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Prevalence, burden and healthcare needs of people living with Osteoarthritis in Portugal: contribution to the development of a Model of Care

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Daniela Sofia Albino Costa

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TUTORIAL COMISSION

Professor Sónia Dias

Escola Nacional de Saúde Pública, Universidade NOVA de Lisboa

Professor Carla Nunes (2019-2021)

Escola Nacional de Saúde Pública, Universidade NOVA de Lisboa

Professor Eduardo Cruz

Escola Superior de Saúde, Instituto Politécnico de Setúbal

Professor Ana Rodrigues

NOVA Medical School, Universidade NOVA de Lisboa

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ABSTRACT

Background: Hip and/or knee Osteoarthritis (HKOA) are a leading and rising cause of disability worldwide. Evidence-based guidelines recommends core non-pharmacological and pharmacological interventions to improve pain, disability and quality of life. However, literature has shown that the outcomes of current care are far from optimal. Current interventions are heterogeneous, centred on symptomatic control with pharmacological interventions and surgical procedures, with a lack of processes to tailor treatment selection according to patient characteristics and preferences. To overcome this reality several countries and regions have implemented Models of Care (MoCs) for OA. These are frameworks that outline what care should be offered and how care should be delivered that aim to decrease the evidence-practice gap and optimize patient-level outcomes, quality of care and sustainability of health systems.

To successful implement an HKOA MoC in a country it is necessary to identify and understand the unmet needs of people living with this disease, the healthcare delivery and the pattern of healthcare utilization of these population. Furthermore, it is needed to map effective solutions based on literature and identify which of them can be successfully applied in a specific setting.

The work presented in this thesis used Portugal as a case-based setting for the future development of an HKOA MoC, with the following specific objectives:

1) to estimate the prevalence of HKOA and factors associated with its clinical and radiographic severity in Portugal.
2) to estimated the prevalence and factors associated with unmanageable pain levels among people with HKOA in Portugal.
3) to determine the trajectories of physical function and HRQoL and the factors associated with different trajectories in a 10-year longitudinal follow-up.
4) to analyse the healthcare services utilization of people with knee OA in Portugal, focusing on behavioral determinants for healthcare utilization.
5) to map and synthesize the literature of MoCs developed and implemented for people with knee OA.

Methods: This thesis has two different phases. In the first phase we analysed data from the nationwide population-based cohort – EpiDoC study (2011-2021) that included a representative sample of the Portuguese population randomly selected. In the first wave of EpiDoC study, after a structured interview where sociodemographic, lifestyle and health-related data were collected, participants were invited to an appointment with a rheumatologist, that validated the diagnosis of rheumatic diseases. These participants were then invited to participate in the subsequent waves (EpiDoC 2, 3 and 4) where structured interviews were again implemented. In the studies of the first phase of this thesis we included participants that were diagnosed with HKOA by a rheumatologist in EpiDoC 1. The second phase – potential solutions – we systematically analysed the published evidence published in peer-review and grey data sources, to perform a scoping review that mapped and synthesized the literature of MoCs developed and implemented for people with HKOA in primary care.

Results: Across the 4 studies of the EpiDoC cohort we concluded that 14.1% (95%CI 12.6-15.7) of the Portuguese population have HKOA, two-thirds self-report unmanageable pain levels. Age, female sex, multimorbidity, overweight/obesity, no regular exercise and education level were identified as factors associated with clinical severity. More than half of the population maintain moderate/low stable trajectories of physical function and HRQoL during 10 years. High users of healthcare services represent approximately 35% of people with HKOA. But, approximately 80% of participants with HKOA do not exercise regularly or are overweight/obese, which suggests a low uptake of evidence-based core interventions. The utilization of healthcare services seems not to be based just on clinical needs, revealing inequities in access to healthcare. The scoping review included 13 MoCs, that were implemented worldwide, delivering the core interventions in stepped care pathways at the primary care level. Despite the promising results at the patient-, organization- and implementation-level, the heterogeneity in the report and the implementation strategies may difficult the transferability to other contexts and demand further high-quality research. Notwithstanding, it was possible to identify care pathways, evidence-based interventions and implementation strategies that could fit into the Portuguese healthcare system

Conclusions: This thesis contributes to understanding the prevalence, characteristics and health-related status of people with HKOA in Portugal, as well as the suggested evidence-practice gap and inequities in the access to care regarding healthcare utilization. These results raise hypotheses about the uptake of core interventions and the access to healthcare by people with HKOA that should concern health authorities and call for future research in this area. Also, our results suggest the need to implement national strategies to optimize outcomes of care, and decrease and prevent future healthcare demands and rising costs related to HKOA, like MoCs. The implementation of a MoC in Portugal maybe challenged by external, local and individual health context features that should be considered in the implementation process.

Keywords: Osteoarthritis, Epidemiology, Models of Care

RESUMO

Introdução: A Osteoartrose da Anca e/ou Joelho (OAAJ) é uma das condições com maior incapacidade associada em todo o mundo. A evidência suporta intervenções não-farmacológicas centrais e farmacológicas para melhorar a dor, incapacidade e qualidade de vida. No entanto, a literatura tem demonstrado que os resultados dos cuidados de saúde atuais estão longe de serem ótimos. As intervenções atuais são heterogéneas e fragmentadas, centradas no controlo sintomático com medicação e cirurgia com ausência de processos de tomada de decisão adaptado às características e preferências do utente. Para ultrapassar esta realidade, vários países têm implementado Modelos de Cuidados (MdC) para pessoas com OA. Os MdC são modelos que esquematizam quais os cuidados de saúde que devem ser oferecidos e como estes devem ser prestados e avaliados nos diferentes níveis. Os MdC têm como objetivo diminuir as lacunas entre a evidência e a prática e otimizar os resultados em saúde ao nível do utente, a qualidade dos cuidados e a sustentabilidade dos sistemas de saúde. Para implementar um MoC com sucesso é necessário identificar as necessidades de melhoria no que toca à prestação de cuidados de saúde, perceber o estado de saúde das pessoas que vivem com OAAJ e identificar o padrão de utilização dos cuidados de saúde desta população. É seguidamente necessário mapear soluções efetivas para estas necessidades baseadas na literatura atual e identificar quais podem ser implementadas e adaptados a um contexto específico.

Objetivos: Esta tese usa o contexto específico de Portugal para o futuro desenvolvimento de um modelo para peossoas com OOAJ e tem os seguintes objetivos específicos:

1) Estimar a prevalência de OOAJ em Portugal e fatores associados à sua severidade clinica e radiológica.
2) Estimar a prevalência e fatores associados ao controlo da dor em pessoas com OAAJ em Portugal.
3) Identificar trajetórias de função física e Qualidade de Vida Relacionada com a Saúde (QVRS) e os fatores associados a diferentes trajetórias num período de 10 anos
4) Analisar a utilização de serviços de saúde em pessoas com OA do joelho, focando os determinantes comportamentos para utilização de cuidados de saúde
5) Mapear e sintetizar a literatura relativa aos MdCs desenvolvidos e implementados em pessoas com OA do joelho.

Métodos: Esta tese está dividida em duas fases. Na primeira fase foram analisados dados da coorte nacional de base populacional – estudo EpiDoC (2011-2021) que incluíram uma amostra representativa da população portuguesa, aleatoriamente selecionada. Na primeira onda do estudo EpiDoC, após uma entrevista estruturada onde foram recolhidos dados sociodemográficos e relacionados com a saúde, os partipantes foram convidados a participar numa consulta com um reumatologista onde o diagnosticou de doença reumática foi validado. Estes participantes foram depois convidados a participar nas ondas subsequentes (EpiDoC 2, 3 e 4), em que as entrevistas estruturadas foram realizadas novamente. Nos estudos desta primeira fase incluímos os participantes que foram diagnosticados com OOAJ no EpiDoC 1. A segunda fase desta tese analisou a evidência publicada em fontes revistas por pares e literatura cinzenta, para desenvolver uma *scoping review* e mapear e sintetizar a literatura relativa a MdCs desenvolvidos e implementados para pessoas com OAAJ.

Resultados: Com os quatro estudos da coorte EpiDoC foi possível concluir que 14.1% (95%IC 12.6-15.7) da população adulta portuguesa tem OAAJ, destes, dois terços reporta níveis de dor não controlados e mais de metade mantém trajetórias estáveis de moderada ou baixa função física e QVRS num período de 10 anos. A idade, sexo feminino, presença de multimorbilidade, excesso de peso ou obesidade, não realizar exercício de forma regular e o nível educacional foram fatores associados com a severidade clínica, trajetórias de moderada/baixa função física e QVRS e com níveis de dor não controlados. Cerca de 35% das pessoas com OOAJ têm uma elevada utilização de serviços de saúde. Aproximadamente 80% dos participantes com OAAJ não realizam exercício de forma regular ou têm excesso de peso/obesidade, o que sugere uma baixa adesão às intervenções centrais baseadas em evidencia para a OAAJ. A utilização dos serviços de saúde está associada não apenas a necessidades clínicas, mas também a fatores relacionados com o status socioeconómico e com áreas geográficas específicas. A *scoping review* incluiu 13 MdC que foram implementados em todo o mundo, que incluem a prestação das intervenções centrais para a OAAJ ao longo de percursos de cuidados escalonados nos cuidados de saúde primários. Apesar dos resultados ao nível do utente, organizacionais e de implementação serem promissores, a heterogeneidade no reporte e nas estratégias de implementação podem dificultar a sua transferibilidade para outros contextos. Por outro lado, são necessários mais estudos de elevada qualidade. Com estes resultados foi possível identivicar percursos clínicos, intervenções baseadas em evidencia e estratégias de implementação que poderão ser adaptadas ao sistema de saúde Português.

Conclusões: Os resultados da presente tese contribuem para o conhecimento da prevalência, características e estado de saúde das pessoas com OAAJ em Portugal, as lacunas entre a evidência e a prática clínica já previamente apontadas na literatura, assim como desigualdades no acesso aos serviços de saúde desta população. Estes resultados levantam hipóteses sobre a adopção das intervenções centrais e o acesso aos serviços de saúde das pessoas com OAAJ que devem ser consideradas pelas autoridades de saúde e que requerem investigação futura nesta área. Mais ainda, os resultados apresentados sugerem a necessidade de implementar estratégias nacionais para otimizar os resultados em saúde dos cuidados atuais, diminuir e prevenir o aumento futuro da procura e necessidade de cuidados de saúde e dos custos associados relacionados com a OAAJ, como os MdC. A implementação de um MdC em Portugal pode ser desafiante por características do contexto em vários níveis – externos, locais e individuais – que devem ser considerados no processo de implementação.

Palavras-Chave: Osteoartrose, Epidemiologia, Modelos de Cuidados

LIST OF STUDIES DEVELOPED

1. Daniela Costa, Eduardo B. Cruz, Catarina Silva, Helena Canhão, Jaime Branco, Carla Nunes, Ana M. Rodrigues. Factors Associated With Clinical and Radiographic Severity in People With Osteoarthritis: A Cross-Sectional Population-Based Study. Front Med (Lausanne). 2021 Nov 15;8:773417. https://doi.org/10.3389/fmed.2021.773417 PMID: 34869491; PMCID: PMC8634437.
2. Daniela Costa, Eduardo B Cruz, David G Lopes, Catarina Nunes da Silva, Ana Rita Henriques, Diogo Luis, Jaime Branco, Helena Canhão, Ana M Rodrigues. Prevalence of and factors associated with unmanageable pain levels in people with knee or hip osteoarthritis: a cross-sectional population-based study. Accepted for publication BMC Musculoskeletal Disorders in November 2022 (Submission ID: 8b2fb46-16bf-4ab2-be4e-be46f23a9d4b). Available at https://doi.org/10.21203/rs.3.rs-1619389/v2
3. Daniela Costa, David G. Lopes, Eduardo B. Cruz, Ana R Henriques, Jaime Branco, Helena Canhão, Ana M Rodrigues. Trajectories of physical function and quality of life in people with osteoarthritis: Results from a 10-year population-based cohort. Submitted to BMC Public Health in August 17th 2022 (Submission ID: 7eeafee3-6e07-43e3-9d2f-f69854963391 | v.1.0), under revision. Available at https://doi.org/10.21203/rs.3.rs-1957027/v1
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CONTENTS

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LIST OF ABBREVIATIONS

ADL: Activities of Daily Living

BIC: Bayesian Information Criteria

BMI: Body mass index

CI: Confidence Interval

EQ-5D-3L: EuroQoL, 5-dimension and 3-level

HADS-A: Hospital Anxiety and Depression Scale subscale for anxiety

HADS-D: Hospital Anxiety and Depression Scale subscale for depression

HAQ: Health Assessment Questionnaire

HKOA: Hip and/or Knee Osteoarthritis

HOOS: Hip Disability and Osteoarthritis Outcome Scale

HRQoL: Health-Related Quality of Life

KOOS: Knee Injury and Osteoarthritis Outcome Score

MPL: Manageable pain levels

MoC: Model of Care

NPRS: Numeric Pain Rating Scale

NSAIDs: Non-steroidal anti-inflammatory drugs

NUTS II: Nomenclature of Territorial Units for Statistical purposes, *Nomenclatura das Unidades Territoriais para Fins Estatísticos*

OA: Osteoarthritis

OR: Odds Ratio

RRR: Relative Risk Ratio

RMD: Rhematic and Musculoskeletal Diseases

SD: Standard Deviation

SORT: Survey of Osteoarthritis Real World Therapies

TJR: Total Joint Replacement

UPL: Unmanageable Pain Levels

1. INTRODUCTION

Osteoarthritis (OA) is the most common type of arthritis and represents a serious public health problem (1) due to the exponential increase in prevalence and associated disability seen in the last decades (2). Hip and Knee together are the most affected joints by OA and represent the greatest burden for healthcare systems (2,3). Costs related to healthcare interventions, occupational constraints, and early retirement constitute a major socio-economic burden to patients and societies worldwide (4). In Portugal, the prevalence of OA was estimated at 15.8% (95%CI 13.5% to 18.0%), 12.4% (95%CI 11.0% to 13.8%) for knee OA and 2.9% (95%CI 2.3% to 3.6%) for hip OA (5), and it represents the 6th leading cause of years lived with disability in Portugal (6). The prevalence of Hip and/or Knee OA (HKOA) together is not known, nor are the direct costs of the disease. The estimated indirect costs due to OA account for an early exit from work due to early retirement or absenteeism (7).

The risk factors for the onset of HKOA are multifactorial (8) and, in the case of ageing and lifestyle habits, such as physical inactivity and obesity, they are in line with world demographic changes (9). These may partially explain the prevalence increase of this disease in the last decades and, therefore, the estimated future increase in healthcare demands for the treatment of people with HKOA (2,10).

HKOA is considered a chronic and progressive disease affecting a diversity of joint structures such as cartilage, subchondral bone, meniscus, peri-articular muscles, synovium, ligaments, and peri-articular fat (11). People with HKOA often experience joint pain, stiffness, and muscle weakness which can affect physical function and health-related quality of life (HRQoL) (12). Pain is the most critical symptom of HKOA (13) and is usually the primary driver of healthcare-seeking behaviour (14). High levels of pain are directly related to reduced function and decreased HRQoL (12), but the HKOA progression over time varies from person to person, which makes the clinical course of pain and physical functioning highly individual and variable (Sadosky et al., 2010. Thus, controlling the pain levels is paramount to preventing disability and worsening HRQoL in the long term (13).

In the early stages of the disease, symptoms are mostly discordant with structural damage seen in radiographs, and episodic pain is predictable. In the long term, there is a tendency for a slow progression of the disease with more distressing pain. This leads to an increasing impact on the physical functionality of the individuals, limiting their ability to realize basic activities of daily living and restricting mobility and social participation, which contributes to a deterioration of their mental health and HRQoL (15,16).

Older age, female sex, high levels of pain intensity, the presence of comorbidities, radiographic severity, muscle weakness and physical inactivity, overweight or obesity, and also socio-economic factors, like low education, have been associated with a poor prognosis on pain, physical function and HRQoL (17).

Since HKOA is considered a chronic condition and no cure is currently known, healthcare interventions have been focused on the maintenance of physical function, symptom reduction, and limiting disease progression. The standard treatment of HKOA usually follows a patient-centred stepped approach, often classified into three stages, with multidisciplinary interventions, including lifestyle behaviour change, to optimize outcomes of care (18–20).

Self-management education, exercise, and weight control, if appropriate, have been consistently recommended as the first line of treatment for HKOA and should be provided throughout the disease continuum for long-term management. Second-line optional or adjunctive treatment includes pharmacological treatment, aimed at relieving pain, together with other conservative treatments such as load-modifying interventions that can be used to supplement first-line interventions. Third-line interventions, namely total joint replacement (TJR), should be considered as a later option, only after all first- or second-line interventions have been tried and failed, and if HRQoL is significantly impaired (18–20).

However, international literature has raised concerns given the maintenance of ineffective or inappropriate interventions and poor health-related outcomes seen in people with HKOA. The interventions provided are often fragmented, regarding the quality, timing, and coordination of care (1,21). Several studies have shown that evidence-based guidelines are seldom reflected in clinical practice (22,23) and that patients with HKOA are often exposed to the overuse of low-value care and underuse of high-value care modalities (23,24). In many countries, pharmacological interventions are the first approach to patients' symptoms and research shows a rapid increase in the number of TJR surgery (25). For example, Portugal was the country with the highest compound annual growth rate in the incidence of knee replacement surgery (26.7%) among the OECD countries between 2005-2011 (25). Therefore, a fundamental change in the manner healthcare services is planned, implemented, delivered, and evaluated is needed to prevent higher levels of pain and future deterioration of physical function and HRQoL in people with HKOA (26–28).

Models of Care (MoC) have been increasingly recognized as an effective driver to facilitate the translation of evidence into health practice. They are defined as "an evidence-informed framework that outlines the optimal manner in which condition-specific care should be made available and delivered to patients and addresses system-level delivery and specific service provision in different parts of the system" (29).

In the last decade, several MoCs have been proposed to facilitate the delivery of evidence-based care and improve patient and service outcomes for people with HKOA, showing promising results at the patient level (e.g. pain, physical function, and HRQoL), organizational-level (e.g. healthcare utilization) and implementation-level outcomes (e.g. fidelity and adoption of recommended care) (28,30–32). However, this is an emerging research area, and no studies with a systematic methodology were found that have mapped the research on MoCs for people with HKOA.

In Portugal the epidemiological data regarding the characteristics of the population with HKOA, the clinical and radiographic severity profile and the long-term course of the disease as well as factors associated with poor prognosis are limited. Additionally, little information is known regarding healthcare utilization and treatments offered to people with HKOA. Therefore, the current needs of this population are barely known and can only be hypothesized based on international evidence, whose transferability to the national context can be misleading. Moreover, identifying and analysing relevant literature is needed to understand what are the best evidence-based solutions that had success in other countries/settings, workforce roles, programs or interventions, and future developments regarding the implementation of MoCs. This leads to the two general research questions of this thesis:

- *How is the health-related status, which are its determinants and the healthcare needs of people living with HKOA in Portugal?*
- *Which characteristics of a Model of Care may target these needs?*

To answer these questions, this thesis is organized into two phases. In the first phase, the studies included in this thesis were focused on evaluating epidemiological data in Portugal to determine a case for change for people with HKOA. To this end, this thesis estimates the prevalence of HKOA and explores associations between severity and the sociodemographic, lifestyle, and clinical factors (study 1); analysis the long-term trajectories of physical function and HRQoL (study 2); estimates the prevalence of people with HKOA with unmanageable pain levels, factors associated, and interventions offered to this population (study 3); the healthcare utilization and factors associated with higher utilization of healthcare services in people with knee OA (study 4). In the second phase, this thesis maps the literature related to the implementation of MoCs for people with knee OA, to understand the characteristics of MoCs that would better fit the identified needs in the first part.

The specific aims of the included studies are identified below.

Phase 1: Define a Case for Change

To estimate the prevalence of HKOA in Portugal, characterize the clinical severity of HKOA in the population, and identify sociodemographic, clinical, and lifestyle factors associated with clinical and radiographic severity.

To estimate the prevalence of unmanageable pain levels (UPL) among Portuguese people with HKOA, identify factors associated with UPL, compare the performance in activities of daily living (ADL), QoL, anxiety and depression symptoms, and therapeutic interventions used between people with UPL versus people with manageable pain levels (MPL).

To identify longitudinal trajectories of physical function and HRQoL on a 10-year period and determine the sociodemographic, lifestyle, and clinical variables associated with different trajectories.

To explore profiles of healthcare services utilization by people with knee OA and to analyse its determinants, according to Andersen's behavioural model and services provided to people with knee osteoarthritis

Phase 2: Potential solutions

To map the literature that developed and implemented MoCs for patients with knee OA in primary healthcare and, analyse their core components and outcomes.

The findings of this thesis will allow us to comprehensively understand the current health status and associated determinants, as well as the healthcare needs of the population living with HKOA in Portugal. This knowledge will raise awareness of the necessity of actions and initiatives directed to the identified needs. The findings of this thesis will also map evidence on current solutions – MoCs – that may respond to the demands of people with HKOA. Together, this knowledge may raise awareness and enable the development of targeted national strategies for the identified needs and contribute to the development and implementation of a MoC for people with HKOA in Portugal.

Thesis Structure

This thesis is divided into 6 main chapters. The **Introduction** (this **Chapter 1**) is an executive summary that introduces the problem of HKOA, the rationale for this thesis, and presents the overall aims and specific goals of the different studies developed.

Chapter 2 presents a narrative overview of the literature with background information on the OA definition, aetiology, diagnosis, and classification of HKOA. Epidemiological data regarding the prevalence, incidence, and socio-economic burden of HKOA, at the international and national levels, is also outlined. Literature regarding the clinical presentation, clinical and radiographic severity and predictors for the severity of the disease as well as for the course of pain, physical function and HRQoL, as the core clinical outcomes of HKOA, are critically analysed. Finally, literature regarding current care will be introduced, with a focus on the current utilization of healthcare resources, to comprehensively understand the gaps between evidence and practice, and to explore the links between outcomes and current care. Existing literature regarding MoCs definitions and principles of implementation, as a strategy to optimize outcomes of care by facilitating knowledge mobilization to practice, is introduced.

Chapter 3 presents and specify the five goals of this thesis and **Chapter 4** “Material and methods” is a summary of the methods used in the different studies of this thesis.

Chapter 5 presents the five studies that were published or submitted in full manuscript form. The first study is a cross-sectional study with data from the EpiDoC 1 cohort that estimated the prevalence of HKOA in Portugal, analysed the characteristics of the population, clinical and radiographic severity profile of the disease and factors associated with the severity – objective I. The second study is a cross-sectional study with data from the EpiDoC 1 cohort that estimated the prevalence of unmanageable pain levels, analysed factors associated with them, and also, interventions offered to people with HKOA with and without unmanageable pain – objective II. The third study is a longitudinal cohort study, that analysed the trajectories of physical function and HRQoL over the 10 years of the EpiDoC Cohort and factors associated with different trajectories – objective III. The fourth study is also a cross-sectional study that analysed the healthcare utilization of people with knee OA, focusing on behavioural determinants for higher healthcare utilization – Objective IV. Lastly, a protocol and the respective scoping review are presented, aiming to map and synthesize the literature of MoCs developed for people with HKOA – Objective V.

Chapter 6 presents a summary of the results with a general discussion of the key findings of this thesis, its clinical and research implications, and the strengths, and limitations of the studies developed. This is followed by a discussion of the challenges and future plans to implement new models of care for people with HKOA.

2. BACKGROUND

2.1. Definition, aetiology, and diagnosis/ classification of osteoarthritis

The Osteoarthritis Research Society International (OARSI), defines Osteoarthritis (OA) as a “disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by a micro and macro injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. At a joint level, OA is firstly manifested by a molecular derangement followed by anatomic and/or physiologic dysfunction that is characterized by cartilage degradation, bone remodelling, osteophytes, joint inflammation, and loss of normal joint function, that culminate in a disease of the whole person” (11).

OA was historically known as a “wear and tear” disease but, current knowledge supports an active dynamic alteration of repair and destruction imbalance of joint tissues. Cartilage composition changes and loses its integrity, increasing its susceptibility to disruption by physical forces. In an attempt to repair, proinflammatory mediators, deregulate chondrocyte function and stimulate a proinflammatory response, accompanied by tissue hypertrophy, bone remodelling and repair, and osteophytes formation(33). By radiographic imaging is possible to observe joint space narrowing, due to loss of articular and meniscal cartilage, osteophytes formation, bone sclerosis, and bone cysts as well as changes in bone contours and joint alignment, as the primary anatomic changes of OA. As consequence, at the joint level, people with OA often complain of pain, low-grade swelling, and stiffness, especially in the morning for periods of less than 30 minutes. Clinical signs of OA include crepitus in the mobilization, peri-articular tenderness and bone enlargement, a decrease in the range of motion, and muscle weakness (34,35).

A multifactorial aetiology is acknowledged in OA, as its onset is probably caused by the combination of several systemic and local risk factors. Systemic risk factors include factors such as age, sex and genetic factors (36). The risk of developing OA increases with age, mostly ≥50 years old (37,38) due to structural changes resulting from the ageing process but also, by cumulative exposure to other risk factors (36). The female sex has been consistently associated with a higher risk of OA when compared to men (37,38).

Local risk factors for OA onset are obesity, previous trauma and occupational activities. Obesity has been associated with an increased risk of incident HKOA (36). Body mass index (BMI) explains 24.6% of new-onset cases of knee pain (37). The risk of knee OA increases by 3.1-fold if overweight and by 4.7-fold in cases of obesity (39). This can be explained by the joint overload and by the presence of adipokines that promote low-grade inflammatory response at the joint level (40). Physical activity level may either be a protective or a risk factor for HKOA onset (41). The systematic review by Alentorn-Geli et al. (2017) concluded that performing recreational running was protective of HKOA (OR = 0.86; 95% CI: 0.69, 1.07). When compared to recreational runners, competition runners had a significantly higher association with HKOA (p<.001 and p=0.005, respectively). These authors suggest that a sedentary lifestyle or long exposure to high-volume and/or high-intensity running are both risk factors for HKOA diagnosis (42). Nevertheless, evidence has supported the role of muscle weakness in the development of knee OA. Knee extensor weakness was associated with an increased risk of knee OA (OR 1.65 95% CI 1.23, 2.21) (Øiestad et al., 2015).

Knee or Hip previous trauma increases the odds of developing knee OA by 4.2 to 6.3 times (44) and of developing hip OA by 5.0 times, respectively, when compared to people who suffer no knee or hip injury (41). The time between injury and onset of hip or knee OA was estimated at 1.5-36 years (41). Occupational activities like farming, floor laying, and brick laying may contribute to HKOA. People with occupational tasks that require squatting or kneeling, standing (>2 hours daily), and walking are at higher risk of knee OA, and those who lift heavy loads have an increased risk of hip and of knee OA (45).

Diagnosis and classification of OA are typically based on structural findings, symptoms or clinical presentations, or a mixture of both (33,35). Structural classifications of OA are based on signs present on imaging exams of the joint. The Kellgren and Lawrence (KL) classification of OA (46) is a widely used radiographic classification system that uses plain anteroposterior X-rays to evaluate joint space, as an indirect measure of cartilage thickness, and structural changes such as osteophyte formation, joint surface deformation and subchondral sclerosis (46,47). This grading system classifies OA into five severity grades (46):

Grade 0: normal
Grade 1: doubtful joint space narrowing (JSN) and possible osteophytic lipping
Grade 2: definite osteophytes and possible JSN
Grade 3: multiple osteophytes, definite JSN, sclerosis, possible bony deformity
Grade 4: large osteophytes, marked JSN, severe sclerosis and definite bony deformity

The clinical diagnostic criteria for symptomatic OA are based on findings from the clinical examination that generally rely on the evaluation of symptoms, like pain, short-period morning stiffness, and functional limitations, and a brief clinical examination to look up for crepitus, restricted painful movement, joint tenderness, and bony enlargement (48–51). These criteria are largely used in research and clinical practice and are often reported as more clinically relevant, because not all persons who have radiographic OA have the clinical disease, and not all persons who have joint symptoms demonstrate radiographic OA at the same extent (52). Thus, studies within this thesis will use clinical diagnosis criteria for selecting study participants.

For the stated reasons above, *The American College of Rheumatology (ACR)* recommend the combination of radiographic with clinical criteria to establish OA diagnosis and initiate appropriate treatment. For hip OA, the ACR diagnostic criteria include hip pain and at least 2 of the following features: erythrocyte sedimentation rate <20mm/hour; radiographic femoral or acetabular osteophytes; radiographic joint space narrowing (superior, axial and/or medial) (48). On the other hand, the ACR diagnosis criteria for knee OA considers knee pain with at least three of the following clinical findings: age > 50 years, morning stiffness < 30 minutes duration, *crepitus* in active motion, tenderness of the bone margins of the joint, bony enlargement noted on physical examination, and lack of palpable warmth of the synovium (49). The use of imaging for the diagnosis of HKOA in clinical practice is only recommended when other diseases are suspected, of differential diagnosis (53).

2.2. Prevalence and incidence of HKOA

OA affects 7% of the global population, which represents approximately 527 million people worldwide in 2019, an increase of 47.8% since 1990. Worldwide, the age-standardized incidence rate was 492.21 per 100 000 inhabitants in 2019. Hip or knee OA is present in 32.99 and 364.68 million people worldwide, respectively, being the knee the most affected joint by OA. Osteoarthritis is also a leading cause of disability, responsible for 18.9 million Years Lived with Disability (YLD), being the 15th on the rank of causes of YLD. Specifically, knee OA and hip OA account for 60.9% and 5.5% of the total YLD due to OA, respectively (54). As illustrated in figure 1, the incidence, prevalence, and YLD have been exponentially rising since 1990, especially for knee OA and OA in general (54).

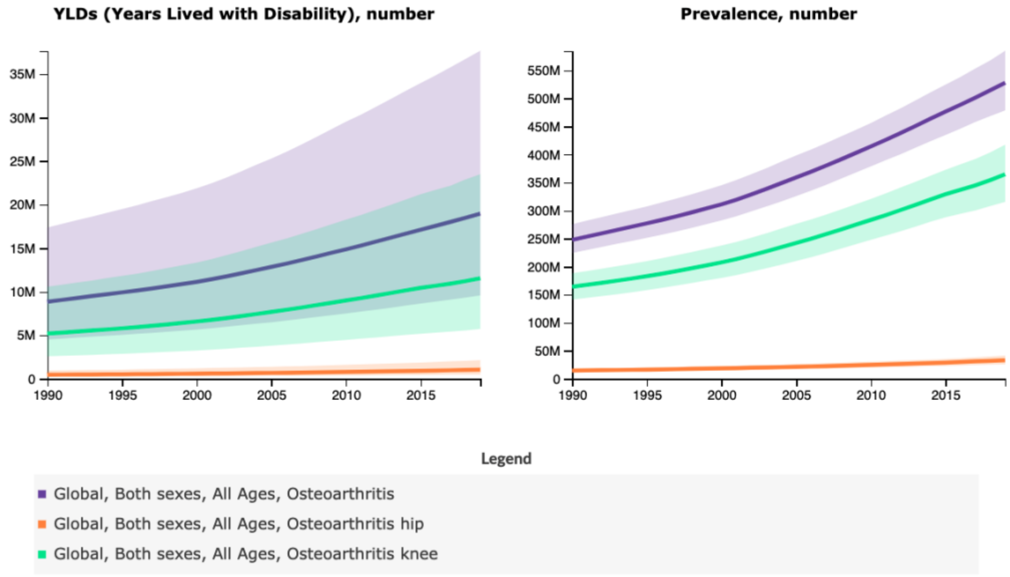


Figure 1 - Years Lived with Disability and Prevalence of Osteoarthritis, Knee Osteoarthritis and Hip Osteoarthritis. Data from the Global Burden of Diseases Study

HKOA together represent the highest burden for healthcare systems, mostly due to the associated disability (2) and total joint replacement surgery needs (4). Data from the GBD study (2) shows that the prevalence and incidence of HKOA were higher in females, when compared to males, in all age groups, and increases with age. The highest prevalence was seen in the group aged 60-64 years old, for both sexes and the highest incidence rate was seen in the 55-59 years old age group (54). Nevertheless, since the GBD study only considers individuals with radiographic OA (2-4 in the KL classification), the results of incidence and prevalence may be underestimated (2).

In Portugal, the population-based study EpiReumaPt, which included a representative sample of the Portuguese population, estimated that 12.4% (95%CI 11.0%, 13.8%) of the Portuguese adults have knee OA, and 2.9% (95%CI 2.3%, 3.6%) have hip OA, ascending to 15.8% (13.7% to 18.0%) and 3.0% (6.9% to 10.3%), respectively, among females. The highest prevalence was observed in the age class 66-75 years old, for both joints, separately. Among the 12 rheumatic and musculoskeletal diseases (RMDs) evaluated, the prevalence of OA was only overcome by low back pain and OA was one of the RMDs most associated with the worst disability, quality of life, and symptoms of depression (5). No data exist on the incidence of OA in Portugal nor the prevalence of HKOA together.

Healthcare costs related to Osteoarthritis

HKOA is a high-cost and high-burden disease. Worldwide, the weighted average annual costs per patient with HKOA are 11.1k€/year, 9.5k€/year for direct costs and 4.4k€/year for indirect costs. The direct costs varied if total joint replacement (TJR) surgery is considered or not, being 6.7k€/year per patient without TJR, 7.4k€/year per patient waiting for TJR and 10.8k€/year per patient with TJR (4). These costs may represent up to 2.5% of the Gross Domestic Product (GDP) in high-income countries (4). In France more than 50% of total direct costs are related to drugs but, only 10.6% of costs are due to OA-related drugs, probably representing the multimorbidity profile of people with HKOA. In the same study, costs of OA-related hospitalizations accounted for 9% of the direct costs, and surgery procedures accounted for 27% of surgery hospitalization costs (55).

In Portugal, there is no data on the direct costs of HKOA. Data from the EpiReumaPt study revealed that the annual indirect costs attributed to an early exit from work due to OA were 1294€ per patient with OA, and 2095€ per patient with OA out-of-work (due to unemployment due to OA or early retirement), representing 656€ million per year, 0.4% of the Gross Domestic Product (7).

The study of Karmarkar et al (2016), used a Markov model to calculate the lifelong costs of people with knee OA in the United States of America. This study shows that the absence of treatment and disparities in the access to healthcare services to manage OA increase indirect and direct long-term costs. When there is no adequate care, indirect costs increase, mostly the ones related to occupational productivity. Additionally, it is shown that $13.28 billion can be saved if there were no inequities in access to treatment. If these inequities were not addressed, these costs with OA will increase to $15.6 billion by 2025. Therefore, the authors conclude that to decrease the costs of OA, waiting for treatment should be minimized and early management should be offered equitably to all patients with knee OA (56).

2.3. Clinical presentation, course and predictors of Pain, Physical Functioning and HRQoL in Patients With HKOA

People with HKOA commonly seek healthcare services for symptoms like pain, joint stiffness, or functional limitations. Pain is the most common symptom reported by people with HKOA, and it explains most of the variance in the associated disability (13). Pain in people with HKOA can be presented either as chronic or acute, frequently in flares with clinical indicators of underlying mechanical or neuropathic pain production mechanisms (12). Approximately 30% of patients with knee OA also present chronic widespread pain (57).

The severity of joint pain and stiffness can undermine basic activities of daily living, such as washing, dressing, shopping, and doing housework, or mobility activities like walking, climbing stairs, and sitting and raising from a chair (58). Moreover, pain due to HKOA contributes to sleep disturbances, mental health issues, and consequently, deterioration of HRQoL (12). Occupational participation is also commonly restricted or impaired which may lead to presenteeism, absenteeism, or early retirement. Additionally, community life and leisure activities are often limited (12). Therefore, people with HKOA may also face exclusion, from familiar or social relationships and activities, due to disability (58).

Although most patients with HKOA present with joint pain and functional limitations (59), the age of disease onset, and disease progression over time vary from person to person, which makes the clinical course of pain and physical functioning highly individual and variable (60,61). People with HKOA have heterogeneous clinical presentations and disease severity depending on factors such as structural joint damage, the presence of non-communicable diseases (e.g., diabetes, obesity), age of symptom onset, and psychosocial factors (17). Therefore, OA ranges from an asymptomatic, incidental finding on clinical or radiologic examination to a progressive disabling disorder eventually culminating in "joint failure" (16).

Radiographic and clinical severity are, therefore, important predictors of individual burden and healthcare service utilization (62). However, there is no consensus on the gold standard for evaluating HKOA severity, therefore the general recommendation is to use a combination of radiographic and clinical severity measures, mostly for research purposes (63).

K-L classification is the most widely used measure to evaluate radiographic severity, as previously stated. Regarding clinical severity, and given the close relationship between high levels of pain and disability and the correspondent impact on HRQoL, pain and functional outcome measures are frequently used as proxies (64).

Clinical severity has been measured with composite tools that capture the short- and long-term consequences of the disease (36,65). Self-reported joint-related problems have been assessed with the Hip disability and Osteoarthritis Outcome Score (HOOS) for the hip (66), and the corresponding Knee injury and Osteoarthritis Outcome Score

(KOOS) for the knee joint (67). These tools have been extensively used both in research and in clinical practice as a clinical severity measure and were developed as an extent of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) (66,67). HOOS/KOOS measure the clinical severity of HKOA in five subscales considered important to patients, such as pain, other symptoms, function in activities of daily living (ADL), function in sport and recreation (Sport/Rec), and hip- or knee-related Quality of Life (QoL).

The information on the severity of HKOA in the population is crucial for obtaining a better understanding of the course and individual burden of HKOA, estimating future increases in health resource demands, and identifying the need for implementing prevention and management strategies for people with HKOA. Over the years researchers have attempted to characterize the clinical course of HKOA. Although, since this is a slow and variable progressive disease over time, long-term follow-up studies, that may capture accurately the long-term course of symptoms and consequences of HKOA, are scarce.

In the long term, patients’ symptoms generally remain stable or worsen, but for some patients, their symptoms may also improve (60,61). Because of this variability, the depiction of the course of clinical severity in symptoms like pain and physical functioning, and the identification of risk factors for the decline of physical function and HRQoL is important and can be used to inform patients of the likely course of their condition, and to target and adapt healthcare interventions to the factors associated with poor prognosis (17).

The systematic review of Rooij et al. (2016) aimed to describe the course of pain and physical function in people with knee OA and included studies with follow-ups from 0.5- to 8 years. This study found that the course of these outcomes was unpredictable, and no conclusions could be drawn due to the studies’ heterogeneity. Looking at large standard deviations of change scores, the authors concluded that there are considerable within-patient differences in the course of pain and physical function (17).

Therefore, literature has shown that people with HKOA have a highly heterogeneous course of clinical symptoms in the long term, supporting the hypothesis of different clinical subgroups of patients and emphasizing the existence of distinct symptom trajectories over time.

The study of Schiphof et al, analyzing 1,002 subjects from the 10-year follow-up multicenter CHECK (Cohort Hip and Cohort Knee) cohort found that, in people with early signs of HKOA at baseline, all WOMAC subscales, pain intensity (numerical pain rating scale - NPRS), health status (SF-36) and HRQoL (EQ-5D) were relatively stable within the follow-up period, for the whole sample. This study also found that individual symptoms may fluctuate over time due to different pain trajectories found: “always high pain trajectory”, “always low pain trajectory”, “decreasing pain trajectory”, and “fluctuating high pain trajectory”. (68). The same study, on the other hand, showed that radiographic severity was progressive over the 10-year follow-up. At the baseline, only 17% and 16% of subjects with knee or hip OA, respectively, had mild radiographic severity with K-L<2. After 10 years of follow-up, 70.9% and 60.4% of people have radiographic knee or hip respectively, with K-L≥2 at least in one joint (68).

The systematic review by Wieczorek et al. 2020 aimed to describe the pain and physical function trajectories in people with HKOA. For hip joint pain, two common trajectories were found across two studies: a stable mild and a stable severe pain trajectory. For knee joint pain mild, moderate and severe patterns with a stable or mild increase over time were found across 9 studies. Similar trajectories were found for physical function course in people with knee OA across five studies, and no studies were found for hip OA. This systematic review also revealed that studies with shorter measurements over time describe high variability in the outcomes measured, resulting from flares of pain and physical function loss. High heterogeneity was seen across studies, but these outcomes were mostly stable over time, and the authors concluded that OA is a slowly progressive disease in the long term (69).

Only one study was found that assessed the course of QoL, measured with KOOS QoL subscale, in an 8-year follow-up cohort. In this study four different trajectories were found: no change (62.9%), slowly worsening (17.1%), improving (10.4%) and rapidly worsening (9.5%) QoL in people with knee OA (70).

In summary, most of the existing studies show that people with HKOA have a prolonged and slow decline of clinical symptoms and structural deterioration, and different trajectories seem to be dependent on baseline values (69). As noted, the literature in this area is heterogeneous and still scarce. More longitudinal studies with long-term follow-ups are needed to identify different trajectories, especially on physical function and HRQoL, as long-term consequences of HKOA.

In line with the course of the disease, some studies have also identified predictors for severity and the progression course of structural and clinical HKOA. These are mostly related to joint structural factors, age, BMI, number of comorbidities, higher clinical and radiographic severity, mental health status, physical performance and physical activity as well as socio-economic determinants.

The systematic review by Bastick et al. (2015), which included cohort studies from 1- to 12 years of follow-up, showed that baseline pain (OR: 2.38 95% CI,1.74–3.27) and presence of Heberden nodes (OR: 2.66, 95% CI, 1.46–8.84) are determinants for knee structural progression, measured by imaging exams. No pooling data was presented for the remaining determinants. Nevertheless, the authors found strong evidence [consistent findings (≥75%) among two or more high-quality studies] for the association of varus alignment, serum hyaluronic acid, and tumour necrosis factor-alpha with radiographic severity progression (71). Another systematic review developed by the same authors, which included cohort studies with follow-ups from 1- to 7 years, reported strong evidence that age, BMI, comorbidity count, magnetic resonance imaging (MRI)-detected infrapatellar synovitis, joint effusion and baseline OA severity (both radiographic and clinical) are factors that predict clinical knee OA progression, including functional decline, defined as the difference in several measurement tools such as WOMAC and KOOS (72).

The systematic review and meta-analysis by Rooij et al. 2016 analysed the predictors of high-intensity pain and deterioration of physical function and included studies with follow-up periods from 0.5- to 8 years. Data from the metanalysis showed that higher pain at baseline (B= -0.48 95%CI, -0.52, -0.44) and female sex (OR=0.76, 95% CI, 0.63, 0.92) are predictors of higher levels of pain in the future. In this study, qualitative evidence synthesis showed strong evidence (consistent significant associations found in at least 2 high-quality studies) that bilateral knee symptoms and depression were also associated with a deterioration of pain in the long term, in people with knee OA. On the other hand, in the same study, the metanalysis showed that bilateral knee pain (risk ratio=0.79, 95%CI 0.63, 0.98) and higher knee pain at baseline (OR=0.90, 95% CI 0.83, 0.99) are predictors for the deterioration of physical function. In the qualitative evidence synthesis, strong evidence showed that higher radiographic severity grade, higher knee pain at baseline, worsening of knee pain, pain on patellofemoral joint compression, lower knee extension muscle strength, higher baseline disability, higher comorbidity count, poor general health, lower vitality, poor mental health, depressive symptoms and lower walking speed were associated with the deterioration of physical function in the long-term (17).

Physical activity level has a dynamic relation with pain severity in people with knee OA. The systematic review and meta-analysis by Burrows et al. (2020) reveal that, although physical activity levels are protective of pain severity, periods of high physical activity levels can proceed with periods of higher symptom severity in the short term (73). An umbrella review found that physical activity level is a predictor of lesser pain and improved physical function (strong evidence – further evidence is unlikely to be modified by more studies for these outcomes) and HRQoL (moderate evidence) in people with lower limb OA. These authors found that even lower levels of physical activity (at least 45 total minutes/week of moderate intensity) were associated with improved or sustained high physical function (74).

A small amount of literature has been published regarding the predictors of the clinical and structural progression course of hip OA. The systematic review by Teirlinck et al (2019) revealed that strong evidence [consistent findings (≥ 75% of the studies showing the same direction of the association) in two or more studies with a low risk of bias] support mostly imaging factors like higher K-L grade at baseline, superior or lateral femoral head migration and subchondral sclerosis as predictors of a faster progression to TJR, or of a higher risk to progress to TJR. Strong evidence was also found for the presence of comorbidities as a predictor of clinical severity progression. This systematic review included studies with follow-ups from 1 to 19 years (75).

Comorbidities have been studied as predictors for HKOA clinical course. The systematic review by Calders & van Ginckel, 2018, showed that the presence of at least one comorbidity is associated with pain intensity (regression coefficient: 0.18, 95%CI 0.14, 0.22) and physical function deterioration (regression coefficient: 0.20, 95%CI 0.10,0.29). Specifically, the presence of musculoskeletal comorbidities (regression coefficient: 0.85, 95%CI 0.06,1.63), and diabetes (regression coefficient: 0.10 95%CI, 0.02,0.17) predicted worsening of pain levels, whereas the presence of back pain (regression coefficient: 0.12, 95%CI 0.04,0.20) and cardiac diseases or hypertension (regression coefficient: 0.08, 95%CI, 0.01,0.16) predicted worsening of physical function when compared to people without these comorbidities (76).

Socio-economic determinants for the prognosis of HKOA were investigated to a lower extent. A recent study, including 971 with HKOA from 28 European countries, followed for 7 years, analysed path models to test the interplay association of psychological and social determinants with pain and activities of daily living, and the mediation effect of cognitive ability, adjusted for confounders. This study showed that high social deprivation before diagnosis predicts greater limitations in activities of daily living after diagnosis, mediated by cognitive ability (standardized coefficient (SDC): 0.006, 95%CI 0.001, 0.011). Additionally, higher educational attainment may protect against limitations in activities of daily living after diagnosis, mediated by better cognitive ability and lower anxiety (SCD: -0.007, 95%CI: 0.007, 0.079) (77).

These systematic reviews consistently reported as a limitation the heterogeneity in the evaluation of clinical course among the included studies and failed to progress to meta-analysis due to studies heterogeneity (17,71,72,75).

More high-quality literature about subgroups of patients with different clinical presentations and their determinants is needed, including different severity subgroups, and different long-term courses of the disease. This would allow us to better identify patients at risk of poor long-term trajectories and of increased clinical and radiographic severity, allocate the appropriate resources and also, and improve the research on the effectiveness of personalized interventions directed to these patients.

In summary, HKOA is a structural and progressive joint disease that results in pain, stiffness, and impaired mobility. The aetiology of HKOA is multifactorial, related to socio-demographic and lifestyle risk factors highly present in the population such as ageing, overweight, sedentarism, previous trauma and comorbidities. Therefore, prevalence is rising as well as associated disability and direct and indirect costs. The structural and clinical severity of the disease is highly variable and it is associated with the estimated healthcare demands for people with HKOA. In the short term, people with HKOA may present flares of symptoms but, in the long term, this disease progresses gradually. Consequently, people with HKOA have a slow and progressive deterioration of physical function and health-related quality of life in the long term. However, the literature regarding the clinical severity and the long-term trajectories of the disease is very heterogeneous, and more data is needed to understand the clinical course of HKOA. Predictors for the course of the disease in clinical outcomes like physical function, pain and HRQoL, and also for structural progression, have been described in the literature, but more high-quality literature is needed. These predictors include ageing, female sex, comorbidities, clinical and radiographic severity, muscle strength and physical activity, overweight or obesity and also socio-economic determinants.

OA in the hip and the knee joints often show up together and have similar individual and socio-economic burdens, however in Portugal the prevalence of OA in these two joints together is not estimated yet.

Epidemiological data on the Portuguese population with HKOA is scarce. Understanding the OA-related health status, as well as the presence of predictors for high severity and course of the disease in the population with HKOA can show up current healthcare needs of this population, as well predict the future increase in healthcare demands. This is an urgent need, regarding the exponentially rising prevalence and the burden for health systems shown internationally. National epidemiological information regarding the prevalence, severity and course of HKOA in Portuguese citizens is needed to understand the real impact and health-related determinants of HKOA in Portugal. This data would set the need for national health policies and national health strategies and programs directed to citizens with HKOA and to the factors that can prevent the disease progression.

2.4. The evidence-based healthcare management for people with Osteoarthritis

Currently, there is no cure for HKOA and no proven effective drugs are recognized that can prevent, stop or restrain the natural course of the disease by preventing, stop or restrain joint structural change (78). Therefore, current effective interventions for the management of HKOA are mostly targeted to the modifiable predictors of poor prognosis of physical function and HRQoL, previously described, and pain management (1,12).

Based on the best current evidence, several clinical practice guidelines for the management of people with HKOA have been published in recent years (18–20). Generally, they consistently recommend a stepped approach in three phases. Conservative non-pharmacological interventions are considered the first-line treatment that should be offered in the early stages and through the progression of the disease. These include education about the disease and self-management of symptoms, exercise programs, with neuromotor, resistance, aerobic training components, and healthy weight management, and are preferably delivered according to individual needs (18–20).

Education programs have relied upon self-management skills, including information about OA, symptoms and medication management and strategies for a healthy lifestyle such as physical activity and healthy weight management (79)

Data from systematic reviews of intervention effectiveness has shown that exercise programs reduce pain, improve physical function and self-efficacy, reduce depression symptoms, improve social function (80), physical performance and QoL (81) in people with HKOA. The effects of exercise programs on pain, function, QoL and physical performance measures, reach a peak in 2 months, and gradually decreases after this time (81). Other systematic reviews comparing different types of exercises showed that short-term, aerobic and neuromotor exercises showed the largest effect sizes on pain and function. Strengthening and flexibility exercises showed to be beneficial in pain, function and QoL, but with smaller effect sizes than aerobic and neuromotor exercises (82).

On the other hand, weight loss interventions alone seem to not produce better results than exercise programs on pain and disability in people with HKOA (83). This may be explained by the few effects of weight management programs on weight reduction in people with HKOA (84). However, current evidence supports those structured programs which include exercise with or without education or diet are cost-effective when compared with physician-delivered usual care, in contrast to education and diet interventions alone (85).

When the core interventions are not enough to control symptoms, pharmacological care should be added. Pharmacological interventions should be given also through a stepped approach at the lowest possible dose, for the shortest time, and taking into account specifically the gastrointestinal and cardiovascular comorbidities (18,19). Topical NSAIDs should be the first pharmacological approach, followed by oral NSAIDs, duloxetine and selective COX-2 inhibitors according to pain severity and inherent risks for side effects in individual patients (18,19). On the other hand, given the toxicity and dependence risk associated with opioids, these drugs are not recommended for people with OA (18,19). International guidelines also consider other conservative interventions like aquatic exercise, cognitive behavioural therapy and gait aids, as adjunctive therapies, that may be considered in selected patients in this phase (18,19).

Primary care is referred to as the most relevant setting for early intervention and through the HKOA disease progression. Collaboration with secondary care should be considered for specialized pain management, differential diagnosis in the presence of red flags, and surgery consideration (18–20). There are no established criteria for surgical referral and evidence suggests that TJR should be considered as a later option when conservative interventions failed and HRQoL is significantly impaired (18,19). Despite TJR is considered a cost-effective intervention, it should be offered to highly selected patients (86) since 20-34% of the patients report dissatisfaction with the outcomes (87), 50% report adverse events (88) and 3-5%, need a new surgery in less than 10 years (89). Moreover, the mortality associated with TJR is approximately 0.2-0.37% (90).

To conclude, evidence-based interventions for people with HKOA should be offered in integrated care settings through the collaboration of multidisciplinary teams across the disease continuum. These interventions should follow a person-centred approach targeting behaviour change to promote long-term adherence to healthy lifestyles, the continuation of exercise and weight management autonomously, as well as adherence to medication and other adjunctive therapies as needed, avoiding or delaying the need for surgery (18,19).

2.5. The Current Management of people with Osteoarthritis

An extensive body of literature has been published in recent years reporting consistent conclusions: the recommendations for OA management are not reaching the patients (22,23,91–95). This has been pointed out as the reason for the negative consequences regarding outcomes at the patient- and societal-level, increasing the burden of the disease worldwide (1,21). Healthcare interventions offered to patients with HKOA have been reported as fragmented, heterogenous and palliative, based on symptoms control with pharmacotherapy, and with an underlying biomedical view of HKOA (96). On the other hand, several authors have advocated the existence of a therapeutic nihilism in HKOA, as healthcare professionals downplay the impact of the disease, with misperceptions that HKOA is an inevitable part of ageing, and no interventions are effective for HKOA management (1,21).

Compliance of current care with the recommendations for HKOA has been measured using validated process quality indicators (97). The systematic review and metanalysis by Basedow et al (2015) concluded that the overall achievement of quality indicators for non-drug treatments was 36.1% (95%CI 27.8 to 44.7) and for drug, treatments was 37.5% (95%CI 30.8 to 44.5) (22). The systematic review and metanalysis by Hagen et al (2016), including only studies with people with HKOA recruited in the community, found similar results: less than half of people with HKOA received care according to quality indicators pass rates analysis - calculated by dividing the number of times the indicator was achieved by the number of eligible persons for that particular indicator (23). A multinational study that included n=135 Portuguese participants with HKOA, revealed that overall, 48% of the self-reported quality indicators were achieved among five domains: patient education and information about disease progression, treatment alternatives, self-management, weight management and exercise. Specifically, referral to services to lose weight was only offered to 20% of patients with overweight/obesity; referral for exercise was offered to 43% of participants; and information/education was given to up to 65% of patients, depending on the issue of the education component (e.g., self-management of symptoms, healthy lifestyle) (93). This was a small Portuguese sample, that included participants from primary care units in the Algarve region. Similar results have been found in other countries (93,95). However, referral for exercise was much lower in Portugal, when compared to Norway where more than 65% of people with HKOA were referred to services for exercise interventions (92).

Besides the low uptake of core conservative non-pharmacological interventions, medication for pain relief has been seen often as a first-line and single intervention before surgery to manage HKOA (98,99). Moreover, despite the current recommendations against the prescription of opioids, due to the reported low effectiveness on pain and adverse effects (100), they continue to be prescribed to patients with HKOA. Between 2007 and 2014, in the United States, 17.0% of patients with any joint OA, 13.4% of patients with hip OA, and 15.9% with knee OA received opioids for their condition (101). In The Netherlands, opioids were prescribed to 18.4% of people with OA between 2008 and 2017 (102). Similar results were found in Sweden, where the 12-month prevalence of opioids prescription reached 23.7% (103).

On the other hand, TJR surgery, which should be the end-stage intervention for HKOA, is often seen as inevitable and given too early in the course of the disease. The incidence of TJR has increased since 2005 around the globe, specifically when it comes to total knee replacement surgery. Between 2005-2011, Portugal was the country with the highest compound annual growth rate in the incidence of knee replacement surgery (26.7%) among the OECD countries and presented a growth rate of more than 13% in each age group. This growth is not fully explained by the demographics and risk factors presented in the population. An interplay between economic variables, healthcare system-factors, reimbursement strategies and patient and surgeon preferences can also explain these data (25)., The rates of inappropriate use of total hip and knee replacement in Spain are estimated at 25% and 26%, respectively, while in the USA the rate of inappropriate total knee replacement is 34% (24). An overuse of other ineffective treatments for knee OA such as glucosamine and arthroscopic surgery has also been reported worldwide (24).

In brief, current evidence suggests that care offered to people with HKOA does not seem to be based on the best current evidence. This has been shown by the type of interventions that are offered to people with HKOA, by the timing that interventions are offered, and also, by the biomedical paradigm approach still present.

To sum up, in Portugal, few epidemiological data have been published that characterize the population with HKOA namely in terms of the severity of the disease, the modifiable factors for the severity and predictors for the course of symptoms. Additionally, the interventions offered to people with HKOA and the utilization of healthcare services are barely known. Given the concerns raised by international literature regarding the outcomes of current care, the future demands for healthcare systems as consequence, and the poor knowledge translation in the management of people with HKOA, there is a need to analyse comprehensively how people live with HKOA regarding their healthcare status, the interventions offered and the utilization of healthcare services. This knowledge will allow us to identify current needs for improvement in patient-related outcomes as well as in healthcare interventions provided and may justify the need to implement improvement strategies accordingly.

2.6. Quality improvement strategies: the need for implementation of Models of Care

The literature review showed that HKOA is a high and increasingly prevalent health condition, with rising associated disability, poor health-related outcomes and consequent burden to the healthcare systems. This can be partly explained by the low quality of care offered to people with HKOA as seen internationally, with the use of low-value interventions, not based on best evidence and not providing additional cost-benefit. Probably, this is a consequence of a lack of organized system-level strategies, based on health policies that failed to tackle health determinants of HKOA severity and progression (21). In face of these problems, several regions and countries have implemented strategies, like Models of Care (MoCs), to optimize patient-related outcomes, improve the quality of care by straightening the evidence-practice gap, and assure the sustainability of the healthcare systems in the management of people with HKOA (Allen et al., 2016b; Andrew M. Briggs & Choong, 2018; Baldwin et al., 2017). This is an emerging area, therefore, heterogeneous definitions and concepts can be found in the literature. In this thesis, we adopted the definition and concepts outlined by Briggs et al (2016) (29) and The Framework to Evaluate Musculoskeletal Models of Care, by the Global Alliance for Musculoskeletal Health of the Bone and Joint Decade, which define the concepts underlying MoCs and support its implementation (105).

What are Models of care

MoCs are defined as “an evidence-informed policy or framework that outlines the optimal manner in which condition-specific care should be made available and delivered to consumers at a system level” (29). MoCs are complex interventions that sketch the delivery and evaluation of care at different levels, from a patient- to system-level with several interacting components (106,107).

MoCs are context-specific, that articulate *what* care should be delivered for people with a given health condition and *how* the local system should deliver care (26). The principles of interventions included in MoCs are based on best evidence (*the “what*”) therefore, for HKOA, these should be based on the literature and clinical guidelines recommendations previously presented (18,19). The recommendations are then tailored to context features, usually with “must-have” elements and adaptable components that are flexible according to local needs (28). Multiple levels of context are taken into account in the development of MoCs, like fiscal environment, health policy and governance, organization of the healthcare system and existent pathways, local clinical expertise, available healthcare professionals and the lived experience of local communities (patients and involved healthcare professionals) (28). The distinction between MoCs, clinical practice guidelines and models of service delivered should be made. MoCs complement clinical practice guidelines by outlining how care should be delivered considering the macro (system), meso (organization) and micro (patient) levels. MoCs include models of service delivery that define how a MoC can be implemented at an operational level, being the next step in the implementation continuum (29) – Figure 2.

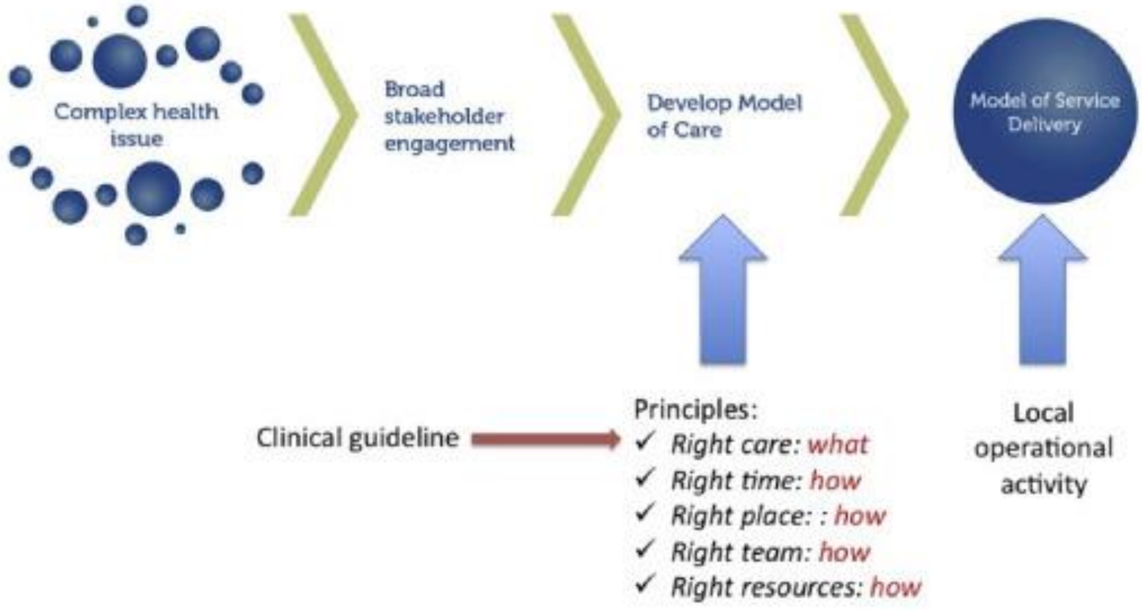


Figure 2 - Models of care, models of service deliver and clinical guidelines and how they are integrated to answer a complex health issue. Reproduced from A.M. Briggs et al. (29), pp362.

The goals of Models of Care for people with HKOA

MoCs are pointed out as a potential solution for health systems to decrease the evidence-practice gaps and support the delivery of high-value care for populations with different health conditions (108). MoCs represent a shift from episodic, poorly coordinated care to meet acute healthcare conditions, to multidisciplinary, integrated, and collaborative care, delivered across the disease continuum and life course, to meet the needs of people with chronic diseases (109).

The development and implementation of MoCs can influence health policy and health strategy priorities, resourcing and health governance decisions (system-level), service design, health professionals' training and capacity to build initiatives (organizational-level) and optimization of patient-level outcomes and patients' participation as well as clinicians practice behaviours (patient and professionals-level) (107). MoCs have, therefore, the quadruple aim to improve healthcare outcomes, improve professionals' and patients' experiences and improve the adequate use of health services resources across the healthcare system (28).

The development and implementation of Models of Care

MoCs for people with OA are designed as a coordinated package of evidence-based care, with an underlying longitudinal care pathway, taking into consideration the need for multidisciplinary and individualized care, and regular review of patient-level outcomes, usually based on the Chronic Care Model and biopsychosocial approach (110) (28). For this, the training of healthcare professionals, to ensure the fidelity and adoption of intervention principles is a crucial element of MoCs. Additionally, organizational-level outcomes like performance indicators should be reported and analysed continuously, to improve the delivery of interventions and guarantee the maintenance and sustainability of Mocs.

The patients' and involved stakeholders' perspectives and experiences have been considered in MoCs development and implementation. Co-design strategies may engage stakeholders from the early phases of the development and optimization of the implementation strategy, to ensure that MoC responds to local needs, to ascertain the optimization of the organizational and patient-level outcomes as well as the sustainability of the implementation (28).

Implementation science methods have been considered in the development, implementation and the evaluation of MoCS, but this is an emerging area in this field and the standards for the implementation of MoCs are not defined (Allen et al., 2016b; Eyles et al., 2019). Implementation theories have underpinned MoCs to describe and guide the process of translating research to practice; to understand or explain the determinants of implementation outcomes; and to evaluate the implementation strategies (Allen et al., 2016b; Nilsen, 2015).

Evidence on Models of Care for people with HKOA

Research on the implementation of MoCs has been escalating in the last decade, however, since MoCs are highly dependent on context features, there are variations in what and how care is delivered across the disease continuum (Allen et al., 2016b; Bowden et al., 2020; Gray et al., 2022). Different MoCS for OA have been found in the literature, as primary prevention models or triaging for TJR and end-stage OA intervention as an alternative to TJR, for example, steered by different healthcare professionals such as GPs, physiotherapists, pharmacists, rheumatologists or nurses, depending on the implementation context (Allen et al., 2016a).

From the current evidence, preliminary data reported in narrative reviews, the implementation of MoCs shows promising results namely on patient-level outcomes like pain, physical function and HRQoL; quality of care, satisfaction with care, reduction of absence from work and costs of care (Allen et al., 2016b; Dziedzic et al., 2016).

Given the intervention and implementation complexity of MoCs for HKOA care, the survey of the "Joint Effort Initiative" endorsed by Osteoarthritis Research International (OARSI) pointed out that "To establish guidelines for the implementation of different OA Management Programmes to ensure consistency of delivery and adherence to international best practice MoC" is the highest priority action for future investigation on MoCs for OA (111).

However, no studies with a systematic methodology have mapped or synthesised the body of literature on the implementation of MoC for people with HKOA. Without this information, guidelines for the implementation of MoCs would hardly be developed, and the transferability of the established MoCs and lessons learned would be hindered. Moreover, without a comprehensive analysis of the literature knowledge on expected outcomes, regarding the effectiveness and cost-effectiveness, the implementation and scale-out of MoCs are concealed.

3. OBJECTIVES

The literature review highlighted the multifactorial aetiology, high prevalence and burden of HKOA, variable severity and course of the disease among individuals and associated determinants. International evidence raises concerns regarding the future increase in the prevalence of HKOA and healthcare demands, as a consequence, enhanced by non-optimal outcomes and questionable quality of care. The implementation of strategies to prevent the escalating of the individual and societal burden of HKOA, as MoCs, is crucial.

The process of developing and implementing innovative MoCs, as context-dependent complex interventions include the three following domains: 1) implementation readiness; 2) strategies to support the optimization of the implementation and 3) evaluation of the success of the implementation (105). This thesis is focused on the readiness domain, targeted to identify the need for change regarding the burden, consequences, and determinants of people living with HKOA, and the review of potential evidence-based solutions to tackle these needs (105).

Thereby, this thesis is divided into two phases aiming to answer the following research questions:

What is the health-related status, which are its determinants and the healthcare needs of people living with HKOA in Portugal?
Which characteristics of a MoC may target these needs?

Phase 1. Define the case for change

To define the case for change, it is necessary to develop a better knowledge of national data that reflects the burden of disease and system impacts, consumer needs, and current local practice behaviours in the sector that are discordant with contemporary evidence (Briggs, Jordan, et al., 2016). As few epidemiological data exist in Portugal that may reflect the prevalence and burden, as well as the health-related status of the citizens with HKOA and its determinants, current healthcare interventions offered and the utilization of healthcare resources and services, the current needs of people living with HKOA are barely known. Epidemiological data may justify the need, and foster the development, of national health policies and implementation of system-level strategies targeted to the specific demands of citizens with HKOA, like MoCs.

Therefore, this thesis intends to comprehensively analyse people with HKOA at a national level through epidemiological lens, with the following objectives:

I. To estimate the prevalence of HKOA in Portugal, characterise the clinical severity of HKOA in the population, and identify sociodemographic, clinical, and lifestyle factors associated with clinical and radiographic severity;

II. To estimate the prevalence of unmanageable pain levels (UPL) among Portuguese people with HKOA, identify factors associated with UPL, compare the performance in activities of daily living (ADL), QoL, anxiety and depression symptoms, and therapies used between people with UPL versus people with manageable pain levels (MPL).

III. To identify longitudinal trajectories of physical function and HRQoL on a 10-year period and determine the sociodemographic, lifestyle, and clinical variables associated with different trajectories

IV. To explore profiles of healthcare services utilisation by people with knee OA and to analyse its determinants, according to Andersen's behavioural model and services provided to people with knee osteoarthritis

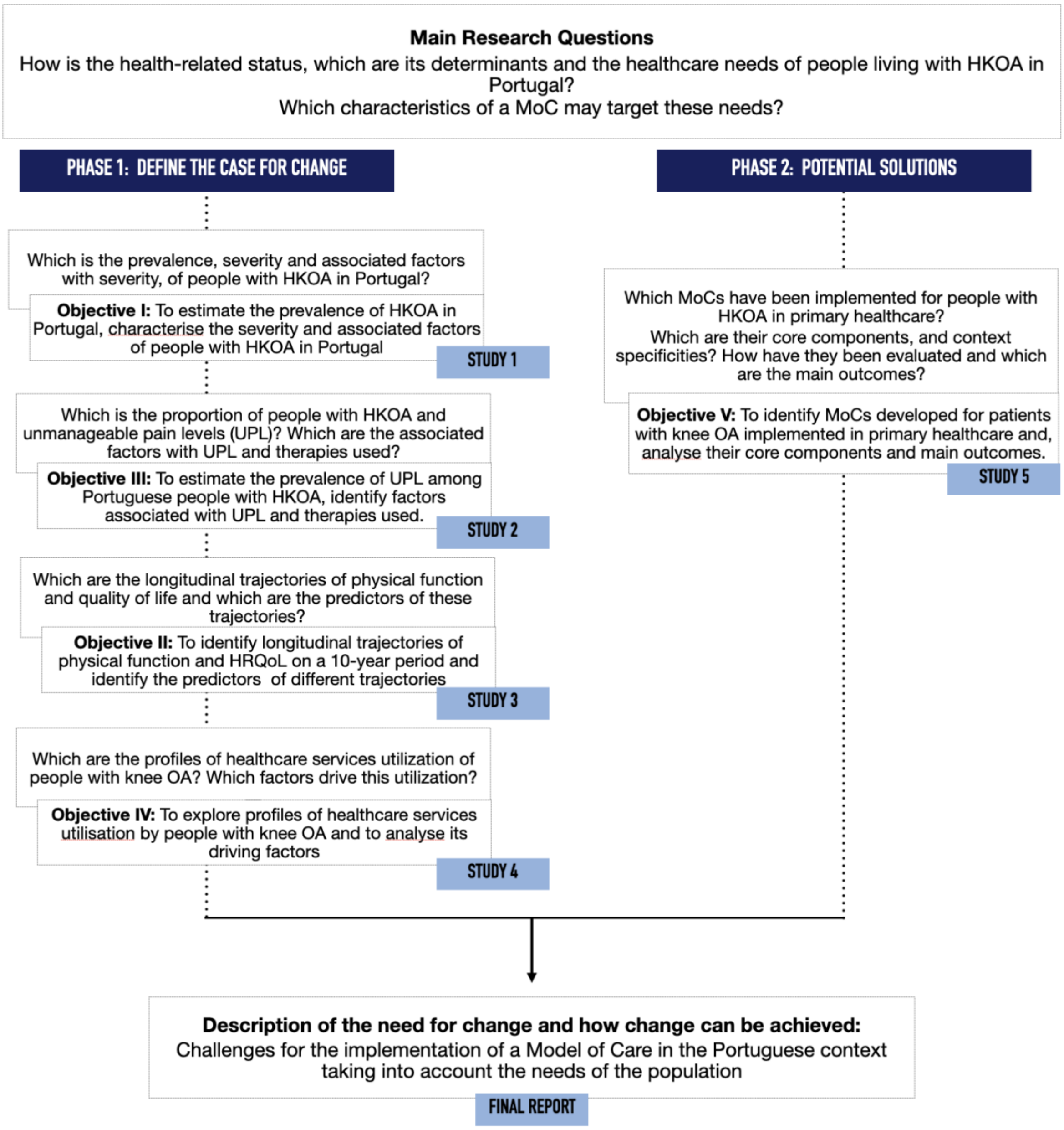
Phase 2. Potential solutions - *mapping the evidence on implemented MoCs*

Mapping literature regarding the implementation of MoCs worldwide may allow us to understand the multi-level components, context and benefits where MoCs were implemented with success, and to what extent this can be adapted to Portugal and other contexts. However, no studies with a systematic methodology that aimed to identify MoCs for people with Osteoarthritis were found.

Therefore, we found that would be crucial to identify MoCs developed for people with HKOA that have been implemented worldwide in primary healthcare, understand what and how care was provided and to what extent the implementation has been successful. As such, the fifth objective of this thesis is:

V. To identify MoCs developed for patients with knee OA implemented in primary healthcare and, analyse their core components and outcomes.

Taking into account the main goal of this study, with the information on what needs to change (Phase 1) and how change can be achieved (Phase 2), we will be able to understand the challenges to implementing a MoC for people with HKOA in the Portuguese context.



Main Research Questions

How is the health-related status, which are its determinants and the healthcare needs of people living with HKOA in Portugal?

Which characteristics of a MoC may target these needs?

Which is the prevalence, severity and associated factors with severity, of people with HKOA in Portugal?

Objective I: To estimate the prevalence of HKOA in Portugal, characterise the severity and associated factors of people with HKOA in Portugal

Which is the proportion of people with HKOA and unmanageable pain levels (UPL)? Which are the associated factors with UPL and therapies used?

Objective III: To estimate the prevalence of UPL among Portuguese people with HKOA, identify factors associated with UPL and therapies used.

Which are the longitudinal trajectories of physical function and quality of life and which are the predictors of these trajectories?

Objective II: To identify longitudinal trajectories of physical function and HRQoL on a 10-year period and identify the predictors of different trajectories

Which are the profiles of healthcare services utilization of people with knee OA? Which factors drive this utilization?

Objective IV: To explore profiles of healthcare services utilisation by people with knee OA and to analyse its driving factors

Which MoCs have been implemented for people with HKOA in primary healthcare?

Which are their core components, and context specificities? How have they been evaluated and which are the main outcomes?

Objective V: To identify MoCs developed for patients with knee OA implemented in primary healthcare and, analyse their core components and main outcomes.

Description of the need for change and how change can be achieved:

Challenges for the implementation of a Model of Care in the Portuguese context taking into account the needs of the population

Figure 3 – Schematic overview of the research questions, objectives and studies of the thesis.

4. MATERIALS AND METHODS

To answer the research questions and accomplish the specific objectives of this thesis five studies, organized in two phases, were conducted. The materials and methods used in each study are described in detail as an integral part of published or submitted articles. A general description of the methods for each study, as well as some noteworthy details that were not presented in the individual articles, is provided below.

Phase I: Define the case for change

All studies (1 to 4) in this first phase used the data from the EpiDoc study (2011-2021) that initially aimed to estimate the prevalence and burden of Rheumatic and Musculoskeletal diseases (RMDs).

Data Source

EpiDoc is a prospective closed cohort study that included a national representative sample of non-institutionalised adults (≥18 years old) that live in private households in Portugal Mainland and Islands (Azores and Madeira). The EpiDoC cohort was conducted in four waves: EpiDoC 1 – EpiReumaPt (September 2011- December 2013); EpiDoC 2 (March 2013 – July 2015); EpiDoC 3 (September 2015-July 2016); and the most recent wave EpiDoC 4 (March-August 2021).

In EpiDoc 1 (EpiReumaPt) there were three stages of data collection. The first stage of EpiDoc 1 (EpiReumaPt) aimed to screen rheumatic and musculoskeletal diseases in the Portuguese population. The participants of EpiDoC 1 were selected through a process of multistage random sampling, and stratified according to the Portuguese statistic regions NUTS and the size of the population. Candidate households were selected through a random selection of addresses on the maps of each locality(115).

Face-to-face structured interviews were conducted by a team of trained interviewers (non-physicians). A structured questionnaire using a computer-assisted personal interview (CAPI) system was used to collect health-related data and screen RMDs. A positive screening for RMDs was considered if the participant mentioned a previously known RMD; if any of the applied disease-specific algorithms for RMD were positive; or if the participant reported muscle, vertebral or joint pain in the previous 4 weeks. This stage enrolled 10 661 participants, of which 7451 participants had a positive screening for RMDs (115).

The participants who screened positive for RMD plus 20% of healthy individuals were invited to participate in the second stage of EpiDoC 1, which consisted of a structured clinical appointment with a rheumatologist, to ascertain the RMD diagnosis, according to validated criteria. The rheumatologists were blinded to the previous information and received instructions on how to conduct the history and physical examination, following a standardized protocol. During the appointments, laboratory testing and radiographic examinations were performed in order to confirm the diagnostic hypothesis (115).

In the third stage of EpiDoC 1, a group of expert rheumatologists review all the collected data (stage 2) and validated the diagnosis. Of the 3877 participants enrolled in clinical appointments, 3198 received a positive diagnosis of RMD. From these, 199 participants received the diagnosis of hip OA, 981 participants received the diagnosis of knee OA, and 1087 had the diagnosis of hip and/or knee OA (115).

For the main sample, sample weights were calculated as the inverse of the inclusion probabilities, taking into account the sampling design, according to CENSUS 2011. The stratification of participants was firstly based on NUTS and the number of inhabitants per locality. Then households were selected by a pseudo-random selection procedure equivalent to the equal probability selection. Weights were calibrated crossing NUTS region, size of locality, gender and age class, to reproduce the known population totals for the crossing margins of these four variables. Considering the inclusion probabilities in the second stage of EpiDoC 1, weights were recalibrated regarding the results of screening and adjusted for non-response (115).

All individuals that participated in the first stage of EpiDoC 1 were invited to the subsequent waves – EpiDoC 2, 3 and 4. Of these, 10 153 (95.2%) signed consent forms and agreed to be contacted by telephone. The data collection in the following waves was performed by trained research assistants, with a telephone interview. This interview was composed of a core questionnaire to collect data on socioeconomic status, a new diagnosis of chronic non-communicable diseases, health-related quality of life, physical function and healthcare resource consumption to gather longitudinal data. Additionally, each wave had also other specific questions regarding lifestyles and health-related data, not used in this thesis (115,116). EpiDoC 2 included n=7591 (71.2% from EpiDoC 1 sample), EpiDoC 3 included n=5653 participants (55.7% from EpiDoC 1 sample), and EpiDoC 4 included 3757 participants (37.0% of the EpiDoC sample).

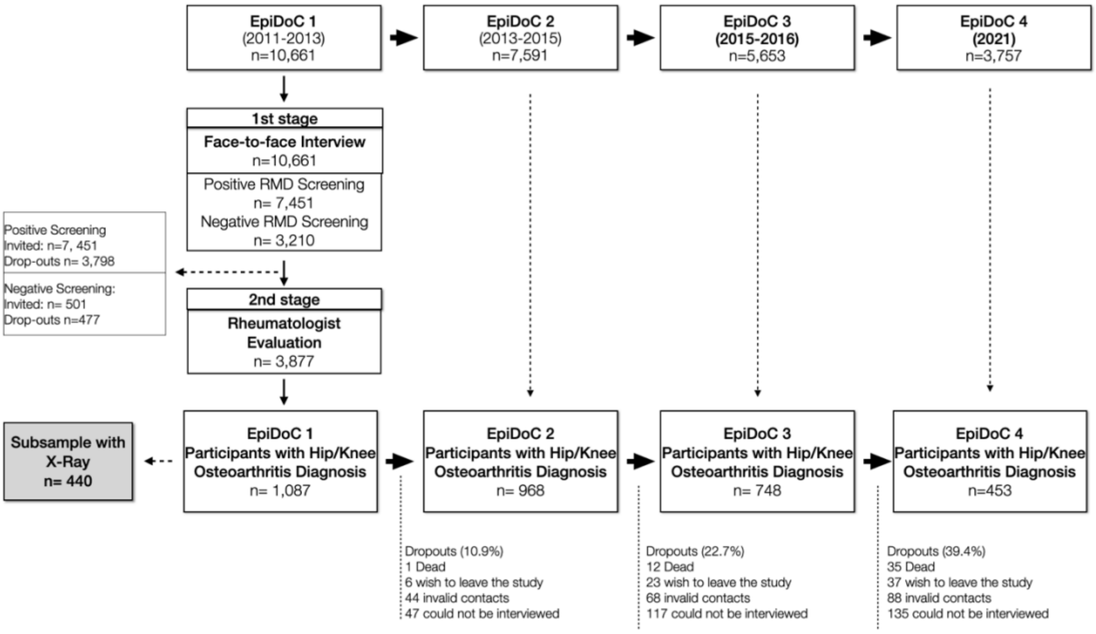


Figure 4 - EpiDoC Cohort study flow diagram

Study Population

In study I-III we analysed a sub-sample of the EpiDoC 1 database that included the participants with a validated diagnosis of hip and/or knee OA by a rheumatologist (stage 3 of EpiDoC 1), according to the ACR criteria, previously defined in the background section (48,49). In study IV, the included sample was limited to participants with a validated diagnosis of knee OA (49).

Methods

In studies I-IV, variables collected with the structured interview in the first stage of EpiDoC 1 in four domains, were included in the analysis:

Sociodemographic and anthropometric: age, sex, geographic location (NUTS II), marital status, years of education, employment status, health insurance, body mass index (m^2/kg)
Lifestyle: alcohol, smoking and physical activity/exercise habits
Health-related: number of comorbidities and multimorbidity, anxiety and depression symptoms, quality of life and physical function
Healthcare services utilization: medical appointments (number and speciality) and if attended to physiotherapy or psychology, had surgery or was hospitalised, considering

the previous 12 months; and regular medication intake (according to the Anatomical Therapeutic Chemical Classification System);

Physical function was measured with the final score of the Health Assessment Questionnaire (HAQ) (117), quality of life was measured with the index score of the European Quality of Life Survey with five dimensions and three levels (EQ-5D-3L) (118) and symptoms of anxiety and depression with the final score of Hospital Anxiety and Depression Scale (HADS-A and HADS-D, respectively) (119).

We also included HKOA-specific variables, collected during the second stage of EpiDoC 1 (clinical appointment) in studies I, II and III. For participants with knee OA, the Knee Injury and Osteoarthritis Outcome Scale (KOOS) – validated Portuguese version (120), and for participants with hip OA the Hip Disability and Osteoarthritis Outcome Scale (HOOS) – validated Portuguese version, was used (121). These instruments evaluate short-term and long-term clinical severity of HKOA, separately in five dimensions: pain, symptoms, activities of daily living, sports and recreation, and quality of life. Scores for each dimension are transformed in a 0-100 scale with zero representing extreme knee problems and 100 no knee problems. A final composite score was calculated with the mean score of each dimension – HOOS5/KOOS5 (122). Pain intensity was evaluated, specifically for each joint, with the Numeric Pain Rating Scale (NPRS), ranging from 0 to 10 where 0 indicates no pain and 10 the worst pain, as the mean level of the last week. Manageable and unmanageable pain levels were considered if <5 or ≥5 points in NPRS, respectively (123).

Simple X-rays were performed to examine 122 hips and 479 knees, among other joints, according to participants' musculoskeletal complaints. The radiographic severity of HKOA was evaluated with X-rays and graded with Kellgren and Lawrence classification (K-L) (47) and included in the analysis of study I.

For HOOS/KOOS, NPRS and K-L X-ray classification, for people with HKOA in more than one joint (left and right and/or hip and knee), the worst score was considered in the studies where these variables were included.

The longitudinal analysis performed in study III included the HAQ scores and EQ-5D-3L index score of the participants with HKOA, collected in EpiDoC 1 and also in the three follow-up waves (EpiDoC 2-4).

Summary of data analysis in each study

Study 1 – Factors Associated with Clinical and Radiographic Severity in People with Osteoarthritis: A Cross-Sectional Population-Based Study – Objective I

The outcomes of this study were clinical and radiographic severity, as described in Section 5.1. Clinical severity was evaluated with the HOOS5/KOOS5 score tertile sample distribution. Participants were categorised into low (65.00–100), middle (45.2–64.80), and high (0.00–45.00) tertiles clinical severity, according to HOOS/KOOS tertile distribution, since there are no validated cut-offs for this measurement tool. Radiographic severity was considered mild if K-L ≤ 2, moderate if K-L = 3, and severe if K-L = 4.

The prevalence of HKOA was estimated as weighted proportions, using the logit transformation method. Two ordinal logistic regressions, adjusted for age, sex, and multimorbidity, were computed, one for clinical and the other for radiographic severity to analyse the associations between sociodemographic, lifestyle and health-related factors.

Study 2 – Prevalence of and factors associated with unmanageable pain levels in people with knee or hip osteoarthritis: a cross-sectional population-based study – Objective III

In this study, we dichotomized participants with HKOA in the MPL subgroup (<5 points) and UPL subgroup (≥5 points), according to the NPRS score.

The prevalence of UPL among people with HKOA was estimated with weighted proportions, using the logit transformation method to calculate 95%CI. Multivariable logistic regression models and linear models, through a backward selection process, were used to identify factors associated with UPL ($p<0.05$), including other clinical outcomes, as stated in Section 5.2. Variables related to the use of therapies were considered namely, regular intake of medication for pain relief, physiotherapy attendance in the last 12 months, and previous hip or knee OA were described in both groups.

Study 3 – Trajectories of physical function and quality of life in people with osteoarthritis: Results from a 10-year population-based cohort – Objective III

This was the only study in which we used a longitudinal analysis of the EpiDoC cohort, including patients from the four waves. The outcomes of this study were the trajectories of physical function (HAQ) and HRQoL (EQ-5D-3L) across the four waves, in the 10 years between EpiDoC 1 (2011-2014) and EpiDoC 4 (2021). The sociodemographic, lifestyle and health-related variables included we collected in EpiDoC 1, as baseline variables. Data analysis included a group-based trajectory modelling analysis to identify different trajectories of physical function and HRQoL over 10 years, using finite mixtures of probability distributions based on maximum likelihood estimation, to identify clusters of individuals with similar trajectories (70). Using trajectories subgroups as outcomes, multinomial logistic regression models were performed for each outcome, as described in Section 5.3.

Study 4 – Driving factors for the utilisation of healthcare services by people with osteoarthritis in Portugal: results from a nationwide population-based study – Objective IV

In this study, we included only the patients with knee OA from the EpiDoC 1. We used healthcare utilization variables as the outcomes of this study, to perform the cluster analysis and explore different profiles of healthcare utilization. Andersen's behavioural model of healthcare utilization was used to frame the sociodemographic, health-related and lifestyle variables in predisposing characteristics, enabling factors and need variables in the statistical analysis, and to give a better practical and comprehensive overview regarding the factors associated with healthcare utilization. A two-step cluster analysis was first performed using the variables related to the healthcare services most used by people with HKOA. This was an exploratory analysis, therefore the final solution was the result of the best cluster solution in terms of statistics and also in terms of practical interpretability. With the final cluster solution as the dependent variable, multinomial regression models were performed, hierarchically using the domains of Andersen's Behavioural Model as independent variables. Further details are presented in Section 5.4.

The analysis of studies 1 and 2 were weighted and performed with SPPS complex samples 26 for macOS (IBM Corp., Armonk, NY, USA). In this procedure, the sampling weights calculated in stage two of EpiDoC 2 which takes into account the multistage sampling design, were considered during analysis. This ensures that the representativeness of the population and the sampling design effect was taken into account in these studies. Study 4 also used SPSS 26 for macOS (IBM Corp., Armonk, NY, USA), however, this study did not use sample weights. Study 3 was performed with STATA v16.1, using the *traj* plugin for the trajectory analysis (124), supported by a statistician from the EpiDoC unit. All the analyses considered a significance level of $p<0.05$ with 95%CI.

Ethical issues

The EpiReumaPt study was approved by the Ethics Committee of NOVA Medical School and the Portuguese Data Protection Authority (*Comissão Nacional de Proteção de Dados*). Written informed consent was obtained from all participants under the Declaration of Helsinki (115). The EpiDoC cohort data analysed in this thesis were provided by the EpiDoC Unit – CEDOC by permission (Appendix 1), after the ethical approval for the data analysis of the Ethics Research Committee NMS|FCM-UNL (nr. 09/2021/CEFCM, Appendix 2).

Phase 2. Potential solutions – mapping the evidence of implemented MoCs

Study V: Models of Care for Patients with Knee Osteoarthritis in Primary Healthcare: A Scoping Review – Objective V

The fifth study of this thesis aims to identify MoCs developed for patients with knee OA implemented in primary healthcare and analyse their core components and outcomes.

Given the expected diversity of healthcare contexts and the heterogeneity of study designs and methods to assess the implementation of proposed solutions, this review aimed to provide a broad overview of the evidence for MoCs for people with knee OA using a scoping review methodology.

In general, scoping reviews aim to map the literature on a particular topic and explore the underpinnings of a research area, as well as identify and clarify the key concepts, theories, sources of evidence, and gaps in the research (125). Scoping reviews differ from systematic reviews in that they do not focus on a narrowly defined question, but usually address broader and emerging topics (126).

In this scoping review, we used a transparent systematic methodology to analyse and synthesize literature regarding the implementation of MoCs for knee OA in primary care. A scoping review protocol was developed and published before starting the main review (127). This scoping review follows the established methodological frameworks proposed by Arksey and O'Malley (126), enhanced by Levac et al (128) and Joanna Briggs Institute (JBI) (129). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension (PRISMA) for Scoping Reviews guided the development of this scoping review to ensure transparency in reporting of the results.

This scoping review aimed to answer the following research questions:

- Which MoCs have been implemented for non-institutionalised patients with knee OA attending primary healthcare units?
- What are the components included in MoCs interventions (care pathway, healthcare interventions, programs duration, healthcare professionals involved and settings considered)?
- Which are the aspects of the included MoCs that are context-specific at external, organisational and population level?
- How was the MoC developed, organized and implemented (theories/models used, health professionals training, coordination of care)?
- How MoCs outcomes have been measured and what are the main results, if any?

Using the mnemonic PCC (Population – people with knee OA; Concept – MoCs and Context – primary care), a comprehensive search on peer-reviewed (PubMed (MEDLINE), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science Core Collection) and grey literature databases (WHO IRIS and Open Grey database) were conducted. As several grey literature databases were unavailable at the time of the search, or the search process in the database was not optimized, the MedNar engine was used to ensure that a systematic search was carried out in grey literature, through a deep web search (130). A hand search in relevant journals and relevant organizations as well as reference screening of relevant reviews and included studies were also performed. Further details are provided in Sections 5.5 and 5.6. With this scoping review, it would be possible to identify types of the available evidence, examine how research has been conducted, identify key characteristics of implemented MoCs, and analyse knowledge gaps, as well as inform the need for a future systematic review on the implementation of MoCs (125).

5. RESULTS

5.1. Study 1: Factors associated with clinical and radiographic severity in people with osteoarthritis: a cross-sectional population-based study

Daniela Costa, Eduardo B. Cruz, Catarina Silva, Helena Canhão, Jaime Branco, Carla Nunes, Ana M. Rodrigues. Factors Associated With Clinical and Radiographic Severity in People With Osteoarthritis: A Cross-Sectional Population-Based Study. Front Med (Lausanne). 2021 Nov 15;8:773417. doi: 10.3389/fmed.2021.773417. PMID: 34869491; PMCID: PMC8634437.

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Factors Associated With Clinical and Radiographic Severity in People With Osteoarthritis: A Cross-Sectional Population-Based Study

Daniela Costa[1,2,3]*, *Eduardo B. Cruz*[2,4], *Catarina Silva*[2,3], *Helena Canhão*[2,3],
Jaime Branco[2,3,5], *Carla Nunes*[1,2] *and Ana M. Rodrigues*[2,3,6]

[1] NOVA National School of Public Health, Public Health Research Centre, Universidade NOVA de Lisboa, Lisbon, Portugal, [2] Comprehensive Health Research Centre, Universidade Nova de Lisboa, Lisbon, Portugal, [3] EpiDoC Unit, Chronic Diseases Research Centre (CEDOC), NOVA Medical School, Universidade NOVA de Lisboa, Lisbon, Portugal, [4] Physiotherapy Department, School of Health, Polytechnic Institute of Setúbal, Setúbal, Portugal, [5] Rheumatology Unit, Centro Hospitalar Lisboa Ocidental (CHLO-E.P.E.), Hospital Egas Moniz, Lisbon, Portugal, [6] Rheumatology Unit, Hospital dos Lusíadas, Lisbon, Portugal

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Edited by:
Francisco Airton Castro Rocha,
Faculdade de Medicina da
Universidade Federal do Ceará, Brazil

Reviewed by:
Ibsen Coimbra,
State University of Campinas, Brazil
Benny Antony,
University of Tasmania, Australia

***Correspondence:**
Daniela Costa
dcosta.ft@gmail.com

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Background: Hip/knee osteoarthritis (HKOA) is a leading cause of disability and imposes a major socioeconomic burden. The aim of this study is to estimate the prevalence of HKOA in Portugal, characterised the clinical severity of HKOA in the population, and identified sociodemographic, lifestyle, and clinical factors associated with higher clinical and radiographic severity.

Methods: Participants with a diagnosis of HKOA from the EpiReumaPt study (2011–2013) were included (n = 1,087). Hip/knee osteoarthritis diagnosis was made through a structured evaluation by rheumatologists according to American College of Rheumatology criteria. Clinical severity was classified based on Hip Disability and Osteoarthritis Outcome Scale (HOOS) and Knee Injury and Osteoarthritis Outcome Scale (KOOS) score tertiles. Radiographic severity was classified based on the Kellgren-Lawrence grades as mild, moderate, or severe. Sociodemographic lifestyle and clinical variables, including the presence of anxiety and depression symptoms, were analysed. Factors associated with higher clinical and radiographic severity were identified using ordinal logistic regression models.

Results: Hip/knee osteoarthritis diagnosis was present in 14.1% of the Portuguese population [12.4% with knee osteoarthritis (OA) and 2.9% with hip OA]. Clinical severity was similar between people with hip (HOOS = 55.79 ± 20.88) and knee (KOOS = 55.33 ± 20.641) OA. People in the high HOOS/KOOS tertile tended to be older (64.39 ± 0.70 years), female (75.2%), overweight (39.0%) or obese (45.9%), and had multimorbidity (86.1%). Factors significantly associated with higher clinical severity tertile were age [55–64 years: odds ratio (OR) = 3.18; 65–74 years: OR = 3.25; ≥75 years: OR = 4.24], female sex (OR = 1.60), multimorbidity (OR = 1.75), being overweight (OR = 2.01) or obese (OR = 2.82), and having anxiety symptoms (OR = 1.83). Years of education was inversely associated with higher clinical severity. Factors significantly associated with higher radiographic severity were age (65–74 years: OR = 3.59; ≥75 years: OR = 3.05) and being in the high HOOS/KOOS tertile (OR = 4.91). Being a female and live in Lisbon or in the Centre region were inversely associated with the higher radiographic severity.

Conclusion: Hip/knee osteoarthritis is present in ∼1.1 million of Portuguese people. Age, educational level, and obesity are independently associated with HKOA clinical severity, whereas age, sex, geographic location, and clinical severity are independently associated with radiographic severity.

Keywords: prevalence, hip osteoarthritis, knee osteoarthritis, clinical severity, radiographic severity

INTRODUCTION

Osteoarthritis (OA), which is the most common articular disease, is a leading cause of chronic disability and a major public health problem (1). Globally, more than 300 million people have hip and/or knee osteoarthritis (HKOA), which is responsible for 9.6 million years lived with disability, and its incidence and prevalence continue to rise (2).

Worldwide, the direct annual mean cost per patient with HKOA is estimated to be 6.7 k€, reaching 10.8 k€ if patients undergo total joint replacement (3). Moreover, the annual indirect cost per patient may surpass the direct cost and is estimated to range from 0.2 k€ to 12.3 k€ (3). Portugal has the highest growth rate of total joint replacement among Organisation for Economic Co-operation and Development countries, with a 20% increase in incidence between 2005 and 2011 (4). Additionally, indirect costs due to premature exit from work represent 0.4% of the Portuguese gross domestic product (5).

Overweight and high body mass index (BMI), physical inactivity, previous joint injuries, and ageing are the main risk factors for the onset and severity of HKOA (6). Data from the EpiReumaPt study reveals that, in the Portuguese population, female sex, higher age, multimorbidity, low levels of physical activity, and physical disability are associated with the diagnosis of OA among adults with ≥50 years old (7). Similar to other middle- and high-income countries (8), Portugal is an ageing country, in which 80% of older adults are overweight and 75% of the adult population is physically inactive (9). Therefore, the prevalence of HKOA and its associated socioeconomic burden is expected to increase exponentially over the next decades (10).

People with HKOA often experience chronic pain, fatigue, sleep problems, disability, impaired quality of life, with a consequent negative impact on mental health, which progressively limits their participation in social, leisure, and occupational activities (1, 11). People with HKOA have heterogeneous presentations and disease severity depending on factors such as structural joint damage, the presence of non-communicable diseases (e.g., diabetes, obesity), risk factor exposure, age of symptom onset, and psychosocial factors (12). Therefore, radiographic and clinical severity are important predictors of individual burden and healthcare service utilisation (13). Although there is no consensus on the gold standard for evaluating HKOA severity, the general recommendation is to use a combination of radiographic and clinical severity measures (14).

Internationally, much attention has been paid to suboptimal outcomes of HKOA at the patient and system levels, as epidemiological data raise concerns about the severity of HKOA and the escalating burden of this disease (15). However, in Portugal, there are little available epidemiological data on the severity of HKOA and its associated factors. Thus, we aimed to estimate the prevalence of HKOA in Portugal, characterise the clinical severity of HKOA in the population, and identify sociodemographic, clinical, and lifestyle factors associated with clinical and radiographic severity. This information is crucial for obtaining a better understanding of the individual burden of HKOA, estimating future increases in health resource demands, and identifying needs for implementing prevention and management strategies for people with HKOA.

MATERIALS AND METHODS

Data Source

This study was developed under the scope of EpireumaPt, a national cross-sectional population-based study that aims to comprehensively assess the burden of rheumatic and musculoskeletal diseases (RMDs) in Portugal. EpiReumaPt includes a representative sample of the Portuguese population that was assessed to identify and characterise the population with RMD in Portugal (16). The study included non-institutionalised adults (≥18 years old) who lived in private households in Portugal Mainland and Islands (Madeira and Azores). Recruitment was conducted between September 2011 and December 2013 through a process of multistage random sampling of private households in Portugal stratified according to administrative territorial units (NUTS II: Norte, Centro, Lisboa and Vale do Tejo, Alentejo, Algarve, Azores, and Madeira) and the size of the population within each locality. In total, 28,502 households were contacted, 8,041 individuals refused to participate, and 10,661 individuals completed the interviews (**Figure 1**).

The EpireumaPt methodology consisted of a three-stage approach (**Figures 2**) (16). In the first stage, participants completed a face-to-face interview to collect sociodemographic and health-related information and to screen for RMDs. A person was considered to have a positive screening if they mentioned a previously known RMD, if any algorithm in the screening questionnaire was positive, or if they reported muscle, vertebral, or peripheral joint pain in the previous 4 weeks. Interviews were conducted by a team of non-medical healthcare professionals

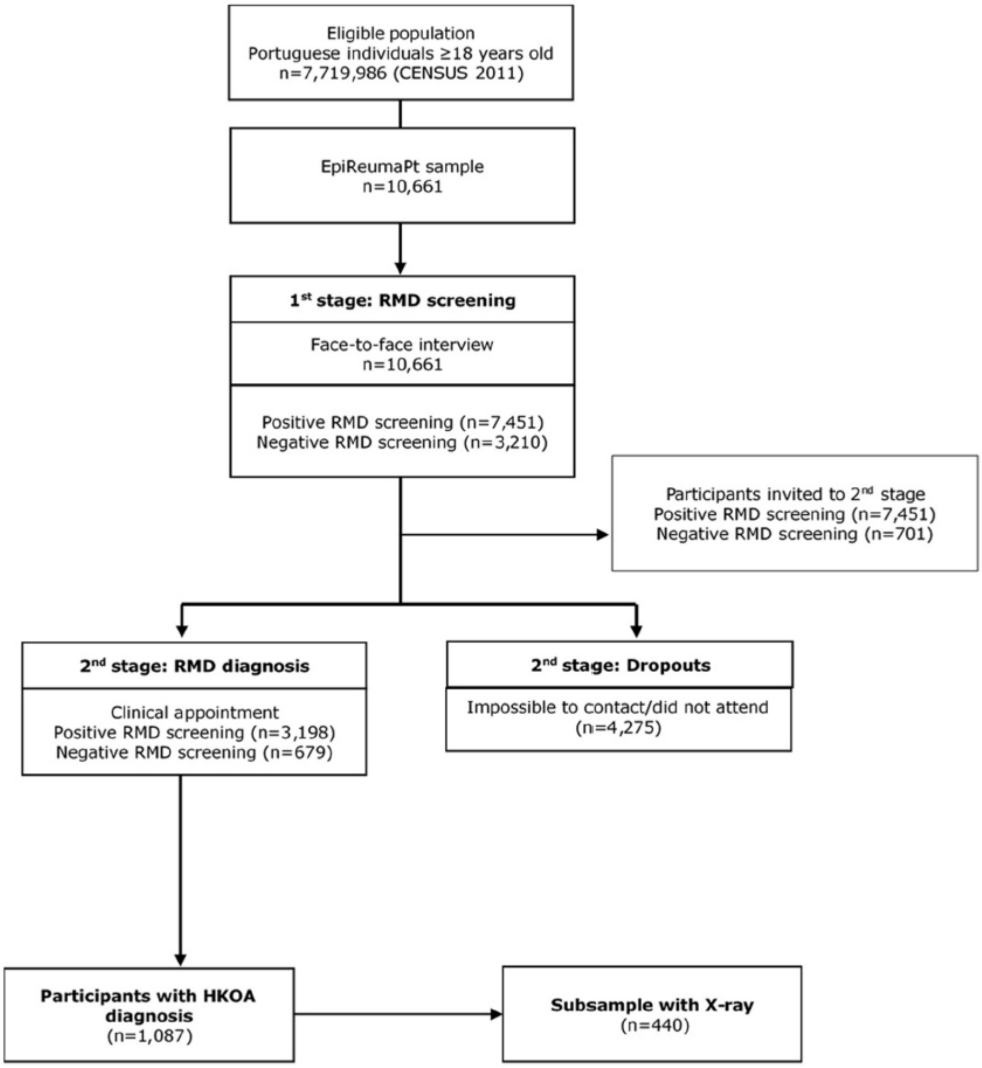

FIGURE 1 | EpiReumaPt study flowchart.

who were trained for this purpose, and data were collected using a computer-assisted personal interview system.

Participants who screened positive for at least one RMD ($n = 7{,}451$) and ∼20% ($n = 701$) of participants with negative screening for RMDs were invited for the second stage, which consisted of a clinical appointment with a rheumatologist. Of these participants, 4,275 did not attend the clinical appointment. Therefore, at the end of stage two, there were 3,877 clinical observations; 3,198 participants received a confirmation of RMD, and 679 did not have an RMD. Clinical assessments were performed at the primary care centre within the participant's neighbourhood by a multidisciplinary team consisting of a rheumatologist, X-ray technician, and nurse. Clinical appointments consisted of a structured evaluation, laboratory, and imaging exams, if needed, to establish the diagnosis and evaluate disease-related information. Simple X-rays were performed for 122 hips and 479 knees, among other joints, according to participants' musculoskeletal complaints. The rheumatologists involved were blind to prior health-related data.

In the third stage, three rheumatologists reviewed all data and validated the diagnoses. Diagnostic agreement among the three rheumatologists was 98.3% with a Cohen's K coefficient of 0.87 [95% confidence interval (CI): 0.83, 0.91] (16). When data were insufficient to fulfil international classification criteria for each RMD, an additional meeting with the rheumatologists took place in order to reach agreement on the final diagnosis. When doubts persisted, the opinion of the rheumatologist who performed the clinical assessment in the second stage prevailed.

As the EpiReumaPt population is similar to the Portuguese population (CENSUS 2011), weights were calculated and calibrated according to age strata, sex, size of locality, and NUTS II in the first stage of the study to reproduce the known population totals for the crossing margins of these four variables. In the second stage, weights were recalibrated taking into account the inclusion probabilities considering the results of screening, and adjusted for non-response, as described in detail elsewhere (16).

Study Population

This study included participants in the EpiReumaPt study with a validated diagnosis of HKOA according to American College of Rheumatology diagnosis criteria (17, 18).

Outcomes

The outcomes of this study were measures of HKOA clinical and radiographic severity, which were assessed in the second stage of EpireumaPt, during clinical appointments. Clinical severity was evaluated with Portuguese versions of the Knee Injury and Osteoarthritis Outcome Scale (KOOS) (19) and Hip Disability and Osteoarthritis Outcome Scale (HOOS) (20). These self-reported outcome measures evaluate short-term and long-term consequences of HKOA in five dimensions: pain, symptoms, activities of daily living, sports and leisure, and quality of life. Scores for each dimension are transformed into a 0–100 scale, with 0 representing extreme hip/knee problems and 100 representing no hip/knee problems (19, 20). A final composite score (HOOS/KOOS) was calculated with the mean score of each dimension as previously recommended (21). Relationships between the core OA domains of pain, function, and quality of life are complex, fluctuate over time, and are intimately related to each other. Therefore, a composite score is considered optimal for capturing the multidimensional features of OA (22). We computed the tertile of the sample score distribution to categorise participants into low (65.00–100), middle (45.2–64.80), and high (0.00–45.00) tertiles of clinical severity, because there are no validated cut-offs for this measurement tool (23).

For radiographic severity, the Kellgren-Lawrence (K-L) system was used to classify joint structural deterioration using antero-posterior X-rays into four severity grades: grade 0 (normal), grade 1 [doubtful joint space narrowing (JSN) and possible osteophytic lipping], grade 2 (definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph), grade 3 (multiple osteophytes, definite JSN, sclerosis, possible bony deformity), and grade 4 (large osteophytes, marked JSN, severe sclerosis, and definite bony deformity) (24). We considered the radiographic severity of HKOA as mild if $\text{K-L} \leq 2$, moderate if $\text{K-L} = 3$, and severe if $\text{K-L} = 4$ (25).

For both outcome measures, if more than one joint was affected, the joint with the worse score/classification was considered.

Sociodemographic, Clinical, and Lifestyle Factors

Sociodemographic, clinical, and lifestyle variables were collected during the first and second phase of EpiReumaPt.

Sociodemographic and Anthropometric Factors

Sociodemographic variables were age, sex, geographic location according to NUTS II territorial units, marital status, and education level. Madeira and Azores were merged in the analysis as the Islands region. Marital status was dichotomized as "with partner" (married or lived in consensual union) or "no partner" (single, widowed, or divorced). Education level was categorised according to years of education completed: <4 years (less than primary education), 4–9 years (primary or secondary education), or ≥10 years (secondary or superior education). Body mass index was categorised as underweight ($\leq$18.49 kg/m^2), healthy weight ($\geq$18.5 and $\leq$24.99 kg/m^2), overweight ($\geq$25 and $\leq$29.99 kg/m^2), or obese ($\geq$30 kg/m^2).

Clinical and Lifestyle Factors

Lifestyle variables included alcohol intake ("never or occasionally" or "daily" intake), smoking ("never" or "occasionally or daily"), and regular exercise/sports ("yes" or "no").

The number of chronic non-communicable diseases was calculated as the numeric count of the following self-reported conditions: high blood pressure, high cholesterol, cardiac disease, diabetes mellitus, chronic lung disease, problems in the digestive tract, renal colic, neurological disease, allergies, mental or psychiatric illness, cancer, thyroid or parathyroid problems, hypogonadism, and hyperuricemia. Multimorbidity was defined as having ≥2 chronic non-communicable diseases (26).

The presence of anxiety and depression symptoms was evaluated using depression (HADS-D) and anxiety (HADS-A) subscales of the Hospital Anxiety and Depression Scale. Both subscales have a range from 0 to 21, with higher values representing more symptoms. Final HADS-A and HADS-D scores were categorised with validated cut-offs as "anxiety symptoms" (HADS-A ≥11) or "without anxiety symptoms" (HADS-A <11) and as "depression symptoms" (HADS-D ≥11) or "without depression symptoms" (HADS-D <11) (27).

Data Analysis

Prevalence estimates were computed as weighted proportions for hip OA, knee OA, and HKOA. The logit transformation method was used to calculate 95% CIs.

Using descriptive statistics, participants with HKOA in each HOOS/KOOS tertile were characterised based on their sociodemographic, clinical, and lifestyle features. Mean scores on HOOS/KOOS subscales (symptoms, pain, activities of daily living, sports and leisure, and quality of life) for people with HKOA were plotted by age, sex, and radiographic severity (**Supplementary Material**, **Supplementary Figure 1**). The independency between HOOS/KOOS tertile and K-L classification was analysed using chi-square independency tests with a significance level based on adjusted F ($p < 0.005$).

Differences between HOOS/KOOS tertiles were analysed using *t*-tests for continuous variables and chi-square independency tests ($p < 0.05$) for categorical variables. As only a subsample of participants received X-rays ($n = 440$), we performed tests for independency of sociodemographic, clinical, and lifestyle characteristics between participants with and without X-rays to better interpret the final results (**Supplementary Material, Supplementary Table 1**).

To analyse variables associated with HOOS/KOOS tertile and K-L classification, two separate ordinal regression models were computed. During this stage of the analysis, age classes were merged as <55 years old, 55–64 years old, 65–74 years old, and ≥75 years old, and BMI categories were merged as normal or underweight (<25.00 kg/m^2), overweight (25–29.99 kg/m^2), and obese (≥30.00 kg/m^2), due to low frequencies in some categories.

For each ordinal regression model, during univariate analysis, a level of significance of 0.25 for relationships between each independent variable and the outcome was considered as the cut-off to enter in the multivariable ordinal regression model, to avoid early exclusion of potentially important variables (**Supplementary Material, Supplementary Table 2**) (28). Sociodemographic and anthropometric, clinical, and lifestyle variables were tested in the univariate analysis. Before running the models, the assumption of proportional odds and multicollinearity were validated, and independent variables with bivariate correlations above $r > 0.75$ were excluded (29).

The logit link function (29) was used because it improved the performed of both multivariable ordinal regression models according to their classification properties and McFadden Pseudo-R^2. This function computed proportional odds ratios (ORs) with 95% CIs. We used a stepwise procedure to construct the final models. Thus, in the first step, all socio-demographic and anthropometric, clinical and lifestyle variables that reached a significance level $p < 0.25$ in the univariate analysis were included. In the following steps, the variables less associated with the outcome were removed one by one, until we reached the final models, where only significant variables remained. The ordinal regression models were adjusted for sex, age, presence of multimorbidity, and BMI, which are known factors associated with HKOA severity, with potential counfounding effect. Therefore, we forced the entry of these variables in all steps. As participants with missing data were automatically excluded from this analysis, K-L classification was not included in the HOOS/KOOS model. Model fit was evaluated using McFadden Pseudo-R^2. All analyses were weighted and performed with SPPS Complex Samples 26 for MacOS (IBM Corp., Armonk, NY, USA).

RESULTS

The weighted prevalence estimate of HKOA in Portugal was 14.1% (95% CI: 12.6, 15.7, weighted n = 1,138,264), with the knee being the most affected joint [knee: 12.4% (95% CI: 11.1, 13.9, weighted n = 1 002 192), hip: 2.9% (95% CI: 2.3, 3.7, weighted n = 238 038)] (**Table 1**). The prevalence of HKOA increased across each age class, being present in 40.9% (95% CI: 34.3, 47.8) of people ≥75 years old, and was more prevalent in women (17.5%, 95% CI: 15.3, 19.9). Clinical severity, according to HOOS/KOOS ($n = 996$), was similar between participants with hip OA and knee OA (HOOS = 55.79 ± 20.88, KOOS = 55.33 ± 20.641).

TABLE 1 | Estimated prevalence of HKOA by sex, age, and severity.

	Hip and/or Knee OA n = 1,087	**Knee OA n = 981**	**Hip OA n = 199**
Total prevalence % (95% CI)	14.1 (12.6–15.7)	12.4 (11.1–13.9)	2.9 (2.3–3.7)
Total prevalence weighted counts (*n*)	1,138,264	1,002,192	238,038
Prevalence by sex % (95% CI)			
Male	10.4 (8.5–12.7)	8.5 (7.0–10.4)	2.9 (1.9–4.3)
Female	17.5 (15.3–19.9)	16.0 (13.9–18.2)	3.0 (2.4–3.8)
Prevalence by age % (95% CI)			
<45 years old	1.8 (1.1–2.8)	1.5 (0.4–0.9)	0.4 (0.2–0.9)
45–54 years old	14.5 (11.3–18.6)	12.0 (9.3–15.3)	3.2 (1.5–6.5)
55–64 years old	24.2 (20.0–28.9)	21.5 (17.9–25.7)	4.8 (2.6–8.6)
65–74 years old	35.5 (30.1–41.4)	31.5 (26.5–36.9)	7.4 (5.7–9.6)
≥75 years old	40.9 (34.3–47.8)	37.1 (30.8–43.8)	8.6 (11.8–23.2)
Clinical severity			
HOOS/KOOS score, mean ± SD	59.6 ± 21.80	55.33 ± 20.641	55.79 ± 20.88
Radiographic severity *n* (%)			
Mild (K-L ≤ 2)	197 (48.3)	177 (48.7)	36 (62.1)
Moderate (K-L = 3)	153 (34.0)	140 (32.1)	14 (35.8)
Severe (K-L = 4)	90 (17.8)	87 (19.2)	3 (3.2)

All percentages and means ± standard deviations (SDs) are weighted.
Radiographic severity non-weighted sub-sample (n = 440): mild n = 197, moderate n = 153; severe n = 90.

Characterisation of Population by Clinical Severity

The mean age of the HKOA population was 64.39 ± 12.90 years old and increased from the lowest (57.82 ± 1.67 years old) to the high (64.39 ± 0.70) HOOS/KOOS tertile (**Table 2**). The largest proportion of the population with HKOA lived in the north of Portugal (n = 271, 35.8%), but clinical severity did not differ across Portugal regions. There was an unequal distribution of education levels across HOOS/KOOS tertiles; the high tertile contained the largest proportion of people with <4 years of education (n = 138, 38.1%) and the smallest proportion of people with ≥10 years of education (n = 18, 6.1%). More than 80% of people with HKOA were overweight (n = 387, 43.6%) or obese (n = 369, 35.8%) and were mostly in the middle and high HOOS/KOOS tertiles.

Regarding lifestyle variables, 10.7% (n = 71) of Portuguese adults with HKOA smoked, and 27.8% (n = 211) drank alcohol

TABLE 2 | Sociodemographic and anthropometric characteristics of participants with HKOA by clinical severity.

	Total	HOOS/KOOS low tertile	HOOS/KOOS middle tertile	HOOS/KOOS high tertile	*p*-Value[a]
Sample size	$n = 996$	$n = 281$	$n = 361$	$n = 354$	
Age (mean ± SD)	64.39 ± 12.90	57.82 ± 1.67	66.24 ± 0.77	64.39 ± 0.70	<0.001
<45 years old, *n* (%)	37 (6.2)	32 (93.8)	3 (3.2)	2 (3.0)	<0.001
45–54 years old, *n* (%)	129 (15.6)	59 (48.1)	47 (34.3)	23 (17.6)	
55–64 years old, *n* (%)	268 (23.4)	74 (32.5)	110 (34.9)	84 (22.9)	
65–74 years old, *n* (%)	340 (31.4)	79 (26.3)	125 (35.4)	136 (38.3)	
≥75 years old, *n* (%)	222 (23.3)	37 (19.6)	76 (34.1)	109 (46.2)	
Female, *n* (%)	720 (65.8)	180 (51.3)	265 (71.1)	275 (75.2)	<0.001
Geographic location, *n* (%)					0.240
North	271 (35.8)	82 (38.6)	88 (32.2)	101 (36.4)	
Centre	243 (27.7)	58 (25.5)	86 (27.7)	99 (30)	
Lisbon	163 (23.5)	56 (25.9)	58 (24.8)	49 (19.9)	
Alentejo	67 (6.5)	9 (3.0)	32 (9.1)	26 (7.6)	
Algarve	21 (1.8)	8 (2.2)	4 (1.0)	9 (2.2)	
Islands	231 (4.7)	68 (4.8)	93 (5.3)	70 (3.9)	
Marital status (partner), *n* (%)	639 (64.4)	191 (61.8)	228 (64.9)	220 (66.4)	0.664
Years of education, *n* (%)					<0.001
<4 years	246 (22.6)	35 (9.7)	73 (20.1)	138 (38.1)	
4–9 years	631 (62.9)	187 (67.9)	247 (65.0)	197 (55.8)	
≥10 years	117 (14.4)	58 (22.3)	41 (14.8)	18 (6.1)	
BMI, *n* (%)					0.003
Underweight	3 (0.2)	1 (0.4)	1 (0.1)	1 (0.3)	
Normal weight	162 (20.5)	66 (28.9)	58 (16.4)	38 (15.1)	
Overweight	387 (43.6)	134 (43.8)	139 (47.6)	114 (39.0)	
Obese	369 (35.8)	72 (26.9)	143 (35.9)	154 (45.9)	

Categorical variables are presented as n (%); continuous variables are presented as mean ± SD. All percentages and means ± SDs are weighted.

[a] *p-value from independency tests: complex samples t-tests for continuous variables and Chi-square tests for categorical variables. Significance level is based on adjusted F.*

daily (**Table 3**). Few people with HKOA performed regular physical exercise ($n = 209$, 21.3%), particularly those in the high HOOS/KOOS tertile ($n = 53$, 14.4%). The overall proportion of people with HKOA who also had multimorbidity was 74.1% ($n = 756$), which was most pronounced in the high HOOS/KOOS tertile ($n = 305$, 86.1%). The proportions of people with anxiety ($n = 95$, 26.0%) and depression ($n = 85$, 23.6%) symptoms also increased in the high HOOS/KOOS tertile.

HOOS/KOOS tertiles were independent of K-L classification [$F_{(3.26;3542.35)} = 33.69$, p=0.002]. Across increasing HOOS/KOOS tertiles, the proportion of people with mild K-L classification decreased and the proportion of people with severe K-L classification increased (**Figure 2**). However, the highest clinical severity tertile was heterogeneous, consisting of 30.75% of people with mild, 39.94% of people with moderate, and 29.31% of people with severe K-L classification. Results regarding the characterisation of the population with hip and the population with knee OA are presented in **Supplementary Material, Supplementary Table 2**.

Factors Associated With Clinical Severity

In the final ordinal regression model for clinical severity, the following factors were significantly associated with a higher HOOS/KOOS tertile: being 55–64 years old (OR = 3.18; 95% CI 1.80, 5.62; $p < 0.001$), 65–74 years old (OR = 3.25; 95% CI: 1.87, 5.67; $p < 0.001$), or ≥75 years old (OR = 4.24; 95% CI: 2.26, 8.00; $p < 0.001$) compared with <55 years old; being female (OR = 1.60; 95% CI: 1.09, 2.35; $p = 0.017$); having multimorbidity (OR = 1.75; 95% CI: 1.13, 2.71; $p = 0.013$); being overweight (OR = 2.01; 95% CI 1.16, 3.48; $p = 0.013$) or obese (OR = 2.82; 95% CI: 1.62, 4.90; $p < 0.001$) compared with normal weight; and having anxiety symptoms (OR = 1.83; 95% CI: 1.20, 2.81; $p = 0.005$) (**Table 4**). On the other hand, having 4–9 years of education (OR = 0.50; 95% CI: 0.32, 0.77; $p = 0.002$) or ≥10 years of education (OR = 0.30; 95% CI: 0.17, 0.52; $p < 0.001$) were significantly and inversely associated with a higher HOOS/KOOS tertile.

Compared with the results of univariate analysis, multimorbidity (OR = 2.90; 95% CI: 1.90; 4.42; $p < 0.001$) and anxiety symptoms (OR = 1.96; 95% CI: 1.33, 2.80; $p = 0.001$), and the age stratas 55–64 (OR = 3.27; 95% CI: 1.81, 5.95; $p < 0.001$) and ≥75 years old (OR = 6.06; 95% CI: 4.33, 1.00; $p < 0.001$) were less strongly associated with clinical severity in the multivariable ordinal regression model (**Supplementary Material, Supplementary Table 3**). By contrast, the age strata 65–74 years old (OR = 2.31; 95% CI: 2.56, 7.29) and BMI (overweight:

TABLE 3 | Lifestyle and clinical characteristics of participants with HKOA by clinical severity.

	Total	HOOS/KOOS low tertile	HOOS/KOOS middle tertile	HOOS/KOOS high tertile	*p*-Value[a]
Sample size	*n* = 996	*n* = 281	*n* = 361	*n* = 354	
Lifestyle variables, *n* (%)					
Smoker	71 (10.7)	31 (17.3)	24 (9.0)	16 (5.6)	0.007
Alcohol intake (daily)	211 (27.8)	70 (33.9)	74 (26.1)	67 (23.3)	0.117
Regular exercise	209 (21.3)	81 (28.5)	75 (20.6)	53 (14.4)	0.007
Clinical variables, mean ± SD					
HOOS/KOOS	55.79 ± 20.88	79.50 ± 9.60	54.35 ± 5.91	33.21 ± 9.87	<0.001
(min–max)	(0.00–100)	(65.00–100)	(45.20–64.80)	(0.00–45.00)	
Multimorbidity (yes), *n* (%)	756 (74.1)	175 (60.0)	276 (76.4)	305 (86.1)	<0.001
Anxiety symptoms (HADS-A), mean ± SD	6.70 ± 4.21	6.0 ± 4.05	6.39 ± 4.18	7.72 ± 4.19	<0.001
HADS-A ≥ 11, *n* (%)	193 (18.5)	40 (12.9)	58 (16.6)	95 (26.0)	0.002
Depression symptoms (HADS-D), mean ± SD	6.04 ± 4.49	4.54 ± 4.07	5.97 ± 4.15	7.63 ± 4.68	<0.001
HADS-D ≥ 11, *n* (%)	159 (16.8)	25(11.5)	49 (15.1)	85 (23.6)	0.028

Categorical variables are presented as n (%); continuous variables are presented as mean ± SD. All percentages and means ± SDs are weighted.

[a] *p-value from independency tests: complex samples t-tests for continuous variables and Chi-square tests for categorical variables. Significance level is based on adjusted F.*

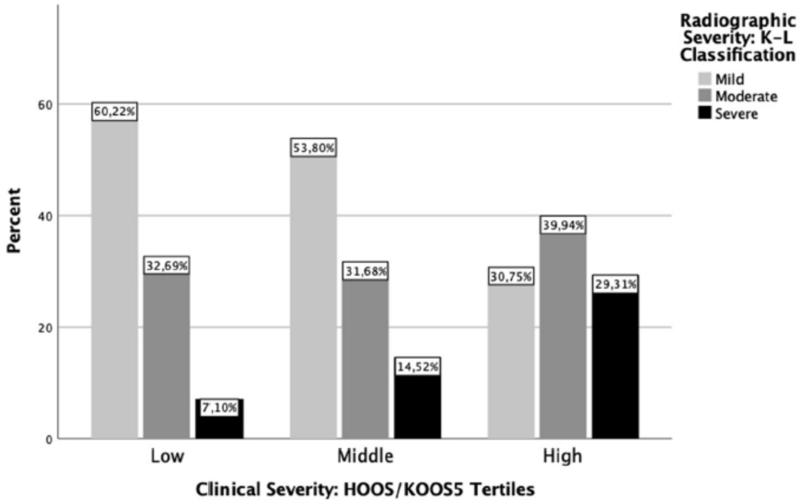

FIGURE 2 | Distribution of radiographic severity classification according to clinical severity tertile. The y-axis indicates the proportion of K-L classification grades within each HOOS/KOOS tertile, and the x-axis indicates HOOS/KOOS tertile. Bars represent K-L classification grade: mild ≥2, moderate = 3, or severe = 4.

OR = 1.87; 95% CI: 1.06, 3.30; p = 0.003; obese: OR = 2.72; 95% CI: 1.53, 4.85; p = 0.001) were more strongly associated with clinical severity in the multivariable ordinal regression model.

Factors Associated With Radiographic Severity

Regarding the subpopulation of participants who received an X-ray ($n = 440$), the final ordinal regression model for radiographic severity showed that a severe K-L classification was associated with being 65–74 years old (OR = 3.59; 95% CI: 1.43, 9.02; p = 0.007) or ≥75 years old (OR = 3.05; 95% CI: 1.13, 8.21; $p = 0.028$) compared with <55 years old and being in a high HOOS/KOOS tertile (OR = 4.91; 95% CI: 2.57, 9.40; $p < 0.001$) compared with a low HOOS/KOOS tertile (**Table 5**). By contrast, a less severe K-L classification was associated with being female (OR = 0.41; 95% CI: 0.24, 0.69; p = 0.001) and living in the Lisbon (OR = 0.23; 95% CI: 0.11, 0.48; $p < 0.001$) or Centre region (OR = 0.35; 95% CI: 0.20, 0.61; $p < 0.001$).

Compared with the results of univariate analysis, the following variables were more strongly associated with radiographic severity in the multivariable ordinal regression model: age (65–74 years old: OR = 2.60; 95% CI: 1.18, 5.71; p = 0.018; ≥75

TABLE 4 | Factors associated with clinical severity in the final multivariable ordinal regression model.

	OR (95% CI)	*p*-Value
Age		
<55 years old[a]	–	–
55–64 years old	3.18 (1.80, 5.62)	<0.001
65–74 years old	3.25 (1.87, 5.67)	<0.001
≥75 years old	4.24 (2.26, 8.00)	<0.001
Sex		
Male[a]	–	–
Female	1.60 (1.09, 2.35)	0.017
Number of non-communicable diseases		
No multimorbidity[a]	–	–
Multimorbidity	1.75 (1.13, 2.71)	0.013
Education level		
<4 years[a]	–	–
4–9 years	0.50 (0.32, 0.77)	0.002
≥10 years	0.30 (0.17, 0.52)	<0.001
BMI (kg/m^2)		
Normal or underweight (<25 kg/m^2)[a]	–	–
Overweight (25–29.99 kg/m^2)	2.01 (1.16, 3.48)	0.013
Obese (≥30 kg/m^2)	2.82 (1.62, 4.90)	<0.001
Anxiety (HADS-A)		
No anxiety symptoms (HADS-A<11)[a]	–	–
Anxiety symptoms (HADS-A≥11)	1.83 (1.20, 2.81)	0.005

Total sample included in the analysis: $n = 968$. Test of parallel lines: Wald $F_{(10)} = 0.630$; $p = 0.789$ (assumption of proportional odds validated); McFadden Psuedo-$R^2 = 0.115$. This model correctly classified 51.4% of cases. All analysis were weighted.

[a]*Reference classes.*

TABLE 5 | Factors associated with radiographic severity in the final multivariable ordinal regression model.

	OR (95% CI)	*p*-Value
Age		
<55 years old[a]	–	–
55–64 years old	1.43 (0.54, 3.79)	0.470
65–74 years old	3.59 (1.43, 9.02)	0.007
≥75 years old	3.05 (1.13, 8.21)	0.028
Sex		
Male[a]	–	–
Female	0.41 (0.24, 0.69)	0.001
Chronic non-communicable diseases		
No multimorbidity		
Multimorbidity	0.71 (0.37, 1.36)	0.300
Geographic location		
North[a]	–	–
Centre	0.35 (0.20, 0.61)	<0.001
Lisbon	0.23 (0.11, 0.48)	<0.001
Alentejo	0.64 (0.30, 1.35)	0.237
Algarve	1.40 (0.27, 7.34)	0.689
Islands	0.80 (0.24, 2.65)	0.717
BMI (kg/m^2)		
Normal or underweight (<25 kg/m^2)[a]	–	–
Overweight (25–29.99 kg/m^2)	1.61 (0.75, 3.44)	0.222
Obese (≥30 kg/m^2)	1.67 (0.77, 3.58)	0.191
HOOS/KOOS		
Low tertile[a]	–	–
Middle tertile	1.69 (0.85, 3.40)	0.137
High tertile	4.91 (2.57, 9.40)	<0.001

Total sample included in the analysis: $n = 376$. Test of parallel lines: Wald $F_{(14)} = 0.789$, $p = 0.681$ (assumption of proportional odds validated); McFadden Pseudo-$R^2 = 0.132$. This model correctly classified 54.1% of cases. All analyses were weighted.

[a]*Reference classes.*

years old: OR = 2.71; 95% CI: 1.16, 6.35; $p = 0.022$), sex (female: OR = 0.65; 95% CI: 0.42, 1.00; $p = 0.052$), and high HOOS/KOOS tertile (OR = 3.68; 95% CI: 1.82, 7.43; $p < 0.001$) (**Supplementary Material**, **Supplementary Table 4**). By contrast, geographic location (Centre: OR = 0.49; 95% CI: 0.29, 0.83, $p = 0.008$; Lisbon: OR = 0.30; 95% CI: 0.16, 0.57; $p < 0.001$) was less strongly associated with radiographic severity in the multivariable ordinal regression model.

DISCUSSION

This study shows that 14.1% of people in Portugal have HKOA, mostly involving the knee, which corresponds to the ~1.1 million people with this disease in Portugal, as previously reported (11). The Portuguese dataset used in Global Burden of Diseases report (GBD) to estimate global prevalence of OA was EpireumaPt, but no data were published on HKOA together in Portugal (11). The prevalence of OA, globally, ranges from 5.4 to 24.2% for the knee and 0.9 to 7.4% for the hip (30). According to the GBD report, Portugal, the United Kingdom, and Finland have the highest age-standardised prevalence of HKOA in Europe (4,000–4,400 per 1,000,000 individuals) (2).

Different from the present study, the cohorts in several previous studies were limited to radiographic-only diagnoses or older age classes (2, 31, 32), which may not encompass people in the early stages of the disease or with early-onset HKOA. For example, the GBD report only included people with HKOA confirmed radiologically with grades 2–4 K-L and, as such, likely underestimates the true prevalence (2, 32). Our data show that the prevalence of HKOA is higher in females and increases across each age class, being present in up to 40% of people who are ≥75 years old, consistent with previous reports (2, 31, 33, 34). Although sex differences in the incidence and prevalence of HKOA have been previously studied, they are not yet fully understood. However, early exposure to oestrogen (i.e., menarche at a younger age), parity, and menopause may provide hormonal and biomechanical explanations for the greater prevalence of OA in females (35). Furthermore, we found that risk factors for the onset and severity of OA are highly prevalent in the Portuguese population, particularly the lack of regular exercise and the presence of overweight or obesity, and are even higher than those previously reported for the overall Portuguese population (9), and compared with international HKOA cohorts (36).

Although the proportion of people with moderate and severe radiographic OA increased with greater clinical severity, we found that people in the high clinical severity tertile had heterogeneous radiographic severity classifications. This finding is supported by previous studies showing that HKOA radiographic severity is correlated with clinical severity but in a non-linear fashion (14) and is an imprecise guide for predicting clinical severity (37).

Regarding radiographic severity, >80% of people in our study had mild or moderate severity, similar to other studies (38). The Chingford Women's study, a 15-year longitudinal cohort study, concluded that 41.5% of knees worsened by at least one K-L grade over this time span, with a 3.9% annual rate of disease worsening (39). Thus, if the prevalence of HKOA is increasing (10), a higher proportion of people with mild and moderate HKOA will progress to moderate or severe HKOA at a considerable rate. People with severe HKOA are 5.3 times more likely to have surgery (13), thus increasing the demand for healthcare resources and the socio-economic impact of this disease (3).

Regarding the factors associated with HKOA severity, age was associated with both clinical and radiographic severity. All older age strata were associated with a high clinical severity tertile compared with the <55 years old stratum, whereas only age strata above 65 years old were associated with high radiographic severity. These results are consistent with the observed impact of pain and functional impairment due to HKOA on social and work activities, which can lead to absenteeism, presentism, or premature work withdrawal and negatively affect the quality of life of adults at younger ages living with HKOA (5, 40). The association of clinical and radiographic OA severity with age is well-documented in the literature (2, 31, 33, 34) and is explained by both cumulative exposure to risk factors including chronic non-communicable diseases and by biological age-related structural joint changes (41). However, we found contradictory results pertaining to the association between sex and HKOA severity. Being female was simultaneously associated with higher clinical severity and milder radiographic severity. Previous literature also reports conflicting associations between sex and the clinical severity of OA (42). Data from the European SHARE cohort reveal that women have overall disadvantages in terms of activity limitations, pain, depression, and self-reported health status compared with men (43). On the other hand, a systematic review by Bastick et al. found strong evidence that sex is not associated with radiographic severity (44). However, male sex is often linked with physically demanding jobs (e.g., firefighting, construction, mining, carpentry) and contact sports, which increases the probability of previous trauma, injuries, and structural joint damage and represents a major joint-level risk factor for OA (22).

We also found that multimorbidity was associated with greater clinical severity. Non-communicable diseases are prevalent in the HKOA population and are associated with greater utilisation of healthcare services (45). A systematic review and meta-analysis by Calders et al. likewise found that a higher non-communicable disease count is associated with the worsening of pain and performance-based physical function. Specifically, the presence of cardiac disease, hypertension, and back pain are important predictors of the deterioration of physical functioning, and diabetes is associated with worse pain (46). In addition, being overweight or obese was associated with greater clinical severity but not radiographic severity in the present study. Similarly, previous research indicates that BMI is a dose-responsive risk factor for OA clinical severity (47). However, other studies report that BMI is associated with both clinical and radiographic severity (48) and that greater mechanical load (49) and systemic inflammation due to a high BMI may play a role in OA onset and clinical and radiographic severity (50).

In addition, we found that anxiety symptoms and socioeconomic factors, such as low education, were associated with clinical severity but not radiographic severity. As previously described, anxiety is associated with worse pain and physical function trajectories (51). Moreover, previous research indicates that education is an important social determinant for several chronic diseases, including OA, and is related to lifestyle factors, a lack of preventive measures, low access to healthcare services, and low literacy levels (42, 52). Psychosocial variables such as a low level of self-efficacy, catastrophising, and pain sensitisation are also associated with poorer clinical outcomes (41). Thus, the lived experience of people with HKOA and its multifactorial influences, such as psychosocial factors, may be distinct from its structural changes, suggesting that HKOA is best framed with a biopsychosocial approach (41).

This study also revealed geographic associations, with people living in the North region having higher radiographic severity than people living in the Lisbon and Centre regions. In the northern region of Portugal, industrial employment is higher than the national average, and agriculture, forestry, construction, and manufacturing industries are important sources of employment (53). A recent systematic review concludes that people in the agriculture, construction, and metal industries have a higher probability of developing knee OA (54). Additionally, due to current sociodemographic characteristics of this region and the projected prevalence of chronic diseases and long-term disability, the northern region of Portugal is expected have a higher proportion of individuals with at least one chronic disease and long-term disability in 2031, mainly due to lower education levels (55).

Limitations

This study has some limitations that should be considered. Its cross-sectional design does not allow the establishment of a temporal relationship between associated factors and HKOA severity, thus it is not possible to establish cause-and-effect relationships between modifiable variables, such as BMI, and HKOA symptoms and physical function. The estimation of prevalence using sample weights is not free from error, although it is considered that weights should be used in all statistics analysis when dealing with complex survey data (56).

Although hip and knee OA may impose similar burdens on the domains of one's life (2, 31), some studies show that people with hip OA have greater disease severity and an earlier requirement for joint replacement (13). However, we did not thoroughly investigate differences in factors associated with hip vs. knee OA.

As HOOS and KOOS scores do not have validated cut-off values, we categorised our sample by tertile distribution. Thus, it should be noted that the low, middle, and high HOOS/KOOS tertiles do not directly correspond to mild, moderate, and severe radiographic severity. Moreover, we did not use any imputation method, given the amount of missing X-ray data, for the overall sample. The subgroup of participants who received X-rays was older, presented higher clinical severity, and had a larger number of non-communicable diseases (**Supplementary Material, Supplementary Table 1**); thus, this should be considered when interpreting the results.

"Regular exercise" was self-reported by participants and did not consider the precise amount and intensity of weekly physical activity. Hence, our data may overestimate the proportion of people who performed exercise and misrepresent the association between exercise and disease severity. Moreover, as HKOA onset and severity is multifactorial (1), several important factors may have not been included in this analysis, namely other psychosocial factors and previous injuries.

Strengths and Implications

This is the first study with a representative sample of the Portuguese population with HKOA that characterised this population and analysed factors associated with disease severity. Unlike most epidemiologic research on HKOA, the radiographic and clinical severity analyses in this study allow a deeper understanding of people with HKOA from their lived experience of the disease as well as from a structural perspective. Moreover, our case definition of people with HKOA also included people with early-onset ($\geq$18 years old) and early stages of the disease (0–4 grade K-L), allowing more accurate results.

Given the risk factors for HKOA onset and greater severity present in this study's sample and also in the overall Portuguese population (9), our study raises concerns regarding the need for preventive measures and political strategies to improve lifestyle factors and specific interventions directed at people with HKOA. Furthermore, sociodemographic and health-related data from our sample of Portuguese individuals suggest that the socioeconomic and individual burden of this disease may increase over the next decades. Clearly, there is a gap between international recommendations for physical activity and weight management in OA and current care given the small proportion of people who exercise and the large proportion of people who are overweight or obese. Adherence to behavioural strategies and access to care have already been identified as barriers to the optimization of health management among people with HKOA. Nonetheless, health professionals' lack of awareness of OA as a serious disease and lack of knowledge of current recommendations should also be taken into account by health politicians and managers to promote a collective approach to preventing and treating this disease (57).

CONCLUSIONS

Hip and/or Knee OA is present in 14.1% of the Portuguese adults. Age, female sex, multimorbidity, lower education, higher BMI, and anxiety symptoms are associated with higher clinical severity of HKOA, whereas age, geographic location, male sex, and clinical severity are associated with higher radiographic severity of HKOA. Given the cross-sectional design of this study, these factors should be interpreted as an association with higher severity, and not a cause of higher severity. Known risk factors for OA severity, such as decreased physical activity, obesity, and multimorbidity, are highly present among the population of people with HKOA in Portugal. Our findings highlight the need for effective prevention and management strategies focused on identified risk factors, namely weight management and exercise programs and control of chronic non-communicable diseases.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by the EpiDoc Unit - CEDOC by permission. Data will be shared upon request to the corresponding author with the permission of EpiDoc Unit group leaders.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of NOVA Medical School and Portuguese Data Protection Authority (Comissão Nacional de Proteção de Dados). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DC and CS contributed to the drafting of the manuscript. DC, EC, CN, and AR contributed to the analysis and interpretation of the data and statistics. HC, JB, and AR contributed to the conception and design of the main project (EpiReumaPt), provision of study materials, obtaining funding for the main project, administrative/logistic support, and collection of data. All authors critically revised and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.773417/full#supplementary-material

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Supplementary Material

SUPPLEMENTARY FIGURES

Supplementary Figure 1. HOOS/KOOS subscale scores by sex, age class, and radiographic severity.

SUPPLEMENTARY TABLES

Supplementary Table 1.

Table S1. Sociodemographic, lifestyle, and clinical characteristics of the total sample and the subsample with X-rays

	Total	**Sample with X-rays**	**p-value^{a}**
Sample size	n=996	n=440	
Age (mean±SD)	64.39±12.90	66.07±10.61	0.010
<45 years old	41 (6.3)	8 (3.1)	0.032
45-54 years old	146 (16.7)	48 (16.0)	
55-64 years old	289 (22.7)	112 (21.5)	
65-74 years old	368 (31.1)	157 (32.3)	
≥75 years old	243 (23.3)	115 (27.1)	
Female sex, n (%)	720 (65.8)	308 (67.6)	0.181
Geographic location, n (%)			<0.001
North	271 (35.8)	190 (45.4)	
Centre	243 (27.7)	109 (22.1)	
Alentejo	67 (6.5)	25 (4.6)	
Algarve	21 (1.8)	6 (0.9)	
Lisbon	162 (23.5)	88 (26.1)	
Islands	231 (4.7)	22 (0.8)	
Marital status (partner), n (%)	639 (64.4)	302 (69.8)	0.009
Education level, n (%)			0.282
<4 years	246 (22.6)	121 (25.0)	
4-9 years	631 (62.9)	275 (61.8)	
≥10 years	117 (14.4)	43 (13.1)	
BMI, n (%)			0.156
Underweight	3 (0.2)	-	
Normal weight	162 (20.5)	65 (17.4)	
Overweight	387 (43.6)	172 (45.9)	
Obese	369 (35.8)	167 (36.6)	
Lifestyle variables, n (%)			
Smoker	71 (10.7)	22 (6.7)	0.016
Alcohol consumption (daily)	480 (54.4)	232 (56.6)	0.483
Regular exercise	209 (21.3)	86 (18.8)	0.087
Clinical variables			
HOOS/KOOS, mean±SD (min-max)	55.79±20.88 (0.00-100)	51.29±19.11 (0.00-100)	<0.001
HOOS/KOOS low tertile, n (%)	281 (33.8)	88 (26.5)	0.004

HOOS/KOOS middle tertile, n (%)	361 (32.8)	131 (33.8)	
HOOS/KOOS high tertile, n (%)	354 (33.4)	169 (39.7)	
Number of non-communicable diseases, mean±SD	2.91±1.96	3.10±1.99	0.011
Anxiety (HADS-A), mean±SD	6.70±4.21	6.96±4.18	0.137
With anxiety symptoms (HADS-A≥11), n (%)	193 (18.5)	87 (18.9)	0.553
Depression (HADS-D), mean±SD	6.04±4.49	5.62±4.14	0.097
With depression symptoms (HADS-D≥11), n(%)	159 (16.8)	82 (19.3)	0.043

[a] Significance level of independency test between the subsamples with and without X-rays: complex samples t-test for continuous variables and Chi-square tests for categorical variables. All percentages and mean±SD were weighted

Supplementary Table 2.

Table S2: Sociodemographic and anthropometric, clinical and lifestyle characteristics of participants with Knee and Hip OA

	Hip OA	Knee OA
Sample size	n=199	n=981
Age (mean±SD)	63.86±12.81	66.62±12.98
<45 years old, n (%)	10 (6.7)	33 (6.2)
45-54 years old, n (%)	22 (17.7)	133 (15.6)
55-64 years old, n (%)	37 (21.4)	270 (22.9)
65-74 years old, n (%)	77 (31.0)	327 (31.3)
≥75 years old, n (%)	53 (23.2)	218 (23.9)
Female, n (%)	119 (53.3)	716 (67.0)
Geographic location, n (%)		
North	60 (37.9)	256 (33.9)
Centre	50 (29.4)	244 (27.9)
Lisbon	42 (22.4)	25.1 (163)
Alentejo	14 (6.1)	65 (6.6)
Algarve	3 (1.5)	19 (1.7)
Islands	30 (2.8)	234 (4.8)
Marital status (partner), n (%)	135 (68.7)	622 (63.6)
Years of education, n (%)		
<4 years	47(18.3)	247 (23.5)
4-9 years	124 (70)	618 (60.9)
≥10 years	27 (11.8)	115 (15.6)
BMI, n (%)		
Underweight	1 (0.6)	2 (0.1)
Normal weight	41 (27.6)	156 (19.2)

Overweight	73 (41.8)	381 (43.4)
Obese	68 (30)	370 (37.3)
Lifestyle variables, n (%)		
Smoker	10 (10.3)	71 (9.9)
Alcohol intake (daily)	61 (34.8)	200 (26.9)
Regular exercise	41 (18.4)	202 (21.2)
Clinical variables, mean±SD		
HOOS/KOOS (min-max)	59.46±21.78 (4-100)	55.33±20.64 (0-100)
Multimorbidity (yes), n (%)	149 (71.9)	747 (74.0)
Anxiety symptoms (HADS-A), mean±SD	6.49±4.30	6.65±4.15
HADS-A≥11, n (%)	35 (17.1)	188 (17.8)
Depression symptoms (HADS-D), mean±SD	5.74±4.30	5.98±4.49
HADS-D≥11, n (%)	31 (12.7)	152 (16.4)

Supplementary Table 3

Table S3. Factors associated with clinical severity in univariate ordinal regression analysis

	OR (95% CI)	**p-value**
Age class		<0.001
<55 years old[a]	-	-
55-64 years old	3.27 (1.81, 5.95)	<0.001
65-74 years old	2.31 (2.56, 7.29)	0.001
≥75 years old	6.06 (4.33, 1.00)	<0.001
Sex		
Male[a]	-	-
Female	2.29 (1.53, 3.42)	<0.001
Chronic non-communicable diseases		
No multimorbiditiy[a]	-	-
Multimorbidity	2.90 (1.90, 4.42)	<0.001
Geographic location		0.120
North[a]	-	-
Center	1.19 (0.52, 2.87)	0.472
Lisbon	0.87 (0.52, 1.44)	0.583
Alentejo	1.70 (1.04, 2.78)	0.034
Algarve	1.09 (0.38, 3.08)	0.875
Islands	0.90 (0.60, 1.36)	0.616
Marital status		
Without partner[a]	-	-
With partner	1.165 (0.79, 1.70)	0.430
Education level		<0.001
<4 years[a]	-	-
4-9 years	0.31 (0.22, 0.45)	<0.001
≥10 years	0.15 (0.09, 0.27)	<0.001
BMI (kg/m^2)		0.002
Normal or underweight (<25kg/m^2)[a]		
Overweight (25-29.99 kg/m^2)	1.87 (1.06, 3.30)	0.003

Obese (≥30 kg/m^2)	2.72 (1.53, 4.85)	0.001
Anxiety (HADS-A)		
No anxiety symptoms (HADS-A<11)[a]	-	-
Anxiety symptoms (HADS-A≥11)	1.96 (1.33, 2.80)	0.001
Depression (HADS-D)		
No Depression symptoms (HADS-D<11)[a]	-	-
Depression Symptoms (HADS-D≥11)	1.94 (1.66, 3.22)	0.011
Smoking habits		
Non-smoker[a]	-	-
Daily or occasional smoker	0.38 (0.19, 0.75)	0.005
Alcohol consumption		
Never or occasionally[a]	-	-
Daily	0.67 (0.44, 1.03)	0.065
Exercise		
No regular exercise[a]	-	-
Regular exercise	0.52 (0.34, 0.80)	0.003

[a] Reference classes

All analyses were weighted.

Supplementary Table 4.

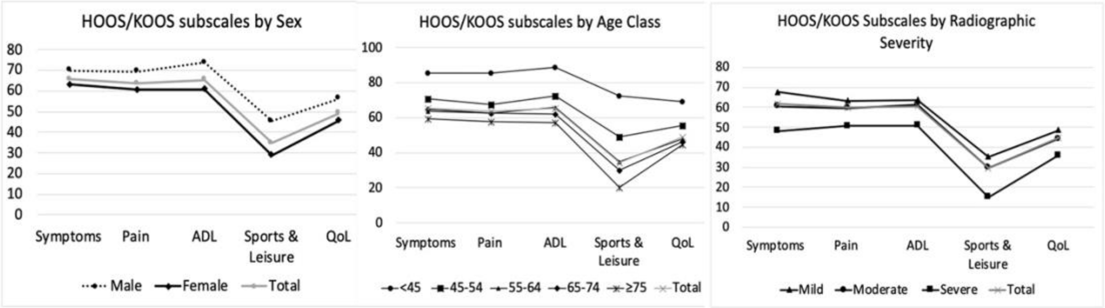
Table S4. Factors associated with radiographic severity in univariate ordinal regression analysis

	OR (95% CI)	**p-value**
Age		0.020
<55 years old[a]	-	-
55-64 years old	1.37 (0.57, 3.26)	0.478
65-74 years old	2.60 (1.18, 5.71)	0.018
≥75 years old	2.71 (1.16, 6.35)	0.022
Sex		
Male[a]	-	-
Female	0.65 (0.42, 1.00)	0.052
Chronic non-communicable diseases		
No multimorbiditiy[a]		
Multimorbidity	1.43 (0.81, 2.55)	0.220
Geographic location		0.003
North[a]	-	-
Center	0.49 (0.29, 0.83)	0.008
Lisbon	0.30 (0.16, 0.57)	<0.001
Alentejo	0.90 (0.46, 1.78)	0.770
Algarve	0.92 (0.25, 3.45)	0.899
Islands	0.49 (0.21, 1.15)	0.099
Marital status	-	-
Without partner[a]	-	-
With partner	0.91 (0.56, 1.48)	0.699
Years of education		0.001
<4 years[a]		
4-9 years	0.48 (0.30, 0.75)	0.002
≥10 years	0.17 (0.07, 0.45)	<0.001
BMI (kg/m^2)		0.136
Normal or underweight (<25kg/m^2)[a]	-	-

Overweight (25-29.99 kg/m^2)	0.27 (1.77, 1.59)	0.270
Obese (≥30 kg/m^2)	2.06 (0.97, 4.45)	0.065
HOOS/KOOS		<0.001
Low tertile[a]	-	-
Middle tertile	1.40 (0.70, 2.94)	0.370
High tertile	3.68 (1.82, 7.43)	<0.001
Anxiety (HADS-A)		
No anxiety symptoms (HADS-A<11)[a]	-	-
Anxiety symptoms (HADS-A≥11)	1.10 (0.64, 1.89)	0.738
Depression (HADS-D)		
No depression symptoms (HADS-D<11)[a]	-	-
Depression symptoms (HADS-D≥11)	0.94 (0.48, 1.83)	0.845
Smoking habits		
Non-smoker[a]	-	-
Daily or occasional smoker	0.44 (0.17, 1.16)	0.097
Alcohol consumption		
Never or occasionally[a]	-	-
Daily	1.25 (0.77, 2.04)	0.369
Exercise		
No regular exercise[a]	-	-
Regular exercise	0.49 (0.27, 0.87)	0.016

[a]Reference classes
All analysis were weighted.

Supplementary figure 1 - HOOS/KOOS subscale scores by sex, age class, and radiographic severity.



5.2. Study 2: Prevalence of and factors associated with unmanageable pain levels in people with knee or hip osteoarthritis: a cross-sectional population-based study

Daniela Costa, Eduardo B Cruz, David G Lopes, Catarina Nunes da Silva, Ana Rita Henriques, Diogo Luis, Jaime Branco, Helena Canhão, Ana M Rodrigues. Prevalence of and factors associated with unmanageable pain levels in people with knee or hip osteoarthritis: a cross-sectional population-based study. Accepter for publication in BMC Musculoskeletal Disorders in 28th November 2022 (Submission ID: 8b2fb46-16bf-4ab2-be4e-be46f23a9d4b | v.2.0),

Available at https://doi.org/10.21203/rs.3.rs-1619389/v2

Abstract

Background: Pain due to knee and / or hip osteoarthritis (HKOA) is the most common symptom for seeking healthcare. Pain interferes on daily activities, social and occupational participation in people with HKOA. The goal of this study is to estimate the prevalence of unmanageable pain levels (UPL) among people with HKOA), characterize this population and identify factors associated with UPL, and compare therapeutic strategies used by people with UPL versus manageable pain levels (MPL).

Methods: We analysed data from the EpiReumaPt study (n=10,661), that included a representative sample of the Portuguese population. Among these, 1081 participants had a validated diagnosis of HKOA by a rheumatologist. Sociodemographic, lifestyle and health-related data were collected in a structured interview. Pain intensity (NPRS) data were collected in a medical appointment. Intake of regular medication for pain relief (last month), physiotherapy and surgery were considered as therapies for pain management. UPL was defined as a mean pain intensity in the previous week of ≥5 points on 11-point numeric pain rating scale. The factors associated with UPL were analyzed with logistic regression (p<0.05, 95%CI). To assess the effects of unmanageable pain levels in the HOOS/KOOS activities of daily living and quality of life subscales and in the presence of anxiety and depression symptoms, linear and logistic regression were used. All analysis were weighted.

Results: The estimated prevalence of UPL among people with HKOA was 68.8%. UPL was associated with being female (odds ratio (OR)=2.36, p<0.001), being overweight (OR=1.84, p=0.035) or obese (OR=2.26, p=0.006), and having multimorbidity (OR=2.08, p=0.002). People with UPL reported worse performance in activities of daily living and lower quality of life (β=-21.28, p<0.001 and β=–21.19, p<0.001, respectively) than people with MPL. People with UPL consumed more NSAIDs (22.0%, p=0.003), opioids (4.8%, p=0.008), paracetamol (2.7%, p=0.033), and overall analgesics (7.3%, p=0.013) than people with MPL. A higher proportion of people with UPL underwent physiotherapy (17.5%, p=0.002) than people with MPL.

Conclusion: Two-thirds of people with HKOA in Portugal have poor management of their pain levels. Clinical and lifestyle factors, that are highly presented in individuals with HKOA, are associated with unmanageable pain. Our results highlighting the need for further research and implementation of effective interventions to improve pain, function and quality of life in people with HKOA.

Keywords: osteoarthritis, pain management, pharmacological therapies, non-pharmacological therapies

Manuscript

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease, affecting more than 300 million people worldwide. The hip and knee joints are the most affected and combined reflect 9.6 million years lived with disability (1). The direct annual costs of hip and/or knee OA (HKOA) per patient are estimated at 6.7K€ worldwide, which reaches 10.8K€ if total joint replacement surgery is considered (2). Indirect annual costs per patient are estimated between 0.2K-12.3K€. In Portugal, indirect costs represent 0.4% of the national gross domestic product (3). Moreover, the incidence of total joint replacement surgery in Portugal has increased by 20% annually in the period between1990-2011, which represents the highest growth rate among Organisation for Economic Co-operation and Development countries (4).

HKOA often results with chronic pain, physical disability, and mental health and sleep problems, which impairs quality of life (QoL) and prevents participation in social and occupational activities (5). Pain is the most disabling symptom of OA and a major driver of clinical decision-making and healthcare resources (5).

Pain severity is more indicative of functional impairment than radiographic severity (6–8). Pain severity is also strongly associated with reported disability, medication use (9,10), healthcare utilization, impact on daily and occupational activities, loss of productivity, early retirement, and absenteeism (11,12). Poor pain management is a major predictor of total joint replacement surgery (13).

Recent literature raises concerns over the pain management and low QoL among people with HKOA (10,14). Current pain management focus on symptomatic control, which incorporate medication as first-line intervention that increases the risk of oipioid over-prescription (14,15). The use of end-stage interventions such as surgery is becoming more common, even among people with early-stage OA (14,15).The knowledge of pain management and therapeutic strategies in Portugal is scarce. There is a critical need to better understand patients' associated risk factors, characteristics, and available therapeutic interventions for people enduring HKOA in Portugal.Therefore, the aims of this study were to: 1) estimate the prevalence of unmanageable pain levels (UPL) among Portuguese population with HKOA, 2) characterize the HKOA population in terms of sociodemographic, lifestyle, and health-related variables and identify factors associated with UPL; and 3) compare performance in activities of daily living (ADL), QoL, anxiety and depression symptoms, and therapies used between people with UPL versus people with manageable pain levels (MPL). This knowledge will help to understand which factors undermine patient's ability to manage pain levels and how associated therapies used either facilitate or fail to facilitate successful management of pain. The results of this study may also indicate whether the associated therapeutic interventions account for the factors associated with poor pain management and if improvements in offered interventions to people with HKOA are needed.

.

METHODS

Data source

We analyzed data from EpiReumaPt, a national cross-sectional, population-based study with a representative sample of the Portuguese population that aimed to analyze the burden of rheumatic and musculoskeletal diseases (RMDs) in Portugal. As described in detail elsewhere (16), participant recruitment was conducted between September 2011 and December 2013 using a random selection of private households in Portugal stratified by administrative territorial units (NUTS II: Norte, Centro, Lisboa and Vale do Tejo, Alentejo, Algarve, Azores, and Madeira) and the size of the population within each locality. In each household, the permantent resident ≥18 years old who most recently celebrated birthday was selected to participate in the study. In total, 28,502 households were contacted, 8,041 individuals refused to participate, and 10,661 were included in the study. The EpiReumaPt population was similar to the Portuguese population (Census 2011) in age strata, sex, and NUTII distribution (16).

EpireumaPt data collection was performed using a three-staged approach. In the first stage, participants completed a face-to-face interview to collect sociodemographic and health-related information and to screen for RMDs. Interviews were conducted by a team of non-medical healthcare professionals trained for this purpose, and data were collected using a computer-assisted personal interview system. Screening was considered positive if a participant mentioned a previously known RMD, if any algorithm in the screening questionnaires was positive, or if the participant reported muscle, vertebral, or peripheral joint pain in the previous 4 weeks.

In the second stage, participants who screened positive for at least one RMD (n=7,451) and approximately 20% of participants who screened negative for RMDs (n=701) were invited to a clinical appointment at the primary care center of the participant's neighborhood. Participants were seen by a multidisciplinary team consisting of a rheumatologist, X-ray technician, and nurse. Clinical assessment consisted of a structured evaluation, laboratory tests, and imaging exams, if needed, to establish a diagnosis and evaluate disease-related information. According to participants' complaints, simple radiographs were performed in 122 hips and 479 knees, among other joints. Rheumatologists were blind to prior health-related data. Of the participants in the second stage, 4,275 did not attend the clinical appointment. Therefore, at the end of the second stage, there were 3,877 clinical observations: 3,198 participants received an RMD diagnosis, and 679 did not receive an RMD diagnosis.

In the third stage, three experienced rheumatologists reviewed all data and validated the RMD diagnosis of individuals that participated in the clinical appointment – second stage. Diagnostic agreement among the three rheumatologists was 98.3%, with a Cohen's K coefficient of 10.87 (95% confidence interval (CI): 0.83, 0.91) (16). When data were insufficient to fulfill international classification criteria for an RMD, five rheumatologists met to reach agreement on the final diagnosis. When doubts persisted, the opinion of the rheumatologist who performed the clinical assessment in the second stage prevailed. From the individuals that participated in the clinical appointment (n=3.877), a total of 1,087 participants had a validated diagnosis of HKOA, 199 had a validated diagnosis of hip OA, and 981 had a validated diagnosis of knee OA (Figure 1). When the overall performance of the RDM screening algorithm was evaluated, using final diagnosis after the third stage as the gold standard, its sensitivity and specificity were 98% and 22% and positive and negative predictive value were 85% and 71%, respectively.

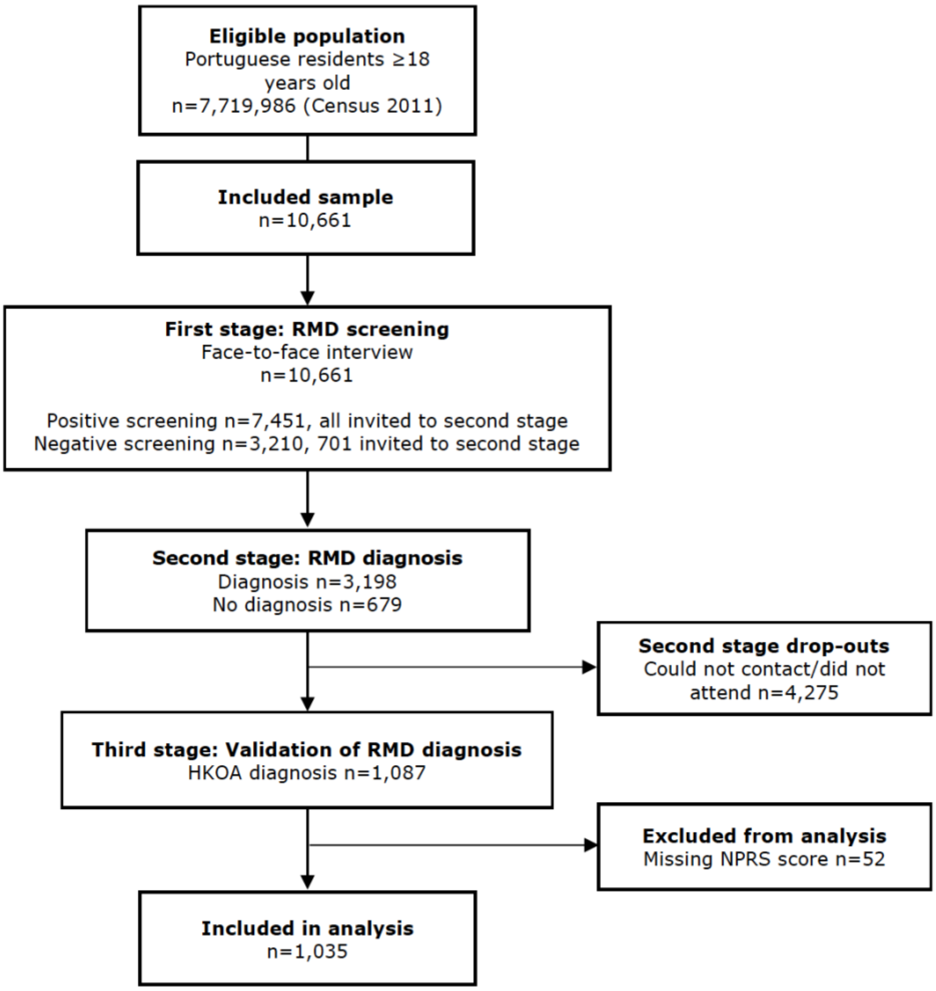


Figure 1. EpiReumaPt study flowchart

Study population

This study included participants of EpiReumaPt with validated a diagnosis of HKOA according to American College of Rheumatology criteria (17,18).

Case definition and measurement

Mean pain intensity in the previous week, measured on a 11-point numeric pain rating scale (NPRS) in the second stage of EpiReumaPt, was used to categorize participants with HKOA into MPL (<5 points) and UPL (≥5 points), which was validated by Zelman et al. (2003) using the question 5 of Brief Pain Inventory (BPI) scale, as the average pain in the previous week on an 11-point NPRS. The optimal cut-off point found for manageable day pain in OA was 5 (F(7, 9)=7.08, p<0.001)(19). In the validation of this cut-off Zelman et al., statistically derived the 11-point NPRS with BPI interference scale measures, WOMAC-physical function and SF-36 and reach the final cut off of 5 in average pain intensity that best separate the groups with manageable pain and not manageable pain. This cut-off represent a “Manageable Day” or, in other words, in people with HKOA, pain intensity less than 5 on a 11-point NPRS permit an increased function and quality of life (19).

When both the hip and knee were affected, the worst score was considered.

Sociodemographic, clinical, and lifestyle variables

Sociodemographic, clinical, and lifestyle variables were collected during the first and second phases of EpiReumaPt. To assure better clinical interpretation, some variables were subjected to categorical transformation.

Sociodemographic and anthropometric variables

Sociodemographic variables were age, sex, and geographic location according to NUTS II territorial units. Madeira and Azores were merged in the analysis as the Islands region. Marital status was categorized as “partner” (married or consensual union) or “no partner” (single, widowed, or divorced). Education level was categorized according to years of education completed: <4 years (less than primary education), 4-9 years (primary or secondary education), or ≥10 years (secondary or higher education).

Body mass index (BMI) was categorized as underweight (≤18.49 kg/m^2), healthy weight (≥18.50 and ≤24.99 kg/m^2), overweight (≥25.00 and ≤29.99 kg/m^2), or obese (≥30.00 kg/m^2).

Lifestyle and clinical variables

Lifestyle variables were alcohol intake (“no” or “occasionally or daily”), smoking habits (“never” and “occasionally or daily”), and regular exercise/sports (“yes” or “no”).

The number of chronic non-communicable diseases was calculated as the numeric count of the following self-reported conditions: high blood pressure, high cholesterol, cardiac disease, diabetes mellitus, chronic lung disease, problems in the digestive tract, renal colic, neurological disease, allergies, mental or psychiatric illness, cancer, thyroid or parathyroid problems, hypogonadism, and hyperuricemia. Multimorbidity was defined as having two or more chronic non-communicable diseases (20).

In addition to pain intensity, other clinical variables were considered: performance in ADL, QoL, and the presence of depression and/or anxiety symptoms. Performance in ADL and QoL related to HKOA were evaluated with the Portuguese version of the Knee Injury and Osteoarthritis Outcome Scale (KOOS) (21) and Hip Disability and Osteoarthritis Outcome Scale (HOOS) (22). These self-reported clinical outcome measures evaluate short- and long-term consequences of HKOA in five dimensions: pain, symptoms, ADL, sports and leisure, and QoL. For this study, we used only the HOOS/KOOS ADL and HOOS/KOOS QoL subscales. Scores for each dimension were transformed on a 0-100 scale, with 0 representing extreme hip/knee problems and 100 representing no hip/knee problems (21,22). For both subscales, if more than one joint was affected, the worst score was considered.

Anxiety and depression symptoms were evaluated using the Hospital Anxiety and Depression Scale subscales for depression (HADS-D) and anxiety (HADS-A). Both scales have a range of 0 to 21, with higher values representing more severe symptoms of anxiety or depression. Final HADS-A and HADS-D scores were categorized using validated cut-offs as: "with anxiety" (HADS-A ≥11) or "without anxiety" (HADS-A <11) and "with depression" (HADS-D ≥11) or "without depression" (HADS-D <11) (23).

Use of therapies

Information on pharmacological therapies, defined as daily medications taken in the previous month, was collected in the first-stage interviews. Medication for pain relief was classified according to the Anatomical Therapeutic Chemical Classification System as: glucosamine (M01AX05); analgesics/antipyretics (N02B), specifically paracetamol (N02BE01); simple (N02A) and combined (N02AJ) opioids; non-steroidal anti-inflammatory drugs (NSAIDs; M01A); and topical agents (M02A). Information on physiotherapy attendance in the previous 12 months, was also collected in the first-stage interviews. Information on any previous hip or knee surgery was collected during the second-stage clinical appointments, which occurred no more than 15 days after the first stage. Surgery variable (yes/no) was related to any hip or knee surgical procedure that the participants have had in their life, this may include, for example, replacement surgery, meniscectomy or ligament reconstruction surgery.

Data Analysis

After participants were categorized into UPL and MPL subgroups, weighted proportions of participants with UPL were computed taking sampling design into account as described in the EpiReumaPt methodologic protocol (16). The logit transformation method was used to calculate 95% CIs. Analysis of the proportion of participants with

UPL and MPL (relative and absolute frequencies) was conducted separately for participants with hip OA and those with knee OA.

Descriptive statistics were used to characterize all participants and separate, the MPL and UPL subgroups, according to sociodemographic, lifestyle, health-related variables as well as use of pain medication, physiotherapy and surgery. Differences between subgroups were analyzed using independent samples t-tests for continuous variables and Chi-square tests for categorical variables.We first analyzed associations between sociodemographic, lifestyle, and health-related variables and pain levels subgroups. Variables with $p<0.25$ were included in a univariate logistic regression model in a forward selection process (24) to avoid early exclusion of potentially important variables (**Additional file 1.**). These variables were selected in this stage since they are previously known associated with HKOA outcomes(25). Variables with $p<0.05$ were then kept in a backward selection process to construct a multivariable model(26).

We next analyzed associations between UPL and clinical outcomes, having MPL subgroup as reference. Associations between UPL and HOOS/KOOS ADL and QoL subscale scores were analyzed using linear regression models adjusted for the variables retained in the multivariable model. Associations between UPL and the presence of anxiety and depression symptoms were analyzed using logistic regression models adjusted for the same variables. This adjustment was made since the variables retained in the first multivariable model have showed statistical associations with the outcome and so, can they can have a confounder effect on the associations between UPL/MPL with other clinical outcomes.

Given the scarcity of data, normal and underweight BMI categories were merged into a single category (<25.00 kg/m^2). A sensitivity analysis was additionally performed for participants with hip OA and for those with knee OA (Additional file 2).

All analyses were weighted and performed with SPSS 26 complex samples for MacOS (IBM Corp., Armonk, NY, USA). Statistical significance was defined as $p<0.05$.

RESULTS

The prevalence of UPL among people with HKOA was 68.8%. People with UPL reported a mean pain intensity of 6.85±1.54 on a 0- to 10-point numeric pain rating scale. The proportions of people with UPL who had hip OA (n=144, 69.7%) or knee OA (n=694, 69.5%) were similar (Table 1).

Table 1. Prevalence of UPL and MPL among people with HKOA

	Total	**UPL** **(NPRS ≥5)**	**MPL** **(NPRS <5)**
HKOA weighted prevalence (95% CI) **Sample size**	100% n=1,035	68.8% (63.9, 73.2) n=765	31.2% (26.8, 36.1) n=270
HKOA weighted count	1,080,633	743,130	337,502
Pain (NPRS), mean±SD	5.55±2.45	6.85±1.54	2.69±1.43
Hip OA, n (%)	199 (2.9)	144 (69.7)	40 (30.3)
Knee OA, n (%)	981 (12.4)	694 (69.5)	247 (30.4)

All percentages and means±SDs are weighted.

MPL, Manageable pain levels; CI, confidence interval; HKOA, hip and knee osteoarthritis; UPL, unmanageable pain levels; NPRS, numeric pain rating scale; OA, osteoarthritis; SD, standard deviation

The proportion of people with UPL increased with age, reaching 73.3% in the oldest age class (≥75 years of age). UPL was more common in female than in male subjects, as shown in Figure 2.

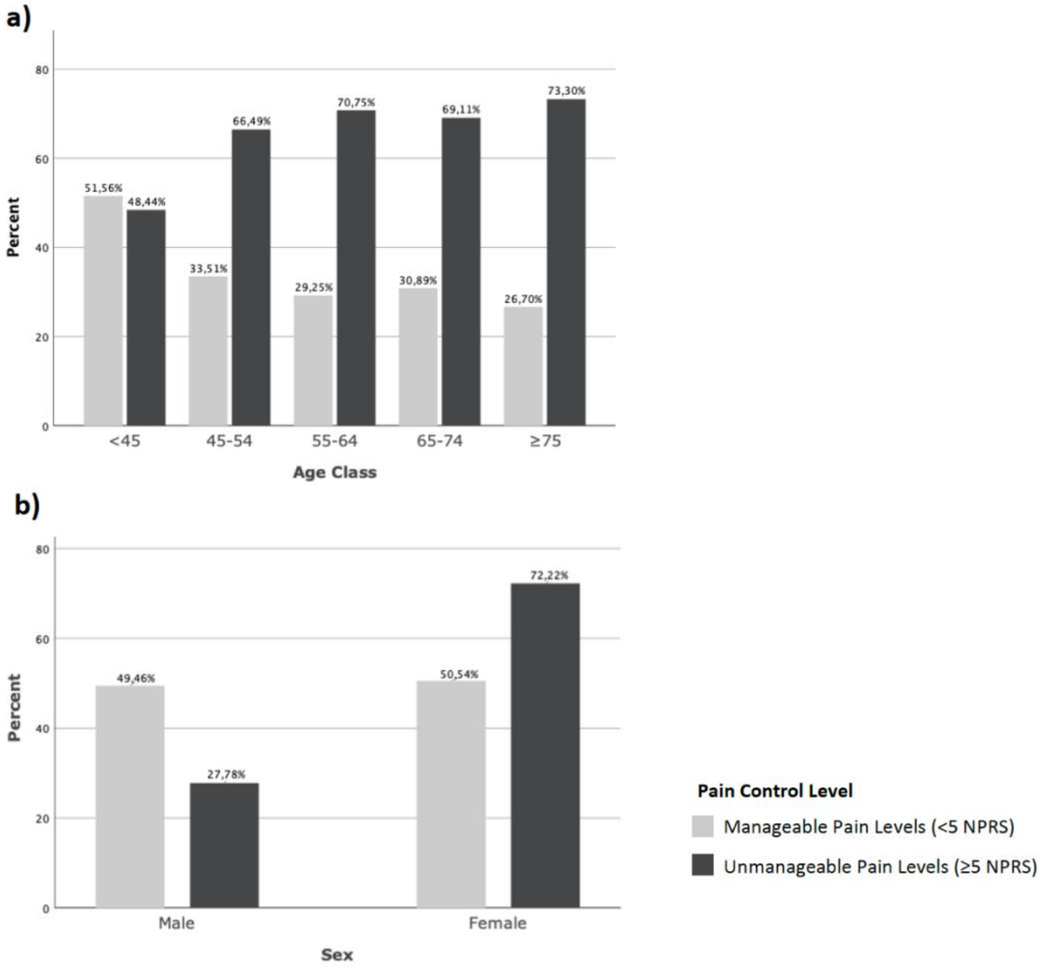


Figure 2. Proportions of people with HKOA and UPL or MPL by (**a**) age class (years) and (**b**) sex.

Mean age and age class distributions were similar between UPL and MPL subgroups (Table 2). The UPL subgroup contained a larger proportion of people with a lower level of education (<4 years of completed schooling) than the MPL subgroup. Overweight and obesity were highly prevalent among people with HKOA and were present at similar proportions between UPL and MPL subgroups.

The UPL subgroup contained smaller proportions of people who smoked or consumed alcohol daily than the MPL subgroup. Although regular exercise was more common within the MPL subgroup than within the UPL subgroup, this difference was not significant. The presence of multimorbidity was more common within the UPL subgroup than within the MPL subgroup.

Table 2. Sociodemographic, lifestyle, and health-related variables for people with HKOA

	Total **n=1,035**	**UPL** **n=765**	**MPL** **n=270**	***p*-value**[a]
Age (mean±SD)	64.33±12.90	65.32±12.04	62.17±14.38	0.091
<45 years, n (%)	38 (6.1)	24 (4.3)	14 (10.2)	0.265
45-54 years, n (%)	138 (6.0)	98 (15.7)	40 (17.4)	
55-64 years, n (%)	279 (23.2)	209 (23.9)	70 (21.7)	
65-74 years, n (%)	351 (31.3)	261 (31.4)	90 (30.9)	
≥75 years, n (%)	229 (23.2)	173 (24.7)	56 (19.8)	
Female sex, n (%)	744 (65.4)	571 (72.2)	173 (50.5)	<0.001
Geographic location, n (%)				0.478
North	281 (35.6)	205 (36.0)	76 (34.8)	
Centre	255 (27.8)	180 (26.2)	75 (21.4)	
Lisbon	171 (23.7)	121 (23.4)	50 (24.4)	
Alentejo	69 (6.4)	53 (7.0)	16 (5.1)	
Algarve	22 (1.9)	18 (2.3)	4 (1.1)	
Islands	237 (4.6)	188 (5.3)	49 (3.3)	
Marital status, n (%)				
With partner	662 (63.8)	477 (64.0)	185 (63.3)	0.893
Years of education, n (%)				0.024
<4 years	257 (23.0)	208 (26.6)	49 (15.1)	
4-9 years	652 (62.2)	474 (58.9)	178 (68.9)	
≥10 years	124 (14.8)	82 (14.2)	42 (16.0)	
BMI, n (%)				0.067
Underweight/normal weight	173 (21.1)	114 (18)	59 (27.8)	
Overweight	404 (43.4)	294 (43.5)	110 (43.3)	
Obese	381 (35.4)	297 (38.5)	84 (28.8)	
Lifestyle factors, n (%)				

Smoker	75 (10.9)	47 (7.9)	28 (17.3)	0.015
Daily alcohol intake	225 (28.5)	152 (24.5)	73 (37.1)	0.016
Regular exercise	220 (21.5)	146 (19.4)	74 (26.2)	0.116
Multimorbidity, n (%)	783 (73.8)	608 (79.4)	175 (61.5)	<0.001

All percentages and means±SDs are weighted.

[a]p-value from independent samples t-tests for continuous variables and Chi-square tests for categorical variables. Significance level (p<0.05) based on adjusted F.

MPL, Manageable pain levels; BMI, body mass index; HKOA, hip and knee osteoarthritis; UPL, unmanageable pain levels; SD, standard deviation

When analyzing associations between UPL and sociodemographic, lifestyle, and health-related variables, female participants, being overweight or obese, and having multimorbidity were independently associated with UPL (Table 3).

Table 3. Multivariable model including factors associated with UPL in people with HKOA

	UPL vs. MPL **OR (95% CI)**	**p-value**
Variables included		
Female sex[a]	2.32 (1.50 to 3.57)	<0.001
BMI[b]		
Overweight	1.84 (1.04 to 3.25)	0.035
Obese	2.26 (1.27 to 4.02)	0.006
Multimorbidity[c]	2.07 (1.33 to 3.20)	0.001

n=1,009. [a]Reference class: male sex; [b]Reference class: underweight/normal weight; [c]Reference class: no multimorbidity. Wald F(5)=8.08, p<0.001; Nagelkerke Pseudo R^2=0.125.

MPL, manageable pain levels ; BMI, body mass index; CI, confidence interval; HKOA, hip and knee osteoarthritis; UPL, unmanageable pain levels; OR, odds ratio

When adjusting for sex, BMI, and multimorbidity, significant negative associations between UPL and HOOS/KOOS ADL and QoL scores remained (Table 4). Thus, people with UPL were more likely to have worse HOOS/KOOS ADL and QoL scores than people with MPL. Although there was a significant association between UPL and anxiety symptoms in the unadjusted model, no significant association was found in the adjusted model, having the MPL subgroup as reference. No statistically significant associations were found in the unadjusted or in the adjusted model between depression symptoms and UPL, having MPL subgroup as reference. No differences were found in the sensitivity analysis (Additional file 2).

Table 4. HOOS/KOOS ADL and QoL subscale scores and anxiety and depression symptoms in people with HKOA and UPL or MPL

Sample size and weighted prevalence (%)	**Total** n=1,035 (100%)	**UPL** n=765 (68.4%)	**MPL** n=270 (31.6%)		**β (95% CI)**	**p-value**	**Adjusted β (95% CI)**	**p-value**
HOOS/KOOS ADL, mean±SD	66.00 ±23.08	58.36 ±21.31	83.06 ±16.96	UPL	-24.70 (-28.60, -20.80)	<0.001	-21.28 (-24.81, -17.76)	<0.001
HOOS/KOOS QoL, mean±SD	50.55 ±22.45	43.09 ±19.37	67.00 ±19.88	UPL	-23.91 (-28.31, -19.51)	<0.001	-21.19 (-25.22, -17.16)	<0.001
					Crude OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Anxiety symptoms, n (%)	198 (18.1)	161 (20.6)	37 (12.8)	UPL	1.76 (1.09, 2.83)	0.020	1.23 (0.77, 1.97)	0.395
Depression symptoms, n (%)	162 (16.5)	130 (18.1)	32 (12.9)	UPL	1.49 (0.77, 2.86)	0.235	1.11 (0.59, 2.12)	0.744

All percentages and means±SDs are weighted. β and OR are adjusted for sex, obesity, and multimorbidity.

ADL, activities of daily living; MPL, manageable pain levels; CI, confidence interval; HKOA, hip and knee osteoarthritis; HOOS, Hip Disability and Osteoarthritis Outcome Scale; UPL, unmanageable pain levels; KOOS, Knee Injury and Osteoarthritis Outcome Scale; OR, odds ratio; QoL, quality of life; SD, standard deviation

Overall, NSAIDs, analgesics, and physiotherapy were the most used therapies by people with HKOA (Table 5). Higher proportions of people within the UPL subgroup regularly took NSAIDS, simple opioids, and analgesics, specifically paracetamol, than within the MPL subgroup. Physiotherapy was also more commonly used by people with UPL than by people with MPL. There were no significant differences in the proportions of people who underwent hip or knee surgery between UPL and MPL subgroups.

Table 5. Pharmacological, conservative non-pharmacological, and surgical therapies used by people with HKOA with UPL or MPL

	Total	**UPL**	**MPL**	**p-value**[a]
Sample size and weighted prevalence	n=1,035 (100%)	n=765 (68.4%)	N=270 (31.6%)	
Pharmacological therapies				
Anti-inflammatory				
NSAIDS, n (%)	239 (19.0)	194 (22.0)	45 (12.5)	0.003
Topical NSAIDS, n (%)	10 (1.2)	7 (1.5)	3 (0.7)	0.410
Opioids				
Simple opioids, n (%)	49 (3.7)	44 (4.8)	5 (1.3)	0.008
Opioids combined with analgesics, n (%)	24 (1.4)	22 (1.8)	2 (0.4)	0.053
Analgesics/antipyretics				
Analgesics (all), n (%)	72 (5.7)	62 (7.3)	10 (2.7)	0.013
Paracetamol, n (%)	25 (2.0)	23 (2.7)	2 (0.6)	0.033
Others				
Glucosamine, n (%)	65 (4.7)	53 (5.1)	12 (3.9)	0.438
Conservative non-pharmacological therapies				
Physiotherapy, n (%)	152 (14.9)	121 (17.5)	31 (8.9)	0.002
Surgery				
Hip surgery[b], n (%)	42 (18.7)	29 (19.1)	13 (17.6)	0.847
Knee surgery[c], n (%)	113 (13.2)	82 (13.4)	31 (13.0)	0.893

All percentages are weighted.

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[a]p-value from Chi-square tests. Significance level is based on adjusted F. [b]Sub-sample with hip OA. [c]Sub-sample with knee OA.

MPL, manageable pain levels; CI, confidence interval; HKOA; hip and knee osteoarthritis; UPL, Unmanageable pain levels; NSAIDS, non-steroidal anti-inflammatory drugs; OA, osteoarthritis

DISCUSSION

Our results indicate that 68.8% of people with HKOA in Portugal live with UPL, which is higher than the prevalence of UPL in Mexico (53%) (29), the Survey of Osteoarthritis Real World Therapies (SORT) cohort from six European countries (54%) (10), and a sample of Portuguese people with knee OA included in the SORT cohort (51%) (28). All three of these earlier studies included people who were ≥50 years old, possibly excluding younger patients with early OA, and who took analgesics regularly, which may explain why we found a higher prevalence of UPL in the present study.Our study included a representative sample of the Portuguese population who live in the community, suggesting that offered interventions do not meet the need for pain control for more than two-thirds of the Portuguese HKOA population.

We found that people with UPL had lower education levels than people with MPL. This finding is consistent with previous literature reporting that low education is associated with more severe OA symptoms, is a social determinant of unhealthy lifestyles and multimorbidity (29,30), is a determinant of lack of access to and delay in seeking healthcare (32), and is associated with increased pain intensity over time (33).

The multivariable model showed that female sex, overweight and obesity, and multimorbidity were associated with UPL, similar to the results of the SORT study (10). In our study being female was associated with higher OA-related pain levels, but gender differences on pain intensity in HKOA remain unclear in the literature. Data from quantitative sensory testing in people with knee OA has shown that women have greater sensitivity to pain but no sex differences were found in clinical pain. These authors suggested that women have an enhanced central pain sensitivity (32). More recently, Mun et al (2020) concluded that women with knee OA have a greater interleukin-6 activation, when compared to men, after laboratory quantitative sensory testing. These authors concluded that this enhanced inflammatory reactivity in women may contribute to exacerbation or maintenance of symptoms (33).

Other factors like psychosocial and genetic factors have been showed as inconsistent in gender differences and pain severity (34). (35). Also, a systematic review of progression phenotypes among people with OA shows that overweight or obesity is a major factor in the progression of OA and is associated with worsening of pain, loss of physical function, and structural deterioration over time (36).

Additionally, our results show that having multimorbidity was associated with UPL. Multimorbidity is associated with chronic pain in a cumulative manner (37) and is related to pain intensity in people with HKOA (38). People with multimorbidity have a higher likelihood of walking impairments, which can contribute to a worsening of OA and other chronic conditions that occurswith an additional consequence of psychological distress (37,38).

We found that UPL was negatively associated with performance in ADL and QoL. Previous research reveals that within the OA population, pain severity explains most of the variability in disability and QoL (39). High pain severity may lead to fear of movement and/or avoidance behaviors, resulting in physical inactivity and less participation in social activities and leading to greater physical disability, psychological distress, and reduced QoL (40).

The sensitivity analysis did not show differences when separating participants with hip OA and with knee OA. This suggests that similar factors were associated with UPL in people with OA in these two joints, separately or together. However, due to the small sample size of participants with hip OA, we were not able to perform multivariable analysis for anxiety and depression symptoms.International clinical practice guidelines recommend that topical NSAIDs be considered before oral NSAIDs consistentwith the least systemic exposure principle, and oral NSAIDs are strongly recommended at the lowest possible dose (41). Given the limited efficacy of paracetamol and its potentially harmful secondary effects, it is only conditionally recommended for people with OA (41). Although tramadol is conditionally recommended, non-tramadol opioids are not recommended for the management of pain in people with OA. Tramadol and non-tramadol opioids can be used only when alternatives have been exhausted. Glucosamine is strongly not recommended for people with HKOA (41). In the present study, oral NSAIDs were the most used medication followed by analgesics/antipyretic medication, whereas topical NSAIDs were the least used pharmacological modality. People with UPL regularly took more medication for pain relief, namely NSAIDS, opioids, and analgesics, specifically paracetamol, than people with MPL, consistent with the results of the SORT study (10). A cohort study from the Netherlands also shows pain severity is positively related to analgesic intake; however, the authors concluded that most reasons for analgesic prescription are unknown (42).

Even though no temporal relationships can be drawn from a cross-sectional design, this study reveals that a higher proportion of people who took daily pain medication in the previous month had UPL. Additionally, our results suggest that medication is taken by a much lower proportion of people with OA in Portugal than in other European countries (12). In Europe, medication use seems to be highly variable across countries. Data from five countries included in the National Health and Wellness Survey (n=37650), reveal that the minimum and maximum proportions of overall pain medication intake by people with OA was 22% in Germany and 53.2% in Spain. Specifically, NSAID’s were at minimum by 46,5% of people with OA in France and at maximum by 81.9% in Germany; Paracetamol was not used by any participants of Germany, but by 6% of participants from Spain. Opioids were used by 1.8% in Italy at minimum and by 54.5% at maximum of people with HKOA in France. These proportions of medication use were much higher than the ones seen in our findings probably because medication intake was asked as “medication used at the moment” (12) rather than daily use of medication in the previous month, as in our study. Similarly, our findings reveal that NSAID’s are the medication most used by people with HKOA. In other European countries opioids are the second most used pain medication, contrarily to our study (used similarly to analgesics). These findings may suggest that opioids are less prescribed in Portugal than in other countries. However, data from the general population reveal that the prescription of opioids in Portugal has increased by 1.5-fold between 2013 and 2017 (43).

Although randomized controlled trials show that analgesic drugs and other recommended interventions effectively manage pain in individuals with OA, adherence to medication and healthy lifestyle behaviors are a real-world concern that prevent the optimization of pain control in this population. A qualitative meta-ethnographic study points out that factors such as the severity of pain, perceived effect of medication, fear related to side effects, acceptability of dose regimens, education and knowledge about OA and the medication regimen, self-efficacy, and locus of control over OA influence medication adherence (44).

Regarding conservative non-pharmacological therapies used by people with HKOA, we found that <20% of people with UPL underwent physiotherapy in the last 12 months or regularly exercised. These values are much lower than other European countries. For example, the proportion of people with OA in national cohorts that used physiotherapy in a 12-month time frame was 53.1% in Germany (45) and 32% in the UK (46).

Crrent clinical guidelines recommend physiotherapy and exercise as first-line treatments. Exercise should be maintained during the progression of the disease for pain management purposes (47,48). Although, similarly to our results, literature suggests that currently exercise and physiotherapy, as part of core non-pharmacological treatments, are uptake by <50% of people with HKOA and that the healthcare interventions are symptom-driven and segmented (49) centered on pharmacological (50,51) and surgical options (52). On the other hand, lack of long-term adherence to behavior-dependent interventions, like exercise has been pointed out as an explanation for poor long-term outcomes in people with HKOA (53,54). Therefore, interventions for the management of HKOA should also target behavior changethrough strategies that optimize motivation and overcome barriers of adherence (55).

Limitations

Our study has several limitations that should be considered. A large proportion of participants included in the first phase of the study and invited for the second phase did not show up in the rheumatologist appointment. Therefore, we should hypothesize a selection bias, since the subjects who were willing to participate in the appointment might be the most severe cases.

Due to its cross-sectional design, no cause-effect relationships can be established between UPL and sociodemographic, lifestyle, and health-related variables. Additionally, identification of variables with direct and indirect effect on the outcome is not possible with this study design and was not accounted in the regression models (56). Also, giving the cross-sectional design of the study, the variables related with the use of therapies were considered only to describe and compare UPL/MPL subgroups and no associations with the outcome variables were explored. Also, estimation of the proportion of people with UPL in the Portuguese population using sample weights is not free from error, although sample weights are recommended for all statistical analyses using complex samples data (57).

(1,45)(58)We used the validated cut-off by Zelman et al (2003), to define people with UPL and MPL. However, in this validation study the eligible criteria included people with HKOA that have at least 1 year pain duration, that have a daily use of some form of analgesic and that reported average daily pain of 4 at least in the 11-point NPRS (19).

Notwithstanding, the cut-off “5” was previously validated in other populations as pain intensity that interferes with function and QoL - musculoskeletal pain in general (59), in patients with knee OA (10) and in those with HKOA waiting for surgery (60). In this late study the authors concluded that the interference of pain in function (using the same cut-off) was independent from pain duration. Therefore, we cautiously believe that this cut-off is valid also in the population of our study.

We asked participants about their use of “regular medication”. However, as people with OA often use analgesic medication sporadically for pain flares rather than daily, our results may underestimate the proportion of people that use medication for symptomatic control. On the other hand, we did not control for other pain conditions like fibromyalgia or widespread pain syndromes, pain duration or pain frequency (e.g. daily or constant pain) that may increase the intake of medication. Also, as physiotherapy attendance in the last 12 months was self-reported, we acknowledge the possibility that memory bias may compromise the accuracy of our results. Additionally, we did not investigate the reason for medication use or physiotherapy.

Surgery procedure was not specified, and this variable (surgery - yes/no) was not related to a specific time frame. Additionally, since the causes of surgery are not known our results were purposively descriptive and no hypothesis can be drawn. “Regular exercise” was self-reported by participants and did not consider the precise amount and intensity. Hence, our data may overestimate the proportion of people who exercised. Moreover, pain intensity is multifactorial (40), and several potentially important factors were not considered in the analysis, such as fear avoidance beliefs, catastrophizing, or coping strategies.

The analyzed data were collected in 2011-2013, but due to few specific strategies directed to RMDs in the last decade in Portugal, we cautiously believe that the current management of OA does not differ from that reflected in this study.

Strengths and implications

This is the first population-based study in Portugal analyzing outcomes of current interventions offered to community-dwelling people with HKOA. The results of this study raise concerns regarding important factors that should be further explored in future research and addressed in national health policies to optimize the outcomes of people with HKOA, namely:

1) The high proportion of people with UPL, suggest a poor control of pain levels in people with HKOA;

2) The high proportion of people with UPL who use pharmacological and non-pharmacological therapiesmay indicate that pain management is suboptimal ;

3) Besides the low proportion of people who use therapy, the interventions offered do not seem to be aligned with international recommendations (41,47) considering the small proportion of people who underwent physiotherapy, exercised, and used pain medication and the large proportion of people who were overweight or obese.

CONCLUSION

Approximately two-thirds of the Portuguese population with HKOA have UPL, despite the higher use of medication and physiotherapy in the UPL subgroup, when compared with theMPL subgroup. Being overweight and having multimorbidity are modifiable risk factors associated with UPL. Overall, recommended management strategies appear to be offered to a small proportion of people with HKOA. Our results may seemingly suggest that current therapies are sub-optimal and that lifestyle behaviour change may be neglected, but longitudinal research is needed to corroborate these hypotheses. Our findings reveal an opportunity for pain management improvement in the HKOA population and highlight the need for further research on effective pain management interventions.

LIST OF ABBREVIATIONS:

ADL: Activities of Daily Living

BMI: Body Mass Index

CI: Confidence Interval

HADS-A: Hospital Anxiety and Depression Scale subscale for anxiety

HADS-D: Hospital Anxiety and Depression Scale subscale for depression

HKOA: Hip and/or Knee Osteoarthritis

HOOS: Hip Disability and Osteoarthritis Outcome Scale

KOOS: Knee Injury and Osteoarthritis Outcome Scale

MPL: Manageable pain levels

NPRS: Numerical Pain Rating Scale

NSAIDs: Non-steroidal anti-inflammatory drugs

OA: Osteoarthritis

OR: Odds Ratio

QoL: Quality of Life

RMD: Rhematic and Musculoskeletal Diseases

SD: Standard Deviation

SORT: Survey of Osteoarthritis Real World Therapies

UPL: Unmanageable Pain Levels

DECLARATIONS

Ethical approval and consent to participate: The EpiReumaPt study was approved by the Ethics Committee of NOVA Medical School and the Portuguese Data Protection Authority (*Comissão Nacional de Proteção de Dados*). This secondary analysis of EpiReumaPt database presented in this study was additionally approved by the Ethics Committee of NOVA Medical School. This study was performed in accordance with the Declaration of Helsinki and revised in 2013 in Fortaleza. Written informed consent was obtained from all participants before entering in EpiReumaPt study, as described elsewhere (16).

Consent for publication: Not Applicable.

Availability of data and materials: The data underlying this article were provided by the EpiDoc Unit - CEDOC by permission. Data will be shared upon request to the corresponding author with the permission of EpiDoc Unit group leaders.

Competing interests: All authors declare no competing interests.

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Authors' Contributions: DC, DGL, and CNS contributed to the drafting of the manuscript. DC, EBC, DL and AMR contributed to the analysis and interpretation of the data. DC, DGL, and ARH contributed to statistical analysis. HC, JB, and AMR contributed to the conception and design of the main project (EpiReumaPt), provision of study materials, obtaining funding for the main project, administrative/logistic support, and collection of data. All authors critically revised and approved the final manuscript.

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Supplementary Material

Additional File 1

Univariate Logistic Regression analysis

Table S1. Factors associated with unmanageable pain levels in univariate logistic regression analysis

	OR (95% CI)	p-value
Age class		0.378
<45 years old	0.34 (0.12, 0.99)	0.047
45-54 years old	0.72 (0.34, 1.54)	0.399
55-64 years old	0.88 (0.47, 1.66)	0.694
65-74 years old	0.82 (0.47, 1.40)	0.459

≥75 years old[a]	-	-
Sex		
Male[a]	-	-
Female	2.54 (1.64, 3.96)	<0.001
Chronic non-communicable diseases		
No multimorbiditiy[a]	-	-
Multimorbidity	2.41 (1.49, 3.91)	<0.001
Geographic location		0.178
North[a]	-	-
Center	0.81 (0.46, 1.39)	0.440
Lisbon	0.93 (0.51, 1.69)	0.802
Alentejo	1.33 (0.67, 2.65)	0.410
Algarve	2.06 (0.64, 6.58)	0.225
Islands	1.53 (0.90, 2.61)	0.115
Marital status		
Without partner[a]	-	-
With partner	1.03 (0.64, 1.66)	0.893
Education level		0.005
<4 years[a]	-	-
4-9 years	0.49 (0.31, 0.76)	0.002
≥10 years	0.49 (0.31, 0.76)	0.038
BMI (kg/m^2)		0.022
Normal or underweight (<25kg/m^2)[a]		
Overweight (25-29.99 kg/m^2)	1.96 (1.08, 3.57)	0.028
Obese (≥30 kg/m^2)	2.36 (1.28, 4.38)	0.006
Smoking habits		
Non-smoker[a]	-	-
Daily or occasional smoker	0.41 (0.20, 0.85)	0.017
Alcohol consumption		
Never or occasionally[a]	-	-
Daily	0.60 (0.39, 0.93)	0.022
Exercise		
No regular exercise[a]	-	-
Regular exercise	0.67 (0.41, 1.10)	0.117

[a] Reference classes

All analyses were weighted.

Sensitivity Analysis of participants with hip OA and with knee OA

Table S.2 a). Sociodemographic, lifestyle, and health-related variables for people with Hip OA

	Total n=184	UPL n=144	MPL n=40	*p*-value[a]
Age (mean±SD)	64.1±12.7	66.1±12.0	59.5±13.2	0.066
<45 years, n (%)	9 (6.5)	7 (6.3)	2 (7.1)	0.490
45-54 years, n (%)	19 (16.7)	15 (12.7)	4 (25.7)	
55-64 years, n (%)	33 (21.5)	27 (19.7)	6 (25.7)	
65-74 years, n (%)	73 (31.3)	53 (31.4)	20 (31.3)	
≥75 years, n (%)	50 (23.9)	42 (29.9)	8 (10.1)	
Female sex, n (%)	114 (55.2)	92 (66.3)	22 (29.8)	0.003
Geographic location, n (%)				
North	55 (37.5)	43 (36.0)	12 (40.8)	0.166
Centre	47 (30.3)	33 (24.2)	14 (44.4)	
Lisbon	13 (5.7)	10 (6.2)	3 (4.8)	
Alentejo	3 (1.6)	3 (2.3)	-	
Algarve	28 (2.9)	23 (3.5)	5 (1.3)	
Islands	38 (22.0)	32 (27.7)	6 (8.7)	
Marital status, n (%)				
With partner	123 (67.7)	95 (69.4)	28 (63.6)	0.709
Years of education, n (%)				
<4 years	46 (19.5)	41 (24.7)	5 (7.4)	0.061
4-9 years	113 (70.1)	86 (65.0)	27 (81.9)	
≥10 years	24 (10.4)	16 (10.3)	8 (10.6)	
BMI, n (%)				
Underweight/normal weight	34 (26.9)	26 (24.8)	8 (31.5)	0.466
Overweight	70 (42.1)	51 (38.7)	19 (49.7)	
Obese	65 (31.0)	55 (36.5)	10 (18.7)	
Lifestyle factors, n (%)				
Smoker	9 (10.7)	7 (6.1)	2 (21.3)	0.154
Daily alcohol intake	55 (34.4)	41 (28.8)	14 (47.4)	0.224
Regular exercise	38 (18.0)	25 (17.2)	13 (19.8)	0.751
Multimorbidity, n (%)	138 (72.3)	116 (81.4)	22 (51.5)	0.030

All percentages and means±SDs are weighted.

[a] p-value from independent samples t-tests for continuous variables and Chi-square tests for categorical variables. Significance level (p<0.05) based on adjusted F.

MPL, Manageable pain levels; BMI, body mass index; UPL, unmanageable pain levels; SD, standard deviation

Table S.2 b) Sociodemographic, lifestyle, and health-related variables for people with Knee OA

	Total **n=941**	**UPL** **n=694**	**MPL** **n=247**	***p*-value**[a]
Age (mean±SD)	64.6±12.9	65.4±11.9	62.8±14.9	0.093
<45 years, n (%)	31 (6.1)	18 (3.7)	13 (11.7)	0.039
45-54 years, n (%)	127 (15.1)	90 (15.3)	37 (14.5)	
55-64 years, n (%)	263 (23.5)	198 (25.3)	65 (19.6)	
65-74 years, n (%)	314 (31.5)	234 (31.3)	80 (32.0)	
≥75 years, n (%)	206 (23.7)	154 (24.4)	52 (22.2)	
Female sex, n (%)	691 (67.9)	531 (73.7)	160 (54.5)	<0.001
Geographic location, n (%)				0.620
North	250 (34.4)	182 (35.2)	68 (32.5)	
Centre	253 (27.7)	165 (26.8)	68 (29.9)	
Lisbon	61 (6.5)	46 (6.9)	15 (5.5)	
Alentejo	19 (1.8)	15 (2.0)	4 (1.2)	
Algarve	224 (4.9)	179 (5.4)	45 (3.6)	
Islands	154 (24.8)	107 (23.7)	47 (27.3)	
Marital status, n (%)				
With partner	597 (63.6)	428 (63.4)	169 (64.1)	0.902
Years of education, n (%)				
<4 years	237 (23.8)	189 (26.6)	48 (17.2)	0.110
4-9 years	593 (60.9)	431 (58.7)	162 (66.0)	
≥10 years	110 (15.3)	74 (14.7)	36 (16.8)	
BMI, n (%)				
Underweight/normal weight	149 (19.6)	97 (16.9)	52 (25.5)	0.144
Overweight	369 (43.5)	270 (44.1)	99 (42.1)	
Obese	353 (36.9)	273 (39.0)	80 (32.4)	
Lifestyle factors, n (%)				
Smoker	69 (10.3)	43 (8.1)	26 (15.2)	0.042
Daily alcohol intake	193 (26.8)	128 (23.0)	65 (35.5)	0.011
Regular exercise	194 (21.5)	130 (19.1)	64 (27.0)	0.090
Multimorbidity, n (%)	718 (74.7)	556 (80.0)	162 (62.7)	0.0004

All percentages and means±SDs are weighted.

[a] p-value from independent samples t-tests for continuous variables and Chi-square tests for categorical variables.

Significance level (p<0.05) based on adjusted F.

MPL, Manageable pain levels; BMI, body mass index; UPL, unmanageable pain levels; SD, standard deviation

Table S.3- Univariable models factors associated with UPL in people with Knee OA or Hip OA

	Hip OA		**Knee OA**	
	UPL vs. MPL OR (95% CI)	p-value	UPL vs. MPL OR (95% CI)	p-value
Female sex[a]	4.64 (1.63; 13.19)	0.004	2.34 (1.51; 3.62)	<0.001
Age group[b]				
<45 years	1.77 (0.11; 27.73)	0.683	0.30 (0.10; 0.91)	0.034
55-64 years	1.54 (0.14; 16.51)	0.719	1.22 (0.67; 2.22)	0.513
65-74 years	2.02 (0.33; 12.51)	0.447	0.93 (0.51; 1.70)	0.810
≥75 years	5.97 (0.87; 41.20)	0.070	1.04 (0.53; 2.03)	0.904
Geographic location[c]				
North	0.68 (0.12; 3.79)	0.659	0.87 (0.44; 1.75)	0.704
Centre	0.42 (0.08; 2.22)	0.305	0.72 (0.35; 1.47)	0.368
Alentejo	1	-	1.31 (0.37; 4.66)	0.679
Algarve	2.11 (0.39; 11.36)	0.383	1.23 (0.60; 2.52)	0.580
Islands	2.44 (0.49; 12.31)	0.277	0.70 (0.32; 1.53)	0.373
Marital status[d]				
With partner	1.30 (0.33; 5.13)	0.709	0.97 (0.61; 1.55)	0.902
Years of education[e]				
4-9 years	0.24 (0.07; 0.82)	0.023	0.58 (0.37; 0.89)	0.014
≥10 years	0.29 (0.07; 1.13)	0.075	0.57 (0.28; 1.13)	0.107
BMI[f]				
Overweight	0.99 (0.18; 5.44)	0.989	1.58 (0.86; 2.90)	0.145
Obese	2.47 (0.46; 13.38)	0.291	1.81 (0.96; 3.43)	0.066
Lifestyle factors				
Smoker[g]	0.24 (0.03; 1.92)	0.178	0.49 (0.25; 0.98)	0.045
Daily alcohol intake[h]	0.45 (0.12; 1.66)	0.228	0.54 (0.34; 0.87)	0.011
Regular exercise[i]	0.84 (0.29; 2.46)	0.751	0.64 (0.38; 1.07)	0.091
Multimorbidity[j]	4.11 (1.10; 15.27)	0.035	2.37 (1.47; 3.84)	<0.001

MPL, manageable pain levels; BMI, body mass index; CI, confidence interval; OA, osteoarthritis; UPL, unmanageable pain levels; OR, odds ratio.

[a]Reference class: male sex; [b]Reference class: 45-55 years; [c]Reference class: Lisboa; [d]Reference class: no partner; [e]Reference class: <4 years; [f]Reference class: underweight/normal weight; [g]Reference class: nonsmoker; [h]Reference class: no alcohol intake; [c]Reference class: no regular exercise; [j]Reference class: no multimorbidity.

Table S.4- Multivariable models factors associated with UPL in people with Knee OA or Hip OA

	Hip OA		**Knee OA**	
	UPL vs. MPL OR (95% CI)	p-value	UPL vs. MPL OR (95% CI)	p-value
Female sex[a]	4.46 (1.51; 13.21)	0.007	2.13 (1.40; 3.25)	<0.001
BMI[b]	Not included	Not included		
Overweight			1.70 (0.92; 3.14)	0.092
Obese			1.90 (1.01; 3.56)	0.046
Lifestyle factors				
Multimorbidity[c]	3.91 (1.22; 12.49)	0.022	2.12 (1.34; 3.36)	0.001

n^{hipOA}=184. Wald F(2)=7.20, p<0.001. n^{kneeoA}=871. Wald F(4)=7.10, p<0.001
MPL, manageable pain levels; BMI, body mass index; CI, confidence interval; OA, osteoarthritis; UPL, unmanageable pain levels; OR, odds ratio.
[a]Reference class: male sex; [b]Reference class: underweight/normal weight; [c]Reference class: no multimorbidity.

Table S.5. HOOS/KOOS ADL and QoL subscale scores and anxiety and depression symptoms in people with Hip OA and UPL or MPL and people with Knee OA and UPL or MPL

	Hip OA				**Knee OA**				**Hip OA**					**Knee OA**			
Sample size and weighted prevalence (%)	**Total** *n*=184 (100%)	**UPL** *n*=144 (69.7%)	**MPL** *n*=40 (30.3%)		**Total** *n*=941 (100%)	**UPL** *n*=694 (69.6%)	**MPL** *n*=247 (30.4%)		**β (95% CI)**	**p-value**	**Adjusted^a β (95% CI)**	**p-value**		**β (95% CI)**	**p-value**	**Adjusted^b β (95% CI)**	**p-value**
HOOS ADL, mean±SD	67.25 ±24.46	57.78 ±21.19	89.09 ±16.21	**KOOS ADL, mean±SD**	65.32 ±22.90	58.30 ±21.51	81.60 ±16.98	**UPL**	-31.31 (-39.74, -22.88)	<0.001	-27.48 (-35.29, -19.67)	<0.001	UPL	-23.31 (-27.17; -19.44)	<0.001	-20.01 (-23.65; -16.37)	<0.001
HOOS QoL, mean±SD	56.48 ±24.36	47.46 ±21.51	77.12 ±16.89	**KOOS QoL, mean±SD**	49.78 ±22.19	42.93 ±19.40	65.46 ±20.16	**UPL**	-29.66 (-37.45; -21.88)	<0.001	-27.45 (-35.81; -19.08)	<0.001	UPL	-22.53 (-27.06; -18.00)	<0.001	-19.83 (-23.99; -15.68)	<0.001
									Crude OR (95% CI)	**p-value**	**Adjusted^a OR (95% CI)**	**p-value**		**Crude OR (95% CI)**	**p-value**	**Adjusted^b OR (95% CI)**	**p-value**
Anxiety symptoms, n (%)	30 (15.9)	29 (22.2)	1 (1.3)		182 (18.2)	146 (19.8)	36 (14.6)	**UPL**	-	-	-	-	UPL	1.45 (0.89; 2.34)	0.132	1.12 (0.67; 1.86)	0.658
Depression symptoms, n (%)	30 (13.2)	28 (17.7)	2 (2.9)		146 (16.6)	116 (17.7)	30 (14.3)	**UPL**	-	-		-	UPL	1.28 (0.65; 2.52)	0.471	0.96 (0.49; 1.90)	0.914

All percentages and means±SDs are weighted. β^a and OR^a are adjusted for sex, and multimorbidity. β^b and OR^b are adjusted for sex, obesity, and multimorbidity.
ADL, activities of daily living; MPL, manageable pain levels; CI, confidence interval; HOOS, Hip Disability and Osteoarthritis Outcome Scale; UPL, unmanageable pain levels; KOOS, Knee Injury and Osteoarthritis Outcome Scale; OR, odds ratio; QoL, quality of life; SD, standard deviation

5.3. Study 3: Trajectories of physical function and quality of life in people with osteoarthritis: Results from a 10-year population-based cohort

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Available at https://doi.org/10.21203/rs.3.rs-1957027/v1

Abstract

Objective: To identify long-term trajectories of physical function and health-related quality of life (HRQoL) among people with hip and/or knee osteoarthritis (HKOA) and the sociodemographic, lifestyle, and clinical factors associated with different trajectories.

Methods: Participants with HKOA from the EpiDoC study, a 10-year follow-up (2011–2021) population-based cohort, were considered. Sociodemographic, lifestyle, and clinical variables were collected at baseline in a structured interview and clinical appointment. Physical function and HRQoL were evaluated with the Health Assessment Questionnaire (HAQ) and EuroQoL, respectively, at baseline and the three follow-ups. Group-based trajectory modeling identified physical function and HRQoL trajectories. Multinomial logistic regression analyzed the associations between the covariates of interest and trajectory assignment ($p<0.05$).

Results: We included 983 participants with HKOA. We identified three trajectories for each outcome: “consistently low disability” (32.0%), “slightly worsening moderate disability” (47.0%), and “consistently high disability” (21.0%) for physical function; “consistently high HRQoL” (18.3%), “consistently moderate HRQoL” (48.4%) and “consistently low HRQoL” (33.4%) for HRQoL. Age ≥75 years, female sex, multimorbidity, and high baseline clinical severity were associated with higher risk of assignment to poorer physical function and HRQoL trajectories. Participants with high education level and with regular physical activity had a lower risk of assignment to a poor trajectory. Unmanageable pain levels increased the risk of assignment to the “consistently moderate HRQoL” trajectory.

Conclusion: The levels of physical function and HRQoL remained stable over 10 years and highlight the importance of tailored interventions that target individuals’ modifiable risk factors associated with low physical function and HRQoL trajectories.

Keywords: Osteoarthritis, Trajectories, Health-Related Quality of Life, Physical Function, Prognosis

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease, affecting 519 million people worldwide in 2019 (1). The hip and knee are the joints most affected by OA, responsible for 9.6 million years lived with disability (2). Hip and/or knee OA (HKOA) comes at the high cost of up to 1%–2.5% of the gross domestic product of high-income countries due to the high utilization of healthcare services, mostly for patients requiring total joint replacement surgery. The high socioeconomic burden of HKOA is also due to the absenteeism, early retirement, and loss of productivity caused by this condition (3).

People with HKOA experience acute and chronic pain and limitations on physical function as well as progressive negative consequences for their mental health, health-related quality of life (HRQoL), and participation in social, leisure, and occupational activities (4). OA is a long-course, fluctuating, and complex disease with varying clinical characteristics and heterogenous progression (5). This multidimensionality challenges the prediction of the evolution of clinical symptoms and the long-term impact of the disease in physical function and HRQoL (6).

However, few studies have analyzed the long-term trajectories of physical function and HRQoL in people with HKOA (7). The disease progression and phenotypes have, however, been suggested as top priorities for OA research (6). Understanding the different trajectories of physical function, HRQoL, and other factors associated with HKOA may allow clinicians to individualize interventions according to clinical progression. Stratifying patients by their risk of high levels of disability and worsening quality of life and delivering targeted treatment interventions has become a key focus for OA research (6).

This study aimed to identify longitudinal trajectories of physical function and HRQoL over 10 years and identify the sociodemographic, lifestyle, and clinical variables associated with different trajectories. Secondarily, this study aimed to describe the patterns of specific dimensions of physical function and HRQoL in the 10-year period.

METHODS

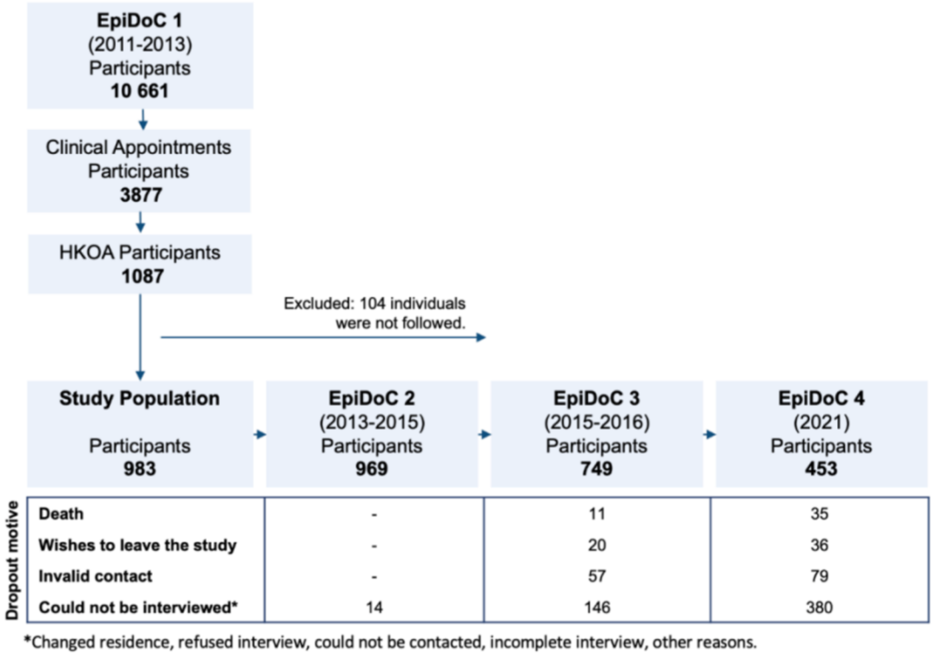
Data Source

This nationwide longitudinal study in Portugal analyzed data from the Epidemiology of Chronic Diseases (EpiDoC) cohort (2011–2021), which was comprised of randomly selected Portuguese adults (≥18 years old) living in private households, as previously described in the literature (8). The EpiDoC cohort had four waves: EpiDoC 1 (N=10,661) collected baseline data from September 2011 to December 2013; EpiDoC 2 (N=7,591) started in March 2013 and ended in July 2015; EpiDoC 3 (N=5,653) started in September

2015 and ended in July 2016; and the most recent wave, EpiDoC 4 (N=3,757), occurred from March to August 2021. The baseline evaluation (EpiDoC 1) aimed to estimate the prevalence of 12 rheumatic and musculoskeletal diseases (RMDs) in Portugal, including HKOA. EpiDoC 1 was performed in two phases. In the first phase, trained research assistants conducted face-to-face interviews with a structured questionnaire to collect data on socioeconomic status, chronic non-communicable diseases, HRQoL, and healthcare resource consumption and screen for RMDs. The second phase integrated a clinical appointment for all participants who screened positive for RMDs and 20% of those with negative RMD screenings who agreed to participate. Each appointment consisted of a structured evaluation with a rheumatologist—including laboratory and imaging exams, if needed—to validate the RMD diagnosis and evaluate the patient's disease-related information (8). In each follow-up wave, trained research assistants performed follow-up evaluations as an interview over the phone. These interviews were guided by a core questionnaire to collect data on socioeconomic status, new diagnoses of chronic non-communicable diseases, HRQoL, physical function, and healthcare resource consumption to gather longitudinal data. Each wave also had specific questions on lifestyles and health-related issues to enable the collection of cross-sectional and longitudinal data (8,9) – Figure 1.

Study population

This study included participants from the EpiDoC cohort with an HKOA diagnosis validated by a rheumatologist according to the American College of Rheumatology OA classification criteria for hip (10) and knee OA (11).



Dropout motive	EpiDoC 2	EpiDoC 3	EpiDoC 4
Death	-	11	35
Wishes to leave the study	-	20	36
Invalid contact	-	57	79
Could not be interviewed*	14	146	380

*Changed residence, refused interview, could not be contacted, incomplete interview, other reasons.

Figure 1. Flowchart of study design for participants with hip/knee osteoarthritis.

Outcome definition and measurements

Physical Function

Physical function was measured with the Health Assessment Questionnaire (HAQ), that is the most widely used questionnaire to assess functional status in patients with arthritis. Although not specific for people with HKOA, it was previously tested in this population, showing good psychometric properties (12). HAQ was used in the first phase of EpiDoC 1, as a baseline and by a phone interview during the three follow-up assessments. This instrument evaluates functional impairments in 20 activities of daily living classified into eight dimensions: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities (e.g., shopping, entering and exiting a car, and doing chores). Each activity was scored from 0 to 3 according to the individual’s difficulty in performing it: 0, “Without any difficulty”; 1, “With some difficulty”; 2, “With much difficulty”; and 3, “Unable to do”. The total possible scores lie between zero, indicating no functional impairment/disability, and 3, indicating complete impairment/disability (12).

Health-Related Quality of Life

HRQoL was measured with the Portuguese version of EuroQoL, with a 5-dimension and 3-level (EQ-5D-3L) descriptive system. The assessment took place in the first phase of EpiDoC 1 at baseline and during the three follow-up assessments, by phone interview. This instrument describes health status in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is scored within three levels (without problems, some problems, extreme problems). Participants were asked to mark the option that would best describe their experience on the day of the interview. A preference-based scoring function was used to convert the descriptive system to a summary index score that ranged from 1 (full health) to 0 or less than 0, which correspond to death or states worse than death, respectively (13).

Covariates of interest

Sociodemographic, lifestyle, and clinical variables were collected during the baseline assessment. Given the scarcity of data in some categories, and to ensure optimal interpretation of the data, several variables were subjected to categorical transformation.

In this study, we considered age class, sex, and geographic location — according to NUTS II territorial units (Lisbon, North, Centre, Algarve, Alentejo, Madeira, and Azores)—as sociodemographic variables. The age classes were <55 years old, 55–64 years old, 65–74 years old, and ≥75 years old. In the analysis of geographic locations, Madeira and Azores were merged to form one “Islands” region. Marital status was categorized as “with partner” (married or consensual union) and “no partner” (single, widowed, or divorced). Education level was categorized according to the years of education completed: “<4 years” (less than primary education), “4–9 years” (primary or secondary education), and “≥10 years” (secondary or higher education). Body mass index (BMI) was categorized as “underweight” (≤18.49 kg/m^2), “healthy weight” (≥18.5 and ≤ 24.99 kg/m^2), “overweight” (≥25 and ≤29.99 kg/m^2), and “obese” (≥30 kg/m^2) according to self-reported height and weight. Lifestyle variables were collected as well, including alcohol intake (“never” and “occasionally or daily”), smoking habits (“never,” “in the past,” and “occasionally or daily”), and whether individuals participated in regular physical activity/sports (“yes”, “no”, and “doesn’t know/doesn’t answer”).

Multimorbidity was defined as having two or more self-reported chronic non-communicable diseases from the following list noted in the baseline assessment: high blood pressure, high cholesterol, cardiac disease, diabetes mellitus, chronic lung disease, problems in the digestive tract, neurological disease, mental disease, allergies, cancer, and hyperuricemia (14).

Clinical severity was evaluated at baseline with the Portuguese versions of the Knee Injury and Osteoarthritis Outcome Score (KOOS) (15) and the Hip Disability and Osteoarthritis Outcome Score (HOOS) (16). HOOS/KOOS are self-reported assessments that evaluate the consequences of HKOA in five dimensions: pain, other symptoms, activities of daily living, sports and leisure, and quality of life. Scores for each dimension were transformed to a 0–100 scale, with 0 representing extreme hip/knee problems and 100 representing no hip/knee problems (15,16). A final composite score was calculated with the mean score of each dimension, as previously recommended (17). For this study, and to facilitate the interpretation of this measure, the final score is reported as the inverted normalized mean score (0–100), with higher values corresponding to higher clinical severity, as previously documented (18). Pain intensity was measured as the mean pain intensity in the previous week with the 11-point Numeric Pain Rating Scale (NPRS) at baseline. Zelman et al. (2003), using question 5 of the Brief Pain Inventory scale to determine the average pain in the previous week on an 11-point NPRS, found 5 points to be the optimal cut-off point to consider a pain day manageable in OA ($F[7, 9]=7.08$, $p<0.001$) (19). Therefore, we divided the population into two subgroups: manageable pain levels (<5 points) and unmanageable pain levels (≥5 points). For HOOS/KOOS and NPRS, if a participant's hip and knee were both affected, the worst score of the two was considered.

Data analysis

We first performed descriptive analysis of the HAQ and EQ-5D-3L dimensions for each of the follow-ups in the 10-year period. The proportions of participants that reported "some difficulty" and "with much difficulty" in each HAQ dimension and "some problems" or "extreme problems" in each EQ-5D-3L dimension were computed and plotted, separately, for better interpretation.

We used a group-based trajectory modeling analysis to identify different trajectories of physical function and HRQoL over the 10-year period. For this, we considered only HKOA patients who participated in both the baseline assessment and at least one of the cohort follow-ups. Group-based trajectory modeling uses finite mixtures of probability distributions based on maximum likelihood estimation to identify clusters of individuals with similar trajectories.

Posterior probabilities were estimated to quantify the likelihood of an individual belonging to a specific trajectory, and participants were placed into their respective trajectories with the highest posterior probability. The final model was chosen based on the log of the

Bayes factor, by comparing changes in the Bayesian Information Criteria (BIC) between models (20). Average posterior probabilities, odds of correct classification, and clinical interpretation of the trajectory groups were also considered in this process. Nagin (2005) recommended that average posterior probabilities should be ≥0.7, as the optimal cut-off (21). A censored normal distribution specification was considered for both outcomes (EQ-5D-3L and HAQ scores). In this approach, negative EQ-5D-3L scores were recoded and attributed a value of 0 for compatibility because, theoretically, 0 and values below 0 represent a low HRQoL state ($n_{recoded}$=63).

Descriptive analysis was performed for the sociodemographic, clinical, and lifestyle characteristics of the study population and each of the trajectory subgroups using absolute and relative frequencies for categorical variables and the mean and standard deviation for continuous variables. The same analyses were conducted separately for the participants included in each wave (Additional file 1: table S1). Independence hypotheses were tested to compare the different trajectory subgroups according to their sociodemographic, clinical, and lifestyle characteristics using non-parametric tests: Chi-squared for categorical variables and Kruskal–Wallis for continuous variables.

Finally, we used a 2-step multinomial logistic regression model to assess the associations between the baseline variables, namely the sociodemographic, clinical and lifestyle variables, and trajectory groups assignment. In the first step, we conducted a univariate analysis, considering a significance level of 0.25 to avoid early exclusion of potentially important variables. Then, with a forward conditional method, we sequentially included the statistically significant variables and compared the models through likelihood ratio tests based on the Akaike Information Criterion until the final models were reached. The relative risk ratio (RRR) was estimated for each variable with a 95% confidence interval (95% CI).

The models' postestimation was evaluated through a generalized Hosmer–Lemeshow goodness-of-fit test (22) under the null hypothesis that the model fit the data correctly, i.e., the observed and expected frequencies did not differ significantly.

The missing data for covariates was below 10% thus, no imputation methods were used. Participants with missing data were automatically excluded in this procedure, constituting a complete case analysis. The adjustment of sex and age was forced in the models. Due to scarcity of data, the normal and underweight BMI categories were merged into one (<25.00 kg/m^2).

All analyses were performed with STATA v16.1 considering a level of significance of 0.05. Trajectory analysis was carried out using the *traj* plugin (21).

RESULTS

We included in this study 983 participants with HKOA from the EpiDoC (96 with hip OA, 803 with knee OA, and 84 with hip and knee OA). Total sample average years of EpiDoC 4 (2021) to baseline (EpiDoC 1) were 8.38±0.61 years – Supplementary table S2.

Patterns of physical function and HRQoL dimensions over time

Considering physical function, EpiDoC 2 was the wave with the highest percentage of people that reported "some" or "much difficulty" in all dimensions of HAQ. Namely, in "reach" this proportion was 78.12% (n=739), in "walking" 70.59% (n=672) and in arising 68.73% (n=655). These were also the dimensions with the highest proportion of people who experienced some or much difficulty in all four waves. "Walking" was the dimension with the largest increase in the proportion of people who reported some or much difficulty between EpiDoC 1 (n=505, 51.37%) and EpiDoC 4 (n=262, 64.37%) – Additional file 1: figure S1, Table S3.

Overall, the patterns in the EQ-5D-3L dimensions over the 10-year period were similar to those in the HAQ dimensions. Pain and mobility were the dimensions for which the largest proportions of people with HKOA reported some or extreme problems: 74.87% (n=715) and 70.87% (n=674) in EpiDoC 2, respectively. Self-care dimension had the greatest increase in the proportion of people reporting some or extreme problems over the 10-year period (EpiDoC 1: n=194, 19.73%; EpiDoC 4: n=125, 30.56%) - Additional file 1: figure S2, Table S3.

Physical function and HRQoL trajectories

Based on the BIC values and clinical interpretation of trajectories, a model with three trajectory groups was achieved for both physical function and HRQoL (Additional file 1: table S4) with an average posterior probability of group membership greater than 0.7 (Supplementary Table S5). Trajectories of physical function in the 10-year follow-up were identified as: 1) "consistently high disability" (n=204, 21.0%); 2) "slightly worsening moderate disability" (n=472, 47.0%); and 3) "consistently low disability" (n=307, 32.0%) – Figure 2 a). For HRQoL, the three trajectories were defined as: 1) "consistently low HRQoL" (n=317, 33.4%); 2) "consistently moderate HRQoL" (n=501, 48.4%); 3) "consistently high HRQoL" (n=165, 28.3%), where participants consistently reported low, moderate and high HRQoL during the follow-up, respectively – Figure 2 b).

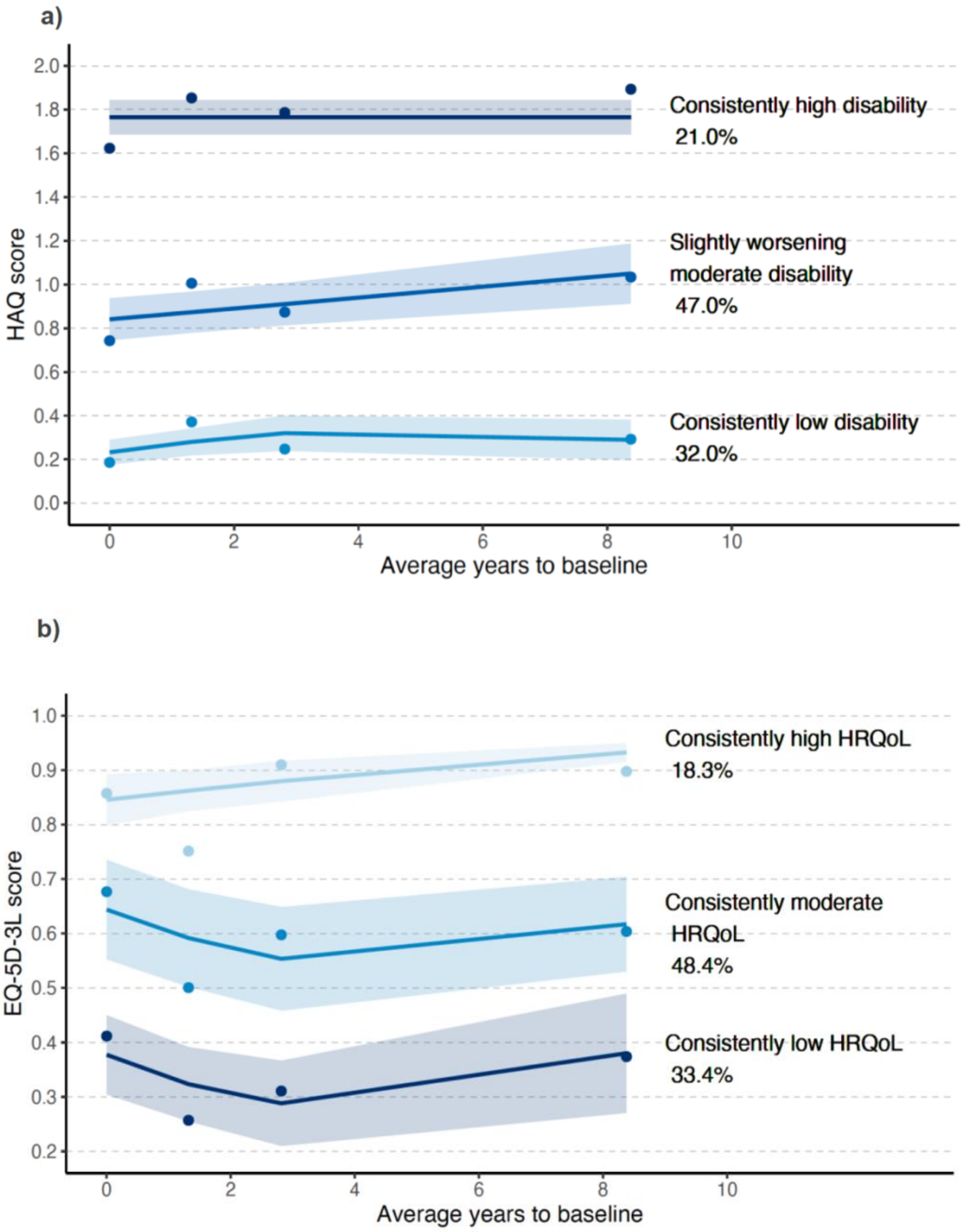


Figure 2. Estimated a) physical function and b) HRQoL trajectories for people with hip and/or knee osteoarthritis, and proportion of individuals in each group. Shapes represent observed group membership and lines represent predicted group membership.

Baseline characteristics of participants with HKOA according to trajectory assignment

The HKOA participants (n=983) had a mean age of 62.2±11.2 years old, 71.3% (n=701) were female, 81.7% (n=751) were overweight or obese, multimorbidity was present in 70.8% (n=634) of the participants, and only 21.6% (n=212) reported regular physical activity (Table 1).

For physical function, the “consistently high disability” trajectory group had the highest mean age (70.9±9.4 years, p<0.001), the largest proportion of female participants (n=176, 86.3%, p<0.001), with low education level (<4 years of education; n=92, 45.1%, p<0.001), obesity (n=83, 46.9%, p<0.001), no regular physical activity (n=23, 11.3%, p<0.001), multimorbidity (n=155, 89.1%, p<0.001), unmanageable pain levels (n=165, 85.0%, p<0.001) and the highest clinical severity (inverted HOOS/KOOS5: 59.4 ±15.1, p<0.001) - Table 1.

Table 1. Baseline sociodemographic, anthropometric, lifestyle and clinical characteristics for the study population and Physical Function trajectory groups.

		Physical Function (HAQ score) Trajectories			
	Total Sample n=983	Consistently low disability n=204	Slightly worsening disability n=472	Consistently high disability n=307	p^a
Sociodemographic					
Age (years)					
Mean (SD)	65.2 (11.2)	70.9 (9.4)	65.4 (10.6)	61.2 (11.5)	<0.001
<55 years old, n (%)	170 (17.3%)	13 (6.4%)	79 (16.7%)	78 (25.4%)	<0.001
55–64 years old, n (%)	265 (27.0%)	34 (16.7%)	128 (27.1%)	103 (33.6%)	
65–74 years old, n (%)	340 (34.6%)	78 (38.2%)	168 (35.6%)	94 (30.6%)	
≥75 years old, n (%)	208 (21.2%)	79 (38.7%)	97 (20.6%)	32 (10.4%)	
Female sex, n(%)	701 (71.3%)	176 (86.3%)	359 (76.1%)	166 (54.1%)	<0.001
Region (NUTS II), n (%)					
North	267 (27.2%)	65 (31.9%)	125 (26.5%)	77 (25.1%)	0.032
Center	238 (24.2%)	47 (23.0%)	118 (25.0%)	73 (23.8%)	
Lisbon	165 (26.8%)	31 (15.2%)	66 (14.0%)	68 (22.1%)	
Alentejo	58 (5.9%)	15 (7.4%)	28 (5.9%)	15 (4.9%)	
Algarve	20 (2.0%)	7 (3.4%)	6 (1.3%)	7 (2.3%)	
Islands	235 (23.9%)	39 (19.1%)	129 (27.3%)	67 (21.8%)	
Marital status, partner **n (%)**	641 (65.2%)	112 (54.9%)	316 (67.0%)	213 (69.4%)	0.002
Educational level, n (%)					
<4 years	230 (23.4%)	92 (45.1%)	107 (22.7%)	31 (10.1%)	<0.001

4–9 years	630 (64.1%)	106 (52.0%)	314 (66.5%)	210 (68.4%)	
≥10 years	123 (12.5%)	6 (2.9%)	51 (10.8%)	66 (21.5%)	
Anthropometric					
BMI (kg/m^2), n (%)					
Underweight/Normal weight	168 (18.3%)	32 (18.1%)	71 (16.0%)	65 (21.9%)	<0.001
Overweight	376 (40.9%)	62 (35.0%)	169 (38.0%)	145 (48.8%)	
Obese	375 (40.8%)	83 (46.9%)	205 (46.1%)	87 (29.3%)	
Lifestyle					
Smoking habits n (%)					
Never	732 (74.5%)	173 (84.8%)	371 (78.6%)	188 (61.2%)	<0.001
In the past	180 (18.3%)	20 (9.8%)	71 (15.0%)	89 (29.0%)	
Daily/Occasionally	71 (7.2%)	11 (5.4%)	30 (6.4%)	30 (9.8%)	
Alcohol consumption n (%)					
Never	497 (50.6%)	126 (61.8%)	251 (53.3%)	120 (39.1%)	<0.001
Occasionally/Daily	485 (49.4%)	78 (38.2%)	220 (46.7%)	187 (60.9%)	
Regular physical activity n (%)	212 (21.6%)	23 (11.3%)	91 (19.3%)	98 (32.0%)	<0.001
Clinical					
Multimorbidity n (%) yes	634 (70.8%)	158 (91.9%)	313 (73.0%)	163 (55.4%)	<0.001
Unmanageable pain levels (≥5 NPRS), n (%)	691 (73.8%)	164 (85.0%)	355 (78.2%)	172 (59.5%)	<0.001
Clinical severity mean(SD) (Inverted HOOS/KOOS)	46.1 (18.8)	59.4 (15.1)	48.8 (16.0)	33.1 (17.1)	<0.001
Physical function (HAQ score) – Mean (SD)	0.75 (0.67)	1.65 (0.50)	0.75 (0.47)	0.15 (0.23)	<0.001
HRQoL (EQ5D score) – Mean (SD)	0.62 (0.27)	0.36 (0.19)	0.61 (0.23)	0.82 (0.20)	<0.001

[a] *p*-values for non-parametric independency tests (Chi-squared for categorical variables, Kruskal–Wallis for continuous variables). BMI: body mass index; NPRS: Numeric Pain Rating Scale; HRQoL: Health-Related Quality of Life. Sample size is not constant due to missing values in some variables at baseline: HRQoL (n=971).

Similarly, the “consistently low HRQoL” trajectory group had the highest mean age (68.4±10.1 years old, p<0.001), the largest proportions of female participants (n=264, 83.3%, p<0.001) and participants with the lowest education level (<4 years of education: n=125, 39.4%, p<0.001), with obesity (n=150, 53.0%, p<0.001), no regular physical activity (n=37, 11.7%, p<0.001), multimorbidity (n=230, 83.3%, p<0.001), unmanageable pain levels (n=256, 84.2%, p<0.001) and the highest clinical severity (inverted HOOS/KOOS: 57.0±15.6, p<0.001) – Table 2.

Table 2. Baseline sociodemographic, anthropometric, lifestyle and clinical characteristics for participants assigned to the HRQoL trajectory groups.

	HRQoL (EQ5D score) Trajectories			
	Consistently low HRQoL	Consistently moderate HRQoL	Consistently high HRQoL	*p*^{a}
	n=317	n=501	n=165	
Sociodemographic				
Age (years)				
Mean (SD)	68.4 (10.1)	64.7 (10.9)	60.5 (12.0)	<0.001
<55 years old, n (%)	35 (11.0%)	92 (18.4%)	43 (26.1%)	<0.001
55–64 years old, n (%)	71 (22.4%)	141 (28.1%)	53 (32.1%)	
65–74 years old, n (%)	114 (36.0%)	172 (34.3%)	54 (32.7%)	
≥75 years old, n (%)	97 (30.6%)	96 (10.2%)	15 (9.1%)	
Female Sex, n(%)	264 (83.3%)	350 (69.9%)	87 (52.7%)	<0.001
Region (NUTS II), n (%)				
North	95 (30.0%)	127 (25.3%)	45 (27.3%)	0.920
Center	75 (23.7%)	127 (25.3%)	36 (21.8%)	
Lisbon	47 (14.8%)	85 (17.0%)	33 (20.0%)	
Alentejo	18 (5.7%)	31 (6.2%)	9 (5.5%)	
Algarve	7 (2.2%)	9 (1.8%)	4 (2.4%)	
Islands	75 (23.7%)	122 (24.4%)	38 (23.0%)	
Marital status :partner, **n (%)**	190 (59.9%)	323 (64.5%)	128 (77.6%)	0.001
Educational level, n (%)				
<4 years	125 (39.4%)	88 (17.6%)	17 (10.3%)	<0.001
4–9 years	179 (56.5%)	344 (68.7%)	107 (64.8%)	
≥10 years	13 (4.1%)	69 (13.8%)	41 (24.9%)	
Anthropometric				
BMI (kg/m^2), n (%)				
Underweight/Normal weight	39 (13.8%)	98 (20.6%)	31 (19.5%)	<0.001
Overweight	94 (33.2%)	199 (41.7%)	83 (52.2%)	
Obese	150 (53.0%)	180 (37.7%)	45 (28.3%)	
Lifestyle				
Smoking habits n (%)				
Never	257 (81.1%)	370 (73.8%)	105 (63.6%)	<0.001
In the past	41 (12.9%)	87 (17.4%)	52 (31.5%)	
Daily/Occasionally	19 (6.0%)	44 (8.8%)	8 (4.9%)	
Alcohol consumption n (%)				
Never	180 (56.8%)	260 (52.0%)	57 (34.6%)	<0.001
Occasionally/Daily	137 (43.2%)	240 (48.0%)	108 (65.4%)	
Regular physical activity n (%)	37 (11.7%)	117 (23.4%)	58 (35.2%)	<0.001
Clinical				
Multimorbidity n (%)	242 (88.3%)	305 (65.9%)	87 (55.1%)	<0.001
Unmanageable pain levels	256 (84.2%)	357 (75.0%)	78 (50.0%)	<0.001

(≥5 NPRS), n (%)				
Clinical severity, Mean (SD) (Inverted HOOS/KOOS)	57.0 (15.6)	44.1 (17.1)	31.4 (17.3)	<0.001
Physical function (HAQ score) – Mean (SD)	1.32 (0.63)	0.545 (0.51)	0.26 (0.38)	<0.001
HRQoL (EQ5D score) – Mean (SD)	0.37 (0.18)	0.70 (21.6)	0.87 (0.18)	<0.001

[a] *p*-values for non-parametric independency tests (Chi-squared for categorical variables, Kruskal–Wallis for continuous variables). BMI: body mass index; NPRS: Numeric Pain Rating Scale; HRQoL: Health-Related Quality of Life. Sample size is not constant due to missing values in some variables at baseline: HRQoL (n=971).

For both outcome measures, participants showed poorer mean scores in the poorer trajectory groups—i.e., “consistently high disability” (HAQ: 1.65±0.50; p<0.001) and “consistently low” HRQoL (EQ-5D-3L: 0.37±0.18; p<0.001) – table 1 and 2.

Baseline factors associated with physical function and HRQoL trajectory groups

Univariate logistic regression analysis is presented in the Additional File 1: tables S6 and S7, for HRQoL and physical function, respectively.

In the final multinomial logistic regression model for the physical function trajectory groups, using “consistently low disability” trajectory as reference, female participants (RRR=2.90; 95% CI: 1.97, 4.28) and people with multimorbidity (RRR=1.66; 95% CI: 1.13, 2.42) had a significantly higher risk of a “slightly worsening moderate disability”. Female participants (RRR: 5.56; 95% CI: 2.99, 10.34), adults aged 75 years and over (RRR=3.93; 95% CI: 1.48, 10.46), and people with multimorbidity (RRR=4.99; 95% CI: 2.49, 10.00) had a higher risk of assignment to the “consistently high disability” trajectory. Baseline clinical severity increased the likelihood of being assigned to the “consistently high disability” (RRR=1.09; 95% CI: 1.07, 1.11) and the “slightly worsening moderate disability” (RRR=1.06; 95% CI: 1.04, 1.07) trajectories. People with a high level of education (≥10 years) (RRR=0.19; 95% CI: 0.05, 0.64) and a baseline report of regular physical activity (RRR=0.35; 95% CI: 0.17, 0.68) were less likely to be assigned in the “consistently high disability” trajectory – table 3.

Table 3. Multinomial logistic regression model for the association of baseline characteristics and physical function (HAQ) trajectories.

	Physical Function Trajectories (HAQ)		
	Consistently low disability	**Slightly worsening moderate disability**	**Consistently high disability**
	RRR (95% CI)	**RRR (95% CI)**	**RRR (95% CI)**

Sex			
Male (ref)	-	-	-
Female	-	2.90 (1.97–4.28)	5.56 (2.99–10.34)
Age class			
<55 years old (ref)	-	-	-
55–64 years old	-	0.57 (0.34–0.97)	0.63 (0.25–1.59)
65–74 years old	-	0.93 (0.55–1.58)	1.41 (0.58–3.41)
≥75 years old	-	1.65 (0.86–3.17)	3.93 (1.48–10.46)
Educational level			
<4 years (ref)	-	-	-
4–9 years	-	1.00 (0.57–1.75)	0.54 (0.28–1.03)
≥10 years	-	0.88 (0.44–1.78)	0.19 (0.05–0.64)
Regular physical activity (yes)	-	0.51 (0.34–0.78)	0.35 (0.17–0.68)
Clinical severity (0 best – 100 worst)	-	1.06 (1.04–1.07)	1.09 (1.07–1.11)
Multimorbidity (yes)	-	1.66 (1.13–2.42)	4.99 (2.49–10.00)

RRR: Relative risk ratio; HAQ: Health Assessment Questionnaire

Goodness-of-fit: $\chi^2(16)=19.2$, df=16, $p=0.259$

Total sample: n=823

For HRQoL, similar baseline variables were significantly associated with poor trajectory groups, using “Consistently high HRQoL” trajectory as reference class. Female sex (RRR=2.11; 95% CI: 1.39, 3.22), older adults aged 75 years old and over (RRR=2.65; 95% CI: 1.18, 5.92), and participants with unmanageable pain levels (RRR=1.85; 95% CI: 1.16, 2.93) were significantly associated with a “consistently moderate HRQoL” trajectory. Female participants (RRR=3.75; 95% CI: 2.16, 6.49) and participants with multimorbidity (RRR=3.83; 95% CI: 2.13, 6.90) were associated with a “consistently low HRQoL trajectory”. A higher baseline clinical severity score was associated with a “consistently moderate” HRQoL (RRR: 1.03 95%CI: 1.02–1.05) and with a “consistently low” (RRR: 1.08, 95%CI: 1.06–1.10) HRQoL trajectory. Participants with a high level of education (≥10 years) (RRR=0.29; 95% CI: 0.10, 0.82) and a baseline report of regular physical activity (RRR=0.36; 95% CI: 0.20, 0.67) had a significantly lower risk of assignment to the “consistently low HRQoL” trajectory – Table 4.

Table 4. Multinomial logistic regression model for the association of baseline characteristics of people with HKOA and HRQoL (EQ-5D-3L) trajectories.

	HRQoL Trajectories (EQ-5D)		
	Consistently high HRQoL (Reference)	**Consistently moderate HRQoL RRR (95% CI)**	**Consistently low HRQoL RRR (95% CI)**
Sex			

Male (ref)	-	-	-
Female	-	2.11 (1.39–3.22)	3.75 (2.16–6.49)
Age class			
<55 years old (ref)	-	-	-
55–64 years old	-	0.94 (0.52–1.68)	0.68 (0.32–1.47)
65–74 years old	-	0.99 (0.55–1.79)	0.71 (0.33–1.52)
≥75 years old	-	2.65 (1.18–5.92)	2.24 (0.87–5.82)
Educational level			
<4 years (ref)	-	-	-
4–9 years	-	1.32 (0.67–2.59)	0.62 (0.30–1.28)
≥10 years	-	1.04 (0.46–2.35)	0.29 (0.10–0.82)
Regular physical activity (yes)	-	0.60 (0.38–0.94)	0.36 (0.20–0.67)
Clinical severity (inverted KOOS/HOOS) (0 low – 100 high severity)	-	1.03 (1.02–1.05)	1.08 (1.06–1.10)
Unmanageable pain level (yes)	-	1.85 (1.16–2.93)	1.36 (0.74–2.48)
Multimorbidity	-	1.28 (0.84–1.96)	3.83 (2.13–6.90)

RRR – Relative risk ratio; HRQoL: Health-Related Quality of Life

Final model goodness-of-fit: $\chi^2(16)=17.9$, $p=0.329$

Total sample: n=817

DISCUSSION

This study identified three different long-term trajectories of physical function (HAQ) and HRQoL (EQ-5D-3L) in people with HKOA, that remained stable over time, according to baseline levels – high, moderate or low. Similar results were found in the Osteoarthritis Initiative cohort studies, using the KOOS quality of life subscale (23,24). One of these studies included more than 3,000 people with mild knee OA and additionally found a rapidly worsening HRQoL trajectory, that made up 9.5% of the participants. These subjects were at higher risk of total joint replacement. Moreover, a small proportion of participants with knee OA reported high HRQoL, similarly to our study (23). Regarding physical function, similar results were found in a recent systematic review, concluding that physical function and also pain trajectories remained stable over time (7). Data from the CHECK cohort, with a 9-year follow-up, reported that poor physical function trajectories were not associated with timing for surgery (25).

Baseline differences in physical function and HRQoL, and subsequent trajectories assignment can be explained by the so-called “horse-racing effect”. This concept describes that the participants who have already started progressing in these outcomes, are likely to be “out in the front” (have worse physical function or HRQoL) at baseline, because they were already in a lower level of physical function or HRQoL before the start of the study, and will keep relative lower/higher levels of physical function and HRQoL through time (26).

In our study, we found that older age, female sex, presence of multimorbidity, high baseline clinical severity, and unmanageable pain levels were associated with low HRQoL and high disability trajectories, similarly to other longitudinal studies that analyzed the course of physical function (7,27–30) and HRQoL (23,24).

However, there is conflicting evidence for the association of older age with low HRQoL trajectories. Data from the Osteoarthritis Initiative showed that being younger was associated with of quality of life (measured with KOOS quality of life subscale) in a population between 45 and 79 years old (24). HRQoL loss in younger people may be explained by the impact of OA on work (31), whereas exposure to risk factors, structural changes and multimorbidity in older adults are also associated with functional and HRQoL decline (32,33). Because we used a generic measurement tool (EQ-5D-3L), our results may capture a broader image of HRQoL.

Previous literature suggest that female sex is associated with poor physical function (34) and HRQoL (23) trajectories, likely due to the gender gap in overall socioeconomic disadvantages of women, when compared to men. Additionally, women often report more activity limitations, multimorbidity, pain, depression, and self-reported health status when compared to men (35). Evidence shows that people with HKOA and multimorbidity, specifically cardiac diseases, hypertension, or back pain, are more likely to have worse physical function (36), mobility and mental health problems (37).

Unmanageable pain was associated with a “consistently moderate” HRQoL trajectory but not with any physical function trajectories. This conflicts with the literature which shows that high pain intensity is an important predictor of HRQoL decline (23) and that pain explains most of the variability in disability and HRQoL (38). On the other hand, higher clinical severity at baseline was associated with poorer physical function and HRQoL trajectories, as previously found in the literature (27). Clinical severity, evaluated with HOOS/KOOS, encompasses several dimensions of OA consequences that fluctuate over time and are closely related to each other, such as pain, stiffness, and activity performance (39). Therefore, not only pain levels, but symptoms conjunction, may influence HKOA trajectories.

We found that participants who reported regular physical activity at baseline had a lower risk of poor HRQoL and physical function trajectories, suggesting a protective effect on the symptoms and structural progression of OA (40). Maintaining regular physical activity is one of the core recommended interventions for HKOA (41) and most people follow improvement trajectories in physical function after physical activity programs (29,42). Therefore, we hypothesize that specific, personalized, and supportive interventions that consider modifiable risks factors for poor trajectories, such as physical activity, may improve HRQoL and physical function in the long term as well as the pattern of progression of these outcomes.

We examined the dimensions of physical function (HAQ) and HRQoL (EQ-5D-3L) in each follow-up evaluation and found poorer levels in the HAQ and in EQ-5D-3L dimensions in the second wave of the study (2013–2015) than in the other three waves. This may be explained by the major economic crisis that occurred in Portugal at the time and led to high unemployment rates, lower monthly incomes, and consequent inequalities in access to healthcare (43). These are factors known to be closely associated with health outcomes (44). Regarding EQ-5D-3L, pain/discomfort, mobility, and usual activities were the most affected dimensions, highlighted previsouly as the dimensions with the most pronounced differences between people with OA and the general population (45). Aligned with our results, a national study in Austria showed that the most impaired daily life activities for people with HKOA were heavy housework, bending or kneeling down, climbing stairs, and walking 500 m (46).

Limitations and Strengths

This study is not free from limitations. First, only four waves were conducted for this cohort, and the last two were separated by a period of 5 years, which restricts the number of observations in the longitudinal analysis and may compromise the sensitivity of the trajectories. Baseline data collection occurred between 2011 and 2013, which placed individuals at different starting points and added variability that wasn’t accounted for. Second, participants’ memory bias in the self-reported questions in the 10 years period might have affected the strength of associations. Moreover, we did not investigate differences between people with hip versus knee OA. Although OA of the hip and OA of the knee may impose similar burdens (2,47), people with hip OA may have greater disease severity and an earlier requirement for joint replacement (48). Lastly, we did not control other potential factors that may influence the classification into different HRQoL or physical function trajectory groups, namely psychosocial factors (e.g., coping strategies or self-efficacy) and interventions used. Furthermore, physical activity was self-reported, not taking into account the amount of time spent per week or the intensity; thus, our results may have overestimated the recommendations for physical activity.

However, this study used data from a large nationwide prospective cohort of adults from the community, and is not confined to people who seek healthcare. To the best of our knowledge, this is the first study to characterize trajectories of physical function and HRQoL among community adults with clinically validated HKOA using group-based trajectory modeling. This approach has been gaining momentum in the longitudinal analysis of clinical patient-reported outcomes, since it allows for the identification of unique subgroups of the population that follow distinct trajectories (49). OA is a progressive chronic disease, a long follow-up period is needed to capture changes in health-outcomes. Few studies have follow-ups longer than 8 years, in opposite to our study (7).

Future research should validate HKOA outcome trajectories in a population-level in other contexts, analyze the interventions that may change trajectories (e.g., exercise, total joint replacement) and consider also the modifiable predictors of poor trajectories in the design of stratified interventions for people with HKOA.

CONCLUSION

During a 10-year follow-up period, physical function and HRQoL trajectories remained stable over time in people with HKOA. Female participants, multimorbidity, baseline high clinical severity, and unmanageable pain levels were positively associated with moderate/low HRQoL and physical function trajectories, whereas, high education level and baseline regular physical activity were protective. Our findings highlight the importance of tailored OA multidisciplinary management programs that target individuals' modifiable risk factors, such as physical activity and multimorbidity.

LIST OF ABBREVIATIONS

BIC: Bayesian Information Criteria

BMI: Body mass index

EQ-5D-3L: EuroQoL, 5-dimension and 3-level

HAQ: Health Assessment Questionnaire

HKOA: Hip and/or Knee Osteoarthritis

HRQoL: Health-Related Quality of Life

KOOS: Knee Injury and Osteoarthritis Outcome Score

NPRS: Numeric Pain Rating Scale

NUTS II: Nomenclature of Territorial Units for Statistical purposes, *Nomenclatura das Unidades Territoriais para Fins Estatísticos*

OA: Osteoarthritis

RRR: Relative Risk Ratio

DECLARATIONS

Ethical approval and consent to participate: The EpiReumaPt study was approved by the Ethics Committee of NOVA Medical School and the Portuguese Data Protection Authority (*Comissão Nacional de Proteção de Dados*). This secondary analysis of EpiReumaPt database presented in this study was additionally approved by the Ethics Committee of NOVA Medical School. This study was performed in accordance with the Declaration of Helsinki and revised in 2013 in Fortaleza. Written informed consent was obtained from all participants before entering in EpiReumaPt study, as described elsewhere (16).

Consent for publication: Not Applicable.

Availability of data and materials: The data underlying this article were provided by the EpiDoc Unit - CEDOC by permission. Data will be shared upon request to the corresponding author with the permission of EpiDoc Unit group leaders.

Competing interests: All authors declare no competing interests.

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Authors' Contributions: DC, DL, ARH, EBC and AR contributed to the drafting of the manuscript. DL, DC, EBC and AMR contributed to the analysis and interpretation of the data. DL, DC and ARH contributed to statistical analysis. HC, JB, and AMR contributed to the conception and design of the main project (EpiReumaPt), provision of study materials, obtaining funding for the main project, administrative/logistic support, and collection of data. All authors critically revised and approved the final manuscript and all agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Supplementary Material

Additional File 1

Figure S1

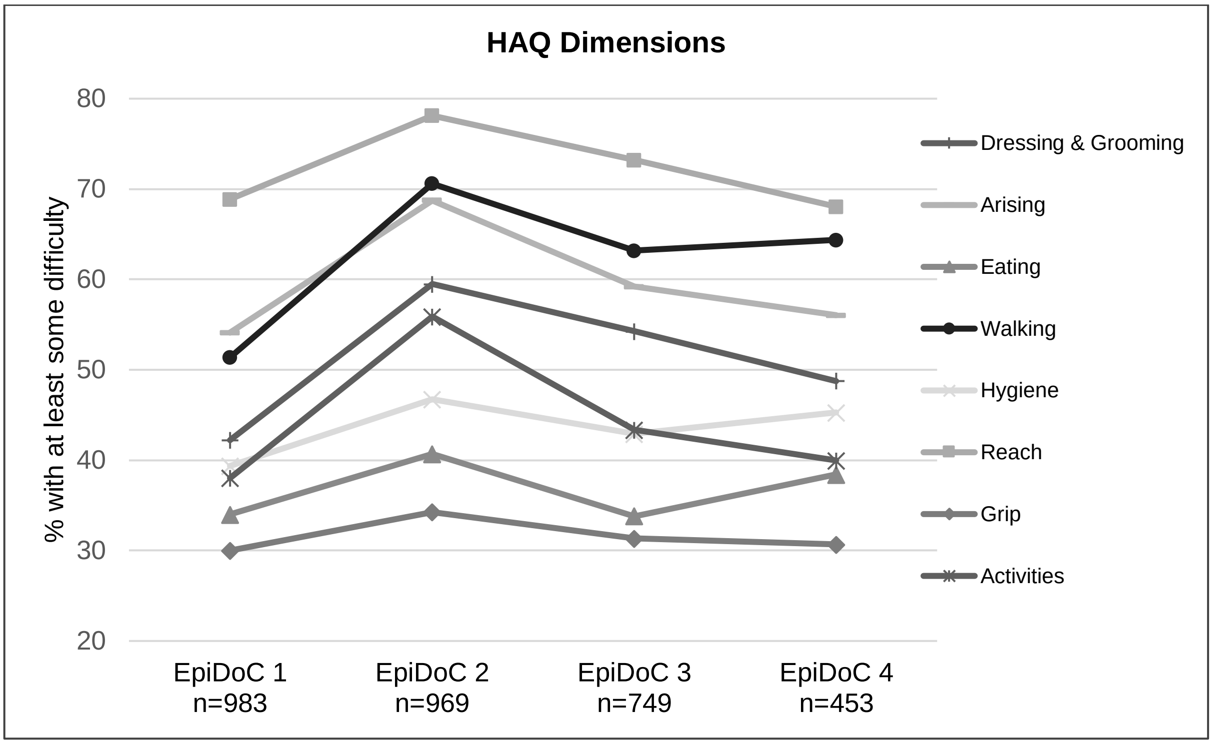

Figure 2. Percentages of people with HKOA with at least some difficulty (%) by HAQ domains at baseline (EpiDoC 1) and in each follow-up (EpiDoC 2, 3, and 4).

Figure S2

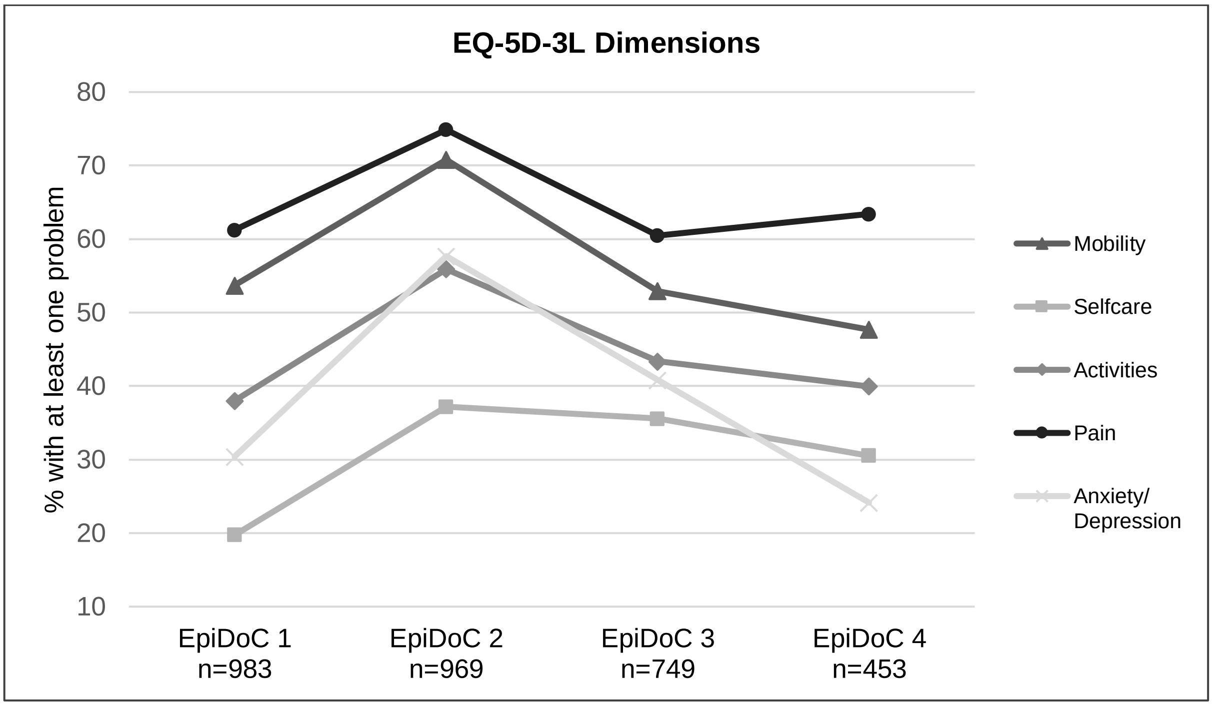

Figure 3. Percentages of people with HKOA with at least one problem (%) by EQ-5D-3L dimensions at baseline (EpiDoC 1) and in each follow-up (EpiDoC 2, 3, and 4).

Table S1. Sociodemographic, lifestyles and clinical characteristics of HKOA participants in each EpiDoC wave

	EpiDoC 1 **(2011-2013)** n=983	**EpiDoC 2** **(2013-2015)** n=969	**EpiDoC 3** **(2015-2016)** n=749	**EpiDoC 4** **(2021)** n=453
Sociodemographic				
Sex, n(%)				
Female	701 (71.3%)	692 (71.4%)	538 (71.8%)	332 (73.3%)
Age (years old**)**				
Mean (SD)	65.2 (11.2)	66.3 (11.2)	67.3 (11.5)	71.6 (11.0)
<55 years old, n (%)	170 (17.3%)	155 (16.0%)	102 (13.6%)	26 (5.7%)
55-64 years old, n (%)	265 (27.0%)	245 (25.3%)	177 (23.6%)	89 (19.6%)
65-74 years old, n (%)	340 (34.6%)	328 (33.8%)	245 (32.7%)	144 (31.8%)
³75 years old, n (%)	208 (21.2%)	241 (24.9%)	225 (30.0%)	194 (42.8%)
Region (NUTSII), n (%)				
North	267 (27.2%)	264 (27.2%)	195 (26.0%)	125 (27.6%)
Centre	238 (24.2%)	233 (24.0%)	175 (23.4%)	107 (23.6%)
Lisbon	165 (26.8%)	163 (16.8%)	122 (16.3%)	91 (20.1%)
Alentejo	58 (5.9%)	57 (5.9%)	48 (6.4%)	22 (4.9%)
Algarve	20 (2.0%)	20 (2.1%)	15 (2.0%)	11 (2.4%)
Islands	235 (23.9%)	232 (23.9%)	194 (25.9%)	97 (21.4%)
Marital status, **n (%)**				
With partner	641 (65.2%)	631 (65.1%)	492 (65.7%)	313 (69.1%)
Educational Level, n (%)				
<4 years	230 (23.4%)	225 (23.2%)	167 (22.3%)	87 (19.2%)
4-9 years	630 (64.1%)	621 (64.1%)	488 (65.1%)	293 (64.7%)
³10 years	123 (12.5%)	123 (12.7%)	94 (12.6%)	73 (16.1%)
Anthropometric				
BMI (kg/m^2), n (%)	n=919	n=891	n=664	n=399
Underweight/Normal weight	168 (18.3%)	177 (19.9%)	137 (20.6%)	82 (20.6%)
Overweight	376 (40.9%)	377 (42.3%)	311 (46.8%)	168 (42.1%)
Obese	375 (40.8%)	337 (37.8%)	216 (32.5%)	149 (37.3%)
Lifestyle				
Smoking habits n (%)				
Never	732 (74.5%)	700 (73.9%)	551 (75.3%)	331 (77.0%)
In the past	180 (18.3%)	187 (19.8%)	133 (18.2%)	76 (17.7%)
Daily/Occasionally	71 (7.2%)	60 (6.3%)	48 (6.6%)	23 (5.3%)
Alcohol consumption n (%)				
Never	497 (50.6%)	546 (57.7%)	324 (44.2%)	224 (52.1%)
Occasionally/Daily	485 (49.4%)	401 (42.3%)	409 (55.8%)	206 (47.9%)
Regular physical activity n (%)				
Yes	212 (21.6%)	374 (39.1%)	270 (36.8%)	159 (37.0%)
Clinical				
Multimorbidity n (%)				
Yes	634 (70.8%)	627 (72.9%)	501 (78.5%)	297 (74.6%)
Clinical severity (inverted HOOS/KOOS score)				
Mean (SD)	46.1 (18.8)	-	-	-
Unmanageable pain levels (≥5 NPRS), n (%)				
Yes	691 (73.8%)	-	-	-

Sample size is not constant due to missing values in some variables: BMI – EpiDoC1 (n=919), EpiDoC2 (n=891), EpiDoC3 (n=664), EpiDoC4 (n=399); Smoking habits – EpiDoC2 (n=947), EpiDoC3 (n=732), EpiDoC4 (n=430); Alcohol consumption – EpiDoC1 (n=982), EpiDoC2 (n=947), EpiDoC3 (n=733), EpiDoC4 (n=430); Regular physical activity – EpiDoC1 (n=982), EpiDoC2 (n=957), EpiDoC3 (n=734), EpiDoC4 (n=430); Multimorbidity – EpiDoC1 (n=895), EpiDoC2 (n=860), EpiDoC3 (n=638), EpiDoC4 (n=398); Clinical severity – EpiDoC1 (n=903); Inadequate Pain Relief – EpiDoC1 (n=936).

Table S2. Average years to baseline in each follow-up wave of total sample and by trajectory group

	HRQoL (EQ-5D score)					Physical Function (HAQ score)			
	Total Sample n=983	Consistently high HRQoL n=165	Consistently moderate HRQoL n=501	Consistently low HRQoL n=317	p^a	Stable high disability n=204	Slightly worsening moderate disability n=472	Consistently low disability n=307	p^a
Years to baseline Mean (SD)									
EpiDoC 1	-	-	-	-	-	-	-	-	-
EpiDoC 2	1.32 (0.62)	1.38 (0.65)	1.35 (0.60)	1.25 (0.62)	0.051	1.30 (0.62)	1.27 (0.59)	1.42 (0.64)	0.004
EpiDoC 3	2.82 (0.65)	2.86 (0.66)	2.84 (0.64)	2.75 (0.65)	0.164	2.75 (0.65)	2.78 (0.62)	2.93 (0.67)	0.008
EpiDoC 4	8.38 (0.61)	8.38 (0.66)	8.49 (0.60)	8.34 (0.60)	0.688	8.33 (0.64)	8.33 (0.58)	8.45 (0.64)	0.203

Table S3. Frequencies of participants reporting at least one problem/difficulty divided by the total number of respondents, for EQ5D dimensions and HAQ Domains.

EQ5D	**EpiDoC 1**	**EpiDoC 2**	**EpiDoC 3**	**EpiDoC 4**
Mobility	528/983 (53.71%)	676/955 (70.79%)	387/731 (52.94%)	195/409 (47.68%)
Selfcare	194/983 (19.73%)	356/957 (37.2%)	260/731 (35.57%)	125/409 (30.56%)
Activities	373/981 (38.02%)	535/957 (55.90%)	317/731 (43.47%)	163/408 (39.95%)
Pain	602/983 (61.24%)	715/955 (74.87%)	442/731 (60.47%)	260/410 (63.41%)
Anxiety/ Depression	296/973 (30.42%)	538/950 (57.68%)	294/720 (40.83%)	99/410 (24.15%)

HAQ	**EpiDoC 1**	**EpiDoC 2**	**EpiDoC 3**	**EpiDoC 4**
Dressing & Grooming	415/983 (42.22%)	567/953 (59.50%)	395/728 (54.26%)	199/408 (48.77%)
Arising	532/983 (54.12%)	655/953 (68.73%)	431/728 (59.20%)	228/407 (56.02%)
Eating	334/983 (33.98%)	387/951 (40.69%)	246/728 (33.79%)	156/406 (38.42%)
Walking	505/983 (51.37%)	672/952 (70.59%)	460/728 (63.19%)	262/407 (64.37%)
Hygiene	387/983 (39.37%)	445/952 (46.74%)	312/727 (42.92%)	182/402 (45.27%)
Reach	677/983 (68.87%)	739/946 (78.12%)	533/728 (73.21%)	277/407 (68.06%)
Grip	295/983 (30.01%)	325/949 (34.25%)	228/728 (31.32%)	124/404 (30.69%)
Activities	373/981 (38.02%)	535/957 (55.90%)	317/731 (43.37%)	163/408 (39.95%)

Table S4. Bayesian Information Criterion (BIC) values and estimated group sizes (%).

Number of groups	**Polynomial order[a]**	**BIC**	**Estimated group sizes**				
	EQ5D						
2	22	-1458.18	66.3	33.7			
3	222	-1440.05	33.5	48.3	18.2		
4	2222	-1367.79	28.2	46.0	10.2	15.5	
5	22222	-1349.87	27.1	40.9	9.9	7.2	15.0
3 (final)	221	-1436.64	33.4	48.4	18.3		
	HAQ						
2	22	-3211.63	60.7	39.3			
3	222	-3098.29	30.2	47.5	22.3		
4	2222	-3077.43	18.8	43.5	27.7	10.0	
5	22222	-3080.47	12.4	32.5	29.7	18.9	6.4
3 (final)	210	-3099.59	32.0	47.0	21.0		

[a] Order shape: 0–intercept, 1–linear, 2–quadratic, 3-cubic. For both EQ5D and HAQ, the optimal number of groups by BIC criterion alone was four. However, the clinical decision was made to keep the models with three groups.

Table S5. Trajectory model diagnostic criteria.

	n	Estimated group probabilities	Proportion classified[a]	APP[b]	OCC[c]
EQ5D Group					
Consistently low	317	0.322	0.333	0.793	8.04
Consistently moderate	501	0.509	0.484	0.759	3.03
Consistently high	165	0.168	0.183	0.817	22.20
HAQ Group					
Consistently low disability	307	0.312	0.320	0.876	15.50
Slight worsening moderate disability	472	0.480	0.470	0.848	6.06
Consistently high disability	204	0.208	0.210	0.883	28.94

[a] Estimated group probabilities should be close to the proportion of individuals classified in the group (proportion based on the assignments for the maximum posterior probability). [b] Average Posterior Probabilities (should be at least 0.7). [c] Odds of Correct Classification (should be ≥5.0).

Table S6. Univariate Multinomial Logistic Regression models for the association of baseline characteristics and physical function (HAQ) trajectories.

	Physical Function Trajectories (HAQ)			
	Consistently low disability RRR (95% CI)	Slightly worsening moderate disability RRR (95% CI)	Consistently high disability RRR (95% CI)	p
Sex				<0.001
Male (ref)	-	-	-	
Female	-	2.70 (1.98, 3.67)	5.34 (3.38, 8.44)	
Age Class				<0.001
<55 years old (ref)	-	-	-	
55-64 years old	-	1.23 (0.82, 1.84)	1.98 (0.98, 4.00)	
65-74 years old	-	1.76 (1.18, 2.64)	4.98 (2.57, 9.63)	
^{3}75 years old	-	2.99 (1.80, 4.97)	14.81 (7.24, 30.33)	
Region (NUTSII)				0.036
North (ref)	-	-	-	
Centre	-	1.00 (0.66, 1.50)	0.76 (0.47, 1.25)	
Lisbon	-	0.60 (0.38, 0.93)	0.64 (0.31, 0.92)	
Alentejo	-	1.15 (0.58, 2.29)	1.18 (0.54, 2.61)	
Algarve	-	0.53 (0.17, 1.63)	1.18 (0.39, 3.55)	
Islands	-	1.19 (0.79, 1.79)	0.69 (0.41, 1.15)	
Marital status				0.002
With partner	-	0.89 (0.66, 1.22)	0.54 (0.37, 0.78)	
Educational Level				<0.001
<4 years (ref)	-	-	-	
4-9 years	-	0.43 (0.28, 0.67)	0.17 (0.11, 0.27)	
^{3}10 years	-	0.22 (0.13, 0.38)	0.03 (0.01, 0.08)	
BMI (kg/m^{2})				<0.001
Underweight/Normal weight (ref)	-	-	-	
Overweight	-	1.07 (0.71, 1.60)	0.87 (0.52, 1.46)	
Obese	-	2.16 (1.42, 3.28)	1.93 (1.15, 3.26)	
Smoking habits				<0.001
Never (ref)	-	-	-	
In the past	-	0.40 (0.28, 0.57)	0.24 (0.14, 0.41)	
Daily/Occasionally	-	0.51 (0.30, 0.87)	0.40 (0.19, 0.82)	
Alcohol consumption				<0.001
Never (ref)	-	-	-	
Occasionally/Daily	-	0.56 (0.42, 0.75)	0.40 (0.28, 0.57)	
Regular exercise (yes)		0.51 (0.36, 0.71)	0.27 (0.16, 0.44)	<0.001
Clinical severity (inverted KOOS/HOOS) (0 low -100 high severity)	-	1.06 (1.05, 1.07)	1.10 (1.09, 1.12)	<0.001
Unmanageable pain levels (yes)	-	2.44 (1.76, 3.37)	3.85 (2.43, 6.09)	<0.001
Multimorbidity	-	2.18 (1.58, 2.97)	9.07 (5.01, 16.41)	<0.001

RRR: Relative risk ratio; HAQ: Health Assessment Questionnaire; p – Wald test p-value.

Table S7. Univariate Multinomial Logistic Regression models for the association of HKOA patients baseline characteristics and HRQoL (EQ-5D) trajectories.

	HRQoL Trajectories (EQ-5D)			
	Consistently high HRQoL (Reference)	Consistently moderate HRQoL RRR (95% CI)	Consistently low HRQoL RRR (95% CI)	p
Sex				<0.001
Male (ref)	-	-	-	
Female	-	2.08 (1.44, 2.98)	4.47 (2.92, 6.83)	
Age Class				<0.001
<55 years old (ref)	-	-	-	
55-64 years old	-	1.24 (0.77, 2.01)	1.65 (0.93, 2.91)	
65-74 years old	-	1.49 (0.93, 2.39)	2.59 (1.49, 4.50)	
³75 years old	-	2.99 (1.56, 5.75)	7.94 (3.93, 16.05)	
Region (NUTSII)				0.921
North (ref)	-	-	-	
Centre	-	1.25 (0.76, 2.07)	0.99 (0.58, 1.68)	
Lisbon	-	0.91 (0.54, 1.55)	0.67 (0.38, 1.19)	
Alentejo	-	1.22 (0.54, 1.54)	0.95 (0.39, 2.27)	
Algarve	-	0.80 (0.23, 2.72)	0.83 (0.23, 2.98)	
Islands	-	1.14 (0.69, 1.87)	0.93 (0.55, 1.58)	
Marital status				<0.001
With partner	-	0.52 (0.35, 0.79)	0.43 (0.28, 0.66)	
Educational Level				<0.001
<4 years (ref)	-	-	-	
4-9 years	-	0.64 (0.38, 1.13)	0.24 (0.14, 0.42)	
³10 years	-	0.33 (0.17, 0.63)	0.05 (0.02, 0.10)	
BMI (kg/m^2)				<0.001
Underweight/Normal weight (ref)	-	-	-	
Overweight	-	0.76 (0.47, 1.22)	0.90 (0.52, 1.57)	
Obese	-	1.27 (0.75, 2.12)	2.65 (1.49, 4.72)	
Smoking habits				<0.001
Never (ref)	-	-	-	
In the past	-	0.47 (0.32, 0.71)	0.32 (0.20, 0.51)	
Daily/Occasionally	-	1.56 (0.71, 3.41)	0.97 (0.41, 2.29)	
Alcohol consumption				<0.001
Never (ref)	-	-	-	
Occasionally/Daily	-	0.49 (0.34, 0.70)	0.40 (0.27, 0.59)	
Regular exercise (yes)		0.56 (0.39, 0.82)	0.24 (0.15, 0.39)	<0.001
Clinical severity (inverted KOOS/HOOS) (0 low -100 high severity)	-	1.04 (1.03, 1.06)	1.10 (1.08, 1.11)	<0.001
Unmanageable pain levels (yes)	-	3.00 (2.06, 4.37)	5.33 (3.44, 8.28)	<0.001
Multimorbidity	-	1.58 (1.09, 2.28)	6.17 (3.80, 10.01)	<0.001

RRR – Relative risk ratio; HRQoL: Health Related Quality of Life; p – Wald test p-value.

5.4. Study 4: Driving factors for the utilisation of healthcare services by people with Osteoarthritis in Portugal: Results from a nationwide population-based study

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Driving factors for the utilisation of healthcare services by people with osteoarthritis in Portugal: results from a nationwide population-based study

Daniela Costa[1,2,3*], Ana M. Rodrigues[2,3,4], Eduardo B. Cruz[2,5], Helena Canhão[2,3], Jaime Branco[2,3,6] and Carla Nunes[1,2]

Abstract

Background: Worldwide, the current management of knee osteoarthritis appears heterogeneous, high-cost and often not based on current best evidence. The absence of epidemiological data regarding the utilisation of healthcare services may conceal the need for improvements in the management of osteoarthritis. The aim of this study is to explore the profiles of healthcare services utilisation by people with knee osteoarthritis, and to analyse their determinants, according to Andersen's behavioural model.

Methods: We analysed a sample of 978 participants diagnosed with knee osteoarthritis from the population-based study EpiReumaPt, in Portugal. Data was collected with a structured interview, and the diagnosis of knee osteoarthritis was validated by a rheumatologist team. With the Two-step Cluster procedure, we primarily identified different profiles of healthcare utilisation according to the services most used by patients with knee osteoarthritis. Secondly, we analysed the determinants of each profile, using multinomial logistic regression, according to the predisposing characteristics, enabling factors and need variables.

Results: In our sample, a high proportion of participants are overweight or obese (82,6%, $n = 748$) and physically inactive (20,6%, $n = 201$) and a small proportion had physiotherapy management (14,4%, $n = 141$). We identified three profiles of healthcare utilisation: "HighUsers"; "GPUsers"; "LowUsers". "HighUsers" represents more than 35% of the sample, and are also the participants with higher utilisation of medical appointments. "GPUsers" represent the participants with higher utilisation of general practitioner appointments. Within these profiles, age and geographic location – indicated as predisposing characteristics; employment status and healthcare insurance - as enabling factors; number of comorbidities, physical function, health-related quality of life, anxiety and physical exercise - as need variables, showed associations ($p < 0{,}05$) with the higher utilisation of healthcare services profiles.

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* Correspondence: dcosta.ft@gmail.com
[1]NOVA National School of Public Health, Public Health Research Centre, Universidade NOVA de Lisboa, Avenida Padre Cruz, 1600-560 Lisbon, Portugal
[2]Comprehensive Health Research Centre (CHRC), Universidade Nova de Lisboa, Lisbon, Portugal
Full list of author information is available at the end of the article

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Conclusions: Healthcare utilisation by people with knee osteoarthritis is not driven only by clinical needs. The predisposing characteristics and enabling factors associated with healthcare utilisation reveal inequities in the access to healthcare and variability in the management of people with knee osteoarthritis. Research and implementation of whole-system strategies to improve equity in the access and quality of care are paramount in order to diminish the impact of osteoarthritis at individual-, societal- and economic-level.

Keywords: Delivery of health care, Osteoarthritis, Socioeconomic factors, Health services, Andersen's behavioural model of healthcare utilisation

Background

Osteoarthritis (OA) is a leading cause of disability worldwide, responsible for 9.6 million years-lived with disability, of which 85% are attributable to the knee joint [1]. The direct costs of knee OA represent 1–2.5% of the GDP of high-income countries, mainly accounted by Total Knee Replacement surgery (TKR) costs. Moreover, the indirect costs can surpass the direct costs, mainly due to work loss or early retirement [2]. In Portugal, 12,4% of the adult population have knee OA [3] and, in 2013, the indirect costs represented 0.4% of the GDP [4]. Portugal has an ageing population, where 80% of the older adults are overweight and 75% of the adult population is physically inactive [5]. This data suggests a progressive and future increase in the prevalence and burden of knee OA, in the same way as in other countries [6].

People with knee OA suffer from chronic pain, fatigue, sleep problems, disability, impaired quality of life and mental health, this limits their participation in social, community and occupational activities [3, 7]. The management of this condition requires integrated multidisciplinary interventions during the progression of the disease to reduce pain, modify the risk factors and improve function, as there is no known cure for OA [7].

Exercise, maintenance of a healthy body weight, education and self-management strategies are recommended as first-line and core interventions during the disease progression. Pharmacological modalities can help with the symptoms control. TKR should only be considered if the core interventions have failed and, if HRQoL is significantly impaired in selected patients [8, 9], due mainly to the rates of surgical complications and adverse events, associated mortality and low levels of satisfaction with the outcomes [10].

However, data from several countries suggests that the current care for knee OA is heterogeneous and discordant with the quality standards [11]. Medication for pain relief is often the first line treatment prescribed by general practitioners (GP's) [12], less than 50% of patients are referred to physiotherapy or weight management programs and referrals to the orthopaedic surgeon is often inadequate [11]. Portugal is the country with highest TKR growth rate among OECD countries, where the incidence rate increased by 20% between 2005 and 2011 for patients both above and below 65 years old [13].

International data has shown that overall healthcare utilisation and related costs are significantly higher in patients with knee OA than in the matched non-OA population, even when adjusted for the number of comorbidities [14]. Moreover, the variability in healthcare utilisation can be driven by determinants other than clinical factors, like sex, education level, income, insurance coverage, perceived needs, area of residence and socio-economic status [15].

: According to the Andersen's Behavioural Model [16], the utilisation of healthcare services levels are influenced by contextual (health organisations provider-related factors and community characteristics, measured at an aggregate rather than individual level) and individual determinants. Contextual and individual determinants may influence health behaviours and outcomes [17]. Individual determinants are classified into the following three domains: 1) predisposing characteristics - demographic variables that influence people to use healthcare services, e.g., age, geographic location, marital status; 2) enabling factors - socio-economic related factors that promote the utilisation of health services, e.g. education level, health insurance; 3) need variables - include risk factors for diseases, individual health states, and experiences of diseases that lead to the utilisation of healthcare services, e.g. self-reported quality of life, functional status or physical activity [15, 16, 18]. In an equitable system, the interventions received would be driven by the clinical needs of the patient [18].

The Portuguese National Health Service (NHS) is a universal coverage, tax-financed system where GP's are required to act as the gatekeeper to other health services. In addition, there are private health insurance for the general population and, health insurance schemes that cover particular professions, which facilitate access to the private healthcare sector [19].

Currently, there is no published data about healthcare utilisation by people with knee OA in Portugal, and literature with national datasets is scarce. Due to the complexity of this condition, the identification of different profiles of healthcare services utilisation and its determinants is critical to identify needs for improvement at individual and system level and, to develop interventional strategies to mitigate these needs. The aim of this study is to explore different profiles of healthcare services utilisation by people with knee OA and to analyse its determinants, according to Andersen's behavioural model. Secondarily, we aim to describe the overall healthcare services used by people with knee OA.

Methods

Data source

This study analyses the *EpireumaPt* project database, a national cross-sectional population-based study with a representative sample of the Portuguese population. *EpiReumaPt* aimed to develop a comprehensive understanding of the burden of Rheumatic and Musculoskeletal Diseases (RMD's) in Portugal. As described in detail elsewhere [20], the *EpiReumaPt* study recruitment used a three-phase approach, over the period September 2011 to December 2013. The sample of *EpiReumaPt* study was recruited from a random selection of private households in Portuguese Mainland and Islands (Madeira and Azores), and was stratified according to the administrative territorial units [(NUTS II) (Norte, Centro, Lisboa and Vale do Tejo, Alentejo, Algarve, Açores Islands (Azores) and Madeira Islands (Madeira)], and the size of the population within each locality (< 2000; 2000–9999; 10,000–19,999; 20,000–99,999; and ≥ 100,000 inhabitants, respectively). In each household, an individual ≥18 years old with permanent residence and the most recently celebrated birthday was selected to be a participant in the study. Each selected household was visited, with no previous contact, up to three times, if no candidate participant was present during the first visit. In the long run, 28,502 households were contacted, 8041 individuals refused to participate in the study, and 10,661 were included. The *EpiReumaPt* population was similar to the Portuguese population (CENSUS 2011) in age strata, sex, and NUTII distribution [20].

In the first phase of the study, the participants completed a face-to-face interview to collect health-related information, which also screened for RMD's, by a team of non-medical healthcare professionals trained for this purpose. The interviews were conducted using a Computer Assisted Personal Interview (CAPI) system. An individual was considered to have a positive screening if the subject mentioned a previously known RMD, if any of the algorithms in the screening questionnaires was positive, or if the subject reported muscle, vertebral or peripheral joint pain in the previous 4 weeks.

The overall performance of the screening algorithm was evaluated (the gold standard was considered the final diagnosis after revision - phase 3) and the overall sensitivity of the screening questionnaire for RMD's was 98%, with a specificity of 22%. The positive predictive value was 85% and the negative predictive value was 71% [20].

The participants who screened positive for at least one RMD ($n = 7451$), as well as approximately 20% ($n = 701$) of participants with negative screening for RMD's, were invited for a second phase, that consisted of a clinical appointment with a Rheumatologist. Of these, 4275 did not attend the clinical appointment. Therefore, at the end of phase 2 there were 3877 clinical observations: 3198 received the validation of RMD'S and 679 did not have an RMD diagnosis. The clinical assessments were performed at the Primary Care Centre of the participants neighbourhood, with a mobile van, fully equipped, to perform imaging and laboratory tests, supported by a multidisciplinary team with a rheumatologist, and X-Ray technician, a nurse, a staff coordinator and a driver. The clinical appointments consisted of a structured evaluation, laboratory and imaging exams, if needed, to establish the diagnosis and evaluate disease-related information. The rheumatologists involved were blind to the prior health-related data. In the third-phase, experienced rheumatologists reviewed all the data and confirmed the diagnosis – Fig. 1 [20]. When data was insufficient to fulfil the international classification criteria for each RMD, an additional meeting of the experts took place in order to discuss and reach an agreement on the final diagnosis. If at this stage no agreement had been reached, the opinion of the rheumatologist that performed the clinical assessment (second phase) prevailed. Diagnostic agreement between the 3 reviewers was 98.3% with a Cohen's K coefficient of 0.87 (95%CI 0.83, 0.91. A total of 981 participants had a validated diagnosis of knee OA [20].

Study population

This study includes the participants of *EpiReumaPt* with knee OA diagnosis, validated in the second phase of *EpireumaPt*, according to the American College of Rheumatology criteria: knee pain with at least three of the following clinical findings: age > 50 years, morning stiffness < 30 min duration, *crepitus* in active motion, tenderness of the bone margins of the joint, bony enlargement noted on examination, and lack of palpable warmth of the synovium [21].

Outcomes

The healthcare services utilisation data is the outcome of interest, collected in the first phase of the study. Participants were asked if they had attended any medical appointments, undergone hospitalisations, surgery, psychology and physiotherapy consultations and, to indicate the number of appointments in the previous 12 months. The number of General Practitioner (GP) appointments was categorised in "no appointments", "1–2

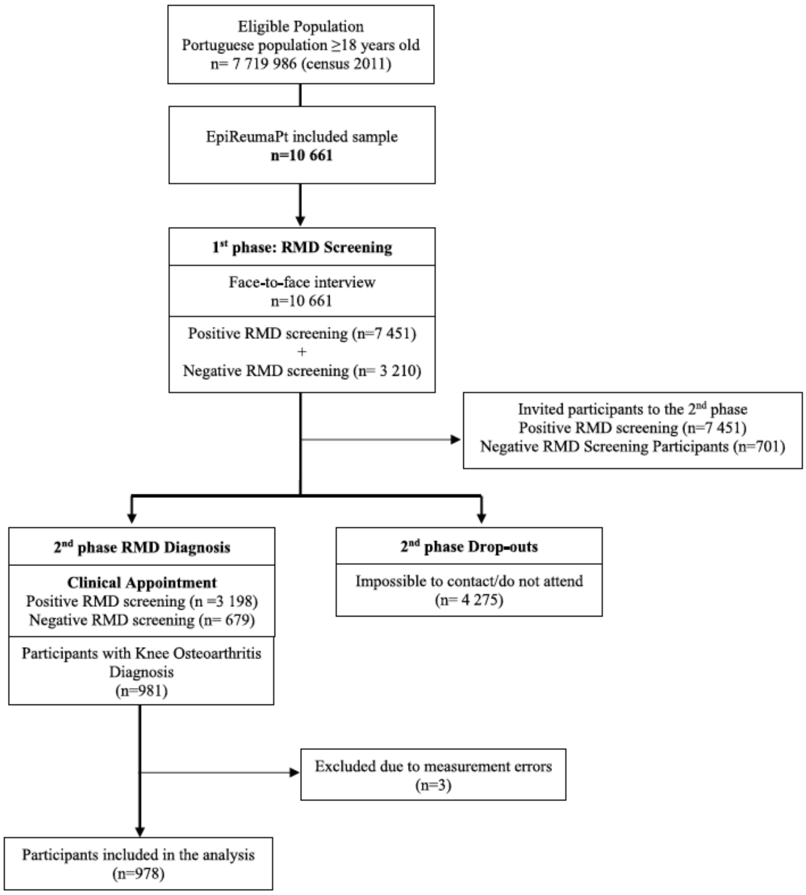

Fig. 1 Flowchart of EpiReumaPt study design. *RMD, Rheumatic and Musculoskeletal Diseases*

appointments" and "3 or more appointments". The reason for hospitalisation was asked. Joint surgery was considered, although the presented variable does not distinguish between joint replacement surgery or other joint surgery. Based on the possible number of medical appointments and physiotherapy sessions within a year, and according to the distribution of number of medical appointments and physiotherapy sessions, the participants with > 60 medical appointments or > 180 physiotherapy sessions were considered to be an error of data insertion and were excluded ($n = 3$).

Determinants

The determinant variables were collected during the first phase of *EpiReumaPt*, and are presented according to Andersen's model, as previously described. Due to the low frequency of response in some of the original categorical variables, and to ensure a better interpretation of the results, some categories of categorical variables were amalgamated and some continues variables were transformed in categorical variables, as described in detail below.

Predisposing characteristics

Predisposing characteristics included: age, sex, geographic location, according to NUTS II territorial units and marital status, previously described [20]. Madeira and Azores were merged in the analysis as Island's region The variable marital status was dichotomized into: "with partner", which includes participants who are married or who live in a consensual union, and "without partner", which includes participants who are single, widowed or divorced.

Enabling factors

These factors included: work status, firstly presented as employed (full or part time), retired, unemployed, incapable of working due to rheumatic disease and others (domestic worker, students, live with revenues) and then categorised as employed and non-employed (unemployed, retired, incapable of working due to rheumatic diseases and others); have or do not have healthcare insurance, additional to NHS coverage; number of years of schooling, that was categorised as having < 4 and ≥ 4 years of schooling, representing the attendance (or not) of at least the first stage of primary education.

Need variables

Need variables included the number of self-reported chronic comorbidities: high blood pressure, high cholesterol, cardiac disease, diabetes mellitus, chronic lung disease, problems in the digestive tract, renal colic, neurological disease, allergies, mental or psychiatric illness, cancer, thyroid and parathyroid problems, hypogonadism, hyperuricemia. The presence of other rheumatic diseases (excluding knee OA), diagnosed by the rheumatologists' team, was added. Body mass index (kg/m^2) was calculated with self-reported height and weight, and categorised as underweight (≤18.49 kg/m^2), healthy weight (≥18.5 and ≤ 24.99 kg/m^2), overweight (≥25 and ≤ 29.99 kg/m^2) and obese (≥30 kg/m^2). Lifestyle variables such as alcohol intake and smoking habits (both categorised as never, occasionally and daily) were noted, as well as past habits of smoking. Regular physical exercise/sports habits were also questioned (yes/no). Health-related quality of life (HRQoL) was assessed using EuroQol, with 5 dimensions and 3 levels (EQ-5D-3L) [22]. The index score ranges from 1, which represents full health, and zero or below that corresponds to death or states worse than death. Anxiety and depression symptoms were evaluated using the Hospital Anxiety and Depression Scale (HADS) for subscales of depression (HADS-D) and anxiety (HADS-A). Both fall into a range from 0 to 21, where higher values represent greater symptoms of anxiety or depression [23]. Physical function was measured based on the Health Assessment Questionnaire (HAQ). Where total scores lying between zero, indicating no functional impairment, and 3 indicating complete impairment [24]. The use of regular medication and number of medicines was also collected.

Statistical analysis

All statistical analyses were performed using SPSS 24 for MacOS (IBM Corp., Armonk, NY, USA).

In the first stage, using descriptive statistic methods, we explored the health services most used by participants with knee OA. With the results of this analysis and the knowledge of the literature previously published in this field We included in the Two Step Cluster procedure (TSC) four variables: 1) number of GP appointments (no appointments, 1–2 appointments and ≥ 3 appointments); 2) orthopaedic specialist appointments (yes or no); 3) physiotherapy sessions (yes or no); 4) hospitalization (yes or no). The categorisation of the variable "GP appointments" was made according to the median value of the distribution of this variable in the sample (x = 3.00).

The TSC procedure is a hybrid approach that uses a distance measure to separate groups, and an agglomerative hierarchical clustering based on best fit to choose the optimal subgroup model. In this procedure, we used the Schwarz's Bayesian information criterion (BIC) as a statistical measure of best fit to determine the number of clusters, the log-likelihood as distance measure and the average silhouette coefficient (ASC) as the silhouette measure of cluster cohesion and separation. We accepted the cluster solution considering the highest ratio of distance measure. Evidence shows that TSC is one of the most reliable procedures in terms of the number of subgroups detected, classification probability of individuals to subgroups and reproducibility of findings on clinical data [25].

We used descriptive statistics and non-parametric tests for independent samples (Kruskal-Wallis for continuous variables and chi-squared test for categorical variables, $p < 0.05$) to describe and compare the determinants and health utilisation in the entire sample and between clusters.

In addition, through a sensitivity analysis to ensure the robustness of our results, we also explored the association between the determinant variables and the cluster membership. First, we conducted a univariate analysis to select the variables for inclusion in the multinomial logistic regression model, with a significance level of 0.2, to avoid early exclusion of potential important variables [26]. Then, in the multinomial regression procedure, we performed a stepwise hierarchical analysis according to the domains of Andersen's model in three steps: 1) inclusion of predisposing characteristics in the model and removal of non-significant variables; 2) inclusion of enabling factors in the previous model and removal of non-significant enabling factors; 3) inclusion of need variables in the previous model and removal of non-significant need variables, resulting in the final model. Odds-Ratio (OR) was estimated for each variable with 95% confidence interval (CI). Participants with missing data were automatically excluded from this analysis. This model was adjusted for sex and age, as important confounder variables for healthcare utilisation.

We evaluated the discriminative capacity of each model in each of the three steps calculating a binomial area under the receiver operating curve (AUC), to analyse the proportion of increment in the discriminative capacity in each step. The binomial AUC was calculated using the estimated classification probability for a given cluster, regarding the reference cluster. The discriminative capacity was considered weak if AUC was between 0.5–0.69; acceptable if between 0.7–0.79 and good if above 0.80. We also analysed the variance of the multinomial model using the McFadden Pseudo-R^2 in each step [27].

EpireumaPt ethical issues

EpireumaPt study was approved by the Ethics Committee of NOVA Medical School and by the Portuguese Data Protection Authority (Comissão Nacional de Proteção de Dados). Written informed consent was obtained from all participants, in accordance with the Declaration of Helsinki, as described elsewhere [20].

Results

Profiles of healthcare utilisation

Among the 978 participants diagnosed with knee OA included in the analysis, we found three different profiles of healthcare services utilisation with the TSC procedure, based on the healthcare services most used – Table 1. We named the clusters according to the attendance to orthopaedic surgeon appointments, physiotherapy sessions, number of GP appointments and hospitalisation.

1. "High Healthcare Users" (*HighUsers*): included all participants from the sample who had at least one appointment in the previous 12 months with the orthopaedic surgeon, who had physiotherapy and who had hospitalisation. In this cluster, the distribution of participants among the three categories of GP appointments was heterogeneous. The participants included in the *HighUsers* cluster represent 35.07% of the sample.
1. "GP users" (*GPUsers*): included only participants who had 3 or more GP appointments in the last 12 months and no use of the other services. Participants included in the *GPUsers* cluster represent 27.8% of the sample.

Table 1 Healthcare utilisation of total sample and Clusters

	Total[f] **n (%)** **978 (100)**	***HighUsers*** **n (%)** **343 (35.07)**	***GPUsers*** **n (%)** **272 (27.80)**	***LowUsers*** **n (%)** **363 (37.11)**	***p*-value**
Cluster Variables[a]					
GP Appointments					
0	126 (12.9)	30 (8.7)	0 (0)	96 (26.4)	< 0.001[d]
1–2	379 (38.8)	112 (32.7)	0 (0)	267 (73.6)	
≥ 3	473 (48.4)	201 (58.6)	272 (100)	0 (0)	
Physiotherapy[b]	141 (14.4)	141 (41.1)	0 (0)	0 (0)	< 0.001[d]
Orthopaedic Surgeon[b]	192 (19.6)	192 (56.0)	0 (0)	0 (0)	< 0.001[d]
Hospitalisation[b]	112 (11.5)	112 (32.7)	0 (0)	0 (0)	< 0.001[d]
Healthcare Use					
GP appointments, mean ± SD	3.14 ± 3.32	3.38 ± 3.38	4.00 ± 1.17	1.27 ± 0.83	< 0.001[e]
Other medical appointments[b]					
Rheumatology	56 (5.7)	29 (8.5)	12 (4.4)	15 (4.1)	0.026[d]
Physiatry	43 (4.4)	39 (11.4)	4 (1.5)	0 (0)	< 0.001[d]
Cardiology	136 (13.9)	72 (21.0)	25 (9.2)	39 (10.7)	< 0.001[d]
Neurology	50 (5.1)	24 (7.0)	17 (6.3)	9 (2.5)	0.015[d]
Internal medicine	77 (7.9)	10.8 (37)	24 (8.8)	16 (4.4)	0.006[d]
Surgery	71 (7.3)	55 (5.6)	8 (2.9)	8 (2.2)	< 0.001[d]
Psychiatry	45 (4.6)	19 (5.5)	15 (5.5)	11 (3.0)	0.197[d]
Other medical appointments[c], mean ± SD	2.41 ± 4.35	4.43 ± 6.65	3.82 ± 4.75	1.82 ± 2.70	< 0.001[e]
Joint Surgery[b]	20 (2.3)	20 (8.0)	0 (0)	0 (0)	< 0.001[d]
Psychology[b]	13 (1.3)	5 (1.5)	1 (0.4)	7 (1.9)	0.228[d]
Technical aids[b]	18 (1.8)	17 (5.0)	1 (0.4)	0 (0)	< 0.001[d]

Categorical variables are presented as n(%); continuous variables are presented as mean ± standard deviation

GP General Practitioner

[a] Variables included in the Two Step Cluster procedure. [b] At least once in the previous 12 months. [c] Number of visits related with the previous 12 months. [d] Chi-square test for independency; [e] Kruskal-Wallis test

[f] Sample Size is not constant due to participants with validated data in the following variables: Joint Surgery (*n* = 885) and Technical aids (*n* = 973)

1. "Low healthcare users" (*LowUsers*): included participants who had less than 2 appointments with the GP in the previous 12 months, and no use of the other healthcare services. Participants included in *LowUsers* cluster represent 37.11% of the sample

This cluster solution presents an ASC of 0.6, which shows a good model fit, and the ratio of distance measures was 1.706.

Regarding the total sample, 87.2% of the participants reported at least one GP visit, 14.4% were enrolled in physiotherapy, 19.6% had visited the orthopaedic surgeon and 11.50% were hospitalised in the last 12 months. *HighUsers* represent the participants with higher number of medical appointments (4.43 ± 6.65, $p < 0.001$) among the majority of medical specialities. *GPUsers* includes participants with a higher utilisation of GP appointments (4.00 ± 1.17, $p < 0.001$), and who take more regular medication (1.12 ± 3.86, $p < 0.001$).

Characteristics of the sample and clusters

Women represent 73% of the sample, the mean age of participants was 65.34 (±11.30) years old, 247 (25.3%) participants have less than 4 years of education, and only 15% of participants were employed. The majority of the participants are overweight (41.8%) or obese (40.8%) and only 20.6% report doing regular physical exercise. Distributions across clusters were statistically different ($p < 0.05$) for the majority of predisposing characteristics, enabling factors and need variables – Table 2.

Determinants of cluster membership

After the univariate analysis (Supplementary file), variables at < 0.2 significance level were considered for the multinomial logistic regression model. The reference category was *LowUsers* cluster. Due to missing data, 146 (14,93%) participants were excluded from this analysis, but the proportion of excluded participants was similar between clusters – Table 3.

As seen in the Tables 3 and 4, in the multinomial logistic model, having *LowUsers* as the reference cluster, the following determinants were associated with *HighUsers* cluster membership: being younger (OR = 0.96, 95% CI 0.95, 0.99) and reside in Portugal mainland, when compared to reside on islands (OR = 0.43, 95% CI 0.24, 0.77) as predisposing characteristics; have additional health coverage (OR = 0.65, 95% CI 0.43, 0.98) and being employed (OR = 0.55, 95% CI 0.31–0.97) as enabling factors; and higher number of comorbidities (OR = 1.12, 95%CI 1.03, 1.21), worse HRQoL (OR = 0.33, 95% CI 0.14, 0.79), worse physical function (OR = 1.59, 95% CI 1.10–2.23) and no regular physical exercise (OR = 0.57, 95% CI 0.37, 0.88) as need variables. The only predisposing characteristic associated with *GPUsers* membership was geographic location. Residing in the centre when compared to reside in Lisbon region (OR = 2.11, 95% CI 1.21, 3.68), and in Portugal mainland when compared to reside in the Islands region (OR = 0.42, 95% CI 0.21, 0.83), increase the probability of being classified as *GPUser*, with *LowUsers* as the reference cluster. No enabling factors had statistical association within *GPUsers* cluster membership. Higher number of comorbidities (OR = 1.22. 95% CI 1.11, 1.33), the presence of anxiety symptoms (OR = 1.09, 95% CI 1.03, 1.14) and have no regular physical exercise (OR = 0.55 95% CI 0.34, 0.89) were the need variables associated with *GPU* cluster membership. A higher variation in the AUC and in the McFadden pseudo-R^2 occurred when need variables were entered in the model.

Discussion

Healthcare services utilisation in Portugal

In this study, we identified three profiles of healthcare utilisation according to the services most used by the participants with knee OA. The profile with the highest healthcare utilisation – *HighUsers*, represents more than 35% of the sample and was characterised by participants with appointments with the GP, orthopaedic surgeon, physiotherapy sessions and/or with hospitalisation. Given the high number of other medical appointments, this profile is possibly responsible for a high proportion of the total costs spent with people with knee OA in Portugal. As Warwick et al. [28] concluded, analysing an insurance database with more than 40,000 of people with knee OA, the top 30% of high-payment patients with OA accounted for more than 70% of overall non-arthroplasty payments.

Primary care is considered the most relevant setting for prevention and management of knee OA, where the conservative non-pharmacological interventions should be considered early, and throughout the progression of the disease [8, 9]. However, in our sample, few participants were enrolled in physiotherapy or regular exercise programmes and a high proportion were overweight. The study of Østeras et al. [29] found similar data, when analysing a sample of Portuguese people with knee OA in primary healthcare: only 20% of participants were referred to weight management programmes, and only 43% were referred to physical exercise programmes, in a similar fashion to other European countries included. However, in our sample, the proportion of participants who had undergone physiotherapy treatments (14.4%) was much lower compared to the 39–52% observed, for example, in the UK [30]. Overall, this data may suggest a weak adoption of the core recommended interventions for the management of knee OA, and possibly, be responsible for suboptimal outcomes and higher health costs, in Portugal. Moreover, Bedard et al. [31] estimated that if health professionals followed current clinical practice guidelines, the

Table 2 Predisposing characteristics, enabling factors and need variables distribution of total sample and clusters

	Determinants	**Total[a]** **n (%)** **978 (100)**	***HighUsers*** **n (%)** **343 (35.07)**	***GPUsers*** **n (%)** **272 (27.80)**	***LowUsers*** **n (%)** **363 (37.11)**	***p-value***
Predisposing	Age	65.34 ± 11.30	65.18 ± 10.51	66.47 ± 10.35	64.74 ± 12.02	0.081[b]
	Female sex	714 (73)	259 (75.5)	209 (76.8)	246 (67.8)	0.017[c]
	Geographic Location					
	North	255 (29.3)	105 (34.0)	60 (28.6)	81 (25.2)	< 0.001 [c]
	Centre	243 (27.9)	85 (27.2)	87 (36.1)	72 (22.4)	
	Islands	127 (14.6)	32 (10.4)	21 (8.7)	74 (23.1)	
	South	84 (9.6)	29 (9.4)	26 (10.8)	29 (9.0)	
	Lisbon	162 (18.6)	59 (19.1)	38 (15.8)	65 (20.2)	
	Married or consensual union	619 (63.3)	222 (64.7)	165 (60.7)	232 (63.9)	0.556 [c]
Enabling	Years of Education	4.96 ± 3.32	5.05 ± 3.36	4.36 ± 3.18	5.32 ± 3.32	< 0.001[b]
	< 4 years of Education	247 (25.3)	79 (23.1)	98 (36.0)	70 (19.3)	< 0.001[c]
	Employment status					0.006 [c]
	Employed (part-time OR full-time)	145 (16.6)	42 (13.5)	31 (12.9)	72 (22.9)	
	Retired	634 (72.4)	222 (71.4)	185 (76.7)	228 (70.2)	
	Unemployed	68 (7.8)	31 (10.0)	18 (7.5)	19 (5.8)	
	Temporarily disabled	17 (1.9)	11 (3.5)	4 (1.7)	2 (0.6)	
	Others[d]	12 (1.4)	5 (1.6)	3 (1.3)	4 (1.2)	
	NHS as only health system	763 (78.0)	236 (74.9)	230 (79.3)	297 (79.6)	0.003[c]
Need	Physical function (HAQ)	0.76 ± 0.69	0.88 ± 0.66	0.77 ± 0.67	0.47 ± 0.59	< 0.001[b]
	HRQoL (EQ-5D-3L)	0.62 ± 0.27	0.57 ± 0.27	0.61 ± 0.26	0.73 ± 0.25	< 0.001[b]
	BMI (kg/m^2)	29.54 ± 5.06	29.71 ± 4.77	29.69 ± 5.14	29.27 ± 4.95	0.366[b]
	Underweight (< 18.5 kg/m^2)	2 (0.2)	0 (0)	0 (0)	2 (0,6)	0.311[c]
	Normal weight (18.5–24.99 kg/m^2)	156 (17.2)	59 (15.2)	40 (16.1)	67 (19.9)	
	Overweight (25–29.99 kg/m^2)	379 (41.8)	135 (41.8)	110 (44.4)	134 (39.9)	
	Obese (≥30 kg/m^2)	370 (40.8)	139 (43.0)	98 (39.5)	133 (39.6)	
	Anxiety (HADS-A)	6.86 ± 4.15	7.08 ± 4.20	7.54 ± 4.23	5.85 ± 3.94	< 0.001[b]
	Depression (HADS-D)	6.09 ± 4.30	5.74 ± 3.96	6.59 ± 4.21	4.94 ± 3.82	0.001[b]
	Number of Comorbidities	4.47 ± 2.44	4.48 ± 2.42	5.11 ± 2.54	3.65 ± 2.19	< 0.001[b]
	Daily alcohol intake	199 (20.4)	70 (20.5)	53 (19.5)	76 (20.9)	0.077[c]
	Active smoker	71 (7.3)	25 (7.3)	16 (5.9)	30 (8.3)	0.519[c]
	Ex-smoker	182 (17.9)	59 (18.6)	38 (14.8)	65 (19.5)	0.312[c]
	Regular physical activity	201 (20.6)	58 (17.0)	41 (15.1)	102 (28.1)	< 0.001[c]

Categorical variables are presented as n (%); continuous variables are presented as mean ± standard deviation

NHS National Health System, *GP* General Practitioner, *HRQoL* Health Related Quality of Life, *EQ-5D-3L* EuroQol with five dimensions and three levels, *HAQ* Health Assessment Questionnaire, *HADS-A* Hospital Anxiety and Depression Scale – Anxiety subscale, *HADS-D* Hospital Anxiety and Depression Scale – Depression subscale

[a] Sample size is not constant due to participants with validated data in the following variables the following: Geographic location (*n* = 871), Years of education (*n* = 977), Employment status (*n* = 876), EQ-5D-3L score (*n* = 965), Alcohol intake (*n* = 977), BMI (*n* = 971), Regular physical activity (*n* = 977)

[b] Kusskall-Wallis test

[c] Chi-squared test

[d] This category includes participants who are students, domestic workers or that lives on revenues

non-inpatient costs with OA would decrease by 45%. This data should sufficiently alarm health politicians regarding the need for the implementation of effective and recommended modalities in the management of people with knee OA at a national level.

Determinants for healthcare services utilisation

Overall, the characteristics of our sample are similar to other data related to people with multimorbidity and the older adult population in Portugal, namely given the high proportion of people with lower education, high

Table 3 Final Multinomial Regression Model

		HighUsers vs. LowUsers			GPUsers vs. LowUsers		
Variables added	**Determinants**	**OR**	**95%CI**	***p*-value**	**OR**	**95%CI**	***p*-value**
Predisposing Characteristics	Age	0.96	0.95–0.99	0.001	0.99	0.96–1.01	0.172
	Male sex[a]	1.05	0.69–1.58	0.826	1.12	0.72–1.76	0.613
	Geographic Location[b]						
	North	1.545	0.93–2.56	0.091	1.23	0.70–2.15	0.475
	Centre	1.50	0.89–2.51	0.130	2.11	1.21–3.68	0.008
	Islands	0.43	0.24–0.77	0.005	0.42	0.21–0.83	0.013
	South	1.49	0.76–2.94	0.250	1.82	0.89–3.75	0.102
Step 1	**AUC[g]**	0.58	0.54–0.61	0.001	0.61	0.57–0.65	0.001
	McFadden Pseudo-R^2 = 0.026						
Enabling Factors	NHS only[c]	0.65	0.43–0.98	0.042	1.34	0.81–2.22	0.249
	< 4 Years of Education[d]	0.90	0.56–1.45	0.900	1.50	0.93–2,43	0.096
	Employed[e]	0.55	0.31–0.97	0.038	0.81	0.44–1.50	0.512
Step 2	**AUC[g]**	0.60 (+ 0.02)	0.56–0.64	0.001	0.63 (+ 0.02)	0.59–0.67	0.001
	McFadden Pseudo-R^2 = 0.040 (+ 0.014)						
Need Variables	Number of Comorbidities	1.12	1.03–1.21	0.011	1.22	1.11–1.33	< 0.001
	HRQoL (EQ-5D-3L index score)	0.33	0.14–0.79	0.013	0.61	0.23–1.57	0.303
	Physical function (HAQ score)	1.59	1.10–2.23	0.013	1.03	0.69–1.53	0.902
	Anxiety (HADS-A)	1.02	0.97–1.07	0.432	1.09	1.03–1.14	0.002
	Regular Physical Exercise[f]	0.57	0.37–0.88	0.010	0.55	0.34–0.89	0.014
Step 3: Final model	**AUC[g]**	0.68 (+ 0.08)	0.64–0.71	0.001	0.69 (+ 0.07)	0.65–0.73	0.001
	McFadden Pseudo-R^2 = 0.098 (+ 0.058)						

NHS National Health System, *GP* General Practitioner, *HRQoL* Health Related Quality of Life, *EQ-5D-3L* EuroQol with five dimensions and three levels, *HAQ* Health Assessment Questionnaire, *HADS-A* Hospital Anxiety and Depression Scale – Anxiety subscale. Reference Categories: [a]Female; [b]Lisbon and Tagus valley; [c] Healthcare insurance along with NHS; [d] ≥ 4 years of education; [e]Non employed or retired; [f] Don't perform regular physical exercise; [g]Area Under the ROC Curve (95% CI) – reference cluster is LowUsers. Differences in discriminatory capacity (AUC) and in variance of the model regarding the previous step is shown in brackets. $\chi^2(28) = 180.328$, $p < 0.001$

This procedure excluded all the participants with missing data. Sample included in the analysis: Total: $n = 838$ (85,69% of the initial sample), HighUsers: $n = 295$ (86.0% of the initial cluster sample); GPUsers: $n = 232$ (85,29% of the initial cluster sample); LowUsers: $n = 311$ (85.67% of the initial cluster sample)

Table 4 Summary of determinants that increase the probability of membership in each healthcare utilisation profile, according to Andersen's Behaviour Model of Healthcare Utilisation

	Determinants	***HighUsers*[a]**	***GPUsers*[a]**
Predisposing Characteristics	Age	Being Younger	–
	Geographic Location	Live in Portugal Mainland	Live in Portugal Mainland Live in the centre region
Enabling Factors	Healthcare insurance	Additional healthcare coverage	–
	Employment status	Being employed	–
Need Variables	Comorbidities	Higher number of comorbidities	Higher number of comorbidities
	Quality of life	Worse HRQoL	–
	Physical function	Worse physical function	–
	Anxiety symptoms	–	More anxiety symptoms
	Physical Exercise	No regular physical exercise	No regular physical exercise

NHS National Health System, *HRQoL* Health Related Quality of Life

[a]Reference Cluster: LowUsers

proportion being overweight or obese, and physically inactive [5, 32].

Our findings show that, regardless of clinical need, predisposing characteristics and enabling factors such as age, geographic location, health insurance and employment status, play an important role in healthcare utilisation. This data may disclose that, possibly, the current management of knee OA is heterogenous, not consistent with the needs of the patients, and also, highlights possible inequities in the access of health care [18].

In our analysis, younger and employed participants were positively associated with *HighUsers* profile. Unlike the data related to general older adults population in Portugal [33], evidence suggests that older adults with knee OA are less likely to be referred to specialised services, like an orthopaedic surgeon, rheumatologist [34] or to physiotherapy [30]. Qualitative data suggests that GP's often consider OA as a normal consequence of ageing, attributing low importance to this condition in older adults [35]. In contrast, knee OA is associated with work-related disability, absenteeism, early retirement, psychological distress and low HRQoL in younger patients [4, 36]. Thus, employed or younger adults with knee OA seem to behave more proactively in seeking help and their physical limitations are generally taken more seriously by GP's, with higher referral rates and consequently, a higher utilisation of healthcare services [35].

Our findings also suggest that geographic location is a determinant to healthcare services utilisation, namely the Islands and Centre region. Both of these regions are far from city centres, with higher proportion of older, less educated and poorer people. These regions experience a shortage of medical specialists such as orthopaedic surgeons. Moreover, Madeira and Azores are underserved by primary care units [37]. International data suggests that the distance from healthcare units, lack of transport and consequent isolation, and the perception of OA as being a self-limited condition, may prevent people from rural areas of seeking healthcare services timely, with lower healthcare resources utilisation as consequence [38, 39].

Participants with additional healthcare coverage were more likely to be *HighUsers*, suggesting that the NHS may not provide optimal access to the appropriate interventions according to the patients' needs, or that the facilitation of access to private sector may enhance the utilisation of healthcare services, regardless of the severity of the disease [40]. In accordance with our study, private health insurance was the most frequently cited enabler in Australia for surgical and conservative OA treatments, such as physiotherapy [41].

Overall, our findings suggest that the delivery of healthcare for Portuguese people with knee OA may be inefficient and unfair, where people with better predisposing and enabling features consume a higher amount of healthcare services, than people without those features. Our findings, with the support of the presented literature, should raise concerns regarding the need to tackle health access inequities in Portugal. In this way, the organisation of the health system should guarantee that people with OA receive effective interventions according to clinical severity, and not according to sociodemographic factors.

For predisposing variables, our findings showed that the number of comorbidities is associated with higher healthcare utilisation profiles, mainly with *GPUsers* profile, as well as anxiety symptoms. People with OA visit primary care mostly in case of multimorbidity [42]. However, evidence shows that, in people with OA and multimorbidity, joint pain is often seen as a low priority problem, brought up late in the consultation, with low referral rates to physiotherapy or specialised care targeted to OA [42, 43]. This information may explain the stronger association of number of comorbidities with *GPUsers* profile, than with *HighUsers*. Regarding anxiety symptoms, contradictory data was found in literature. Anxiety is associated both negatively and positively with the utilisation of healthcare services [44, 45]. However, it is well known that mental health comorbidities, like anxiety and depression, as well as cardiovascular and metabolic comorbidities are associated with higher severity symptoms and poor outcomes in people with OA [45, 46]. Thus, the management of people with OA, especially with anxiety and/or multimorbidity, should be multidisciplinary personalised and targeted [8, 9], which would justify a higher utilisation of healthcare, mostly specialised services, partly in contrast to our data. Thus, we may argue that this subpopulation of patients with knee OA is undertreated in Portugal, recognising the urge to organise services across healthcare sectors to pursue the delivery of recommended and more effective interventions, mainly to people with poor prognosis.

In our study, physical inactivity was associated with both profiles of higher healthcare utilisation. Sedentary behaviour and being overweight in people with knee OA is associated with poor physical function, higher risk of cardiovascular comorbidities [7], higher healthcare consumption and higher health-related costs [47]. Barriers to physical exercise have been identified in literature that justify the low adherence of patients, namely the misbeliefs of health professionals regarding exercise and physiotherapy [48].

As expected, low levels of physical function and HRQoL are associated with *HighUsers*. A 10-year UK survey reported that disability was the strongest predictor for referral to specialised care and for TKR in people with knee pain [34]. Similarly to our data, poor physical function, associated comorbidities, and also radiologic severity were also associated with higher direct and indirect costs as reported in a Spanish survey [49]. Considering physical function and quality of life, the results of this study suggest that a higher healthcare utilisation does not reflect better outcomes.

Strengths and limitations

This is the first study in Portugal analysing the health services utilisation by people with knee OA at a national level. The large sample, the multi-domains of the dataset and its framing on An dersen's model, provides a comprehensive view of the current healthcare utilisation profiles and its determinants.

Nevertheless, it has some limitations. The cross-sectional design does not does not allow the establishment of a temporal relationship between determinants and healthcare utilisation; thus, cause and effect can be overestimated mainly in modifiable variables like physical function or HRQoL. Other potential important psychosocial variables, that may influence healthcare utilisation behaviours were not controlled in this study (e.g., coping behaviour, self-efficacy) [50]. The physical activity variable did not take into account the amount of time spent per week, nor its intensity, thus our results may be, even so, overestimated when comparing to the recommendations for physical activity. Public or private appointments, were not distinguished, which could increase the importance of predisposing characteristics and enabling factors in the variance of healthcare utilisation. As self-reported healthcare utilisation is related to the previous 12 months, we acknowledge that the possibility of memory bias may compromise the accuracy of the outcome of this study (utilisation of healthcare services). In this study, we did not account for the reason for medical appointments or physiotherapy attendance, which could increase the accuracy of the results. The data used was collected in 2011–2013 but, due to the few specific strategies directed to musculoskeletal diseases in the last decade in Portugal, we cautiously believe that the actual management of OA does not differ from this study.

Implications of the findings

The results of this study highlight the importance of addressing the inequalities of access and heterogeneity in care, as well as the need to tackle adherence to exercise and enhancement of self-management strategies, e.g., with physiotherapy in primary care, to a much larger proportion of the population with knee OA. A whole system approach needs to consider primary prevention, early detection, cost-effective interventions and appropriate referral, as well as personalised interventions taking into account other comorbidities that are often present in these patients [51].

Conclusion

We identified three different healthcare services utilisation profiles. The *HighUsers* profile accounted for more than one third of people with knee OA and it includes GP utilisation, orthopaedic surgeon appointments, physiotherapy and/or hospitalisation. Need variables explained a considerable proportion of the variance in healthcare utilisation, although determinants like younger age and geographic location, having additional healthcare coverage and being employed were associated with higher utilisation of healthcare services. These facts suggest the need for improvement in the access of healthcare services, in the quality of care and, implementation of international recommendations according to the clinical severity in all people with knee OA.

Abbreviations

BMI: Body Mass Index; CI: Confidence Interval; EQ-5D-3L: EuroQol Questionnaire with 5 dimensions and 3 levels; GBP: Gross Domestic Product; GP: General Practitioner; GPUsers: General Practitioner Users profile; HADS-A: Hospital Anxiety and Depression Scale – Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale – Depression subscale; HighUsers: High Healthcare Users profile; HRQoL: Health Related Quality of Life; LowUsers: Low Healthcare Users profile; NHS: National Health Service; OA: Osteoarthritis; OR: Odds Ratio; TKR: Total Knee Replacement

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12913-021-07045-4.

Additional file 1 : **Table S1.** Univariate association analysis between the determinant variables and cluster membership.

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Authors' contributions

DC contributed to the drafting of the manuscript. DC, EBC, CN and AMR contributed to the analysis and interpretation of the data and statistics. HC, JB and AMR contributed to the conception and design of the main project (*EpiReumaPt*), for the provision of study materials, obtaining funding for the main project, administrative/logistic support and in collection of the data. All of the authors critically revised and approved the final manuscript.

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Availability of data and materials

The data underlying this article were provided by the EpiDoc Unit - CEDOC by permission. Data will be shared on request to the corresponding author with permission of the EpiDoc Unit group leaders.

Declarations

Ethics approval and consent to participate

This is a secondary analysis of the EpiReumaPt study database, requested by the authors, authorized and provided by EpiDoC Unit - CEDOC staff. The provided database was anonymized, without any contact information of individual participants.

Consent for publication

Not applicable.

Competing interests

The authors report no conflict of interests.

Author details

[1]NOVA National School of Public Health, Public Health Research Centre, Universidade NOVA de Lisboa, Avenida Padre Cruz, 1600-560 Lisbon, Portugal. [2]Comprehensive Health Research Centre (CHRC), Universidade Nova de Lisboa, Lisbon, Portugal. [3]EpiDoC Unit, CEDOC, NOVA Medical School, Lisbon, Universidade NOVA de Lisboa, Lisbon, Portugal. [4]Rheumatology Unit, Hospital dos Lusíadas, Lisbon, Portugal. [5]Physiotherapy Department, School of Health, Polytechnic Institute of Setúbal, Setúbal, Portugal. [6]Centro Hospitalar Lisboa Ocidental (CHLO- E.P.E.), Serviço de Reumatologia do Hospital Egas Moniz, Lisbon, Portugal.

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Supplementary Material

Table S1 – Univariate association analysis between the determinant variables and cluster membership

	Determinants (eligible participants)	**Chi-square**	**DF**	**p-value**
Predisposing Characteristics	Age (n=978)	3.99	2	0.136
	Sex (n=978)	8.08	2	0.018
	Geographic Location (n=871)	39.53	8	<0.001
	Marital Status (n=978)	1.16	2	0.558
Enabling Factors	Healthcare Insurance (n=978)	12.63	2	0.002
	Years of Education (n=977)	23.60	2	<0.001
	Employed (n=964)	11.05	2	0.004
Need Variables	Number of Comorbidities (n=978)	55.20	2	<0.001
	Body Mass Index (n=907)	7.64	6	0.266
	HRQoL (EQ-5D-3L index score) (n=965)	56.28	2	<0.001
	Physical function (HAQ score) (n=978)	63.67	2	<0.001
	Depression (HADS-D) (n=978)	22.09	2	<0.001
	Anxiety (HADS-A) (n=978)	31.84	2	<0.001
	Physical Exercise (n=977)	19.92	2	<0.001
	Alcohol Intake (n=977)	8.41	4	0.078
	Smoking Habits (n=978)	1.34	2	0.512

DF, degrees of freedom; HRQoL, Health Related Quality of Life; EQ-5D-3L, EuroQol with five dimensions and three levels; HAQ, Health Assessment Questionnaire; HADS-D, Hospital Anxiety and Depression Scale – Depression subscale; HADS-A, Hospital Anxiety and Depression Scale – Anxiety subscale

Only variables at <0.2 significant level were considered for inclusion in the multinomial logistic regression analysis.

5.5. Study 5: Models of Care for People with Knee Osteoarthritis in Primary Healthcare: A Scoping Review

5.5.1. **Published protocol:** Daniela Costa, Eduardo B Cruz, Ana M Rodrigues, Daniela Gonçalves-Bradley, Luís A Gomes, Helena Donato, Carla Nunes, Models of care for patients with knee osteoarthritis in primary healthcare: a scoping review protocol. *BMJ Open* 2021;**11:**e045358. doi: 10.1136/bmjopen-2020-045358

BMJ Open

Models of care for patients with knee osteoarthritis in primary healthcare: a scoping review protocol

Daniela Costa ,[1,2,3] Eduardo B Cruz ,[2,4] Ana M Rodrigues,[2,3]
Daniela Gonçalves-Bradley,[5] Luís A Gomes,[2,3,4] Helena Donato ,[6] Carla Nunes[1,2]

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- ► Prepublication history and additional online supplemental material for this paper are available online. To view these files, please visit the journal online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-045358).

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For numbered affiliations see end of article.

Correspondence to
Daniela Costa;
dcosta.ft@gmail.com

ABSTRACT

Introduction Knee osteoarthritis (OA) is a prevalent condition with associated high disability and healthcare costs. Evidence of major gaps in the implementation of evidence-based interventions in people with knee OA led several healthcare systems to implement models of care (MoCs) in order to improve knowledge translation and guaranty their economic sustainability. Nevertheless, there are few studies that analyse the existing body of evidence of MoCs for patients with knee OA in primary healthcare settings. Therefore, we aim to identify MoCs developed for patients with knee OA implemented in primary healthcare and, analyse their core components and outcomes. This scoping review will create knowledge about the components and outcomes of these MoCs which, in the future, will facilitate their transferability to practice.

Methods and analysis We will include studies that developed and implemented an MoC for people with knee OA in primary healthcare. We will use the PCC mnemonic, being 'Population'—people with Knee OA, 'Concept'—the MoCs and 'Context'—the primary healthcare setting. We will conduct the search on PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Scopus, Web of Science Core Collection, as well as grey literature databases and relevant institutions and organisations websites, for articles published after 2000. Two independent reviewers will screen titles and abstracts followed by a full-text review to assess papers regarding their eligibility. We will evaluate the methodological quality of the included studies with the Mixed Methods Appraisal tool and apply a data abstraction form to describe and interpret the evidence.

Ethics and dissemination As a secondary analysis, this scoping review does not require ethical approval. Findings will be published in peer-review journal, presented in scientific conferences and as a summary through primary healthcare units.

Strengths and limitations of the study

- ► To our knowledge, this is the first scoping review that aims to map the literature about models of care developed and implemented for patients with knee osteoarthritis.
- ► We will undertake a comprehensive search strategy for published and unpublished studies in peer-reviewed journals databases, grey literature databases, handsearch in relevant journals, organisation and institution websites and conference proceedings, with the support of a research librarian.
- ► This scoping review is limited to articles written in English, Spanish and Portuguese, since 2000.
- ► The quality appraisal of the included studies, although not common on scoping reviews, will provide a better interpretation of the results and will identify the gaps in evidence in this topic.
- ► This scoping review will generate hypothesis for the development of new models of care and support future intervention research studies.

INTRODUCTION

Osteoarthritis (OA) affects approximately 250 millions of people worldwide,[1] and is responsible for 9.6 million years lived with disability.[2] Alongside the impairments in physical function,[3] people with OA often experience chronic pain, depression and sleeping problems.[4] Worldwide, healthcare costs related to OA represent approximately 0.9% of national healthcare systems,[5] representing 1%–2.5% of the Gross Domestic Product (GDP) of high-income countries.[6]

The knee is the most affected joint and it is responsible for approximately 85% of the burden of OA.[2] The worldwide increase of obesity, alongside with the proportion of people with low levels of physical activity, are associated with the rising prevalence and incidence of knee OA.[7]

There is no known cure for OA. Currently, evidence-based approaches aim to improve joint function and patients' quality of life, relieve pain and modify risk factors for disease progression. Clinical practice guidelines recommend exercise, education, self-management and healthy weight maintenance as core interventions for knee OA, during all stages of this disease. Pharmacological management is recommended for symptom control, and total knee arthroplasty (TKA) is considered a latter option, when quality of life is significantly impaired, even

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with the implementation of conservative interventions.[8 9] Although TKA is considered to be a cost-effective intervention,[10] patient-reported outcomes highlight its shortcomings. Evidence reveals that 5% of patients report postoperative complications,[11] 50% report adverse events in the first year after surgery,[12] 20%–34% report dissatisfaction with surgery,[13] and 3%–5% need surgery revision in less than 10 years.[14] Furthermore, the mortality rate associated with TKA is approximately 0.2%–0.37%.[15]

Despite international recommendations, evidence across several countries report that conservative non-pharmacological interventions are offered to less than 50% of patients.[16 17] Moreover, TKA incidence rate has been rising exponentially in the Organisation for Economic Co-operation and Development (OECD) countries, for patients both above and below 65 years old. The reported annual growth rate of 5.5% is disproportional even when the epidemiological changes are taken into account.[18] Furthermore, qualitative studies reveal that healthcare professionals see OA as a trivial condition with an unavoidable progression, and often believe that conservative treatments lack efficacy.[19]

Taking this data into account, there are major gaps in the translation of evidence to practice, and the care of patients with OA has been characterised by symptom-driven and segmented interventions,[20] centred on pharmacological,[16 17] surgical options.[21] The complex and multidomain target for knee OA treatment can only be achieved by person-oriented intervention models that are multidisciplinary, if needed, and include a timely integration of evidence-based interventions.[20] This knowledge has driven national health policies in several countries to create strategies to improve intervention outcomes, guarantee the sustainability of healthcare systems and the cost-effectiveness of interventions of patients with OA.[22] These strategies encompass the implementation of models of care (MoCs) that are used as facilitators to bridge the gap between evidence and care delivery and practice, by describing not only the principles of care for a given condition (what to do), but also to guide how these principles can be implemented in a local setting (the 'how').[23]

MoCs for musculoskeletal diseases are showing promising results in overall patient satisfaction with care,[24] improvement of patient-level outcomes and adherence to guidelines recommendations,[25] and appropriate use of medication and reduction of absence from work.[26]

Several MoCs for OA have been implemented and published worldwide,[24–27] mainly in primary healthcare settings. Usually, MoCs are complex interventions thus, its transferability into practice is challenging due to their context dependency. Moreover, in 2018 a group of researchers and clinicians established the 'Joint Effort Initiative', endorsed by Osteoarthritis Research Society International, which mission includes the investigation of the most effective OA Management Programmes, that are MoCs for OA, and the development of long-term strategies for effective implementation in different socio-economic and cultural environments. The first action of this initiative was to identify and prioritise future work, with a survey with delegates with known interest on OA Management Programmes. The highest priority ranked action statement identified was 'to establish guidelines for the implementation of different OA Management Programmes to ensure consistency of delivery and adherence to international best practice MoC'.[28] Therefore, creating knowledge of and clarifying which intervention components have been included in the MoCs, as well as exploring their outcomes is paramount and needed worldwide.

Few studies have synthesised evidence on MoCs for OA. The narrative review by Allen *et al*.[2929] shares some preliminary evidence about the characteristics of selected MoCs designed for patients with OA. This is, to our knowledge, the only study that synthesised the evidence on this topic. This review identified several MoCs for prevention, management in the disease continuum and specific for advanced OA, namely directed for total joint replacement surgery. The authors concluded that there are emerging efforts in multiple countries to implement MoCs, mostly focused on non-pharmacological interventions. Additionally, it is concluded that there is a need to examine the impact of these MoCs, and to explore how this MoCs can be adapted and implemented in other contexts.[29] Due to its inherent methodological limitations, such as the absence of a search strategy, methodological quality assessment of the included studies and a standardised method for data extraction, it is not possible to replicate this review nor to understand how studies were selected. Notwithstanding its importance, this study provides a biased depiction of the literature of MoCs developed for patients with OA.

With this scoping review, we aim to map the existing literature of MoCs developed for people with knee OA through a systematic methodology. Our primary objective is to identify MoCs developed for patients with knee OA in primary healthcare and describe their components. The secondary objectives are to describe the outcomes of MoCs and to identify specific aspects of the context reported related with the implementation of the MoC. These context-related aspects, which can influence the success and transferability of the MoCs, will be divided in three categories: external (e.g., supportive national/local policies, governmental financial incentives, dominant paradigms in society as evidence-based practice or patient-centred care, support of stakeholders), organisational (e.g., presence of a culture of innovation, leadership characteristics, organisational readiness, resources available and professional relationships among team and patients) and population-level (e.g., specific geographic areas with different access to health services, subpopulations with special sociodemographic and clinical characteristics).[30] Although qualitative assessment is not usually performed on scoping reviews,[31 32] we will include it to describe the quality of research in this field.

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METHODS AND ANALYSIS

A scoping review is a valid, comprehensive and transparent method for mapping the body of evidence underpinning a research area, main sources and type of evidence available. Scoping reviews are mainly made for complex and heterogeneous research topics or for those which were not previously comprehensively reviewed.[32 33] Given the stated objectives of this review, the topic of interest is the identification, mapping, reporting and discussion of the characteristics of MoCs. Therefore, our purpose is better aligned with a scoping review, instead of systematic review, considering the criteria described by Munn *et al*[34]

The methodology of this scoping review will be guided by established methodological frameworks, as outlined by Arksey and O'Malley[33], and enhanced by Levac *et al*[31] and Joanna Briggs Institute (JBI).[35] The Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension (PRISMA) for Scoping Reviews will guide the development of the scoping review to ensure transparency of the results uptake.[36] To our knowledge, and after a search in relevant databases, this is the first protocol for a scoping review that aim to identify the MoCs developed and implemented for people with knee OA.

Research questions

According to the objectives previously formulated, this review will attain to answer the following research questions

1. Which MoCs have been implemented for non-institutionalised patients with knee OA attending primary healthcare units?
2. What are the core components included in the MoCs (these include, but are not limited to, interventions and their characteristics, healthcare professionals involved, programmes duration, funding)?
3. What are the MoCs outcomes and how have they been measured (patient-level outcomes, system-level outcomes and implementation outcomes)?
4. Which are the aspects of the included MoCs that are context-specific at external, organisational and population level (as described in the introduction section)?

Identification of the relevant literature

Inclusion criteria

To guide the identification and inclusion of the studies we will use the mnemonic 'PCC' referring to Population, Concept and Context, as proposed by JBI.[35]

Population

We will consider studies that included non-institutionalised adults (that live in the community, and are not residents/inpatients in any institution, like hospitals, psychiatric centres, nursing homes, military institutions or prisons), diagnosed with knee OA who have not undergone, or scheduled, TKA. Studies that involve patients with other types of arthritis or patients with OA in multiple joints will be included if more than 50% of the patients have diagnosis of knee OA.

Concept

The concept of interest in this review is MoCs designed for patients with knee OA. In this study, we will use the definition by Briggs *et al* that defines an MoC as 'an evidence-informed policy or framework that outlines the optimal manner in which condition-specific care should be made available and delivered to consumers at a system level'.[23] Therefore, 'a MoC aims to describe the principles of care for a given condition (the 'what') as well as guidance on how those principles could be implemented in a local setting (the 'how')'. A distinction should be made between MoCs, clinical guidelines and models of service delivery. MoC serve as guides that complement clinical practice guidelines, describing how best evidence can be implemented as a sector-wide model of service delivery by clinicians, consumers and health systems across the disease continuum, tailored to the specificities of local context. Thus, a model of service delivery converts the principles of an MoC into operational activity and operational recommendations, relevant to the local context, modes of service delivery and evaluation, considering resources, infrastructure and workforce capacity requirements. As mentioned, the concept of interest of this scoping review is MoC, and we will only consider the model of service delivery of a specific MoC to describe its organisational components.[23]

To guide the inclusion of the studies in this review we develop operational a priori criteria to distinguish a model of care from other types of interventions based on The Framework to Evaluate Musculoskeletal MoC, Briggs *et al*[37] and Eyles *et al*[28] .[23 28 37] Only studies that address the implementation in a real-world setting of MoC's and that fulfil all the following criteria will be considered for inclusion:

- Defines the optimal care manner to deliver care for people with OA, with an underlying evidence-informed strategy, framework or pathway.
- Describes the operationalisation of the MoC, for example, who deliver care, when and where care is best delivered and how it is to be delivered.
- The MoC is tailored according to context.
- Care is coordinated, with longitudinal progression and reassessments.
- The implementation of the MoC has patient-level, organisational-level and/or implementation-level goals.

In this scoping review, we will consider the identified MoC as the unit of interest thus, several studies that report the outcomes of the same MoC will be considered.

According to the stated research questions as well as the recommendations for implementation of MoC's,[37] we will a priori include studies that describe, but are not limited to: (1) Which MoC was implemented: identification of MoC and/or frameworks/theory used; (2) What and how care is provided, and by whom: underlying interventions at patient level, professionals training, services involved, organisation of care, among others; (3) How the MoC is assessed and what were its outcomes at patient's

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level (e.g., pain, function or quality of life, satisfaction, collected with self-reported questionnaires or interview questionnaires or performance measures), at system level: (e.g., rate of referral or prescription for exercise, rate of prescribed exams, healthcare costs, waiting times, quality indicators, perceptions/perspectives of stakeholders) and implementation outcomes (e.g., acceptability, adoption, feasibility, fidelity, penetration, sustainability) and (4) What are the aspects, if any, of the MoC that are context-specific at external, organisational and population level, as described in introduction section. We will include MoCs that consider non-pharmacological interventions (for example, exercise, patient education, behavioural change programmes, self-efficacy and self-management programmes), combined or not with pharmacological interventions, integrated in an MoC. We will exclude MoCs that focus only on pharmacological interventions, or that includes surgery or complementary and alternative medicine interventions.

Context

This review will be focused on primary healthcare context. WHO defines primary healthcare as a 'whole-of-society approach to health'.[38] According with guidelines recommendations, primary care is the most relevant setting worldwide for both research and management of patients with OA for prevention and across the disease continuum.[8 9]

We will include studies that have implemented MoCs focused on primary care services, but we will consider also MoCs that include interventions at other levels of healthcare delivery as long as it includes primary care services in the patient's pathway. The inclusion of primary healthcare in the pathway may be referred as the first contact with the healthcare system, for direct provision of care, point of referral to other levels of care or services or continuity of care. Primary care services may cover all the full continuum of health promotion and disease prevention, treatment and rehabilitation, delivered at individual or community-oriented approach. Thus, MoCs that consider in the pathway services such as, but not limited to, community pharmacies, physiotherapy and nutrition outpatient services, physical activity community services as well as hospitals or other secondary care settings linked with primary care will be included.[38]

Types of sources

We will include quantitative studies with comparative (randomised controlled, cohort, quasi-experimental) and non-comparative methods (narrative, policy reports, audit) related with the implementation of MoCs for patients with knee OA, that report outcomes of the implementation of the MoC. Qualitative or mixed-methods study designs will also be considered only if they report outcomes of the implementation for example, qualitative evaluation studies.

We will exclude studies that aim to test clinical effectiveness or efficiency of specific clinical interventions that do not undertake implementation interventions. In order to distinguish typical clinical intervention trials and implementation intervention trials related to MoCs (e.g., pilot studies, cluster or pragmatic randomised controlled trials) during title and abstract screening, we will consider studies for full text screening when the experimental group is compared with usual care, at the same or at another healthcare unit, wait list or no treatment whenever the title and abstract suggests an underlying MoC.[39] We will assume overinclusion of clinical intervention studies for full-text screening whenever doubts arise.

Literature published between 2000 and 2020 written in English, Portuguese or Spanish, in peer-reviewed and grey literature will be included in order to capture the most recent evidence on the implementation of MoC aligned with current paradigms of healthcare delivery.[40]

Search strategy

We will run the search query in PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL), Scopus (including conference proceedings), Web of Science Core Collection (including conference proceedings). Then, we will conduct a hand search in relevant peer-reviewed journals: Osteoarthritis and Cartilage, Best Practice and Research Clinical Rheumatology, BMC Musculoskeletal Disorders, Arthritis Care and Research, Implementation Science, Health Services and Delivery Research, JBI Evidence Synthesis and BMC Health Services Research.

We will perform the search in Open Grey, Grey Literature Report databases and MedNar search engine to identify grey literature records. We will also search websites of relevant institutions and organisations, such as WHO, Arthritis Australia, American College of Rheumatology, Osteoarthritis Research Society International, European League Against Rheumatism, Agency for Clinical Innovation Musculoskeletal Network, Arthritis Community Research & Evaluation Unit, National Institute for Health Research, and Bone and Joint Initiative.

We will screen the reference lists of the selected articles for inclusion to identify additional potentially eligible primary studies. Additionally, we will check reference lists of previous published reviews. We will contact authors of the included studies to clarify any questions we might have about their published reports and to seek unpublished data related to the MoC. Different reports of the same MoC will be collated, as each MoC is the unit of interest.[41]

We undertook a preliminary search in PubMed in September of 2020, which was built according to the 'PCC' mnemonic. The search terms included 'osteoarthritis', 'models of care' and 'primary care' and their synonyms, in title or abstract. We used the text words of relevant articles on this topic and the index terms used to describe these articles to develop a full search strategy (online supplemental file). As MoC are often poorly defined in the literature, and used interchangeably, as 'service improvement frameworks', 'models of service

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delivery', 'clinical frameworks' or 'care pathways', we will use a broad search strategy to cover all relevant studies. We will adapt the search strategy to each of the included databases. This process will be held in collaboration with a research librarian. We will conduct the searches from May to June 2021.

Study selection

Two independent reviewers (DC and LAG) will screen abstracts and titles of the search records. We will adopt maximum sensitivity during title and abstract screening, and retrieve full texts for all records included by at least one reviewer. The review team will perform a pilot testing of source selectors with the selection of a sample of 25 random titles/abstracts. We will screen this sample using the defined eligibility criteria, discussing discrepancies and making any necessary modifications. Screening will start only when we achieve an agreement of 75% or more.[41] For full-text screening we will note specific reasons for exclusion.

All identified articles will be collated and uploaded, duplicates will be removed, potentially relevant papers will be extracted in full and their citation details will be uploaded using EndNote X7.8 (Clarivate Analytics, USA). We will report a narrative description of the process of the search in the final scoping review accompanied by a PRISMA flow diagram.[36]

As previously stated, the unit of interest is the identified MoC, therefore we expect that, during the study selection, we will identify more than one study for the same MoC. Thus, all papers with a MoC that respects the inclusion criteria for population and context will be investigated for additional papers and then aggregated. In the end of full-text screening, we will collate information of different single studies related with the same MoC.

Data charting

Two reviewers (DC and LAG) will independently complete a standard data abstraction form to extract data from each study using a pilot-tested data abstraction form. Charting is a technique for organising and interpreting the data by screening, charting and sorting material according to the main issues and themes. The reviewers will apply the pilot-test data abstraction form in at least five articles to test and ensure consistency of the form in line with the purpose of the study, as presented in table 1. Changes will be made and discussed with the team prior to extracting data from the remaining articles. As an iteractive process, during the data extraction some items can be added according with studies found.[32] We will detail these modifications in full in the scoping review.

Quality assessment

Performing quality assessment is not common and is also a controversial issue in scoping reviews. The absence of quality appraisal is usually referred as a methodological limitation,[42] and, at the same time, a necessary component.[43] By qualitatively appraising the included studies, we will be able to map the quality of the literature in this field. Therefore, not only will we identify where research is lacking, but also the gaps in evidence base, identify the types of available evidence, and how research has been conducted in this area.[34] Additionally, quality appraisal is of paramount importance for the interpretation and dissemination of the results of this scoping review, enhancing their usefulness to practice, policy-making and for future research.[44]

Two independent reviewers will analyse the methodological quality of the retrieved studies using the Mixed Methods Appraisal Tool, 2018 version, since we expect to find a wide range of study types. This is a validated tool to evaluate qualitative research, randomised controlled trials, non-randomised studies, quantitative description studies and mixed-methods studies. Any disagreements between reviewers will be solved by consensus or decision of a third reviewer. We will report results in a narrative form and in a table that will contain the accomplishment information of each item of the checklists, described as

Table 1 Data extraction according to scoping review research questions

	Data to be extracted
Summary	Authors Title Year of publication Citation Source of Information (peer-review or grey literature) Study designs
Research question 1: identification of the MoC	MoC Identification (name, if applicable) Country Population addressed and sample size, including proportion of participants with Knee OA (n/% of total)
Research question 2: core components	Theory/framework Interventions components and their characteristics Organisational components (eg, healthcare professionals involved, workforce capacity, programmes duration, funding, care coordination)
Research question 3: outcomes and outcome measures used	Outcomes addressed and outcome measures Main results of MoC (outcomes at organisation and patient level Evaluation of implementation success (if applicable)
Research question 4: context-specific components	Context-specific external factors Context-specific organisational factors Context-specific population factors

MoC, models of care; OA, osteoarthritis.

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'yes', 'no' and 'can't tell'.[45] This appraisal will provide a structured and thorough analysis the range of quality of studies of knee OA MoCs that has been published, leading to a better interpretation of the results.

Synthesis and presentation of results

We will perform a descriptive qualitative content analysis that will be presented in a tabular form, aligned with the objectives and research questions of this scoping review. This will include the identification of the MoC, the core intervention components, professionals involved and inherent training, services involved, organisation components, context-related specificities, outcome measures used and outcomes at organisational and patient level and evaluation of implementation success. We will report also as quantitative data, using a descriptive numerical summary, the overall number of studies, study designs, years of publication, types of intervention, characteristics of the study population and geographical distribution of studies. Meta-analysis is not planned.

Additionally, a narrative summary will accompany the tabulated results and will describe how the results relate to the research questions and objectives. As stated before, the data extraction may be updated during the data extraction process.

Consultation with relevant stakeholders

Two members of the research team (EBC and AMR) have developed and implemented MoCs for musculoskeletal diseases and will be involved throughout the analysis process. This involvement will provide additional sources of information, perspectives, high level of meaning content, expertise and it will enhance the applicability of this scoping study.

Author affiliations
[1]NOVA National School of Public Health, Public Health Research Centre, Universidade NOVA de Lisboa, Lisbon, Portugal
[2]Comprehensive Health Research Center (CHRC), Universidade Nova de Lisboa, Lisboa, Portugal
[3]EpiDoC Unit - Epidemiology of Chronic Diseases Unit, CEDOC, NOVA Medical School, Universidade Nova de Lisboa, Lisboa, Portugal
[4]Physical Therapy Department, School of Health, Polytechnic Institute of Setúbal, Setúbal, Portugal
[5]Nuffield Department of Population Health, University of Oxford, Oxford, UK
[6]Documentation and Scientific Information Service, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

Twitter Eduardo B Cruz @EBCRUZ64

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ORCID iDs
Daniela Costa http://orcid.org/0000-0001-8469-6356
Eduardo B Cruz http://orcid.org/0000-0003-1812-1815
Helena Donato http://orcid.org/0000-0002-1905-1268

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Models of Care for Patients with Knee Osteoarthritis in Primary Healthcare: A Scoping Review Protocol

Supplementary file

MEDLINE (PubMed) Search strategy

Search conducted in May 2021

Search	**Query**	**Records retrieved**
#1	(“osteoarthritis"[MeSH] OR “osteoarthritis"[tiab] OR “osteoarthritides"[tiab] OR "arthritis"[MeSH] OR "arthritis"[tiab] OR “arthritides"[tiab] OR ("arthritis"[tiab] AND "degenerative"[tiab]) OR "arthritis degenerative"[tiab])	349 039
#2	((“model of care”[tiab] OR “care model”[tiab] OR “Models, Organizational”[MesH]) OR (theor*[tiab] OR concept*[tiab] OR **framework*[tiab] OR model*[tiab] OR program*[tiab] OR approach*[tiab]))** **AND** (((“critical pathways”[MeSH] OR “functional integration”[tiab] OR “clinical integration”[tiab] OR “**case management**”[MeSH] OR “delivery of health care, integrated”[MeSH] OR “disease management”[MeSH] OR “patient care management”[MeSH] OR “patient-centered care”[MeSH] OR “continuity of patient care”[MeSH] **OR** “comprehensive health care”[MeSH] OR “managed care program*”[tiab] **OR** “multidisciplinary care”[tiab] OR “interdisciplinary care”[tiab] OR “inter-**disciplinary** care”[tiab] OR “cross disciplinary care”[tiab] OR “cross-**disciplinary** care”[tiab] OR “**multiple interventions**”[tiab] OR “care chain”[tiab] OR “care chains”[tiab] OR “**care continuity**”[tiab] OR “**care continuation**”[tiab] OR “care transition*”[tiab] OR “chain of care”[tiab] OR “continuity of care”[tiab] OR “cross sectoral care”[tiab] OR “integrated health care”[tiab] OR “integrated medicine”[tiab] OR “integrated social network*”[tiab] **OR** “integration of care”[tiab] OR “intersectoral care”[tiab] OR “linked care”[tiab] OR “**management model**”[tiab] OR “service network*”[tiab] OR “transition of care”[tiab] OR “transitional care”[tiab] OR “transmural care”[tiab] OR “holistic care”[tiab])))	3111 501
#3	**("primary health care"[MeSH Terms] OR ("primary"[tiab] AND "health"[tiab] AND "care"[tiab]) OR "primary health care"[tiab] OR**	560 685

	("primary"[tiab] AND "care"[tiab]) OR "primary care”[tiab]) **OR** ("general practice"[MeSH Terms] OR ("general"[tiab] AND "practice"[tiab]) OR "general practice"[tiab] OR ("general"[tiab] AND "medicine"[tiab]) OR "general medicine”[tiab]) **OR** ("family practice"[MeSH Terms] OR ("family"[tiab] AND "practice"[tiab]) OR "family practice"[tiab] OR ("family"[tiab] AND "medicine"[tiab]) OR "family medicine”[tiab]) **OR** (("primaries"[tiab] OR "primary"[tiab]) AND "servic*"[tiab])	
#4	#1 AND #2 AND #3	893
Limited to: from 2000, English, Portuguese and Spanish		802

5.5.2. **Manuscript**: Daniela Costa, Luís A Gomes, Helena Donato, Ana M Rodrigues, Daniela Gonçalves-Bradley, Eduardo B Cruz, Models of Care for People with Knee Osteoarthritis in Primary Healthcare: A Scoping Review (To be submitted)

Models of Care for People with Knee Osteoarthritis in Primary Healthcare: A Scoping Review

ABSTRACT

Objective: To map the existing literature of models of care (MoCs) designed for people with knee osteoarthritis (OA) in primary healthcare.

Design: This scoping review identified MoCs studies via PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Scopus and Web of Science Core Collection, hand search in relevant peer-reviewed journal, gray literature databases and in arthritis relevant organizations. We included MoCs designed for people with knee Osteoarthritis in primary healthcare, that reported patient, organization or implementation-level outcomes. Title and abstract screening as well as full text and data extraction was performed by two independent reviewers. Data was charting through a content analysis given the objectives of this scoping review.

Results: Thirteen MoCs were included, all implemented in high-income countries. Most of MoCs presented a stepped care pathway. Education and structured exercise programs were the most included interventions. Integration of primary care with community services, hospital-based and outpatient clinics was observed. Physiotherapists and General Practitioners were the professionals most considered in MoCs. Context features have been reported, as well as professionals training and coordination of care. Few MoCs report the use of theories for the development or for the implementation process. Thirty different patient-level intervention outcomes domains were noted across MoCs. Compared to usual care, MoCs have reported benefits in physical function, pain intensity, health-related quality of life and physical activity level; healthcare utilization and quality of care, and in implementation outcomes, like fidelity and adherence.

Conclusions: This scoping review gives a broad and comprehensive view of MoCs implemented in primary care for people with knee OA worldwide. These MoCs have been designed to the local context, mostly according to national system organization and underlying health policy, however, the evaluation and report of MoCs are heterogeneous. Our results highlight the need for more research regarding the effectiveness and process evaluation of MoCs implementation, as well as guidelines for the development and report the components and implementation features of MoCs.

Key words: Osteoarthritis, Models of Care, Implementation Science

BACKGROUND

Over 500million people worldwide suffer with OA, representing 9.6million years-lived with disability, of which 85% are due to knee OA (1). Prevalence, associated disability and healthcare demands have been raising exponentially worldwide as consequence of the high rate of risk factors for onset and severity progression of knee OA, like previous injuries, ageing, overweight and obesity, physical inactivity and multimorbidity (2–4).

No cure or disease modifying interventions has been found for OA. Given the multidomain and complexity of this disease, clinical practice guidelines have recommended a stepped, integrated, person-centred and multidisciplinary interventions that should be offered in primary care through the disease continuum (5,6). Self-management, exercise and weight control have shown short-to-medium term effectiveness in improving pain, function, and HRQoL (7–9), and are considered core interventions and first-line strategies for people with knee OA (5,6,10). Pharmacological interventions have shown short to mid-term effectiveness for symptoms control (11). Joint replacement surgery (TJR) showed cost-effectiveness but (12), given the associated adverse events (13), rates of dissatisfaction with the outcomes (14) and rates of surgery revision needs (15) it has been considered a latter option in selected patients, when all other interventions fail (12).

However, literature shows evidence-practice gaps in the management of people with knee OA, with symptom-driven and segmented interventions, that are poorly based on recommendations (16,17), namely with low uptake of core interventions (18–20). In contrast, medication is often offered as first-line treatment, and surgery has been rising exponentially in last decades (18–20), and seems to be seen as inevitable (21).

In face of these problems, research on the implementation of Models of Care (MoCs) has been emerging, aiming to optimize outcomes, guarantee the quality of care and sustainability of healthcare services in the management of people with knee OA around the world (Allen et al., 2016b; Andrew M. Briggs & Choong, 2018; Baldwin et al., 2017). MoCs have been defined as evidence-informed framework that describes the principles of care for a given condition (what to do) and guide how these principles can be implemented, considering the local setting and context (the ‘how’) (25).

The need for guidelines to support the implementation of MoCs for people with OA and ensure consistency of delivery and adherence have been pointed out as a top priority action for future investigation on MoCs for OA (26). Narrative reviews shared some preliminary evidence on the characteristics and promising results of selected MoCs

(Allen et al., 2016b; Bowden et al., 2020; Gray et al., 2022) but, the body of literature in this field is markedly unknown.

No studies with a systematic methodology have mapped or synthesize the body of literature on the implementation of MoCs for people with knee OA, which may hinder the development of implementation guidelines and the transferability of established MoCs, given its context dependency. The effectiveness and cost-effectiveness of MoCs are unclear and without this knowledge the implementation and scale-out of MoCs are concealed.

The aim of this scoping review is to map the existing literature of MoCs developed for people with HKOA in primary care. Specifically, we aim to 1) identify MoCs developed and implemented for people with HKOA in primary healthcare; 2) describe their intervention components (*what care*); 3) describe the specificities of the context and the features of implementation reported in the identified MoCs (*how care is delivered*); 4) to describe the outcomes measured at patient, organizational and implementation level; 5) describe the main outcomes of MoCs. To understand the quality of evidence published, we will appraise the quality of the studies included, although not usually performed in scoping reviews (29,30).

METHODS

This scoping review was guided by established methodological frameworks, outlined by Arksey and O'Malley (2005) (32), and enhanced by Levac et al. (2010) (29) and Joanna Briggs Institute (JBI) (33), as previously reported in the published protocol (34)**.** The Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for scoping reviews (PRISMA-ScR) guided this report to ensure transparency of the results uptake (35).

Research Questions

According to the objectives previously stated, this review aims to answer the following research questions:

1. Which MoCs have been implemented for non-institutionalised patients with knee OA attending primary healthcare units?

2. What are the components included in MoCs interventions (care pathway, healthcare interventions, programs duration, healthcare professionals involved and settings considered)?

3. Which are the aspects of the included MoCs that are context-specific at external, organisational and population level?
4. How was the MoC developed, organized and implemented (theories/models used, health professionals training, coordination of care)?
5. How MoCs outcomes have been measured and what are the main results, if any?

Study Selection and inclusion criteria

The identification and inclusion of the studies were based on the PCC mnemonic, referring to Population, Concept and Context, as proposed by JBI (33). Further details in the published protocol (34)**.**

Population: People with knee OA, with no TJR scheduled. We included MoCs with >50% participants with knee OA diagnosis.

Concept: Models of Care, defined by Briggs et al (2016), as “an evidence-informed policy or framework that outlines the optimal manner in which condition-specific care should be made available and delivered to consumers at a system level”. Using The Framework to Evaluate Musculoskeletal MoCs, (36) we develop operational criteria to distinguish a model of care of other type of interventions. Only MoCs implemented in a real-world setting and that fulfil all the criteria were considered for inclusion (Additional file 1).

Context: Primary healthcare included in the care pathway, as the first contact with the healthcare system, for direct provision of care, point of referral to other levels of care or services, or continuity of care.

Types of Studies

Quantitative studies with comparative, non-comparative methods, qualitative and mixed methods design, that report outcomes from the implementation of the MoC were included. Each MoC was considered as the unit of interest of this study, thus the studies that report outcomes of the same MoC were considered for inclusion. We included peer-reviewed and grey literature published between 2000 and July 2021 written in English, Portuguese or Spanish to capture the most recent evidence on the implementation of MoC aligned with current healthcare recommendations for OA management.

Search Strategy

The search was conducted in PubMed (MEDLINE), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus (including conference proceedings) and Web of Science Core Collection (including conference proceedings) databases – additional file 2. Additionally, we performed a hand search in relevant peer-reviewed journals: Osteoarthritis and Cartilage, Best Practice and Research Clinical Rheumatology, BMC Musculoskeletal Disorders, Arthritis Care and Research, Implementation Science, Health Services and Delivery Research, JBI Evidence Synthesis and BMC Health Services Research.

The search was also conducted in the grey literature databases WHO IRIS and Open Grey, and also using the deep web search engine MedNar. We also searched for records in relevant organizations: WHO, Arthritis Australia, American College of Rheumatology, Osteoarthritis Research Society International, European League Against Rheumatism, Agency for Clinical Innovation Musculoskeletal Network, Arthritis Community Research & Evaluation Unit, National Institute for Health Research, and Bone and Joint Initiative.

We screened the reference lists of included studies and relevant reviews to identify additional potentially eligible primary studies. We contacted authors and forward screened the included studies and protocols that suit the eligibility criteria, using ISI Web of Science, to seek unpublished data or additional papers related to each MoC. This process was held in a collaboration with an experienced research librarian.

Source of evidence selection

All identified records were uploaded to Mendeley reference manager software and duplicates were removed. The retrieved records were screened by two independent reviewers (DC and LG). After a pilot test of title/abstracts, refinements in the inclusion criteria were made and the screening started after an agreement > 75% between reviewers (33). We adopted a maximum sensitivity in this phase and retrieve the full texts for all records included by at least one reviewer. During the full-text screening phase, in case of discrepancies, a third reviewer (EBC) was consulted.

For all the MoCs identified in the full-text phase, we searched for additional documents, like theoretical papers, protocols, or description reports. These were not included in the review but were consulted to clarifyMoC components, context and implementation features. When grey literature records did not add new information to the peer-reviewed literature already included, these papers were excluded from the analysis.

Data charting, summarizing, and reporting results

Two reviewers (DC and LG) independently extract the data taking into account the goals of the study and the data extraction form. This form was developed through an initial pilot-test in 5 included studies. The main changes made to the pilot form were related with the extraction of coordination of care (37), context (38), and description of intervention components.

All the data extracted was summarized in a tabular form and organized according to the research questions. Interventions components were described using the 'Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide'(39).

For context features, when available, data extraction and description were guided according to the dimensions defined by Nielsen et al. (2019)(38). Data related to coordination of care were identified according to Shultz et al. (2014), that define coordination of care as "the deliberate organization of patient care activities between two or more participants (including the patient) involved in a patient's care to facilitate the appropriate delivery of health care services" and "is often managed by the exchange of information among participants responsible for different aspects of care". Core elements of coordination of care were extracted, when available: interdependence, roles and resources of participants (patients and healthcare professionals), information exchange and articulation of a goal (integration of care activities aiming to facilitate appropriate healthcare delivery).

Outcomes were categorized according to Hakkennes et al. (2006)(40) and Proctor et al. (2011) (41) taxonomies:

- Patient-level: changes on patients' health-status (e.g. pain, function or quality of life, self-efficacy).
- Organizational-/health providers-level: changes in healthcare practice, health service or health-system (e.g. compliance with recommendations, healthcare services utilization, rate of prescription of treatments/exams, quality of care, healthcare costs, waiting times.
- "After" Implementation outcomes: the effects of deliberate and purposive actions to implement new treatments, practices, and services (acceptability, adoption, feasibility; fidelity; penetration; sustainability (41).

Outcome domains and measurements were preferability categorized as patient-level or organizational-level, since, for example, effectiveness and healthcare utilization measures can be used also as implementation outcomes.

Quality assessment

Two independent reviewers (DC and LG) analysed the methodological quality of the included peer-reviewed records, using the Mixed Methods Appraisal Tool (MMAT), 2018 version (42). MMAT allows the evaluation of different study designs with two common screening questions and additional 5 questions specific to each type of study. In case of disagreements between reviewers, these were solved by consensus. For quantitative randomized and non-randomized studies, question 3 is related to "complete outcome data". We accepted <20% of dropout rates, as suggested by the tool (42). The final score of each study is presented as the proportion of positive achievement criteria (0-100%). Gray literature and economic studies were excluded from this analysis.

RESULTS

Of the 3588 records identified by the search in peer-reviewed and gray literature, 30 records met the eligibility criteria and were included in this scoping review (Figure 1).

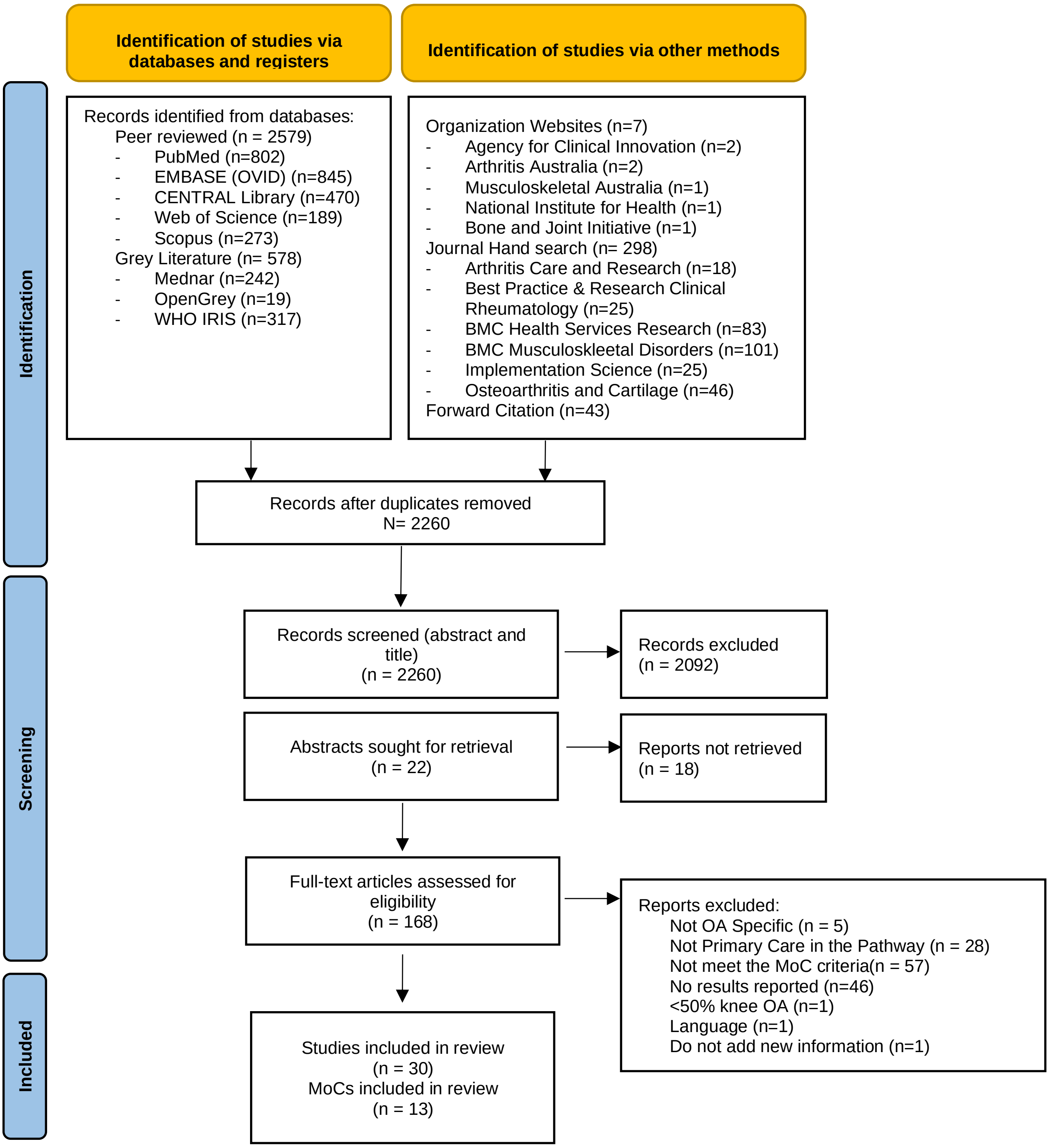

Figure 1. Flow chart for the articles and MoCs included in the scoping review

The included studies are related to 13 MOCs, all implemented in high-income countries, 8 in Europe, 1 in Asia, 2 in Oceania, and 4 in North America. We included research papers and reports related to the implementation of GLA:D® MoC in three countries: Denmark, Australia and Canada. The MoCs studies were published between 2009 and

2021 and include 14 observational cohorts, before and after studies, 9 cluster randomized controlled trials (including two economic analysis studies, secondary to cluster RCTs), 3 mixed-methods studies, two reports, 1 feasibility study and 1 quasi-experimental study. Mixed-methods studies were focused on the implementation analysis of the MoCs, while cluster RCTs and before and after studies were focused on the effectiveness or change at patient- and organizational-level – Table 1

Table 1. MoCs identification and corresponding studies

MoC designation & Geographic location	Studies	Goal	Type of study
ARTIST France	Ravaud, P et al. (2009) (72)	To compare ARTIST MoC with usual care in weight management and physical activity among people with knee OA	Cluster RCT
ARTROACAS Spain	Loza, E et al. (2011) (50)	To evaluate the effects of the program, integrated with daily practice in patient-level outcomes, and satisfaction of patients and health professionals	Observational Cohort, Before and after study
BART Beating osteoarthritis The Netherlands	Smink et al. (2014) (44)	To examine the association between BART consistent stepped care strategy (SCS) and patient-level health outcomes	Observational Cohort, Before and after study
	Smink et al. (2014) (47)	To measure the extent to which health care in general practice is consistent with the BART after its implementation.	Observational Cohort, Before and after study
	Smink et al. (2014) (46)	To describe healthcare use after the implementation of BART	Observational Cohort, Before and after study
BOA Better management of patients with OsteoArthritis Sweden	Jönsson et al., 2019 (45)	To evaluate the changes in outcomes related to the aims of the BOA program in patients with knee/hip OA after participation in the program	Observational Cohort, before and after study registry-based
	Dell'Isola et al., 2021 (49)	To assess the proportion of participants reconsidering their willingness to undergo surgery after 3 and 12 months of BOA	Observational Cohort, before and after study registry-based
	Thorstensson et al, 2015(50)	To explore the feasibility of BOA program	Observational cohort, before and after study, registry-based
CONnACT Collaborative Model of Care between Orthopaedics and Allied Healthcare Professionals Singapore	Tan et al., 2020 (51)	To determine the feasibility of a full randomized controlled trial; To optimize the intervention and study design through a process evaluation in preparation for a full RCT	Feasibility RCT with mixed methods approach
Durham VA USA	Allen et al,. 2020(52)	To evaluate implementation metrics and changes in patient-level measures following implementation of the Group PT program	Observational Cohort, before and after
GLA:D® Good Life with Osteoarthritis	Roos et al. (2021)	To report outcomes and proportion of responders across the three first countries to implement GLA:D	Observational Cohort, before and after study registry-based

Denmark	(61)		
Canada Australia	Skou et al., 2017 (54)	To evaluate the specific aims of the GLA:D initiative in patients with knee and hip OA. To evaluate the equality of access to care, according to the guidelines across Denmark regions.	Observational Cohort, before and after study registry-based
	Davis et al., 2018 (55)	To cross-culturally adapt the GLA:D therapist training and patient education materials for the Canadian context; To evaluate implementation outcomes.	Mixed methods feasibility study
	Report Australia, 2020 (57)	Presents an overview of the GLA:D® Australia program and reports the results from the data registry	Report (grey literature)
	Report Denmark 2020(56)	Present the status of GLA:D® for knee/hip osteoarthritis and GLA:D® Back, including information about GLA:D® clinician, patients, research activities and other national and international activities	Report (grey literature)
Joint Clinic New Zealand	Gwynne-Jones et al, 2018 (58)	To determine the effectiveness of an individualized multidisciplinary nonoperative program for patients with hip or knee OA who were initially assessed as being below the threshold for surgery.	Observational Cohort, before and after study
	Gwynne-Jones et al., 2018 (59)	To assess the effectiveness of the Joint Clinic in prioritizing those patients deemed most in need of first specialist assessment (FSA) and optimizing non-operative management for those who may not need surgical assessment.	Observational Cohort, before and after study registry-based
	Gwynne-Jones et al., 2020 (60)	To report the patient-reported functional outcomes of patients with knee OA managed nonoperatively through the JC at 5-year follow-up after their initial assessment	Observational Cohort, before and after study registry-based
	Gwynne-Jones et al., 2020 (61)	To determine long-term outcomes following nonoperative treatment coordinated through the JC.	Observational Cohort, before and after study registry-based
	Abbott et al., 2019 (62)	To conduct a comprehensive, longitudinal program evaluation of the implementation of the Joint Clinic initiative.	Mixed Methods
MOSAICS Managing OSteoArthritis In ConsultationS **UK**	Dziedzic et al., 2018(63)	To investigate the effectiveness of MOSAICS on clinical outcomes, and on the uptake of core NICE OA core recommendations in participants consulting their GP with peripheral joint pain	Cluster RCT
	Jordan et al., 2017 (64)	To assess the effectiveness of MOSAICS on the quality of primary care for patients consulting with clinical OA;	Cluster RCT

		To assess the impact, feasibility and acceptability of the model OA consultation in primary care.	
	Oppong et al., 2018(65)	Report the economic evaluation alongside the MOSAICS trial to assess the cost-effectiveness of MOSAICS compared with usual care.	Cluster RCT – economic analysis
OA-PCP, Osteoarthritis physical activity care pathway USA	Allen et al,. 2020(66)	To obtain information on feasibility and acceptability, as well as preliminary data on efficacy of OA-PCP	Pilot before and after study feasibility
PhIT-OA, Pharmacist-Initiated Intervention Trial in OA Canada	Marra et al., 2012 (67)	To evaluate whether pharmacists could address the gaps in OA patient care as measured using quality of care indicators and health-related quality of life markers	Cluster RCT
	Marra et al., 2014(68)	To show which treatment strategy provides the best value for money in participants with previously undiagnosed knee OA	Cluster RCT – economic analysis
SAMBA, SAMhandling for Bedre Artrosebehandling i kommunehelsetjenesten Sweden	Østeras et al., 2019 (69)	To assess the effectiveness of SAMBA in primary care	Cluster RCT – stepped wedge
	Moseng et al., 2019 (70)	To explore patient reported response to treatment between the intervention and control group. Comparing the proportion of responders among participants completing the exercise programme vs. the proportion among the non-completers	Cluster RCT – stepped wedge
	Moseng et al., 2019 (71)	To evaluate the uptake of recommended core treatment and fidelity to the implementation strategy and intervention in the SAMBA study	Cluster RCT – stepped wedge
START - STavanger osteo-ARThritis Norway	Østerås et al, 2021 (72)	To evaluate the effectiveness of an intervention aimed to increase provision of core OA treatment prior to referral for surgery, rational use of imaging for assessing OA and improve communication between healthcare professionals.	Quasi-Experimental study - interrupted time series design

Of the 13 included MoCs, 9 used a stepped care approach, in which all participants receive at least an initial/minimal intervention, and progress through more advanced/specific interventions (43–48). In two MoCs patients were firstly stratified according to clinical severity (49)(15–19), and two of the MoCs offer an intervention package to all patients.

In 6 of the MoCs, GPs consultations were the entry point for MoC referral. Self-referral (44,55–61), referral from healthcare providers in general (44,55,56,62) emergency department (45), secondary care specialists' consultation (57–62) or community pharmacists (46,63) were also used as entry point of referral to the MoC considered.

The re-evaluation of patients was considered in all MoCs after the intervention or at least after 3 months – Table 2. In the case of non-improvement with conservative intervention, surgery was described as a referral option in 3 MoCs (n=3). Criteria for discharge are not objectively defined in most of the MoCs (n=9).

Health interventions components

All the MoCs considered education as an intervention strategy that included, general, information about the disease, physical activity promotion and weight management advice, self-management or behavior change strategies. Education was delivered in group sessions in six MoCs (44,55,56). Education written materials like booklets, to support education sessions were considered (n=8). MOSAICS included a previously validated guidebook for patients (64–66), that was also used in START MoC (48).

Ten MoCs included an exercise program, with a duration from 4-12 weeks, delivered in group, individual or as a home-based program. Four of the MoCs considered the patients' preference to choose between group or home-based programs (43,47,48,57–61,67–70), and two MoCs between supervised individual or group exercise (50–54,62).

Pharmacological interventions were included in eight of the MoCs. ARTROACAS (49) and BART (43,67,68) considered specific and progressive pharmacological strategies along with intervention steps. Five MoCs considered dietitian referral. Psychology interventions were reported only in CONnACT (45) as part of the MoC pathway – Table 2.

Settings and professionals

The main intervention was provided at primary care level in 8 MoCs, in 3 of them, itwas the only setting considered in the MoC pathway. Outpatient physiotherapy clinics were included in 5 MoCs. Referrals for community care were also considered namely:

community-based rehabilitation center (45,71) and physical activity providers (50–54). GLA:D was designed to be delivered in primary, outpatient clinics and hospital/specialized care (Davis et al., 2018; GLA:D® Denmark, 2020; GLA:DTMAustralia, 2020; Roos et al., 2021; Skou & Roos, 2017). – Table 2.

As showed in Table 2, the professionals most included in the MoCs were physiotherapists and GPs. Physiotherapists were mostly responsible for the main intervention (n=8), and GPs were often responsible for initial contact for MoC referral, first consultation of the MoC, and/or for pharmacological intervention. In MOSAICS(64–66), nurses are responsible for the education of patients. Dietitians are included in two MoCs and (44,55,56) considered for referral in 4 (43,67,68) (50–54) (47,69,70)(48). As showed in table 1 and 2, in OA-PCP (71) the background profession of the health professional coach responsible for the intervention is not defined. Rheumatologists are the only healthcare professional considered in ARTIST (72) and pharmacists are responsible for identification/diagnosis, education and referral in Phit.OA (46,63).

Table 2 – Summary of MoCs core components, settings and professionals included

MoCs and settings	Referral to MoC	STEP 1	STEP 1 Intervention content	Referral to step 2	STEP 2 Intervention content	Referral to step 3	STEP 3 Intervention content	Discharge from the MoC
ARTIST (72) Primary care	Rheumatologists in primary care.	Education+ educational booklet + Medication Note: intervention package to all	Rheumatologists Self-management (3 sessions, 30 days); Progressive exercise program (3x/week), depending on patient preference; Information on weight loss; Analgesics/NSAIDs as co-interventions, according to care providers decision	Not described	Not described	Not described	Not described	Not described
ARTROACAS (49) Primary care and specialized medical departments	GPs	Education + Exercise + medication Note: Stepped/stratified strategy: patients can start in phase 1 or 2 according to disease severity	Physiotherapists: 4 weeks education and exercise program Education: disease information, healthy lifestyle, weight loss, gait modifications, walking aids, self-management Exercise: home-based program GP: Acetaminophen	If no improvement: Readjust pharmacotherapy + 6 weeks in step 1, and then step 2	Education and exercise program GPs: NSAID/Coxib and GI risk evaluation (adjust dose at 4th and 12th if improved)	Referral to Rheumatologist	Rheumatologist: Add Steroid injection If no improvement in 2 weeks, add hyaluronic acid injections	12 weeks after step 3: Orthopaedic surgeon - Consider surgery
BART (43,67,68) Primary and secondary care – specialized medical departments	GPs	Education+ medication + self-management booklet Note: Multidisciplinary team involved, no	Lifestyle advice, paracetamol (advised), glucosamine sulphate (optional) Evaluation after 3 months	If no improvement: Referral to radiological assessment; pain coping and psychosocial	Physical therapy, dietary therapy (if overweight), NSAIDS, tramadol.	If no improvement: Referral to consultation specialist	Multidisciplinary care, intra-articular injections, and transcutaneous electrical nerve stimulation	Not described

		specific professional defined for education: GPs, nurse practitioners, occupational therapists or physical therapists		factors; adjust goals	Evaluation after 3-6 months		Patient sets the interval for the evaluation	
BOA (44,55,56) Primary Care	Healthcare providers or self-referral	Minimal intervention: education group sessions	PT or OT, and dietitian Education group sessions (2-3 sessions, 7-12 participants): Information about OA, exercise and weight management and self-management strategies. Participation of a patient representative. Minimal intervention could not be modified, PT could adjust the content to suit clinical routines and resources.	Patients choice: Exercise program	PT or OT*:* One session (one-to-one) – individual exercise program or Home-based or supervised group sessions, using the individual program – 2 x/week, in 6 weeks; progression according to capacity and pain tolerance	If improved	Incorporate physical activity and exercise routines in daily life	Not described
CONNACT (45) Primary care, secondary care – specialized medical departments (outpatient clinic at orthopedic	Primary healthcare or emergency medicine doctor	Medication + Education + exercise therapy	Orthopaedic surgeon: Pharmacologic intervention and 2 group educational sessions - Orthopaedic surgeon Physiotherapist: Exercise Therapy (NEMEX with ACSM principles - 6 group sessions, 12 weeks; 8-10 participants)	If: BMI>23.5: dietitian referral Anxiety and depression symptoms (PHQ-4 > 5) and/or pain intensity interference on activity (PEG > 4	According to triage add: - Education and self-efficacy strategies for weight loss (3 group sessions) (Dietitian) - Acceptance and commitment therapy principles; pain coping	If improvements with step1/step2	Flexible post-intervention program (continue exercise in groups) Support group session 3 months after program completion	Not described

surgery department) and community care (community-based rehabilitation centre)				on all scales): psychology referral	strategies; behavioural change (3 group sessions) (Psychologist and Medical Social Worker)			
Durham VA (62) Primary care (referral) and secondary care - specialized medical department (intervention delivered at Physical Medicine and Rehab Service)	Any primary care or specialty medical provider or physical therapists on staff	Education + exercise program Note: intervention package to all	Group exercise - PT 6 sessions (1hour), 10 participants maximum Group discussion: exercise successes and barriers (3 sessions), overview of exercises for knee OA (1 session); joint protection (1 session) and activity pacing (1 session); stretch and strengthening exercises (1 session). Progression in repetitions, sets or resistance Handouts of each session and therapy band for at home exercises Encourage to stretch daily and strength exercises 3 times a week – with progression Evaluation in the last group session	Not described	Not described	Not described	Not described	Not described

GLA:D® (57–61) Denmark: Primary care with physiotherapy outpatient clinics Canada: Primary and secondary care – specialized medical department	GP, orthopedic surgeon or self-referral	Education + exercise program	Physiotherapists 8-week program: - Education (2 group sessions, + 1 session with an expert patient): Information about OA, exercise, coping with pain, self-management strategies and treatment options - Exercise program (12 sessions, 60 min, 2/week), individualized program based on NEMEX - Home-based or supervised group sessions (6-12 patients), or the combination of both (choice of patients)	Not described	Follow-up Encouragement to stay active	Not described	Not described	Not described
Joint Clinic (50–54) Primary care, secondary care - specialized medical department (orthopedic department and outpatient clinic); community care referral (physical activity providers)	Referral from GP to orthopaedic service triage: Joint clinic intervention and referral to support services OR First specialist assessment (FSA) in outpatient clinic: consider surgery OR Decline and refer back to GP	Education + Exercise + manual therapy	6 physiotherapy sessions that include: Education: lifestyle modifications and optimization of analgesia Exercise therapy and manual therapy (optional) - delivered individually or in group, progressive according with patient level	Re-evaluated every 6 months for discharge (GP) or surgical referral, if condition deteriorated.	Referral to support services: Individual chronic disease management program could include community physical activity providers, orthotist, dietetics.			Patient is stable or need to be referral elsewhere

MOSAICS (64–66) Primary Care	GP consultation	Education + guidebook	GP consultation: - Assessment and clinical diagnosis without x-ray; education about OA and first line analgesia. - Guidebook: self-management, core treatments and living with OA Nurse consultation: Education and self-management with guidebook. Goal setting: need for pain relief, healthy eating, physical activity and exercise – 2-4 weeks after GP consultation 3 Follow-up nurse consultations at 3, 6, 12 months: guide in self-management and adherence, exercise plan definition	Referral to multidisciplinary care, if needed	Not described	Not described	Not described	Not described
OA-PCP (71) Primary care and community care referral for continuity of physical activity	GP Note: Intervention Package to all Phase 2: Physical activity coach (PA) coaching call; review progress in 2 weeks, check in emails Phase 3: Identification/Referral	Education + exercise	Chronic Care Management counselors: Education phone call, tailored to patient stage of change for PA: benefits, preferences and identification of PA resources; goal-setting; written materials about exercise; identification of local and internet-based PA programs; Review progress in 2 weeks, check in emails	Add referral to community care	Chronic Care Management counselors: Link to other PA community programs to continue physical activity (PA instructors, Physiotherapists; other health professionals)	Not described	Follow-up call - counseling; review/set goals	Not described

	to community services to continue the process Phase 4: follow-up call after 3 months							
PhiT-OA (46,63) Community care, primary care and outpatient physiotherapy clinics (NHS)	Community pharmacists	Education + self-management program + medication	Pharmacist consultation: education (about knee OA), medication review. Arthritis Self-management program (optional).	GP consultation: validate diagnosis and approve PT referral	PT individualized program: (1hour) Assessment – identify goals; Home exercise individualized program (based on ACSM); Personalized education, including exercise related; Recommendations of walking aids, if necessary Exercise group sessions (1/week, 6 weeks), with prescribed exercises	Re-assessed in 3-6 weeks	Not described	Not described
SAMBA (47,69,70) Primary care, private outpatient clinics within	GP	Education + exercise + medication	GP's consultation: education about OA and intervention options; pharmacological treatment PT program (AKtivA):	Not described	Optional healthy eating program	After 3 months (GP), decide if: 1) Self-management - discharge; 2) New referral; 3)Referral surgery evaluation –		GP consultation (3 months)

the primary care system (NHS)			- 1 education group session (about OA, risk factors, lifestyle and self-management) – booklet to support education - 8-12 week exercise program: 2 sessions/week: exercise group sessions (5-10 patients) prescribed individually with progressions; addition of a third home-based session – cardiorespiratory exercise			orthopaedic surgeon	
START (48) Primary care, physiotherapy outpatient clinics within the primary care system (NHS), specialized medical department	Physiotherapists	Education + exercise	PT education and exercise program (AKtivA), based on SAMBA: Patient education program (3h) Exercise program – 6 weeks, twice weekly, 1h supervised OA guidebook (see MOSAICS)	Referral to GP	Not described	GP referral to OS, if needed	Not described

GP: general practitioner; PT: Physiotherapist; NHS: National Health Service

Implementation and Organizational Characteristics of the MoCs

Context Specificities

At an external-level, Table 3 shows that most of MoCs included are implemented in the context of the national healthcare system (n=10), and varied according the organization structure of healthcare. In France, Rheumatologists work in primary care centers, and patients can self-refer to Rheumatology appointments. (72). GLA:D is implemented in private practices in Denmark (61), but also in a center of excellence for TJR in Canada (57). In Canada, community pharmacists can refer directly to GPs or to PTs (Physiotherapists) (46). The organization of the primary care in Norway include private outpatient clinics of Physiotherapy that work in collaboration with GPs at primary health facilities (47,48,69,70). Additionally, GLA:D MoC was registered as trademark (61). Financial resources context specificities were reported in four MoCs. Health insurance covered most of the costs in BOA (44,55,56) and in Denmark, GLA:D costs are reimbursed depending on how the patient is referred (self-referral, GP or orthoapedic surgeon) (61). At a patient-level context, two records report that MoCs were implemented in urban (46) or in urban, rural areas and multicultural areas (60).

Theories, models and frameworks used for MoC development and implementation

Theories, models and frameworks were specified in seven MoCs. These were used for: 1) the development and evaluation of the implementation process, like RE-AIM (45,57); for the development of healthcare interventions, like the transtheoretical model of behaviour change, self-determination theory, relapse prevention model (44,55,56); and 3) for the development of health professionals training, like the normalisation process theory and theoretical domains framework (64–66) – Table 3.

Professionals Training

Seven of the twelve MoCs report training programs for health professionals, including multi or uni-professional seminars and/or workshops that lasted for 1-4 days. Five MoCs report the availability of supporting material to help deliver the intervention – Table 3.

Coordination of Care

Exchanging information was carried out by national OA registry tools in five MoCs. In Phit-OA, care is coordinated by pharmacists that are responsible to refer patients to the GP along with the baseline evaluation, while GPs are responsible for physiotherapy referral approval, after the referral of pharmacists (46). Three of included MoCs have systems to ensure that the care is accurately delivered like a case report form to guide the steps of the intervention (72), decision support system tools (49), summarized recommendations, telephone reminders or outreach visits (47,69,70). Diaries for patients to record weight (72) and exercise (47,48,69,70,72) were implemented in one and three MoCs, respectively – Table 3.

Table 3. Implementation and Organizational Characteristics of the MoCs – How it has been implemented?

MoC	Context Features	Theories, models or frameworks used	Professionals Training	Additional Coordination of Care elements
ARTIST (72)	NHS; Rheumatologists in primary care	Not described	Not described	Case report form guide Data collection form Booklet to record weight and exercise (patients)
ARTROACAS (49)	NHS NHS politics that promote appropriate and rational use of resources Expert panel set up diagnosis and management recommendations	Not described	Healthcare professionals involved: explanatory meetings	Decision support system Electronic tools to data collection
BART (43,67,68)	NHS Developed according to resources availability (protocol) Reimbursement if additional health coverage (43) Note: The model takes contextual factors to a minor extent, asstated by the authors (43)	Based on behaviour change implementation strategies summarized by Grol & Grimshaw (2003) (73)	Healthcare professionals involved: educational visits with information about patient's booklet. GPs, orthopaedic surgeons and rheumatologists: reminder material GPs: seminar and interactive workshop PTs: seminar (67)	Coordinated by GPs through referral and follow-up appointments schedule. Methods of information exchange not described.
BOA (44,55,56)	NHS Supported financially by the National Social Insurance Office from the Swedish government with the aims to reducing costs to society and improve health related QoL. NHS provide 120USD maximum fee per outpatient visit MOC developed, stimulated, funded and integrated in the Swedish national health program.	Intervention based on behaviour change theories: - Transtheoretical model of behavior change - Self-determination theory - Relapse prevention model	PTs or OT's: One or 2-day training course. Access to support digital material	BOA Registry: national quality register for collection of OA outcome measures before and after treatment Digital material to support the intervention
CONNACT (45)	Expert advice from other implemented MoCs (GLA:D and OACCP); local experts adapted to local context.	MoC implementation and assessment (future RCT):	Not described	Referral letters from GPs to secondary care

		- Medical Research Council framework for developing and evaluating complex interventions: - RE-AIM - Global Alliance for MSK Health (GMUSC) framework		
Durham VA (9)	Primary care (referral) and secondary care - specialized medical department (intervention delivered at Physical Medicine and Rehab Service) - Veterans Durham VA Healthcare System <u>External level:</u> Part of the project Optimizing Function and Independence Quality Enhancement Research Initiative program	Not described	Not described	Electronic referral from treating healthcare provider and triage by physiotherapists for inclusion; Referral notes; Physiotherapist responsible for the decision of group/individual for included based on individual assessment and medical record review
GLA:D® (58–61)	Denmark: Non-profit initiative at University of Southern Denmark; Financtial support: - Referred from general practitioner – 40% of the costs reimbursed - Self-Referral – patients pay full - Referred from orthopedic Surgeon – 100% of the costs are reimbursed Most of GLA:D units are private (61) Registered trademark to ensure quality of care. Physiotherapists educated in GLA:D should follow the principles of GLA:D and contribute to the national GLA:D registry in Denmark. (60) Canada (57) Intervention delivered in a center of excellence for TJR - patients are referred for consideration of joint replacement Canada, Australia and Denmark implementation: participants from urban and rural settings; different culture and healthcare systems (60).	Canada Implementation: Evaluation framework: RE-AIM Program fidelity: framework by Carroll et al. (2007) (74)	PT's: Two-day course regarding the intervention and use of GLA:D registry; Access to a digital toolbox with intervention information	Denmark: National registry integrated with other healthcare data

Joint Clinic (50–54)	Rationale resource allocation: centred on local unmet need of access to orthopaedic First Specialist Assessment (FSA) and wait times for surgery National health policy, workforce recommendations, and local needs supported the rationale for the program. National criteria to rate the need for surgery.	Program evaluation: Framework described by Hollander et al, 2010. (75) Intervention (self-management): Wagner Chronic Care Model	Not detailed: Experienced physiotherapist with training for JC	Monthly report of department referrals, patient visits and pathways of care. National registry: New Zealand Joint Registry
MOSAICS (64–66)	NHS Health professional’s participation on applied research is stated by the author as a readiness to change feature. Support from the UK National Institute of Health Research Clinical Research Network	Intervention – self-management: Whole system Informing Self-management Engagement (WISE) model Implementation development – healthcare professionals training - Calgary-Cambridge framework: consultation skills enhancement - The Normalisation Process Theory: to embed complex interventions in routine clinical practice - Theoretical domains framework: behavior change	GPs: four training sessions, included simulated patients. Nurses: four days of training on OA, recommendation for on OA, OA guidebook, goal setting, pain management.	E-template registry to record quality indicators and assessment of patients OA consultation template
OA-PCP(71)	University primary care clinic Developed to be compatible with healthcare delivery in Center for Medicare and Medicaid Services Chronic Care Management services context	Intervention: Social Ecological Model of Health Behavior	Not described	Electronic records to identify patients Physical activity coaches are responsible for the entire PA program: endorsement of primary care providers, deliver the PA intervention, engagement of patients, inclusion of follow-up contacts and tailored feedback, and integration with community-based and other PA resources.
PhiT-OA (46)	NHS Community pharmacist can directly refer to GP and physiotherapy.	Not described	Not described	Pharmacists responsible to initiate care and referral. Pharmacists’, record and faxed

	Participants included limited to the metropolitan area of Vancouver			patient consultation outcomes to GP; GP evaluation determined the inclusion in PT.
SAMBA (47,69,70)	NHS GPs and physiotherapists work in private clinics, within the context of primary care (NHS). Healthy living centres in the pathway. Developed under the Norwegian Health Care Coordination Reform, regarding national needs to improve quality of care. Primary care: main responsibility for OA treatment, under the healthcare reform(protocol information). Collaborative project with six municipalities, one hospital department, and two national research environments.	Based on MOSAICS study theories.	GP's and PT's workshop (1.5 hours): PTs workshop (1-day): including patient OA education program and exercise database access	Project coordinator - visits and phone calls to health professionals. Strategies to facilitate the use of the SAMBA model: summarized treatment recommendations, regular telephone reminders, quarterly letters with feedback, and biannual outreach visits Exercise diary for patients National quality register
START (48)	NHS GPs and physiotherapists work in private clinics, within the context of primary care.	Based on MOSAICS study theories.	GP's and PT's workshop (1.5 hours) – see SAMBA PT workshop (1 day) – as SAMBA	PT discharge template to the GPs Referral letter by GPs to OS

GP: general practitioner; PT: Physiotherapist; NHS: National Health Service

Outcomes evaluated and outcome measures

We found 30 different outcome domains at patient-level across the 13 MoCs included in the review, that were categorized and presented in table 4. Due to the high variability and number of outcomes domains and measurement tools found, we aggregate the outcomes domains, at patient-level, in “symptoms and disease severity” (e.g. pain, function HRQoL), “lifestyle-related” (e.g. physical activity, weight) and “psychosocial” (e.g. self-efficacy, coping with pain). The organizational outcomes domains were categorized in “quality of care assessment” (e.g. measurements of quality of care, compliance with the recommendations), “healthcare services utilization” (e.g. referral to surgery, specialized medical appointments) and costs (e.g. total costs, cost-effectiveness). Implementation outcomes were categorized with the taxonomy by Proctor et al. (2011) previously described. A detailed list of outcomes domains and measurement tools used in each MoC is provided additional file 3.

Outcome measures related to symptoms and disease severity were evaluated in all MoCs, except START. Lifestyle related outcome measures were measured in 8 MoCs, and psychosocial variables in 6 MoCs. Most of the follow-up assessments occurred between 3-12 months. Organizational outcomes were evaluated in 7 MoCs, 4 with the evaluation of quality of care, and 3 evaluated healthcare utilization and also costs. Eight MoCs conducted process evaluations, reporting evaluation of the MoCs implementation, using qualitative methods as focus groups interviews, self-reported tools, defined indicators in medical registries or direct observation (supplementary material). Although nomenclature for implementation outcome domains varied across studies, these outcomes were defined using RE-AIM framework (GLA:D Canada(57)), or with the taxonomy defined by Proctor et al (2011)(40).

Table 4 – Outcomes measures considered in MoCs studies

Outcomes Dimensions	**Follow-Up**	**Artist**	**ARTROACAS**	**BART**	**BOA**	**CONNACT**	**Durham VA**	**GLA:D®**	**Joint Clinic**	**MOSAICS**	**OA-PCP**	**Phit-OA**	**SAMBA**	**START**
Patient-level														
Symptoms and disease severity	<3mo					X	X							
	3-12mo	X	X	X	X			X	X	X	X	X	X	
	>12mo			X										
Lifestyle-related	<3mo					X								
	3-12mo	X			X			X	X	X	X		X	
	>12mo								X					
Psychosocial	<3mo					X	X							
	3-12mo			X	X			X		X				
	>12mo			X										
Organizational Level														
Quality of Care assessment	<3mo													
	3-12mo									X		X	X	X
	>12mo											X		
Healthcare services utilization	<3mo													
	3-12mo		X	X										
	>12mo			X										
Costs	<3mo								X					
	3-12mo									X		X		
	>12mo													
Implementation Level														
	<3mo													

Acceptability (satisfaction included)	3-12mo		X											
	>12mo													
Adoption (uptake, utilization)	<3mo													
	3-12mo												X	
	>12mo					X								
Appropriateness	<3mo								X					
	3-12mo										X			
	>12mo													
Feasibility	<3mo								X					
	3-12mo										X			
	>12mo													
Fidelity (implementation, delivered as intended, adherence)	<3mo							X						
	3-12mo		X		X		X		X				X	
	>12mo													
Penetration/ sustainability	<3mo							X						
	3-12mo				X		X							
	>12mo													

MoCs studies characteristics and main outcomes

Participants with a diagnosis of hip and/or knee OA were included in 16 studies. Seven studies included only patients with knee OA, and the three studies related to the MoC MOSAICS (64–66), included patients with multi-joint OA – Table 5.

Five MoCs have included patients with OA with no strict eligibility criteria. Other MoCs considered age (n=8), radiographic (n=1) and clinical severity (n=2), and BMI (n=2) as eligibility criteria. The sample size ranged from n=20 participants in a pilot feasibility study (45) to n=72 131 in a large registry-based study (44). Cluster RCTs included n=73 (46,63) to n=1015 (66) participants in the intervention arm.

All cluster RCTs (ARTIST, MOSAICS, Phit-OA and SAMBA MoCs) reported statistical significative differences in pain at 3- and 4-months, when compared to a control group (participants from other settings or evaluated before the implementation). Those results were maintained at 6-months only in Phit-OA and SAMBA. ARTIST and MOSAICS did not show any differences between groups in physical function, in contrast to Phit-OA and SAMBA, that showed statistical significative differences at 3- and 6-months follow-up. ARTIST and MOSAICS showed between group statistical significative differences in physical activity levels at 4-months and at 3-/6-months, respectively. SAMBA showed a decrease in time spent on sitting position at 3- and 6-months. SAMBA also showed statistically significant differences in HRQoL at 3- and 6-months, when compared to usual care. At organizational-level, MOSAICS, PHIT-OA and SAMBA reported statistically significant differences in quality of care, namely in the referral/uptake of core treatments like education/information and exercise, when compared to usual care. However, only Phit-OA reported statistically significant differences in the referral to weight loss programs. Adequate prescription of medication according to recommendations was improved in MOSAICS, and in SAMBA there were less referrals to Orthopedic Surgeon in the intervention group. Phit-OA reported incremental cost-effectiveness ratio benefiting Phit-OA, at societal and governamental level, while MOSAICS showed that the intervention was less costly, but also, less effective.

At implementation-level, MOSAICS showed a higher proportion of patients referred to a consultant nurse, showing fidelity to the recommendations, when compared to usual care. SAMBA showed higher uptake of core interventions when compared to usual care. SAMBA also showed high adherence rates of healthcare professionals to MoC training and fidelity in the referral and intervention recommendations. However, a low proportion of PT tailored the patient exercise program and the patients' adherence rate to cardiorespiratory exercise was low – Table 5.

Table 5 – Characteristics of included studies and main results of MoCs

MoC	**Reference**	**Study type**	**Eligibility criteria**	**Sample Size** **Experimental (E) and Control (C) group**	**Outcome Domain**	**Follow-up**	**Main Results** Patient: Pain, physical function, HRQoL, physical activity Organizational: quality of care, healthcare utilization, costs
ARTIST	Ravaud, P et al. (2009) (72)	Cluster RCT	People with knee OA, 45-75 years old Pain 3-7 NPRS NSAIDs intake BMI ≥25, <35	Total Sample n=327 (E) n=146; (C) n=181	P	4-monts	Between groups, MD (SD) Pain (NPRS): (E) −1.65 (2.32); (C) −1.18 (2.58), p=0.041 Physical activity (Baecke index): (E) 0.20 (0.65); (C) 0.04 (0.78), p=0.013 Physical function: no significant differences (p<0.05)
MOSAICS	Dziedzic et al., 2018(65)	Cluster RCT	People with OA (knee, hip, foot, wrist or multiple joints), age ≥45 years old	Total Sample n=525 (E) n=288; (C) n=237	P	3-, 6- and 12-months	Between groups, MD (95% CI) – knee Pain (NPRS): 3mo: -0.49 (-0.94, -0.05), p=0.031 ; 6mo: -0.20 (-0.74, 0.34), p=0.468 ; 12mo: 0.04 (-0.71, 0.80), p=0.909 Physical activity (PASE): 3mo: -22.1 (-35.7, -8.5), p=0.001; 6mo: -18.3 (-34.0, -2.6), p= 0.022; 12mo: - 17.0 (-38.2, 4.1), p=0.127 Physical function (WOMAC): no differences in any follow-up (p<0.05)
					O	6-months	Between groups, QI pass rates, OR (95%CI): Education, advice and access to information: 2.67 (1.62, 4.40), p= 0.010 Muscle strengthening exercises: 1.91 (1.20, 3.20), p= 0.007 Oral NSAIDs: 0.51 (0.31, 0.85), p= 0.010 Community pharmacy: 1.84 (1.02, 3.34), p=0.043 Walking aids: 0.57 (0.34, 0.94, p=0.027 No differences in the remain QI pass rates
					I	3-months	Between groups Fidelity: Higher proportion of participants that consulted a practice nurse: (E)=28.9%; (C)=13.5%
	Jordan et al., 2017 (66)	Cluster RCT	Same	Total sample n=1960 (E) n=1015; (C) n=836	O	6-months	Between groups, QI pass rates, OR (95%CI): Physiotherapy referral: 5.30 (2.11, 13.34) Paracetamol prescription: 1.74 (1.27, 2.38)

							Information: 26.92 (6.33, 114.51) Exercise advice: 40.49 (5.64, 290.56) No differences in the remain QI pass rates
	Oppong et al., 2018(65)	Cluster RCT – economic evaluation	Same	Total Sample n=525 (E) n=288; (C) n=237	O	12-months	Between groups, Cost-utility, MD (E-C) NHS costs £: 13.11, p=0.705 QALYs: 0.003, p=0.786 Net monetary benefits £: 33.63, p=0.887 Intervention less costly and less effective
PhIT-OA	Marra et al., 2012 (46)	Cluster RCT	People with knee OA, ≥50 years old With pain, aching, or stiffness in or around the knee(s) on most days of the last month; BMI ≥25 kg/m^2; self-reported difficulty in ADL due to knee pain	Total Sample= n=139 (E) n=73; (C) n=66	P	3- and 6-months	Between groups, ED (95% CI) Pain (WOMAC): 3mo: -0.78 (-1.40, -0.16); 6mo: -0.93 (-1.59, -0.28) Function (WOMAC): 3mo: -0.65 (-1.20, -0.10); 6mo: -0.84 (-1.45, -0.24) Quality of life (PAT-5D score) - daily activities domain: 3mo: 3.28 (0.38, 6.19); 6mo: 4.09 (0.95, 7.23)
					O	6-months	Betwee groups, QI pass rates, (E) passing n(%) vs (C) passing n(%): Pain and functional assessment: (E) 13 (76.5) vs. (C) 6 (26.1) p= 0.002 Exercise: (E) 56 (94.9) vs. (C) 6 (10.7), p<0.0001 Education: (E) 36 (73.5) vs. (C) 5 (12.5), p<0.0001 Weight loss: (E) 11 (50.0) vs. (C) 4 (13.3), p=0.004 Radiographs: (E) 38 (52.1) vs. (C) 8 (12.1), p<0.0001 No differences in the remain QI pass rates
		Cluster RCT – economic evaluation	Same		O	6-months	Between groups, Incremental cost-effectiveness ratio (ICER) (95%CI) HUI3 Societal: 14.395 (7.826, 23.132) Ministry of Health: 232 (-1.530, 2.154) PAT-5D Societal: 14.903 (6.669, 30.116) Ministry of Health: 431 (-1.604, 2.901)

SAMBA	Moseng et al., 2019 (70)	Cluster RCT, secondary analysis	People with hip/knee OA, >45 years old Symptomatic, confirmed by GP	Total Sample: n=393 (E) n=284 (C) n=109	P	3- and 6-months	Between group differences (95%CI) Pain (NPRS), 3mo: b: −0.65 (−1.26,−0.04), p=0.04; 6mo: b: − 0.98 (−1.59, −0.37), p=0.002 Function (NRS), 3mo: b: −0.67 (−1.28, − 0.06), p=0.03: 6mo: b: − 1.17 (−1.78, − 0.56), *p*< 0.001 Quality of life (H/KOOS): 3mo: b: 5.43 (0.59, 10.27), *p*=0.03; 6mo: b:5.11 (0.28, 9.95), p=0.04 Time spent on sitting position: 3mo: b:-1.17 (−2.04, −0.31), p=0.008; 6mo: b: −1.47 (− 2.33, −0.60), p=0.001
	Østeras et al., 2019 (47)	Cluster RCT	Same	Total Sample: n=393 (E) n=284 (C) n=109	O	3- and 6-months	Between groups QI overall pass rates, mean difference (95%CI): 3mo: 16.5 (10.3, 22.6), p<0.001: 6mo: 18.9 (12.7, 25.1), p<0.001 Specific QI pass rates, OR (95%CI) Referred to PT: 3mo: 2.5 (1.08, 5.73); 6mo: 0.7 (0.28, 1.52) Referred to OS: 3mo: 0.2 (0.06, 0.73): 6mo: 0.3 (0.08, 0.80) Fullfilling PA recommendation: 3mo: 3mo: OR: 28.4 (8.30, 97.08); 6mo: OR: 9.3 (2.87, 30.37) Referred to MRI, and being overweight or obese indicators did not show significant differences between groups.
	Moseng et al., 2019 (69)	Cluster RCT, secondary analysis	Same	Total Sample: n=393 (E) n=284 (C) n=109 + 40 GPS and 37 PTs	I	3- and 6-months	Between groups - adoption: Uptake of recommended treatment OR (95%CI) Participated in patient education: 82.2 (24.6, 274.7), p<0.001 Received information: 3.5 (1.6, 8.0), p<0.05 Performed resistance exercise: 5.0 (2.1, 12.3), p<0.001 Performed cardiovascular exercise: 5.7 (2.5, 13.1), p<0.001 Performed only passive treatments: 0.05 (0.01, 0.4), p<0.05 Referral to services to support weight reduction: 3.5 (1.3, 9.4), p<0.05 Fidelity: Adherence to SAMBA % GPs and PTs that attend workshops: 50% GPs, 50%-100% PTs

							PT knowledge towards evidence-based statements: >81% Physios that adjust exercise program: 16% Patients: Received PT: (E) 95% vs (C) 46%, p<0.001 Completed education+exercise period: 64% Exercised according to recommendations: resistance exercise: 39%, cardiorespiratory exercise: 9%
ARTROACAS	Loza, E et al. (2011) (49)	Observational Cohort, Before and after study	People with knee OA, 40-75 years old No pharmacological treatment K-L: 1-3	ARTROACAS n=226 Secondary analysis: ARTROACAS n=226 ARTROCAD (standard care) n=201	P	12-months	Within group Pain (WOMAC), MD=-25.7; P<0.001 Physical Function (WOMAC), MD=-29.1; P<0.001
					O	12-months	ARTROACAS vs. ARTROCAD Use of healthcare resources: Decrease in primary care visits, specialist visits, prescription of NSAIDS, symptomatic slow acting drugs, hyaluronic acid injection, no difference in steroids prescription and increase in analgesic prescription and blood analysis (p<0.05)
				ARTROACAS n=226	I	12-months	Within group Adherence to education program: 84% attended of whom 94% followed given recommendations.
BART	Smink et al. (2014) (43)	Observational Cohort, Before and after study	People with hip/knee OA, ≥18 years old Have visited GP for a new episode	Total Sample n=280 Consistent with BART (E) n=117 Non-consistent with BART (C) n=163	P	24-months	Total Sample, before and after total differences (95%CI) Pain (WOMAC): 7.0 (4.2 to 9.8); p<0.001 Physical Function (WOMAC): 5.6 (3.2 to 8.0); p<0.001 No statistically significant differences (p<0.05) in the remain outcomes between consistent and inconsistent subgroups
					O	24-months	Healthcare use by patients who received consistent vs. inconsistent BART care Utilization according to step-1 modalities: education (p<0.001), lifestyle advice (p<0.001); paracetamol (p=0.05), glucosamine sulfate (p=0.18) Utilization according to step-2 modalities: exercise therapy (p=0.02); NSAIDs (oral or topical) (p=0.42); tramadol (p=0.70) dietary therapy (p= 0.02)

							Utilization according to Step-3 modalities: Multidisciplinary care (p= 0.16); Intra-articular injections (p<0.01); TENS (p=0.22); Rheumatologist referral (p= 0.37); Orthopaedic surgeon referral (p=0.79) Surgical modalities (p=0.82)
	Smink et al. (2014) (68)	Observational Cohort, Before and after study		Total Sample: n=313	O	6- and	Within group X-ray n (%) – 6-mo: 172 (55%); 24mo: 212 (72%), X-ray consistent with BART (24mo): 92 (44%)
	Smink et al. (2014) (67)	Observational Cohort, Before and after study		Total Sample: n=313	O	24mo	Within group Specialized care consultations: Rheumatologist: baseline-6mo: 8%, 18-24mo: 16% OS: baseline-6mo: 21%, 18-24mo:45% Cumulative percentages of surgery: 5%(6mo), 10% (12-mo), 14%(18-mo), and 18%(24-mo).
BOA	Jönsson et al., 2019 (44)	Observational Cohort, before and after study registry-based	People with hip/knee OA, no age defined	Total Sample: n=72 131	P	3- and 12-months	Within group, MD (95%CI): Pain (NPRS): 3-mo: 1.18 (1.15–1.20); 12-month: 0.92 (0.89–0.95) Quality of life (EQ-5D): 3-mon: 0.065 (0.063–0.068); 12-mo: 0.039 (0.036–0.042) Physical activity (yes), n (%): baseline: 15 152 (60) vs. 3-mo: 9 999 (39), p<0.001; baseline: 10,125 (58) vs. 12-mo: 6,812 (39), p= 0.902
	Dell'Isola et al., 2021 (55)	Observational Cohort, before and after study registry-based	People with hip/knee OA; referred to BOA program between 2008 and 2016, that willing to undergo TJR	Total Sample: n=30,578			No selected outcomes reported
	Thorstensson et al, 2015(56)	Observational cohort, before and after study, registry-based		N=20, 000	I	3- and 12-months	Satisfaction: 3mo: MoC rated as good or very good by 94% participants; 12mo: rated as good or very good by 83% participants At 3-months: Penetration: 30,700 patients

							Patient adherence: 97% education, 81% exercise program
CONnACT	Tan et al., 2020 (45)	Feasibility RCT with mixed methods approach	People with knee OA, no age defined Activity related pain; K-L>1; KOOS4 <75 Walking independently	Total Sample: n=20 (E) n=10 vs. (C) n=10	P	12-weeks	Pain, Physical Function and QoL (KOOS subscales): no statistically significant differences between groups (p<0.05) HRQoL (EQ-5D): no statistically significant differences between groups (p<0.05)
Durham VA	Allen et al,. 2020(62)	Observational cohort, before and after	People with knee OA, >50 years old Veterans at DVAHCS; no history of falls, no neurologic deficits, cognitively intact Knee OA diagnosed by imaging	Total Sample: n=80	P	Post intervention	Within group, MD (SD) Physical function (WOMAC), baseline: 56.9 (18.8) vs. post-intervention: 46.9 (14.0) Pain intensity (NPRS), baseline: 6.4 (2.0) vs. post-intervention: 5.5 (1.9)
					I	12-months	Penetration: 80 participants included out of 152 referred) Adherence: mean sessions: 4.1 (0-6), 61.3% of patients attended at least 5 sessions
GLA:D®	Roos et al. (2021) (60)	Observational longitudinal, registry-based, before and after study	People with hip/knee OA	Total sample n= 38 925	P	8-weeks	Within group Pain intensity (VAS/NRS), MD (95%CI) - Denmark: -1.2 (-1.2, 1.2) - Canada: -1.5 (-1.6, -1.3) - Australia: -1.4 (-1.6, -1.3) Quality of Life (H/KOOS), MD (95%CI) - Denmark: 5.7 (5.5, 5.8) - Canada: 7.8 (6.9, 8.7) - Australia: 11.3 (10.2, 12.3)
	Skou et al., 2017 (61)	Observational longitudinal, registry-based, before and after study		Total Sample: n=9,825	P	3- and 12-months	Within group Pain (NPRS), mean improvement (95% CI): 3mo: 12.4 mm (11.8 to 13.1); 12mo: 13.7 mm (12.6 to 14.9) QoL (H/KOOS), mean improvement (95% CI): 3mo: 5.4 (5.0 to 5.9); 12mo: data not showed Physical activity (nr of days/week), OR (95%CI): 3mo: 1.18 (1.10 to 1.27); 12mo: 1.10 (0.99 to 1.23)

GLA:D® Canada	Davis et al., 2018 (57)	Mixed methods feasibility study	People with hip/knee OA, ≥30 years old	Total sample: n=59	P	3-months	Within group, MD (95%CI) Pain (NPRS): 2.1 (-2.7, -1.5) Physical Function (KOOS ADL): 6.8 (2.3, 11.3) Quality of life (KOOS QoL): 7.3 (2.9, 11.6)
					I	3-months	Fidelity: 3-4 observation results completely met accross 9 criteria Adherence: 89% of participants use information on daily basis, 52% willing to pay ≥251$ to attend GLA:D™
Joint Clinic	Gwynne-Jones et al, 2018 (54)	Prospective Observational Cohort, before and after study	People with hip/knee OA All patients seen and subsequently reviewed at JC, not referred to surgery	Total sample: n=218	P	12mo	No selected outomes considered.
	Gwynne-Jones et al., 2018 (53)	Prospective observational Cohort, before and after study	People with Knee OA Patients seen and subsequently reviewed at JC, not referred to surgery	Total sample: n=358	P	12-months	No selected outomes considered
	Gwynne-Jones et al., 2020 (52)	Prospective Observational Cohort, before and after study		Total Sample: n=120, 78 non-surgical	P	5-years	Within group, non-surgical Physical Function (SF-12 PCS), mean change from baseline (95%CI): -1.9 (-26.0 to 24.1), p=0.26
	Gwynne-Jones et al., 2020 (51)	Prospective observational Cohort, before and after study		Total Sample: n=337	P	7-years	No selected outcomes considered
	Joint Clinic Abbott et al., 2019 (50)	Mixed Methods	People with end-stage hip/knee OA	Total sample: n=358	I	Post-intervention	- Acceptability: satisfaction of GPs (≥60%) and patients (≥70%) - Fidelity and adherence: concordance with the model and well accepted by stakeholders and by the interdisciplinary team - Appropriateness: patients perceived benefits; patients and GPs valued the service - Penetration: 358 patients attended out of 376 referred

OA-PCP	Allen et al,. 2020(71)	Pilot before and after study feasibility	People with hip/knee OA diagnosis, ≥65 years old Other chronic health care condition	Total sample: n=67	P	4-months	Between groups, mean difference (95%CI) Minutes of moderate to vigorous intensity PA per week (accelerometer): 0.78 (−1.6, 3.2), p=0.5145 Minutes of light intensity activity (accelerometer): −0.63 (−17.3, 16.0), p=0.9392 Pain (WOMAC): −1.9 (−2.7, − 1.0), p<0.0001 Function (WOMAC): −6.1 (− 8.7, − 3.4), p<0.0001
					I	4-months	Within group Feasibility: 88% of patients completed follow-up Acceptability/apropriateness: helpfulness of OA-PCP: mean 7.65±2.5 (0-10)
START	Østerås et al, 2021 (48)	Quasi-Experimental study - interrupted time series design	People with hip/knee OA, That received physiotherapy treatment for at least 2 weeks (4–6 sessions) due to symptomatic OA	Pre-implementation N=208 Post-implementation N=125	O	12-months	Individual QI pass rates, OR (9%CI) between pre- and post-implementation: Information about different treatment alternatives: 1.8 (1.04, 3.14), p=0.037 Information on self-management: 2.6 (1.43, 4.79), p=0.002 The remain QI did not show statistical differences

P: patient-level outcomes; O: Organizational-level outcomes; I: implementation-level outcomes; QI: quality indicators

Quality appraisal of the included studies

All of the studies positively achieved the two screening criteria: 1) clearness of research questions and 2) if data collected allow to answer those question. Of the quantitative non-randomized studies, n=10 achieved at least 3 of the 5 criteria, and two achieved a score over 3. The criteria least achieved by quantitative non-randomized studies were the complete outcome data, with proportions of dropout rates above 20%, and account for confounders. Of the quantitative RCTs analysed with MAAT (n=7), 6 studies positively achieved at least 3 of 5 criteria and only 1 study achieve less than 3 criteria. Most of these studies did not consider an outcome accessor blinded to the intervention (n=5) and do not have complete outcome data (n=4). All of the mixed methods studies positively fulfilled the five criteria. Therefore, the interpretation of the outcomes should account for a possible risk of attrition and detection bias. Detailed information on quality appraisal is provided in additional file 4.

DISCUSSION

MoCs, by definition, are frameworks for the delivery of evidence-based interventions for people with OA (as well as for other chronic diseases) across the disease continuum (76). Our results show that care pathways of MoCs for people with knee OA are preferably designed as stepped care, as recommended by clinical guidelines (5,6). However, the care pathways of included MoCs seem to be focused on a first-step intervention program, and more specialized interventions are poorly described or absent. Furthermore, criteria for steps change along the pathway are often not described, and few MoCs reported criteria for discharge.

Coordination of care across the pathway is a fundamental element for the success of the implementation on MoCs (77). However, our results show that the report on coordination of care was scarce and often limited to the exchange of information through electronic tools. Therefore, the communication within the multidisciplinary teams, the involvement of patients, the leadership, dependent roles of health professionals, discussion and adjustment of treatment plans and shared decision making is markedly unknown (36).

Context features have a paramount importance in the implementation of MoCs, and its transferability is highly dependent on these features (37), however heterogeneity and lack of information in the report across the included studies was noted. For example, information on the finance system that underlies MoCs and how health system ensures its long-term sustainability has not been reported. Likewise, the external validity of the results and the transferability of MoCs may be limited.

As a probable consequence of context-dependency, the organization of care across health settings and providers considered were highly variable among MoCs. For example, rheumatologists, GPs, nurses and PTs in primary care as well as Community Pharmacists had similar roles in the MoCs included in this study. Transversal healthcare professional competences have been recognized and are recommended in OA care, mostly on the delivery of education regarding lifestyle and self-management support (78). However, most of MoCs that reported health professionals training did not seem to account the need for multidisciplinary team training (25), and it was often limited to the health professionals who delivered the exercise and education program.

Nevertheless, the professionals training included in MoCs may be partially responsible for the fidelity of the intervention and success of the implementation. For example, SAMBA (69) and MOSAICS (66), when compared with a match period of time before the training, reported an increase in the delivery of evidence-based recommendations, by the achievement of quality indicators. Moreover, previous literature has supported that the training of GPs regarding OA pain may lead to improvement in patient-level outcomes and guideline-consistent behaviour (79).

Our results show that, as expected, MoCs patient-level interventions followed evidence-based recommendations for the management of people with knee OA. However, these interventions were often limited to education and exercise, that were delivered in multiple modes (5,6). Education was the only intervention considered on step 1 in two MoCs, although, evidence has previously suggested that education as a standalone intervention have little to no effect on patient-level outcomes like pain and function (80), and has failed to show cost-effectiveness (8). Structured exercise programs included in MoCs have different combinations of strength, aerobic and/or motor control exercises, as supported by literature (81). Few MoCs reported the principles of exercise prescription used, like the American College of Sports Medicine recommendations (82), which may support the replication of such programs. None of the MoCs considered structured weight management or psychological support programs, that have been recommended in patients with knee OA with overweight/obesity or, in the presence of persistent pain and important psychosocial determinants (5,6), respectively. Besides core interventions, MoCs often left other health interventions, like medication, for health professionals' decisions according to patients' needs (66), and were not strictly included in the MoC.

Only OA-PCP have considered a remote mode of delivery of intervention with the use of phone calls (71). The exponentially increasing evidence and use of digital health may emphasize the inclusion of e-health tools in future MoCs patient-level interventions (83). E-health interventions have shown that can be as effective as in-person care (84), increasing the accessibility and guarantee the sustainability of health resources (83), which are aligned with MoCs underlying general goals.

Since the results of interventions for people with knee OA often dissipate with time, long-term adherence to lifestyle interventions should be guaranteed across the disease continuum (85). Even though, few MoCs describe discharge plans with strategies to facilitate the long-term adherence to healthy behaviours. The inclusion of community services for the continuation of exercise, for example, was reported only in two MoCs (45,71).

Stepped care, as mentioned before, seems to be the preferably design of care pathways in most of the included MoCs. Theoretically, stepped care guarantees that all patients receive first-line interventions and progress to more specific treatments in case of need. However, this may lead to under or over treatment, since not all patients need all interventions selected for the first step, and others would need more specialized interventions in the first place, given the individual clinical needs and health-status (88). Stratified care may allow tailored and more individualized management programs, based on risk factors for poor prognosis (88). Although, to our knowledge, no validated risk/prognosis stratification tool have been validated to OA. Recently, the Octopus study attempted to test a stratified exercise program based on muscle strength and BMI, however it failed to produce better results at patient-level, when compared to usual care (89).

Given that MoCs are evidence-based interventions, the frameworks need to be dynamic and updated accordingly with new knowledge. For example, the use of paracetamol as first line medication is now questionable, since recent literature showed that the risks of paracetamol surpass its benefits (11) and was withdrawn from clinical guidelines (5,6). However, no update plans or strategies were reported in any MoC, and this should be considered in future MoCs.

Our results show that, few MoCs reported the theories or models used in the development of the intervention (including health professionals training) and in the implementation strategy. This hinders the knowledge of the determinants taken into account that may be responsible for the success/ failure of the implementation process (90).

Yet, the implementation of MoCs has scale-out to a national level in Sweden, Norway and Denmark, as well as its training programs that have been responsible for the update of healthcare professionals (91). In addition, GLA:D™ has scaled out also to an international level, and have trained health professionals for the delivery of OA and back pain care across the globe (92,93). National registry tools have been implemented in four countries within the context of MoCs (53,61,69,94). This may foster the collection of large-scale registry data, that may improve the scientific knowledge of OA and justify the implementation of MoCs around the globe (95).

Even though a high heterogeneity was noted, the majority of MoCs included the core set outcome domains for people with OA (41), mostly pain and function. Knee OA is a multidimensional disease and its impact can be measured at multiple domains (25). The evaluation of a MoC impact can be dependent on the prioritization given by different stakeholders and knowledge users, the main goal of each study, but also, the main goal of each MoC (91). Nevertheless, he reasons for such heterogeneity should be further investigated.

Our results also show that the implementation of MoCs have been evaluated mostly with observational studies but, real-world RCTs can more accurately evaluate the effectiveness of MoCs interventions. The results reported in the few cluster RCTs studies included showed that the implementation of MoCs improved pain, and increase physical function, HRQoL and physical activity levels, when compared to patients that attended other units/facilities where MoCs were not implemente. These studies also reported effects on pass rates of quality indicators, but cost-effectiveness results were mixed. The outcomes of the included studies in this scoping review should be further investigated on a systematic review of cluster RCTs.

The MoCs included also reported promising results in most of the implementation outcomes analysed but, maintenance/sustainability was less explored. Therefore, the long-term success of the implementation process and the long-term change in health professionals' behaviour regarding the fidelity and adherence to MoCs interventions is unknown. Furthermore, MoCs should be implemented and evaluated periodically to be optimized in the long term, but we did not find any information on long-term process evaluation and adjustment plan of the implementation approach (91).

To our knowledge this is the first review with a systematic methodology that identified and synthesized published literature of MoCs developed for people with OA. Understanding the attributes of MoCs implemented for people with knee OA and its benefits to patients and to health services may foster the research on implementation and refinement in this field as well as the development of guidelines for MoCs implementation. Given the heterogeneity found in the included studies, guidelines for the report and development of MoCs are needed, namely regarding criteria used to different management approaches in a stepped pathway, the report of context features, training of healthcare professionals, the use of implementation theories, coordination of care elements, the evaluation of implementation-level outcomes and the multi-level outcome domains that should be accounted for to test the success of the implementation of MoCs.

Stakeholders and patient-involvement are key features for the success of the implementation of a MoC. Although we did not include pre-implementation studies, the needs for change that underpins the development of each MoC, as well as barriers and facilitators that were taken into account in the implementation were not explored in this scoping review, and should be further investigated in future research.

Limitations

The results of this scoping review should be interpreted taking into account its limitations. Firstly, some studies may be missing in this scoping review due to: 1) the search query and search process fallibility, despite the comprehensive search strategy; 2) although we kept an auto-tracking in the main peer-reviewed databases other studies maybe published since may 2021; 3) the eligibility criteria, given unclear definition of MoC concept found in literature and the greyness between the reports of MoCs and clinical interventions (96); 4) Language restrictions. Our population eligibility criteria included only people with knee OA, but most of MoCs studies included considered people with hip and/or knee OA and did not separate the results in these two populations. However, we believe that it may affect our results to a minor extent since the evidence-based interventions for people with hip or with knee OA are similar as well as its outcomes (97). Due to the heterogeneity found in the report on information across studies, mostly related to context features and coordination of care, we acknowledge that some information may be missing. We attempt to accomplish this issue with the use of frameworks in the data analysis and report.

CONCLUSION

Several MoCs have been implemented in primary care worldwide and include evidence-based core interventions, mostly education and exercise. The overall organization of MoCs are highly dependent on context features, including the organization of health systems where are implemented. High heterogeneity was found in the report of the implementation process, MoCs components, and in the evaluation of MoCs outcomes. More high-quality effectiveness studies are needed as well as implementation studies. The outcomes of MoCs may be further investigated in a systematic review of cluster RCTs.

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Supplementary Material

Additional File 1 - Guidance for Full-text Screening

1.1. Eligibility Criteria

	Criteria	Y/N
Population	1. MoC is **specifically** targeted to the **management** people with OA	
	2. ≥50% of the participants included have with knee OA	
	3. Non-institutionalised and **do not** have scheduled or undergone TKR.	
Context	4. Primary care is included in the pathway	
Concept	5. Intervention defines a new way of a service to deliver healthcare, at least for that context;	
	6. Has an underlying evidence-informed strategy, framework or pathway that **defines the optimal manner to deliver care**;	
	7. Describes its **operationalization**: who deliver care, when and where care is best delivered and the details of how it is to be delivered and re-evaluated, for example.	
	8. Address service planning, implementation, delivery and/or evaluation according to context;	
	9. Care is integrated and coordinated longitudinally;	
	10. Multi-**interventions** are considered even if for a single profession;	

	11. Has clear organizational level and/or patients level goals	
	12. Analyses patient, organizational or implementation outcomes (process, summative evaluation)	
Type of study	13. Quantitative a. Comparative: RCT's, cluster or pragmatic RCT, before-after, cohort, quasi-experimental; b. Non-comparative: narrative, policy reports, audits 14. Qualitative or mixed methods – qualitative evaluation (report implementation outcomes – after implementation studies – summative evaluation)	
	Language: English, Portuguese or Spanish; Published after 2000	

2. INCLUSION AND EXCLUSION CRITERIA

2.1. Population

Include if:

- Targeted **specifically** to individuals with OA, even if other conditions are included;
- Non-institutionalized adults diagnosed with knee OA;
- Not undergone, or scheduled, TKA.
- More than 50% of the patients have diagnosis of knee OA.

2.2. Concept

Model of care: "overarching design for the provision of a particular type of healthcare service that is shaped by a theoretical basis, evidence-based practice and defined standards. It consists of defined core elements and principles and has a framework that provides the structure for the implementation and subsequent evaluation of care"

Consider for inclusion if address a MoC and fulfil all the following criteria:

1. It defines a new way of a service to deliver healthcare, or different from the standard practice in that context;

2. Has an underlying evidence-informed strategy, framework or pathway that defines the optimal manner to deliver care;

3. Describes its operationalization: who deliver care, when and where care is best delivered and the details of how it is to be delivered and re-evaluated, for example;

4. Address service planning, implementation, delivery and/or evaluation according to context;

5. Care is integrated and coordinated longitudinally;

6. Multi-interventions are considered even if for a single profession;

7. Has clear organizational level and/or patients level goals

Unit of Interest – Model of care

- As the unit interest is the Model of Care, if several studies are included for the same MoC they will be **collated in the end of full-text screening**.
- As the unit of interest is the "model of care", different studies can arise for the same MoC. Thus, all papers**, including protocols or theoretical papers**, related to a MoC that respects the inclusion criteria for population and context will be investigated for additional papers and then aggregated.

2.3. Context:

Include if:

- MoC's implemented on primary care services **or**,
- MoC's that include interventions at other levels of healthcare delivery, as long as it includes primary care services in the patient's pathway.

3. TYPES OF STUDIES:

- Quantitative
  - Comparative: RCT's, cluster or pragmatic RCT, before-after, cohort, quasi-experimental;

    - Non-comparative: narrative, policy reports, audits
- Qualitative or mixed methods – qualitative evaluation (report implementation outcomes – after implementation studies – summative evaluation)
- Protocols and theoretical papers will be considered **ONLY** if aggregated with MoC intervention/implementation studies, once they can be a source of descriptive information about the MoC.

Consider of inclusion studies that report any of the following outcomes:

- **Patient-level**: impact of the model of care on patients
    - e.g. pain, function or quality of life, satisfaction, collected with self-reported questionnaires or interview questionnaires or performance measures.
- **Organizational/system-level:** impact on health services, providers or on health-system
    - E.g. rate of referral or prescription for exercise, rate of prescribed exams, healthcare costs, waiting times – collected with administrative/clinical databases, quality indicators, questionnaires or interviews with providers.
- **"After" Implementation outcomes**: Acceptability; Adoption; Feasibility; Fidelity; Penetration; Sustainability - (106,131–133)

Data from qualitative/mixed-methods studies will be used both for context-specific features of each model of care as well as to describe implementation outcomes of success of the MoC – **exclude formative evaluation**.

Exclude studies that:

- Test clinical effectiveness or efficiency of specific clinical interventions that do not undertake implementation interventions

Additional file 2

Search Strategy – May 2021
Pubmed = 802

Search	Query	Records

		retrieved
#1	(“osteoarthritis"[MeSH] OR “osteoarthritis"[tiab] OR “osteoarthritides"[tiab] OR "arthritis"[MeSH] OR "arthritis"[tiab] OR “arthritides"[tiab] OR ("arthritis"[tiab] AND "degenerative"[tiab]) OR "arthritis degenerative”[tiab])	349 039
#2	((“model of care”[tiab] OR “care model”[tiab] OR “Models, Organizational”[MesH]) OR (theor*[tiab] OR concept*[tiab] OR framework*[tiab] OR model*[tiab] OR program*[tiab] OR approach*[tiab])) **AND** (((“critical pathways”[MeSH] OR “functional integration”[tiab] OR “clinical integration”[tiab] OR “case management”[MeSH] OR “delivery of health care, integrated”[MeSH] OR “disease management”[MeSH] OR “patient care management”[MeSH] OR “patient-centered care”[MeSH] OR “continuity of patient care”[MeSH] OR “comprehensive health care”[MeSH] OR “managed care program*”[tiab] **OR** “multidisciplinary care”[tiab] OR “interdisciplinary care”[tiab] OR “inter-disciplinary care”[tiab] OR “cross disciplinary care”[tiab] OR “cross-disciplinary care”[tiab] OR “multiple interventions”[tiab] OR “care chain”[tiab] OR “care chains”[tiab] OR “care continuity”[tiab] OR “care continuation”[tiab] OR “care transition*”[tiab] OR “chain of care”[tiab] OR “continuity of care”[tiab] OR “cross sectoral care”[tiab] OR “integrated health care”[tiab] OR “integrated medicine”[tiab] OR “integrated social network*”[tiab] OR “integration of care”[tiab] OR “intersectoral care”[tiab] OR “linked care”[tiab] OR “management model”[tiab] OR “service network*”[tiab] OR “transition of care”[tiab] OR “transitional care”[tiab] OR “transmural care”[tiab] OR “holistic care”[tiab])))	3111 501

#3	("primary health care"[MeSH Terms] OR ("primary"[tiab] AND "health"[tiab] AND "care"[tiab]) OR "primary health care"[tiab] OR ("primary"[tiab] AND "care"[tiab]) OR "primary care"[tiab]) **OR** ("general practice"[MeSH Terms] OR ("general"[tiab] AND "practice"[tiab]) OR "general practice"[tiab] OR ("general"[tiab] AND "medicine"[tiab]) OR "general medicine"[tiab]) **OR** ("family practice"[MeSH Terms] OR ("family"[tiab] AND "practice"[tiab]) OR "family practice"[tiab] OR ("family"[tiab] AND "medicine"[tiab]) OR "family medicine"[tiab]) **OR** (("primaries"[tiab] OR "primary"[tiab]) AND "servic*"[tiab])	560685
#4	#1 AND #2 AND #3	893
Limited to: from 2000, English, Portuguese and Spanish		802

Cochrane Central Register for Control Trials, n=470

	Search Query	**Records Retrieved**
#1	arthritis:ti,ab OR osteoarthritis:ti,ab OR arthrides:ti,ab OR osteoarthritides:ti,ab OR (arthritis AND degenerative):ti,ab OR (arthritisNEARdegenerative):ti,ab	
#2	Mh osteoarthritis - explode all	
#3	Mh arthritis - explode all	
#4	#1 OR #2 OR #3	34195
#5	Mh models, organizational - explode all	

#6	(model of care):ti,ab OR (care model):ti,ab	
#7	#5 OR #6	
#8	theor*:ti,ab OR concept*:ti,ab OR framework*:ti,ab OR model*:ti,ab OR approach*:ti,ab	
#9	mh critical pathways . Explode all	
#10	Mh case management - explode all	
#11	mh delivery of health care - explode all	
#12	Mh Disease management - explode all	
#13	Mh patient care management - explode all	
#14	Mh patient centred care - explode all	
#15	mh continuity of patient care - explode all	
#16	mh comprehensive health care - explode all	
#17	(functional integration):ti,ab OR (clinical integration):ti,ab OR (managed care program):ti,ab	
#18	{OR #9-#16}	
#19	(multidisciplinary care):ti,ab OR (interdisciplinary care):ti,ab OR (inter-disciplinary care):ti,ab OR (cross disciplinary care):ti,ab OR (cross-disciplinary care):ti,ab OR (multiple interventions):ti,ab OR (care chain):ti,ab OR (care continuity):ti,ab OR (care continuation):ti,ab OR (care transition):ti,ab OR (chain* of care):ti,ab OR (continuity of care):ti,ab OR (cross sectoral care):ti,ab OR (integrated health care):ti,ab OR (integrated	

	medicine):ti,ab OR (integrated social network):ti,ab OR (integration of care):ti,ab OR (intersectoral care):ti,ab OR (linked care):ti,ab OR (management model):ti,ab OR (service network) OR (transition of care):ti,ab OR (transitional care):ti,ab OR (transmural care):ti,ab OR (holistic care):ti,ab	
#20	#7 OR (#8 AND (#19 OR #19))	72584
#21	mh primary care - explode all	
#22	(primary health care):ti,ab OR (primary care):ti,ab	
#23	mh general practice - explode all	
#24	(general practice):ti,ab OR (general medicine):ti,ab	
#25	mh family practice - explode all	
#26	(family practice):ti,ab OR (family medicine):ti,ab	
#27	(primaries OR primary):ti,ab AND (service*):ti,ab	
#28	{OR #20-#26}	106773
#28	#4 AND #19 AND #27	472
Limits to 2000-2021		470

EMBASE, n=845

('models organizational':ab,ti OR theor*:ab,ti OR concept*:ab,ti OR framework*:ab,ti OR 'model* OR program*':ab,ti OR ‘approach* AND critical pathways OR functional integration OR clinical integration OR case management OR delivery of health care, integrated OR disease management OR patient care management OR patient-centered care OR continuity of patient care OR comprehensive health care OR managed care program* OR multidisciplinary care OR interdisciplinary care OR inter-disciplinary care OR cross disciplinary care OR cross-disciplinary care OR multiple interventions OR care chain OR care chains OR care continuity OR care continuation OR care transition* OR chain of care OR continuity of care OR cross sectoral care OR integrated health care OR integrated medicine OR integrated social network* OR integration of care OR intersectoral care OR linked care OR management model OR service network* OR transition of care OR transitional care OR transmural care OR holistic care':ab,ti)
AND
(osteoarthritis :ab,ti OR osteoarthritis:ab,ti OR osteoarthritides:ab,ti OR arthritides:ab,ti OR arthritis:ab,ti) AND (degenerative:ab,ti OR 'arthritis degenerative':ab,ti) AND ('family practice':ab,ti OR 'family medicine':ab,ti OR 'general practitioner':ab,ti OR 'general practice':ab,ti OR 'general medicine':ab,ti OR 'primary health care':ab,ti OR 'primary care’:ab,ti)

Web of Science, n=189

Population:
TS= (osteoarthritis OR osteoarthrosis OR osteoarthrides OR arthritis OR arthrosis OR arthrides OR (degenerative NEAR/6 arthritis))

Concept:

TS=((models NEAR/2 care) OR ((theor* OR concept* OR framework* OR model* OR program* OR approach*) AND ("critical path*" OR "care path*" OR clinical path* OR "functional integration" OR "clinical integration" OR "case management" OR "managed *care program*" OR "Patient *care plan*" OR "integrated delivery systems" OR "integrated health*care systems" OR "disease management" OR "*care management" OR "comprehensive NEAR/2 *care" OR "Patient*Cent*red NEAr/2 *Care" OR "Patient*Focused NEAR 2 *Care" OR "continuity of patient *care" OR "Continuity NEAR/2 care" OR "continuum NEAR2 *care" OR "multidisciplinary *care" OR"inter*disciplinary *care" OR "cross*disciplinary care" OR "multiple intervention*" OR "*care NEAR/2 chain*" OR "*care NEAR/2continuity" OR "*care NEAR2 continuation" OR "*care NEAR/2 transition*" OR "chain NEAR/2 *care" OR "continuity NEAR/2 *care" OR "cross sectoral *care" OR "integrated NEAR/2 *care" OR

"integrated medicine" OR "integrated social network*" OR "integrat* NEAR/2 care" OR "intersectoral *care" OR "linked *care" OR "management NEAR/2 model" OR "service network*" OR "transition NEAR/2 *care" OR "transitional NEAR/2 *care" OR "transmural NEAR/2 *care" OR "holistic *care")))
Context:
TS=((primary NEAR/3 care) OR “primary care” OR “primary health*care” OR “general practice” OR “general medicine” OR “family practice” OR “family medicine” OR (("primaries" OR "primary") AND (service* OR servicing)))

Scopus, n=273

TITLE-ABS-KEY (osteoarthritis OR osteoarthrosis OR osteoarthrides OR arthritis OR arthrosis OR arthrides OR (degenerative W/2 arthritis)) AND

TITLE-ABS-KEY (("model W/2 care" OR "care model") OR ((theor* OR concept* OR framework* OR model* OR program* OR approach*) AND ("critical path*" OR "care path*" OR "clinical path*" OR (delivery W/2 care) OR "functional integration" OR "clinical integration" OR "case management" OR "managed *care*" OR "Patient *care plan*" OR "integrated delivery system*" OR "integrated *care*" OR "disease N2 management" OR "*care management" OR "care management" OR (comprehensive W/2 care) OR (comprehensive W/2 health*care) OR "Patient*Cent*red Care" OR "Patient Focused Care" OR (continuity W/2 care) OR (continuity W/2 *care) OR (continuum W/2 care) OR (multidisciplinary W/2 care) OR (inter*disciplinary W/2 care) OR ("cross*disciplinary" W/2 care) OR "multiple intervention*" OR (care W/2 chain*) OR (care W/2 continuity) OR (*care W/2 continuation) OR (*care W/2 transition*) OR (chain AND w/2*care) OR (continuity W/2 care) OR "cross sectoral *care" OR "integrated medicine" OR "integrated social network*" OR (integrat* W/2 care) OR "intersectoral care" OR "linked care" OR (management W/2 model) OR (servic* W/2 network*) OR (transition W/2 care) OR (transitional W/2 care) OR (transmural W/2 care) OR (holistic W/2 care))))) AND TITLE-ABS-KEY ((primary AND n3 AND care) OR "primary care" OR "primary health*care" OR "general practice" OR "general medicine" OR "family practice" OR "family medicine" OR (("primaries" OR "primary") AND (service* OR servicing)))

Grey Literature

OpenGrey n=19

((primary NEAR/3 care) OR “primary care” OR “primary health*care” OR “general practice” OR “general medicine” OR “family practice” OR “family medicine” OR “primar* servic*”) AND ("model of care" OR "care model" OR ((theor* OR concept* OR framework* OR model* OR program* OR approach*) AND (critical pathways OR functional integration OR clinical integration OR case management OR delivery of health care, integrated OR disease management OR patient care management OR patient-centered care OR continuity of patient care OR comprehensive health care OR managed care program* OR multidisciplinary care OR interdisciplinary care OR inter-disciplinary care OR cross disciplinary care OR cross-disciplinary care OR multiple interventions OR care chain OR care chains OR care continuity OR care continuation OR care transition* OR chain of care OR continuity of care OR cross sectoral care OR integrated health care OR integrated medicine OR integrated social network* OR integration of care OR intersectoral care OR linked care OR management model OR service network* OR transition of care OR transitional care OR transmural care OR holistic care)) AND (osteoarthritis OR osteoarthrosis OR osteoarthrides OR arthritis OR arthrosis OR arthrides OR (degenerative NEAR/3 arthritis))

WHO – IRIS, n=317

(“model of care” OR “clinical pathway” OR “care pathway” OR “service delivery” OR “Integrated care” OR “care management” OR “comprehensive care”) AND (“Primary care” OR “primary healthcare” OR “primary health care” OR “general practice” OR “general medicine” OR “primary service”) AND osteoarthritis

1. Language: English
2. Data - ≥2000

MedNar, n=242

Search: Full Record: (osteoarthritis OR arthritis) AND (“model of care” OR “clinical pathway” OR “care pathway” OR “service delivery” OR “Integrated care” OR “care management” OR “comprehensive care”) AND (“Primary care” OR “primary healthcare” OR “primary health care” OR “general practice” OR “general medicine” OR “primary service”) / From: 2000 / To: 2020

Additional File 3

Table S1 – Detailed description of outcome domains and outcomes measures considered in each MoC

MoC	**Patient-Level outcome (outcome measure)** **Follow-up**	**Organizational-Level outcome (outcome measure)** **Follow-up**	**Implementation-Level outcome (outcome measure)** **Follow-up**
Artist (134) **France**	**Patient-level** **4-months and 1-year follow-up** - Weight - Time spent on physical exercise (Baecke index) - Pain on movement (NPRS) - Physical function (WOMAC) - Global assessment of the disease (0-10 NRS) - Quality of life (SF-12 PCS and MCS) **Only at 4-months** - Patient satisfaction (0-10 NRS) - Patient knowledge (0-10 NRS)	**Not considered**	**Not considered**
ARTROACAS (135) **Spain**	**Patient-Level** **One year follow-up** - Rate of OARSI responder criteria - Rate of OMERACT-OARSI responder criteria - Physical function and stiffness (WOMAC) - Health Status: SF-36 - Pain intensity (VAS) - Changes in OA clinical severity (WOMAC pain) - Patients satisfaction	**Not considered**	**Implementation Level** **One year follow-up** - Proportion of >70% compliance rate with the programme recommendations **Questionnaire:** - Professionals satisfaction - Healthcare services/resources utilization Rate of adherence
BART, Beating osteoARThritis (136–138) **The Netherlands**	**6, 12, 18 and 24 months follow-up** **Patient-Level** (136) - Pain (WOMAC) - Physical function (WOMAC) - Self-efficacy (Dutch General Self-Efficacy Scale) - Pain coping (Pain Coping Inventory)	**Organizational-level** (136–138) **6, 12, 18 and 24 months follow-up** Self-report questionnaire: - Healthcare services/interventions used in the last 6 months - Sequence of non-surgical treatment - Radiological assessment: Proportion of patients who received; No of radiological assessments per patient;	**Not considered**

		Proportion of patients with timely assessment - Healthcare services/interventions used in the last 6 months **24-months follow-up** (138)**:** **Related to the previous 6 months** Radiological assessment: - Proportion of patients who received - No of radiological per patient - Proportion of patients with timely assessment Sequence of non-surgical treatment	
BOA, Better management of patients with OsteoArthritis (139–141) **Sweden**	**Patient-level outcomes** (139): **Baseline, 3 and 12 month follow-up** - Pain: NPRS and frequency - QoL: EQ5D - Self-efficacy: Arthritis Self-Efficacy Scale (ASES) - Pain killers intake (yes/no) - Fear avoidance (yes/no) - Physical activity (<150 or 150 min/week) - Willingess to go to surgery (yes /no) (139,140) - Sick leave - Waliking difficulites - Satisfaction with the program	**Not considered**	**Implementation-level** (141) **Baseline, 3 and 12 month follow-up** National registry: - Penetration – nº included patients Patients adherence
CONNACT, Collaborative Model of Care between Orthopaedics and Allied Healthcare Professionals (142) **Singapore**	**Patient-level outcomes** **Follow-up: 12 weeks** - Knee Injury and Osteoarthritis Outcome Score (KOOS4); - Clinical severity: KOOS4 subscales - Quality of life: EQ-5D-5L - Physical Function tests: 30s chair stand, 10m fast paced walk, stair climb, timed up-and-go - Body Mass Index (BMI) - Food intake: Modified Semi-Quantitative Food Frequency Questionnaire (FFQ) - Mental-health related symptoms: Patient Health Questionnaire 4 (PHQ-4); Pain-related functional interference: Pain, Enjoyment, General Activity Scale (PEG); Acceptance and Action Questionnaire 2 (AAQ-II); Chronic Pain Acceptance Questionnaire 8 (CPAQ-8)	**Not considered**	**Implementation-level** **Follow-up: 12 weeks** Interviews with patients: Benefits with the program (appropriateness) Feasibility for a larger trial

	- Global Impression of Change (GIC)		
Durham VA (143) **USA**	**Patient-level** **In the 6th session** - Pain, stiffness and function: WOMAC - Pain intensity: NPRS - Physical function tests: 30 second chair stand test, single leg stand - Satisfaction with care – 5-point scale - Cope with ADL – 5-point scale - Recommended the program – 4 point scale	**Not considered**	**Implementation Level** **One-year after implementation** Electronic Records - Penetration: Referrals to the program - Fidelity: Attendance at Group PT sessions
GLA:D® Good Life with Osteoarthritis (144–148) **Denmark, Canada, Australia**	**Patient-level** (144–148) **After treatment, at 3- and 8-months follow-up** - Pain intensity: VAS or NRS - Pain KOOS/HOOS - Physical function: 30s chair-stand test; 40m fast paced walk test, KOOS ADL - Joint-related quality of life (QOL): KOOS QoL - Physical activity: days with >30 min/week of moderate activity, KOOS sports - Self-efficacy: Arthritis Self-Efficacy Scale - Medication intake: 4-point scale - Perceived benefit and perceived satisfaction - Responders: NPRS, walking speed, chair stand, KOOS QoL cut-offs - Sick leave (yes/no) - Willingness to go to surgery, after intervention	**Organizational-level** (145) **After treatment, at 3- and 8-months follow-up** - Healthcare costs - Nr of patients on sick leave - Access to care: number of GLA:D units; number of active Gla:D units; number of patients	**Implementation-level** (146) **Post-implementation:** RE-AIM framework outcomes Records, direct observation and structured interviews with physiotherapists: - Reach: absolute nr; proportion of elegible patients that participated - Efficacy: patient-level outcomes - Implementation: fidelity and clinical processes - Individual-level maintenance: self-reported use of recommendations (scale 0-5) and willingness to pay - Adherence – % of people who participate in at least 10 sessions (148)

Joint Clinic (149–153) **New Zealand**	**Patient-level** (149–153) **12-months, 5- and 5-7-years follow-up** - Joint-specific impairment: Oxford Knee Score (OKS) - Health status: SF-12 PCS e MCS Rate of responders: improvement greater than the MCID for each score above - Questionnaire (yes/no): Use of walking aids, analgesia, and physical therapy exercises. - Global change and satisfaction – question - Need for surgery – registry/question - Time to surgery (registry) - Health status: SF-6D utility score	**Organizational-Level** (149) **Post-Implementation** - Costs –financial report - Service level statistics: department referrals, patients visits and pathways of care	**Implementation-level:** (149) **Post-implementation:** - Satisfaction GPs and staff (survey) – perception about the joint clinic - acceptability. Feasibility, appropriateness and efficiency of the model's implementation: semi-structured interviews with staff and GPs
MOSAICS, Managing OSteoArthritis In ConsultationS (154–156) **UK**	**Patient-level** (154,155) **3-, 6- and 12-months follow-up** - Health status, physical component: SF-12 PCS - Pain intensity: NPRS - Physical function: WOMAC - OARSI/OMERACT responder criteria - Self-efficacy: Arthritis Self- Efficacy pain subscale) - Patient enablement (PEI) - Physical activity (IPAQ, Physical Activity Scale for the Elderly [PASE]) - Global Assessment of Change – 5-point scale - Mental health (SF-12 mental component summary (MCS), Patient Health Questionnaire depression scale (PHQ) and seven-item Generalised Anxiety Disorder Questionnaire (GAD7)) - Quality of Life: EQ-5D	**Organizational-Level**(155,156) **6-months follow-up** Achievement of quality indicators (self-reported): - Assessment (pain, function, body mass index (BMI), X-ray use) - Core interventions (OA information, exercise advice, weight loss advice) - Other non-pharmacological management (physiotherapy referral) - Pharmacological management (paracetamol, topical non-steroidal anti-inflammatory drugs (NSAIDs), gastroprotection) Cost-Utility at **12-months follow-up** Health status: SF-6D utility score, QALY's	**Implementation level** (154) **6-months follow-up** Case report forms and medical records: Fidelity: Content, number and percentage of participants in the intervention arm having had a practice nurse consultation for OA - case report forms and medical records.
OA-PCP (157) **USA**	**Patient-level:** **4 months follow-up** - Physical activity level: Minutes of moderate to vigorous intensity PA per week + minutes of light intensity – Actigraph G3TX+ device to measure PA during 7 days. - Pain and physical function: WOMAC	**Not considered**	**Implementation-level:** **4 months follow-up** Feasibility: - Proportion eligible participants and who consented to participate; - Proportion of screened patients who met the PA eligibility criteria (< 150 min per week); - Proportion of participants who completed each phase of the program.

			Acceptability/appropriateness: How helpful was this program in supporting you to increase your physical activity? – 0-10 scale
PhiT-OA, Pharmacist-Initiated Intervention Trial in OA (158,159) **Canada**	**Patient-level** **3- and 6-month follow-up** - Function: WOMAC and Lower Extremities Function Scale (LEFS). - Quality of life: Paper Adaptive Test-5D (PAT-5D) and the Health Utilities Index Mark 3 (HUI3)). - Pain: WOMAC pain scale	**Organizational-level** **3- and 6-month follow-up** - Quality of Care - Arthritis Foundation QI pass rates: Self-reported questionnaire (158) **6-months follow-up** Direct costs (ministry of health perspective), indirect and out-of-pocket costs (societal perspective): self-reported data (159)	**Not considered**

SAMBA, SAMhandling for Bedre Artrosebehandling i kommunehelsetjenesten (160–162) **Norway**	**3- and 6-months follow-up** **Patient Level** (160,162) - Patient satisfaction (5-point scale) - Self-reported physical activity – frequency, duration and intensity questionnaire – 3-iten questionnaire - Self-reported high and weight - BMI - Pain intensity (11 -point NPRS) - Function last week - 11-Point NRS - Stiffness – 11-point NRS - Global assessment of disease activity – 11-point NRS - OMERACT-OARSI responders - n (%) - KOOS ADL - KOOS QoL - Daily hours in sitting position	**Organizational-level** (160) Patient Reported quality of care: Quality indicators questionnaire (OA-QI v2) pass rates	**Implementation-level** (161) Uptake: proportion of people who received the recommended core OA treatment: Information, exercise, weight management – self-reported Fidelity to the implementation strategy: GPs and PTs - Attendance the workshops - study records - PT knowledge and attitudes after the workshop: PT reported questionnaire - No of times the PT adjusted exercise programmes - Patient reported exercise diary OA patients - Proportion of patients which received physiotherapy - Patient reported questionnaire - Adherence: Proportion of patients which completed the patient education and exercise period - Study records, Patient reported questionnaire and exercise diary - Proportion of patients which exercised according to dose recommendations from ACSM Patient reported exercise records
START (163) **Norway**	**Not considered**	**Organizational Level** 12 months follow-up - Patient report quality of care: OA-QI v2 pass rates - Number of discharge reports (PT) - GP referral letters information: medication list and comorbidity – included/non-included (registry) - Sequence of treatment: Proportion of people used core interventions prior to OS referral; used MRI prior to x-ray for TJR decision	**Not considered**

Additional File 4

Table S2 - Quality Appraisal of the included studies with the Mixed Methods Appraisal Tool (MMAT)

Study	Study Type	Screening questions		MMAT Criterion, by study type					Quality rating
		S1	S2	1	2	3	4	5	
ARTIST **Ravaud, P et al. (2009)** (134)	Quantitative RCT	Y	Y	Y	Y	N	N	Y	3
ARTROACAS **Loza, E et al. (2011)** (135)	Quantitative non-randomized	Y	Y	N	Y	Y	N	Y	3
BART **Smink et al. (2014)** (136)	Quantitative non-randomized	Y	Y	Y	Y	Y	Y	Y	5
BART **Smink et al. (2014)** (138)	Quantitative non-randomized	Y	Y	CT	Y	Y	N	Y	3
BART **Smink et al. (2014)** (137)	Quantitative non-randomized	Y	Y	Y	Y	N	N	Y	3
BOA **Jönsson et al., 2019** (139)	Quantitative non randomized	Y	Y	Y	Y	N	N	Y	3
BOA **Dell'Isola et al., 2021** (140)	Quantitative non-randomized	Y	Y	Y	Y	Y	N	Y	4
BOA **Thorstensson et al, 2015** (141)	Quantitative non-randomized	Y	Y	Y	Y	N	N	CT	2
CONnACT, **Tan et al., 2020** (142)	Mixed Methods	Y	Y	Y	Y	Y	Y	Y	5
Durham VA, **Allen et al,. 2020**(143)	Quantitative non-randomized	Y	Y	CT	Y	Y	Y	N	3
GLA:D® **Roos et al. (2021)**(144)	Mixed Methods	Y	Y	Y	Y	Y	Y	Y	5
GLA:D® **Skou et al., 2017** (145)	Quantitative non-randomized	Y	Y	Y	Y	N	N	CT	2
GLA:D® **Davis et al., 2018** (146)	Quantitative non-randomized	Y	Y	Y	Y	N	Y	N	3
Joint Clinic **Abbott et al., 2019** (149)	Mixed methods	Y	Y	Y	Y	Y	Y	Y	5
Joint Clinic **Gwynne-Jones et al., 2020** (150)	Quantitative non-randomized	Y	Y	CT	Y	Y	Y	CT	3
Joint Clinic **Gwynne-Jones et al., 2020** (151)	Quantitative non-randomized	Y	Y	CT	Y	N	N	CT	1
Joint Clinic **Gwynne-Jones et al., 2020** (152)	Quantitative non-randomized	Y	Y	CT	Y	Y	N	CT	2
Joint Clinic **Gwynne-Jones et al., , 2018** (153)	Quantitative non-randomized	Y	Y	CT	Y	Y	Y	CT	3
MOSAICS **Jordan et al., 2017** (156)	Quantitative RCT	Y	Y	Y	CT	Y	Y	Y	4
MOSAICS **Dziedzic et al., 2018**(154)	Quatnitative RCT	Y	Y	Y	Y	N	N	Y	3
OA-PCP **Allen et al,. 2020**(157)	Quantitative non-randomized	Y	Y	CT	Y	N	N	Y	2
PhIT-OA **Marra et al., 2012** (158)	Quantitative RCT	Y	Y	N	Y	Y	Y4	Y	4
SAMBA **Østeras et al., 2019** (160)	Quantitative RCT	Y	Y	Y	Y	Y	N	N	3

SAMBA **Moseng et al., 2019** (162)	Quantitative RCT	Y	Y	Y	Y	N	N	N	2
SAMBA **Moseng et al., 2019** (161)	Quantitative RCT	Y	Y	Y	Y	Y	N	N	3
START **Østerås et al, 2021** (163)	Quantitative non-randomized	Y	Y	N	Y	Y	N	CT	2

6. OVERALL DISCUSSION

The work presented in this thesis used Portugal as a case-based setting to understand the needs and challenges for the development of an evidence-based MoC for people with HKOA. First, we estimated the prevalence, burden, and health care needs of the Portuguese population with HKOA using a population-based cohort study to establish priorities in terms of community-based MoCs. Then, we mapped the literature on MoCs developed for people with HKOA through a scoping review to provide the best evidence-based solutions that had success in other countries/settings and that can be adapted to Portugal.

This thesis encompasses five major contributions to HKOA management and to the development and implementation of a community-based MoC:

1) We determined the relative importance of HKOA in Portugal and identified modifiable risk factors associated with its clinical and radiological severity.
2) We contributed to increasing knowledge about the factors associated with unmanageable pain levels among people with HKOA.
3) We provided further insights in terms of long-term trajectories of physical function and quality of life of people who live with HKOA.
4) We identified determinants and the pattern of healthcare services utilisation among hip and knee osteoarthritis citizens in Portugal
5) We mapped the current literature on MoCs implemented for people with HKOA in community-based healthcare to identify the best paths to be implemented in a community-based MoC in Portugal.

Since the results of individual studies were already discussed in each paper, in this discussion section the main results of the studies will be presented and discussed broadly emphasizing the main challenges of the implementation of a new MoC for people with HKOA in the Portuguese context.

6.1. Main Findings

Phase 1 – Define the case for change.

The studies of phase 1, based on the data from the EpiDoC cohort, provided an overview of the prevalence, characteristics and health-related status regarding the severity of the disease, course of physical function and HRQoL, healthcare interventions and services utilization and factors associated with each of these outcomes.

Across the studies, the results of this thesis show that 14.1% (95%CI 12.6-15.7) of Portuguese adults have HKOA (study 1); 68.8% (95%CI 63.9-73.2) of the population with HKOA have unmanageable pain levels (≥5 NPRS) (study 2); over 10 years 21% maintain a stable trajectory of low levels of physical function and 47% moderate worsening physical function, 33.4% maintain a stable trajectory of low HRQoL and 48.4% of moderate HRQoL (study 3); and 35.1% of the people with knee OA are high users of healthcare services (study 4).

The prevalence of HKOA founded in Portugal is similar to other high-income countries, which have projected an increase in the prevalence in the next decades. In Sweden, it was estimated that, in 2032, the prevalence of knee OA will increase from 13.8% to 15.7% and with hip OA from 5.8% to 6.9%, based on ageing and overweight/obesity trends and sex demographic structure (10). Similar results were found in Australia (164), where the increase in TJR incidence was estimated by 276% for the knee and 208% for the hip, based on obesity trends (165). In Canada, given the trends of ageing, sex, BMI and socio-economic determinants, the direct costs with HKOA were projected to increase from $2.9 billion in 2010 to $7.6 billion in 2031 (166). However, these projection models did not account for the incidence of joint traumatic injuries, physical activity habits or multimorbidity (17,42). Therefore, they can be underestimated.

Risk factors for the disease onset are markedly present in the general Portuguese population, namely the ageing of the population, rates of overweight and obesity, physical inactivity, and multimorbidity (168,169). Therefore, if no primary and secondary preventive measures take place, it is possible that the future prevalence and associated burden of HKOA in Portugal will continue to rise in the next decades (54).

In study 2 we found that two-thirds of people with HKOA from the community report mean pain intensity of five or more (NPRS), considered as unmanageable pain levels that interfere with functional activities (123). Literature, across multiple countries, including Portugal (174), reveal that approximately 50% of people with HKOA, that are taking analgesic medication, maintain pain levels of 5 and above (NPRS) (174–176). Moreover, people with HKOA-related pain, in comparison with people without pain, and adjusting for confounders, may incur two-fold higher total costs ($15,047 for people with OA pain versus $8,175 for people without OA pain; $p < 0.0001$). Of these, 75% are related to a decrease in productivity in the workplace (177).

In study 3 we found that up to 68.8% of people with HKOA were assigned to stable trajectories of low/moderate physical function and 81.8% of low/moderate HRQoL levels over a 10-years period, similarly to previous literature related not only with physical function and HRQoL but also, with pain trajectories (60,70,170,171). On the other hand, some studies show that 6% and 9.5% of people with OA may have a rapid decline in function (170) and quality of life (70), respectively, and 8% and 10.4% can improve pain (60) and quality of life, respectively (70).

Among other factors, we found that low baseline levels of physical function and HRQoL were predictors of stable low physical function and low HRQoL trajectories, respectively, over a 10-year period. This was explained before by the literature on the trajectories of symptoms of long-term chronic conditions, with the horse-racing effect (172), as explained in study 2. Moreover, our results show that people assigned to the consistently low HRQoL trajectory (n=317, 33.4%), have much lower levels of HRQoL (EQ-5D index=0.37±0.18) than the normative value for the Portuguese population with 70 years old or more (EQ-5D index=0.600, SE=0.18) (173). Similar findings are shown in the stable low physical function trajectory, regarding baseline values of HAQ. Therefore, our findings are aligned with current literature, showing that HKOA is a slowly progressive disease for the great majority of patients, although they maintain decreased physical function and HRQoL through time.

In studies 1-3, several factors were consistently associated with most of the health-related outcomes evaluated. These include modifiable factors, like physical activity levels, overweight/obesity and multimorbidity, and non-modifiable factors like age, sex and education level. Similar results were found also in the literature, as presented in the background section (41,71,72,75,76). Physical activity level can be seen as a health-related behaviour that a person can maintain consistently but also, but it can be seen as a health outcome since the decrease in physical activity level over time may be a consequence of clinical symptoms severity (178). Improvements in symptoms may not spontaneously increase physical activity levels (179) therefore, the promotion of long-term adherence to exercise/physical activity as a health behavior is crucial and it should be seen as an outcome of care (80,81).

The findings of this thesis showed that multimorbidity was associated with poorer outcomes of HKOA. Similar results were found in current literature, mostly when OA is presented concomitantly with cardiovascular or diabetes conditions (76). Physical inactivity and high BMI have shared risk factors for cardiovascular diseases, diabetes and hypertension onset and severity (180). Since the major consequences of multimorbidity are loss of physical function and quality of life (181), in the presence of

HKOA, these health-related indicators can be exacerbated in both ways (180,181). Furthermore, literature has shown that OA is associated with an increased risk of all-cause mortality. A prospective cohort study of 10 years follow-up, using Cox proportional hazard modelling, has shown that people with OA have a higher risk of dying (adjusted hazards ratio (HR): 1.14 95%CI 1.00 to 1.29) when compared to the non-OA population. This higher risk was mediated by walking frequency (HR: 1.06; 95% CI 1.04-1.08) (183), which may be seen as an indicator of physical activity levels (184). This information may raise hypothesis on the need for further research on effectiveness and, probably, on implementation of public health programs and individually tailored interventions to older adults with HKOA and multimorbidity that include health behaviours like physical activity levels and weight management (12,185,186). These interventions may optimize not only OA-specific symptoms and consequences but also the outcomes of other high-burden and highly prevalent diseases, like diabetes and cardiovascular diseases (187).

Our findings show that older age is associated with higher disease severity and low/moderate physical function and HRQoL trajectories. Despite the structural changes that occur with age and the exposure to risk factors (17,36), we cannot exclude the role of multimorbidity, which is more prevalent with ageing (180,182). Therefore, with the increasing life expectancy of the population (168) and the projected increase in the prevalence of HKOA (10), our results raise the hypothesis that the proportion of older adults with HKOA may increase in the next decades, as well as the complexity of these patients alongside with the increase of healthcare providers' needs and health services demands.

Our results showed that ~85% of the population with HKOA reported less than 9 years of education, which was associated with poorer outcomes. There is a recognized interplay between education level and multimorbidity and health behaviours like overweight/obesity and low physical function. Low education levels and low socio-economic status are seen as a proxy, and literature has shown that they are important social determinants for the risk of multimorbidity, for the adoption of poor lifestyle behaviours and have been associated with poor outcomes in people with HKOA (188). The study of Kouraki et al (2022) that included >1000 patients with OA over a 7-year period found that higher educational attainment before diagnosis was protective against impairment on instrumental activities in daily living after diagnosis (SD coefficient: -0.011 95%CI: -0.019, -0.003). This association was mediated by cognitive ability and lower anxiety. These authors concluded that the direct effects of education on impairments of activities of daily living can be mitigated by improving cognitive ability and managing anxiety (77). Moreover, health literacy has been shown as a mediator between low education levels and low health status (189). Overall, these three non-modifiable factors associated with poor outcomes in the studies of this thesis, older age, low education level and female sex, have also been associated with low literacy levels in Portugal (190).

The findings of study 2 show that a high proportion had overweight or obesity (~80%), and a small proportion of people used to exercise regularly (~21%), attended physiotherapy (~15%) or had a regular intake of pain relief medication (19.0% for NSAIDs, 5.7% for analgesics). On the other hand, a high proportion of people have consulted an orthopaedic surgeon (19.6%, study 4), which should be left to a later stage of the disease to evaluate the potential for surgery when core interventions fail. These results suggest that probably, similarly to the literature presented in the background section (1,22,23,93,95), most people with HKOA are not receiving or not adhering to evidence-based core interventions – exercise (including physiotherapy/therapeutic exercise) and weight management. Instead, more people self-reported visits to the orthopaedic surgeon, for example, than to physiotherapy. Together with the low adherence to exercise and the high rates of overweight and obesity, these findings suggest that modifiable factors associated with the severity of the disease and poor health-related outcomes are probably not being addressed by the current healthcare practices. Previous literature has attempted to explain the barriers regarding the uptake/provision of evidence-based interventions to patients with HKOA. The systematic review of qualitative studies by Egerton et al. (2017) shows that general practitioners often trivialize HKOA due to perceived inevitability and as less important comorbidity; GPs showed a lack of knowledge and confidence in the guideline's recommendations, doubt about its effectiveness and feel that core interventions are discordant from patient's expectations (191). Seeking care behaviour in people with HKOA seems to be driven by flares of pain and loss of physical function (14,192). As a probable consequence, medication for pain relief is often prescribed as a first-line treatment, instead of non-pharmacological interventions (98,99). However, data from real-world evidence suggests that the reasons for medication prescription are unclear and the pattern of prescription is heterogeneous regarding the need for symptom relief (193). A recent scoping review, regarding the implementation of physical activity and weight management programs in people with OA, found some barriers to its adoption by healthcare professionals: non-optimal interdisciplinary collaboration between healthcare professionals; lack of time in the consultation; lack of accessibility to these programs; lack of knowledge or skills on delivering conservative interventions, as well as lack of behaviour change skills; patient's negative attitudes towards these behaviour-dependent interventions and low levels of literacy of patients (194). Barriers to patients' adherence to interventions based on physical activity were also depicted in the literature. The findings of the systematic review by Kanavaki et al. (2017) showed several barriers from the patient's perspective: the physical capacity to exercise; associated symptoms; maladaptive beliefs about OA and doubtfulness effectiveness or harmfulness of exercise; lack of motivation or resignation to OA; lack of behavioural regulation; OA-related distress; lack of advice and encouragement from healthcare professionals; lack of social support or social comparison and lack of motivation (178).

Similarly, in study 4, the number of comorbidities, worse physical function and HRQoL, anxiety symptoms and no regular exercise were associated with higher utilization of healthcare services. However, despite the clinical needs, other variables were also associated with high utilization of healthcare services that may reveal inequities in access to healthcare. Older age, additional health coverage and living in the centre region and the Islands regions was negatively associated with high utilization of healthcare.

Our results show that being younger is associated with higher utilization of healthcare services (study 4). This may be explained by the impact of OA in occupational activities, leading to presenteeism, absenteeism or early retirement in younger patients, who may seek care more actively and whose symptoms may be taken more seriously (195,196). On the other hand, these results may also be explained by the poor knowledge of the navigation of the healthcare system by people with HKOA. Portuguese data from the Health Literacy Population Survey Project 2019–2021 reveal that navigation in the healthcare system seems to be a challenge for 65.5% of the population (190). Since older age was previously associated with lower levels of literacy, and regarding the proportion of older adults in the population with HKOA, a lack of knowledge of how to navigate the healthcare system may explain the negative association between age and higher healthcare utilization (190).

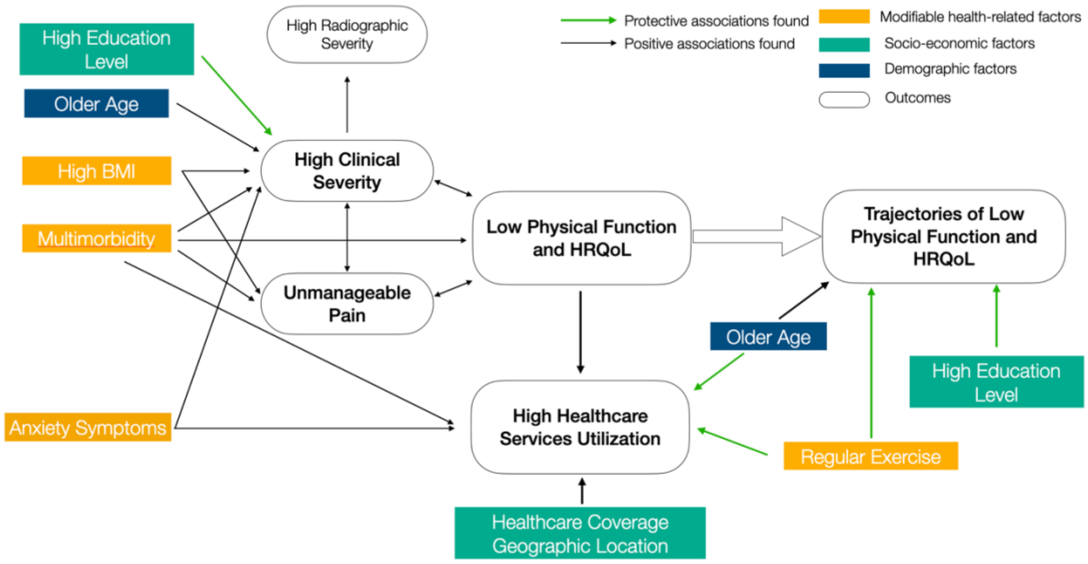
No additional health coverage was negatively associated with the high utilization of healthcare. Consequently, we carefully hypothesize that additional health coverage is a facilitator of the utilization of healthcare services, independently of clinical needs – study 4. These findings may be explained by two different perspectives. On one hand, our results may suggest that national health service may not provide optimal access to care or, on the other hand, that the facilitated access to the private sector may increase the utilization of specialized services, with overuse of healthcare services, regardless the clinical needs (197). Data from the National Health Survey (2014) corroborate these perspectives (198).

Moreover, results of study 4 reveal that geographic location seems to be also a barrier to access to care. Islands and Center region shortages of specialized care and primary care units may partly explain the lower utilization of healthcare services when compared to healthcare units that exist in the Lisbon area (168). On the other hand, Portuguese data show that these are rural areas with a higher proportion of older adults, with lower socio-economic status and lower education, when compared to people who live in urban areas (168). Previous studies showed that differences in the utilization of healthcare services between people from rural and urban areas may be explained by the distance to specialized healthcare centres, the lack of transport facilities, isolation, and the perception of OA as a self-limited condition (199,200). Therefore, our results suggest that the access of people with HKOA to healthcare may be marked by inequities and should be further evaluated by researchers and policymakers.

In summary, the findings of Phase 1. raise hypothesis regarding the need for improvement in several domains of HKOA management. Our results suggest that HKOA in Portugal is highly prevalent, and the population with this disease has a health status far from optimal, with ~70% with unmanageable pain levels, ~60% of the population that have and maintaining moderate to low levels of physical function and HRQoL in the long-term and with ~35% with high utilization of healthcare services. The determinants associated with high severity, trajectories of low physical functional and HRQoL and unmanageable pain levels seem to be highly present in the population with HKOA, namely, older age, female sex, multimorbidity, overweight or obesity, physical inactivity and low levels of education – Figure 5. On the other hand, our results suggest that core non-pharmacological conservative interventions, like exercise and weight management, may be poorly considered by healthcare professionals and patients, regarding the high proportion of people who are overweight or obese, who do not exercise regularly and the few people who are referred to physiotherapy. Therefore, we may hypothesise that the current best evidence-based strategies are not reaching patients with HKOA, which may partly explain the poor outcomes seen across these studies. Our results also suggest that there are inequities in access to specialized and primary care, mostly for older people, people who live in rural areas and who do not have additional healthcare coverage.

However, these are preliminary results that should be further investigated. Our results raise the hypothesis that future interventions, at a patient-level, may be designed to effectively optimize self-management of symptoms, physical activity and diet adherence in the disease continuum, probably with behaviour change approaches to surpass individual barriers. Therefore, patient barriers and facilitators for core-interventions adherence should be further explored. Further research, with a longitudinal design, is needed to understand the impact of current healthcare interventions delivered for HKOA in health-related outcomes, like pain levels, physical function and HRQoL, as well as its cost-effectiveness. Moreover, more research is needed at an organizational-level, regarding the analysis of the quality of current care, patients' care pathways across the healthcare sector, utilization of healthcare services and prescription/referral patterns, physiotherapy referral and management, as well as the suitability of patients with HKOA to replacement surgery. Health professionals' barriers to the delivery of evidence-based healthcare interventions may also be explored in the future.

Facing international literature and our preliminary results we can cautiously suggest that there is a need for a national strategic plan to improve outcomes and quality of care for all people with OA that should be implemented and directed to patients, healthcare professionals and healthcare organizations. This plan should be focused on education about the disease and treatment options, promotion of physical activity and healthy diet and weight management, and also control of joint pain. Moreover, inequities in access to healthcare should be considered regarding mostly older adults and female sex, people with lower socioeconomic status, and covering all geographic areas.



Results from ordinal, linear, multivariable and multinomial regression models, adjusted at least for sex, age and comorbidities.
Female sex was positively associated with all outcomes; Radiographic severity was evaluated in a subsample of patients.

Figure 5 - Factors associated with health-related outcomes accross Phase 1. studies

Phase 2 – Potential Solutions

The implementation of a MoC can be a potential solution to tackle the presented needs elicited in the first phase of this thesis. Given the lack of knowledge about the body of literature published on the development and implementation of MoCs for people with OA, the final study of this thesis aimed to map the literature published regarding the MoCs implemented in primary care for people with knee OA.

As previously stated, MoCs are defined as “an evidence-informed policy or framework that outlines the optimal manner in which condition-specific care should be made available and delivered to consumers at a system level” (36). These are often underpinned by intersectoral multidisciplinary integration and coordination of care in the delivery of evidence-based interventions across the disease continuum, according to context features (114).

Currently, this was the first known study that used a systematic methodology to synthesize the literature about MoCs implemented for people with knee OA. In this scoping review, we included 13 MoCs, among 29 studies, implemented mostly in Europe.

Stepped care pathways were the preferred approaches in the MoCs included. All patients are included in a first-step intervention and patients who do not have satisfactory outcomes proceed to more specific interventions. The progression criteria for the pathway steps as well as discharge criteria were often poorly defined, as well as follow-up plans.

Across the MOCs analysed, the care pathway was focused on a main first-line program, that often-included education (e.g. information about the disease, and treatment options like exercise and weight management) and personalized structured exercise programs. Exercise is offered individually, with or without supervision, in groups, and/or home-based. Some of these exercise programs follow the current recommendations for exercise prescription. Some MoCs accounted for referral for dietitians or psychological support, but any reported the inclusion of specific programs targeted to people with OA obesity or persistent pain, as recommended by current guidelines (18,19).

Primary care was often considered the main setting for the delivery of healthcare interventions across the care pathway, but some MoCs implemented a cross-sectoral pathway, including hospital-based, outpatient clinics and/or community settings. GPs and PTs were the professionals most considered for assessment and delivery of main interventions but, in the case of education, different professionals were included, like rheumatologists, nurses or pharmacists.

MoCs differ regarding the context where they were implemented, and this can explain the variability of settings considered, steps of the pathway and health professionals involved. Implementation theories, that may explain the determinants taken into account for the success of the implementation process, were reported in few MoCs (112). The coordination of care elements reported relied mostly on tools to exchange information. But, national registries on OA have been implemented in the context of MoCs' national dissemination process. Professionals' training seems to have paramount importance on the delivery of health interventions, however, the training of the whole multidisciplinary team involved and important stakeholders are barely considered in the MoCs included.

High heterogeneity was found in the outcome domains considered, mostly on the patient-level. Only four MoCs considered a cluster RCT design, comparing the implementation of MoC to a control group (participants from other settings or evaluated before the implementation). These studies showed between group statistically significant differences in pain, physical function, physical activity level, and HRQoL between 3- and 6-months follow-up at patient-level. At the organizational-level, between groups statistically, significant differences were found in the achievement of quality indicators, but cost-effectiveness results were mixed. At the implementation-level, fidelity and adherence, specifically, were the outcomes most reported by MoCs.

The overall quality of the evidence was fair. Twelve studies reach a final score of 3/5, and seven ≥4/5. Only mixed methods studies fulfilled all the criteria. The least achieved items were related to drop-out rates (randomized and non-randomized studies) accounting for confounders (non-randomized studies) and blindness of accessors (quantitative RCTs).

The results of the scoping review show that implemented MoCs for knee OA at primary healthcare worldwide share some limitations regarding the underpinning definition of MoCs, mostly regarding the steps of the pathways, the discharge criteria and the follow-up plan. Coordination of care is poorly reported, as well as the role of the multidisciplinary team across the care pathway. Strategies for implementation are often not highlighted in the studies included as well as context features considered in the implementation, which may hinder the possibility to transfer these MoCs to other contexts.

The MoCs included show, on the other hand, promising results at patient-relevant outcomes and organizational-level, which may be further explored in a systematic review. The results of this scoping review allow us to foresee cautiously how MoC may be implemented in different contexts, taking into account the multiple different healthcare systems and countries included.

6.2. Strengths and limitations

The findings of this thesis should be interpreted given its strengths and taking into account its limitations.

Strengths

The first part of this thesis – define the case for change – analysed national data from a population-based cohort that included a large representative sample of the Portuguese population. Few epidemiological data have been published before in the Osteoarthritis field with a representative sample of the Portuguese population. The study population included participants from the EpiDoC cohort with a validated diagnosis of HKOA by a rheumatologist. The validated criteria used for the diagnosis (48,49) also included people with early onset (participants ≥18 years old) and in the early stages of the disease without restrictions of clinical or radiographic severity.

Comprehensive socio-demographic, clinical and lifestyle data were collected with the EpiDoC cohort that enables an overarching analysis of prevalence, characteristics and health-related status, as well as utilization of healthcare resources and services of people with HKOA in Portugal. This allowed a complex analysis of the people with HKOA, and its determinants, in multiple domains. Study 3 included data from the EpiDoC cohort that were collected over a 10-year period, in the four waves of this study. Few studies have followed people with HKOA regarding the course of physical function and HRQoL for such long periods (60,69). To our knowledge, Study 3 was the first study that analysed the trajectories of HRQoL and physical function using group-based trajectory modelling. The study of trajectories of clinical symptoms is a top research priority in the OA field (202).

The participants included in the EpiDoC study were recruited from the community which allows for more accurate representativeness of the population with this disease. When studies limit the recruitment of participants to healthcare services, for example, this can lead to selection bias and may not frame the reality of living with HKOA in Portugal. For example, the results of study 3 and 4 show that there are a considerable proportion of people with HKOA that may not seek healthcare services for their health condition.

To our knowledge, the scoping review is the first study that uses a systematic methodology to map the literature regarding MoCs for OA. This study allows a comprehensive overview of the core components of MoCs, their results and also the context features that may optimize the research on the development and implementation of MoCs worldwide.

A comprehensive search strategy was developed in peer-reviewed, grey literature, with a hand search of relevant journals and organizations. Several methods to reach the maximum number of relevant research papers were conducted like forward screening, contact with the authors and also a deep web search engine (MedNar). Although not commonly performed in a scoping review, we conducted a quality appraisal of the evidence. This allows us to better understand the quality of the literature published, and the evidence gaps in this field, but also to better interpret our results.

Limitations

Despite the strengths highlighted, the studies of this thesis have several limitations that should be taken into consideration when interpreting the results.

Population with hip and/or knee OA were included in studies 1, 2 and 3, whereas in study 4 only participants with knee OA were included, and the scoping review (study 5) included only MoCs designed for people with knee OA (not excluding other joints). These five studies were developed at different time points within this research project. OA of the hip or of the knee impose similar burdens on the health system and on individuals and are often presented as a single population in the literature (203,204). On the other hand, we acknowledge that literature shows also that people with hip OA may present greater severity of the disease and an earlier requirement for total joint replacement (62). For this reason, in study 2, we performed a sensitivity analysis of the results in the population specifically with knee OA and with hip OA (presented in the supplementary material of this manuscript), which showed minor differences between the two populations. Thus, we carefully believe that it would not change our results to a major extent.

In studies 1 and 3 we used a composite score of HOOS and KOOS, calculated with the mean score of the five subscales. Although used before in research, a composite score of both instruments was not previously validated. Some authors acknowledge the utilization of the HOOS/KOSS composite score as a primary outcome in RCTs, as the average of the five subscales scores, as long as the scores of the subscales are also presented separately (67). Moreover, in these studies, HOOS and KOOS were aggregated, using the worst score of both scales, or subscales, in the case of people with hip and with knee OA. Although previous studies have performed the same procedure (205,206), no literature was found regarding the validity or accuracy of this procedure. Therefore, we may acknowledge measurement bias in studies 1-3.

HOOS and KOOS are OA-specific measures, although we also measured physical function and HRQoL in studies 3 and 4 with HAQ and EQ-5D, respectively. HAQ and EQ-5D are validated measures but they are not disease-specific, therefore these outcome measures capture physical function and HRQoL at a general health level (117,118). This was accounted for by including comorbidities/multimorbidity as adjustment variables in the analysis of the results of these studies. However, we cannot conclude that the results of HAQ and EQ-5D are related only to OA.

Since study 3 and study 4 did not account for sample weights, we noted small differences in the characterization of the population with descriptive statistics. Therefore, given the sample size included, we cautiously believe that adding weights to these studies would not have a major impact on the results and conclusions.

Other specific limitations, previously acknowledged in the studies of the first phase, should be considered:

- The limitations of self-reported measurement tools, such as misunderstandings, social desirability, and memory bias (207).
- The inherent error of use of sample weights in the analysis of studies 1 and 3 (208).
- The loss of participants between stage 1 (structured interviews) and stage 2 (clinical appointments) of EpiDoC 1. This may lead to selection bias.
- The cross-sectional design of studies 1, 2 and 4, that do not allow to test temporal or cause-effect relationships.
- Other psychosocial variables that may influence self-reported clinical severity of the disease, pain levels, medication intake and healthcare services utilization (March et al., 2016), that were not accounted for.
- The regular exercise variable was self-reported and asked only if the person use to perform regular exercise/sports. We did not account for the intensity or frequency of exercise, therefore, the proportion of participants who regularly exercise may be overestimated and may not correspond to the recommendations for physical activity for example.
- Reasons for healthcare services utilization (study 4) or reason for the intake of pain medication (study 2) was not taken into account, so we are not sure if this consumption was related to OA specifically.

- In study 2, regular pain medication was asked as the daily intake of analgesics in the previous month. Medication can be taken in the context of pain flares for a short period of time (14,192). Because of this, our results can be underestimated.
- Data from the study 1, 2 and 4 were collected in 2011-2013. However, since no national health policies targeted to optimization of outcomes or quality of care of HKOA were implemented, we believe that our findings closely reflect the current health status of the population with HKOA.

Regarding the second phase of this thesis, the final search of the scoping review was made in May of 2021, although we tracked for new studies, we acknowledge that some other articles may have been published meanwhile and were not included. Given the complexity of the definition of the concept – model of care – and the associated evidence, as well as the extent of the information retrieved by the published studies, this review was a dynamic process in which eligibility criteria and data extraction was reviewed several times. Since the information was highly heterogeneous, different frameworks were selected to ensure transparency and the homogeneity of the results report across studies. Nevertheless, we acknowledge that some information may be missing mostly related to context features and coordination of care.

Some other limitations are considered in the manuscript, namely:

- After the initial search strategy, we did not perform any auto-tracking on grey literature or scientific organizations. Thus, some papers may be missing.
- We focused only on knee OA. However, most of the included studies reported hip and/or knee OA results together.
- The complexity of the concept and the definition used, may had contribute to the exclusion of other MoCs, due to the greyness between specific intervention programs and MoCs (209).
- The language restriction that was used to select documents for the review may had exclude some MoCs (English, Portuguese and Spanish).

6.3. Challenges to implement a Model of Care for Osteoarthritis in Portugal

This thesis identified that HKOA is very common among Portuguese adults and that the majority live with unmanageable pain levels and poor health-related status. Modifiable factors such overweight and obesity, physical inactivity and multimorbidity are present in a high proportion of people with HKOA in Portugal and are associated with unmanageable pain levels, long term physical disability, low HRQoL and high health care services utilization. Community-based MoCs in Portugal should target these factors. Our results suggest that Portugal has an evidence-practice gap in terms of HKOA management. A low proportion of people receives the recommended core treatments, such physiotherapy or pain medication. Also, few people received health care promotion interventions to assure regular physical exercise and healthy BMI. This may partly explain the previously stated poor outcomes. Inequities of the access of healthcare were also noted, mainly related with additional health coverage and geographic areas that facilitates care despite clinical needs.

Considering our findings, we suggest that in Portugal interventions with the goal to optimize multi-level outcomes among people with HKOA, to close the evidence-practice gap and to guarantee the sustainability of healthcare system should be implemented.

The implementation of these complex interventions, like MoCs, can face several barriers that should be accounted for. The systematic review of reviews by Lau et al. (2016) aimed to explore the barriers and facilitators for the implementation of complex interventions in primary care. These authors developed a framework that summarizes key factors that influence the implementation of change in primary care at four different levels: 1) the external context in which implementation was taking place; 2) organizational features; 3) characteristics of health professionals involved and 4) characteristics of the intervention (210) - Figure 7.

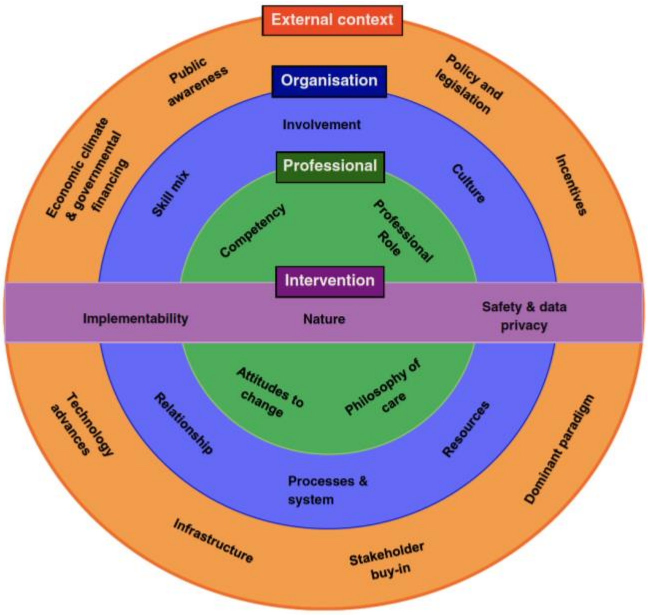


Figure 6 - Key elements to achieve change in primary care. Reproduced from Lau et al. (2015) (210)

At an external context-level the implementation of MoCs, as multi-sector interventions, may be facilitated by national health policies and national health programs targeted to OA, assuring the quality of care, optimizing patient-level outcomes and assuring the sustainability of healthcare services in the long-term.

Facing similar epidemiological data, as the hypothesis raised by this thesis, in the USA, the *Centers for Disease Control and Prevention* and the *Arthritis Foundation* create a collaborative effort to reduce the burden of OA via public health interventions, policies (systems and environmental), and communication strategies. These had the following goals: make OA a public health priority through policymakers and reflect this in decisions and funding allocation; disseminate information about prevention and management of OA in the community; mobilise health professionals to address OA in their clinical practice; engage patients and families to adopt self-management strategies; prevention strategies on injuries and weight management. The OA Action Alliance worked collectively to increase awareness about the need for the prevention and management of OA; to provide educational resources; to expand access to evidence-based programmes for individuals with OA and related stakeholders, including policymakers (186). Similarly, MoCs included in the scoping review of this thesis like SAMBA in Norway (161), Joint Clinic in New Zealand (149) and BOA in Sweden (139) were also implemented in the context of national healthcare reforms, aiming to optimize patient-level outcomes, to improve quality of care and to decrease the economic burden of OA in these countries.

However, in Portugal, despite the national priority programs of physical activity and healthy eating (211–213), the national healthcare system seems to be focused on infectious and acute diseases, according to the indicators to be achieved in the 2021-2030 National Health Plan (6). The absence of national health policies for RMDs as well as guidance in service delivery for decision-makers as planners, coordinators or funders about which interventions offer the greatest value in HKOA, and that align the health system with the best practice recommendations, may constitute an important barrier for the implementation of a MoC directed to HKOA (26,28).

Given the multidimensionality of the disease (18,19), training of healthcare professionals in primary care regarding the delivery of evidence-based interventions recommended for HKOA is crucial and it has been considered in MoCs for HKOA (141,145,214–217). Previous literature has suggested and adopted behaviour change approaches in health professionals' training to assure the uptake and long-term adherence to guideline recommendations (154–156). This may ensure the success of the MoC implementation and fidelity to the intervention, since training and interventions may account for the barriers identified in the delivery of evidence-based care (218,219).

The organization of care pathways in several MoCs included in the scoping review, like SAMBA (162) and MOSAICS (154), seem to be aligned with the organization of healthcare in Portugal. In these MoCs GPs act as gatekeepers and are the first point of contact, responsible for the primary diagnosis and evaluation of people with OA, primary education regarding the disease and treatment options, the referral to core interventions, and for first-line analgesia, as needed. Physiotherapists were the professionals most considered for the delivery of structured exercise but also participated in the patient's assessment and in the education component in several MoCs. Physiotherapists seem to be the professionals whose competencies are most aligned with the assessment of physical function, with the delivery of education and support the self-management, as well as with the delivery of structured and personalized exercise programs (96).

Referral to a dietitian, in case of overweight/obesity or referral to pain management specialists, rheumatologists or orthopaedic surgeons was also considered often in MoCs for people with HKOA. The organization of healthcare in Portugal allow this referral and, intersectoral care may be enhanced through Local Health Units, or through established integration of care between primary units and hospitals, in general (220). However, shortages of physiotherapists and dietitians at the primary care level, the wait lists for GPs and specialized medical appointments and the lack of intersectoral coordination of care may challenge the success of the implementation of such care pathway in the Portuguese context (220,221). As recommended, at an organizational level, the development of care pathways, principles of intervention programs and mode of delivery should be co-designed, engaging coordinators and health managers, medical and non-medical healthcare professionals and patients. Therefore, an in-depth analysis of the barriers and facilitators for the implementation of a MoC, the analysis of the organizational structure of healthcare delivery regarding, for example, the availability of health professionals and other resources, and the engagement of stakeholders, including patients, throughout the implementation process is crucial for the implementation of a MoC for people with HKOA.

The majority of MoCs interventions were limited to the healthcare units and also limited in time. Facing current literature, since maintaining physical activity levels should be a goal of the interventions for HKOA (178), integration of primary care with community services may be considered. Although, discharge to community services for exercise was considered only in Joint Clinic (149) and OA-PCP (222). Current literature has shown that the benefits gained with exercise, namely in pain and physical function may be dissipated with time (81). Long-term adherence to exercise/physical activity levels according to recommendations should be invoked as a goal of OA health interventions (223). Therefore, community services that support adherence to exercise programs, like community exercise groups, senior universities, gyms, and municipal swimming pools, among others, can be included in the pathway to support and promote this long-term adherence and taking out the patients from healthcare units. This can be achieved for example, through social prescribing programs that have taken the first steps in Portugal in the late years, promoting healthy ageing (224).

At an intervention level, the strategies to manage HKOA included in MoCs focused on core evidence-based interventions: education and support for self-management, exercise interventions and weight management when needed, based on the best available evidence (18,19). The education and exercise programs were considered to be delivered as individually supervised, in groups or as home-based. On the other hand, few MoCs interventions have focused on behaviour change approaches regarding the education for healthy lifestyles and uptake of self-management strategies. Current literature has highlighted the importance of behaviour change for long-term adherence to exercise and a healthy diet in people with HKOA (225). This approach takes into consideration not only the capacitation of the person to have regular exercise and lose/maintain weight with education but also the motivations and opportunities to accomplish the lifestyle change (225). Interventions that underlie behaviour change theories identify individual facilitators and barriers that may be targeted. These allow developing of individualized intervention programs using different behaviour change techniques, embedded in the education and exercise programs, for example, with a goal to increase the adherence to exercise or maintain high levels of physical activity, optimizing also the patient-level outcomes like pain, function and HRQoL (225).

6.4. Implications for future research

The epidemiological findings of this thesis, and also the literature presented, suggest that in Portugal there is a need to face HKOA as a major public health problem, and justify further research. Therefore, investigations on direct costs of HKOA, current pathways of care through the healthcare system, quality of current care at the primary and secondary level of care, the adequacy and rates of TJR and related costs and outcomes, would be needed to understand more comprehensively the evidence-gap in HKOA care, the need for change and also, to develop indicators to be targeted with future system-level interventions.

Future research should also be focused on the implementation of a MoC in the Portuguese context. The implementation of MoCs requires cycles of mixed methods studies for needs evaluation (formative evaluation), aligned with the evaluation of the implementation strategy (process evaluation) to interactively understand how the implementation of the MoC can be optimised in a given context, and be responsive to changing circumstances, before initiating a summative (impact) evaluation (28,105). Future research on MoCs for HKOA in Portugal may include hybrid research projects (effectiveness and implementation studies), to develop, and test the effectiveness and cost-effectiveness of the intervention and evaluate the success of the implementation strategy (106). This process may start on pilot healthcare units, with the co-design of stakeholders, including patients to target the needs of the context as well as the barriers and facilitators that determine the success of the interventions. The information on the effectiveness and cost-effectivess of this MoC may be a drive to scale out a MoC to national-level, supported by national health authorities (28), especially to geographic areas where inequities in HKOA care were identified, like in the Centre region and in Azores and Madeira.

7. CONCLUSION

The findings of this thesis identified the burden and health care needs of people with HKOA in Portugal. We found a high prevalence of HKOA in Portugal and a poor health-related status of people living with this condition, which informs future healthcare demands for this population. We identified that the majority of people with HKOA have a long-term trajectory of moderate/high physical disability and low health related quality of life. Modifiable factors such overweight and obesity, physical inactivity and multimorbidity are present in a high proportion of people with HKOA and are associated with unmanageable pain levels, long term physical disability, low health related quality of life and high health care services utilization. Community-based MoCs in Portugal should target these factors. Our results also suggest that Portugal has an evidence-practice gap on HKOA management. A low proportion of people receives the recommended core treatments, such as long-term physical activity plan, healthy weight maintenance or physiotherapy, as well as pain medication. This may partly explain the previously stated poor outcomes. Inequities of the access of healthcare were also noted, mainly related with additional health coverage and geographic areas that facilitates care despite clinical needs.

Finally, in this thesis we verified that MoCs for people with HKOA in primary care implemented internationally have included stepped care pathways focused on core interventions and have promising results at patient- and at organizational-level. MoCs are complex and context dependent interventions, and heterogeneities in frameworks and in the report were identified. Nevertheless, the transferability of care pathways and health interventions of the identified MoCs, may be cautiously adapted to other contexts, and these may respond to the needs identified in the Portuguese people with HKOA. The absence of national health policies for RMDs and the need for implementation research in the field of community-based MoCs are the major barriers to tailor a successful implementation of a community-based MoC for people with HKOA in Portugal.

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9. APPENDIXES

9.1. Appendix I – EpiDoC Unit authorization to access to anonymized database

EpiDoC Unit
Epidemiologia em Doenças Crónicas
Epidemiology of Chronic Diseases

NOVA Medical School
Faculdade de Ciências Médicas

To whom it may concern,

I, Helena Canhão, as Principal Investigator of the EpiDoC Unit, declare, for due effects, that:

- the EpiDoC Unit accepts and welcomes the study "Hip and Knee Osteoarthritis in Portugal: characterization of the population, current management and outcomes";

- the EpiDoC Unit will provide anonymised EpiDoC Cohort data for the referred study.

Lisbon, January 11th 2021

Helena Canhão

Helena Canhão, MD, PhD

Investigadora Principal da Unidade EpiDoC

NOVA MEDICAL SCHOOL | FACULDADE DE CIÊNCIAS MÉDICAS
UNIVERSIDADE NOVA DE LISBOA
CEDOC_ Centro de Investigação em Doenças Crónicas
Campus Sant'Ana |Pólo de Investigação, NMS, UNL. Edifício Amarelo
Rua do Instituto Bacteriológico, nº5 | 1150-082 Lisboa
Tel.: +351 218 803 110
http://cedoc.unl.pt/epidoc-unit/

9.2. **Appendix 2.** Ethics research committee approval

Decisão final sobre o projeto

"*Hip and Knee Osteoarthritis in Portugal: characterization of the population, current management and outcomes*"

A Comissão de Ética da NMS|FCM-UNL (CEFCM) decidiu, por unanimidade, aprovar, do ponto de vista ético, o projeto de investigação intitulado *“**Hip and Knee Osteoarthritis in Portugal: characterization of the population, current management and outcomes** "* (nº 09/2021/CEFCM), submetido pela Profa. Doutora Ana Maria Rodrigues.

Lisboa, 24 de fevereiro de 2021

O Presidente da Comissão de Ética,

(Professor Doutor Diogo Pais)

TO WHOM IT MAY CONCERN

The Ethics Research Committee NMS|FCM-UNL (CEFCM) has unanimously, approved the Project entitled " ***Hip and Knee Osteoarthritis in Portugal: characterization of the population, current management and outcomes***" (nr. 09/2021/CEFCM), submitted by Ana Maria Rodrigues, MD, PhD.

Lisbon, February 24th 2021

The Chairman of the Ethics Research Committee,

(Diogo Pais, MD, PhD)