ORIGINAL ARTICLES

Prevalence of undiagnosed rheumatic and musculoskeletal diseases and its association with health-related quality of life and with physical function

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ABSTRACT

Aim: To estimate the disease specific prevalence of undiagnosed rheumatic and musculoskeletal diseases (RMDs) in Portugal and determine if people with undiagnosed RMDs have worse quality of life, physical function and higher health resources consumption, than people without RMDs.

Methods: A subgroup analysis of EpiReumaPt was made that included all participants≥18 years evaluated by a rheumatologist. Participants were stratified into three groups: undiagnosed RMDs; previously diagnosed RMDs; non-RMDs. A descriptive analysis of the three groups was performed. To estimate the prevalence of undiagnosed RMDs, weighted proportion were computed considering the sample design. The three groups were compared (Undiagnosed RMDs vs non-RMDs; Previously diagnosed RMDs vs non-RMDs) for health related quality of life (HRQoL) (EQ5D), physical function (HAQ), mental health (HADS) and health resources consumption. The effect of being undiagnosed for these outcomes was assessed in multivariable models adjusted for age, gender, geographical region and years of education (reference: non-RMD).

Results: A total of 3877 participants were included. The prevalence of undiagnosed RMDs was 29%. Compared to participants without RMDs, undiagnosed participants had lower HRQoL (EQ-5D: β (95% CI)=-0.07 (-0.103,-0.043)) and physical function (HAQ: β (95% CI)=0.10 (0.05, 0.15)), more anxiety (OR (95% CI)=2.3 (1.4, 3.7)) and depression symptoms (OR (95% CI)=1.4 (0.8, 2.4)). Undiagnosed RMDs participants were more likely to visit an orthopedist (OR (95% CI)=2.0 (1.1, 3.5)) and had a higher number of orthopedic appointments (IRR (95% CI)=2.5 (1.3, 4.9)) than participants without RMDs.

Conclusion: Patients with undiagnosed RMDs are frequent in Portugal, have worse HRQoL, physical function and mental health than people without RMDs. Undiagnosed patients are nonetheless consumers of health resources and tend to seek help from specialties other than rheumatology. Increasing the awareness of RMDs might promote their early identification and treatment leading to both personal and societal benefits.

Keywords: Epidemiology; Depression; Quality of life; Health policies; Health economics; Quality of health care.

INTRODUCTION

Rheumatic and musculoskeletal diseases (RMDs) are the most common cause of severe long-term pain and physical disability and affect hundreds of millions of people around the world[1]. RMDs affect all aspects of life through pain and by limiting activities of daily living typically by affecting mobility. They affect one in four adults across Europe resulting in a considerable consumption of health resources[2,3]. However, the enormous and growing impact of RMDs is not yet widely recognised and health policies to countermeasure it are still not prioritized. One reason is RMDs' broad demographic and symptomatic spectrum and their association with ageing and pain that eventually leads to an acceptance of these conditions among affected individuals. Millions of citizens live with undiagnosed RMDs and with no medical care for their disease.

Undiagnosed RMDs occur due to the failure to recognize or to correctly diagnose a disease. This can be due to a lack of access to medical facilities, not seek-

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ing help early in disease's course, when a patient is not adequately referred or when signs and symptoms are wrongly interpreted. This failure to diagnose RMDs present a problem because if left untreated, many RMDs can cause permanent structural damage and deformities early in its course, which ultimately results in decreased health related quality of life[4,5]. The absence of a plan of action to prioritize early diagnosis, prevention and effective management of RMDs can result in unnecessary irreversible disability that puts a burden on individuals, their families and carers and society.

The Portuguese national survey of RMDs in 2011-2013 (EpiReumaPt[6]) already showed that RMDs were frequently undiagnosed in Portugal. However, there is no data regarding the impact on HRQoL, physical function, mental health and health resources consumption while having undiagnosed RMDs. To better understand the burden of undiagnosed RMDs in Portugal, the present study aims to estimate the disease specific prevalence of undiagnosed RMDs and to determine if undiagnosed RMDs are already associated with worse quality of life, physical function and higher health resources consumption, as it was already seen in the RMDs population. Such information could stress the need to improve public health strategies in terms of early detection and adequate management of RMDs.

METHODS

Data source and study population

This project was conducted under the scope of EpiReumaPt6, a national cross-sectional study elaborated in Portugal from September 2011 to December 2013 with the main goal of estimating the prevalence of a subset of 12 RMDs in Portugal (hand, knee and hip osteoarthritis (OA), low back pain (LBP), rheumatoid arthritis (RA), fibromyalgia (FM), gout, spondyloarthritis (SpA) (and its subtypes), periarticular disease (PD), systemic lupus erythematous (SLE), polymyalgia rheumatica (PMR) and osteoporosis (OP)). To obtain a representative sample of Portuguese population, participants were selected by a process of multistage random sampling. The sampling was stratified across the country in seven regions, according to the Nomenclature of Territorial Units for Statistics II (NUTS II) - Norte, Centro, Lisboa e Vale do Tejo, Alentejo, Algarve, Região Autónoma dos Açores (the Azores) and Região Autónoma da Madeira (Madeira).

The study involved a three-stage approach. In the first stage, a face-to-face survey performed by trained interviewers screened for RMDs and their symptoms and collected several variables. Participants were considered to have RMDs if they mentioned previously known RMDs, if they were positive for the screening self-questionnaires related to specific RMDs (algorithms that covered disease characteristics and respective signs and symptoms) or if participants reported muscle, vertebral or peripheral joint pain in the previous four weeks. The second stage of the study was conducted by rheumatologists blinded to information collected on the first stage. A total of 3,877 participants (all participants positive for the RMDs screening plus 20% randomly selected who tested negative) were evaluated in order to gather clinical information and establish a diagnosis of RMDs. The final and third stage was performed by a team of three experienced rheumatologists who reviewed all gathered information and confirmed the existence of the diagnosis of RMDs. A detailed review of the methods of the EpiReumaPt study was already published[7].

In this cross-sectional study, we included all individuals aged 18 years or older who participated in the second and third phases of EpiReumaPt and answered, in the first phase, the question "Did any doctor tell you that you suffered from a rheumatic disease?".

Case definition

In order to determine which participants had undiagnosed RMDs, data gathered through the self-report questionnaires during the first phase of EpiReumaPt was compared with the final diagnosis of RMDs during the third phase. Three groups were formed: Undiagnosed RMDs - participants who reported having no diagnosis RMDs or didn't know in the self-report questionnaire in the first phase of EpiReumaPt but had the diagnosis of RMDs by the rheumatologist at the end of the third phase of EpiReumaPt; Previously established RMDs – participants who reported RMDs in the self-report questionnaire in the first phase and the diagnosis was confirmed by a rheumatologist in the third phase; Non-RMDs – participants who finished stage three without a diagnosis of RMDs, regardless of their answer in the self-report questionnaire.

Measurement, assessment and instruments

All participants were asked for their sociodemographic data (age, gender and years of education), socioeconomic profile (current professional status) and lifestyle habits (alcohol intake, current smoking status and physical exercise). To measure healthcare resource consumption, participants were also asked about the number and type of outpatient clinic visits, number of hospitalizations, the need for home care assistance or other healthcare related services, in the 12 months prior to the interview. In order to evaluate generic health related quality of life (HRQoL), the European Quality of Life questionnaire with five dimensions and three levels (EQ-5D-3L[8]) was used. As for physical function, assessment was made through the Health Assessment Questionnaire (HAQ[9]). Anxiety and depression were

assessed by the Hospital Anxiety and Depression Scale (HADS[10]), which is divided into Anxiety and Depression subscales (HADS-A and HADS-D, respectively). All the previously mentioned questionnaires are validated for the Portuguese population. Self-reported anthropometric data (weight and height) were collected as well as self-reported chronic diseases (high cholesterol level, high blood pressure, allergy, gastrointestinal disease, mental disease, cardiac disease, diabetes, thyroid and parathyroid disease, urolithiasis, pulmonary disease, hyperuricemia, neoplastic disease, neurologic disease, hypogonadism), along with current non-pharmacological and pharmacological therapies. A medical history and physical examination were performed. Specific questions were asked, regarding current medication and the need for medical visits due to RMDs symptoms in the previous 12 months.

Statistical analysis

A national weight was used to determine the prevalence of undiagnosed RMDs in Portugal and to stratify them by sociodemographic and socioeconomic characteristics.

An adjusted analysis compared the undiagnosed RMDs, previously established RMDs and non-RMDs groups regarding their sociodemographic and health-related characteristics. Chi-Squared tests of independence were performed in order to investigate whether there is an association between RMDs and the various demographic characteristics. The association between having an undiagnosed RMD and a previously diagnosed RMD as compared to not having RMDs (reference) on HRQoL, physical function (EQ5D and HAQ) and mental health (presence of symptoms of anxiety (HADS-A <11 vs HADS-A ≥11)[11]and presence of symptoms of depression (HADS-D<11, HADS-D≥11)[11]was tested in multivariable linear/binomial regression models. Multinomial logistic regression models were used to compare health resources consumption (physician visit, home care and hospitalization in the past 12 months) in the three groups (Undiagnosed RMDs vs Non-RMDs and Previously established RMDs vs non-RMDs). A Poisson model was employed to investigate the number of physician visit in the past 12 months. All models were adjusted for age, gender, education level and NUTSII.

All statistical analysis were performed using the R software (R version 4.2.0, 2022)[12] and its *survey* package (R Core Team (2022))[13].

RESULTS

Prevalence of undiagnosed RMDs in the Portuguese adult population

The weighted analysis concluded that 29% of the Portuguese population had at least one undiagnosed RMDs. There was a higher prevalence of undiagnosed RMDs in females (53%) and in people between 46 and 55 years old (20%) (Figure 1). Most undiagnosed Portuguese people had a low education level (34%), were working (52%), had other chronic diseases (70%), were overweight (42%) and were sedentary (67%). The "Norte" region had the highest prevalence of undiagnosed RMDs (41%), followed by the "Lisboa e Vale do Tejo" (24%) and "Centro" (22%) regions, as shown in Figure 2.

The prevalence of each undiagnosed RMDs, overall and stratified by gender and NUTSII region, is shown in Table I. The most undiagnosed RMDs was periarticular disease (33%), followed by knee OA (17%) and hand OA (11%) and OP (11%). Undiagnosed inflammatory RMDs (SpA, Gout, RA, SLE; PMR) were uncommon. Undiagnosed RMDs were more prevalent in women, except for low back pain, hip osteoarthritis and gout. All RMDs were more undiagnosed in the Norte Region, except for hand OA ("Lisboa"), low back pain ("Lisboa"), SpA ("Lisboa") and SLE ("Algarve").

Comparison of the sociodemographic and socioecomic characteristics of the undiagnosed RMDs, previously established RMDs and non-RMDs groups

In total, 3877 participants were included. Sociodemographic and socioeconomic characteristics comparing the three groups are shown in Table II. All considered demographic variables are associated with the designated participants' RMDs status. Undiagnosed RMDs were present in 39% (n=1514) of participants of whom 64% (n=968) were female. Female participants were also the majority in the previously diagnosed RMDs and non-RMDs groups. Participants of the [46-55] and [56-65] age stratums were more frequently undiagnosed (24%, n=359 in both), while the previously established RMDs group had a higher prevalence of RMDs in the [56-65] (25%, n=367) and [66-75] (29%, n=426) age groups. The northern region of the country had the highest account for undiagnosed RMDs (29%, n=440) and of previously established RMDs (25%, n=367). Both undiagnosed RMDs and previously established RMDs were more frequent in participants with a low education level (47%, n=711 and 69%, n=1000, respectively) and body mass index in the overweight range (42%, n=605 and 41%, n=554, respectively). Most participants with undiagnosed RMDs have an active employment status (48%, n=725), while most with previously established RMDs are retired (61%, n=872).

HRQoL, HAQ, presence of anxiety and depression symptoms in participants with undiagnosed RMDs, previously established RMDs and without RMDs

The association between participants' health status and having undiagnosed RMDs and previously diagnosed RMDs when compared to not having RMDs is shown in Table III. Participants with undiagnosed

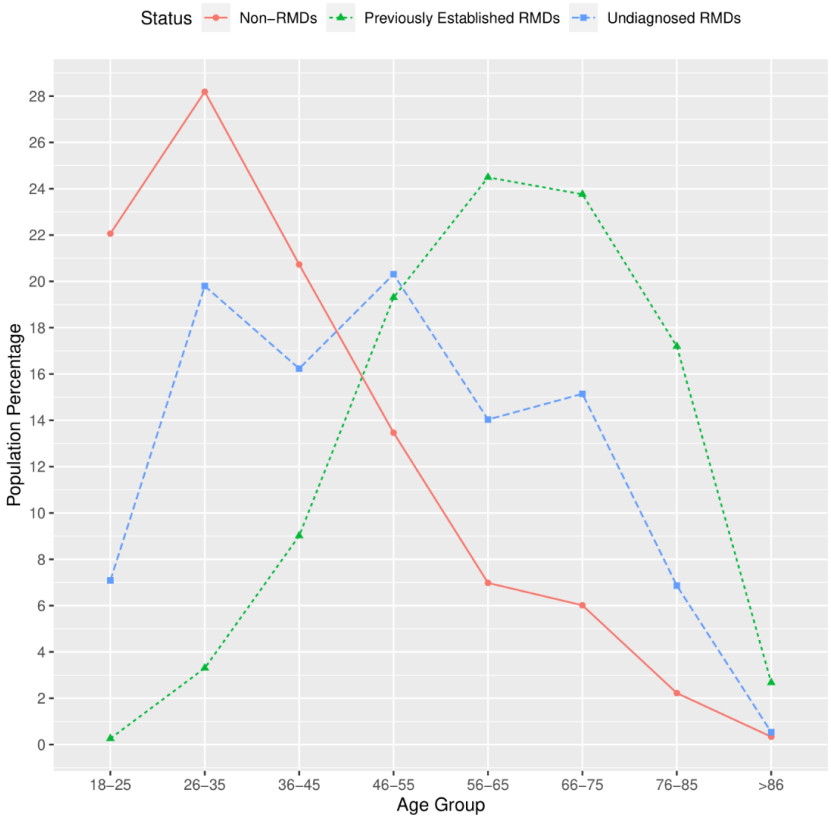

Figure 1. Distribution of undiagnosed RMDs, previously established RMDs and non-RMDs by age groups of the adult Portuguese Population. RMDs: rheumatic and musculoskeletal diseases

RMDs showed significantly worse HRQoL and physical function when compared to the non-RMDs population, with significant worse EQ5D (β (95% CI)=-0.07 (-0.103,-0.043)) and HAQ (β (95% CI)=0.10 (0.05, 0.15)) scores. As for mental health, undiagnosed participants were more likely to show anxiety (OR=2.3; (1.4, 3.7)) and depression (OR=1.4; (0.8, 2.4)) symptoms. Patients with previously diagnosed RMDs had even worse EQ5D scores (β=-0.23; (-0.27, -0.20)), HAQ score (β=0.40; (0.33, 0.47)) and anxiety (OR=4.8; (2.8, 8.0)) and depression (OR=2.3; (1.4, 4.0)) symptoms when compared to participants with no RMDs.

Health resource consumption in participants with undiagnosed RMD, previously established RMDs and without RMDs

The association between participants' health resources consumption and having undiagnosed RMDs and previously diagnosed RMDs when compared to not having RMDs is shown in Table IV. The undiagnosed RMDs population, when compared to those without RMDs, was more likely to visit an Orthopedist (OR (95%CI) =2.0 (1.1, 3.5)), while being less likely to visit a Rheumatologist (OR (95%CI) =1.7 (0.8, 3.8)) and had more Orthopedic appointments per year (incidence rate ratio (IRR)=2.5 (1.3, 4.9)). They also had less general practitioner visits in the past 12 months (IRR (95% CI) =0.4 (0.1, 1.4)). There was also a high likelihood for undiagnosed people to receive home care (OR (95%CI) =11.5 (4.4, 30.2)) and to have hospitalizations (OR (95%CI) = 2.0 (1.2, 3.6)).

DISCUSSION

In this study we found that undiagnosed RMDs were frequent in Portugal. Possible explanations for this finding include the low number of rheumatologists existing in Portugal (1:100 000)[14], the lack of awareness of the population for RMDs or even the acceptance of RMDs symptoms as part of aging. Undiagnosed people were frequently female, which is expected, since RMDs generally have a higher prevalence in women[6].

The "Norte" region had the highest prevalence of undiagnosed RMDs, which can be explained by its high population density and a low number of rheumatologists available to the population in this region. It is also worth noting that this region has a high number of blue-collar jobs[15] and most undiagnosed participants had a low education level, which may make then sus-

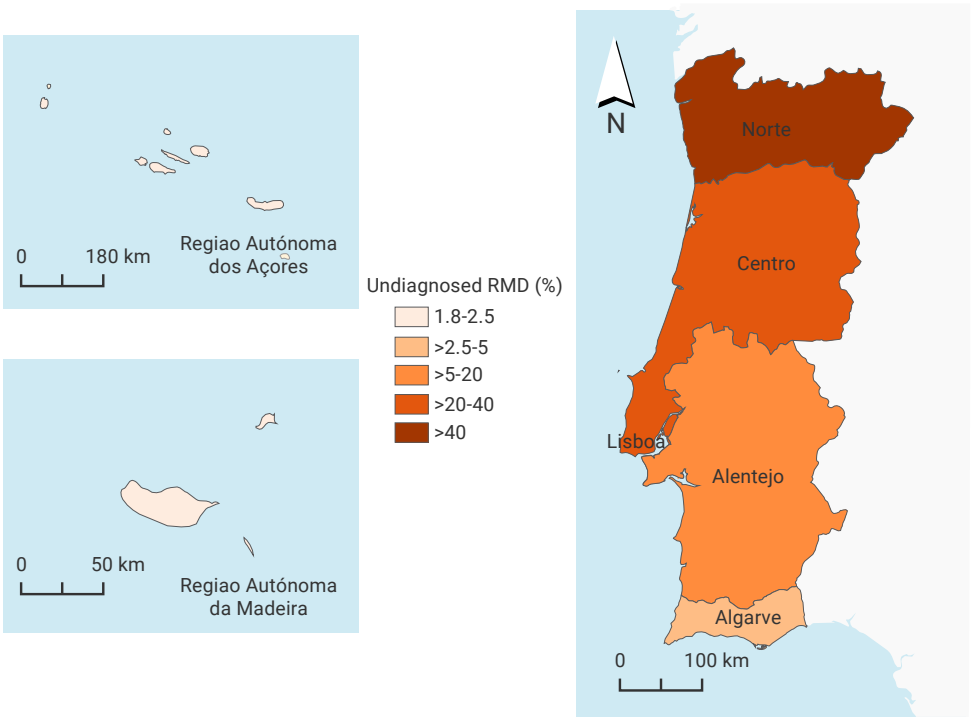

Figure 2. Prevalence of undiagnosed RMDs in Portugal by NUTSII.
RMDs: rheumatic and musculoskeletal diseases; NUTSII: Nomenclature of Territorial Units for Statistics II (Norte, Centro, Lisboa, Alentejo, Algarve, Lisboa, Madeira and Azores)

Table I. Prevalence of undiagnosed RMDs in Portugal, overall, stratified by gender and NUTSII

	Total* 1528 n (%)	Women 968 (53) n (%)	Men 546 (47) n (%)	NUTSII territory with higher prevalence *per* undiagnosed RMDs n (%)
Periarticular disease	481 (34)	336 (59)	145 (41)	Norte 129 (36)
Knee Osteoarthritis	343 (17)	210 (55)	133 (45)	Norte 95 (35)
Hand Osteoarthritis	209 (11)	166 (82)	43 (18)	Lisboa 50 (42)
Osteoporosis	241 (11)	194 (79)	47 (21)	Norte 67 (31)
Low back Pain	58 (5)	28 (29)	30 (71)	Lisboa 9 (41)
Hip Osteoarthritis	64 (5)	33 (39)	31 (61)	Norte 19 (37)
Spondyloarthritis	41 (3)	29 (77)	12 (23)	Lisboa 8 (38)
Gout	47 (3)	2 (4)	45 (96)	Norte 15 (35)
Fibromyalgia	30 (1)	29 (99)	1 (2)	Norte 8 (39)
Rheumatoid Arthritis	10 (1)	8 (79)	2 (22)	Norte 4 (36)
SLE	4 (0.1)	3 (93)	1 (8)	Algarve 2 (86)
Polymyalgia Rheumatica	0	0	0	-

Percentages were calculated using a national weight
NUTSII: Nomenclature of Territorial Units of Statistics (Norte, Centro, Lisboa, Alentejo, Algarve, Lisboa, Madeira and Azores)
RMDs: rheumatic and musculoskeletal diseases; SLE: Systemic lupus erythematosus
*Sample size is not constant due to some participants having more than one undiagnosed RMD

ceptible to having undiagnosed RMDs. Low socioeconomic status has already been associated with a higher likelihood of missing medical appointments and having a poorer health outcome[16]. Combined, all these sociodemographic and socioeconomic characteristics may be a cause for the high prevalence of undiagnosed RMDs in Portugal, particularly in the northern region. We also found that the NUTSII region "Lisboa e Vale do Tejo" also had a high prevalence of undiagnosed patients, most likely due to high population density.

Table II. Sociodemographic characteristics across participants with undiagnosed RMDs, previously diagnosed RMDs and no RMDs in the adult Portuguese population

Demographic characteristics	Undiagnosed RMDs n (%) 1514 (39)	Previously Established RMDs n (%) 1459 (38)	Non-RMDs n (%) 904 (23)	*p*-value
Gender Female	968 (64)	1142 (78)	518 (57)	*<0.001*
Age group				
18-25	31 (2)	1 (1)	80 (9)	
26-35	98 (6)	13 (1)	137 (15)	
36-45	242 (16)	89 (6)	240 (26)	<0.001
46-55	359 (24)	246 (17)	177 (20)	
56-65	359 (24)	400 (27)	134 (15)	
66-75	278 (18)	426 (29)	93 (10)	
76-85	135 (9)	249 (17)	34 (4)	
>86	12 (1)	35 (2)	9 (1)	
NUTSII				
Norte	440 (29)	367 (25)	243 (27)	
Centro	343 (23)	341 (23)	172 (19)	
Lisboa	274 (18)	256 (18)	178 (20)	0.005
Alentejo	106 (7)	116 (8)	51 (6)	
Algarve	46 (3)	57 (4)	41 (4)	
Azores	158 (10)	167 (11)	95 (10)	
Madeira	147 (10)	155 (11)	124 (14)	
Education Level (years)				
>12	208 (14)	95 (7)	205 (23)	<0.001
10 – 12	227 (15)	130 (9)	218 (24)	
5 – 9	363 (24)	221 (15)	191 (21)	
0 – 4	711 (47)	1000 (69)	286 (32)	
Employment Status				
Active	725 (48)	416 (29)	548 (61)	
Unemployed	183 (12)	112 (8)	139 (15)	<0.001
Retired	561 (38)	872 (61)	203 (23)	
Sick leave	30 (2)	38 (2)	12 (1)	
Other Chronic Disease(s)	1195 (79)	1343 (92)	622 (69)	<0.001
Body Mass Index				
Underweight	22 (1)	10 (1)	14 (2)	
Normal	461 (32)	361 (27)	412 (47)	0.021
Overweight	605 (42)	554 (40)	326 (37)	
Obese	359 (25)	435 (32)	130 (14)	

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Table II. continuation

Demographic characteristics	Undiagnosed RMDs n (%) 1514 (39)	Previously Established RMDs n (%) 1459 (38)	Non-RMDs n (%) 904 (23)	*p*-value
Physical Exercise	471 (31)	372 (26)	339 (38)	<0.001
Alcohol consumption				
Never	631 (42)	809 (56)	354 (39)	<0.001
Occasionally	528 (35)	403 (28)	374 (41)	
Daily	353 (23)	245 (16)	175 (20)	
Smoking	263 (17)	132 (9)	198 (22)	<0.001

Undiagnosed RMDs sample size is not constant due to missing data in: Education level (n=1509), Employment status (n=1499), Body mass index (n=1447), Physical exercise (n=1513), Alcohol consumption (n=1512), Smoking (n=1513).
Previously established RMDs sample size is not constant due to missing data in: Education level (n=1446), Employment status (n=1438), Body mass index (n=1360), Physical exercise (n=1458), Alcohol consumption (n=1457).
p-values were obtained from Pearson Chi-squared tests of indepence.
Non-RMDs sample size is not constant due to missing data in: Education level (n=900), Employment status (n=902), Other chronic diseases (n=902), Body mass index (n=882), Physical exercise (n=903), Alcohol consumption (n=903), Smoking (n=903).
NUTSII: Nomenclature of Territorial Units of Statistics (Norte, Centro, Lisboa, Alentejo, Algarve, Lisboa, Madeira and Azores); RMDs: Rheumatic and musculoskeletal diseases

The most prevalent undiagnosed RMDs was periarticular disease (PD), followed by knee and hand OA, probably due to the high prevalence of both these diseases in Portugal[6]. This can explain why most patients are between 46 and 55 years old since PD and OA usually start at these ages[17,18]. Most participants of the undiagnosed population were overweight, which may put them at risk of having PD and OA, since this finding is a known risk factor for these diseases[17-19]. Osteoporosis was also frequently undiagnosed. Since it is a silent disease, its diagnosis is even more difficult and usually delayed. In fact, many patients are undertreated and many are diagnosed only after having a fragility fracture[20]. An effort must be made in order to identify patients before the occurrence of fractures or, in the event of fracture, to promptly begin OP treatment. The high prevalence of other chronic diseases and sedentary lifestyle in the undiagnosed population dictates the need to amplify

Table III. Association between having undiagnosed RMDs and previously diagnosed RMDs compared to not having a RMD (reference) on health status

HRQoL and physical function	Undiagnosed RMDs mean (SD)	Previously Established RMDs mean (SD)	Non-RMDs mean (SD)	β estimates; 95% CI (Undiagnosed RMDs vs Non- RMDs)	β estimates; 95% CI (Previously established RMDs vs Non- RMDs)
EQ5D (0-1)	0.80 (0.23)	0.61 (0.26)	0.89 (0.18)	-0.07 (-0.10, -0.04)	-0.23 (-0.27, -0.20)
HAQ (0-3)	0.28 (0.53)	0.72 (0.69)	0.09 (0.29)	0.10 (0.05, 0.15)	0.404 (0.33, 0.47)
Mental health	**Undiagnosed RMDs n (%)**	**Previously Established RMDs n (%)**	**Non-RMDs**	**OR; 95%CI (Undiagnosed RMDs vs Non-RMDs)**	**OR; 95%CI (Previously established RMDs vs Non- RMDs)**
Anxiety (yes)	235 (13.1)	325 (23.6)	103 (6.2)	2.3 (1.4, 3.7)	4.8 (2.8, 8.0)
Depression (yes)	111 (5.1)	221 (14.1)	46 (1.9)	1.4 (0.8, 2.4)	2.3 (1.4, 4.0)

Multivariable linear regression models were used to evaluate the association on HRQoL and physical function (outcomes were EQ5D and HAQ, respectively).
Multivariable logistic regression models were used to evaluate the association on mental health – anxiety and depression symptoms (outcomes were anxiety score (yes/no) and depression score (yes/no), respectively). Each model was adjusted for age, gender, nomenclature of Territorial Units of Statistics, years of education
Sample size is not constant due to missing data: Undiagnosed RMD: EQ5D (n=1497), HAQ (n=1514); Established RMD: EQ5D (n=1450), HAQ (n=1459); Non-RMD: EQ5D (n=899)
EQ5D: European Quality of Life questionnaire five dimensions three levels; HAQ: Health Assessment Questionnaire; HRQoL: health-related quality of life; RMDs: rheumatic and musculoskeletal disease.

Table IV. Association between having undiagnosed RMDs and previously diagnosed RMDs compared to not having RMDs (reference) on health resources consumption

Healthcare resources consumption	Undiagnosed RMDs n (%)	Previously Established RMDs n (%)	Non-RMDs n (%)	OR; 95%CI (Undiagnosed RMDs *vs* Non-RMDs)	OR; 95%CI (Previously established RMDs *vs* Non- RMDs)
Physician visit in the past 12 months (yes)					
General practitioners	1205 (77)	1277 (85)	681 (71)	0.9 (0.6, 1.5)	1.1 (0.6, 2.1)
Rheumatology visits	37 (2)	157 (9)	23 (1)	1.7 (0.8, 3.8)	9.1 (4.0, 20.7)
Orthopaedic visits	175 (12)	277 (22)	69 (7)	2.0 (1.1, 3.5)	4.7 (2.8, 8.0)
Other visits	813 (58)	825 (57)	467 (54)	1.2 (0.8, 1.8)	1.0 (0.7, 1.5)
Healthcare resources consumption	**Undiagnosed RMDs mean (sd)**	**Previously Established RMDs mean (sd)**	**Non-RMDs mean (sd)**	**IRR; 95%CI (Undiagnosed RMDs *vs* Non-RMDs)**	**IRR; 95%CI (Previously established RMDs *vs* Non- RMDs)**
Number of physician visit in the past 12 months					
General practitioners	2.13 (3.21)	3.26 (6.84)	3.71 (28.06)	0.4 (0.1, 1.4)	1.0 (0.7, 1.3)
Rheumatology appointments	0.03 (0.28)	0.21 (0.98)	0.02 (0.23)	1.6 (0.7, 3.8)	8.0 (3.5, 18.0)
Orthopaedic appointments	0.30 (1.06)	0.50 (1.37)	0.12 (0.63)	2.5 (1.3, 4.9)	4.0 (2.1, 7.7)
Other appointments	1.62 (2.76)	2.40 (10.38)	1.55 (2.53)	1.0 (0.8, 1.2)	1.3 (1.0, 1.8)
Healthcare resources consumption	**Undiagnosed RMDs n (%)**	**Previously Established RMDs n (%)**	**Non-RMDs n (%)**	**OR; 95%CI (Undiagnosed RMDs *vs* Non-RMDs)**	**OR; 95%CI (Previously established RMDs *vs* Non- RMDs)**
Home care in the past 12 months	38 (3)	58 (4)	9 (0.2)	11.5 (4.4, 30.2)	10.6 (4.1, 27.4)
Hospitalisations in the past 12 months	133 (11)	170 (13)	74 (6)	2.0 (1.2, 3.6)	2.3 (1.4, 3.9)

Multivariable logistic regression models were used for the outcomes "Physician visit in the past 12 months" (yes/no), "Home care in the past 12 months" (yes/no), "Hospitalizations in the past 12 months" (yes/no). Multivariable Poisson regression models were used for the outcomes "Number of physician visit in the past 12 months". Each model was adjusted for age, gender, nomenclature of Territorial Units of Statistics, years of education
Other considered visits were: Internal Medicine, Neurology, Cardiology, Nephrology, Physical medicine and rehabilitation, General surgery, Psychiatry, Urology, Ophthalmology.
RMDs: rheumatic and musculoskeletal disease.; IRR: incidence rate ratio.

primary care and prevention in the Portuguese population. Interestingly, there is a low prevalence of undiagnosed inflammatory RMDs. This may be because these diseases are less prevalent in the population[6], and their initial presentation can be very debilitating, prompting the rapid need for medical help, resulting in early diagnosis. A continued effort must be made in order to maintain early recognition of these diseases to reduce structural damage and thus, the disease burden.

We have shown that patients with undiagnosed RMDs have worse HRQoL, physical function and mental health than people without RMDs, which is in agreement with previous studies[6]. These findings were even more marked in the previously diagnosed population. Maybe the undiagnosed population has milder symptoms or less disease duration and progression with less structural damage, which cannot be confirmed by this study.

Several studies have already demonstrated the association between RMDs and anxiety and depression symptoms[21-23]. This study demonstrates thatthis is also true for patients with undiagnosed RMDs. Having an undiagnosed disease increases the prevalence of psychiatric symptoms leading to a decreased QoL[24]. Early diagnosis may be a tool to avoid the potential mental burden of RMDs and its consequences on QoL.

Participants with undiagnosed RMDs are frequent users of health resources. However, these patients are recurring to specialties other than rheumatology, such as orthopedics. In fact, these patients have an increased likelihood of consulting an orthopedist. Although this can be explained by the fact that the most undiagnosed

RMDs are PD and OA, which are diseases that are treated by both specialties, surgical treatment is usually considered as a last resort option. The population´s lack of awareness that rheumatologist also treat these diseases may be a leading cause for higher orthopedic visits seen in the undiagnosed group. Non-RMDs participants are users of other specialties but not of Rheumatology, which may delay a correct diagnosis and adequate treatment. It can be important to reinforce to other specialties the signs and symptoms of the presentation of RMDs so other clinicians can recognize RMDs early in their course and promptly refer these patients to a Rheumatology appointment. An unexpected finding is that undiagnosed patients have a low number of general practitioner appointments. Since primary care is of key important for the early recognition and referral of RMDs, this can explain, in part, the prevalence of undiagnosed RMDs in Portugal.

Being undiagnosed is also associated with a higher chance of needing home care or hospitalization. Recognition of existing RMDs is mandatory in order to properly treat and avoid unnecessary healthcare resources consumption and disease burden. The burden of RMDs comes from the combination of high incidence, low lethality and low probability of cure that culminates in a high prevalence. This results in a high health and QoL impact with very high direct and indirect costs to society[24]. With the increasing age of the population in the western world, it is also expected an equal rise in RMDs, culminating in higher healthcare service costs, to a system that is not prepared to deal with this increase. RMDs prevention, diagnosis and treatment should be applied to either primary (general population), secondary and tertiary levels. A proper articulation between all healthcare providers is key to improve its objectives. Due to the nature of RMDs and the common links between several other specialties, the collaboration of other medical societies, such as primary care physicians, orthopedic, physical rehabilitation medicine and occupational medicine is also required, to promote an efficient cooperation between specialties in the clinical setting.

A probable major contributor to the high prevalence of undiagnosed RMDs in Portugal is the absence of a national priority program against RMDs, encompassing all ages, to promote the early diagnosis and treatment of these diseases. This program would also help to control the morbidity and mortality of RMDs, improve the QoL of RMDs patients and manage the associated costs. Consequently, patients would also become more independent with less need of health and social care services, consequently reducing health care associated costs. The necessary conditions to prove the need to implement such a program were already met: RMDs have a high prevalence in Portugal, which is expected to rise, have a high disease burden on the population and are recognized as public health problem. The fact that there still exists a large numer of undiagnosed RMDs in Portugal, as proved by this study, strengthens the need to enforce this program, which should be included in the national political agenda. Policies should be made at all levels: health care providers, social care and support, employers and population, in order to prioritize health promotion, mobilize the necessary resources and deploy cost-effectiveness strategies. A shift to long-term sustainable solutions is advisable, to invert the rising tendency of RMDs prevalence and diminish the pressure to health services. Health promotion measures need to be readily applied and reinforced in the community and primary care settings in order to prevent RMDs. Obesity, for example, is an important modifiable factor for RMDs. A national report[25] concluded that the prevalence of obesity doubled in a 10-year span period. Not surprisingly, our study supports a high prevalence of overweight and obese participants with either undiagnosed RMDs or previously established RMDs. Campaigns to educate the population about prevention and detection of early signs of RMDs are important and teach patients when and where to seek medical help. Primary care units should have the necessary resources to give better access and proper care to patients with RMDs, with a shorter referral time-period to secondary and tertiary centers, when needed. An adequate program against RMDs must ensure access to health services occurs in a timely fashion. The development of existing rheumatology centers and the creation of new ones in deprived regions of Portugal should also be promoted, in order to create a reliable network for provision of rheumatology services able to respond to the crescent prevalence of RMDs. Divulgation of the location and services provided by rheumatologists should be a periodically diffused to both the general population and health care professionals. Healthcare professionals should have continued education and training regarding RMDs. Existing national (and international) guidelines for the approach, diagnosis and treatment of RMDs are already accessible and may facilitate this process. Research agendas to better understand the causes and consequences of RMDs are fundamental and a continued effort must be made in order to pursue the proven the burden of RMDs and that adequate strategies of prevention, diagnosis and treatment are beneficial to both the patients and society.

Limitations of this study are inherently related to those previously appointed on the EpiReumaPt study. These include the recruitment selection method (last birthday within-unit respondent), a large dropout rate during its phase one and two, the definition of PD or

the diagnosis of OP lacking a densitometric measurement. However, as stated, the presence of RMDs was validated by experienced rheumatologists, with numerous clinical measurements characterizing their burden, ultimately strengthening the collected data and the diagnosis of new RMDs and associated health-related consequences.

CONCLUSION

In conclusion, undiagnosed RMDs are frequent in Portugal and are associated with low HRQoL, physical function and mental health. Socioeconomic and lifestyle factors seem to contribute to being undiagnosed. There is an imperative need to promote awareness of RMDs since early diagnosis and treatment may lead to both personal and societal benefits. This strategy should be implemented in the National Health Care Program to maximize the available resources and accommodate the expected growing prevalence of RMDs in order to help prevent its associated burden.

REFERENCES

1. World Health Organization - Global status report on noncommunicable diseases 2010. http://apps.who.int/iris/bitstream/handle/10665/44579/9789240686458_eng.pdf?sequence=1. Accessed in August 2nd 2022
2. Badley EM, Rasooly I, Webster GK. Relative importance of musculoskeletal disorders as a cause of chronic health problems, disability, and health care utilization: findings from the 1990 Ontario Health Survey. J Rheumatol 1994;21:505–514.
3. Yelin E, Callahan LF. The economic cost and social and psychological impact of musculoskeletal conditions. National Arthritis Data Work Groups. Arthritis Rheum 1995;38:1351–1362.
4. Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS, Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. Ann Rheum 2002, 61:290-297
5. Kwiatkowska B, RAciborski F, Klak A, Maslinska M, Gryglewicz J, Ealry diagnosis of rheumatic diseases: an evaluation of the present situation and proposed changes, Reumatologia 2015; 53/1:3-8
6. Branco JC, Rodrigues AM, Gouveia N, Eusébio M, Ramiro S, Machado PM, da Costa LP, Mourão AF, Silva I, Laires P, Sepriano A, Araújo F, Gonçalves S, Coelho PS, Tavares V, Cerol J, Mendes JM, Carmona L, Canhão H; EpiReumaPt study group. Prevalence of rheumatic and musculoskeletal diseases and their impact on health-related quality of life, physical function and mental health in Portugal: results from EpiReumaPt- a national health survey. RMD Open. 2016 Jan 19;2(1):e000166. doi: 10.1136/rmdopen-2015-000166.
7. Rodrigues AM, Gouveia N, da Costa LP, et al. EpiReumaPt- the study of rheumatic and musculoskeletal diseases in Portugal: a detailed view of the methodology. Acta Reumatol Port. 2015 Apr-Jun;40(2):110-124.
8. Ferreira LN, Ferreira PL, Pereira LN, Oppe M. EQ-5D Portuguese population norms. Qual Life Res 2014; 23: 425-430.
9. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980; 23: 137-145.
10. Pais-Ribeiro J, Silva I, Ferreira T, Martins A, Meneses R, Baltar M. Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale. Psychol Health Med 2007; 12: 225- -235; quiz 235-237
11. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70,
12.
13. R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/. Accessed in August 2nd 2022
14. T. Lumley (2004) Analysis of complex survey samples. Journal of Statistical Software 9(1): 1-19
15. Administração Central do Sistema de Saúde I. Actuais e Futuras Necessidades Previsionais de Médicos (SNS). 2011. https://saudeimpostos.files.wordpress.com/2011/10/actuais-e-futuras-necessidades-previsionais-de-mc3a9dicos-sns-acss-9-2011.pdf, Accessed in August 2nd 2022
16. Resultados definitivos dos Census 2011, Portugal, 2012 https://censos.ine.pt/ngt_server/attachfileu.jsp?look_parentBoui=148313382&att_display=n&att_download=y, Accessed in August 2nd 2022
17. Ellis D, McQueenie R, McConnachie A, Wilson P, Williamson A. Demographic and practice factors predicting repeated non-attendance in primary care: a national retrospective cohort analysis. The Lancet Public Health. 2017;2(12):e551-e559.
18. Losina E, Weinstein A, Reichmann W, et al. Lifetime Risk and Age at Diagnosis of Symptomatic Knee Osteoarthritis in the US. Arthritis Care & Research. 2013;65(5):703-711.
19. Kaux JF, Forthomme B, Goff CL, Crielaard JM, Croisier JL. Current opinions on tendinopathy. J Sports Sci Med. 2011 Jun 1;10(2):238-53.
20. Vina E, Kwoh C. Epidemiology of osteoarthritis: literature update. Current Opinion in Rheumatology. 2018;30(2):160-167.
21. Kanis J, Cooper C, Rizzoli R, Reginster J. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporosis International. 2018;30(1):3-44.
22. Hyphantis T, Kotsis K, Tsifetaki N, et al. The relationship between depressive symptoms, illness perceptions and quality of life in ankylosing spondylitis in comparison to rheumatoid arthritis. Clin Rheumatol 2013;32:635–644.
23. Poleshuck EL, Bair MJ, Kroenke K, et al. Psychosocial stress and anxiety in musculoskeletal pain patients with and without depression. Gen Hosp Psychiatry 2009;31:116–122
24. Krishnan KR, France RD, Pelton S, et al. Chronic pain and depression. II. Symptoms of anxiety in chronic low back pain patients and their relationship to subtypes of depression. Pain 1985;22:289–294.
25. Waserstein G, Partin C, Cohen D, Schettler P, Kinkead B, Rapaport MH. The prevalence and impact of psychiatric symptoms in an undiagnosed diseases clinical program. PLoS One. 2019 Jun 6;14(6):e0216937. doi: 10.1371/journal.pone.0216937
26. World Health Organization (WHO), The Burden of Musculoskeletal Conditions at the Start of the New Millenium: Report of a WHO Scientific Group. http:// whqlibdoc.who.int/trs/WHO_TRS_919.pdf. Accessed in August 2nd 2022
27. Prevalência de excesso de peso e de obesidade em Portugal: resultados do primeiro Inquérito Nacional de Saúde com Exame Físico (INSEF 2015). http://www.insa.min-saude.pt/wp-content/uploads/2020/01/BEO_11_Especial.pdf. Accessed in August 2nd 2022