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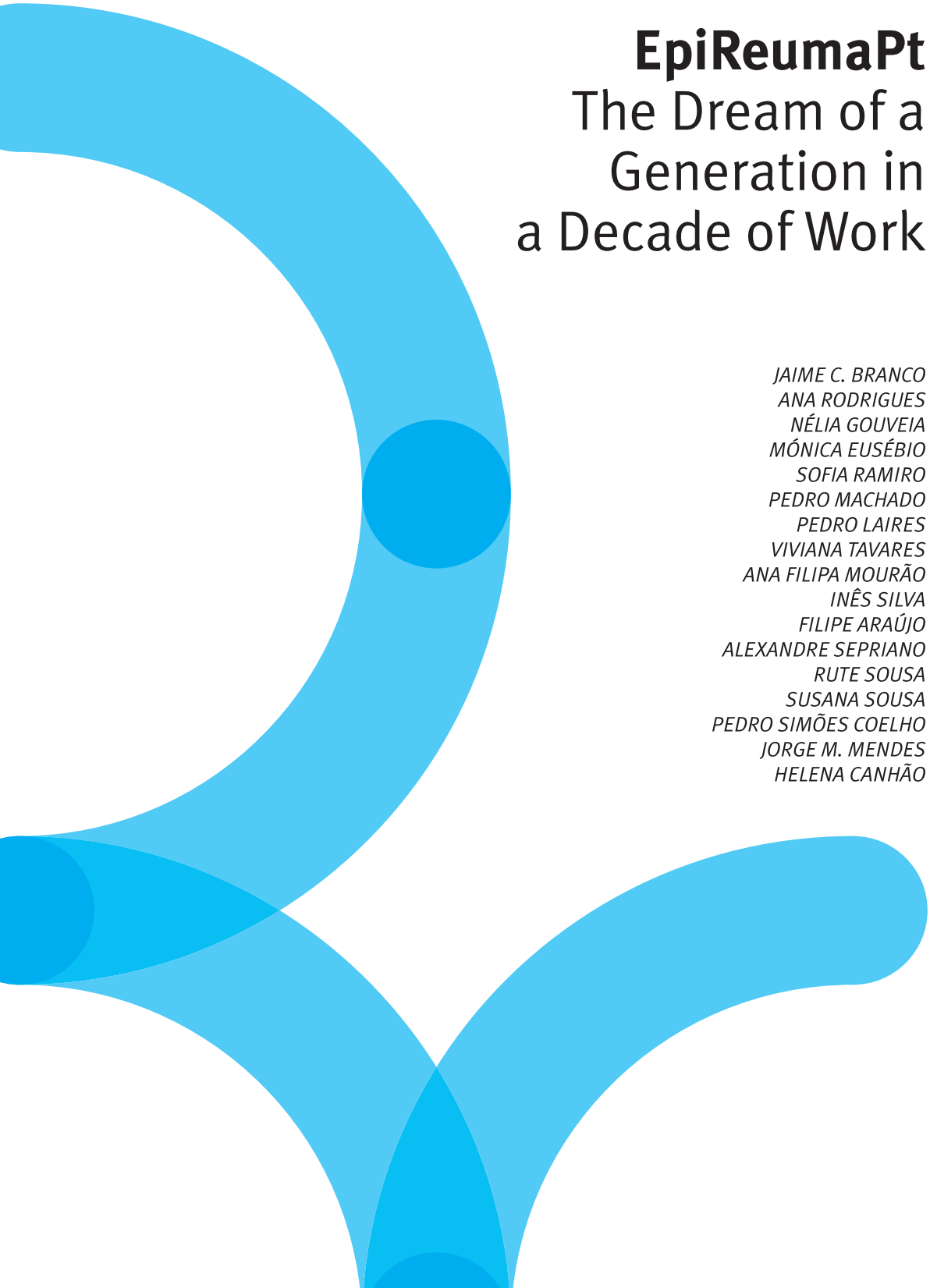
EpiReumaPt
The Dream of a Generation in a Decade of Work

JAIME C. BRANCO
ANA RODRIGUES
NÉLIA GOUVEIA
MÓNICA EUSÉBIO
SOFIA RAMIRO
PEDRO MACHADO
PEDRO LAIRES
VIVIANA TAVARES
ANA FILIPA MOURÃO
INÊS SILVA
FILIPE ARAÚJO
ALEXANDRE SEPRIANO
RUTE SOUSA
SUSANA SOUSA
PEDRO SIMÕES COELHO
JORGE M. MENDES
HELENA CANHÃO



Epidemiology
of Rheumatic Diseases

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Mónica Eusébio, Sofia Ramiro, Pedro Machado,
Pedro Laires, Viviana Tavares, Ana Filipa Mourão,
Inês Silva, Filipe Araújo, Alexandre Sepriano,
Rute de Sousa, Susana Sousa, Pedro Simões Coelho,
Jorge M. Mendes, Helena Canhão

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Short Biography

Jaime da Cunha Branco
was born in 1955 in Lisbon, and graduated by the School of Medicine – Lisbon University in 1978.

Hospital Assistant of Rheumatology in 1992 and Head of Rheumatology Department since 1998, is Director of the Rheumatology Service of CHLO | Egas Moniz Hospital since 2006.

He as a PhD title from NOVA Medical School in 1997, was hired as Assistant Invited Professor in 1999, performed aggregation tests in 2003, was hired as Associate Professor in 2007, and in 2012, made competition for Full Professor of this Medical School of which he is Director since 2013.

He is the author or co-author of hundreds of scientific papers, being Principal Investigator in the area of Rheumatology, of the CEDOC of NMS | FCM. He has received 42 scientific awards, namely the Prémio BIAL de Medicina Clínica 2008 and the Grande Prémio BIAL de Medicina 2016. He has been a Reuméritus of the Sociedade Portuguesa de Reumatologia since 2010 and he is title-holder of the chair number XXV of the Medicine National Academy of Portugal, since 2017.

Ana Rodrigues is investigator of the EpiDoc Unit at CEDOC, the Chronic Diseases Research Centre at Nova Medical School. She is an assistant Lecturer on the disciplines of Rheumatology and Introduction to the Clinic, from Faculdade de Medicina da Universidade de Lisboa. She also is the head of Rheumatology Unit from Hospital do Santo Espirito de Angra do Heroísmo. She graduated in Medicine (Rheumatology) from the Lisbon School of Medicine, University of Lisbon. She also completed the Clinical Scholars Research Training I and II from Harvard Medical School- Portugal Program, a two-year training program on clinical research. She is finishing her Phd in Rheumatology from faculdade de Medicina da Universidade de Lisboa. Her research is focuses on the EpiDoC cohort a population-based study on chronic diseases in particular Rheumatic diseases (osteoporosis) and aging. She also studies the use of ICTs for elderly health promotion.

Nélia Gouveia is pharmacist and holds a PhD in Clinical Research from NOVA Medical School|Faculdade de Ciências Médicas da Universidade Nova de Lisboa (NMS|FCM). In 2015, she starts the NOVA Clinical Research Unit project - which is the Clinical Trial Unit of Universidade NOVA and aims to support academic research, providing national and international networking. Before this, she was the project Manager of the Portuguese Epidemiological Study of Rheumatic Diseases (2011-2016), and also of the Cohort Study of Rheumatic Diseases (2013-2016).
Nélia also collaborated in National Ethics Committee for Clinical Research (2009-2011).
Currently, Nélia Gouveia is Investigator in NOVA Chronic Diseases Research Center (Lisbon, Portugal) as well, the NOVA Clinical Research Unit (NOVA-CRU) manager. She also is the Coordinator of the Master Course - Management of Clinical Research (MEGIC), provided by Universidade NOVA and Universidade de Aveiro. Nélia Gouveia also collaborates at Doctoral Programme in Medicine and also at PhD Programme in Mechanisms of Disease and regenerative Medicine.

Moreover, she is the Clinical Research Consultant of the Portuguese College of Pharmacists (Ordem dos Farmacêuticos).

Nélia Gouveia is also author of scientific articles in national and international publications and has wan the "Prémio Dor - Grunenthal 2015" and was also distinguished with honorable mentions in "Prémio Dor - Grunenthal 2014" and also "Prémio de Investigação Científica Professora Doutora Maria Odette Santos-Ferreira 2015" (Portuguese College of Pharmacists - "Ordem dos Farmacêuticos").

Mónica Eusébio Currently working at the Portuguese Rheumatology Society as a Biostatistician and junior programmer, divides the time between developing Reuma.pt (The Rheumatic Diseases Portuguese Registry) and data analysis. PhD candidate in Statistics and Operational Research since February 2018.

Sofia Ramiro, MD, Msc, PhD, is a rheumatology fellow at Zuyderland Medical Center, Heerlen, and a senior researcher at the Leiden University Medical Center, Leiden, the Netherlands. Sofia Ramiro graduated from Medical School in the Nova Medical School, New University of Lisbon, Portugal. She has done a Master in Epidemiology at Maastricht University. She obtained her PhD, with cum laude distinction, at the University of Amsterdam on long-term outcomes in ankylosing spondylitis under the supervision of Prof. Landewé and Prof. van der Heijde. Her research focuses in axial spondyloarthritis, rheumatoid arthritis, imaging and outcomes research. Sofia Ramiro currently has an appointment at Nova Medical School in Lisbon as a Visiting Professor. She is currently the Past Chair of EMEUNET, the Emerging EULAR Network, and also a member of the EULAR Scientific Committee. Sofia Ramiro has authored more than 120 peer-reviewed manuscripts.

Pedro M. Machado is a Researcher at University College London (UCL) and Consultant Rheumatologist at University College London Hospitals (UCLH) and Northwick Park Hospital (NPH), in London, United Kingdom. He trained in musculoskeletal imaging and clinical epidemiology during his PhD research at the Leiden University Centre (LUMC), The Netherlands.

His research interests include the investigation of new therapeutic strategies and the assessment and prediction of outcomes in rheumatic diseases, with a focus on muscle diseases and axial spondyloarthritis. He has authored over 85 articles and 4 book chapters. He has been awarded 4 fellowships and 13 scientific prizes. He is the chair-elect of the European League Against Rheumatism (EULAR) Standing Committee on Epidemiology and Health Services Research (SCEHSR), member of the EULAR Executive Committee and past-chair of the Emerging EULAR Network (EMEUNET).

Pedro Laires, MSc, PhD
Epidemiologist
Head of Health Economics & Outcomes Research

Pedro Laires is the head of HE&OR at Novartis. He holds a PhD in Epidemiology from the Faculty of Medicine of Lisbon, where he also earned his Master and worked as an invited lecturer in Epidemiology. He has a Degree in Biology (specialty in Genetics) from the Faculty of Science of Lisbon. Pedro also did several courses in health economics, in particular advanced modelling by Glasgow/York Universities. He has over 25 published articles and over 100 oral communications/ posters presented in health sciences conferences. Pedro is a member of the National Public Health Research Center (CISP – Centro de Investigação em Saúde Pública). Presently is a postdoctoral researcher at the National School of Public Health (ENSP - Escola Nacional de Saúde Pública).

Viviana Tavares Graduated in Medicine in 1981 at Faculdade de Medicina da Universidade de Lisboa and completed Rheumatology training in Hospital de Santa Maria, Lisboa in 1991.
Since 1996 is Consultant Rheumatologist at Serviço de Reumatologia Hospital Garcia de Orta where she work since 1991
President of Associação Nacional contra a Osteoporose – APOROS, since 1994
Past President, Sociedade Portuguesa de Reumatologia (2012-2014)
Consultant for Osteoporosis – General Directorate of Health (2009-2014)
Member of the European Union Osteoporosis Consultation Panel (2002 -2012)
Member of the Working Group for the National Plan against Rheumatic Diseases – General Directorate of Health

Ana Filipa Mourão Rheumatologist in Egas Moniz Hospital, Centro Hospitalar de Lisboa Ocidental, Lisbon, and Coordenator of the Pediatric Rheumatology Clinic in this hospital. Assistant of Rheumatology and Investigator at Center for Chronic Diseases (Centro de Estudos de Doenças Crónicas (CEDOC)) in Nova medical School. PhD with the project intitled "Susceptibility and prognostic factors in Portuguese patients with Juvenile Idiopathic Arthritis". Author of 4 chapters in books of rheumatology and first author of 19 papers indexed in pubmed. Coauthor of more than 40 international papers.

Inês Silva Clinical activity: Rheumatologist (MD) at Centro Hospitalar Lisboa Ocidental, EPE – Hospital Egas Moniz (CHLO, EPE – HEM); 2008-2013: Rheumatology Residency at CHLO, EPE – HEM; 2011: Clinical fellowships at Lariboisière Hospital (Paris) and *Azienda Ospedaliera di Padova* (Padova); 2010: Clinical fellowship at Rangueil Hospital (Toulouse). Graduation: 2006 - Medical degree at Faculty of Medicine of the University of Lisbon.
Scientific activity: assistant lecturer at Nova Medical School; author of several papers and communications in the field of Rheumatology. Awards: 2016 – Bial Merit Award in Medical Sciences; 2016 – Honorable Mention: Janssen Innovation Award; 2014 – Honorable Mention: Grunenthal Pain Award. Scientific Societies: member of the Portuguese Society of Rheumatology.

Filipe Araújo Graduated in Medicine from Faculdade de Medicina da Universidade de Lisboa in 2008. Rheumatology residency at Centro Hospitalar de Lisboa Ocidental - Hospital de Egas Moniz EPE, from 2010 to 2015. Rheumatology and Osteoporosis Unit coordinator at the Hospital de Sant'Ana, SCML since 2015. Assistant Teacher of Clinical Microbiology at Faculdade de Medicina da Universidade de Lisboa since 2007.

Alexandre Sepriano MD, is a rheumatologist at Hospital Egas Moniz, Lisbon, Portugal, a research collaborator at CEDOC, NOVA Medical School, Universidade NOVA de Lisboa, and a PhD applicant at the Rheumatology Department, Leiden University Medical Center, The Netherlands.

Rute Dinis de Sousa is EpiDoC Unit Manager at CEDOC, the Chronic Diseases Research Centre at Nova Medical School. She has a master in Clinical Psychology and is finishing her International MBA. Her main focus are projects related to EpiDoC cohort - a population-based study on chronic diseases – and ageing. She is also interested innovation and the use of ICTs for health intervention.

Susana Maria Pereira de Sousa was born in Lisbon on the 8th of March, 1970.
Graduated in Communication Sciences in 1994, with a specialization in Marketing and Advertising from the Autonomous University of Lisbon, she finished the course with a final classification of 14 values.
At the same time she attended the German course at the German Institute of Lisbon.
Her professional activity began in 1995 when she became Account Executive at the advertising agency HPP Comunicação. In 1996 she became a Supervisor of Accounts at the same agency and in 1997, when the agency merged with the EuroRSCG group, she became the Director of Customer Service, a position which was held until 2001.
Simultaneously, between 1996 and 1997 she completed her Master in Image Management from the Group GCI Comunicação and the Universidad Complutense de Madrid.
From 2001 until 2005 she was the Marketing Director of Pousadas de Portugal (Grupo Pestana Pousadas).
Between 2006 and 2011 she was Marketing Director and Partner Manager at MegaRede.
In parallel, between 2006 and 2007 she attended an Italian course at the Italian Institute of Culture Lisbon.
From 2011 to 2013 she was a member of the EpiReumPt team - Epidemiological Study of Rheumatic Diseases in Portugal, working as a Project Assistant. The project "EpiReumaPt - the dream of a generation in a decade of work won the" won the Grand Medicine Bial Award 2016.
In 2014 she started working as Secretary of the Dean of NOVA Medical School|Faculdade de Ciências Médicas of the Universidade Nova de Lisboa. She carried that function until the August of 2014. Presently she is responsible for the Institutional Communication of NOVA Medical School|Faculdade de Ciências Médicas of the Universidade Nova de Lisboa.

Pedro Simões Coelho is Full Professor, Dean and President of the Scientific Board of the NOVA Information Management School (NOVA IMS) of Universidade Nova de Lisboa. He is senior expert near the European Commission for the area of statistical methods and sampling techniques. He is member of the Portuguese Health Technologies Commission and head of information and statistics in NOVA Clinical Research Unit (NOVA CRU). He is author of about 200 studies and projects, resulting in more than 500 research reports and author of more than 100 refereed publications. Pedro S. Coelho has been consultant for several organizations, namely for the European Commission, Eurostat, the Portuguese Statistical Office, the Portuguese Central Bank and several National Statistical Offices around the world.

Jorge M. Mendes is currently Assistant Professor at Information Management School (NOVA IMS). He is member of Management Information Centre (MagIC) at NOVAIMS. He was awarded with a bachelor degree in Statistics and Information Management from NOVA University of Lisbon, MSc in Probability and Statistics and PhD in Statistics and Operations Research from University of Lisbon. He is author of several scientific publications both in national and international outlets, being invited as referee on a regular basis. At NOVAIMS he has been coordinating several research and development projects. He supervises, on a regular basis, MSc and PhD students.

Helena Canhão, MD, PhD
Head of EpiDoC Unit, CEDOC, NOVA Medical School, Universidade Nova de Lisboa (http://cedoc.unl.pt/epidoc-unit/).
Full Professor of Medicine, Epidemiology and Clinical Research, NOVA Medical School and National School of Public Health,Universidade Nova de Lisboa, Lisbon, Portugal.
Senior Consultant of Rheumatology at CHLC-Hospital Curry Cabral, Lisbon.
Vice-President of the Portuguese Society of Rheumatology, Vice-President of the Portuguese League Against Rheumatism and Elected President of the Medical Sciences Society of Lisbon. Co-leader and Chief Medical Officer at the Project Patient Innovation.
Graduated, PhD and Habilitation in Medicine from Lisbon Medical School, Lisbon University and Master in Medical Sciences and Clinical Research from Harvard Medical School, Harvard University, Boston, USA.
Author and co-author of several papers in peer-reviewed journals, book chapters and books.

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Glossary

AAL. Active and Assisted Living
ACR. American College of Rheumatology
ACSS. Central Administration of Health System
ANAFRE. Associação Portuguesa das Juntas de Freguesia
ANDAI. Associação Nacional de Doentes e outros Reumatismos Infantis e Juvenis
ANDAR. Associação Nacional de Doentes com Artrite Reumatoide
ANEA. Associação Nacional de Espondilite Anquilosante
APO. Associação Portuguesa de Osteoporose
APOROS. Associação Nacional contra a Osteoporose
APR. Associação Portuguesa de Reumatologia
ASAS. Assessment of SpondyloArthritis International Society
BD. Bodily Pain
BMA. Bone Microanalysis
BMI. Body Mass Index
CAPI. Computer Assisted Personal Interview
CARD. D. Cardiovascular Disease
CESOP. Centro de Estudos e Sondagens de Opinião
CHPC | NTNU. Centre for Health Promotion Research of Norges Teknisk-Naturvitenskapelige Universitet
CI. Confidence Interval
CINDI. Countrywide Noncommunnicable Disease Intervention
CLBP. Chronic Low Back Pain
CLSBE | UCP. Católica Lisbon School of Business and Economics
CoReumaPt. The Portuguese Cohort of Rheumatic Diseases
CNC. Comissão Nacional de Coordenação
DEXA. Dual Energy Bone Densitometry
DGS. Direção Geral de Saúde
ECTS. European Calcified Tissue Society
EIP on AHA. European Innovation Partnership on Active and Healthy Ageing
EpiReumaPt. Portuguese Epidemiology Study of Rheumatic Diseases
EQ5D. European Quality of Life Questionnaire Five Dimensions Three Levels
EULAR. European League Against Rheumatism
FM. Fibromyalgia
FMUC. Faculdade de Medicina, Universidade de Coimbra
FMUL. Faculdade de Medicina, Universidade de Lisboa

FMUP. Faculdade de Medicina, Universidade do Porto
GAST. D. Gastrointestinal Disease
GBD. Global Burden of Disease
GDP. Gross Domestic Product
GH. General Health
HAQ. Health Assessment Questionnaire
HRQoL. Health-Related Quality of Life
ID. Identification Code
ISPUP. Public Health Institute, Universidade do Porto
KOOS. Knee Injury and Osteoarthritis Outcome Score
LBP. Low Back Pain
LPCDR. Liga Portuguesa Contra Doenças Reumáticas
LUPUS. Associação Nacional de Doentes com Lupus
MH. Mental Health
MRI. Magnetic Resonance Imaging
MSK. Musculoskeletal
MVQ. Professor Mário Viana Queiroz
MYOS. Associação Nacional contra a Fibromialgia e a Síndrome de Fadiga Crónica
NEOPLASM. Neoplastic Disease
NEUR. D. Neurologic Disease
NUTS II. Nomenclature of Territorial Units for Statistics II
OA. Osteoarthritis
ONDOR. Observatório Nacional das Doenças Reumáticas
OP. Osteoporosis
PD. Periarticular Disease
PF. Physical Functioning
PI. Principal Investigator
PIXI. Peripheral Instantaneous X-ray Imager
PMR. Polymyalgia Rheumatica
PNCDR. Programa Nacional Contra as Doenças Reumáticas
PULM. D. Pulmonary Disease
PYWLL. Potential Years of Working Life Lost
RA. Rheumatic Arthritis
RD. Rheumatic Disease
RE. Role Emotional
RMD. Rheumatic and Musculoskeletal Disease
RMDs. Rheumatic and Musculoskeletal Diseases

RP. Role Physical
SF. Social Functioning
SLE. Systemic Lupus Erythematosus
SPA. Spondylarthropaties
SPR. Sociedade Portuguesa de Reumatologia
UN. United Nations
UNL. Universidade Nova de Lisboa
VT. Vitality
WHO. World Health Organization
YWLL. Years of Working Life Lost

Abstract

EpiReumaPt (Epidemiologic Study of Rheumatic Diseases in Portugal) presents the effort and activities developed for over more than a decade to document in a robust, valid and unquestionable manner the prevalence and burden of rheumatic diseases (RMDs) in Portugal. In this initiative, we have irrefutably established the RMDs impact on quality of life, physical function, psychological status, healthcare resources consumption, and socio-economic costs. The body of knowledge obtained with this work has already contributed for new decisions and health policies changes that improve the healthcare of RMDs patients. In parallel, the team has gathered a large cohort of subjects – the EpiDoC Cohort –, representative of Portuguese population, for long-term follow-up. Data collected refers not only to RMDs but also to other non-communicable chronic diseases and lifestyles, their determinants, associated factors and consequences. In fact, either the cross-sectional study of 10,661 subjects in EpiReumaPt (from September 2011 to December 2013) and the longitudinal data obtained in two more waves of data collection of the same participants RMDs (wave CoReumaPt in 2013 and 2015; and wave Saúde. Come in 2015 and 2016) had built a valid and useful source of knowledge regarding health and health related issues of the Portuguese population. These population-based datasets can support decision-making towards a sustainable and efficient healthcare system.

RMDs are, in western countries, the more frequent group of diseases and represent an important medical, social and economic problem and challenge. The concept of RMDs is not clear-cut. This disease group includes more than 100 entities, very distinct among them. EpiReumaPt covered the most frequent and important RMDs from this vast list.

EpiReumaPt was the first national, large-scale epidemiological population-based study evaluating the prevalence, determinants and burden of RMDs in Portugal. 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. Positive screenings for ≥1 Rheumatic and Musculoskeletal Disease (RMDs) 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.

This study determined the prevalence of 12 target diseases (low back pain (LBP), fibromyalgia (FM), osteoporosis (OP), periarticular disease (PD), hand, knee and hip osteoarthritis (OA), rheumatoid arthritis (RA), spondylarthropaties (SpA), systemic lupus erythematosus (SLE), gout and polymyalgia rheumatic (PMR)) and the impact of RMDs on physical and mental health and the economic burden of these diseases.

The disease-specific estimated 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%). In this study we had verified that subjects with RMDs had significantly lower quality of life (QoL)-EQ5D scores (ß=-0.09; $p<0.001$) and higher disability (HAQ) scores (ß =0.13; $p<0.001$) than subjects without RMDs after adjustments for confounders. We found that PMR, RA and FM were the conditions with the worst impact on physical function and QoL.

When we compared participants with and without RMDs regarding mental distress symptoms, we found a significantly higher proportion of RMDs patients with anxiety symptoms (OR=3.5; $p=0.006$).

Another interesting finding of our study was the high proportion of individuals presenting typical features of one or more RMDs, who did not have a previous diagnosis (1,532 subjects out of 3,877 observed in rheumatologist appointments). This could be explained by the scarce number of rheumatologists in Portugal (1:100000 inhabitants) and by the lack of awareness of the population about these diseases, being frequently accepted as part of the normal aging process.

Finally, in EpiReumaPt we have verified that the economic burden

of RMDs is very high. Con-sidering healthcare resource consumption, we found that Portuguese inhabitants with RMDs were significantly more hospitalized and in need for more homecare support when compared to those with no rheumatic disease (OR=2.45, p=0.032 and OR=12.78, p=0.002, respectively).

In terms of indirect costs evaluation, the early exit from work attributable to rheumatic diseases may represent a problem to be addressed in future policy measures. In fact, RMDs may lead to premature retirement. We estimated that annually this sort of productivity loss may amount to 910 million euros, which is equivalent to 0,5% of our GDP.

In summary, RMDs are highly prevalent in Portugal and are associated not only with a significant physical function and mental health impairment but also with a poor quality of life, leading to more health resources consumption and higher early retirement.

All results together emphasize the burden of RMDs in Portugal and the need to develop RMDs awareness, building a strong rational to encourage policy makers to increase the amount of resources allocated to the treatment of rheumatic patients. EpiReumaPt can provide valuable data to researchers, healthcare providers and patient organizations to future research.

Obviously, the fulfilment of these objectives in itself would be a very important achievement with great consequences, but what this study represents and entails truly surpasses those goals.

First of all, it was showed that it is possible to develop an undertaking of this size in Portugal with the accuracy, prolific ability and professionalism necessary for its success. And this fact alone represented a gratifying reward for all the "patrons" who - and this shouldn't go unnoticed risked pursuing the social importance and national relevance of what was then just a simple project.

It also revealed that it is possible to motivate towards a common goal, a large number of doctors who, despite their many obligations and professional affairs, were able to mobilize so as not to jeopardize in the slightest the tight and demanding schedule of appointments that moulded the 2nd phase of EpiReumaPt.

Finally, EpiReumaPt was the kick-off to the constitution of an organized research team that built the EpiDoC Cohort that followed for five years EpiReumaPt participants.

In the following two data collection, we repeated most of the questions but also asked about new diseases and therapies, death, adverse events, hospitalizations, medical appointments and have more specific questions about life habits, nutrition, food security, exercise and health innovation.

We think that this work is an excellent example of how a very demanding organization and fieldwork can boost the acquisition of knowledge on the health of the Portuguese population as well as other important aspects like work, income, health costs, life habits and many other. This model can be used to learn more about other non-communicable chronic diseases, beyond rheumatology.

This work proves that is possible to develop and produce high quality clinical and epidemiological research in Portugal, obtaining results that can be translated to clinical practice of individual patients, as well as in a socio-economic dimension, to inform and help the design of new policies, collaborating to the improvement of the healthcare and health system.

Preamble

EpiReumaPt was always considered a fundamental necessity, however was continually postponed.

The delay in the study's implementation was due to its major overall complexity, high demand for human, material and financial resources and extraordinary time requirement inherent to a project of this magnitude.

These intrinsic characteristics plus the small number of rheumatologists and the short time elapsed since Ordem dos Médicos [Medical Association] has recognized this specialty have turned this demanding assignment into an astonishing, but unlikely to success, epopee.

The dream overlapped the anticipated strains and abysmal barriers that the old voices from "Restelo" had announced.

And, as the need sharpens the wit, we dared to start navigating (19/09/2011) in the complex craft we had methodically built and carefully equipped for more than 6 years.

This long 27 months journey led us across the country, from the mainland (which we crossed from south to north and interior to coast) to the autonomous regions of Azores and Madeira.

The immense data we eventually collected had to be filtered, verified, tested and aligned so that the results could be managed without fear of error or inaccuracy.

The onset of the first wave of results came naturally and responded to some, and yet only a few, of the many and diverse questions that directed to this adventure.

The study of EpiReumaPt data originated more knowledge we wish to see multiplied in the future. In fact, this is the only way for this point of arrival to be also a starting place to expand the information available on the frequency and weight of RMDs in Portugal. Make no mistake, EpiReumaPt is not limited to the exceptional epidemiological data collection on RMDs.

The size and diversity of EpiReumaPt database can, and should, equip many other research projects that reveal further important dimensions of RMDs.

Altogether, more than ten thousand participants obtained in EpiReumaPt become a Cohort (EpiDoc Cohort) whose extent and unique

population will provide us with several indications and some answers about not only the origin and evolution of RMDs, but also other chronic non-communicable diseases.

This extraordinary opportunity to obtain a variety of information is not only unique in the national scientific scene but also provides a remarkable opportunity to supply other lines of investigation.

The new research directions mentioned have already begun to be explored and its pursuit will surely intensify in the future.

Chapter 1

The Dream

1.1. Conceptual Overview

The "Bone and Joint Decade: 2000-2010" was inspired by the great international success ex-perienced in the previous decade's (1990 to 2000) dedicated to the process of neurosciences.

The concept originated in Lund, Sweden, in 1996, and received immediate support from several national and international institutions - such as United Nations (UN), World Health Organization (WHO), Scientific Institutions, Patient's Associations, Professional Organizations, several foundations and scientific magazines. In 1998 an assembly took place in Lund, where a consensus document and a continued action plan were produced. The aim for the Decade 2000-2010 was to "improve the quality of life of individuals all over the world suffering from musculoskeletal diseases" (1).

RMDs may be defined as non-traumatic functional disorders or alterations of the musculoskeletal system, that comprise a group of more than one hundred entities with numerous subtypes which include inflammatory diseases of the musculoskeletal system, peripheral and axial joint diseases, bone and joint metabolic diseases, changes in the periarticular soft tissues and disorders in other organs and/or systems related to the above (2).

These diseases can be acute, recurrent or chronic and affect individuals of all ages. RMDs are a frequent cause of disability and when not diagnosed or treated early and correctly, can have severe and unnecessary physical, psychological, family, social and economic repercussions (2).

The clinical manifestations of RMDs (eg, joints and/or soft tissue pain and swelling, limited mobility and more or less marked functional disability) are very common in the general population and particularly prevalent among women, elderly and people with lower incomes and lower literacy (2).

Thus, as a whole, this wide-ranging and diverse group of diseases is among the main contributors for direct and indirect health expenses due to its high frequency, morbidity and costs (3).

Although the "rheumatic reality" varies considerably from one country to another, the point is that, in all countries, the overall rheumatic condition was worse than in every other medical specialty. While there were asymmetries between countries, globally the population was very unaware of RMDs. Indeed, patients did not know when, where and to whom they should appeal and most doctors, and other health professionals, did not have enough knowledge on how to address the disease or under what circumstances they should refer the patients to rheumatologists (4).

Health authorities did not perceive RMDs the same way as they In the majority of these countries, labour or social legislation did disadvantages caused by these diseases (1). Often, RMDs were Schools or given insufficient curricular value (5).

For these reasons, the Decade 2000-2010 established itself in a very fast, sustained and assured manner.

The European League Against Rheumatism (EULAR), which supported the decade 2000 - 2010 since the beginning, converted its congress in an annual event (until 1999 occurred once in every 4 years). Thus, since EULAR 2000 (Nice, France, 20-24/06/2000) the congress has happened annually and in 2003 it took place in Lisboa, Portugal (18 - 21/06/2003) (6).

Also in 2003, the World Health Organization asserted an urgent need to fight against musculoskeletal diseases, considering their elevated and rising prevalence, high diversity and consequences - mainly functional inability, work absenteeism and other direct and indirect health expenses- which weakened a lot of countries' already feeble Health Systems (1).

In this context, the association and cooperation of related medical and scientific fields (e.g., rheumatology, orthopaedics, rehabilitation, public health) raised awareness and encouraged international and national policy-makers to define preventive strategies (primary, secondary and tertiary) capable of reducing the risk of RMDs and decreasing its consequences and/or complications' effects (1).

Several international authorities acknowledged the need for epidemiological data that allowed clinical decisions to be scientifically sustained and presented good cost-effectiveness ratio (1). Similarly, this happened in Portugal through the Ministry of Health's support to the Decade 2000-2010.

1.2. Portuguese Context

Rheumatology in Portugal was born in 1948, when Dr. Manuel Assunção Teixeira, Professor Pulido Valente's disciple, and other honourable physicians founded the Associação Portuguesa de Reumatologia (APR) [Portuguese Rheumatology Association]. In 1954 the association was extinct when Dr. Assunção Teixeira, Professor Luis de Pap and other APR members created the Instituto Português de Reumatologia [Portuguese Rheumatology Institute].

In 1957, the request was made to officially establish the specialty of Rheumatology but it was only in 1977 that the Ordem dos Médicos [Portuguese Medical Association] approved this specialty (Regulatory Decree No 07/77, June 5th). The first internship began in 1981 and since then the Rheumatology training has specialized more than 120 rheumatologists (7).

The implementation and implantation of Rheumatology in hospitals, while still incomplete, presented some progress through the application of several national rheumatologic actions. But undoubtedly it was the Programa Nacional Contra as Doenças Reumáticas (PNCDR, 2004-2014) [National Program Against Rheumatic Diseases] that best impelled the development of Rheumatology in our country (in terms of assistance, prevention, instruction, divulgation and investigation). This Program was developed by a group of rheumatologists led by Professor Mário Viana Queiroz (MVQ) under the aegis of Direção-Geral da Saúde (DGS) [Directorate-General of Health] (2).

PNCDR was incorporated into the 2004-2014 National Health Plan and represented the Ministry of Health's contribute to the Decade 2000-2010 international movement (1,4).

Despite its great clinical, social and economic importance the true scale of the problem caused by RMDs was undetermined in Portugal. The clinical experience and data obtained in other countries allowed us to understand that, although the mortality caused by these diseases was low, at least 30% of the population suffered musculoskeletal symptoms, 20% had a RMD, 7% would exhibit some degree of incapacity as a result of a RMD and 0.5% would even become invalid (2).

In our country, several epidemiological studies had already been conducted, although purely at a regional level (e.g., Lisboa, Oporto, Setubal, Azores and Madeira) and/or regarding just one disease/syndrome (e.g., osteoporosis, osteoarthritis).

Dr. João Figueirinhas was the first rheumatologist who studied the association between RMDs epidemiology and work absenteeism (8,9).

In the late 80s, early 90s of last century, MVQ's team conducted a rheumatologic questionnaire and clinical exam to the entire sample group (n=1381) of CINDI (Countrywide Noncommunicable Disease Intervention) study, randomly selected from Setubal Peninsula's population. This study, which resulted from a WHO initiative, was carried out in several countries and intended to do an epidemiological analysis of cardiovascular disease, dietary habits and diabetes. Portugal was the only country where RMDs, as well as the ocular pathology, were studied (10).

Later, osteoporosis and fragility fractures, due to the development of new and effective therapies, were the predominant topic of multiple regional epidemiological studies, either strictly national or integrated into international projects (11).

For the same reason, rheumatoid arthritis would undergo a similar epidemiological investigation, a few years later (12,13). Several years later, the same occurred with fibromyalgia (14).

Despite the relatively abundant scientific literature on the epidemiology of RMDs, rheumatologists and its Scientific Society, Sociedade Portuguesa de Reumatologia (SPR) [Portuguese Society of Rheumatology] felt the need to get credible national data on the most relevant RMDs (15,16).

PNCDR was responsible for assembling the necessary and appropriate conditions for not only reinforce the need for a national RMDs epidemiological study, but also for partially setting its goals and methods.

Indeed, the program postulated that RMDs are a diverse nosological group that, as a whole, causes high morbidity, significant temporary disability, frequent work absenteeism and premature permanent incapacity, resulting in large numbers of early retirement due to disability, reduced life expectancy and negative economic and social impact (2).

PNCDR also marked the existence of evidence that a correct and early

diagnosis and an appropriate and timely treatment of RMDs significantly reduces its consequences, regarding both physical disability and therapeutic intervention, which made it imperative to encourage the diffusion and teaching of RMDs to professionals from different areas of the health system (2).

PNCDR aimed for a 10-year time horizon and had three overall goals - 1) to control the morbidity and mortality caused by RMDs; 2) to improve the quality of life of rheumatic patients, and 3) to control costs associated with RMDs - and five specific goals, four of which were quantitative – to know the prevalence of RMDs covered by the program and also the incidence of soft-tissue rheumatic diseases, low back pain and osteoporotic fractures. These could only be properly established by conducting an epidemiological study nationwide (2).

This program defined 21 national, regional and local development strategies. Of these, 11 were intervention approaches, 8 concerned training and 2 referred to information collection and analysis. In order to fulfil the latter, it advocated the development of multi-sectorial partnerships with the aim of creating an observatory for rheumatic diseases, which should include systems for data collection, to enable not only the gathering and analysis of information (on RMDs prevalence and incidence, temporary and/or permanent disability and work absenteeism it causes) but also the monitoring of potential health gains resulting from the Program itself (2).

PNCDR COMPRISED THE FOLLOWING RMDs (7)

1. Osteoarthritis
2. Back Pain
3. Soft-tissue Rheumatic Diseases
4. Work related musculoskeletal injuries
5. Osteoporosis
6. Fibromyalgia
7. Microcrystalline Arthropathies
8. Rheumatoid Arthritis
9. Spondyloarthropathies
10. Systemic Rheumatic Diseases
11. Juvenile Idiopathic Arthritis

All actions that comprised the strategies were scheduled on a trimestral incidence timeline that covered the first five years of its implementation (2).

The PNCDR anticipated its own monitoring and evaluation to be carried out by Regional Health Administrations. Its national coordination was performed by the DGS through a Comissão Nacional de Coordenação (CNC) [National Coordination Committee] created by Ministerial Dispatch (2).

This periodic evaluation assessed indicators of prevalence, incidence, disability and mortality caused by RMDs (2).

SPR and the Serviço de Higiene e Epidemiologia da Faculdade de Medicina da Universidade do Porto [Department of Hygiene and Epidemiology, Faculty of Medicine, University of Oporto], created the Observatório Nacional das Doenças Reumáticas (ONDOR) [National Observatory of the Rheumatic Diseases] in partnership, through a protocol signed in June 2003 (17).

ONDOR's mission was to maintain a permanent and continued attention to the reality and developments of Portuguese rheumatology and its insertion in the international context, in order to produce good quality information for the general public, the interested health pro-fessionals and health authorities.

According to the PNCDR, ONDOR should therefore fulfil their information collection and analysis strategies and quantify the health gains resulting from the program's implementation (2,18).

Thus, ONDOR's tasks included a wide range of activities, from the assembly and processing of routine information, resorting to diverse and wide health, demographic and social statistics produced in Portugal and abroad, to information production through the collaboration with several healthcare providing entities (1,18).

Among the multiple initiatives, international and national communications and publications, ONDOR (17). Produced three reports of great technical, scientific and political significance: "Relatório de Actividades 2003-2005" [Activities Report 2003-2005], issued during the XIII Congresso de Reumatologia (Ponta Delgada, 27-29 April 2006) (17).

O Estado da Reumatologia em Portugal" [The State of Rheumatology in Portugal], issued in April 2010 (1).

"Doenças Reumáticas em Portugal: Da Investigação às Políticas da Saúde" [Rheumatic Diseases in Portugal: from Research to Health Policies], issued in April 2014 (available online since 2012) (19).

Despite all this immeasurable and extraordinary work, PNCDR's CNC and SPR maintained that it was essential to conduct an epidemiological study of RMDs in Portugal. Only a study of this sort could provide most of the key instruments to successfully implement PNCDR.

Professor Henrique de Barros and Professora Raquel Lucas, in charge of ONDOR, shared this view and were important consultants in the study that was to be conducted.

1.3. Research Team

Following the PNCDR publication and its first Coordinator nomination (MVQ), several work groups were created, under its coordination structure.

The long-lasting need, identified by rheumatologists and by the SPR, of an accurate knowledge of RMDs prevalence in Portugal, was now integrated as a specific objective of PNCDR, with the creation of a working group devoted to epidemiology. Two of the authors of PNCDR - Jaime Branco and Helena Canhão - started, in the beginning of 2005, drafting the methodology and the scientific protocol for the desired epidemiological study, gathering and analysing relevant national data on RMDs.

A review of the work developed in Portugal up to the beginning of the millennium, showed homogeneous and coherent numbers, revealing RMDs as the most prevalent medical condition (between 28% to 37% of the population) and the main reason for general practice/family medicine appointment (20% of these consultations) (15,20).

Using the EpiPorto cohort (n=2485 adults of Oporto), ONDOR identified at least one diagnosis of RMDs (among the most frequent and/or main diseases) in 23% of this population. Women (28.7%) had at least one of these diseases, more frequently than men (13.1%) (21).

An earlier publication had already revealed that musculoskeletal pain complaints were also very common in children and adolescents. In a sample of 762 students between 6 and 17 years, selected in two schools of Lisboa, the prevalence of musculoskeletal pain in the 3 months prior to evaluation was 28.4%. These conditions were more frequently mentioned by female students (62.8%) and were mostly referred to the lower limbs (22).

In a 2005 study of the Observatório Nacional de Saúde [National Health Observatory], the self-reported prevalence of RMDs was 24%, more frequent in women (29.1%) than in men (18.3%) and also increased with age (23).

In the 4th National Health Survey (2005/06), the prevalence of self-declared RMDs throughout life, was 16.9% for the continental population. This number was surpassed merely by High Blood Pressure reported by 20% of the population. The frequency of RMDs in the autonomous regions, was lower - 12.9% in the Azores and 6% in Madeira. Throughout the country the RMDs were more prevalent at older ages and women for all age groups (24).

In the WHO sponsored CINDI program conducted in Setúbal Península, rheumatologists observed a randomized population of 1,381 adults of both genders. Table 1 summarizes the prevalence found in this study for some inflammatory RMDs. Until 2005, this study, conducted nearly 30 years ago, was the one that involved the largest population sample with the specific goal of studying the prevalence of RMDs in our country (25).

Table 1. Frequency of some Inflammatory RMDs in CINDI population

RMDs	PREVALENCE
Uric Gout	1.5%
Rheumatoid Arthritis	0.36%
Ankylosing spondylitis	0.22%
Psoriatic Arthritis	0.14%
Juvenile Idiopathic Arthritis	0.07%

Regrettably for a number of reasons, this important data was published twice simply in the form of abstract in the context of two oral presentations, in Funchal, Madeira (VI Portuguese Congress of Rheumatology, 1991) and Budapest, Hungary (XIIth European Congress of Rheumatology, 1991).

Many other reviewed epidemiological studies were designed to characterize just a specific pathology, were either carried out in smaller geographic areas or failed to assemble a representative sample.

The extensive and thorough review concluded the existence of diverse and important gaps in epidemiological knowledge on RMDs in Portugal; the data was neither reliable nor updated.

Consequently, EpiReumaPt - Portuguese Epidemiology Study of Rheumatic Diseases started to be planned and designed by PNCDR's group responsible for epidemiology.

A review of analogous studies conducted in Europe, particularly in similar countries (Southern Europe), and the rest of the world was conducted aiming to find a model that would eventually be applied to the Portuguese reality and/or to identify methodologies and questionnaires that could serve our needs (26,27,28).

The analysis revealed that, unlike us, many European countries, like Spain and Greece, had well-designed and consistent epidemiological studies of RMDs (27,28).

However, it also showed that none of the methods used would be able to meet our goals (29).

It was therefore necessary to design and develop a new and innovative methodology for EpiReumaPt.

In 2009, in order to prepare EpiReumaPt's Protocol, the team was reinforced by Dr. Sofia Ramiro, who despite her youth had great national and international epidemiological experience.

The resulting work was published in mid-2010 and was fundamental for the success of the funding campaign (30).

Early in 2011, with the certainty that EpiReumaPt would be a reality, out of more than 60 candidates we selected the project manager (Dr. Nélia Gouveia) and reinforced the study team with Dr. Pedro Machado and Dr. Pedro Laires, later joined by Dr. Ana Filipa Mourão and Dr. Inês Silva.

The services of the Centro de Estudos e Sondagens de Opinião (CESOP), Universidade Católica Portuguesa [Opinion Studies and Surveys Centre, of the Portuguese Catholic University] were hired due to their expertise in population - based studies. In fact, CESOP had a relevant previous experience among clinical studies provided by the National Epidemiological Study of Mental Diseases (31). We highlight the work of Eng. Jorge Cerol (Executive Director of CESOP and the Project's General Coordinator), Dr. Leonor Pereira da Costa (Project's Operational Coordinator) and Dr. António Vale (Fieldwork Coordinator Assistant).

Engineer Jorge Ventura and Dr. Fernando Martins (responsible for SPR's informatics systems) were responsible for the development of the software assisting the whole project.

For the fieldwork we hired a total of seven nurses, three radiology technicians and five drivers (32,33).

The management board's structure (Professor Jaime Cunha Branco, Professor Helena Canhão and Dr. Nélia Gouveia) was flexible, but endowed with strong decision-making capacity. This was one of the ingredients that contributed to the success of EpiReumaPt (32,33).

The Executive Secretariat, coordinated by the Project Manager, included Dr. Susana Sousa and Dr. Tânia Rego (radiology technician also responsible for the mobile unit's coordination).

EpiReumaPt is a cross-sectional epidemiological study capable of providing an accurate representation of RMDs in Portugal. Nonetheless, the constitution of Cohorts (CoReumaPt) for different purposes was one of the secondary goals of the study. The CoReumaPt working group included EpiReumaPt's research team, some of its consultants (Professor João Eurico Fonseca, Professor José António Silva and Dr. Viviana Tavares) and other invited rheumatologists (Dr. Domingos Araújo, Dr. José Carlos Romeu, Dr. Maria José Santos and Dr. Elsa Sousa) (32,34).

Most of the rheumatology appointments were performed by Dr. Ana Maria Rodrigues, who was later included in EpiReumaPt management team mainly for processing data collected in the field.

After all data collection, Dr. Filipe Araujo and Dr. Alexandre Sepriano were recruited to, under Dr. Inês Silva coordination, conduct the analysis

of all electronic records from the rheumatology appointments.

The research group also included a total of 95 rheumatologists, who volunteered to perform unpaid medical consultations, conducting all 3,886 of EpiReumaPt's clinical observations.

1.4. Funding

Funding, or rather its scarcity, has always been one of the major difficulties that prevented carrying out an epidemiological study of RMDs in Portugal, despite its necessity being widely acknowledged (2).

But this time there was a PNCDR, propelled by DGS and with a hard-working coordinating structure, in line with SPR, its five successive Boards and most of its members (35).

This agreement meant not only the recognition of the need of this study, but also, and above all, the recognition of the excellence of the moment when multiple wills and environments prone to resolving constraints came together.

PNCDR's epidemiology group based its entire project on the assumption that EpiReumaPt would be held exclusively in our mainland. This interim scenario was mainly due to the fact that the extension of the study to the autonomous regions (AR) of Madeira and the Azores, would mean an approximately 40% increase on the continental budget (1.6 million € instead of 1.15 million).

However, our desire for EpiReumaPt to truly be a nationwide study was such, that, after several meetings with multiple authorities during the XV Congresso Português de Reumatologia, held in Funchal, in April of 2010, it was finally decided that the study would cover the entire national territory.

The fundraising began in this Congress with the expressed donation of a rheumatologist (Dr. José Bravo Pimentão). It was merely the symbolic beginning of a long, difficult but fruitful campaign.

The second part of the funding was more substantial (about 1/3 of the budget forecast) and resulted from a special Pfizer International call

for product/drug free 5 yearlong research projects for which we applied (March 2010), in a crucial collaboration with Dr. Eduardo Ribeiro (Medical Director of Pfizer Portugal at the time) and won (July 2010). This was the key breath we needed to keep undertaking without fear. We had reached the point of no return.

In May 2010, we took the opportunity of a DGS call opening for non-profit public interest entities (SPR was the formal candidate) to submit projects integrated into one of the National Health Plan programs (as was the case of PNCDR). Our application obtained the requested funding (about half of EpiReumaPt's budget) distributed in equal shares for 4 years.

Having this key financial support in perspective and with EpiReumaPt's Protocol already published (30), presenting the project and requesting support for its execution became easier. We did it with several companies and entities (see list of financing and support) and we were getting positive responses either in cash (for example, the pharmaceutical industry companies and Fundação Calouste Gulbenkian) or services (e.g. GALP, Açoreana Seguros, Happy Brands, Germano de Sousa, Cal Clínica, Fundação Champalimaud).

In the latter group we cannot fail to include all 95 rheumatologists who willingly and graciously collaborated with EpiReumaPt in carrying out medical consultations that took place in different health centres.

The fund-raising process for EpiReumaPt implementation was so successful that the end result exceeded the required for its completion. The surplus was used in the early phases of CoReumaPt.

Despite this success, there were moments of pronounced capital struggle, especially in the early stages of the project as the funds were received in parcels and to put through the fieldwork we had considerable expenses to cover. SPR Board (President, Dr. Luís Maurício) provided the amount required to address these demands (70 000€) and was later reimbursed.

EpiReumaPt obtained the necessary funding for its implementation in such a distinctive moment, just before the consequences of the global financial crisis started, that it would be perhaps unrepeatable.

1.5. Institutional and Scientific Support

Right from the conception and drafting of the article in which the EpiReumaPt protocol was published, the Scientific Committee was defined.

It was constituted by Professor Loreto Carmona (responsible for the epidemiological study of RMDs in Spain - EpiSER), Professor Henrique de Barros (Epidemiologist, FMUP - Faculdade de Medicina, Universidade do Porto, later ISPUP - Public Health Institute, Universidade do Porto, and re-sponsible for ONDOR), Dr. Viviana Tavares (Rheumatologist, Hospital Garcia de Orta), Professor João Eurico Fonseca (Rheuma-tologist, FMUL - Faculdade de Medicina, Universidade de Lisboa) and Professor José António Pereira da Silva (Rheumatologist, FMUC - Faculdade de Medicina, Universidade de Coimbra) (30).

Figure 1. EpiReumaPt Kick-off ceremony in September 2011. From left to right Jaime C Branco (EpiReumaPt PI), Francisco George (Director-General of Health),), Luís Maurício (President of Sociedade Portuguesa de Reumatologia at the time) and João Carvalho das Neves (President of Administração Central dos Serviços de Saúde(ACSS) at the time)

After finishing the fieldwork and processing millions of data, there was a need for more specific and specialized statistical support. Thus, Professor Pedro Simões Coelho and Professor Jorge Mendes, from NOVA Information Management School, Universidade NOVA de Lisboa (UNL), were invited as scientific consultants for EpiReumapPt (36).

The promoters of EpiReumaPt were DGS (PNCDR's Coordination Headquarters), SPR, CESOP-UCP (whose services, although remunerated, far exceeded contractual obligations) and the NOVA Medical School, UNL (Institution to which belongs the principal investigator of EpiReumaPt and that enabled some of the financing).

Moreover, the study received support from other Portuguese medical schools that have undergraduate rheumatology education, performed by rheumatologists (such as FMUP, FMUC and FMUL) and the Sociedad Española de Reumatología [Spanish Rheumatology Society].

EpiReumaPt's social partners were LPCDR (Liga Portuguesa Contra as Doenças Reumáticas), rheumatic diseases patient's associations such as ANEA (Associação Nacional de Espondilite Anquilosante) [National Association for Ankylosing Spondylitis], ANDAI (Associação Nacional de Doentes com Artrite e outros Reumatismos Infantis e Juvenis) [National Association for Patients with Arthritis and other Child and Juvenile Rheumatisms], ANDAR (Associação Nacional de Doentes com Artrite Reumatoide) [National Rheumatoid Arthritis Patients Association], APO (Associação Portuguesa de Osteoporose), APOROS (Associação Nacional contra a Osteoporose) [Portuguese Osteoporosis Associations] and MYOS (Associação Nacional contra a Fibromialgia e a Síndrome de Fadiga Crónica [National Association against Fibromy-algia and Chronic Fatigue Syndrome]. LUPUS (Associação Nacional de Doentes com Lupus) [National Association of Patients with Lupus] was likewise invited to support EpiReumaPt but declined the request.

RESPONSIBLE ENTITIES

SPONSOR

Chapter 2

The Journey

2.1. Methodology Overview

This chapter describes the design in detail, methodology and the field challenges of EpiReumaPt - a population-based study (36). 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 (30).

The secondary aims were to determine the impact of RMDs on function, quality of life, mental health, work status and use of healthcare resources, in line with the objectives of the PNCDR.

EpireumaPt needed to be a valid and well-designed cross-sectional population-based study. All details of the methodology were carefully planned, designed and discussed from 2005 to 2009 and the study protocol was published in 2010 (30). EpiReumaPt recruitment started in September 2011 and finished in December 2013. The study involved a three-stage approach. The first step was a face-to-face survey performed by trained interviewers at the household of 10,661 subjects who were randomly selected by a stratified multistage sampling and were representative of the Portuguese population.

A highly sensitive screening questionnaire for RMD 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. Subjects participating in this second phase 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 rigorous methodology and large scale of the study were

unprecedented in Portugal and represent an important contribution of rheumatology as a specialty towards excellence standards of epidemiological and clinical research in Portugal (36).

2.2. Objectives

EpiReumapt was a cross-sectional population - based study that had the following aims:

PRIMARY OBJECTIVE

Estimate the prevalence of the different RMDs in Portugal

SECONDARY OBJECTIVES

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

2.3. Geographical Setting

Portugal is a Southwestern European country that includes the mainland and the two archipelagos of Madeira and Azores. According to the National Census 2011, Portugal had a resident population of 10,562,178

inhabitants, of which 8,657,240 were adults (4,072,122 men and 4,585,118 women) (37). As in other European countries, the age gap between young and older people has increased in the last decade. In fact, the percentage of young adults (18-29 years-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 (37).

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 (Azores) and Região Autónoma da Madeira (Madeira). At the NUTS II level, the Norte region has the largest population (34.7 %) followed by Lisboa e Vale do Tejo (26.6%) and Centro (22.4%) (Figure 2).

The other NUTS II regions (Alentejo, Algarve, Azores and Madeira) encompass small towns and villages with a lower population density and higher desertification rates.

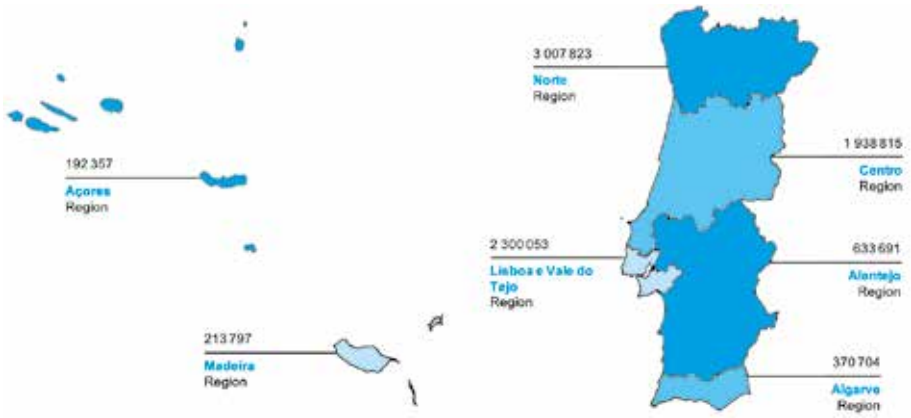


Figure 2. Portuguese population density distribution according to NUTS II(36). NUTS II- Nomenclature of Territorial Units for Statistics (Norte, Centro, Alentejo, Algarve, Lisboa, Madeira and the Azores)

2.4. Study Population

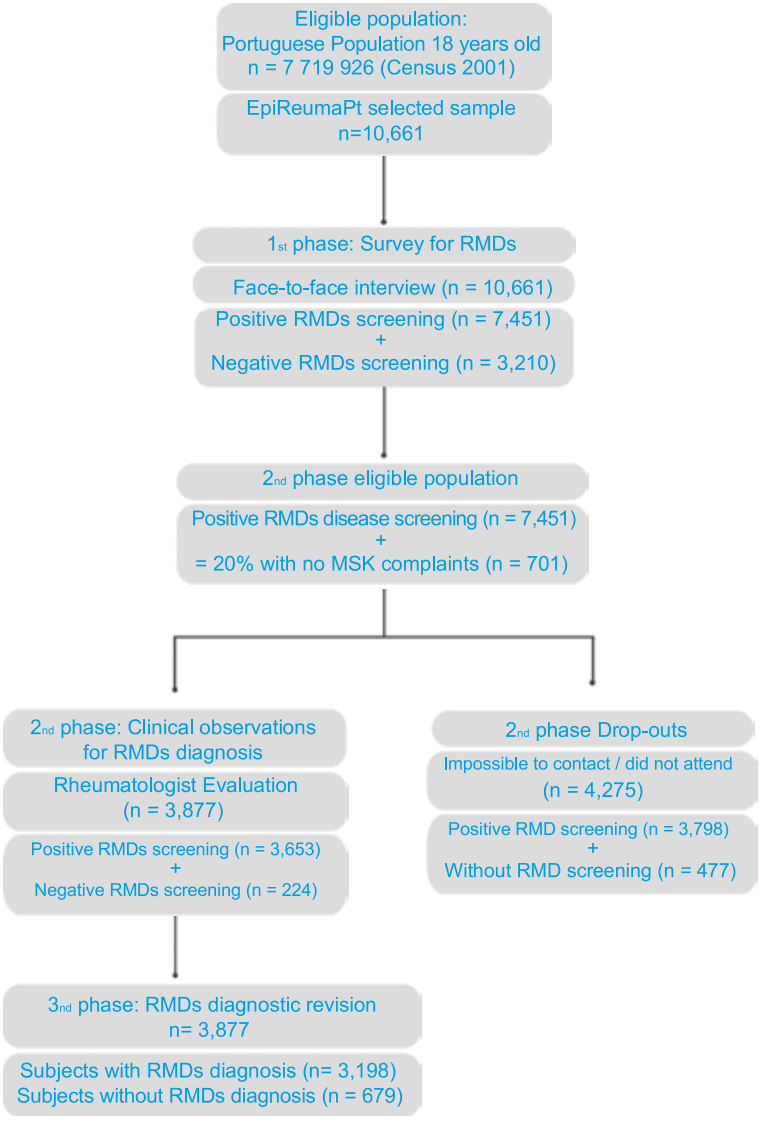
The population of EpiReumaPt study was composed by non-institutionalized adults (≥18 years-old) living in private households in Portugal (Mainland and the Autonomous Regions of Madeira and Azores). Therefore, residents in hospitals, nursing homes, military institutions or prisons were excluded, as well as individuals unable to speak Portuguese or unable to complete the questionnaire, despite being aided (30).

2.5. Sample Size Estimate

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

2.6. Planning, Development and Analysis

EpiReumaPt was a national, cross-sectional, population-based study conducted across all country from September 2011 to December 2013, involving a three-stage approach (36) (Figure 3). In phase 1 – Survey for RMDs screening –, there was a face-to-face interview performed at participants' households, selected by random route methodology. In phase 2 – Clinical observations for RMDs Diagnosis - all subjects who screened positive for at least one MSK symptoms disease during phase 1, and also 20% of individuals with no rheumatic complaints, were observed by a rheumatologist. Finally, in phase 3 – RMDs Diagnosis Revision -, cases were defined after revision of all the clinical data from each participant by a team of 3 experienced rheumatologists considering previously validated criteria.



RMDs- Rheumatic and Musculoskeletal diseases

Figure 3. Flowchart of recruitment in the EpiReumaPt Study (36)

2.6.1. Phase 1 - Survey for RMDs Screening

In phase 1, the disease screening was performed by a face-to-face interview that was carried out by CESOP of Portuguese Catholic University. Moreover, CESOP was also responsible for the recruitment of EpiReumaPt sample.

CESOP had a relevant previous experience among clinical studies provided by the National Epidemiological Study of Mental Diseases (31).

CESOP TEAM

CESOP team had a coordination board composed by the CESOP Executive-Director and the Staff Coordinator who was responsible for organizing the fieldwork. Coordination board also was responsible for the recruitment and training of the interviewers.

Non-physicians candidates were subjected to a recruitment selection process composed of 2 stages: interview selection and training session. Only the candidates that successfully went through two phases were selected.

Five teams of interviewers (10-15 elements) worked all over the country during the recruit-ment period: Lisboa team (assured the recruitment in Lisboa & Setúbal, Alentejo, Algarve, Estremadura, Ribatejo, Beira Baixa), Coimbra team (provided the recruitment in Beira Alta, Beira Litoral), Porto team (was responsible for the recruitment in Douro Litoral, Minho, Trás-os-Montes & Alto Douro), Azores Islands team and Madeira Island team.

For each interviewer team a training session was provided and it included topics related to:

- study design
- study features
- logistical
- ethical and legal issues
- random-route methodology (field training)
- interview procedures (role-play exercises)
- survey and software training (computer training).

Each team was on the field every day (including weekends) in groups, each one with a different route. During the first visit if no subject was found in the selected household he/she could not be replaced. This could only be done after the household had been contacted in three different times (which included evenings and weekends). The most successful schedules were in the evenings and at the weekends (33).

QUALITY CONTROL

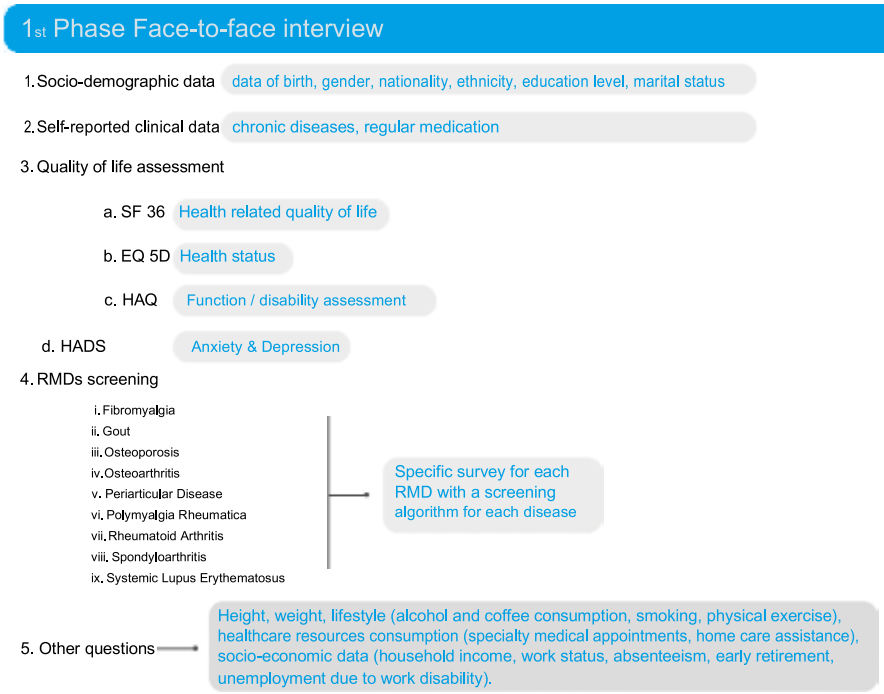
Quality control of interviews was performed through a random evaluation of the interviews and interviewers and recheck of the participants´ eligibility criteria. Specifically, each interviewer had 25% of his interviews submitted to a quality control through a telephone contact to the participants, in order to assess the reliability of the answers. The selection of households and the selection of respondents were also submitted to a quality control. In fact, every day CESOP Staff Coordinator was responsible for checking all the data collected by each inter-viewer through remote control; on the other hand, the Staff Coordinator also selected random participants who were contacted by telephone to check interviewers´ performance.

QUESTIONNAIRE DESIGN FOR DISEASE SCREENING

EpiReumaPt research team designed detailed and comprehensive questionnaire including a screening for RMDs symptoms. Subjects were inquired about sociodemographic, socioeconomics, lifestyle, healthcare resource consumption, functional status, quality of life, mental health, work status, and comorbidities. Participants were also asked about several rheumatic symptoms.

The EpiReumaPt research team developed algorithms for the screening of specific RMDs, covering disease characteristic and respective signs and symptoms. An individual was considered to have a positive screening if the subject mentioned a previously known RMD, if any of the specific disease algorithms in the screening questionnaires was positive, or the subject reported muscle, vertebral or peripheral joint pain in the previous 4 weeks (38).

The questionnaire was applied at each participant's household with the support of a Computer Assisted Personal Interview (CAPI) system. The software was provided by CESOP and all the survey and software performance was tested and validated by the EpiReumaPt research team before it was used by the interviewers (Figure 4).



RMD- Rheumatic and musculoskeletal disease SF36 – short form (36) form health survey; EQ5D - measure of health status from the EuroQol Group; HAQ – Health Assessment Questionnaire; HADS – Hospital Anxiety and depression scale

Figure 4. Phase 1 survey for RMDs screening (33)

PLANNING FACE-TO-FACE INTERVIEW

Planning of Phase 1 was a joint work of CESOP and EpiReumaPt research team during the first semester of 2011.

CESOP recruitment was sequentially done by regions: Lisboa & Vale do Tejo, Alentejo, Algarve, Centro, Norte, Azores Islands and Madeira Island. The timeline was defined as showed in the section "EpiReumaPt in

the field- timeline". Recruitment started in Lisboa region as an option to test all the logistic and managing procedures.

Clinical observations to the phase 2 were performed at the Primary Care Centres of participant's neighborhood. All Health Administrations Regions (Lisboa & Vale do Tejo, Alentejo, Algarve, Centro, Norte) and the Regional Government of Azores Islands and Madeira Islands were previously contacted and agreed with the study. They also provided the name and contact person in each Primary Care Centres identified.

To plan and execute phase 1, the CESOP team had to be completely coordinated with EpiReumaPt management team. Since success of phase 2 was wholly dependent of phase 1, the 2 teams work together as follows:

1. Locations of the recruitment were identified by CESOP.
2. At the same time, the Coordination Team of EpiReumaPt identified the correspondent Primary Care Centres where the clinical appointments would occur.
3. The EpireumaPt Coordinator Team contacted all Primary Care Centres identified. In Lisboa Region, all of them were previously visited to ask authorization and to confirm the conditions that were needed to phase 2. Across the country, all contacts and confirmations were done by phone.
4. CESOP sent every week the information of participants recruited in each location as well as the identification of those selected for an invitation to be observed by a Rheumatologist. These participants were contacted again by the EpiReumaPt Coordination Team to schedule the outpatient visit, which occurred in the Healthcare Centre closer to the participant's household.

These tasks were performed in all the locations, with the same sequence. The method was very efficient and provided 100% of success in the project execution, without breakages of productivity throughout the recruitment period (27 months).

EPIREUMAPT SAMPLING AND RECRUITMENT

The EpiReumaPt participants were selected through a process of multistage random sampling. The sample was stratified according to the Portuguese statistic regions NUTS II in the Census 2001 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. We increased the sample size (oversampling) from Madeira and Azores to have sufficient power to do separate analysis in these distinct regions. In the national analysis, weights take into account the islands oversampling.

In Portugal, there are no listings/databases for residents and addresses available for research. Thus, households were selected using the random route methodology.

This procedure, random route or random walk method, allows assigning each household an equal probability of being chosen, and thus each individual equally likely to be inquired.

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. Each interviewers team worked daily, seven days a week, on the field in groups of 4 or 5 elements, covering different routes. 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 (33).

2.6.2. Phase 2 - Clinical Observations for RMDs Diagnosis

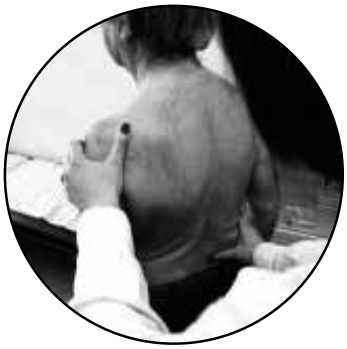


Figure 5. Clinical observation for RMD diagnosis

PLANNING AND DEVELOPMENT

In order to ascertain the RMDs diagnosis, those subjects who screened positive for at least one RMDs or one MSK symptom during phase 1, were invited for a clinical assessment by a rheumatologist. The same procedure was applied to a random 20% sample of the individuals without rheumatic or MSK complaints in phase 1 of the study.

The phase 2, the clinical observation performed by the rheumatologist, used a blinded methodology - the positive screening of the 1st phase was unknown to the rheumatologist. Rheumatologists were instructed about how to conduct the clinical observation following a standard protocol. This protocol included the following steps: 1) written signed consent, 2) clinical history, 3) physical examination, 4) data register through a computer assisted software and 5) imaging and laboratory request (if necessary).

The computed assisted software, specifically designed for the study, was used to support clinical appointment registries. The software contained a checklist of data, in order to verify if the patient fulfill the pre-established diagnostic criteria and specific questionnaires that included medication, disease activity and severity that were to be completed according to diagnostic hypothesis chosen by the rheumatologist.

The pre-establish diagnostic criteria of RMDs were performed according to the American College of Rheumatology (ACR)/European

League Against Rheumatism (EULAR) classification criteria for RA; the ACR criteria for knee OA, hip OA, hand OA, FM, SLE and gout; the Assessment of SpondyloArthritis international Society (ASAS) criteria for axial and peripheral SpA; and the Bird criteria for PMR (39-50). 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. PD diagnoses were established based on expert opinion after reviewing clinical history, physical exam, ultrasound and electromyography (when available). OP was defined by rheumatologist's decision based on the presence of at least one of the following: previous fragility fracture, previous OP diagnosis, current OP treatment or fulfilment of the WHO criteria when lumbar and/or femoral neck dual energy X-ray absorptiometry (DEXA) was available. Low back pain (LBP) was defined solely by self-report (Table 2).

Table 2. RMDs diagnostic criteria

RMD'S	Diagnostic Criteria
Fibromyalgia	ACR criteria, Wolfe F, et al, 2010 (43)
Gout	ACR criteria, Wallace SL, et al, 1977 (45)
Hand osteoarthritis	ACR criteria, Altman R, et al, 1990 (42)
Hip osteoarthritis	ACR criteria, Altman R, et al, 1991 (41)
Knee osteoarthritis	ACR criteria, Altman R, et al, 1986 (40)
Rheumatoid arthritis	ACR criteria, Aletaha D, et al 2010 (39)
Systemic lupus erythematosus	ACR criteria, Hochberg MC, et al 1997 (44)
Polymyalgia Rheumatica	Bird criteria, Bird HA, et al, 1979 (47)
Spondyloarthritis	ASAS criteria, Rudwaleit M, et al, 2009 (46,49) and Rudwaleit M et al 2011 (50)
Low back pain	Self-reported
Periarticular diseases	Expert opinion after clinical history, physical exam and imaging (when available)
Osteoporosis	Previous fragility fracture and/or previous OP diagnosis and/or current OP treatment and/or Who criteria when DEXA available (48)

In mainland, when laboratory test or imaging was required, they were performed at the mobile unit that supported all the clinical appointments

(Figure 6). In Azores and Madeira Islands it was necessary the support of local hospitals or clinics to provide these tests.

Finally, in order to minimize any potential disturbances in participants' daily life, all the study evaluations (face-to-face interview, clinical appointment, laboratory test and imaging examinations) were performed nearby the participants' residences in a schedule chosen by them.

IDENTIFICATION OF PRIMARY CARE CENTRES FOR CLINICAL APPOINTMENTS

Before the fieldwork started in each region, the EpiReumaPt management team identified the primary care centres and contacted all of them in order to plan and schedule the days of clinical appointments and to make sure that all the needs were fulfilled: 1 or 2 consultation rooms 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 in the Islands).

Figure 6. EpiReumaPt mobile unit at a primary care centre

SCHEDULING CLINICAL OBSERVATIONS

All participants selected in phase 1 by the CESOP were contacted by phone to schedule the clinical observations. The time lapse between the CESOP interview and the clinical appointment never exceeded 1 month (in most cases was around 2 weeks).

Usually clinical appointments were schedule twice a week, but sometimes it was necessary to schedule more days. For instance, in Trás-os-Montes, Azores Islands (S. Miguel, Terceira and Faial) and Madeira Island, clinical appointments were schedule during the entire week (including weekends) in order to optimize team journeys. In total, the EpiReumaPt team went to 254 primary care centres and rheumatologists performed 3,886 clinical appointments (Figure 13). Out of the 3,886 clinical appointments, 9 subjects were not participants of the EpiReumaPt sample. In fact, the clinical appointments were performed under subjects´ special request and were not included in the analysis and data set.

RHEUMATOLOGISTS CONTRIBUTION

Table 3. Rheumatologists that collaborated in EpiReumaPt

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

The schedules of medical teams were planned according to their availability. To promote physician adhesion, local rheumatology teams were invited according to the several regions of recruited sample people.

Rheumatologists of the research team were also schedule whenever needed and assured 38% of clinical appointments. To standard clinical appointments and procedures, a training handbook was provided to each rheumatologist (Figure 7).

EpiReumaPt staff provided a short review of all the study procedures and supported the rheumatologists in their needs and with details regarding software and logistical issues on the first day of each rheumatologist clinical appointment.

95 experienced rheumatologists were graciously and voluntarily involved, during more than 250 days of clinical appointments (Table 3).

Figure 7. Reumatologist handbook for clinical observation (phase 2)

MOBILE UNIT AND MULTIDISCIPLINARY TEAM

A mobile unit was built and fully equipped (Figures 8, 11 and 12) before the study started. It was built to perform imaging and laboratory tests: X-ray of the affected body segments, peripher-al dual energy x-ray absorptiometry and draw of blood samples (Figure 9, 10).

Figure 8. Mobile Unit that supported clinical appointments in mainland (phase 2)

A multidisciplinary team constituted by a X-ray technician (only in mainland), a nurse, a staff coordinator and a driver, supported all the clinical appointments across the country. The EpiReumaPt management team was responsible for scheduling these professionals and also rheumatologists (according to their area of residence and availability) and planning their work every week (33).

2.6.3. Phase 3 - RMD Diagnosis Revision

The third phase was the validation of RMDs diagnosis. After having the results from the laboratorial and imaging tests previously requested at the medical observation (phase 2), a team of three experienced rheumatologists reviewed all the clinical data from each participant. The aim was to validate the diagnosis decision established in the second phase. Moreover, when a patient was referred, in the second phase, to a rheumatology centre due to a suspected inflammatory rheumatic disease, follow-up information from that centre was also requested and used. A specific protocol was developed to support these tasks.

When data were insufficient to fulfil pre-established diagnostic criteria (Table 2) 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 who performed the clinical assessment (second phase) prevailed (36).

Figures 9, 10. Imaging acquisition inside the mobile unit

2.6.4. Data Analysis

PARTICIPATION ANALYSIS

The EpiReumaPt study recruited 10,661 subjects and 64% had a positive screening for at least one RMDs. 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 (36). These variables were considered in the weighted model used to calculate the prevalence of RMDs. 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 (36).

WEIGHT DEVELOPMENT

EpiReumaPt was designed to obtain a representative sample of the

Portuguese population. To guarantee its representativeness, the design effect was taken into account. This was 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 – 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 RMDs 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 (36).

2.6.5. Study Information Release to the Portuguese Population

In Portugal, large-scale epidemiological studies are not common. Therefore, at the beginning of the EpiReumaPt it was necessary to promote the project among the Portuguese population. Certain aspects had to be overcome:

1. It was necessary to distinguish EpiReumaPt methodology (randomized sample) from a screening program and explain to the population why it was not possible to recruit everyone.

2. It was also necessary to clarify among the recruited subjects that the main aim of this kind of study was general public health, rather than individual benefits.

3. To minimize lack of confidence and uncertainties in specific population subgroups (eg. the elderly population), strategic partnerships were established, namely with the National Association of Local Councils (Associação Portuguesa das Juntas de Freguesias - ANAFRE), to promote and disseminate EpiReumaPt through the population. It was also necessary to establish liaisons 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 face-to-face interview) in order to gain the trust of the population and consequently improving compliance.

4. The relative lack of availability of the active population to participate in the study (especially in larger cities), led CESOP to plan the field work to be carried seven days a week and also during the evenings.

5. A promotional event of EpiReumaPt - including a public session and a press release - was held on September 9th 2011, before starting recruitment.

6. A website was also developed and automatically updated all over the EpiReumaPt recruitment (http://www.reumacensus. org/) (Figure 13).

A monthly newsletter was created and sent to a large mailing list, which included national and local authorities (health and social authorities), media, sponsors, and other public decision makers.

Figures 11, 12. Mobile unit equipment

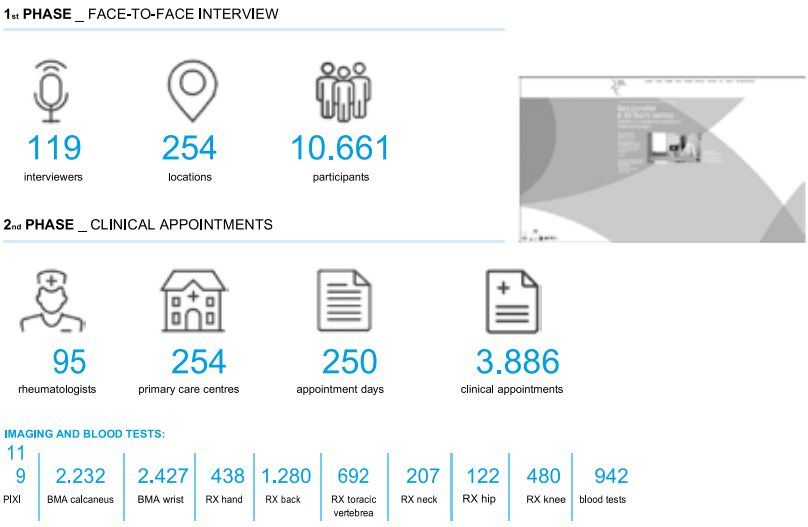


Figure 13. Website and EpiReumaPt field numbers

2.6.6. EpiReumaPt in the Field - Timeline

2011

MARCH

· Finishing of Informed Consents and major documents
· Submission to ethical and legal Portuguese Authorities
· First edition of the monthly Newsletter edition
· Starting to plan the field work
· Consultation of authorities for the mandatory requirements of the mobile Unit

APRIL, MAY, JUNE

· Development and testing of the software for data collection of phase 1

APRIL, MAY, JUNE, JULY AND AUGUST

· Development and testing of the software for data collection of phase 2

JUNE, JULY, AUGUST

· Design, planning and construction of the Mobile Unit

JULY

· Getting the approval of ethical and legal Portuguese Authorities

JULY, SEPTEMBER, NOVEMBER AND DECEMBER

· Training of CESOP interviewers

JUNE, JULY AND AUGUST

· Planning and organization of phase 2 field work
· Submission to the Ethics Committee of each Regional Administration of Health

AUGUST

· Development of the Rheumatologist handbook
· Scheduling of clinical appointments with Rheumatologists until the end of 2011

SEPTEMBER – until the end of clinical appointments (Dec 2013)

· Rheumatologists Training in loco (physicians support in all Clinical appointments)

SEPTEMBER 19TH

· Starting the recruitment in Lisbon city (phase 1)

SEPTEMBER 30TH

· Starting clinical appointments (phase 2)

SEPTEMBER TO DECEMBER

· Optimization of clinical appointments software
· Phase 1 and phase 2 in Lisbon City and Cascais region

OCTOBER

· Planning and organization of logistic aspects of CoReumaPt

DECEMBER

· First interim analysis of EpiReumaPt data

2012

JANUARY TO APRIL

· Phase 1 and phase 2 in Vale do Tejo region

APRIL TO JUNE

· Phase 1 and phase 2 in Alentejo region

JUNE AND JULY

· Phase 1 and phase 2 in Algarve region

AUGUST AND SEPTEMBER

· Phase 1 and phase 2 in Ribatejo and Oeste regions

OCTOBER TO DECEMBER

· Phase 1 and phase 2 in Beira Interior region

OCTOBER 14TH

· Second interim analysis of EpiReumaPt data

2013

JANUARY

· Planning and organization of Azores field work

· Starting the CoReumaPt phone calls

· Phase 1 and phase 2 in Beira Litoral region

JANUARY TO MARCH

· Providing the Interim Report of EpiReumaPt (Sep 2011 to March 2013)

FEBRUARY TO MAY

· Recruitment in Azores (phase 1): São Miguel, Terceira and Faial Islands

· Clinical Appointments (Phase 2): April 8th to 21th (S. Miguel), May 7th to 13th (Terceira) e May 15th to 17th (Faial)

· Phase 1 and phase 2 in North region

JUNE TO AUGUST

· Continuing phase 1 and phase 2 in North region

JULY, AUGUST, SEPTEMBER

· Planning and organization of Madeira field work

SEPTEMBER AND OCTOBER

· Continuing phase 1 and phase 2 in Trás-os-Montes region

OCTOBER, NOVEMBER AND DECEMBER

· Recruitment in Madeira Island (phase 1)

· Clinical Appointments (Phase 2): October 21th to 26th , November 18th to 23th, December 9th to 13th

NOVEMBER AND DECEMBER

· Continuing phase 1 and phase 2 in Minho region

DECEMBER 20TH

· End of the study – last clinical appointments

2014

JANUARY TO MAY

· Data cleaning and data management of phase 1 EpiReumaPt database

· Providing the codebook of phase 1 EpiReumaPt database

FEBRUARY TO MAY

· Phase 3 (diagnosis revision)

· Data analysis EpiReumaPt

JUNE

· Validation of interobserver rate – results of phase 3

JUNE TO SEPTEMBER

· Compilation of phase 1 with phase 2

· Databases

· Data analysis

· Medical writing of princeps paper

AUGUST

· External consulting to weight definition assuring the representativeness of EpiReumaPt sample of Portuguese population

SEPTEMBER 22TH

· Public presentation of EpiReumaPt data

2.6.7. Data Protection and Ethics

EpiReumaPt was performed according to the principles established by the Declaration of Helsinki (Finland), revised in Seul (South Korea), in 2008, and in 2013, in Fortaleza (Brazil) (World Medical Association, 2013), and according to the Portuguese law at the time that study began (Law n. 46/2004, of 24th August).

Behind the Declaration of Helsinki and the Portuguese law for Clinical Research, EpiReumaPt was complied with the following laws and standards:

• Protection of Personal Information (Law n.67/98 de 26th of October (DR L. n., 1998) (51). and National Committee for Data Protection deliberation n.227/2007 (CNPD, 2007)) (52).

• Genetic, clinical and health personal information (Law n.12/2005, of 26th January (DR L. n., 2005)) (53).

As an observational study it was reviewed and approved by the

Portuguese authorities: National Committee for Data Protection, and by NOVA Medical School Ethics Committee. The study was also reviewed and approved by the Ethical Committees of Regional Health Authorities.

Data protection was assured by data encryption according to the Portuguese law and according to National Committee for Data Protection deliberation nº 227/2007 (CNPD, 2007), which provided guidelines to the processing of personal data carried out under scientific clinical research (52).

Data encryption process keeps the confidentiality and anonymity of each subject. In phase 1, participants were identified with a code (ID) which was anonymous, and was always the same throughout the study procedures. In phase 2, personal data (ID, name, address and contacts) were accessible to the Rheumatologist and Technical Team (nurse and X-ray Technician) when clinical data was collected.

During both phases (phase 1 and phase 2), data was collected on a computer assisted platform and after exported to a major database. Decryption process of IDs was only possible with a secret password belonging to the principal investigator (PI). All the computers that were used during the study procedures (phase 1, phase 2 and phase 3) had very restricted access.

CESOP interviewers in phase 1 provided informed consents of EpiReumaPt study and of the EpiDoC cohort. Rheumatologists at clinical observation provided Biobank and EpiDoC Cohort informed consents (figures 14, 15). In every situation, participants received clear information about the study (oral information and a specific flyer - main study, cohort study and biobank), and they were given enough time to decide whether to participate or not in the study. Subjects were only asked to participate after they assured that they fully understood the study.

When a subject accepted to participate in the study, he/she was then asked to sign the consent form (33).

Figure 14. Informed consent signature of a EpiReumaPt participant

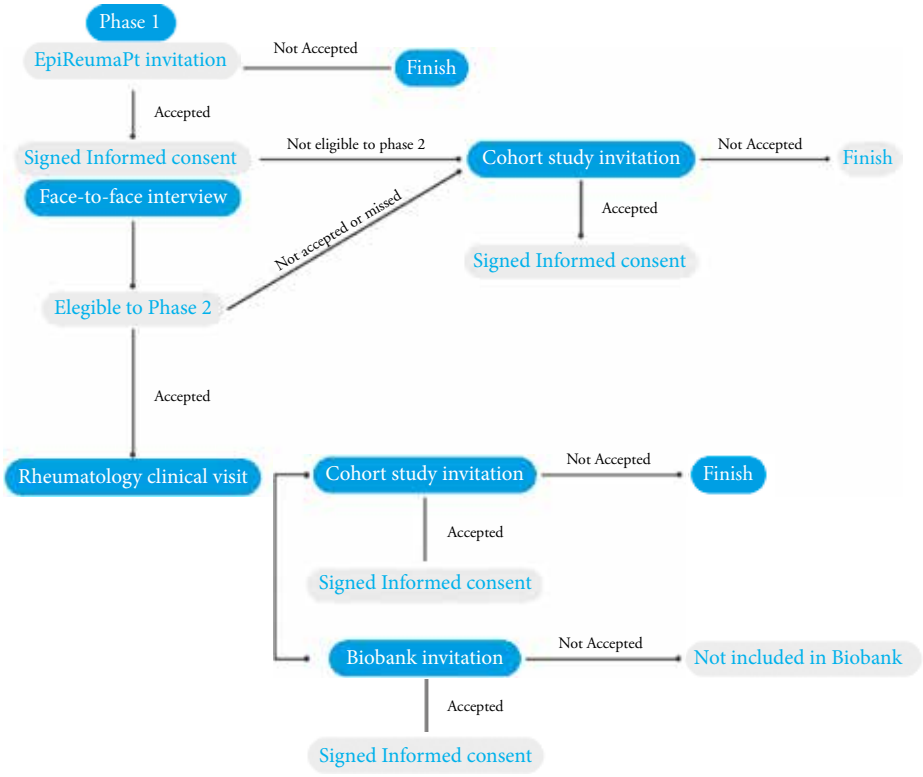


Figure 15. Informed consent flowchart

2.6.8. Reporting RMDs Diagnosis and Test Results to the Participants

During the assessment by rheumatologist in phase 2, all patients with a new diagnosis of a chronic inflammatory rheumatic disease were referred to a rheumatology centre 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 (36).

Chapter 3

The Work

3.1. Sociodemographic, Economic and Lifestyle Characterization of the Portuguese Adult Population

EpiReumaPt study's population is representative of the Portuguese population, as confirmed by data from the Portuguese National Institute of Statistics Census 2011 (54) (Table 4). In this study we were able to capture sociodemographic, economic and health-related data of the Portuguese adult population during the economic crisis, 2011-2013 (Table 4).

The Portuguese adult population was mostly Caucasian (n=10,342; 96.0%) and married (n=6,111; 50.2%). With respect to educational level, a high proportion of participants (n=6,899; 55.8%) had less or equal to 9 years of education. Portuguese adult population was mostly employed at full-time (42.8%), however 12 % were unemployed and 24.9% retired. Moreover, 19.9% of the Portuguese adult population lived with a mean monthly household income lower than 500 €.

With respect to health-related characteristics, the observed mean number of chronic diseases was 1.55 ± 1.80. Regarding cardiovascular risk factors, Portuguese frequently reported high cholesterol level (24.4%) and high blood pressure (23.0%). Moreover, diabetes was reported by 8.3% of the adult Portuguese population.

The most frequently reported non-communicable chronic diseases were RMDs (21.2%) and allergy (22.8%). Anxiety and depression symptoms were also reported by a high proportion of the population (11.7% and 5.2 respectively). Prevalence of overweight and obesity was 52.2% (35.1% for overweight and 17.1% for obesity).

Regarding lifestyle habits, namely in terms of alcohol intake and smoking habits, 20.2% of the individuals had reported a daily intake of alcohol beverages and 23.2% were current smokers. Only 37% of the Portuguese adult population reported to be physical active.

Table 4. Sociodemographic and health related characteristics of the adult Portuguese population: EpiReumaPt (1st and 2nd phase) and Census 2011 populations (Portuguese population)

	1st phase study population n=10,661	2nd phase study population n=3,877	CENSUS 2011
Demographic characteristics			
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%)	

(to be continued)

	1st phase study population n=10,661	2nd phase study population n=3,877	CENSUS 2011
Socio-economics Household income*			
<500€	1,994 (19.9%)	795 (21.8%)	No comparable data
501€ to 750€	1,707 (21.7%)	710 (20.4%)	
751€ to 1000€	1,268 (18.8%)	511 (18.9%)	
1001€ to 1500€	1,141 (17.2%)	403 (15.9%)	
1501€ to 2000€	657 (9.9%)	246 (10.3%)	
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%)	No comparable data
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%)	
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%)	No comparable data
1 to 3	6,364 (59.1%)	2,331 (59.5%)	
More than 3	908 (11.9%)	277 (10.4%)	
Current alcohol intake			
Daily	2,050 (20.2%)	773 (20.8%)	No comparable data
Occasionally	3,967 (42.6%)	1,305 (46.0%)	
Never	4,625 (37.1%)	1,794 (33.2%)	
Current smoking habits			
Daily	51,854 (23.2%)	5526 (20.8%)	No comparable data
Occasionally	246 (2.7%)	67 (2.2%)	
Never	8,554 (74.1%)	3,282 (77.0%)	

(to be continued)

	1st phase study population n=10,661	2nd phase study population n=3,877	CENSUS 2011
Physical exercise			
Comorbidities (self reported)	3,499 (37.0%)	1,182 (37.3%)	No comparable data
Number of Comorbidities	1.55±1.80	1.71±1.83	
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%)	
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), 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 QuestionnaireThe estimated values for the characteristics were obtained considering study design (36).

3.2. Rheumatic Diseases Prevalence and Under-Diagnosis

The EpiReumaPt study included 10,661 adult subjects. Sixty-four percent had a positive screening for at least one RMD. Applying the eligibility criteria, 8,152 subjects were invited and 3,877 entered the second phase and were evaluated by a rheumatologist. Rheumatologists detected 1,532 new RMDs diagnosis out of 3,877 subjects evaluated (Figure 16).

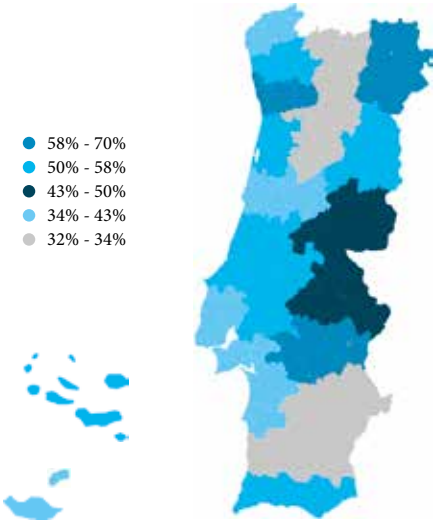


Figure 16. Distribution of the new RMDs diagnosis established during EpiReumaPt according to NUTS II

Moreover, 2,670 individuals were found to have more than one RMDs. Of the 3,877 subjects evaluated in the second phase, only 85 previously reporting a RMDs had no identifiable target disease (Figure 16). The prevalence of each RMDs, overall and stratified by gender is shown in Table 5.

The RMDs 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 5). 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 17). Interestingly, the Norte and Centro region of Portugal, composed mainly by rural regions, had the highest prevalence of LBP (30.4% and 33.2% respectively) (Table 5).

PD was also a frequent RMDs 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). These RMDs had the highest prevalence in the working-age population (46-55 years) (21.5%; 95%CI 17.4 to 25.5%) (Figure 17).

OA was also common among Portuguese individuals; particularly

knee OA, with a prevalence of 12.4% (95%CI 11.0% to 13.8%). Of note, the combined prevalence of hip and/or knee and/ or hand OA in Portugal is 19.1% (95%CI 17.1 to 21.1%).

Moreover, the Centro region of Portugal, had the highest prevalence of this disease (17.4%) (Table 6). Noteworthy, gout had an overall prevalence of 1.3% (95%CI 1.0% to 1.6%) (Table 5). 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 19).

As expected, men had the highest gout prevalence (2.6% versus 0.1% in women, p<0.001). Additionally, 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 preceding 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, anky-losing spondylitis (AS) 29.6%, psoriatic arthritis 18.7% and SpA associated with inflammatory bowel disease 12.0%.

These results correspond to a national prevalence rate of 0.7% (95%CI 0.4% to 1.0%) for undifferentiated spondyloarthritis, 0.5% (95%CI 0.3% to 0.7%) for AS, 0.3% (0.1% to 0.5%) for psoriatic arthritis and 0.2% (0.0% to 0.4%) for SpA associated with inflammatory bowel disease. Of note, SpA had an important variance among Portuguese regions being the Centro region the one with the highest prevalence (2.4%; 95%CI 1.3 to 3.5) (Table 6). The prevalence of RA was of 0.7% (95%CI 0.5% to 0.9%). As expected, women had the highest RA prevalence (1.2% versus 0.3% in men, p<0.001) (Table 5).

Table 5. Prevalence of RMDs in Portugal, overall and stratified by gender

	Total prevalence (95% CI) n=3,877	**Women (95% CI) n=2,630**	**Men (95% CI) n=1,247**
Low Back Pain (n=1,393)	26.4% (23.3%;29.5%)	29.6% (25.8%;33.5%)	22.8% (17.9%;27.8%)
Periarticular Disease (n=929)	15.8% (13.5%;18.0%)	19.1% (16.2%;22.0%)	12.0% (8.4%;15.6%)
Knee Osteoarthritis (n=981)	12.4% (11.0%;13.8%)	15.8% (13.7%;18.0%)	8.6% (6.9%;10.3%)
Osteoporosis (n=858)	10.2% (9.00%;11.3%)	17.0% (14.7%;19.2%)	2.6% (1.9%;3.4%)
Hand Osteoarthritis (n=625)	8.7% (7.5%;9.9%)	13.8% (11.6%;15.9%)	3.2% (2.2%;4.1%)
Hip Osteoarthritis (n=199)	2.9% (2.3%;3.6%)	3.0% (2.3%;3.7%)	2.9% (1.7%;4.1%)
Fibromyalgia (n=149)	1.7% (1.3%;2.1%)	3.1% (2.4%;3.9%)	0.0% (-0.0%;0.2%)
Spondyloarthritis (n=92)	1.6% (1.2%;2.1%)	2.0% (1.3%;2.7%)	1.2% (0.7%;1.8%)
Gout (n=92)	1.3% (1.0%;1.6%)	0.1% (-0.0%;0.2%)	2.6% (1.9%;3.3%)
Rheumatoid Arthritis (n=61)	0.7% (0.5%;0.9%)	1.2% (0.8%;1.5%)	0.3% (0.1%;0.4%)
SLE (n=13)	0.1% (0.1%;0.2%)	0.2% (0.1%;0.4%)	0.0% (-0.0%;0.1%)
Polymyalgia Rheumatica (n=8)	0.1% (0.0%;0.2%)	0.13% (0.0%;0.2%)	0.1% (-0.0%;0.2%)

The sample was calculated considering a minimum prevalence of 0.5%. For rare diseases the estimated number of Portuguese subjects with the disease could be overestimated (38).

Table 6. Prevalence of RMDs in Portugal stratified by NUTs II

	Norte (95% CI) n=1,050	**Centro (95% CI) n=856**	**Lisboa e Vale do Tejo (95% CI) n=708**	**Alentejo (95% CI) n=273**
Low Back Pain (n=1,393)	30.4% (24.4%; 36.4%)	33.2% (27.3%; 39.0%)	20.3% (15.0%; 25.6%)	21.5% (13.8%; 29.1%)
Periarticular Disease (n=929)	14.3% (10.5%; 18.2%)	18.8% (15.3%; 22.4%)	15.1% (10.2%; 20.0%)	15.3% (9.5%; 21.1%)
Knee Osteoarthritis (n=981)	11.3% (9.2%; 13.5%)	17.4% (14.2%; 20.7%)	10.5% (7.7%; 13.3%)	14.1% (8.7%; 19.5%)
Osteoporosis (n=858)	8.6% (6.9%; 10.3%)	10.9% (8.6%; 13.3%)	9.5% (7.1%; 12.0%)	15.7% (9.5%; 21.9%)
Hand Osteoarthritis (n=625)	7.0% (5.3%; 8.6%)	10.3% (8.2%; 12.5%)	9.7% (6.7%; 12.8%)	10.5% (6.1%; 14.8%)

(to be continued)

	Norte (95% CI) n=1,050	**Centro (95% CI) n=856**	**Lisboa e Vale do Tejo (95% CI) n=708**	**Alentejo (95% CI) n=273**
Hip Osteoarthritis (n=199)	3.0% (1.8%; 4.2%)	4.4% (2.4%; 6.3%)	2.2% (1.3%; 3.2%)	3.1% (1.2%; 5.0%)
Fibromyalgia (n=149)	1.3% (0.8%; 1.9%)	2.4% (1.5%; 3.2%)	1.4% (0.6%; 2.2%)	1.3% (0.3%; 2.4%)
Spondyloarthritis (n=92)	1.3% (0.6%; 2.0%)	2.4% (1.3%; 3.5%)	1.3% (0.4%; 2.2%)	2.3% (0.4%; 4.1%)
Gout (n=92)	1.0% (0.5%; 1.5%)	1.7% (1.0%; 2.4%)	1.0% (0.4%; 1.6%)	2.3% (0.7%; 4.0%)
Rheumatoid Arthritis (n=61)	0.6% (0.3%; 0.9%)	0.7% (0.2%; 1.1%)	0.7% (0.3%; 1.1%)	1.8% (0.3%; 3.3%)
SLE (n=13)	0.1% (-0.0%; 0.2%)	NA	0.2% (0.0%; 0.4%)	NA
Polymyalgia Rheumatica (n=8)	NA	NA	0.2% (-0.0; 0.4%)	0.2% (-0.2%; 0.7%)

	Algarve (95% CI) n=144	**Azores (95% CI) n=420**	**Madeira (95% CI) n=426**
Low Back Pain (n=1,393)	10.7% (5.5%; 16.0%)	22.8% (16.3%; 29.2%)	18.9% (13.8%;23.9%)
Periarticular Disease (n=929)	24.7% (6.5%; 43.0%)	14.6% (9.5%; 19.7%)	9.3% (6.2%; 12.4%)
Knee Osteoarthritis (n=981)	6.7% (3.2%; 10.2%)	13.4% (9.8%; 17.1%)	13.2% (9.7%; 16.8%)
Osteoporosis (n=858)	16.7% (10.2%; 23.2%)	8.5% (6.0%; 11.0%)	15.2% (11.3%; 19.2%)
Hand Osteoarthritis (n=625)	10.2% (5.5%; 14.9%)	4.7% (3.1%; 6.3%)	7.2% (4.8%; 9.7%)
Hip Osteoarthritis (n=199)	1.4% (-0.3%; 3.1%)	2.4% (1.1%; 3.6%)	1.3% (0.3%; 2.3%)
Fibromyalgia (n=149)	2.9% (0.1%; 5.7%)	3.0% (1.7%; 4.3%)	3.7% (0.5%; 6.9%)
Spondyloarthritis (n=92)	2.1% (0.3%; 4.0%)	2.3% (0.7%; 3.9%)	1.5% (0.3%; 2.7%)
Gout (n=92)	1.2% (-0.2%; 2.5%)	0.3% (-0.2%; 0.9%)	3.7% (-0.1%; 7.5%)
Rheumatoid Arthritis (n=61)	1.2% (-0.2%; 2.5%)	1.1% (0.2%; 2.0%)	0.2% (-0.1%; 0.5%)
SLE (n=13)	1.5% (-0.2%; 3.2%)	0.1% (-0.1%; 0.2%)	0.2% (-0.1%; 0.6%)
Polymyalgia Rheumatica (n=8)	0.5% (-0.4%; 1.4%)	0.1% (-0.1%; 0.3%)	0.3% (-0.1%; 0.7%)

The sample was calculeted considering a minimum prevalence of 0.5%. For rare diseases the estimated number of Portuguese subjects with the disease could be overestimated.

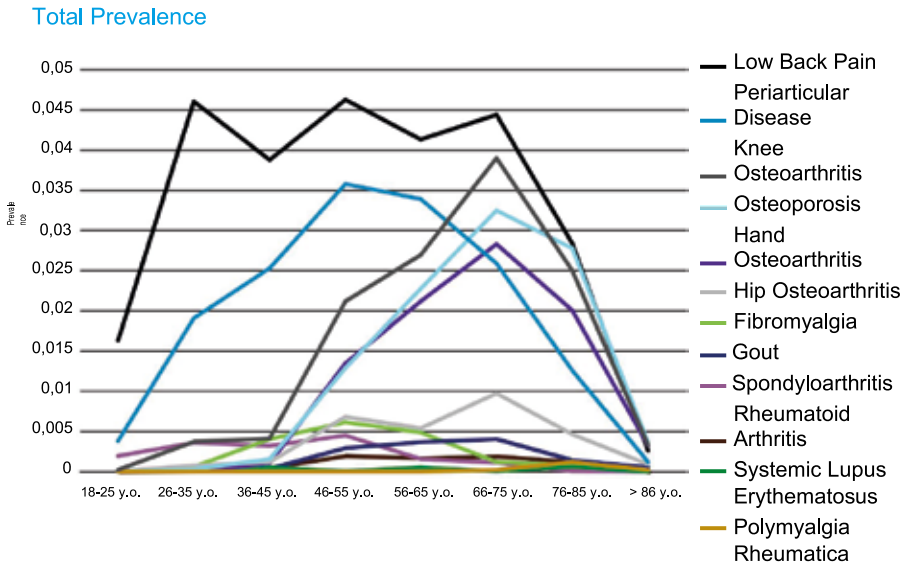


Figure 17. Prevalence of RMDs, stratified by age group (38)

In conclusion, in EpiReumaPt we have demonstrated that RMDs are highly prevalent in Portugal, similarly to other southern European countries.

Furthermore, LBP and osteoarthritis are the most prevalent diseases and their prevalence increase with age and differs across country region.

3.3. The Burden of Rheumatic Diseases

RMDs are the leading cause of disability in developed countries and consume a large amount of health and social resources (55, 56). In fact, according to the Global Burden of Disease (GBD) study, rheumatic and musculoskeletal disorders are the second most common cause of disability in the world (57). In fact, the burden of RMDs is not only associated with the high prevalence of these diseases, but also with their impact on individual's disability, as well as with their economic impact (27, 57). In EpiReumaPt we assessed these two dimensions of the burden of RMDs: 1) the physical and mental impact of RMDs at individual level (quality of life and disability of RMDs and depression and anxiety symptoms) and 2) the economic impact of RMDs (healthcare resources consumption and early retirement).

3.3.1. The Physical and Mental Impact of Rheumatic Diseases

ASSESSING QUALITY OF LIFE AND DISABILITY OF RMDs PATIENTS.

Patients with RMDs have been associated with lower health-related quality of life and also with mental health disturbances (56). In fact, estimates of RMDs-related disability show a 45% in-crease from 1990 to 2010, especially due to osteoarthritis (OA), and it is expected to keep rising with the increasingly obese, sedentary and ageing population (58, 59). In EpiReumaPt study we have verified that RMDs are among the most common noncommunicable chronic diseases in Portugal and the ones that lead to the poorest quality of life and disability (Figure 18).

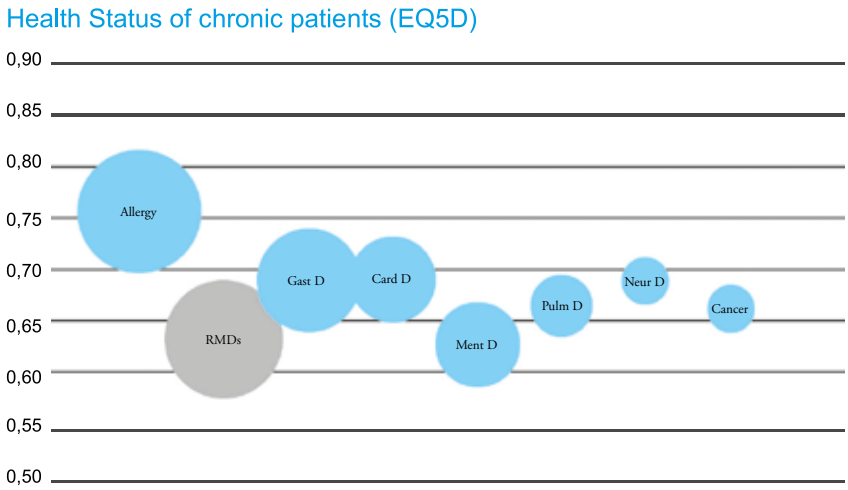


Figure 18. Self-reported non-communicable chronic disease prevalence and quality of life (EQ5D) among portuguese adult population

Allergy- self-reported allergic disease, RMDs – Rheumatic and musculoskeletal diseases; Gast Dgastrointestinal disease; CardD- Cardiovascular disease; Pulm D- Pulmonary disease; Neur D- Neurologic disease; cancer-neoplastic disease

When we analysed the Portuguese population that had a previous diagnosis of a RMD, we found that the participants that self-reported RMDs have a lower self-perception of their health status than others who do not had the knowledge of having a rheumatic disease. This difference is highly significant for all dimensions (Figure 19). However, it is higher among physical dimensions than among mental ones. The comparison between self-reported RMDs (from our sample) and the estimate of the general Portuguese population based on the published norms, resulted in differences ranged between 25% (role physical) and -19% (bodily pain) in physical dimensions and between -12% (mental health) and -7% (role emotional) in mental dimensions. In what concerns general health, the difference was -20% (60).

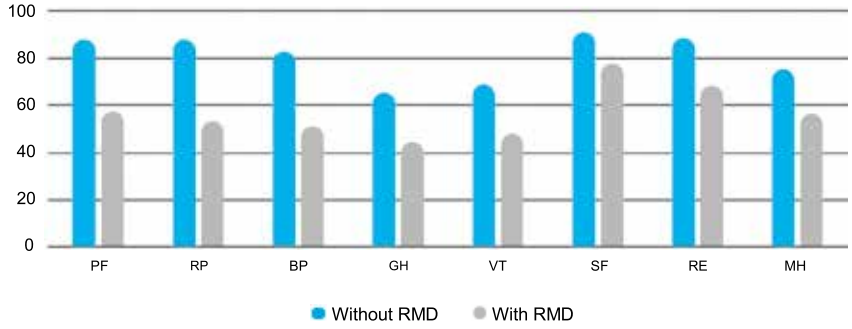


Figure 19. Estimative of the average of the SF-36 dimensions (61).

PF-Physical functioning; RP-Role physical; BP-Bodily pain; GH-General Health; VT-Vitality; SF-Social functioning; RE-Role emotional; MH-Mental health; RMDs-Rheumatic disease. PF-Physical functioning; RP-Role physical; BP-Bodily pain; GH-General Health; VT-Vitality; SF-Social functioning; RE-Role emotional; MH-Mental health; RMDs-Rheumatic Musculoskeletal disease

Regarding the health-related quality of life (HRQoL) instruments, the EQ-5D descriptive system showed that, for each dimension, the intensity of problems was significantly more evident in the self-reported RMDs group, when compared to the Portuguese general population, and to the sample without self-reported RMDs (Table 7) (62). The problems reported are higher in the so called "activity dimensions" (mobility, usual activities and pain/discomfort). There is as well an evidence of a ceiling effect in EQ-5D, that is, few patients placed themselves at level 3 of the five dimensions. In fact, for all dimensions, except for pain/discomfort, more than a half of the respondents with self-reported RMDs still placed themselves at level 1 (no limitations). Looking at EQ-5D-3L index and VAS we also observe statistically significant lower levels for patients with self-reported RMDs, when compared to the Portuguese general population and with the sample without self-reported RMDs (Table 7).

Table 7. Population estimative according to the EQ-5D-3L dimensions (n=10,661)

EQ-5D-3L		PT General Populationa (%)	Without self-reported RMD (%)	With self-reported RMD (%)
Mobility	Without problems	83.3	91.9	57.5*
	Some problems	16.2	8.0	42.0
	Extreme problems	0.5	0.1	0.5
Self-Care	Without problems	95.2	97.7	80.4*
	Some problems	4.4	2.0	18.6
	Extreme problems	0.4	0.3	1.0
Usual Activities	Without problems	83.7	94.2	61.8*
	Some problems	13.9	5.3	35.7
	Extreme problems	2.4	0.5	2.5
Pain/ Anxiety / Depression	No pain or discomfort	55.3	80.0	39.4*
	Moderate pain or discomfort	40.0	19.1	53.8
	Extreme pain or discomfort	4.7	0.9	6.8
	Not anxious or depressed	65.6	84.7	66.9*
	Moderately anxious or depressed	30.1	14.2	29.7
	Extremely anxious or depressed	4.3	1.0	3.4
EQ-5D-3L index mean (SD)		0.76	0.88 (0.19)	0.66* (0.27)
VAS mean (SD)		74.9	77.5 (17.1)	60.7* (19.3)

RMD- rheumatic and musculoskeletal disease; PT - Portuguese; VAS: Visual analog Scale; SD-standard deviation a source: Ferreira et al, 2014. *p<0.001 (61).

Furthermore, the same result was also verified when we evaluated subjects with confirmed RMDs. Indeed, subjects with confirmed RMDs had significantly lower EQ5D scores (ß=-0.09; p<0.001) when compared to subjects without RMDs, adjusted for demographic factors, so-cio-economic factors, lifestyle and comorbidities (Table 8). When we analysed the independent associations of QoL, we found that several RMDs were significantly associated to worse QoL in the Portuguese population. By decreasing order of effect, PMR (ß=-0.33; p=0.027), RA (ß=-0.13; p=0.001), FM (ß=-0.10; p<0.001), LBP (ß=-0.07; p<0.001), knee OA (ß=-0.06; p<0.001) and PD (ß=-0.04; p=0.029) were associated with worse QoL. Moreover, subjects retired or in sick leave (ß=-0.04; p=0.016)

and with a higher number of comorbidities (ß=-0.03; p<0.001) were also associated with worse QoL (Table 9). The presence of anxiety and depressive symptoms (HADS≥11) were also associated with worse QoL (ß=-0.14; p<0.001 and ß=-0.14; p<0.001, respectively). On the other hand, alcohol consumption was significantly associated with better QoL (ß=0.045; p<0.001) (Table 9) (38).

Table 8. Comparison of quality of life, function and anxiety and depression symptoms between subjects with and without RMDs: adjusted analysis

HRQoL and physical function	**RMDs n=3,195**	**Non-RMDs n=682**	**ß estimates**		**95% CI**	**Adjusted p-value**
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	**RMDs**	**Non-RMDs**		**OR**	**95% CI**	**Adjusted p-value**
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

Sample size is not constant due to missing data in RMDs: EQ5D (n=3168), Non-RMDs: EQ5D (n=678). 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, Lisboa, Madeira and the Azores), years of education, work status, household income, alcohol intake, physical exercise, Body Mass Index, and number of comorbidities. For continuous 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 (38).

In addition, patients with confirmed RMD had also significantly higher disability (HAQ score) (ß=0.13; p<0.001) (Table 8). Regarding the HAQ score, and by decreasing order of effect, PMR (ß=1.03; p<0.001), RA (ß=0.38; p<0.001), FM (ß=0.27; p=0.001), knee OA (ß=0.11; p=0.002), LBP (ß=0.09; p<0.001), OP (ß=0.08; p=0.033) and PD (ß=0.06; p=0.019) were significantly associated with disability (Table 9) (38).

Certain characteristics, such as female gender (ß=0.11; p<0.001), low educational level (ß=-0.01; p=0.002) and sick leave or retirement (ß=0.14; p<0.001) were significantly associated with higher HAQ scores. The number of comorbidities (ß=0.06; p<0.001) and symptoms of anxiety

(ß=0.15; p<0.001) or depression (ß=0.32; p<0.001) were also significantly associated with disability. Daily or occasional alcohol intake was significantly associated with lower HAQ scores (ß=-0.06; p=0.023) (Table 9) (38).

Table 9. Factors associated with health-related quality of life (EQ5D) and physical function (HAQ) considering each RMD as variables of interest: multivariable models

	EQ5D		HAQ	
	ß coef (95% CI)	**p-value**	**ß coef (95%CI)**	**p-value**
Demographic characteristics				
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†

(to be continued)

	EQ5D		HAQ	
	ß coef (95% CI)	**p-value**	**ß coef (95%CI)**	**p-value**
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, Lisboa, Madeira and the Azores); BMI -Body Mass Index; SLE- systemic lupus erythematosusTwo multivariable regression models were used: one to identify possible factors that have an impact on the HRQoL, 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 (38).

ASSESSING DEPRESSION AND ANXIETY SYMPTOMS IN RMDs PATIENTS

Regarding anxiety and depression symptoms we found that in subjects with RMDs there was a significantly higher prevalence of anxiety symptoms (OR=3.5; p=0.006) but no significant differences were found concerning depressive symptoms (OR= 1.9; p=0.173) (Table 8). In fact, several RMDs were significantly and independently associated with the presence of anxiety (HADS-A ≥11) and depressive symptoms (HADS-D ≥11). 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 11). 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 10).

Table 10. Factors associated with anxiety and depression symptoms (HADS) considering each RMDs as variables of interest: multivariable models

	Anxiety		Depression	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Demographic characteristics				
Gender (female)	3.1 (1.7; 5.9)	0.001†	2.8 (1.6; 4.9)	<0.001†
Age (years)	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
Regular 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, Lisboa, Madeira and the Azores); BMI -Body Mass Index; SLE-systemic lupus erythematosus. Two logistic regression models 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 consider-ing study design. † adjusted p-value<0.05 (38).

In conclusion, regarding the impact of RMDs on HRQoL, physical function and mental health of the Portuguese population, we verified that patients with RMDs have significantly worse HRQoL and more disability when compared to subjects without RMDs. We found that PMR, RA and FM were the conditions with the worst impact on function and HRQoL. Moreover, when we compared subjects with and without RMDs regarding mental distress symptoms, we found a significantly higher proportion of RMDs patients with anxiety symptoms but not with depressive symptoms.

3.3.2. The Economic Impact of Rheumatic and Musculoskeletal Diseases

The worldwide economic burden caused by RMDs is significant, both via direct and indirect costs. The direct costs reflect the variety of resources consumed towards the diagnosis, treatment and management of the illness. It includes medical expenditures (e.g. medical appointments, hospitalizations, exams, other out- and inpatient resource consumption, pharmaceutical drugs, and the extra costs due to the side effects of drugs) and non-medical ones (formal caregiver, travelling, and community services).

Indirect costs on the other hand, are productivity losses or the illness-related morbidity and mortality that render human resources unavailable for productive uses (63).

Major cost components for the indirect costs include productivity losses of employed patients because of short or long-term work disability (including absenteeism and presentism) and early retirement due to the disease.

DIRECT COSTS

ASSESSING HEALTHCARE RESOURCE CONSUMPTION OF RMDs IN PORTUGAL

Considering healthcare resource consumption Portuguese inhabitants with RMDs were significantly more hospitalized and in need for more homecare support in the previous 12 months when compared to those with no rheumatic disease (OR=2.45, p=0.032 and OR=12.78, p=0.002,

respectively) (Table 11) (38).

Table 11. Comparison of health resources consumption between subjects with and without RMDs: adjusted analysis

Healthcare resources consumption	RMD	Non-RMD	ß estimates	95% CI	Adjusted p-value
Physician visits in the last 12 months					
General practitioners	2,661 (78.8%)	502 (71.5%)	0.5	[0.3;0.8]	0.010†
Rheumatology visits	206 (4.6%)	11 (1.0%)	30.5	[7.4;126.2]	<0.001†
Orthopedic visits	475 (14.9%)	46 (6.5%)	3.2	[1.3;7.8]	0.010†
Other visits	1,758 (57.1%)	347 (53.5%)	0.9	[0.6;1.5]	0.825
Number of physician appointments in the last 12 months					
General practitioners	2.5±5.9	4.0±19.0	-4.01	[-11.37;3.34]	0.285
Rheumatology appointments	0.1±0.8	0.0±0.1	0.08	[0.05;0.11]	<0.001†
Orthopedic appointments	0.4±1.4	0.1±0.4	0.27	[0.10;0.43]	0.002†
Other appointments	1.9±8.0	1.5±1.5	0.01	[-0.47;0.50]	0.961
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	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 RMDs:, 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-RMDs), 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). p-values were adjusted for age, gender, for Nomenclature of Territorial Units for Statistics (Norte, Centro, Alentejo, Algarve, Lisboa, Madeira and the Azores), years of education, work status, household income, alcohol intake, physical exercise, Body Mass Index, and number of comorbidities. For continuous variables a multivariable regression was used to assess the differences between the groups (individuals with Rheumatic and Musculoskeletal Diseases, and without Rheumatic and Musculoskeletal Diseases). The estimated values were obtained considering study design. † adjusted p-values<0.05 (38).

INDIRECT COSTS

ASSESSING EARLY RETIREMENT DUE TO RMDs IN PORTUGAL

Early retirement places a great burden to society due to its concomitant productivity loss. It generates a serious problem for social and economic sustainability in developed countries where, in recent decades, there has been a substantial rise in the percentage of the labour force out of work because of sickness or disability and consequently in the related social protection benefits (64). The combination of an ageing population and widespread early retirement puts severe strains on our social security systems' capacity to maintain today's standard of living for future generations of older people. Portugal is already among the oldest countries in the world, with one of the highest old-age dependency ratios, and it is in the forefront of this general concern regarding premature work withdrawal (65). RMDs may play a key role on early retirement because they are usually both highly prevalent and disabling.

In EpiReumaPt, we compared subjects with RMDs confirmed by the rheumatologist with the ones with no RMDs and found no differences between the two groups regarding the prevalence of sick leave or early retirement due to disease (Table 11) (38).

However, when we analysed specifically the participants between 50 and 64 years old near the official retirement age, we found that 29.9% of the Portuguese population within this range of ages was retired and 13.1% self-reported retirement due to RMD. In fact, we estimated that almost seventy thousand Portuguese people had early retirement due to a claimed RMDs. The observed mean age of early retirement attributed to RMD was 54.8 years old. Despite the considerable variation throughout the years, in the recent past there was an overall trend for early retirement occurs at late ages (Figure 20) (66).

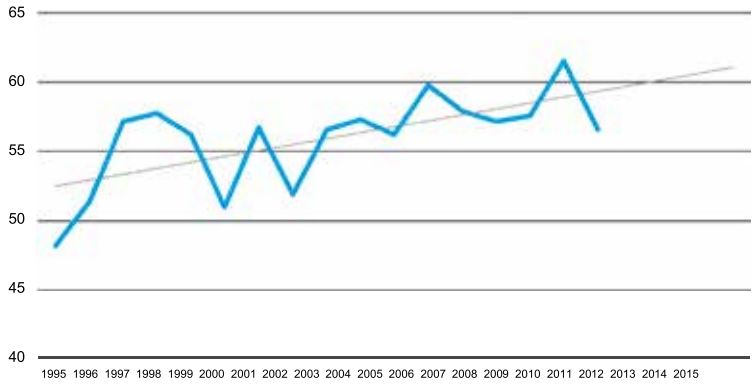


Figure 20. Evolution of mean age of retirement caused by self-reported RMDs (66)

Considering only those who retired prematurely in the last five years, the mean age of retirement due to RMD is 58.2 years old. Projecting this trend over time, and estimate that by year 2050, this figure could reach 65 years old. Of interest, we found a straight relation-ship between disability and odds of being retired and RMDs patients with higher values of disability have the highest risk of early retirement (Figure 21) (66).

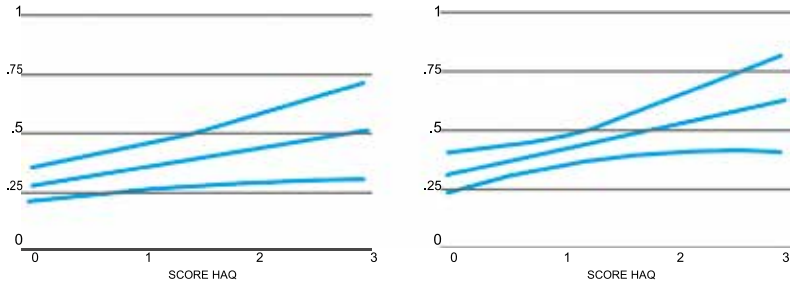


Figure 21. Relationship between disability levels and probability of early retirement (by presence of self-reported RMD) (66)
Y axis: probability of early retirement; X-axis: disability level measured by the HAQ Score. (A) Without self-reported RMD; (B) With self-reported RMD.
The confidence interval consists of the space between the two dashed lines.HAQ, Health Assessment Questionnaire.

The estimated annual indirect cost following premature retirement attributed to RMDs was €910 million (€555 per capita; €1625 per self-reported RMDs patient and €13,592 per early retiree due to RMDs) (Figure 22). Females contributed with the clear majority for these costs (€766 million; €882 per capita versus €187 from males) (Figure 23). To put these estimates into perspective, we measured that early retirement attributed to self-reported RMDs amounts to approximately 0.5% of the national gross domestic product (GDP) in 2013. We also observed a total number of 389,939 accumulated years of working life lost (YWLL) (228 per 1000 inhabitants) and 684,960 potential years of working life lost (PYWLL) (401 per 1000 inhabitants) (Figure 24). The mean YWLL and PYWLL inactivity ratios were 12% and 21%, respectively (66).

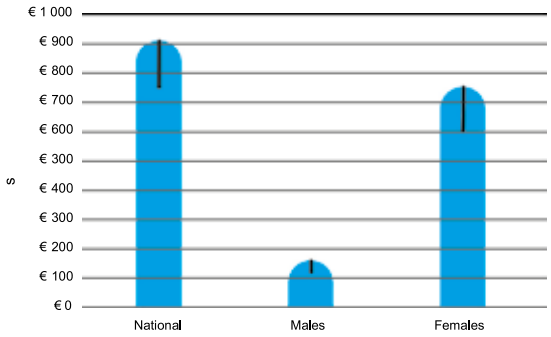


Figure 22. Annual indirect costs of early retirement due to self-reported RMD (66)

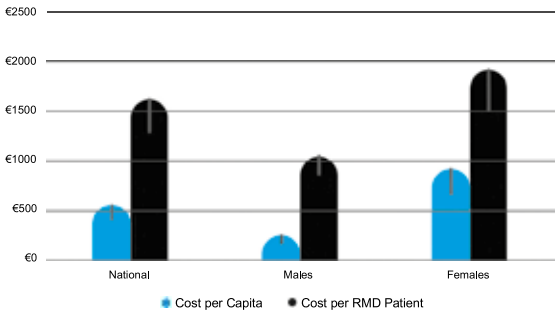


Figure 23. Annual indirect costs of early retirement caused by self-reported RMDs (per capita) (66)
*Line inside bars refers to the lowest estimate

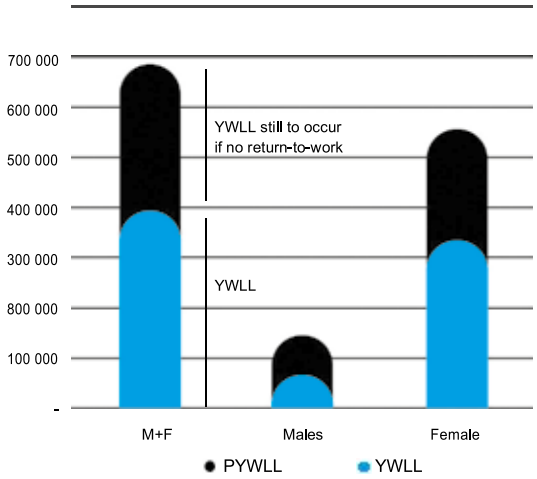


Figure 24. Years of working life lost due to self-reported RMDs (66)
YWLL: years of working life lost; PYWLL: potential years of working life lost.

We also looked at the association of one of the most prevalent and disabling RMDs – osteoarthritis (OA) - with early exit from work and calculated its economic burden (productivity loss). We verified that OA was associated with early exit from paid employment, specifically knee OA (OR: 2.25; CI: 1.42-3.59; p=0.001) (Table 12) (67).

Other OA locations did not have a statistically significant effect on work loss. Knee OA seems to be particularly associated with long-term unemployment which is seems to be pushing the individuals suffering from this musculoskeletal pathology out of the Portuguese labour market in considerable extent (67).

Table 12. Logistic regression analysis by type of early exit from paid employment

	Unemployment		**Early Retirement**		**Early Exit From Paid Employment**	
	Univariable OR (95% CI)	Multivariable OR (95% CI)a	Univariable OR (95% CI)	Multivariable OR (95% CI)a	Univariable OR (95% CI)	Multivariable OR (95% CI)a
Knee Osteoarthritis	1.97* (1.25-3.10)	2.68* (1.58-4.53)	1.37 (0.90-2.08)	-	2.22* (1.49-3.29)	2.25* (1.42-3.59)
Age	0.99* (0.97-1.00)	0.98* (0.97-1.00)	1.03* (1.01-1.04)	1.03* (1.01-1.04)	1.01 (1.00-1.03)	1.01* (1.00-1.03)
Gender (Female)	1.31 (0.83-2.09)	1.06 (0.61-1.84)	0.75 (0.47-1.18)	0.64 (0.41-1.00)	1.27 (0.80-2.00)	1.23 (0.79-1.93)
Educational level (Ref: Primary or less)						
Medium	0.89 (0.51-1.56)	-	0.47* (0.26-0.84)	0.46* (0.23-0.92)	0.41* (0.22-0.74)	0.31* (0.18-0.55)
High	0.77 (0.44-1.34)	-	0.46* (0.26-0.80)	0.62 (0.36-1.06)	0.29* (0.17-0.49)	0.49* (0.27-0.89)
Marital Status (Ref: Single)						
Married / Consensual union	0.85 (0.36-1.99)	-	4.38* (1.81-10.57)	4.21* (1.62-10.92)	3.11* (1.30-7.43)	5.28* (2.24-12.45)
Divorced	0.97 (0.36-2.57)	-	2.89 (0.97-8.63)	2.99 (0.97-9.22)	1.77 (0.64-4.87)	1.78 (0.69-4.58)
Widowed	0.41 (0.13-1.29)	-	6.14* (2.23-16.93)	6.08* (2.00-18.48)	3.93* (1.50-10.29)	4.04* (1.34-12.17)
Chronic Diseases						
Cardiovascular	0.88 (0.55-1.42)	-	0.97 (0.58-1.62)	-	1.04 (0.64-1.68)	-
Diabetes	0.87 (0.47-1.61)	-	2.25* (1.30-3.89)	1.92* (1.09-3.41)	2.78* (1.67-4.65)	-
Pulmonary	0.98 (0.43-2.24)	-	2.08 (0.83-5.21)	-	2.08 (0.84-5.15)	-
Allergy	0.86 (0.51-1.44)	-	0.70 (0.41-1.20)	-	0.76 (0.43-1.33)	-
Gastrointestinal	1.02 (0.63-1.66)	-	1.40 (0.89-2.23)	-	1.45 (0.91-2.31)	-
Neoplasic	1.27 (0.50-3.26)	-	1.61 (0.70-3.70)	-	1.51* (0.62-3.65)	-
Mental	1.04 (0.64-1.70)	-	0.82 (0.54-1.23)	-	1.34 (0.91-1.99)	-
Neurologic	0.50 (0.15-1.59)	-	4.83* (2.19-10.66)	5.00* (1.95-12.83)	4.17* (1.83-9.50)	4.58* (1.40-15.00)

(to be continued)

	Unemployment		Early Retirement		Early Exit From Paid Employment	
Household Income (Ref: ≤€500)						
>€500 and ≤€1000	0.31* (0.18-0.55)	0.36* (0.20-0.64)	0.84 (0.43-1.62)	-	0.43* (0.23-0.80)	0.40* (0.23-0.69)
>€1000 and ≤€2000	0.10* (0.04-0.24)	0.12* (0.05-0.28)	0.98 (0.45-2.12)	-	0.26* (0.12-0.54)	0.25* (0.12-0.53)
>€2000	0.15* (0.06-0.43)	0.18* (0.06-0.50)	0.79 (0.34-1.81)	-	0.22* (0.10-0.49)	0.25* (0.10-0.65)
Regional Controls		YES		YES		YES

OR odds ratio, CI confidence interval, *p<0.05. a - All multivariable models were adjusted for age, gender, geographic region (7 main regions: Norte, Centro, Lisboa region, Alentejo, Algarve, Azores and Madeira), marital status, education level, household income, body mass index and chronic diseases. Cofactors were excluded in the stepwise method if p>0.05 (except for age and gender) (67).

Musculoskeletal pain plays a key role in the risk of workforce withdrawal. In particular, a significant association was seen between pain interference and premature work loss, especially within the knee OA population (OR: 1.52; CI: 1.16-1.99; p=0.002). Those who scored worse in pain interference with work and domestic activities were more frequently out of work (Figure 25) (67).

In fact, not only the OA population was more likely to score worse (p=0.02) in this parameter, but also the aforementioned association between knee OA and exit from work becomes non-significant if only the subset of population with low pain interference is analyzed (i.e. none to moderate pain interference. OR: 1.55; CI: 0.97-2.48) (67).

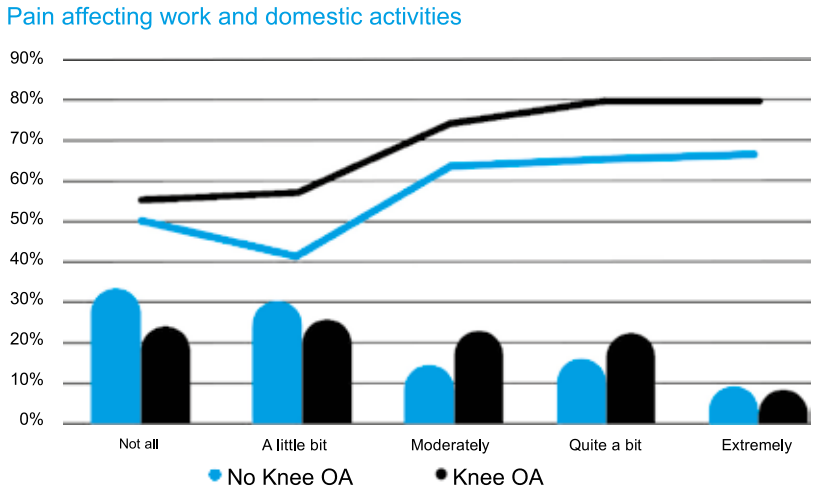
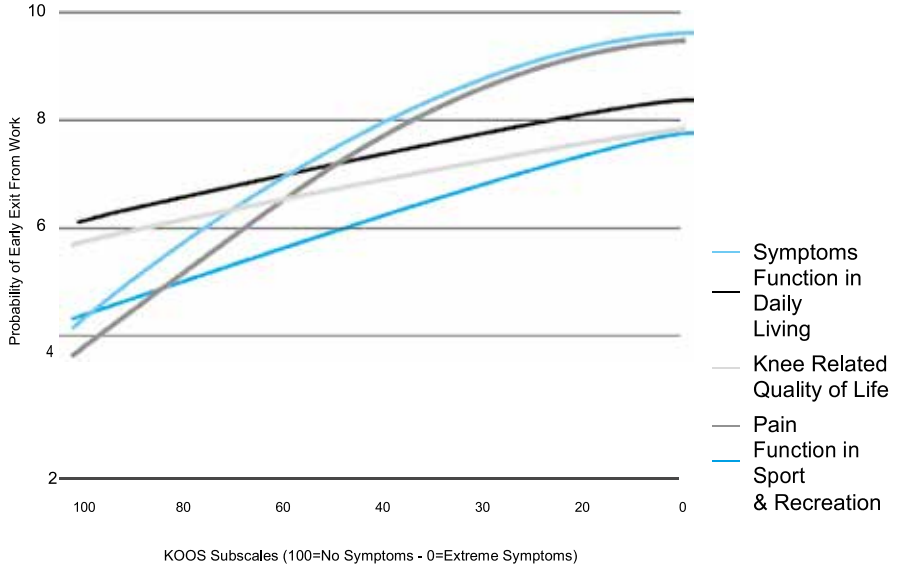


Figure 25. Pain Affecting Work and Domestic Activities & Early Exit from Work
Lines indicate Early Exit from Work (all p-values of Knee OA versus No Knee OA groups are non-significant) (67)
Bars indicate Pain Interference distribution by intensity levels (p=0.02) with corresponding 95% confidence intervals (vertical lines). OA, Osteoarthritis)

Furthermore, looking specifically at the knee location, worse symptoms and more impactful forms of OA are strongly associated with premature work loss. We observed this by using the KOOS subscale scores, where it was possible to verify that knee OA with poorest scores on OA symptoms, pain, quality of life, ability to perform activities of daily living and function in sport and recreation increased the likelihood of individuals being out of work. Consistently this particularly applies for pain and OA symptoms (Figure 26) (67).

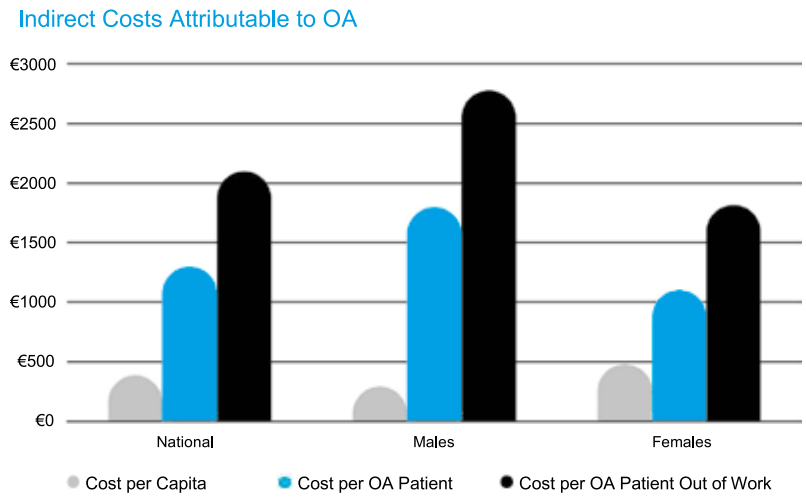


KOOS, Knee injury and Osteoarthritis Outcome Score

Figure 26. Probability of early exit from work according with KOOS subscales Levels (67)

Early exit from paid employment due to OA led to a total of 143,262 YWLL and 338,822 PYWLL (84 and 198, respectively, per 1,000 inhabitants in the age group 50-64). The estimated annual indirect cost attributable to OA was €656 million (€384 per capita; €1,294 per OA patient and €2095 per OA patient out of work) (Figure 27).

Once again, females contributed with most of these costs (€404 million). We thus found that a considerable amount of working life loss and indirect costs were associated with OA. Premature withdrawal from employment attributable to OA amounted to approximately 0.39% of the national GDP (67).



OA, Osteoarthritis

Figure 27. Indirect costs per capita in the 50-64 population, per OA patient and per OA patient out of work (67)

In conclusion, with the EpiReumaPt study we observed that there are a meaningful number of people who claimed to be retired prematurely due to RMDs (66). This translates in many years of working life already lost and many others still potentially to be lost. Indirect costs due to self-reported RMDs are also substantial, equivalent to at least 0.5% of the GDP. By specifically analysing OA, one of the most prevalent and disabling joint disorder, it was possible to verify that the productivity loss due to RMDs is potentially even higher than the one obtained when analysing self-reported RMDs as a whole (67). Regardless the exact magnitude of the estimates, it seems undisputable that the foregone productivity caused by RMDs is enormous. Both the public health concern and the economic impact highlight the need to prioritize investments in health and social protection policies targeting patients with rheumatic conditions (66).

In particular, the high prevalence and the impact of this disabling group of chronic diseases stress the need to focus on policies targeting early retirement in RMDs and research on the cost-effectiveness of interventions aiming to reduce such economic burden.

3.4. Characterization of Specific Rheumatic Diseases

In EpiReumaPt we have analysed two important specific rheumatic diseases – low back pain and fragility fractures. EpiReumaPt research team considered these diseases a priority because of its prevalence and social and individual burden. In fact, the Global Burden of Disease Study showed that low back pain is among the top ten high burden diseases and injuries (68). Moreover, low back pain is one of the most common causes of disability and social burden among people with rheumatic and musculoskeletal complaints in the developed world (27, 68). Physical disability and loss of functional resulting from low back pain reduce quality of life and increase morbidity risk (69).

The prevalence and burden of chronic low back pain was poorly defined in Portugal and no population-based study has addressed this question. In order to overcome this lack of information, the EpiReumaPt research team considered low back pain characterization a priority and the reader can find the main results in the next few pages. On the other hand, in EpiReumaPt we have also looked specifically to high-risk population for fragility fractures.

A fragility fracture is one that occurs as a result of a fall from own height or smaller, and in some cases without associated trauma (70). We have determined the prevalence of fragility fractures and their impact in the quality of life and health resources consumption of this specific vulnerable population that we also will describe in this chapter.

3.4.1. Active Chronic Low Back Pain

In Portugal the prevalence and burden of chronic low back pain (CLBP) were unknown. EpiReumaPt allowed determining the prevalence of CLBP in the adult Portuguese population to compare the population with and without CLBP in terms of healthcare consumption, quality of life, functional capacity and anxiety symptoms. It had also allowed to explore factors associated with active CLBP.

EpiReumaPt confirmed that active chronic LBP in Portugal was

very prevalent, affecting more than 1 million of subjects (10.4%, 95% CI 9.6% to 11.9%) (71), which was similar to the global prevalence of LBP reported in the Global Burden of Disease 2010 study (68) [(9.4%, (95% CI 9.0%-9.8%)]. This finding was also consistent with results of previous studies in industrialized countries (72-75). The mean age of the active chronic LBP population was 58.9 (SD 17.2) years old. Active chronic LBP was significantly more prevalent among women (14.1% vs 6.3% in men). The prevalence of active chronic LBP increased with age (Figure 28).

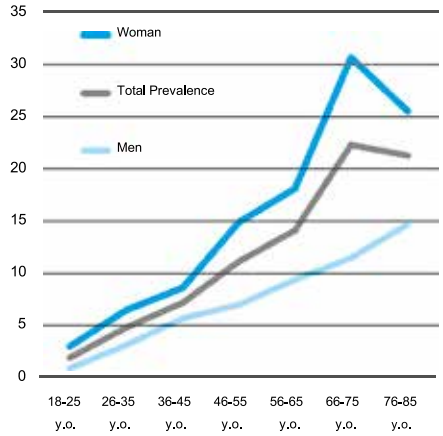


Figure 28. CLBP by age and gender

A substantial proportion of the subjects (68.7%) with active chronic LBP 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 chronic LBP (47.8%). Furthermore, 65.5% self-reported a household income ≤1500€; 50.2% were retired; and 22.3% of the patients with chronic LBP were retired due to RMD. For those with active life, the self-reported mean time of weekly working hours was 42.7 (SD 12.16) hours (Table 13).

Table 13. Crude analysis of sociodemographic and socio-economic characteristics, healthcare consumption and health status of the population with active CLBP and the remaining population with no CLBP (active or non-active)

Demographic characteristics	Mean ± SD or n (%) active CLBP n=1,487	Mean ± SD or n (%) Population without CLBP (active or non-active) n= 8,671	p-value
Age (years)	58.90±17.21	44.75±17.46	<0.001
Female Gender	1,126 (71.4%)	5,047	<0.001
Education level (%) (n=1,462)			
>12 years	85 (7.8%)	1,627 (22.1%)	<0.001
10-12 years	158 (15.3%)	1,707 (25.2%)	
5-9 years	236 (17.2%)	1,856 (23.3%)	
0-4 years	983 (59.8%)	3,433 (29.3%)	
Population size of the place of residence (%)			
< 2,000 habitants	740 (47.8%)	3,651 (38.5%)	<0.001
2,000 – 9,999 habitants	270 (15.3%)	1,630 (16.0%)	
10, 000 – 19, 999 habitants	124 (7.9%)	858 (8.9%)	
20, 000 – 99, 999 habitants	153 (13.6%)	1,210 (17.2%)	
≥100, 000 habitants	200 (15.5%)	1,322 (19.3%)	
BMI (kg/m2) (%) (n=1,346)			
Underweight (<18.50 Kg/ m2)	9 (1.1%)	154 (2.4%)	<0.001
Normal (18.5 – 24.99 Kg/ m2)	396 (30.4%)	3,532 (47.7%)	
Overweight (15.00 – 29.99 Kg/ m2)	522 (38.8%)	3,071 (34.5%)	
Obese (≥ 30 .00 Kg/ m2)	419 (29.8%)	1,538 (15.4%)	
Socio-economic characteristics			
Household income in the last month (%)			
< 500€	396 (21.2%)	1,458 (18.3%)	<0.001
501€ to 1,500€	600 (43.8%)	3,322 (57.7%)	
1,501€ to 2,500€	93 (7.9%)	903 (16.7%)	
2,501€ to 4,000€	19 (1.5%)	339 (5.2%)	
> 4,000€	8 (0.6%)	91 (2.1%)	

(to be continued)

Demographic characteristics	Mean ± SD or n (%) active CLBP n=1,487	Mean ± SD or n (%) Population without CLBP (active or non-active) n= 8,671	p-value
Employment Status (%)			
Full-time Employed	302 (26.0%)	3,571 (45.3%)	<0.001
Part-time employed	30 (1.7%)	299 (5.0%)	
Domestic worker	121 (6.1%)	487 (3.5%)	
Unemployed	115 (9.2%)	927 (12.4%)	
Retired	823 (50.2%)	2,694 (21.2%)	
Student	5 (0.5%)	414 (9.5%)	
Temporary disabled	44 (3.1%)	108 (0.9%)	
Other	47 (3.1%)	170 (2.1%)	
Retirement attributable to RMDs (%) (n=653)	157 (22.3%)	190 (8.3%)	<0.001
Age of Retirement (years) (n=155)	50.78±11.01	54.46±9.57	0.028
Unemployment attributable to RMDs (%) (n=102)	15 (13.4%)	11 (0.9%)	<0.001
Maximum weekly working hours (hours) (n=328)	42.68±12.16	41.14±10.29	0.068

SD - standard deviation; CLBP - Chronic low back pain; BMI - Body Mass Index; RMDs - Rheumatic Musculo-skeletal Diseases; % - percentage; € - euro

After adjustment, active chronic LBP subjects had a higher likelihood for anxiety symptoms (OR=2.77), early retirement due to disease (OR=1.88), and more medical appointments (ß=2.65). Factors significantly and independently associated with the presence of active chronic LBP were: female gender (OR=1.34), overweight/obesity (OR=1.27), presence of self-reported RMDs (OR=2.93), anxiety symptoms (OR=2.67), age (OR=1.02), and higher number of self-re-ported comorbidities (OR=1.12) (71).

The mean intensity of pain, using the numeric pain rating scale (NPRS) among subjects that self-reported active chronic LBP, was 6.0 (SD 2.14); women self-reported high level of pain (6.2 SD 2.53 vs 5.7 SD 2.29 from men); in the previous 12 months, 97.7% had LBP and reported a mean of 233 days (SD 187.15) with pain, and were unable to perform daily activities among an average for 45.4 days (SD 125.58); 52.6% had persistent limitation of mobility; 60.9% of subjects referred pain irradiation and 69.7% reported progressive, slow or insidious onset;

74.4% reported relief with rest; 82.0% characterized the pain as constant and progressive; 69.2% reported progressive weakness of the legs or walking difficulties (71).

Among subjects with active chronic LBP, 63.1% sought medical care and 75.1% had already used analgesic or another pain relief drug, of which 58.5% with parenteral administration. The self-reported average treatment time was 142.3 days (SD 384.43) (71).

EpiReumaPt research team further analysed the profile of analgesic and other pain relief drugs intake among adult Portuguese population with active chronic LBP, taking into account the WHO analgesic ladder and pain intensity. The analgesic drugs intake profile in the population with active chronic LBP was also compared with the remaining Portuguese population in the study (76).

We concluded that analgesic and other pain relief drugs intake among adult Portuguese population with active chronic LBP was very low (18.8%). Most of the subjects with active chronic LBP did not take any analgesic drug regardless pain intensity. Estimated prevalences of main therapeutic groups were: anxiolytics, 14.1%; NSAIDs, 12.3%; antidepressants, 10.1%; analgesic antipyretic, 6.6%; anticonvulsants, 3.4%; central muscle relaxants, 2.6%; analgesic opioids, 1.6% (Figure 29).

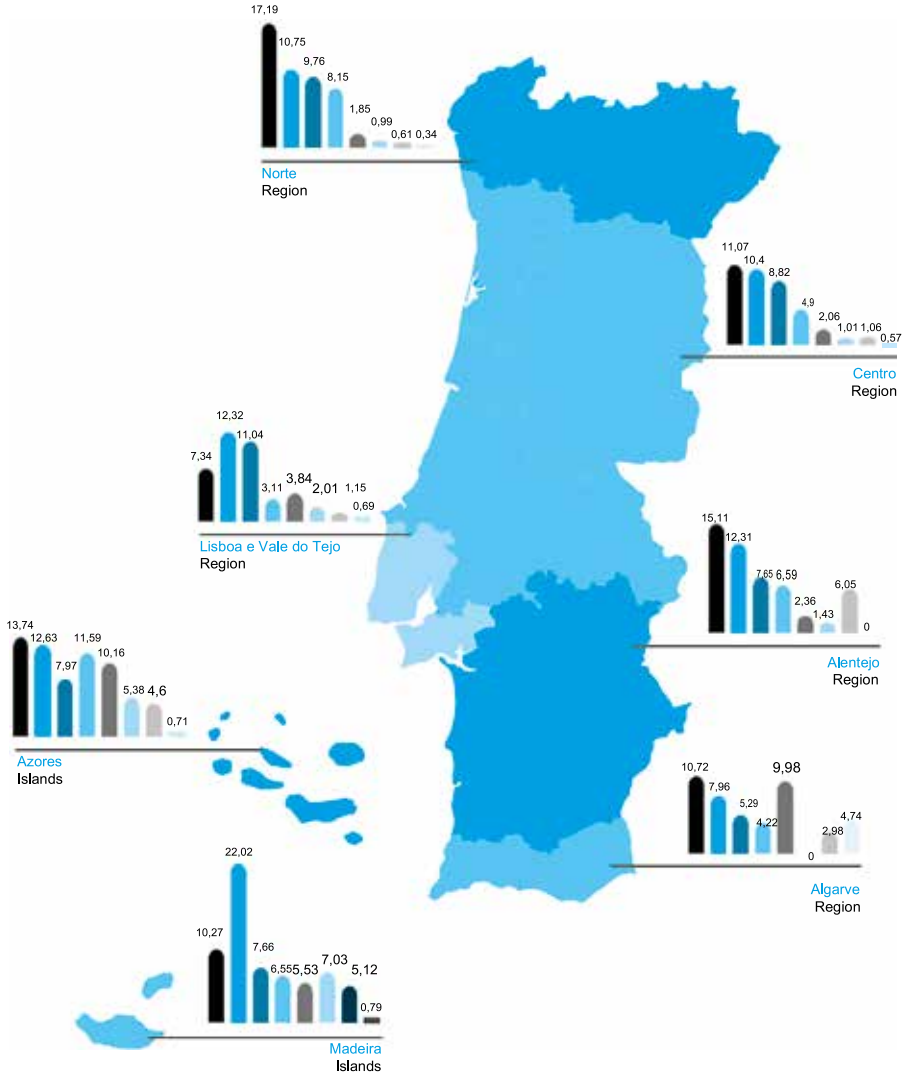


Figure 29. Prevalence of analgesic and other pain relief drug intake by NUTS II; from left to righ: 1st anxiolytics, sedatives and hypnotics; 2nd NSAIDs; 3rd antidepressants; 4th analgesics, antipyretics; 5th anticonvulsants; 6th central muscle relaxants; 7th analgesics; and 8th corticosteroids.

The intake of all therapeutic groups analysed (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 (76).

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.

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.

The presence of active chronic LBP was significantly associated with the intake of all therapeutic groups: antidepressants (OR=12.56; $p<0.001$); centrally acting muscle relaxants (OR=12.01;$p<0.001$); anticonvulsants (OR=9.27;$p<0.001$); anxiolytics, sedatives and hypnotics (OR=8.86;$p<0.001$), NSAIDs (OR=8.56;$p<0.001$) and analgesic opioids (OR=8.13; $p<0.001$) (76).

To summarize, in EpiReumaPt we showed that Portuguese subjects with moderate or severe active chronic LBP were suffering from pain and were under treated. This fact must be linked to loss of productivity and absenteeism verified in this population (71). Moreover, it seems that these subjects do not use regularly pain control drugs and when they use the WHO analgesic ladder is not respected (76).

3.4.2. Fragility Fractures among Elderly Women in Portugal

Osteoporosis (OP) is a metabolic skeletal disease characterized by low bone mass and microarchitecture deterioration (77). Its clinical consequence is the occurrence of fragility fractures (low impact fractures), which represents a public health problem and results in increased mortality, morbidity and disability and also in a major and growing economic burden on healthcare systems (78). Osteoporosis is the most frequent metabolic bone disease with a world prevalence of 11% in women and 2% in men. It is more frequent between postmenopausal women, affecting up to 40% of these women (79).

Following these results, we looked specifically to a high-risk population for fragility fractures, women with ≥ 65 years old and determined the prevalence of fragility fractures and their impact in the quality of life and healthcare resources consumption in this specific vulnerable population.

In EpiReumaPt we could capture sociodemographic, economic and health-related data of elderly women (Table 14). The Portuguese elderly women were mostly Caucasian (n=851; 99.12%) and married (n=447; 47.94%) or widow (n=341; 38.66%). With respect to educational level, a high proportion of participants (n=719; 78.57%) had less or equal to 4 years of education. Moreover, 38.7% of the elderly women lived with a mean monthly household income lower than 500 € (Table 14) (80).

With respect to health-related characteristics, and particularly the cardiovascular risk factors, elderly women frequently reported high cholesterol level (56.15%) and high blood pressure (59.38%). Also, diabetes was reported by 20.9% of the adult Portuguese population. The most frequently reported chronic disease was RMD (67.07%). Prevalence of overweight and obesity was 69.50% in elderly women (47.42% for overweight and 21.68% for obesity). Regarding lifestyle habits, namely in terms of alcohol intake and smoking habits, only 1.96% of the individuals had reported a daily intake of alcohol beverages and 1.81% were current smokers (Table 14) (80).

Finally, we have observed that a significant proportion of elderly women are physical inactive (81.3%). We have also compared sociodemographic, economic and health related data of women≥ 65 years old with and without a self-report of a fragility fracture (Table 14) (80).

Table 14. Comparison of sociodemographic, economic and health related data among elderly women with or without a fragility fracture (crude analysis)

	Post-menopausal women (n=884)	With any self-reported fragility fracture (n=192)	Without any self-reported fragility fracture (n=651)	p-value
Sociodemographic				
Age				
65-69Y	295 (31.52%)	54 (24.52%)	238 (35.46%)	
70-79 Y	443 (51.40%)	95 (47.61%)	318 (50.32%)	0.0142†
> 80 Y	146 (17.08%)	43 (27.87%)	95 (14.21%)	
NUTS II				
Norte	235 (33.82%)	56 (32.23%)	160 (32.34%)	
Centro	201 (22.81%)	37 (21.46%)	151 (22.98%)	
Lisboa	150 (25.60%)	36 (28.78%)	108 (25.68%)	
Alentejo	71 (8.45%)	17 (9.14%)	54 (8.92%)	0.7203
Algarve	46 (5.36%)	9 (4.36%)	36 (5.88%)	
Azores	88 (1.46%)	12 (0.99%)	74 (1.65%)	
Madeira	93 (2.50%)	25 (3.06%)	68 (2.55%)	
Ethnicity/race				
Caucasian	851 (99.12%)	167 (99.44%)	644 (99.13%)	
Black	3 (0.33%)	0 (0%)	3 (0.44%)	
Other	2 (0.23%)	0 (0%)	2 (0.31%)	0.2998
Asian	0 (0%)	0 (0%)	0 (0%)	
Gipsy	0 (0%)	0 (0%)	0 (0%)	
Doesn't know/ doesn't answer	3 (0.32%)	1 (0.56%)	1 (0.13%)	
Education Level (years)				
>12	46 (7.35%)	9 (4.37%)	33 (7.51%)	
10-12	32 (5.89%)	5 (2.58%)	25 (6.82%)	0.1415
5-9	69 (8.20%)	19 (13.67%)	46 (6.85%)	
0-4	719 (78.57%)	150 (79.38%)	540 (78.81%)	

(to be continued)

	Post-menopausal women (n=884)	With any self-reported fragility fracture (n=192)	Without any self-reported fragility fracture (n=651)	p-value
Marital status				
Single	46 (5.99%)	7 (3.61%)	36 (6.56%)	
Married	425 (47.94%)	74 (40.06%)	331 (49.58%)	
Divorced	46 (7.38%)	7 (3.41%)	36 (8.44%)	0.0217†
Widow(er)	341 (38.66%)	80 (52.92%)	246 (35.38%)	
Consensual union	1 (0.03%)	0 (0%)	1 (0.0.4%)	
Household income				
<500€	285 (38.67%)	66 (35.45%)	211 (39.29%)	
501€ to 750€	186 (25.72%)	40 (31.00%)	141 (24.22%)	
751€ to 1000€	73 (9.74%)	17 (11.95%)	53 (8.86%)	
1001€ to 1500€	62 (12.83%)	16 (15.46%)	44 (12.38%)	
1501€ to 2000€	35 (7.44%)	6 (4.45%)	29 (8.51%)	0.3111
2001€ to 2500€	11 (3.85%)	1 (0.68%)	10 (4.83%)	
2501€ to 3000€	7 (0.91%)	2 (1.01%)	4 (0.82%)	
3001€ to 4000€	4 (0.55%)	0 (0%)	4 (0.71%)	
>4000€	2 (0.29%)	0 (0%)	2 (0.37%)	
Non-communicable chronic diseases (self-reported)				
High blood pressure	554 (59.38%)	129 (64.15%)	405 (58.73%)	0.416
Diabetes	199 (20.99%)	45 (27.92%)	148 (20.01%)	0.109
High cholesterol level	512 (56.15%)	105 (51.19%)	379 (56.74%)	0.368
Neurologic disease	68 (7.20%)	15 (8.38%)	49 (6.95%)	0.547
Neoplasic disease	74 (8.06%)	16 (8.51%)	53 (7.74%)	0.776
Thyroid and parathyroid disease	166 (19.86%)	42 (24.84%)	116 (17.63%)	0.117
Hypogonadism	11 (1.58%)	4 (1.94%)	6 (0.90%)	0.283
Rheumatic disease	603 (67.07%)	144 (76.39%)	437 (65.21%)	0.061
Quality of life and physical function				
EQ5D score (mean±sd)	0.63±0.40	0.55±0.42	0.66±0.39	0.002†
HAQ score (0-3) (mean±sd)	0.81±1.04	1.04±1.20	0.74±0.99	0.001†
Healthcare Consumption				
Had home care in the past 12 months	54 (6.09%)	17 (8.39%)	33 (5.38%)	0.208
Hospitalizations in the past 12 months	99 (12.74%)	25 (18.84%)	65 (10.21%)	0.077
Went to medical appointments in the past 12 months				
General practitioners	755 (83.97%)	150 (82.01%)	569 (83.98%)	0.673
Rheumatology appointments	65 (5.84%)	12 (5.70%)	52 (6.15%)	0.839
Orthopedic appointments	130 (15.13%)	24 (12.49%)	97 (15.09%)	0.459
Other appointments	472 (56.48%)	107 (62.97%)	341 (55.17%)	0.186

(to be continued)

	Post-menopausal women (n=884)	With any self-reported fragility fracture (n=192)	Without any self-reported fragility fracture (n=651)	p-value
Number of medical appointments in the past 12 months (mean±sd)				
General practitioners	3.11±5.00	3.20±0.27	3.00±4.76	0.510
Rheumatology appointments	0.13±0.93	0.13±0.94	0.14±0.97	0.892
Orthopedic appointments	0.40±1.88	0.45±2.20	0.37±1.84	0.628
Other appointments	2.51±17.65	2.31±5.67	2.52±20.00	0.718
Lifestyle Habits				
Body Mass Index (kg/m2)				
Underweight	7 (0.81%)	3 (1.58%)	4 (0.67%)	0.1422
Normal weight	228 (28.69%)	51 (29.51%)	160 (27.30%)	
Overweight	379 (47.82%)	80 (40.20%)	285 (50.98%)	
Obesity	251 (22.68%)	53 (28.72%)	189 (21.05%)	
Current Smoking				
Yes	17 (1.81%)	2 (1.15%)	13 (1.77%)	0.581
No	866 (98.19%)	190 (98.85%)	637 (98.23%)	
Alcohol (3 or more units/day)				
Yes	15 (1.96%)	3 (1.55%)	11 (1.55%)	0.988
No	868 (98.04%)	189 (98.45%)	639 (98.45%)	
Physical activity				
Inactive	524 (81.30%)	112 (86.93%)	388 (80.93%)	0.4252
Moderate	24 (4.33%)	4 (2.75%)	17 (3.68%)	
Active	69 (14.37%)	12 (10.33%)	55 (15.39%)	

NUTS II- Nomenclature of Territorial Units for Statistics (Norte, Centro, Alentejo, Algarve, Lisboa, Madeira and the Azores); EQ5D - European Quality of Life questionnaire five dimensions three levels; HAQ - Health Assessment Questionnaire. Sample size is not constant due to: Post-menopausal women – Ethnicity (n=859); Education level (n=866);Marital status (n=859); Household income (n=665); High blood pressure (n=873); Diabetes (n=872); High cholesterol level (n=870); Neurologic disease (n=875); Neoplasic disease (n=879); Thyroid and parathyroid disease (n=869); Hypogonadism (n=852); Rheumatic disease (n=845); EQ5D score (n=874); Had home care in the past 12 months (n=861); Hospitalizations in the past 12 months (n=883); Body Mass Index (n=865); Current Smoking (n=883); Alcohol (n=883); Physical activity (n=617); With any self-reported fragility fracture – Ethnicity (n=168); Education level (n=183); Marital status (n=168); Household income (n=148); High blood pressure (n=188); Diabetes (n=187); High cholesterol level (n=186); Neurologic disease (n=188); Neoplasic disease (n=190); Thyroid and parathyroid disease (n=188); Hypogonadism (n=182); Rheumatic disease (n=186); EQ5D score (n=189); Had home care in the past 12 months (n=169); Hospitalizations in the past 12 months (n=191); Body Mass Index (n=187); Physical activity (n=128); Without any self-reported fragility fracture - Ethnicity (n=650); Education level (n=644); Marital status (n=650); Household income (n=498); High blood pressure (n=645); Diabetes (n=645); High cholesterol level (n=644); Neurologic disease (n=647); Neoplasic disease (n=649); Thyroid and parathyroid disease (n=641); Hypogonadism (n=631); Rheumatic disease (n=620); EQ5D score (n=646); Body Mass Index (n=638); Current Smoking (n=650); Alcohol (n=650); Physical activity (n=460). †p-value<0.05. From Rodrigues AM, et al. (80)

The estimated prevalence of fragility fractures among Portuguese elderly women was 21.1% and the prevalence rises up to 34.4% in women with ≥ 80 years old (Figure 30). Madeira (24.3%) and Lisboa e Vale do Tejo (23.06%) were the regions one with more prevalent fragility fractures

(Figure 31). The wrist was the most frequent fracture site reported (18.25%) followed by spine (5.18%) and finally hip (6.53%) (Figure 32) (80).

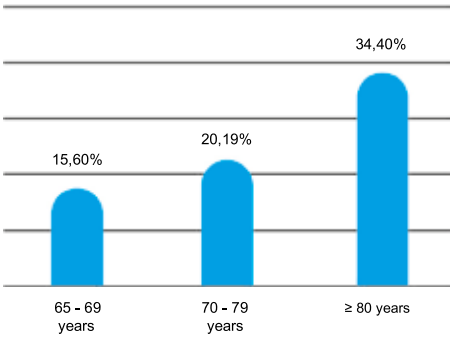


Figure 30. Prevalence of self-reported fragility fracture among elderly women, by age group (80)

Only 7.0% of the elderly women that self-reported a fragility fracture were under/had been under OP treatment. Self-reported fragility fracture among elderly women was associated to worst quality of life (ß= -0.09, 95%CI -0.17, -0.02; p= 0.018), physical function (ß=0.41 95%CI, 0.21, 0.61 p=<0.001) but not with healthcare consumption (Table 15). Regarding clinical risk factors for fracture 7.10% of elderly women reported history of parent hip fracture and 2.72% secondary osteoporosis. In addition, hypovitaminosis D (<30ng/ml) was present in 32.55% of the elderly women (Table 16) (80).

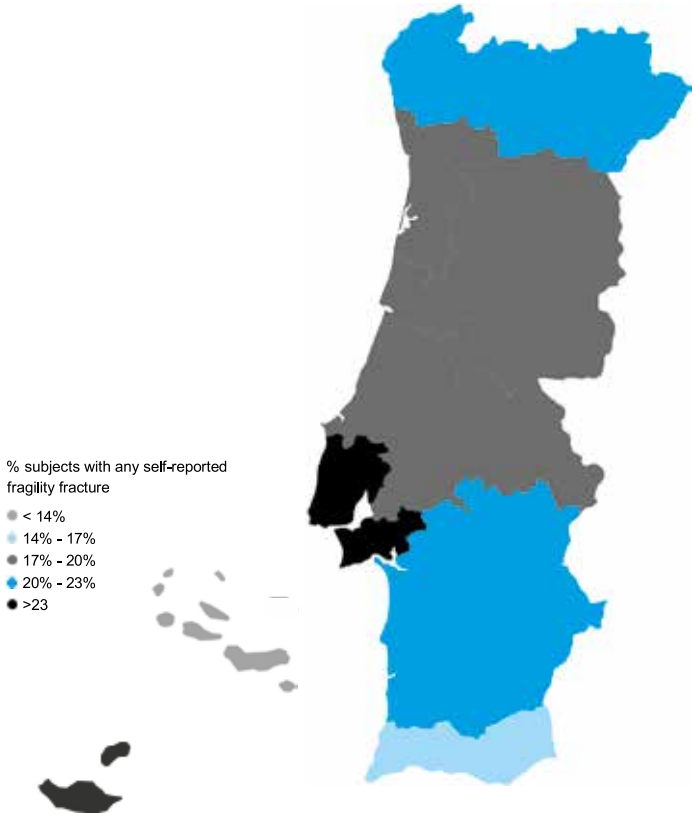


Figure 31. Prevalence of fragility fractures among elderly women according to NUTs II region (80)

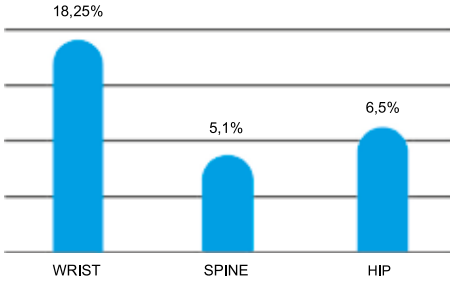


Figure 32. Fragility fractures relative frequency according to the site of fracture (80)

Table 15. Multivariable regression analysis performed to determine the independent association of fragility fracture with quality of life, physical function and healthcare consumption among elderly women

Dependent Variables	Crude Analysis ß [95% CI]	p-value	Adjusted* Analysis ß [95% CI]	Adjusted* p-value
EQ5D	-0.10 [-0.17;-0.04]	0.003†	-0.09 [-0.17;-0.02]	0.018†
HAQ	0.30 [0.11;0.49]	0.002†	0.41 [0.21;0.61]	<0.001†
Total number of medical appointments in the past 12 months	0.06 [-1.56;1.67]	0.944	-0.20 [-2.35;1.95]	0.858
Dependent Variables	**Crude Analysis OR [95% CI]**	**p-value**	**Adjusted* Analysis OR [95% CI]**	**Adjusted* p-value**
Hospitalizations in the past 12 months (y/n)	0.71 [-0.08;1.50]	0.077	1.24 [0.52;2.95]	0.634
Home care in the past 12 months (y/n)	0.48 [-0.27;1.22]	0.208	0.93 [0.27;3.19]	0.908

EQ5D - European Quality of Life questionnaire five dimensions three levels; HAQ - Health Assessment Questionnaire. *Adjusted for: Age, NUTII (Nomencla-ture of Territorial Units for Statistics), years of education, married/consensual union vs single/widow(er)/divorced, and categorical BMI.†p-value<0.05 (80).

Table 16. Comparison of risk fractures for fracture between elderly women with and without a fragility fracture (crude analysis)

Risk factures for fracture	Post-menopausal women (n=884)	With any self-reported fragility fracture (n=192)	Without any self-reported fragility fracture (n=651)	p-value
Age				
65-69Y	295 (31.52%)	54 (24.52%)	238 (35.46%)	0.0142†
70-79 Y	443 (51.40%)	95 (47.61%)	318 (50.32%)	
> 80 Y	146 (17.08%)	43 (27.87%)	95 (14.21%)	
Body Mass Index (kg/m2)				
Underweight	7 (0.81%)	3 (1.58%)	4 (0.67%)	0.1422
Normal weight	228 (28.69%)	51 (29.51%)	160 (27.30%)	
Overweight	379 (47.82%)	80 (40.20%)	285 (50.98%)	
Obesity	251 (22.68%)	53 (28.72%)	189 (21.05%)	
Years since menopause				
≤15	92 (13.74%)	15 (8.92%)	77 (15.22%)	0.1872
Between 15 and 25	283 (47.51%)	60 (44.86%)	222 (48.55%)	
Between 25 and 30	107 (17.04%)	20 (15.01%)	85 (17.49%)	
>30	118 (21.71%)	30 (31.21%)	86 (18.74%)	

(to be continued)

Risk factures for fracture	Post-menopausal women (n=884)	With any self-reported fragility fracture (n=192)	Without any self-reported fragility fracture (n=651)	p-value
Parent Hip Fracture				
Yes	55 (7.10%)	13 (6.75%)	36 (6.83%)	0.976
No	828 (92.90%)	179 (93.25%)	614 (93.17%)	
Current Smoking				
Yes	17 (1.81%)	2 (1.15%)	13 (1.77%)	0.581
No	866 (98.19%)	190 (98.85%)	637 (98.23%)	
Alcohol (3 or more units/day)				
Yes	15 (1.96%)	3 (1.55%)	11 (1.55%)	0.998
No	868 (98.04%)	189 (98.45%)	639 (98.45%)	
Physical activity				
Inactive	524 (81.30%)	112 (86.93%)	388 (80.93%)	
Moderate	24 (4.33%)	4 (2.75%)	17 (3.68%)	0.4252
Active	69 (14.37%)	12 (10.33%)	55 (15.39%)	
Glucocorticoids				
Yes	35 (3.79%)	6 (3.00%)	26 (3.83%)	0.625
No	848 (96.21%)	186 (97.00%)	624 (96.17%)	
Rheumatoid Arthritis				
Yes	15 (1.40%)	4 (1.17%)	11 (1.57%)	0.696
No	868 (98.60%)	188 (98.83%)	639 (98.43%)	
Secondary Osteoporosis				
Yes	29 (2.79%)	6 (2.93%)	22 (2.78%)	0.930
No	854 (97.21%)	186 (97.07%)	628 (97.22%)	
Chronic Renal Insufficiency				
eGFR<30 ml/min/1.73m2	16 (2.11%)	4 (2.70%)	12 (2.11%)	0.672
eGFR≥30 ml/min/1.73m2	656 (97.89%)	141 (97.30%)	484 (97.89%)	
Peripheral Bone Mineral Density (g/cm2)				
Wrist (mean±sd)	0.36±0.12	0.35±0.12	0.37±0.12	0.112
Peripheral Tscore				
Wrist (mean±sd)	-2.10±1.87	-2.27±1.84	-2.05±1.90	0.269
<-2.5	233 (36.35%)	64 (42.96%)	158 (35.38%)	
Between -2.5 and -1	341 (42.80%)	69 (39.58%)	256 (42.35%)	0.5337
>-1	157 (20.85%)	25 (17.46%)	126 (22.27%)	
Deficiency (<10)	19 (2.03%)	5 (3.18%)	14 (1.88%)	
Insufficiency (Between 10 and 30)	223 (32.55%)	44 (31.85%)	167 (33.10%)	0.850
Normal (≥30)	402 (65.42%)	84 (64.97%)	299 (65.02%)	

Sample size is not constant due to: Post-menopausal women – Body Mass Index (n=865); Years since menopause (n=600); Parent Hip fracture (n=883); Current Smoking (n=883); Alcohol (n=883); Physical activity (n=617); Glucocorticoids (n=883); Rheumatoid Arthritis (n=883); Secondary Osteoporosis (n=883); Creatinine clearance (n=672); Bone Mineral Density Wrist (n=759); Tscore Wrist (n=731); Vitamin D (n=644);); With any self-reported fragility fracture – Body Mass Index (n=187); Years since menopause (n=125); Physical activity (n=128); Creatinine clearance (n=145); Bone Mineral Density Wrist (n=162); Tscore Wrist (n=158); Vitamin D (n=133); Without any self-reported fragility fracture - Body Mass Index (n=638); Years since menopause (n=470); Parent Hip fracture (n=650); Current Smoking (n=650); Alcohol (n=650); Physical activity (n=460); Glucocorticoids (n=650); Rheumatoid Arthritis (n=650); Secondary Osteoporosis (n=650); Creatinine clearance (n=496); Bone Mineral Density Wrist (n=563); Tscore Wrist (n=540); Vitamin D (n=480); †p-value<0.05

In conclusion, fragility fractures are a significant public health problem in Portugal and elderly women are a particular vulnerable group. In fact, 1 out of 4 elderly women have a fragility fracture but only 7 out of 100 are under medical treatment. Elderly women that reported a fragility fracture have a poorer quality of life and higher disability than the ones that did not report a fragility fracture (80). EpiReumaPt findings increase the body of knowledge regarding fragility fractures in elderly women and should help public health policies to address this problem.

Chapter 4

Arriving

4.1. Discussion

EpiReumaPt was the first large-scale epidemiological population-based study evaluating the prevalence, determinants and burden of RMDs in Portugal. This study determined the prevalence of 12 target diseases (LBP, FM, OP, PD, hand, knee and hip OA, RA, SpA, SLE, gout and PMR). It also aimed to determine the impact of RMDs on physical and mental health and the economic burden of these diseases. Subsequently analysis allowed the study of specific RMDs as well as other studies focused on therapies and other non-communicable chronic diseases.

In developed countries, RMDs are the most frequent group of diseases among humans and represent a major economical, medical and social problem (81). The concept of RMDs has no clear borders. This group of diseases comprises more than one hundred extremely different entities, which includes those studied in EpiReumaPt (30). Generally, RMDs are more frequent in females, affect all races transversally and, despite targeting all age groups, are more common in the elderly due to its chronic nature (81). These characteristics were also found in Portugal (38). The sampling design of EpiReumaPt was a success as the population is comparable to the one from Census 2011, from the National Institute of Statistics, and therefore is representative of the Portuguese population (36, 54).

Epidemiology studies the frequency and the reasons behind the onset and progression of certain diseases in different groups of the population (82). In fact, epidemiological research lies on seeking clarification on certain characteristics of a target population. For various reasons assessing the entire target population is rarely doable, so the most common procedure is the observation of a sample group extracted from that population as it happened in EpiReumaPt.

In EpiReumaPt we have characterized the socioeconomic features of the Portuguese adult population. From a social and health point of view a very astonishing and alarming result was the fact that a fifth of the adult Portuguese population mentioned a monthly family income of less than 500€. Considering Portuguese health and health-related characteristics,

we have found that RMDs were one of the most frequent chronic non-communicable diseases. In fact, RMDs are highly prevalent in Portugal and their prevalence is similar to the figures reported in other countries (68, 83-86-90), namely our close neighbor Spain (27).

In EpiReumaPt, LBP was the most prevalent RMD as opposed to the findings in other countries (84,85,91) where osteoarthritis was the most prevalent disease. This finding may be due to the different methodology and case definition used in EpiReumaPt study in which OA was considered separately according to body region (hand, knee, hip). In fact, if we consider the combined prevalence of hip and/or knee and/or hand OA it reaches 19.1% which is indeed similar to one reported in other epidemiological studies. In fact, one of the difficulties associated with epidemiological studies is the lack of standardized diagnostic criteria for OA, which is most often defined by radiological criteria - e.q. those of Kellgren and Lawrence, 1957 (92). However, significant clinical and radiological dissociation is mostly present in joint OA. Nevertheless the prevalence, either its total or by gender, of knee OA in Portugal (Total: 12.4%; Women: 15.8%; Men: 8.6%) (38) is similar to that of Spain (T: 10, 2%; W: 14.0%, M: 5.7%) (30); the overall frequency (26.4%) and by gender (W: 29.6% and M: 22.8%) of LBP are similar to the ones in England (T: 23%, W: 24%, M: 22%) and incongruent with those portrayed in Spain (T: 14.8%; W: 17.8%; M: 11.3%) and in Greece (T: 11.0%; W: 12.5%; M: 9.4%) (28, 93, 94).

The observed frequency of hand OA (T: 8.7%; M: 17.0; H: 3.2%) is close to the one found a decade earlier in Spain (T: 6.2%) but the difference among men (2.3%) and women (9.5%) was less marked than we described (27).

As mentioned above, most of the epidemiological studies published indicate the global incidence of peripheral OA, they are not joint specific, which makes it difficult to do reliable comparisons between the results we found for hip OA (T: 2.9%, W: 3.0%; M: 2.9%) and those from other countries.

Periarticular diseases were the second most frequent RMDs in the Portuguese population (T: 15.8%; M: 19.1%; H: 12.0%). As it is

a predominantly acute pathology, it must be present at the time of the inquiry/clinical observation performed in epidemiological studies in order to be considered in this context.

In this type of study, clinical information prevails as the basis for defining each case of periarticular RMD. All these precautions and standards were considered in EpiReumaPt (36).

Because of these difficulties, references regarding the prevalence of periarticular pathology are rare to find in the literature. In Greece, Andrianakos et al. found a much lower prevalence (T: 4.3%; W: 5.0%, M: 3.6%) (28). A review article on the epidemiology of RMDs in 12 developing countries had shown that, in general, the overall PD prevalence rates are similar to those of Greece (28). The exceptions are Indonesia, with a total prevalence (15.0%) almost equal to ours, and Kuwait, where the prevalence of these conditions is three times higher than the Portuguese rate (i.e. 45.6%). In neither case gender information is provided (95).

Osteoporosis (OP) can be defined through the occurrence of a fragility fracture (e.q., due to low energy injury) or by measuring of the bone's mineral density, ideally using the dual energy X Ray bone densitometry (DEXA) method and WHO's operational definition (96).

The wide definition of OP that was used in EpiReumaPt may justify the differences between our results (T: 10.2%; W: 17.0%; M: 2.6%) and those defined in Spanish (T: 3.4%) and Greek (T: 3.0%, W: 5.7%; M: 0.3%) studies (27,28).

One of EpiReumaPt's subsidiary studies, presented herein after its overall results, refers to fragility fractures in elderly women. The estimated prevalence of fragility fractures among Portuguese elderly women was 21.1% and the prevalence rises up to 34.4% in women with ≥ 80 years old. However, only 7.0% of the elderly women that self-reported a fragility fracture were under/had been under OP treatment. These results should create awareness to the undertreated high-risk patients and must be urgently addressed (80).

Fibromyalgia showed a prevalence of 1.7%, occurring almost exclusively in women (3.1%) and virtually non-existent in men (0.0%) (38). These figures do not differ much from those found in Spain (T:

2.4%; W: 4.2%; M: 0.2%) (27), USA (T: 2.0%; W: 3.4%; M: 0.5%) (97) and Italy (T: 2.2%) (98). They are however much lower than the numbers found in the Portuguese population (T: 3.7%; W: 5.1%; M: 2.3%) in another study with a completely different methodology (99).

In the EpiReumaPt study we have used the new ACR/EULAR classification criteria for RA (39) and the ASAS criteria for SpA (46, 50) and found a prevalence of 0.7% for RA and 1.6% for SpA. Global prevalence values for SpA calculated before the introduction of the ASAS criteria were reported to be approximately 1% (100) but ranged substantially from 0.001% in Japan (101) to 2.5% in Northern Artic Natives (102). In fact, the new ASAS classification criterion for axial SpA covers 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 (46). To our knowledge, only one study has used the ASAS classification criteria to estimate the overall prevalence of SpA (103).

Costantino et al used a large population-based cohort - the GAZEL cohort - to estimate SpA prevalence in the French population (0.43%) (103). Unlike the study by Costantino et al, in EpiReumaPt the use of the new criteria confirmed a higher prevalence of SpA in Portugal than the previously reported (25).

The ACR's classification criteria for RA, published in 1988 (104), were used in the most recent epidemiological studies with which we can compare our results (T: 0.7%; W. 1.2%, M: 0.3%). These were slightly higher than the Spanish (T: 0.5%; W: 0.8%; M: 0.2%) (105), but similar to those found in New Zealand (T: 0.79%) (106), Greece (T: 0.68%, W: 1.0%; M: 0.5%) (28) and the USA (T: 0.6%) (86).

The values mentioned above regarding the prevalence of RA in the CINDI study (WHO's program) were half (T: 0.36%) of the ones we now found (10). Although the CINDI study used the 1958's American Rheumatism Association criteria for the diagnosis of RA (107), the value (i.e., 0.36%) was in line with the estimated prevalence for RA in France (T: 0.31%; W: 0.51%; M: 0.09%) (108) and Italy (T: 0.33%; W: 0.51%; M: 0.13%) (109).

The prevalence of gout (T: 1.3%) was higher in EpiReumaPt than the estimated for Europe in the Global Burden of Disease study (T: 0.8%) (110) but similar to the one in UK (T: 1.4%) (111) and New Zeland (T: 1.38%) (106). This finding may relate to the increasing prevalence of metabolic syndrome in Portugal, as a result of recent dietary changes including the decline of the Mediterranean food pattern (112).

Systemic Lupus Erythematosus and Polymyalgia Rheumatica are both systemic RMDs that occur respectively in young or middle-aged females or in seniors of both genders. Because of their low prevalence, few epidemiological studies refer to these two entities.

The overall prevalence for both SLE and PMR was 0.1%. Concerning SLE, this value is identical to that published for Spain (T: 0.09%) (27) and Greece (T: 0.15%) (91) and, regarding PMR, similar to that described in other study in Greece (T: 0.15%) (28).

Another interesting finding of our study was the high proportion of individuals presenting typical features of one or more RMDs that did not have a previous diagnosis (1,532 subjects in a total of 3,877) (38). This could be explained by the scarce number of rheumatologists in Portugal (1: 100000 inhabitants) (113) and by the lack of awareness of the population to these diseases, being frequently accepted as part of the normal aging process.

Regarding the impact of RMDs on HRQoL, physical function and mental health of the Por-tuguese population, we confirmed that patients with RMDs have significantly worse HRQoL and more disability when compared to subjects without RMDs. We found that PMR, RA and FM were the conditions with the worst impact on function and HRQoL (38). When we compared subjects with and without RMDs regarding mental distress symptoms, we found a significantly higher proportion of RMDs 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 (38). 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 (38). In contrast, several other studies have shown higher prevalence of anxiety and depressive symptoms associated with several RMDs (114-116). One explanation could be that many of these studies were performed in a hospital environment and were not population-based studies.

The economic burden of RMDs is very high. RMDs are associated not only with significant physical function and mental health impairment but also with poor HRQoL (60, 61), leading to more healthcare resources consumption (38). Moreover, in EpiReumaPt study we observed that there are a meaningful number of people who claimed to be retired prematurely due to RMDs (66). This translates in many years of working life already lost and many others still potentially to be lost. Indirect costs due to self-reported RMDs are also substantial, equivalent to at least 0.5% of the GDP. By specifically analyzing OA, one of the most prevalent and disabling joint disorder, it was possible to verify that the productivity loss due to RMDs is potentially even higher than the one obtained when analyzing self-reported RMDs as a whole (67).

The results emphasize the burden of RMDs in Portugal and the need to develop RMDs awareness, being a strong argument to encourage policy makers to increase the amount of resources allocated to the treatment of rheumatic patients.

Results of EpiReumaPt emphasize the burden of RMDs in Portugal and the need to increase RMDs awareness, being a strong argument to encourage policy makers to increase the amount of resources allocated to the treatment of rheumatic patients.

The data collected in the EpiReumaPt study can be used along with other patients' clinical in-formation (e.g., lab tests, imaging studies, clinic notes) to inform decision, health policy makers, the medical community and health managers on the impact of RMDs on quality of life.

EpiReumaPt can provide valuable data to researchers, healthcare providers and patient organizations to future research.

4.2. Strengths and Limitations

We had a high number of non-participants loss of follow-up between the first and the second phase of the study. In order to assure that we did not over/underestimate the disease prevalence due to potential sample bias, we performed a detailed participation analysis considering several subject domains (demographic, socio-economic, lifestyle, health-care resources consumption, RMDs screening result and self-report of other chronic diseases) (36).

Other issue was that densitometric measurements were not included in the OP definition, which could have led to an underestimation of the prevalence.

This study has also several strengths, namely it is the first large national population based study on RMDs in Portugal. RMDs were assessed and confirmed by a rheumatologist using validate tools and international classification criteria. The variables captured were very distinct, embracing several domains with clinical, socio and economic measurements that allow ad-dressing the burden of these diseases.

4.3. Impact National Health Policies

In EpiReumaPt's protocol it was considered that this study would be decisive for the future of Portuguese rheumatology and, even more, for patients with RMDs (30).

We recall outlined goals that have been achieved: primary objective - to estimate the prevalence of the different RMDs in Portugal; secondary objectives - to estimate the prevalence of the different RMDs according to sociodemographic characteristics; identify the sociodemographic and clinical variables associated with the diagnosis of some of RMDs; estimate the frequency of RMDs not previously diagnosed; determine the impact of RMDs on quality of life and functional and work capacity; investigate RMDs patients' access to healthcare; compare the reality of RMDs in Portugal with other countries'; define follow-up cohorts (30).

Obviously, the fulfilment of these objectives in itself was a very important achievement with great consequences, but what this study represents and entails truly surpasses those goals.

First of all, it comes to show that it is possible to develop and undertaking a study of this size in Portugal with the accuracy, prolific ability and professionalism necessary for its success. And this fact alone represented a gratifying reward for all the "patrons" who - and this shouldn't go unnoticed - risked pursuing the social importance and national relevance of what was then just a simple project.

Therefore, and taking into consideration the uniqueness of this large epidemiological study, we chose to publish an article exclusively dedicated to its procedures and organization that elucidates on how it was done and that can instruct those who want to venture into conducting another study of this nature for other purposes (33).

It also revealed that it is possible to motivate towards a common goal a large number of doctors who, despite their many obligations and professional affairs, were able to mobilize so as not to jeopardize in the slightest the tight and demanding schedule of appointments that moulded the 2nd phase of EpiReumaPt.

This study has also multiple goals that go beyond the extent of RMDs, therefore establishing itself as an extraordinary and eclectic collection of data, which will forever be available to researchers, universities, companies, scientific societies, authorities and media.

The vast quantity and quality of data and its population representativeness constitute a unique heritage in the national scene that will constantly be expanded through the continuous construction and follow-up of the resulting cohorts (please see New Horizons Chapter).

Finally, plenty of EpiReumaPt's results have an undeniably high medical and socio-economic impact, granting them an explicit power of reference for our Health Authorities to address political and administrative decisions.

Considering only EpiReumaPt's initial results, one can easily conclude that in Portugal the number of rheumatologists is scarce and its geographical distribution is poor.

Consequently, the physical, financial, human and material means available to the health care of RMDs patients in our country is precarious and, unless something is done, the expected increase in the prevalence of at least some of these diseases will worsen this situation.

Of course, there may be several judgments on this matter, and among us there are always highlighted and diversified opinions, but facts are facts and those, thanks to EpiReumaPt, are irrefutable.

Chapter 5

New Horizons

5.1. New Projects

EpiReumaPt allowed the characterization and the study of the impact of RMDs in Portugal. At the same time we achieved two other distinct goals. The first one was to ground EpiReumaPt as the first wave of a more ambitious study that aims to constitute a longitudinal study to follow the participants over time. This cohort is called Epidemology of Chronic Diseases - EpiDoC cohort – has already two other waves of cross-sectional evaluations (performed to the same subjects) called CoReumaPt and Saúde.come, described below.

The second aspect is that in the three waves of the study, we collected much more information than the information on RMDs described in this work. In fact, a large bulk of information was also collected regarding the most important non-communicable chronic diseases and it is now possible to pursue different lines of research based on these data.

5.1.1. CoReumaPt

The cross-sectional study EpiReumaPt finished the collection of data on December 2013. Between March 2013 and July 2015, we developed CoReumaPt, assessing through phone call interviews the same participants included in EpiReumaPt (EpiDoC cohort) (34). This study allowed to systematically collect and analyse longitudinal outcomes and to add new questions like food patterns and health innovation.

The team included specially trained research assistants to perform the phone interviews and also biostatistician and informatics with expertise and experience in conducting large cohorts.

Specific domains beyond RMDs were addressed for all population, such as sociodemographic & socioeconomic data; anthropometric measures; non-communicable chronic diseases and risk factors for cardiovascular events; anxiety, depression, physical function and quality of life; falls and bone fractures; hospitalizations, home care assistance and medical appointments; medication and other treatment; alcohol and

smoking habits; physical exercise and lifestyles; mortality information; habits regarding new technologies; search for health information; development and adoption of health innovation, trust in conventional healthcare system; alternative medicine; adverse events.

In this study we collected data from 7,591 subjects already interviewed in EpiReumaPt, representative of the adult Portuguese population. We already developed some studies involving this wave results, namely calculating the determinants of dietary patterns and its association with socioeconomic factors, lifestyles behaviors and health status in Portugal. Other papers will come soon.

5.1.2. Saúde.come - Promoting Food Security

Between April 2015 and July 2016 we performed another wave of telephone interviews to EpiDoC participants, included in a more comprehensive study, the Project Saúde.come.

The Project Saúde.come - Promoting Food Security, was developed under the Public Health Initiatives of Program, EEA-Grants (www.eeagrants.gov.pt). This program results of the Memorandum of Understanding signed between Portugal and Donor Countries (Iceland, Liechtenstein, and Norway) of the Financial Mechanism of the European Economic Area and aims to contribute to reduce economic and social inequalities in health areas designated as priorities, and the establishment of bilateral relations between the Donor Countries and the Beneficiaries.

In order to develop the study, it was set up an independent consortium which brought together leading institutions in the field of clinical research. The consortium was led by the Portuguese Society of Rheumatology (Helena Canhão, MD, PhD) and also has the following institutions: Nova Medical School, NOVA Medical School (Jaime Branco, MD, PhD), Catolica-Lisboa School of Business and Economics (Pedro Oliveira, PhD), Instituto de Saúde Pública da Universidade do Porto (Ana Cristina Santos, PhD), and Research Centre for Health Promotion and Resources HiST-NTNU Norges Teknisk-Naturvitenskapelige Universitet

Trondheim, Norway (Geir Espnes, PhD).

The objectives of Saúde.Come – Promoting Food Security were to characterize food insecurity in Portugal and its determinants; to increase the body of data and knowledge on several nutrition aspects and related factors; to promote the exchange of knowledge and experience with Norwegian partners and collaboratively study and compare the differences and similarities between the two countries; and to develop for the first time in Portugal, a personalized and sustainable nutritional program using innovative tools (phone apps and interactive television programs), easy to disseminate at a low cost and that contribute to reduce social inequalities in health.

The investigation team gathered and analysed data from pre-existing Portuguese and Norwegian cohorts studies (large-scale population samples with demographic, socioeconomic, health related, nutrition indicators and other life style information): EpiReumaPt a national population-based study (10,661 subjects); EpiPorto: 2485 adults followed since 1999; EpiTeen: 2160 young adults, and a Norwegian cohort - the HUNT study (126.000 participants) - a largest database of personal and family medical histories.

It was possible to determine associations between dietary habits, obesity and sedentarism with non-communicable chronic diseases; to compare life styles, nutrition patterns and comorbidities between both countries and to identify vulnerable nutrition populations according to demographic and socioeconomic characteristics. The best questionnaires were refined to be applied in National Survey on Food Insecurity and its determinants in order to maximize the acquisition of data regarding dietary patterns according to population strata. To optimize these exploratory analyses, outstanding bioinformatics, statistical modelling and database handling support were followed.

Other aim of the project was to perform a survey on food insecurity. The SPR research team developed a structured questionnaire that was included in the third wave of evaluation of EpiDoC cohort. Also, ISPUP performed simultaneously a similar questionnaire to young adults of EpiTeen Cohort.

The third wave of EpiDoC cohort collected data on sociodemographic & socioeconomic data; anthropometric measures; non communicable chronic diseases (were RMDs were also considered) and risk factors for cardiovascular events; anxiety, depression, physical function and quality of life; falls and bone fractures; hospitalizations, home care assistance and medical appointments; medications and other treatment; alcohol and smoking habits; physical exercise and lifestyles; and mortality information. But also more detailed data on food consumption, Mediterranean diet, food insecurity, healthcare system data and oral health.

The third wave of questions was finished on July 2016, but the project is still ongoing. We are analysing data and expect have more results very soon.

Using acquired knowledge in the previous steps, interventional pilot studies were developed in predetermined high-priority vulnerable groups (teenagers and elderly) to improve specific energy balance-related behaviours at 6 months follow-up.

We developed a personalized and sustainable nutritional and physical exercise program that was delivered to the interventional groups using interactive technology tools (phone apps, internet platforms and interactive television programs).

The elderly intervention was a controlled study in subjects ≥60 years old with food insecurity, identified in Primary Care Centres. Primary outcome was changes in participants' food insecurity score (Household Food Insecurity Scale) from baseline to 3 months. Subjects were followed 6 months and intervention lasted 3 months. Data collection was performed in three timepoints (baseline, end of intervention (3 months) and follow-up at 6 months). Intervention was based on an inter-active TV application with an educational/motivational program developed for elderly with daily contents in video format: 1) Nutrition tips, 2) Healthy and low-cost recipes, 3) Physical exercise programs and 4) Brief reminders on health behaviours. This tool consists in a structured and valid reservoir of information on healthy lifestyles that could be access whenever the participant wanted. Moreover, this new technology also allowed to monitor dietary and physical exercise habits and also several health-related variables.

We are analysing data and expecting have the first results very soon.

In this context, we've also published a book* in cooperation with the Directorate-General of Health that includes the intervention program (mentioned above) and new themes such as cognitive aging, cognitive stimulation exercises, sleep, visual and auditory acuity, sexuality, the importance of socialization, among other themes of interest to this population.

* *Viver com Saude – Depois dos 60 anos. Saude.Come*. Eds Rodrigues A, Canhão H, Branco J C, Gregorio MJ, Sousa RD. EpiDoc Unit (2017). ISBN: 978-989-98576-8-1

5.1.3. Ageing

The dramatic increase in life expectancy ranks one of the greatest achievements of the modern societies. However, many of these later years may be spent with increasing disability and compromised quality of life due to chronic illnesses such as heart disease, cancer, stroke, diabetes and rheumatic and musculoskeletal diseases (RMDs) (117). With the rapid growth of older populations throughout the world - and the high costs of managing people with disabilities emerge the following challenges and questions: How can we encourage and maintain an active and independent life in elderly? How can we promote health in this age group?

Health behaviours (poor diet, physical inactivity, smoking, and alcohol abuse) are considered important risk factors for preventable chronic conditions, namely some RMDs (e.g. osteoarthritis). In fact, several factors might contribute to inadequate health behaviours patterns in elderly, such as poor socioeconomic status, social isolation typical among older people, physiological decline, age-related diseases, use of medication, functional limitations and health illiteracy (119, 120). There is a need to provide a continuum of care that includes prevention, early detection of disease and also integrative treatment in this multimorbidity age group in order to maintain or improve their health and well-being (120).

A tremendous opportunity exists to engage millions of senior adults in programs and initiatives that can reduce behavioural risk factors for

chronic diseases and help them to improve illness in a more specialized way. Promoting health among elderly is a challenge that several health professionals should address.

In fact, EpiDoC Unit is devoted to analysing the elderly population regarding chronic non-communicable diseases and their impact in quality of life and healthcare resources consumption. As we increase the body of knowledge of the senior adult population in Portugal we will be able not only to develop innovative and tailored tools to improve health in a person-centred perspective but also help to redirect health policies toward the identified needs.

5.2. New Partnerships

INTERNATIONAL

EIP on AHA - http://ec.europa.eu/research/innovation-union/index_en.cfm?section=ac-tive-healthy-ageing - The European Innovation Partnership in Active and Healthy Ageing (EIP on AHA) is a pilot initiative hurled by the European Commission to nurture innovation in the field of active and healthy ageing. The notion of European Innovation Partnerships (EIPs) is a new attitude to EU research and innovation. It brings together all pertinent players at EU, national and regional levels through different policy areas to handle with specific societal challenges and includes all the innovation chain stages. We are developing an European project proposal integrated in this consortium.

AAL - http://www.aal-europe.eu - The Active and Assisted Living (AAL) program's general goal is to improve the quality of life of elder while consolidating the industrial base in Europe through the use of ICT. Since 2008, it sponsors projects in public-private collaboration in the field of ICT for active and healthy ageing. We presented a workshop in Switzerland in September 2016 with the results of our work, to the group members, having in mind our availability to develop new projects.

CHPC | NTNU - http://www.ntnu.edu/chpr - The Centre for Health Promotion Research of Norges Teknisk-Naturvitenskapelige Universitet

takes part in the scientific investigation of what stimulates, keeps and reestablishes good health in healthy but also in vulnerable and diseased populations. Through these research activities, CHPC aims to produce information which can be applied to empower people to rise control over, and to improve, their well-being and health, by this means allowing people to lead an active and fruitful life, enhancing health and quality of life. We started to collaborate with NTNU as partners in the Project Saúde. come but this collaboration has grown and now we have 3 more projects ongoing.

NATIONAL

ISPUP - http://ispup.up.pt/?lang=pt - Instituto de Saúde Pública da Universidade do Porto aims to contribute to the development, dissemination and application of new knowledge in the field of public health, stimulating research and training excellence to improve and protect the health of the human population. Its mission is achieved by providing the necessary conditions for the pursuit of graduate programs, scientific production created from highly relevant research, innovative in response to needs local, national and international and creative partnerships. In the context of Saúde.Come, we established a valuable partnership not only to compare data from EpiDoC Cohort, EpiTeen and EpiPorto but also to assess food insecurity in young adults living in Oporto area.

CLSBE | UCP - https://www.clsbe.lisboa.ucp.pt/ - Católica-Lisbon School of Business and Economics is dedicated to intellectual leadership in rising exceptional individuals with high-level professions in management and economics, proposing business frontrunners an extraordinary lifelong learning atmosphere, and progressing to the understanding of economic decision making. This partnership was particularly important to support the development of new ICTs tools to perform an intervention program to promote healthy lifestyles among elderly.

DGS - https://www.dgs.pt/ - The Directorate-General of Health (DGS) is a public organization of the Ministry of Health that constitutes a reference for all those who think and work in the healthcare field. We developed our partnership with the Division of Healthy Lifestyles and

together we are developed a book Saúde.Come. This book includes the intervention content developed for TV application dedicated to elderly, and adds new themes such as cognitive aging, cognitive stimulation exercises, sleep, visual and auditory acuity, sexuality, the importance of socialization, among other themes of interest to this population.

ACSS - http://www.acss.min-saude.pt/ - Central Administration of Health System is a public institute implanted under State administration, which accomplishes the tasks of the Ministry of Health, under its supervision with powers over national territory. ACSS was the Program Operator for Public Health Initiatives Programme (EEA Grants) that funded Project Saúde. Come. Being so, we have developed an important partnership responding to their main goals through the vast activities of this project.

Chapter 6

The Harverst

6.1. Scientific Production

6.1.1. Publications

FULL PAPERS

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PRIZES AND DISTINCTIONS

2015

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2016

Prémio de Melhor Comunicação Livre - SPODOM - X Congresso Português de Osteoporose

Prémio Assunção Teixeira de Melhor Artigo de Reumatologia - XXIV Jornadas Internacionais do Instituto Português de Reumatologia

Grande Prémio Bial de Medicina – Fundação Bial

2017

Janssen Immunology Real World Evidence Award - Janssen Portugal

1st Prize - HealthyBone TV Project - Pfizer/ Sociedade Portuguesa de Reumatologia

2nd Prize - Reuma Heart Project - Pfizer/ Sociedade Portuguesa de Reumatologia

1st Prize – Best Original Poster - XIX Congresso Português de Reumatologia

6.1.2. Presentations

ORAL PRESENTATIONS

XVI Portuguese Congress of Rheumatology, Vilamoura, 1-5 May 2012

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Grande Prémio Bial de Medicina 2016

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Na edição de 2016, a obra "EpiReumaPt - the dream of a generation in a decade of work", um estudo coordenado pelo Prof. Jaime da Cunha Branco, foi galardoada com o GRANDE PRÉMIO BIAL DE MEDICINA.

O PRÉMIO BIAL DE MEDICINA CLÍNICA 2016 foi atribuído ao trabalho "Pé Di@bético - soluções para um grande problema" de autoria da Dra. Maria de Jesus Dantas.

Na décima sexta edição deste galardão foram também distinguidas duas obras com Menções Honrosas.

O júri do PRÉMIO BIAL 2016 foi presidido por António Sousa Guerreiro e constituído por João Cerqueira, Ana Félix, Maria Dulce Madeira, José Martinez de Oliveira, José Melo Cristino, Joaquim Murta, Isabel Palmeirim e António de Sousa Pereira.

Em 2017, a FUNDAÇÃO BIAL reformulou o PRÉMIO BIAL, cindindo-o, com o intuito de alargar o seu âmbito de atuação e de reconhecer o que de mais notável e relevante tem sido descoberto na área biomédica, criando um novo galardão, o BIAL AWARD IN BIOMEDICINE. As candidaturas são submetidas pelos membros do Júri, pelos membros do Conselho Científico da Fundação e por Sociedades Científicas. Esta distinção será atribuída, a partir de 2019, em anos alternados com o PRÉMIO BIAL DE MEDICINA CLÍNICA, que mantém o propósito de premiar um trabalho original, de índole médica, dirigido à prática clínica e em que pelo menos um dos autores tem de ser médico nacional de um país de expressão oficial portuguesa.

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