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PREVALENCE OF KNEE OSTEOARTHRITIS IN PORTUGUESE ADULTS WITH OBESITY: AN EPIDEMIOLOGICAL APPROACH

Dissertação com vista à obtenção do grau de Mestre em Exercício e Saúde

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que estejam onde estiverem,
espero que estejam orgulhosos.

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Abstract

Background: The relationship of Knee Osteoarthritis (KOA) and Obesity is explained by mechanical overloading on the cartilage and also by some systemic factors that participate in the pathogenic process. Since six in each ten individuals are overweight or obese in Portugal, this study's goal is to estimate KOA's prevalence in the Portuguese population with obesity. **Methods:** 655 volunteers (age 46,1±13,8; BMI 29,4±5,9kg/m^2) answered to a Knee Osteoarthritis Pre-Screening Questionnaire (KOPS) Online version. Descriptive statistics and Pearson Correlation Coefficient were used for analyses and the coefficient of determination was used to interpret r and was obtained by squaring the correlation coefficient r (r^2). Independent t-test and Analysis of Variance (ANOVA) were used to compare continuous variables between groups. **Results:** From total sample, 36,5% were male (age 46,1±13,9; BMI 29,6±4,7 kg/m^2) and 63,5% were female (age 46,1±13,8; BMI 29,3±6,5kg/m^2) while 50,25% had obesity (age 47,8±13; BMI 34,6±3,9kg/m^2). In the Obese Group, KOA's prevalence was 56,6% (KOPS Total Score 18,3±9,3) while in the Non-Obese was 23,6% (KOPS Total Score 12±7,1). **Conclusion:** KOA's prevalence in the population with obesity is significantly higher than the prevalence in general population reported by literature.

KEY WORDS: Knee Osteoarthritis; Obesity; On-line Survey, Prevalence, Non-Obese, Functional pain, Burden

Resumo

Introdução: A relação entre Osteoartrose do Joelho (OAJ) e Obesidade é explicada pela sobrecarga mecânica na cartilagem e também por alguns fatores sistémicos que participam no processo patogénico. Dado que seis em cada dez indivíduos têm excesso de peso ou obesidade em Portugal, o objetivo deste estudo é estimar a prevalência de OAJ na população portuguesa com obesidade. **Métodos:** 655 voluntários (idade 46,1±13,8; IMC 29,4±5,9kg/m^2) responderam à versão on-line do *Knee Osteoarthritis Pre-Screening Questionnaire (KOPS)*. A estatística descritiva e o coeficiente de correlação de *Pearson* foram usados para análise e o coeficiente de determinação foi usado para interpretar r, e foi obtido através do coeficiente de correlação r ao quadrado (r^2). Teste T e Análise de Variância foram utilizados para comparar variáveis contínuas entre grupos. **Resultados:** Da amostra total, 36,5% eram homens (idade 46,1±13,9; IMC 29,6±4,7kg/m^2) e 63,5% eram mulheres (idade 46,1±13,8; IMC 29,3±6,5kg/m^2), enquanto 50,25% tinham obesidade (idade 47,8±13; IMC 34,6±3,9kg/m^2). No grupo com obesidade, a prevalência de OAJ foi de 56,6% (Score Total KOPS 18,3±9,3), enquanto no não-obeso foi de 23,6% (Score Total KOPS 12±7,1). **Conclusão:** A prevalência de OAJ na população com obesidade é significativamente maior que a prevalência na população em geral relatada na literatura.

PALAVRAS-CHAVE: Osteoartrose do Joelho; Obesidade; Questionário On-line, Prevalência, Não-obesos, Dor Funcional, Custos

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Abreviations

BMI	Body Mass Index
KOA	Knee Osteoarthritis
KOPS	Knee Osteoarthritis Pre-Screening Questionaire
OA	Osteoarthritis
WHO	World Health Organization
QoL	Quality of Life
ACR	American College of Rheumatology
EKOA	Early Knee Osteoarthritis
DKOA	Definitive Knee Osteoarthritis
RD	Rheumatic Diseases
KOOS	Knee Injury and Osteoarthritis Outcome Score
WOMAC	Western Ontario and McMaster Universities Arthritis Index

Chapter 1: Introduction

This chapter presents the Study: Scope, Problem, Goals, Assumptions, and the Dissertation Structure.

1.1 Study Scope and Problem

Rheumatic diseases (RD) are characterized by chronic discomfort and functional limitation due to progressive joint and soft-tissue involvement. Manifestations associated with this group of diseases frequently cause varying degrees of physical disability, which means a high cost for patients, their families, and society. Reported prevalence rates seem to change according to diagnosis, ethnicity, age, and gender. Of these, osteoarthritis (OA) is the most frequent joint disease (Rodriguez-Amado et al., 2011).

Worldwide, OA's prevalence ranges from 6.3% in Greece (Andrianakos et al., 2006) to 70.8% in Japan (Oka et al., 2009) and the most prevalente type of OA is on the knee. Knee osteoarthritis (KOA) is the eleventh highest disability globaly, thereby, causing a large economical burden to the society. Part of these costs arise from the current clinical inability to systematically diagnose the disease at an early stage when it might still be possible to slow down its progression or at least reduce the impact of its future disability. It is estimated that 51% of people aged between 50 and 64 are not working. Of these, 30% have osteoarthrosis, of which 18.6% are in the knee (26% women and 11.5% men) (Tiulpin, Thevenot, Rahtu, Lehenkari, & Saarakkala, 2018).

In Portugal, KOA's prevalence is 12,4% being higher in female (15,8%) than male (8,6%). In a sub-study of EpiReumaPt, which aimed to determine the economic impact of OA and its reflection in terms of early abandonment of professional activity, it was found that, "especially KOA, causes a high rate of disability for the job. The other types of arthrosis do not have such a significant impact in terms of work" (EpiReumaPT, 2013).

Identifying KOA symptom pathways and modifiable risk factors related to them could help identify people who are at risk of suffering a worsening of their quality of life (QoL) and who could benefit from early interventions targeting modifiable risk factors.

This would enhance clinical outcomes and allow a more efficient use of limited health care resources. Knowledge about these patient groups and the quantitative impact of each modifiable risk factor in a personalized manner is of major importance (Tormalehto et al., 2019).

For several authors, Obesity is the most important modifiable risk factor for the development and progression of KOA (Cooper et al., 2000; Davis, Ettinger, & Neuhaus, 1990; Felson, 1990; Felson, Anderson, Naimark, Walker, & Meenan, 1988; Felson, Zhang, Anthony, Naimark, & Anderson, 1992; Hartz et al., 1986; Hochberg et al., 1995; Spector, Hart, & Doyle, 1994; Sturmer, Gunther, & Brenner, 2000) due to the mechanical impact and inflammatory process associated. Even when KOA is asymptomatic and without visible changes (in the initial stages for example), the degenerative process, despite being slow over several years, is underway and hence the need to detect risk factors such as obesity that can contribute to faster wear and tear.

Once that six in each ten Portuguese are overweight or obese, according to the World Health Organization (WHO) criteria (Oliveira et al., 2018), it's possible to generate several questions:

- Comparing individuals with obesity and wihout obesity, is there a higher prevalence of KOA in the first ones?
- In individuals with obesity, is there a significant difference in KOA's prevalence between obesity rates?
- In individuals with obesity, how do risk factors behave?
- What are the main symptoms felt by individuals with obesity that also have KOA?

Considering the impact of KOA on disability and the subsequent unavoidable economic burden, there is a need to quantify the severity of KOA during the early stages of development. KOA's severity level helps establishing appropriate treatment decisions for the monitoring of disease progression (Braun & Gold, 2012). In addition, exercise interventions are often complex and multifaceted, which places a significant obligation on researchers to provide clear, complete, and replicable details of their study interventions (Bartholdy et al., 2019).

1.2 Study Goals

In Portugal most of the studies are a national screen and obese people are almost three times more at risk of incident KOA compared to those of normal weight (Blagojevic, Jinks, Jeffery, & Jordan, 2010), thus, the aim of this study is to estimate the prevalence of KOA in Obese Portuguese Adults, portraying the main signs, symptoms and pain in functional activities felt by these inviduals.

The specific objectives of this study are:

- To understand the prevalence of KOA between individuals with obesity and non-obese individuals;
- To explore the potential factors that could contribute to such differences;
- To analyse KOA's prevalence and its signs and symptoms according to different obesity grades.

1.3 Study Assumptions

While carrying out this study the following assumptions were considered:

- All subjects are able to correctly answer the questions in Portuguese language when filling out the questionnaires;
- No occurrences of pregnancy or mental illness that could influence the responses.

1.4 Dissertation structure

This dissertation is organized with the goal of establishing a fluid and logical reasoning regarding the prevalence and characterization of KOA in Portuguese Adults with Obesity. To fulfill this purpose, this dissertation is presented as follows.

Chapter 1 provides a general framework for the initial definition of the problem that led to the establishment of the study objectives and supports its relevance. Assumptions and limitations are also presented.

Chapter 2 includes a literature review of the topic where rheumatic diseases are first characterized, then OA and finally KOA. This description always bears in mind a definition of the pathophysiology and etiology of the disease, as well as epidemiological data regarding its prevalence, economic, social, mental costs, etc. Finally, the risk factors for KOA, including Obesity, are presented and a categorization of the interaction effects of these two variables, already described in the literature, is made.

Starting with a study design, description of the sample calculation and its recruitment process, Chapter 3 - Methods also includes the questionnaire that served as an instrument for carrying out this study, the scores that served as outcomes and the statistical analysis used.

In Chapter 4, results are presented into five parts. The first one presents sample characterization and the second has the analysis of the outcomes for Obese and Non-Obese volunteers. Later, the same outcomes were analyzed, but according to the presence or absence of KOA and then according to the level of obesity. Finally, the results of the correlations between risk factors and disease were obtained.

Chapter 5 provides a summary and integrated discussion of the main findings of this study.

Chapter 6 includes the conclusion, main research findings, practical implications, study limitations and suggestions for future studies.

Bibliographic references and Appendices are at the end of the present document and include two articles that are cited over this dissertation and are essential to the integrity of the work presented.

Chapter 2: Literature Review

Topics in the literature review are presented from a general overview of Rheumatic Diseases and Osteoarthritis and, thereafter, literature support of KOA’s epidemiology, socioeconomic burden and pathophysiology.

2.1 Rheumatic Diseases

RD include over 150 disorders and are one of the primary causes of compromised QoL and absence from work, with significant economic and social consequences, although death rates are low. ("Rheumatic diseases. Report of a WHO Scientific Group," 1992)

In Portugal, RDs are responsible for 40 to 60% of cases of prolonged physical incapacity in daily activities, 43% of absences from work, and 35 to 41% of early retirement due to illness. The prevalence of rheumatic diseases, both in Portugal and worldwide, is increasing, with significant repercussions for public health (EpiReumaPT, 2013).

According to the WHO, from all RDs, OA is already one of the ten most disabling diseases in developed countries. OA is the RD with the greatest impact on society and represents the major risk to the individuals QoL, once that 80% of those with OA will have limitations in movement, and 25% cannot perform their major daily activities of life (WHO, 2020).

Throughout the last decade, some authors believed that by 2020 the number of people with OA would have doubled, due largely to the exploding prevalence of obesity and the graying of the “baby boomer” generation (Hunter, Neogi, & Hochberg, 2011) and that by 2040 an estimated 78.4 million (25.9% of the projected total adult population) adults over 18 years are expected to have physician-diagnosed arthritis (Hootman, Helmick, Barbour, Theis, & Boring, 2016), the majority of whom will have OA.

Regardless of the definition used, OA’s prevalence ranges from 6.3% in Greece (Andrianakos et al., 2006) to 70.8% in Japan (Oka et al., 2009). Based on self-reported, there are six studies with estimations ranging from 7.1% in Norway (Grotle, Hagen, Natvig, Dahl, & Kvien, 2008b) to 15.0% in the Netherlands (Tukker, Visscher, &

Picavet, 2009). Between 1.3 and 1.75 million people in the UK have OA (Loza et al., 2009), whereas in France, each year, 6 million new diagnosis of OA are made (Levy, Ferme, Perocheau, & Bono, 1993). In conlusion, it gets clear that OA prevalence differs by country and ethnicity (Andrianakos et al., 2006; Bremner, Lawrence, & Miall, 1968; Cvijetic, Campbell, Cooper, Kirwan, & Potocki, 2000; Du et al., 2005; Felson et al., 1987; Haara et al., 2003; Hassett, Hart, Manek, Doyle, & Spector, 2003; Kellgren & Lawrence, 1958; Lethbridge-Cejku et al., 1994; Nakagawa, Hyakuna, Otani, Hashitani, & Nakamura, 1999; Nevitt et al., 2002; Odding et al., 1998; Quintana et al., 2008; van Saase, van Romunde, Cats, Vandenbroucke, & Valkenburg, 1989; van Schaardenburg, Van den Brande, Ligthart, Breedveld, & Hazes, 1994; Yoshimura et al., 2009; Zhang et al., 2001; Zhang et al., 2003) and racial or geographical differences may provide valuable clues about potential etiologic factors.

Nevertheless, the burden of OA relates not only to its prevalence but also to the costs of the disease to individuals and health care systems. Given this, illness cost studies have revealed the great economic impact of OA (Gabriel, Crowson, Campion, & O'Fallon, 1997b; Gabriel, Crowson, & O'Fallon, 1995; Lanes et al., 1997; MacLean, Knight, Paulus, Brook, & Shekelle, 1998). Data from a Canadian cohort found an average annual cost of 11200€ per patient (12200 US dollars) (Gupta, Hawker, Laporte, Croxford, & Coyte, 2005). Moreover, in France, using a macroeconomic approach, OA direct costs in 2002 contributed to 1.7% of expenses of the health insurance system (Le Pen, Reygrobellet, & Gerentes, 2005). Even among employed persons, the total costs attributable to OA are substantial, as reported in a Belgian cohort (Rabenda et al., 2006). In addition to this, some studies have shown a significant impact of OA on premature work loss in terms of long-term sick leave and disability (Hubertsson, Petersson, Thorstensson, & Englund, 2013; Wilkie, Phillipson, Hay, & Pransky, 2014) reduced employment (Sayre et al., 2010) and early retirement (Bieleman, Oosterveld, Oostveen, Reneman, & Groothoff, 2010; Palmer, Milne, Poole, Cooper, & Coggon, 2005). Sharif et al. showed that OA patients have a significantly higher rate of work loss, i.e., leaving employment, due to illness or disability compared to non-OA individuals using a matched cohort design (Sharif et al., 2016). Although a fraction of those experiencing work loss may go back to work, periods of unemployment that are associated with OA have a large societal burden in terms of loss of income and psychosocial burden (Bieleman, 2014).

Other than the societal impact is the impact on QoL which can also be used as a measure of the burden of OA. OA was estimated to be the eighth-leading cause of nonfatal burden in the world in 1990, accounting for 2.8% of total years lost due to disease, approximately the same percent-age as schizophrenia and congenital anomalies (Woolf & Pfleger, 2003). In 1998, the Global Burden of Disease 2000 study was published in the World Health Report 2002 (Lopez & Murray, 1998) and reported OA as the fourth-leading cause of years lost due to disease worldwide.

OA may also impose a significant mental health burden on afflicted individuals (Stubbs, Aluko, Myint, & Smith, 2016; Veronese et al., 2017). Besides affecting patients activity and QoL, OA will further cause depression and anxiety, as well as a great economic burden (Shen & Chen, 2014). Simultaneously, a considerable proportion of OA patients live with co-existing medical conditions. For example, in a meta-analysis, Hallet al. (A. J. Hall, Stubbs, Mamas, Myint, & Smith, 2016) reported that approximately 40% of the patients suffered from a cardiovascular disease. Obesity and metabolic syndrome are also prevalent which likely contributes to an average 10–14% of this specific population having diabetes (Eymard et al., 2015; Louati, Vidal, Berenbaum, & Sellam, 2015).

Until the beginning of the century, OA was not interesting enough: a simple and natural result of the wear and tear on the cartilage. A disorder of elderly people with hardly any treatment options. Conventionally, OA was regarded as a mild disease relative to rheumatoid arthritis, which has served as a benchmark for severe arthritis (Pincus et al., 2019).

From then until now, the public and the medical community realized that this "conventional wisdom" was not based on systematic analysis of disease burden. Many reports indicate that OA is associated with substantial morbidity (Dieppe, Cushnaghan, Tucker, Browning, & Shepstone, 2000), costs (Gupta et al., 2005; Yelin & Callahan, 1995), and increased mortality rates (Cleveland et al., 2019; Hawker et al., 2014; Nuesch et al., 2011; Pincus, Gibson, & Block, 2015), suggesting that OA is indeed a severe disease.

This different point of view (Felson et al., 2000), along with the development of a wider, biopsychosocial perspective on OA (Hunt, Birmingham, Skarakis-Doyle, & Vandervoort, 2008) and its diverse personal and social consequences, have attracted more attention to research and clinical practice. The insight that OA could cause productivity loss, and eventually work loss, in working age individualshas raised awareness for the socio-economic component of the disease (both for individuals and society), since a large increase in prevalence of OA was anticipated (Bieleman, 2014).Therefore, OA turned into this major public health concern and as a result of its high prevalence, its treatment costs, and its association with pain and chronic disability, numerous efforts to identify the associations between patient factors and OA prevalence have been made.

At first sight, once OA is the most common joint disease worldwide, being a leading cause of disability among individuals above 40 years old, it seems questionable why the majority of surveys on the prevalence of OA have been performed in Europe and the United States (Andrianakos et al., 2006; Bremner et al., 1968; Cho, Morey, Kang, Kim, & Kim, 2015; Felson et al., 1987; Haara et al., 2003; Hassett et al., 2003; Kellgren & Lawrence, 1958; Lethbridge-Cejku et al., 1994; Odding et al., 1998;

Quintana et al., 2008; van Saase et al., 1989; van Schaardenburg et al., 1994) knowing that it has been estimated that by 2050, almost four fifths of the world's older population (65 years and older) will be living in less-developed regions of the world (Zhang et al., 2001). At the same time, other authors acknowledge that *"While OA was historically considered a condition of older persons, today it is commonly recognized to affect younger adults as well"* (Ackerman et al., 2015) based on data that supports the idea of an *"(…) evolving contemporary view of OA as a disease that affects not just older adults but also millions of younger and middle-aged adults"* (Deshpande et al., 2016).

Regarding its pathophysiology, OA is a chronic joint disease characterized by cartilage breakdown associated with hypertrophy of the bone (osteophytes and subchondral bone sclerosis), thickening of the capsule (Lawrence et al., 1998; Zhang et al., 2001), synovium inflammation and narrowing of the joint interline (Loeser, Goldring, Scanzello, & Goldring, 2012).

According to the 2010 Global Burden of Disease Study, the most common site of OA is KOA (Lawrence et al., 2008). KOA is more prevalent in over 60 year old women compared to males of the same age (13% vs 10%) (Abedin et al., 2019). Its severity among females above 55 years old is higher compared to their male counterparts, while the severity of KOA is higher compared to other types of OA (Peat, McCarney, & Croft, 2001; Zhang & Jordan, 2010). Approximately one in every six patients consults with a general practitioner in their first year of a KOA episode (Peat et al., 2001; Zhang & Jordan, 2010). The incidence of KOA has a positive association with age and weight and the prevalence is more common in younger age groups, particularly those who have obesity problems (Bliddal & Christensen, 2009).

As a chronic and painful condition, KOA holds significant economic costs (Gabriel, Crowson, Campion, & O'Fallon, 1997a; Gabriel et al., 1995; Lanes et al., 1997;

MacLean et al., 1998; Mapel, Shainline, Paez, & Gunter, 2004) and affects 9.3 million adults over 45 years old in the United States (Lawrence et al., 2008). United States data indicate that the incidence of KOA peaks in the 55 - 65 year old group, at around 0.4% annually, and has an average incidence of approximately 0.25% from age 25 to 85 years (Abbott, Usiskin, Wilson, Hansen, & Losina, 2017). Going worldwide, a wide range of results were found with radiographic case definition, from 7.1% in Croatia (Cvijetic et al., 2000), to 70.8% in Japan (Oka et al., 2009). Based on symptomatic definition the lowest estimate is found in Italy (5.4%) (Salaffi, Carotti, Stancati, & Grassi, 2005) and the highest 24.2% in Korea (I. Kim et al., 2010). Cohort studies carried out in Spain have shown a high prevalence of KOA of 10% (Carmona, Ballina, Gabriel, Laffon, & Group, 2001) and a huge impact on health care costs: more than 4,700 million euro in 2007, equivalent to a 0.5% of the national gross product that same year (Loza et al., 2009).

Tabela 1. Reference to the main KOA's studies used in this dissertation

Study		**Study Subject**	**Type**
Authors	**Year**	**KOA's…**	
Wallis *et al.*	2019	Quality of Life	Systematic Review
Charlesworth *et al.*	2019	Safety Implications	Systematic Review
Pacca *et al.*	2018	Prevalence in Obesity	Published Article
Deveza *et al.*	2017	Phenotypes	Systematic Review
Yazigi *et al.*	2016	Pre-Screening Questionnaire	Published Article
Gomes-Neto *et al.*	2016	Quality of Life	Published Article
Collins *et al.*	2016	Questionnaire - KOOS	Meta-Analysis
Silverwood *et al.*	2015	Risk Factors	Meta-Analysis
Puig-Junoy *et al.*	2015	Socio-economic costs	Systematic Review
Ackerman *et al.*	2015	Prevalence in Youth	Published Article
Shen *et al.*	2014	Research	Published Article
Cross *et al.*	2014	Global Burden	Published Article
Sellam *et al.*	2013	Metabolic effects	Published Article
Felson *et al.*	2013	Mechanics	Published Article
Berenbaum *et al.*	2013	Inflammation and Obesity	Published Article
Loeser *et al.*	2012	Disease	Published Article
Braun *et al.*	2012	Imaging diagnosis	Published Article
Heidari *et al.*	2011	Prevalence and pathogenesis	Published Article
Zhang *et al.*	2010	Epidemiology	Published Article
Blagojevic *at al.*	2010	Risk Factors	Meta-Analysis

2.2 Knee Osteoarthritis

Swelling, joint pain, and stiffness are the prominent symptoms in KOA among others, such as restrictions in movement including walking, stair climbing, and bending (Heidari, 2011). The symptoms worsen over time and elderly patients are affected more frequently than patients in other age groups.

In the past century, The American College of Rheumatology (ACR) has started to develop different criteria for the classification of KOA in order to promote uniformity in reporting OA in epidemiological and intervention studies. These criteria were developed using combinations of clinical, clinical/ laboratory, and clinical, laboratory and radiographic criteria (Altman et al., 1991; Altman et al., 1986). Although these criteria were developed primarily for epidemiological purposes rather than for clinical use, the ACR criteria were commonly used as a diagnostic tool in secondary care. Furthermore, it has been suggested that the criteria were probably mainly diagnostic for late-stage KOA (Peat et al., 2006).

In 2012, the first international Early Knee Osteoarthritis (EKOA) workshop proposed new criteria for EKOA diagnosis (Leyland et al., 2012). This new proposal marked the beginning of a new approach in the diagnosis of KOA. It had become imperative to look for tools that would make diagnosis as early as possible. In that workshop, whilst definitive knee osteoarthritis (DKOA) was defined by the presence of radiographic osteophyte formation or joint space narrowing, EKOA shows no osteoarthritic changes in radiographs. The new criteria for EKOA include knee injury and OA outcome score (KOOS), joint line tenderness and crepitus. Luyten et al. emphasised the necessity of the concept and application of EKOA criteria to change from the current reactive approach of OA management to a more proactive one.(Sasaki et al., 2019)

Besides the always required routine clinical examination of the symptomatic joint, X-ray imaging (plain radiography) is the current gold standard for diagnosing

KOA. However it cannot be a reasonable option because it is well known that radiography is impractice, expensive and (even more importante) insensitive when attempting to detect early KOA changes (Tiulpin et al., 2018). Moreover, some studies were carried out comparing X-ray and arthroscopy where the differences that are often found in the scenario between the examination and the intrasurgical findings were highlighted (AlOmran, 2009; Rupprecht, Oczipka, Luring, Pennekamp, & Grifka, 2007). Given this, some questionnaires started to emerge in the scientific comunity as an alternative option to diagnose and characterize KOA. Additionally, for epidemiology studies in particular, it seems that prevalence evaluation using a specifically designed screening questionnaire is a less costly and more feasible approach (Leung et al., 2018).

The available KOA-related questionnaires can be organized into two groups: patient outcomes and screening instruments. The first group includes questionnaires related to patient outcomes (functionality, signs, symptoms and quality of life) (Bellamy et al., 2007; Bellamy, Buchanan, Goldsmith, Campbell, & Stitt, 1988; Goncalves, Cabri, Pinheiro, Ferreira, & Gil; Greco et al.; Rat et al., 2005; E. M. Roos, Roos, Lohmander, Ekdahl, & Beynnon, 1998), while the Western Ontario and McMaster Universities Arthritis Index (WOMAC) (Bellamy et al., 1988) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) (E. M. Roos et al., 1998; E. M. Roos & Toksvig-Larsen, 2003) are widely used screening instruments.

The WOMAC has been validated with three types of scales: visual analog (Bellamy et al., 1988), Likert (Bellamy et al., 1988) and a numerical rating scale (Theiler et al., 2002).

Considered an extension of the WOMAC, KOOS covers five dimensions that are reported separately: pain, symptoms, activities of daily living, sport and recreation function, and knee related QoL. KOOS proved to be a measure of sufficient reliability, validity, and responsiveness for surgery and physical therapy after reconstruction of the anterior cruciate ligament (E. M. Roos et al., 1998). Given the previously presented need for a change on the approach of diagnosing KOA, both instruments do not seem to serve the purpose of an early diagnosis.

Facing this need in 2016 the Knee Osteoarthritis Pre-Screening Questionaire (KOPS) (Appendix 1) was developed and validated (Yazigi, Carnide, Espanha, & Sousa, 2016). It was developed for KOA screening situations before radiologic diagnostic tests and proved to be user-friendly (it did not require specialist supervision) and quick to complete. According to the authors, KOPS can *"(…) distinguish individuals with KOA from others without KOA, indicating that this instrument has valid constructs*." (Yazigi et al., 2016).

Total joint replacement surgery is the most favorable option to treat advanced stage KOA. However, identifying the status of KOA at an early stage and providing behavioral interventions could be beneficial to extend the healthy life of a patient (Karsdal et al., 2016).

2.2.1. Symptoms, Signs and Health Related QoL

Recent research has shown that the KOA pathway is heterogeneous and patients may present different symptoms (Deveza et al., 2017).

Distinctive subgroups have been identified in the evolution of knee pain and also in the functional limitations experienced by persons with KOA (Ackerman et al., 2015; Bastick et al., 2016; J. E. Collins, Katz, Dervan, & Losina, 2014; Holla et al., 2014; Nicholls, Thomas, van der Windt, Croft, & Peat, 2014). These studies have modeled trajectories of knee pain intensity, knee pain persistence, and the level and evolution of physical activity limitation. The pain and disability are associated with functional restrictions, morphological changes in the subchondral bone, articular cartilage degeneration and damage to the surrounding soft tissue (L. Fernandes et al., 2013; Heiden, Lloyd, & Ackland, 2009).

As a chronic disease with a long “silent” period, KOA has severe emotional consequences as one of the most weakening diseases that affect humanity (Patra & Sandell, 2011). Fatigue, pain and disability affect social and romantic relationships and emotional well-being, subsequently, reducing QoL (Corti & Rigon, 2003). Fatigue is a common complaint by people having rheumatic diseases (as it is an important indicator of QoL) (Murphy, Schepens Niemiec, Lyden, & Kratz, 2016; Power, Badley, French, Wall, & Hawker, 2008) and pain increases with activity and decreases at rest in the early stage of the disease, becoming more intense and resistant as the disease progresses (Fertelli & Tuncay, 2019).

Pain is a clinical trademark of KOA and the management of the patient with KOA related pain is challenging (Foucher, Chmell, & Courtney, 2019). As a universal but subjective experience, pain may be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. It can serve as a warning to protect us from further harm, but it can also contribute to persistent suffering, when it surpasses its underlying cause to become a disease in its own domains and dimensions (De Oliveira Paes Leme, Yuan, Oliveira Magalhaes, Ferreira de Meneses, & Marques, 2019). KOA's pain is complex and somewhat paradoxical due to the often reported structure symptom discordance (Neogi, 2013).

Neurobiological mechanisms likely contribute to chronic pain in KOA and it is now well-established that central and peripheral sensitization are present (Arendt-Nielsen et al., 2010; Arendt-Nielsen, Skou, Nielsen, & Petersen, 2015; Bartley et al., 2016; Courtney, Steffen, Fernandez-de-Las-Penas, Kim, & Chmell, 2016; Courtney, Witte, Chmell, & Hornby, 2010; Fingleton, Smart, Moloney, Fullen, & Doody, 2015; Glass et al., 2014; Graven-Nielsen, Wodehouse, Langford, Arendt-Nielsen, & Kidd, 2012).

Peripheral sensitization is defined as the facilitated response of nociceptive neurons located at the site of tissue injury or disease; it is limited to these nociceptors and will resolve as tissues heal and inflammation recedes. Central sensitization is mediated via amplification of signaling to the central nervous system, potentially at both spinal and supraspinal levels, and is associated with heightened pain, spontaneous pain without trigger, expanded distribution of pain, and potentially the presence of altered non-nociceptive findings, including diminished vibration perception threshold particularly in the most painful region (Courtney, Fernandez-de-Las-Penas, & Bond, 2017). Depending on KOA's stage, patients report a chronic pain most of the time.

Chronic pain is defined as pain that persists past the normal time of healing. Three months has been suggested as the most convenient cut-off between acute and chronic pain (Chou et al., 2007; De Oliveira Paes Leme et al., 2019). According to the biopsychosocial model, chronic pain is the subjective experience of nociception, and derives from the complex interaction of biological changes, psychological status and sociocultural context (Gatchel, Peng, Peters, Fuchs, & Turk, 2007).The prevalence of chronic pain in the general population is high. A systematic review including 19 studies in 34 countries estimated a worldwide prevalence of 30.3% (Elzahaf, Tashani, Unsworth, & Johnson, 2012).

It is important to realize that, althought emotional and psychosocial reactions to pain are clinically significant (De Oliveira Paes Leme et al., 2019), chronic pain is a major health problem, which seriously affects the patients daily activities, social and working lives, and poses an economic burden on patients, healthcare services and society (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006).

Emotionally speaking, living with KOA was described as being ‘difficult’ and often as having a negative impact on the participant’s mood, resulting in feelings of loss, anxiety, inadequacy, frustration, irritability, emotional distress, embarrassment, fear for the future and uncertainty of the outcomes of knee pain and depression (Wallis, Taylor, Bunzli, & Shields, 2019). In fact, depression is seen in two-thirds of chronic rheumatologic patients (Stebbings, Herbison, Doyle, Treharne, & Highton, 2010) and its risk is further increased in patients if OA is accompanied by chronic pain, which is the case for the majority of KOA’s patients.

Regarding to functional impairment, the knee is the eleventh highest disability factor worldwide (Cross et al., 2014). KOA accounts for more dependence in walking, stair climbing and other lower-extremity tasks that any other disease (March & Bagga, 2004). The risk of mobility disability (defined as needing help walking or climbing stairs) attributable to KOA alone is greater than that related to any other medical condition in people over 65 years old (Guccione et al., 1994). The gait of KOA patients is also characterized by higher knee adduction moment, a marker of medial joint loading and known risk factor for progression of arthritis (Foroughi, Smith, & Vanwanseele, 2009; M. Hall et al., 2017; Ro et al., 2018). Such gait changes in KOA can directly or indirectly affect adjacent weight-bearing joints, that is, the hip and ankle joints

(Astephen, Deluzio, Caldwell, & Dunbar, 2008; Mundermann, Dyrby, & Andriacchi, 2005; Schmitt, Vap, & Queen, 2015). In fact, we often encounter KOA patients with ankle and hip joint pathology. Epidemiological studies also showed that significant numbers of patients have pathologies in more than two of the three weight-bearing joints, which may indicate that problems with one joint are biomechanically related to problems in the others (Allen & Golightly, 2015; Arden & Nevitt, 2006).

2.2.2. Risk Factors

While exploring the complexity of KOA, it becomes clear that there are multiple phenotypes that can influence both the beginning and progression of the disease. Especially in the last decade, KOA has been characterized as a disease of mechanics (Felson, 2013) with a metabolic phenotype (Sellam & Berenbaum, 2013) and substantially influenced by inflammatory mediators (Berenbaum, Eymard, & Houard, 2013; Sohn et al., 2012; Q. Wang et al., 2011) as well as a disease that is driven by abnormal joint structure (Rao et al., 2013), morphology (Quinn, Hauselmann, Shintani, & Hunziker, 2013) and genetics (Ryder et al., 2008).

In 2015, a meta-analysis summarised the effect of major risk factors, including modifiable risk factors (such as obesity, joint injury and occupational risk) and non-modifiable risk factors (e.g., Heberden's nodes, age and female gender) (Silverwood et al., 2015).

2.2.3. KOA and the Obesity Cycle

Since 1995 that Western World's obesity has become a major issue for obesity specialists (James, 2008) and, fueled by economic growth, industrialization, mechanized transport, urbanization, an increasingly sedentary lifestyle, and a nutritional transition to processed foods and high calorie diets over the last 30 years, obesity prevalence has doubled or even quadrupled in some cities worldwide (Hruby & Hu, 2015). Being that obesity is a disease with epidemic proportions, it was declared by WHO as the largest global chronic health problem in adults (Capodaglio, Ventura, Petroni, Cau, & Brunani, 2018). Contributing for this statement, a 2014 study estimated that 3.8 percent of the global burden of disease could be attributed to high BMI (including 3.3 million deaths and 93 million disability-adjusted life years in 2010 alone) (Herington, Dawson, & Draper, 2014). At the same time, worldwide prevalence of overweight obesity has doubled since 1980 to an extent that nearly a third of the world population is now classified as overweight or obese (Chooi, Ding, & Magkos, 2018) and the proportion of adults with a BMI of 25 or greater increased from 28.8% in 1980 to 36.9% in 2013 for men and from 29.8% to 38.0% for women, in both developed and developing countries (Oliveira et al., 2018). Totally, 1.9 billion and 609 million adults were estimated to be overweight and obese in 2015, respectively, representing approximately 39% of the world's population (Chooi et al., 2018). Current trends suggest that by 2030, only 10 years from now, approximately half the population of the United States, the United Kingdom, and Australia— and almost a fifth of the world as a whole— will be obese (Wang, McPherson, Marsh, Gortmaker, & Brown, 2011).

America and Europe were the two continents with the highest prevalence of obesity. Between 1980 and 2015, the prevalence of obesity increased from 12.9% to 28.3% in the Americas, being the US and Mexico the countries with the highest prevalence rates, and from 14.5% to 22.9% in the European region (Chooi et al., 2018). Still regarding to Europe, since 2018 the obese accounted for 53.1%. The estimates indicate that the countries with the highest prevalence were Slovenia (20.8%), Estonia (19.7%) and the United Kingdom (19.2%) (Marques, Peralta, Naia, Loureiro, & de Matos, 2018). These recent results are similar with previous regional trends within Europe that showed a higher obesity prevalence in southern Italy, southern Spain and Eastern European countries rather than in Western and Northern European countries (Berghofer et al., 2008).

In Portugal, the national obesity prevalence is 22.3%, being significantly higher in women (24.3%). It increases with age, with the lowest prevalence in children (7.7%) and the highest in the elderly (39.2%). Nationally, the overweight prevalence is 34.8%, being higher in men (38.9%) than in women (30.7), and in the elderly (41.8%). Approximately 40% of the Portuguese population is underweight/normal weight. Going further, the estimate for Portugal is even higher than the worldwide prevalence, which puts into perspective the importance and priority of this public health challenge in our country (Oliveira et al., 2018).

Widespread obesity poses a serious challenge to health outcomes in the developed world (Herington et al., 2014) and is threatening health improvements in many countries (Collaborators et al., 2017; Sidney et al., 2016). One meta-analysis of obesity in trauma care concluded that obesity was associated with 45% increased odds of mortality, longer stays in the intensive care unit and higher rates of complications, and tended to be associated with longer durations of mechanical ventilation and longer stays in the hospital overall compared to non-obese patients, despite equivalent injury severity (Liu, Chen, Bai, Zheng, & Gao, 2013). Simultaneously, obesity is associated with an increased risk of temporary work loss such as sick leave and reduced productivity while being present at work. It is also associated with permanent work loss, which includes disability pension and premature death (Neovius, Johansson, Kark, & Neovius, 2009; Neovius, Johansson, Rossner, & Neovius, 2008). In the US, it has been estimated that the health costs incurred by a single obese individual was €1732 per annum in 2014, extrapolating to €136 billion at the national level (D. D. Kim & Basu, 2016). In 2002, in Europe, it was estimated that the direct and indirect obesity cost was €32.8 billion, whereas the cost of funding healthy food was €10 billion, a third of the obesity cost (Fry & Finley, 2005). Later, in 2011, this cost was already equivalent to 0.47 - 0.61% of gross domestic product (von Lengerke & Krauth, 2011).

Obesity is an excess of body fat leading to ill health. Its impact on risk of stroke and cardiovascular disease, certain cancers and OA is significant (Hruby & Hu, 2015) and it is also a major risk factor for sleep apnea and poor physical health(S. H. Kim, Despres, & Koh, 2016). Althought most of the obesity definitions talk about an etiologically complex phenotype primarily associated with excess adiposity, or body fatness, it is also true that it can be metabolically manifested in spite of body size (Hruby & Hu, 2015). As an example, a study in Pennsylvania (USA) trauma centers showed that in-hospital mortality and risk of major complications of surgery were increased in obese patients as compared to non-obese patients. Severely obese patients had upwards of 30% increased risk of mortality from their trauma than non-obese patients, and double the risk of major complications (Hruby & Hu, 2015). In another study, male and female non-smokers who were obese at age 40 died 6 - 7 years earlier than their non-obese counterparts (Peeters et al., 2003). Attempts at quantifying this health impact suggest that obese individuals stand to lose five to seven healthy life years from the comorbidities and early mortality (Muennig, Lubetkin, Jia, & Franks, 2006).

USA, for example, took over half a century to achieve the immense success they had with regard to smoking, and still they are not tobacco-free yet, while other parts of the world continue to wrestle with it to a greater degree. It has only been a couple decades since we first deeply appreciated that obesity was epidemic (Hruby & Hu, 2015) and may be the first step to stop its prevalence from increasing is knowing that it is a major contributor to preventable disease and death across the globe. It poses a nearly unprecedented challenge not just to those tasked with addressing it at the public health level, or at the healthcare provider level, but to each of us as individuals for none of us are immune (Hruby & Hu, 2015).

Obesity is one of the strongest predictive and prognostic factors for OA, particularly in knee joints (Glyn-Jones et al., 2015). Some authors assume that the majority of patients with KOA are overweight or obese (Marks, 2007) and obesity seems to further increase KOA's risk (Silverwood et al., 2015). The relationship between obesity and KOA was primarily explained by mechanical overloading on the cartilage (Eymard et al., 2015), because the load on the knee joint increases as body weight increases (Bindawas, 2016). However, considering the epidemiological association of obesity and KOA, some systemic factors may participate in the pathogenic process, for example: adipose tissue products, or "adipokines", may have a systemic impact at a distance on joints (Abella et al., 2014; Chauffier et al., 2012; Laiguillon et al., 2014).

Finally a model has emerged claiming that the high body mass promotes development and progression of KOA via two possible mechanisms: mechanical stress beyond the physiological capabilities of the weight-bearing knee joint and on the other hand, altered metabolic and humoral profile resulting in elevated adipocytokine levels and associated pro-inflammatory response (as it was referred already). This is called the vicious circle of the complex cause-and-effect relationship between KOA and obesity (Kulkarni, Karssiens, Kumar, & Pandit, 2016).

This well established evidence associating obesity and KOA (Flego, Dowsey, Choong, & Moodie, 2016) was already represented on The Chingford study, showing that for every two units increase in BMI the odds ratio for developing radiographic KOA increases by the factor 1.36 (Hart & Spector, 1993).

The issue with obesity and KOA is that the two conditions often coincide, working synergistically to perpetuate poor function and a greater likelihood of sedentary lifestyles, which inevitably lead to higher levels of disability and a reduction in quality of life (Ackerman & Osborne, 2012). The burden of KOA has been rising in the past two decades with increasing prevalence of obesity and aging populations (Cross et al., 2014) and obese individuals experiencing frequent knee pain tend to experience higher levels of knee pain than their non-obese counterparts (Summers, Haley, Reveille, & Alarcon, 1988).

There is a substantial body of evidence focusing on the relationship between obesity and KOA from a variety of perspectives. This includes investigation of the causal relationships between obesity and KOA through biomechanical (Messier, Gutekunst, Davis, & DeVita, 2005), physiological (Stannus et al., 2015) and inflammatory mechanisms (Sanchez, Gabay, Salvat, Henrotin, & Berenbaum, 2009), quantification of the impact of obesity on KOA outcomes (Messier et al., 2005) and its negative influence on disease outcomes such as the need for surgery (Wendelboe et al., 2003). In summary, obesity can be classified as having both systemic and local mechanical effects on KOA.

Chapter 3: Methods

This chapter includes the methodology used in the present study.

3.1 Study Design

This was a cross-sectional study with a transversal design. To attend the main goal of the study, KOPS was the selected instrument. Total and Components Scores were the primary outcomes, while the item's frequencies and some characterization variables of the sample are the secondary outcomes.

Althought KOPS was validated by the authors and considered useful for this purpose (Appendix 2), there was a geography problem claiming: how could the questionnaire be spread for all the country to accomplish a sample that was big enough but at the same time from as many different regions of the country as possible? Given this challenge, and using LimeSurvey (an online platform), KOPS was created on an Online version so that just through a link people could answer it quickly and whithout effort on a mobile phone or on a computer.

The Online Version of KOPS was evaluated by a panel of judges from Human Kynetics Faculty (Lisbon, Portugal) that ensured the correspondence between paper and online version of the questionnaire. The panel was composed by a Computer Center Director, a specialist in development and validation of self-reported questionnaires, a teacher responsible for PICO Project (Intervention Program Against Osteoarthritis) and another teacher responsible for KOPS's development and validation

This study was carried out within the scope of the PICO project (Yazigi et al., 2013) whose protocol was approved by the Ethical Committee of the Faculdade de Motricidade Humana, Universidade de Lisboa.

3.1.1. Sample Calculation

Sample size was calculated based on a cross-sectional study from 2017 in Lisbon, where a 14,1% KOA's prevalence was reported by the authors (Marques, 2017). Expecting to obtain at least the same prevalence, 194 volunteers (95% confidence interval) was this study's sample size needed. Considering that outlyers would mean 10-15% of all sample, a statistical confort number was established for conducting this analyses: 230 volunteers with obesity (minimum) according to BMI classification (Pescatello, 2014).

3.1.2. Sample Recruitment

In order to promote KOPS to as many people as possible, insititutional comunications were done with strategic partners: Sociedade Portuguesa para o Estudo da Obesidade (SPEO), Hospital da Luz, Hospital Lusíadas, CUF (Hospitais e Clínicas), for example) and the survey was delivered by email for more than 3000 nutritionists and exercise physiologists using social network platforms (Facebook and Linkedin). Through this email, these professionals were asked to disclose the questionnaire to their patients.

All volunteers had to ensure these following inclusion criteria:

- No pregnancy
- No mental disease
- Age ≥ 18

3.2 Outcomes and Instruments

KOPS was the only istrument used in this study. It was validated for Portuguese population and the receiver operating characteristic curve revealed a KOPS score of 16 with sensitivity of 86.96, specificity of 75.82 and an AUC of 0.880 ($p<0,001$) (Yazigi et al., 2016).

KOPS is a self-report questionnaire composed of closed-ended questions with nominal and ordinal response options. The first part includes sociodemographic information, the second part has risk factor information, the third part is about signs and symptoms and the last part has additional information related to mobility, exercise and clinical supervision. KOPS addresses physical function, activity level, co-morbid diseases, KOA risk factors and symptoms, height and weight (to determine BMI) and caregiver status.

3.2.3. Knee Osteoarthritis Pre-Screening Questionnaire (KOPS)

The maximum value that could be scored on the KOPS is 54 (Fig. 1). As the value increases from zero, there is a greater possibility of having KOA. The suggested threshold value with the highest specificity/sensitivity is 16, which means that participants with a KOPS score ≥ 16 had a greater probability of KOA. This Total Score is composed by two Dimensions: Symptom and Risk Factors.

Symptom Dimension (30 is the maximum possible score) is composed by 4 Components: Functional Pain and Signs and Other Symptom (scored from 0 to 1, where one represented a positive answer) and two Pain components (scored from 0 to 10).

Regarding Risk Factors Dimension (24 is the maximum possible score), to enable the construction of a score, the load for each item was determined by the authors. To avoid an overload of some items, the discrete variables (age, BMI and the amount of years in sports) were transformed into ordinal variables (Yazigi et al., 2016). Age (years) was categorized into seven intervals (≤ 39 = 0; 40–49 = 1; 50–59 = 2; 60–69 = 3; 70–79 = 4; 80–89 = 5; ≥ 90 = 6); BMI was categorized into six intervals (underweight = 1; healthy = 2; overweight = 3; grade 1 obesity = 4; grade 2 obesity = 5 and grade 3 obesity = 6) (ACSM, 2017); and sports volume (years x weekly frequency of sports activity) was categorized into seven intervals (no sports = 0; 1–15 = 1; 16–29 = 2; 30–44 = 3; 45–59 = 4; 60–74 = 5; 75– 89 = 6; ≥ 90 = 7).

Given this, this dimension is organized by 2 Components: Biological Risk (age, menopause and BMI) and External Risk (lower body injury and job posture scored from 0 to 1, and sports volume).

Dimensions (2)	Components (6)	Items (18)	Score
Symptom	Functional pain (FP)		4
		Walking pain	1
		Standing position	1
		Stepping pain	1
		Chair pain	1
	Pain intensity – month (MP)	Last month	10
	Pain intensity-year (YP)	Last year	10
	Signs/others symptoms (SOS)		6
		Morning stiffness	1
		Position stiffness	1
		Swelling	1
		Creaking	1
		Knee extension	1
		Deformity	1
Risk factors	Biological risk (BR)		13
		Age interval	6
		Menopause	1
		BMI classification	6
	External risk (ER)		11
		Lower limb injury	1
		Job posture: stand position	1
		Job posture: sitting position	1
		Job posture: squat position	1
		Sports volume	7
KOPS total score			54

Fig. 1. Dimensions, components, items and maximal scores of the KOPS questionnaire

3.3 Statistical analysis

Descriptive statistics consisted on frequencies for categorical variables and means with standard deviations (SD) for continuous variables.

Independent t-tests were used to compare the continuous variables for the Obese and Non-Obese Groups and for male and female while Analysis of Variance (ANOVA) was used to compare continuous variables between three Obesity Groups.

For continuous variables, normal distribution was tested by Kolmogorov-Smirnov test and equality of variance was tested by Levene Test. Also between continuous variables, correlation was analyzed using Pearson correlation coefficient (r) interpreted as strong ($r \geq 0.7$), moderate ($0.5 < r < 0.7$) and weak ($0.3 < r < 0.5$), and the coefficient of determination was used to interpret r and was obtained by squaring the correlation coefficient r (r^2) (Chinchilli & Gruemer, 1994).

Statistical analysis was performed using IBM SPSS Statistics 25.0 and statistical significance was set at $p<.05$ (2- tailed) for all analyses.

Chapter 4: Results

This chapter is organized by: Sample Characterization, KOA's presence in Obese and Non-Obese groups (through KOPS Scores and correlations) and according to Obesity Grade.

4.1 Sample Characterization

Results were organized regarding the main goals of this study. After 4 months of KOPS online application, a total of 1357 individuals had fulfilled the questionnaire, being that 702 (51,7%) were excluded, due to incomplete or incorrect answers. The final sample included 655 volunteers (age 46,1±13,8) and the mean BMI was 29,4±5,9 kg/m^2 , while almost half of the total sample (46,6%) had obesity (BMI≥30 Kg/m^2) (Table 2).

Still regarding age, 82,6% had less than 60 years and and the mean age of women, who represent almost twice the sample (63,5%) compared to men (36,5%), was equal to the average age of the total sample.

Most of the volunteers finished university or an even higher degree (48,7%), only 14,1% were retired and 61,4% reported that did not practice any sport. Regarding geographic distribution, most of the volunteers were from Lisbon (23,6%). The remaining representativeness municipalities in decreasing order were: Oeiras (18,2%), Sintra (8,1%), Cascais (5,4%), Almada (4,4%), Setúbal (4,1%) and the other cities had frequencies ≤2,5% each.

Mean KOPS Total Score was 14,9±8,8, while in Symptoms Dimension was 7,3±7,4 and in Risk Factors Dimension was 7,7±2,7.

Both in male (KOPS Total Score 14,5±9,2) and female (KOPS Total Score 15,1±9,1) the prevalence of KOA was 38,9%.

With a high level of significance ($p<0,01$), all risk factors and KOPS Total Score were weakly correlated (Age r^2=0,177; BMI r^2=170; Sports Volume r^2=0,027).

Table 2. Descriptive analyses according to KOA's Risk Factors of total sample.

Variables (n=655)		n (%)
Age Interval (Years)	≤39	184 (28,1)
	40-49	194 (29,6)
	50-59	163 (24,9)
	60-69	82 (12,5)
	70-79	28 (4,3)
	80-89	4 (0,6)
Sex	Male	239 (36,5)
	Female	416 (63,5)
Menopause		78 (18,8)
BMI Classification	Underweight	7 (1,1)
	Normal Weight	168 (25,6)
	Overweight	176 (26,9)
	Obesity I	195 (29,8)
	Obesity II	77 (11,8)
	Obesity III	32 (4,9)
Functional Pain	Walk	218 (33,3)
	Chair	228 (34,8)
	Step	258 (39,4)
	Stand	167 (25,5)
Signs/Other Symptoms	Morning Stifness	246 (37,6)
	Position Stifness	286 (43,7)
	Swealling	133 (20,3)
	Creaking	344 (52,5)
	Knee Extension	103 (15,7)
	Deformity	85 (13,0)
Job Posture	Stand	283 (43,2)
	Sitting	333 (50,8)
	Squat	65 (9,9)
Sports Volume	1-15	90 (13,7)
	16-29	86 (13,1)
	30-44	57 (8,7)
	45-59	28 (4,3)
	60-74	28 (4,3)
	75-89	12 (1,8)
	≥ 90	25 (3,8)
Previous Lower Limb Injury		219 (33,4)

Legend: BMI=Body Mass Index; Sports Volume = years of practice X week frequency

4.2 KOA in Obese and Non-Obese Groups

In order to estimate KOA's prevalence in Obese volunteers, the total sample was divided into two groups (Obese and Non-Obese) and their KOPS scores were analyzed (Table 3).The mean BMI was 34,6±3,9 kg/m^2 for the Obese and 24,9±3 Kg/m^2 for the Non-Obese.

Results revealed a KOA's prevalence of 56,6% for the Obese individuals and 23,6% for Non-Obese individuals. The most prevalent items in the Obese Group were knee creaking (60,9%) and working in sitting position (49,3%), respectively.

Most of the Obese (29,3%) were 39 years old or less while most of the Non-Obese (36,5%) were in 40-49 years old age interval. Both groups had more women (61,2% of Obese and 65,5% of Non-Obese) and from these 13,2% of the Obese and 10,8% of Non-Obese were already in menopause.

43,8% of Obese and 24,5% of Non-Obese reported previous injury in the lower limbs. Regarding to work, 83,9% of the Obese and 22,8% of the Non-Obese reported job overload and sitting was the most reported position in both groups (52,6% for Obese and 49,3% for Non-Obese) followed by stand position (46,7% for Obese and 40,2% for Non-Obese).

Analyzing Sports Volume, most of the individuals didn't practice any sport (62,2% of Obese and 39,9% of Non-Obese) but, of the ones who did it, the majority of the Obese had a volume between 1-15 (12%) and the majority of the Non-Obese had a volume between 16-29 (17,7%).

66,4% of Obese and 57,2% of Non-Obese reported knee pain. Considering Last month and Last Year items, most of them felt more than 3 pain episodes in the last year (50,8% of Obese and 31,5% of Non-Obese) but the most significant frequency difference was obtained in the Last Month item with 46,1% for Obese and 25,8% for Non-Obese.

Stepping was also the most prevalent functional pain for both groups and the item with the most significant frequency difference in this component (52,3% of Obese and 28,2% of Non-Obese).

Considering gender, in the Obese group female had 58,6% (KOPS Total Score 19,2±9,6) prevalence of KOA and male had 53,4% (KOPS Total Score 17±8,7) while in the Non-Obese group female had 23% (KOPS Total Score 12±7,2) prevalence of KOA and male had 24,8% (KOPS Total Score 12,1±6,9).

Comparing male and female in the Obese group, T-test revealed significant differences in these scores: Biological Risk (p<0,01), Functional Pain, Month Pain, and Signs/Other Symptoms (p<0,05). In the Non-Obese group the same T-test revealed significant differences only in External Risk score (p<0,01).

Table 3. Comparison analysis of KOPS Scores for Non-Obese and Obese volunteers

		Obese (n=304)	**Non-Obese (n=351)**	**Mean Difference**	
Components		Mean (SD)	Mean (SD)	Mean (SD)	*p*-value
Symptom	Functional Pain	1,7 (1,5)	1,0 (1,4)	0,7 (0,1)	<.001***
	Paint intensity - month	2,7 (3,3)	1,1 (2,3)	1,6 (0,2)	<.001***
	Paint intensity - year	2,1 (3,3)	1,7 (2,8)	1,3 (0,2)	<.001***
	Signs/other symptoms	2,4 (1,8)	1,3 (1,5)	1,1 (0,1)	<.001***
Risk factors	Biological risk	6,0 (1,5)	3,9 (1,5)	2,1 (0,1)	<.001***
	External Risk	2,5 (1,9)	3,0 (2,3)	-0,5 (0,2)	<0.01**
KOPS Total Score		18,3 (9,3)	12,0 (7,1)	-6,3 (0,7)	<.001***

Legend: Functional Pain is 0-4 points; Pain Intensity - Month and Year are 0-10 points; Signs and Other Symptoms is 0-6 points; Biological Risk is 0-13 points; External Risk is 0-11 points
*p<0.05, **p<0.01, ***p <0.001.

4.2.1. KOPS Scores for Obese volunteers

In order to describe the determinants that influence the presence or absence of KOA the Obese group, this group was organized in two subgroups according to their KOPS Total Score: Obese<16 and Obese≥16 (Table 4).

Table 4. Comparison analysis of KOPS Scores for Obese volunteers according to KOPS Total Score

		Obese<16 (n=132)	Obese ≥16 (n=172)	Mean Difference	
Components		Mean (SD)	Mean (SD)	Mean (SD)	*p*-value
Symptom	Functional Pain	0,5 (0,8)	2,7 (1,1)	-2,1 (0,1)	<.001***
	Paint intensity - month	0,1 (0,8)	4,6 (3,2)	-4,5 (0,3)	<.001***
	Paint intensity - year	0,5 (1,6)	4,9 (3,1)	-4,4 (0,3)	<.001***
	Signs/other symptoms	1,1 (1,2)	3,4 (1,4)	-2,4 (0,2)	<.001***
Risk factors	Biological risk	5,2 (1,3)	6,7 (1,5)	-1,4 (0,2)	<.001***
	External Risk	1,9 (1,4)	3,0 (2,0)	-1,1 (0,2)	<.001***
KOPS Total Score		9,4 (3,3)	25,2 (5,9)	-15,8 (0,5)	<.001***

Legend: Functional Pain is 0-4 points; Pain Intensity - Month and Year are 0-10 points; Signs and Other Symptoms is 0-6 points; Biological Risk is 0-13 points; External Risk is 0-11 points

*p<0.05, **p<0.01, ***p <0.001.

At Functional Pain Component, stepping was the most reported functional pain in both groups (18,2% for the Obese<16 and 78,5% for the Obese≥16). For the other items, 10% of the Obese<16 and 66,3% of the Obese≥16 reported walking pain; 8,3% of the Obese<16 and 51,7% of the Obese≥16 reported standing pain and 20% of the Obese<16 and 69,2% of the Obese≥16 reported chair pain.

From the ones who reported knee pain, most of the volunteers of Obese≥16 (20,3%) evaluated their pain intensity as 6 in the last year and most of the volunteers in the Obese<16 (3,0%) evaluated as 4.

The most reported item in the SOS Component was creaking (39,4%) for the Obese<16 and position stiffness for the Obese≥16 (80,8%). Obese≥16 had frequencies >75% in three items: morning stiffness, position stiffness and creaking.

At Biological Risk Component, the majority of Obese<16 volunteers were less than 39 years old (50%) with a mean of 41±11,9 and the majority of Obese≥16 volunteers were in the 50-59 years old age interval (38,4%) with a mean of 53±11,3. from this last group 18% had already entered menopause, which started at a mean age of 52±3,3.

Analyzing External Risk Component, 26,5% of the Obese<16 and 58,1% of the Obese≥16 reported lower limb injury. 62,9% of the Obese<16 did not practice any sport and, from the group who did most (18,2%) were in the 1-15 practice volume interval. For Obese≥16, 61,6% didn´t practice any sport and most of the ones who did (11%) were in the 30-44 practice volume interval.

Independent t-tests revealed significant differences of all components and KOPS Total Score between both groups.

4.2.2. Correlations between KOPS Total Score and Risk Factors

This subsection provided important information about how KOPS Total Score was associated with Risk Factors for Obese and Non-Obese volunteers (Fig. 2). Althought all risk factors were weakly correlated with both groups, age and sports volume had a stronger correlation regarding Obese group in comparison with Non-Obese Group, while in the latter BMI had a stronger correlation.

Gender was weakly correlated with KOPS Total score both in the Obese group (r^2=0,01) and Non-Obese (r^2<0,01).

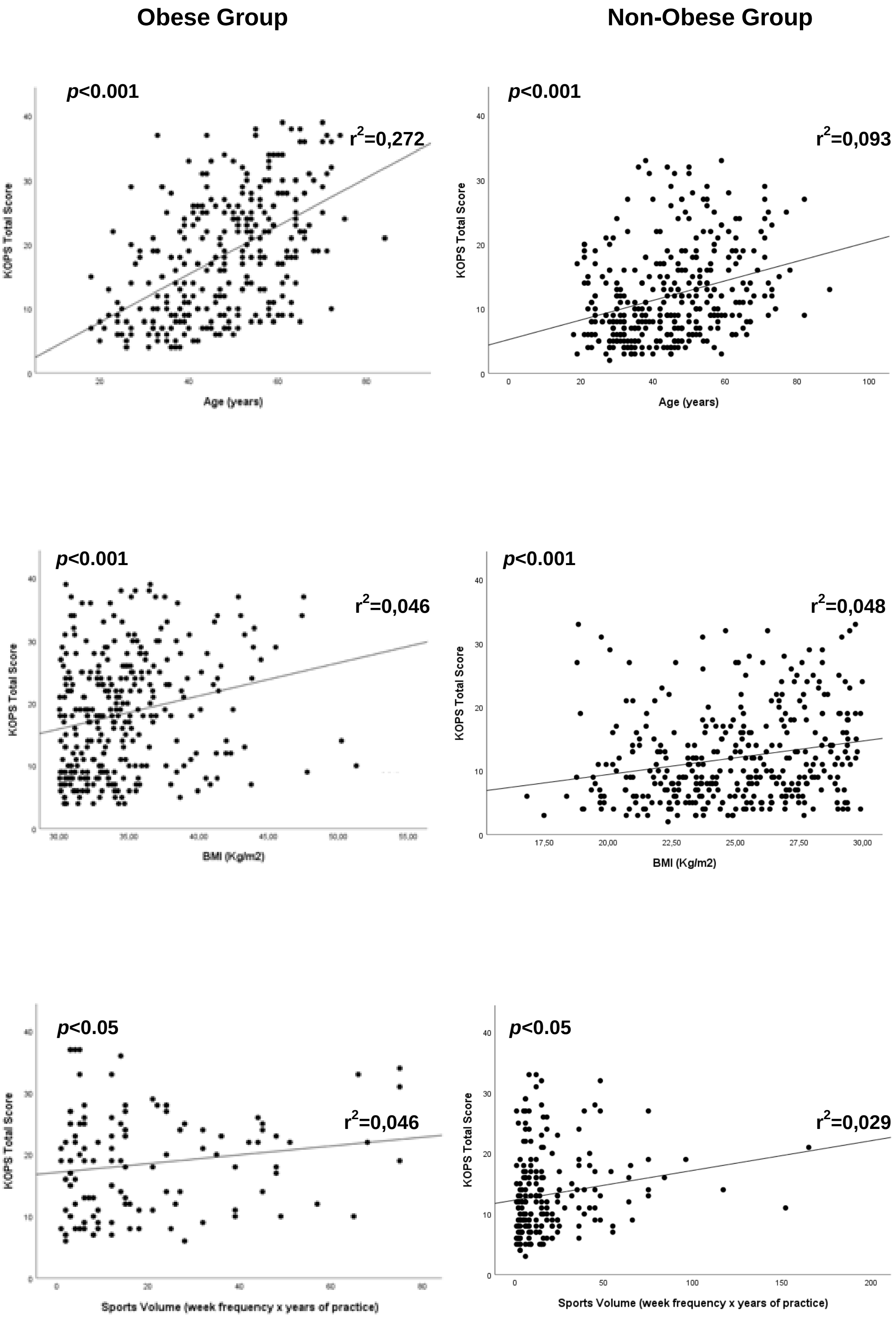

Fig. 2. Linear Regression between KOPS Total Score and Risk Factors (Age, BMI and Sports Volume) for Obese and Non-Obese Groups

4.3 KOA according to Obesity Grade

In order to analyze the way the scores behave in relation to the grade of obesity, the Obese group was divided in 3 according to their Obesity Level (Table 5). KOA's prevalence was 50% for ObesityI, 71,1% for ObesityII and 62,5% for ObesityIII.

Table 5. Comparison analysis of KOPS Scores according to Obesity Grade

		Obesity I (n=195)	Obesity II (n=77)	Obesity III (n=32)	ANOVA	
Components		Mean (SD)	Mean (SD)	Mean (SD)	*F*	*p*-value
Symptom	Functional Pain	1,5 (1,4)	2,0 (1,4)	2,4 (1,6)	7,8	<.001***
	Paint intensity - month	2,2 (3,1)	3,4 (3,5)	3,4 (3,8)	4,5	<0,05*
	Paint intensity - year	2,6 (3,2)	3,7 (3,3)	4,0 (3,8)	4,9	<0.01**
	Signs/other symptoms	2,2 (1,7)	2,8 (1,8)	2,7 (1,9)	4,0	<0,05*
Risk factors	Biological risk	5,5 (1,4)	7,0 (1,4)	7,2 (1,2)	43,8	<.001***
	External Risk	2,6 (2,0)	2,5 (1,8)	2,0 (1,1)	1,7	0,2
KOPS Total Score		16,6 (8,8)	21,4 (9,2)	21,7 (9,9)	10,2	<.001***

Legend: Functional Pain is 0-4 points; Pain Intensity - Month and Year are 0-10 points; Signs and Other Symptoms is 0-6 points; Biological Risk is 0-13 points; External Risk is 0-11 points

*p<0.05, **p<0.01, ***p <0.001.

Regarding to Functional Pain Items, the majority of the volunteers in the three groups answered stepping (46,4% of ObesityI, 61,8% of ObesityII and 65,6% of ObesityIII).

Analyzing Pain Intensity, the highest frequency was obtained in ObesityIII, where 78,1% reported knee pain, and, comparing Month and Year Pain, the last one was the most reported in all groups (44,5% of ObesityI, 62,7% of ObesityII and 61,3% of ObesityIII).

In all the items analised until now there was a directly proportional relation between frequencies and obesity level: as long as you increased the Obesity Level, the frequencies reported also increase.

The most reported item of Signs/Other Symptoms component was creaking for ObesityI (60,7%), ObesityIII (65,6) and Position Stifness for ObesityII (67,1%). Morning stiffness and deformity were the most reported by ObesityII volunteers (64,5% and 23,7% respectively), while swealling and knee extension were the most reported by ObesityIII volunteers (46,9% and 31,3% respectively).

Considering Biological Risk and analyzing female volunteers, 11,2% of ObesityI, 21,1% of ObesityII and 6,3% of ObesityIII were already going through menopause. According to age intervals, the majority of ObesityII volunteers (32,9% in the 50-59 years old interval) were older than the majority ObesityI volunteers (32,1% in the ≤39 years old interval) and ObesityIII volunteers (37,5% in the ≤39 years old interval).

Regarding to External Risk component, the prevalence of previous lower limb injury or surgery was higher in the ObesityII (51,3%) in comparison with ObesityI (43,4%) and ObesityIII (28,1%). The most reported work position in ObesityI was standing (46,4%), in Obesity II was sitting (63,2%) while in ObesityIII these were both items (56,3%). Considering Sports Volume, most of ObesityI (14,8%) and ObesityIII (9,4%) volunteers were in the 1-15 interval while ObesityII volunteers obtained the higher frequency in 1-15 and 30-44 interval (9,2% in both).

Considering ObesityII and ObesityIII as one group (Severe Obesity) T-test revealed significant differences ($p<0,01$) between ObesityI and Severe Obesity ($n=109$) for all components and KOPS Total Score except for External Risk.

Chapter 5: Discussion

This chapter presents the discussion according to the results organization.

5.1 General Discussion

This study was easy to idealize due to its relevance and avant-garde, but the first barrier occurred when the questionnaire was disseminated to obtain answers. The option of switching the questionnaire to the online format, despite the challenges it created and the hours of dedication it required, was in fact an asset for carrying out this study. Otherwise, it would have never been possible to obtain a sample so significant and from so many geographical points in the country so quickly and effectively.

It is also important to strengthen the idea that when studies turn into a digital format it increases the risk of incorrect or incompete answers and this study was no exception. 51,7% of excluded answers is a significative number but it is the price to pay for disclosuring the questionnaire for all country. Most of these answers corresponded to someone that opened the link for the questionnaire but didn’t answered or did answered but didn’t finish it.

In spite of this fact, sample size and the way in which its recruitment was made are two of the great strengths of this study. Most studies choose to carry out recruitment from health units and hospitals, running the possibility of biasing the results due to the fact that many times the disease is already diagnosed. Although some contacts have been established with hospitals for the spread of KOPS, most of the volunteers are derived from clients of nutritionists or personal trainers who are physically functioning at the outset and the significant majority of them without diagnosed disease. On the other hand, there are few cross-sectional studies in the literature with such a significant number of volunteers, especially considering the few resources available and the low cost of carrying out the study.

At the beginning of the study the main limitation of it has emerged: the fact that weight and height were auto reported, which may induce some bias in the BMI carachterization.

The BMI, being the goal-standard measure to identify obesity levels, is calculated as mass divided by height squared (measured in meters). BMI and obesity prevalence calculated from self reported weight and height may exhibit unpredictable types of bias. For example, just because mean BMI is similar does not mean that the prevalence of obesity will be similar. Thus, the net effect of misreporting on obesity prevalence may vary depending on the age and gender composition of the population and other characteristics related to misreporting. Patterns of misreporting of height and weight and their effects on BMI and obesity prevalence are complex (Flegal et al., 2019).

Maukonen and his colleagues reviewed studies published between 2006 and 2017 and revealed a tendency for underestimation of self-reported weight and overestimation of height compared with the measured values. These biases were evident for both genders. Furthermore, BMI derived from self-reported height and weight was underestimated and consequently, a clear tendency for underestimation of the prevalence of overweight and obesity was found. The bias tended to be greater for those in the higher BMI groups (Maukonen, Mannisto, & Tolonen, 2018). This review showed that people overestimated their height and underestimated their weight in a wide range of different populations compared to measured values. In particular, women and participants who were overweight or obese underestimated their weight, whereas men and participants in older age groups overestimated their height. Height overestimation among older age groups is common as people may report height that had been measured when they were younger and with increasing age people tend to become shorter due to changes in bone and muscle structures (Maukonen et al., 2018).

Once that BMI, being self-reported, appear to be underestimated, this will enhance our results once that they should be even lower than reality.

Doing this kind of investigations through epidemiologic studies it seems clear that researchers can assess the role and influence of risk factors, providing valuable information to aid policymaking in national health care systems.

5.2 Total Sample

Concerning to the representativeness of the present study, sample size (n=605) is similar to other studies in the literature (Demirag et al., 2017; Khan, Khan, Zehra, Azhar, & Fatima, 2020; Raud et al., 2020) and, for this reason, many different phenotypes of KOA must be present.

Regarding to age, the present study is also representative since the mean age of the Portuguese population is 45,2 years (PORDATA, 2019), which is very similar to the mean age of this study's total sample (46,1±13,8).

Portuguese population is characterized by 53% of women and 47% of man (PORDATA, 2019). This means that, comparing with our total sample gender distribution, this study has a major presence of female volunteers (63,5%). Knowing that there are significant correlations between female gender and KOA in females (Lu et al., 2019), this fact may contribute to increase KOPS Total Score. Nevertheless, it is importante to notice that only 11,9% of these females have entered menopause and, even though menopause and KOA are correlated (Mohan, 2001), it is a low prevalence that it's not expected to influence this studys results.

In Portugal, overall prevalence of obesity is 28.6% (Gaio et al., 2018). Due to the objectives of this study, a higher obesity prevalence was presented (46,6%).

All the items in Functional Pain had no significant frequencies differences, which shows the similar distribution these disorders have in Total Sample. However, it is well known in the literature that KOA is associated with self-reported impairment in physical function and the effect is mostly mediated by pain (Zambon et al., 2016).

Creaking was the most reported symptom by the volunteers, probably influenced by the ones who are obese. Using another questionnaire that not KOPS, some studies (Tamura, Cazzo, Chaim, & Piedade, 2017) showed the impact of obese pain and other symptoms compared with the mean values in Non-Obese individuals reported in a systematic review (N. J. Collins et al., 2016).

As a resource to obtain volunteers auto-report, questionnaires, are one of the possible techniques for measuring work physical demanding (R. C. P. Fernandes, Cunha, Lima, & Santos, 2019). Althought there are different methods to accomplish that goal, limits and advantages have been explored by many authors that point some challenges in their application (Gardner, Lombardi, Dale, Franzblau, & Evanoff, 2010; Jacobs, Berduszek, Dijkstra, & van der Sluis, 2017). Given this, in Total Sample stand and sitting were the most reported job postures, with frequencies far away from the values reported for squat (9,9%). This significative difference may cancel possible bias between reported job postures.

Althought some researchers (Cibere et al., 2010; Klussmann et al., 2010) have suggested that participation in select sports may increase the risk of KOA, given that most of the volunteers didn't practice any sport (61,4%) and 26,8% of the ones who did it report a sports volume between 1 and 29, it is possible to assume that this item does not contribute significantly to KOPS Total Score. This result comes along with the literature reporting that the percentage of the Portuguese population engaged in regular physical activity is among the lowest in the European Union (Baptista et al., 2012; Varo et al., 2003).

Although it is reported in the literature that being female seems to be a stronger predictor for KOA's presence than being male (Cho et al., 2011) this fact should not influence data due to the fact that KOA's prevalence is equal in both male and female (38,9%) and KOPS Total Score mean's for both genders are under the threshold (16).

5.3 KOPS Scores for Obese and Non-Obese

Regarding to Obesity Group, the KOA prevalence of 56,6% reported by this study is much higher than the 12,4% referred by the Reuma Census 2011-2013 (EpiReumaPT, 2013). It is important to notice that KOA prevalence in the Non-Obese group (23,6%) was also higher than the national prevalence, probably influenced by overweight volunteers.

In the projection of this study, this was another challenge that emerged: will overweight be enough to express the influence of BMI on KOA? Since it is easier for an individual to move from a "normal weight" classification to "overweight" than "normal weight" for "obesity" and, on the other hand, it is reported in the literature that the higher the BMI the greater the harmful effects on the knee joint (Reina et al., 2017), the option was obesity classification (BMI≥30) thus increasing the BMI amplitudes between the two groups.

The obesity prevalence obtained, when in comparison with a recent study in Brazil reporting 63,1% of KOA prevalence in morbidly-obese volunteers (Pacca, GC, Zorzi, Chaim, & JB, 2018), is lower but not significantly different. The main reasons of these differences are the purpose of this discussion. To accomplish this goal we will discuss each KOPS Component and their most relevant items comparing them with the literature.

Study findings demonstrated that obesity is associated with self-reported physical function limitations (Zambon et al., 2016), which comes along with the fact that

Functional Pain Items had always higher frequencies in the Obese group that in the Non-Obese group. These results are in line with other studies suggesting that clinical consequences of KOA are graded with individual's BMI classification in a dose-response relation (Raud et al., 2020). The biggest frequency difference in these components items occurs in stepping. Although it is the most reported item in both groups, there is a nearly 24% difference between them, which may indicate that obesity causes an intensification of the stepping pain as some studies already reported (Heo, Pietrobelli, Wang, Heymsfield, & Faith, 2010). The further question, for another analysis, is whether it is felt when climbing or coming down the stairs. Eitherway, we can assume that stepping was the main item responsible for the score differences of this component between groups.

Although Month and Year Pain Scores were always higher in the obese group and there were a statistically significant difference between them, it was a very low mean in both groups. Frequencies in the Obese group were much higher than in the Non-Obese, which is consistent with results from other studies (Alfieri, Silva, & Battistella, 2017), but that did not produced a much higher pain scale value. This result may suggest that knee pain associated with KOA was not intense but, in opposition, it is consistent. This ideia is strengthened by the results of Year Pain Component, where 50,8% of the obese and 31,5% of the Non-Obese answered “Yes”.

In the Signs/Other Symptoms component the biggest differences were both of the stiffness items. The Obese frequencies were much higher than the Non-Obese in the Morning Stifness and Position Stifness Items, although Creaking was the most reported in both groups. Considering the BMI classification differences between both groups, it is possible to assume that another variable may be contributing to the Creaking frequency and the real difference incremented by Obesity happens in Stifness (Morning and Position). This seems relatively unclear in the literature since some other studies with obese and non-obese volunteers shown greater differences in pain and disability

(Gomes-Neto et al., 2016) while others showed differences only in pain, but none in functionality and stiffness (Alfieri et al., 2017). Pain as we have seen is a complex multifactorial subject that is not totally understood on its causes and consequences yet.

In this Component the lowest frequencies were obtained in Deformity Item for both groups which may suggest that, whether KOA is present or not, the knee image or his degree of deformity is not a valuable way of evaluating KOA presence if it is used as a singular method.

Regarding Biological Risk, once that the majority of the Obese were younger (≤39 years old interval) than the majority of the Non-Obese (40-49 years old interval) and menopause frequencies were very similar in both groups (10,8% for Non-Obese and 13,2% for obese), it is possible to assume that the significant differences registed in this components score are mainly influenced by the BMI classification.

External Risk is the only component where Obese presented a lower mean than Non-Obese. Althought 43,8% of Obese reported a previous injury or surgery against the 24,5% of Non-Obese and all Obese frequencies in Job Posture items were higher than Non-Obese, the significant differences occured in Sports Volume. While 62,2% of the Obese and 39,9% of the Non-Obese didn't practice any sport, which contributes to a low obese frequency, 19,4% of the Non-Obese reported a sports volume ≥45. For the same sports volume, Obese were only 8,2% (less than a half). These results are in line with other studies and enhance the ideia of an inverse relationship between BMI classification and sports participation (Annesi & Gorjala, 2010).

All of this contributes to a higher Total Score mean of the Obese (18,3±9,3), which is above the KOPS threshold for KOA's presence (≥16), in comparison with the Non-Obese (12±7,1).

Spliting the Obese volunteers according to their KOPS Total Score allowed the understanding that all means components in the Obese≥16 were higher than the Obese<16 and had statistically significant differences.

The majority (78,5%) of the Obese≥16 reported step in Functional Pain soon followed by chair (69,2%) which definitely lead to assume that these are the main functional pains felt by the Obese with KOA.

Month and Year Pain had means much higher in the Obese≥16, but still less than 5 in a 1-10 scale. This fact reinforces the idea that Obese with KOA may express pain as a consistent/permanent one and not as as an intense one.

Obese≥16 reported high frequencies for both stiffness and creaking items but swelling also comes along with a high difference against Obese<16 frequency. Beyond the symptoms, swelling seemed to be the main sign that establish a difference between Obese with or without KOA.

Regarding Biological Risk, the main difference in the items was the menopause. While menoapause female volunteers in Obese<16 represented 6,8%, in the Obese≥16 they represented 18,6%. This fact may promote an increased bias and was definitely the major item contributing to statistically significant differences between both groups in this component.

External Risk component enabled the perception that there was a higher frequency of previous injury ou surgery in the Obese≥16 group (57%) in comparison with the Obese<16 (26,5%). This fact may expose a positive correlation between this item and KOA prevalence. It was also possible to acknowledge that this was the item that contributed the most for this component’s score (once that Job posture items showed sitting as the most prevalent in Obese≥16, but with no big differences in comparison with Obese<16) and Sports Volume frequency was the only item where Obese<16 was higher than Obese≥16.

Since KOA presents itself as a complex and multifactorial disease that sometimes acts silently and doesn't always behave the same way nor presents the same symptoms (it doesn't only unfold in elderly people), is of the utmost importance to try and understand KOA's correlation with its risk factors.

Age is a strong predictor of KOA's development (Felson et al., 1995). Considering the estimated median KOA's age diagnosis is 55 years (Losina et al., 2013), the fact that the mean age of the Obese volunteers was 47,8±12,99 and more than a half of them (51%) had less than 49 years may have influenced negatively the weak correlation presented between this risk factor and KOPS Total Score. In any case, it is essential to mention that the diagnosis of KOA at increasingly younger ages has been reported in science mainly throughout the last decade (Kao et al., 2016; E. Roos & Lohmander, 2009; Turkiewicz, Timpka, Thorlund, Ageberg, & Englund, 2017).

The appearance of KOA in individuals with obesity (diagnosed through BMI classification) and the relationship between these two conditions are well documented in the literature (Abbate et al., 2006; Blagojevic et al., 2010; Felson et al., 1988; Felson et al., 1997; Gelber et al., 1999; Grotle, Hagen, Natvig, Dahl, & Kvien, 2008a; Hart, Doyle, & Spector, 1999; Jarvholm, Lewold, Malchau, & Vingard, 2005; Lohmander, Gerhardsson de Verdier, Rollof, Nilsson, & Engstrom, 2009; Manninen, Riihimaki, Heliovaara, & Makela, 1996; Reijman et al., 2007). These studies enhance the relationship between high BMI and KOA over time, which supports that most them are longitudinal (follow-up of 10 or more years) and differentiates them from the design of this study (cross-sectional). This type of study design can explain the weak correlation obtained between these two variables.

Sports participation is another risk factor that may increase the risk of KOA (Cheng et al., 2000; Cibere et al., 2010; Cooper et al., 2000; Klussmann et al., 2010), but it is unclear whether this is due to the specific sport, a sport-related injury, or some other unknown factor. In an attempt to clarify these questions, Jeffrey and his colleagues found a high correlation between certain types of sports and the prevalence of KOA in a systematic review, but claimed that data related to the professionalism of this practice, as well as its duration (volume), are still lacking (Driban, Hootman, Sitler, Harris, & Cattano, 2017). These results come along with the weak correlation found in this study between sports volume and KOA, which may reinforce the ideia that this relationship is still not well enough characterized.

Regarding to KOA's prevalence, it gets higher from ObesityI to ObesityII but decreases to ObesityIII. These outcomes come along with the idea that KOA's prevalence increase with BMI when it concerns obese individuals (Hart & Spector, 1993). Despite this, KOA's prevalence decreases from ObesityII to ObesityIII, which may be explained by the differences in both group sizes. ObesityIII was composed by 32 volunteers, less than half of the 76 volunteers ObesityII group. Analyzing Score's means by Obesity Level it seems that there was a much significant difference between ObesityI and ObesityII than ObesityII and ObesityIII.

Analyzing Functionl Pain, several studies report obesity as having an important association with low levels of walking in people with or at high risk of KOA independent of knee pain (Felson et al., 1992; Strath, Holleman, Ronis, Swartz, & Richardson, 2008; White et al., 2012). This evidence was also present in these results since walking and standing were the items with the lowest frequencies in spite of the obesity level.

On the other hand, the fact that stepping was the most reported functional pain comes along with the study of Sanchez-Ramirez *et. al* from 2016 that, analyzing a stepping down task executed by volunteers with KOA, showed evidence of many muscules disabilities and a 32% pain prevalence. The frequencies from this study were higher than this on all obesity levels probably due to the mechanical obesity impact and the present inflammatory process.

From all the KOPS components analyzed, Biological Risk should probably be the one with more bias. Between the three items, BMI naturally influences the component score according to the obesity level but the other two items may be responsible for some differences between groups. Regarding age, most of the volunteers in ObesityI and ObesityIII were in the same interval (≤39) while most of the volunteers in ObesityII were in the 50-59 interval. In addition to this, ObesityIII presented a 90,6% prevalence of females against 55,6% and 63,2% in ObesityI and ObesityII, respectively. regarding females, while only 11,2% of ObesityI and 6,3% of ObesityIII were already in menopause, the same frequency in ObesityII was much higher (21,1%).

Being already exhaustively featured in the literature the relation between aging (Demehri & Shakoor, 2018; Magnusson, Kumm, Turkiewicz, & Englund, 2018; Takacs, Carpenter, Garland, & Hunt, 2013) and menopause (Mohan, 2001; Nadkar, Samant, Vaidya, & Borges, 1999; Song, Weng, Qiu, Yu, & Lin, 2002) in KOA's prevalence, these two items were clearly influencing these components score in ObesityII.

Regarding to Pain Month and Year components, this study reported higher frequencies in all Obesity grades than some studies in the literature. The study founded with higher pain prevalence in obese volunteers (n=141) was 63,1% (Thomazeau et al., 2014).

Althought in the literature some studies enhance the increased prevalence of stiffness, sewlling or pain as the Obesity level raises (Heo et al., 2010), the results from this study were different. It is possible to assume that positive relation from ObesityI to Obesity II since all the frequencies in Signs/Other Symptoms Items increased their prevalence, but that is not true from ObesityII to ObesityIII. That could be partially explained by the small number of volunteers with ObesityIII (n=32) in comparison with sample size of other two Obesity levels. Other studies with a bigger ObesityIII sample size should be enhanced.

In short, these study's results strengthened the idea that KOA is a multifactorial phenomenon. It is suggested that isolated risk factors are not directly related to the presence of KOA, but it leaves an open vacancy for the idea that the disease occurs when there is a synergistic, negative and progressive presence of these risk factors in obese individuals.

Chapter 6: Conclusions

This chapter presents the research findings wich could be concluded according to the results.

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6.1 Main research findings

This study was based on the premise that KOA and obesity are closely correlated and the higher the level of obesity (expressed through BMI) the greater the prevalence of KOA. This study provides very pertinent information regarding the assessment of the prevalence of KOA among Portuguese adults with obesity and also allows a characterization regarding which are the functional pains, signs and symptoms most present in everyday life of individuals and which naturally influence their QoL negatively.

Another relevant aspect in carrying out this study is that, at least to the best of our knowledge, this was the first time an assessment of the prevalence of KOA in obese individuals was done in Portugal regardless of whether the diagnosis already existed and using the criteria defined by EULAR. This alone is vital, because as widely cited in the literature there is an increasingly need to make early interventions to deal with this disease.

This study strengthens the idea that KOA is highly present in obesity regardless of the level but leaves open the possibility that the onset of the disease will appear more at levels 1 and 2 than at level 3.

The weak correlation obtained between the presence of KOA and each risk factor individually seems to support the idea that the disease is in fact complex and multi-factorial, and it is not entirely clear which of these symptoms and pains are really just symptoms or are in fact the cause of the disease.

6.2 Practical implications and future directions

In this section the practical findings derived from the present dissertation were summarized and their practical application to the real-world of professionals and scientists was considered.

As others studies this one concluded that obesity is significantly associated with KOA. Despite this, the significance to characterize the phenomenon of the relationship between these two diseases, not knowing exactly which of the two tend to appear first, still remains. Anyway, any physiologist can safely assume that if an individual has one of the diseases, it is a matter of time before he develops the other (if he does not already have it, just not yet diagnosed).

It is therefore of the utmost importance that professionals seek through their practices to improve the symptoms of both diseases simultaneously, almost as if we are talking about a syndrome, in order to enhance their results. Otherwise, without this holistic, integrated view, there will always be risk factors that are not being controlled.

Regarding other researchers who are dedicated to these themes, it would be pertinent to take care of the following questions:

- Increase the sample size of people with obesity, mainly obesityIII;
- Make experimental research, realizing if a non-pharmacological intervention through exercise improves scores;
- Analyze the previous injuries reported with a more detailed study;
- Include quality of life questions for participants;
- Perform functional aptitude tests.

The main limitations of the study were:

- The fact that most of the subjects were from Lisbon, which can be a limiting factor in the extrapolation of results to the general Portuguese population;
- The reduced number of volunteers with Obesity level III, which may cause differences and produce a highstandard deviation for some variables;
- The fact that weight an height were auto-reported, which may induce some bias in the body mass index (BMI) carachterization.

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Appendixes

Appendix 1: Knee Osteoarthritis Pre-Screening Questionnaire (KOPS)

Epidemiologia da Osteoartrose

PROJECTO PICO: Programa de Intervenção contra a Osteoartrose

INFORMAÇÕES GERAIS

Está a ser convidado(a) a participar no estudo de investigação científica que pretende caracterizar a prevalência da Osteoartrose (Artrose) na população portuguesa, bem como a identificação precoce de sintomas que possam indicar a existência desta patologia. Este estudo está a ser desenvolvido no âmbito do **Projeto PICO (Programa de Intervenção Contra a Osteoartrose).**

Neste sentido, solicitamos a sua colaboração no preenchimento deste questionário, com o objectivo de recolher o maior número de informações possíveis e deste modo dar o seu contributo neste estudo sobre a **Epidemiologia da Osteoartrose (Artrose) em Portugal.** A duração prevista de resposta ao questionário é cerca de 8-10 minutos.

1. A informação obtida neste questionário será anonimizada.
2. Os resultados serão apresentados de forma confidencial.
3. A participação no estudo é voluntária. É livre de abandonar o questionário em qualquer altura, sem qualquer penalidade e podendo ainda, se o desejar, recusar que os dados recolhidos sejam tratados e publicados.
4. Os questionários são aplicados por uma equipa de entrevistadores que depois remeterão todos os dados apenas para os investigadores e equipa associada ao Projeto PICO da Faculdade de Motricidade Humana (FMH).
5. **No caso de habitar na Grande Lisboa**, poderá no futuro ser convidado a participar gratuitamente num programa de exercício físico, na FMH, concebido para o tratamento da Osteoartrose.

Em caso de dúvida ou de necessidade de informações adicionais poderá contactar a equipa do **Projecto PICO** a partir do e-mail **fyazigi@fmh.ulisboa.pt sua colaboração é imprescindível para o aprofundamento do conhecimento nesta área. Obrigada pela disponibilidade!**

Flávia Yázigi (Responsável do Estudo)

CONSENTIMENTO INFORMADO

Declaro que li as informações no texto acima e que me foram explicados os objectivos deste questionário no qual sei que não sou obrigado(a) a preenchê-lo.

1. Sei que não é me devida qualquer compensação monetária pelo preenchimento deste questionário e que sou livre desistir do estudo a qualquer momento.
2. Declaro que são verdades as respostas dadas por mim neste questionário
3. Aceito que os resultados deste estudo possam ser divulgados ou publicados, mas o meu nome ou identidade não serão revelados sem a minha autorização. Os meus dados são confidenciais.

Nome completo:____

Data: ____ de _______ de 20____ Assinatura____________________________________

QUESTIONÁRIO

Cod:

Nome:____

Telefone: __________________ E-mail:__________________________________

Morada:____

Freguesia:_________________Concelho*:___________________________ Cod. Postal:_______-_________

Data de Nascimento*: _______/_______/_______ Sexo* F ☐ M ☐

Escolaridade*:_____________ Profissão atual ou a que se dedicou a maior parte da vida*:________________

Se for reformado(a), indique a idade com que se reformou*: _________ Estado Civil*:____________________

Se está na menopausa, indique a idade de início*:______ Altura*:________ cm Peso*: ________ Kg

Há quanto tempo tem este peso?* Há menos que 5 anos ☐ Entre 5-10 anos ☐ Há mais que 10 anos ☐ Não sei ☐

*Os campos assinalados são de preenchimento obrigatório; os campos referentes ao nome, contacto e morada são importantes no caso de pretender ser contactado para participação em programas de exercício ou educacional que possam vir a ser realizados.

1. Já alguma vez teve dor persistente ou repetitiva não associada a um traumatismo em alguma articulação?

☐ Não ☐ Sim

1.1. Se respondeu sim, assinale o(s) local(is) onde costuma sentir dor:

Coluna cervical (Pescoço)	☐	Ombro	☐	Anca	☐
Coluna dorsal (Costas)	☐	Cotovelo	☐	Joelho	☐
Coluna lombar	☐	Mão	☐	Tornozelo	☐

2. O seu médico já lhe diagnosticou Osteoartrose (Artrose)? ☐ Não ☐ Sim ☐ Não sei

2.1. Se respondeu sim, assinale com um "x" a(s) região(ões) que tem diagnóstico de Osteoartrose.

Coluna cervical (Pescoço)	☐	Ombro	☐	Anca	☐
Coluna dorsal (Costas)	☐	Cotovelo	☐	Joelho	☐
Coluna lombar	☐	Mão	☐	Tornozelo	☐

2.2. Se assinalou que tem <u>Osteoartrose no joelho</u>, indique há quantos anos:________

3. Já sofreu alguma fractura, intervenção cirúrgica ou lesão grave no(s) membro(s) inferior(es) que o obrigasse a afastar-se temporariamente das suas actividades diárias (trabalho, desporto, etc...)? ☐ Não ☐ Sim

3.1. Se respondeu sim, preencha o quadro com o tipo, membro lesionado e ano de ocorrência:

Tipo de lesão ou cirurgia nos membros inferiores	Membro	Ano
1º		
2º		

3.2. Se respondeu sim, refira durante quanto tempo esteve afastado das suas actividades diárias após a lesão reportada?

Tempo de afastamento	1ª Lesão	2ª Lesão
Menos do que 1 semana		
Mais do que 1 semana		
Mais do que 15 dias		
Mais do que 1 mês		
Mais do que 3 meses		

4. Exerce ou exerceu alguma(s) profissão(ões) em que permaneça muitas horas em pé, sentado ou agachado?

☐ Não ☐ Sim

4.1. Se sim, qual(is) ?____

Predominantemente em pé ☐ Predominantemente sentado ☐

Predominantemente agachado ☐ Todas as anteriores ☐

5. Pratica ou praticou algum(ns) desporto(s) regularmente (futebol, voleibol, ténis, natação, basquetebol, andebol, atletismo, ciclismo, hóquei, ginástica desportiva, corrida ou outro)? ☐ Não ☐ Sim

5.1. Se sim, preencha o quadro com o desporto que praticou:

Desporto	**Anos de prática**	**Frequência semanal (média)**	**Foi federado?**

6. Costuma sentir dor no Joelho? ☐ Não ☐ Sim ☐ Às vezes

6.1. Se respondeu sim na questão 6, assinale qual (is) o(s) joelho(s) em que sentiu ou sente mais dor?

☐ Direito ☐ Esquerdo ☐ Ambos

6.2. Se respondeu sim na questão 6, escolha uma ou mais afirmações que melhor represente o caso dos seus joelhos:

☐ Durante o último ano teve mais de três episódios de dor. Considera-se "episódio de dor" a situação de dor intensa que pode durar horas ou dias, desaparecendo depois completamente (marque um "X" sobre o número que corresponde a máxima intensidade da dor que sentiu).

Sem Dor | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | **Dor Máxima**

☐ Durante os últimos seis meses pelo menos uma vez a dor durou mais que uma semana.

☐ Durante o último mês teve dor (marque um "X" sobre o número que corresponda a máxima intensidade da dor que sentiu).

Sem Dor | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | **Dor Máxima**

7. Sentiu no último mês, dor no(s) joelho(s) em alguma destas situações? (Assinale com "x" a intensidade da dor)

7.1. Ao caminhar ☐ Não ☐ Sim Sem Dor | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Dor Máxima

7.2. Ao subir/descer escadas ou rampas? ☐ Não ☐ Sim Sem Dor | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Dor Máxima

7.3. Ao levantar-se da cadeira? ☐ Não ☐ Sim Sem Dor | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Dor Máxima

7.4. Ao manter-se de pé? ☐ Não ☐ Sim Sem Dor | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Dor Máxima

8. Sente dificuldade em realizar alguma(s) das tarefas abaixo citadas? ☐ Não ☐ Sim

8.1. Se sim, assinale aqueles que mais sente dificuldade em realizar:

Caminhar ☐ Levantar-se ☐ Subir/Descer escada ☐ Manter-se de pé ☐

9. Rigidez é uma sensação de dificuldade em iniciar o movimento (sensação de articulação presa). Sentiu no último mês, rigidez no(s) joelho(s) de manhã ao acordar com duração inferior a 30 minutos?

☐ Não ☐ Sim ☐ Às vezes

10. Sentiu no último mês, rigidez no(s) joelho(s) depois de estar muito tempo sentado(a) ou em pé?

☐ Não ☐ Sim ☐ Às vezes

11. Teve no último mês, o(s) joelho(s) inchado(s) ?

☐ Não ☐ Sim ☐ Às vezes

12. No último mês sentiu ou ouviu o(s) seu(s) joelho(s) ranger, crepitar (pequenos ressaltos) ou a fazer estalos quando se movimenta ou se dobra? ☐ Não ☐ Sim ☐ Às vezes

13. Consegue fazer a extensão completa do(s) seu(s)joelho(s) (mantê-los esticados quando está deitado ou sentado sem apoio)? ☐ Não ☐ Sim ☐ Às vezes

14. Considera-se um joelho deformado quando este apresenta uma alteração no seu aspecto (formato diferente do normal que não deve ser confundido com inchaço temporário).
Tem algum dos joelhos deformado? ☐ Não ☐ Sim ☐ Não sei

14.1. Se sim, qual(is)? ☐ Direito ☐ Esquerdo

SE RESPONDEU SIM EM ALGUMA DAS QUESTÕES SOBRE SINTOMAS NO SEU JOELHO(6-14), RESPONDA AS QUESTÕES 15-16; SE RESPONDEU NÃO, SALTE PARA A QUESTÃO 17.

15. No último ano procurou o médico por causa desses sintomas acima referidos (dor, rigidez ou inchaço) tendo-lhe sido prescritos exames ou tratamento? ☐ Não ☐ Sim

16. Está a tomar algum medicamento para o alívio da dor no(s) seu(s) joelho(s)? ☐ Não ☐ Sim

16.1. Se sim, qual? ☐ Anti-inflamatório ☐ Analgésico ☐ Outro ☐ Não sei

Dor Máxima

Devido ao seu problema no(s) joelho(s) utiliza algum equipamento para o auxílio da marcha? ☐ Não ☐ Sim

16.2. Se sim, qual? Canadiana ☐ Bengala ☐ Andarilho ☐ Outro ☐

17. Está a frequentar algum programa de exercício (ginástica, hidroginástica, manutenção, musculação, etc.)?

☐ Não ☐ Sim Se sim, qual? _________________ Quantas vezes por semana?_______

Appendix 2: KOPS Validation

International Journal of Rheumatic Diseases

DEVELOPMENT OF THE KNEE OA PRE SCREENING QUESTIONNAIRE (KOPS)

For Review Only

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Abstract
Self-report questionnaires are still considered to be a useful instrument for disease screening and for epidemiological studies. Few questionnaires have been developed for the purpose of screening for knee osteoarthritis (KOA). **AIM:** The aim of this study was to develop a KOA screening tool that is useful for health and exercise professionals who do not have access to advanced and costly diagnostic instruments. **METHODS:** This study comprised five steps: content validity, reliability, criterion validity, construct validity and responsiveness. Internal consistency was verified using Cronbach's alpha and the Intraclass Correlation Coefficient (ICC). Reproducibility was analyzed using the ICC (one week). Criterion validity was assessed by comparing the KOPS score *with the* SF-12, the Knee Injury and Osteoarthritis Outcome Scores questionnaire and the 6MWT. Construct validity was verified using the ROC curve (ACR clinical criteria and x-ray). Responsiveness was analyzed over 3 months of an aquatic exercise program using the pooled effect size. **RESULTS:** The overall KOPS score yielded a Cronbach's alpha of 0.747 and an ICC of 0.646. KOPS was considered reproducible (ICC: 0.895-0.992; Cronbach's alpha: 0.894-0.979). The ROC curve revealed a sensitivity of 86.96 and a specificity of 75.82. The KOPS demonstrated medium responsiveness in terms of the total score and the pain and symptoms components. **CONCLUSION:** The KOPS questionnaire is valid for the purposes for which it was created, and its translation into English should be considered.

KEYWORDS: questionnaire; construction; validation; knee; osteoarthritis; screening; KOA

1. Introduction

Knee osteoarthritis (KOA) is one of the most important public health problems in many countries[1, 2]. The situation in Portugal is similar, where the prevalence of KOA is 11.1 % (CI 95%: 9.4-13.1)[3], and it is expected that this value will increase because of the ageing of the population[4] and the rise of obesity[5]. Because of this situation, it is necessary to diagnose the condition in the early stages to manage the main symptoms and avoid disease progression.

The American College of Rheumatology (ACR) established 3 levels of diagnostic criteria for KOA: clinical only (92% sensitivity; 75% specificity), clinical and radiological (95% sensitivity; 69% specificity) or clinical and laboratorial (91% sensitivity; 86% specificity)[6]. Considering financial constraints, the clinical criteria are the most viable option for primary care.

According to the ACR clinical criteria, the KOA diagnosis should be based on the presence of knee pain in combination with at least three of the following variables: age>50, short-lived morning stiffness (<30 min), crepitus, tenderness, bony enlargement and no palpable warmth[6]. The more recent recommendations from the European League Against Rheumatism (EULAR) for clinically diagnosing KOA are based on three symptoms (persistent knee pain, morning stiffness and functional impairment) and three clinical signs (crepitus, restricted movement and bony enlargement)[7].

Laboratory and imaging methods are costly, and their associations with symptoms are not clear, particularly in the initial stages (pre-radiographic KOA, Kellgren-Lawrence radiographic grade 1)[8]. Although x-rays only provide a bone overview, the K-L severity index is considered a useful method for KOA detection in epidemiological studies[9]. Magnetic resonance imaging (MRI) is a sensitive tool that can identify joint components and some cartilage degeneration in the early stages[10, 11], but it is a very expensive technique and more studies are necessary to verify which MRI findings in early OA are clinically important[12].

For public health purposes, it is necessary to improve diagnostic instruments so that interventions can occur in earlier stages. For this purpose, self-report questionnaires are still considered a valid and accessible method for KOA screening, mainly in clinical, epidemiological and exercise field.

The available KOA-related questionnaires can be organized into two groups: patient outcomes and screening instruments. The first group includes questionnaires related to patient outcomes (functionality, signs, symptoms and quality of life)[13-18]; the Western Ontario and McMaster Universities Arthritis Index (WOMAC)[13] and the Knee Injury and Osteoarthritis Outcome Score (KOOS)[15, 19] are widely used.

The WOMAC has been validated with three types of scales: visual analog[13], Likert[13] and a numerical rating scale (NRS)[20]. The NRS allows an immediate evaluation and can be used on the phone or with a computerized touch screen (pain: ICC = 0.915, rho = 0.88; stiffness: ICC = 0.745, rho = 0.77, function: ICC = 0.940, rho = 0.87).

The KOOS is considered an extension of the WOMAC domains and is a specific instrument developed to assess patients' perceptions about their knees, their functional status and their knee-related quality of life. The KOOS was validated with a sample of 21 participants with Anterior Cruciate Ligament (ACL) injuries. Its test-retest reliability after a 9-day interval showed an ICC of 0.75 for the Daily Living subscale (ADL), 0.81 for the Sport and Recreation subscale (Sport/Rec), 0.86 for the knee-related Quality Of Life subscale (QOL), 0.85 for the Pain subscale and 0.93 for the Others Symptoms subscale[15]. The KOOS's responsiveness over 6 months was verified by assessing the effect size (QOL = 1.65; Pain = 0.84; ADL = 0.94; Symptoms = 0.87 and Sport/Recreation = 1.16)[15]. The construct validity of the KOOS was assessed in comparison to the SF-36 questionnaire[19].

Regarding the second group, there are few questionnaires related to KOA screening, possibly because the risk factors associated with KOA incidence and progression are still under discussion. In addition, failures in the validation and reliability assessment processes have prevented the development of good questionnaires [21]. In the following paragraphs, we present the main KOA-screening questionnaires that have been previously published.

The Knee and Hip Osteoarthritis Screening Questionnaire (KHOA-SQ) [22] includes 11 questions for KOA screening and different dimensions that evaluate pain, other symptoms and functionality, but it does not include risk factors in the total score, which may be one of the causes of the high false-positive rate. The validation process included 7,577 older adults (60-90 yrs) and revealed high sensitivity (94.5%) and moderate specificity (43.8%).

The Community-Oriented Program for the Control of Rheumatic Diseases (COPCORD) created the APLAR-COPCORD English questionnaire, a tool for risk factor identification[23]. Although it was used in Asia, only its content validity and reliability were checked. In addition, the authors suggested improving some items, the questionnaire shortness and performing trans-cultural validation.

The Thai Knee Osteoarthritis Screening Questionnaire (Thai-KOA-SQ)[24] addresses three factors that are associated with KOA: knee pain, age and body mass index (BMI). Although this questionnaire showed 79.2% sensitivity, 78.4% specificity and 85.1% for the area under the ROC curve (AUC), other risk factors and symptoms should be considered to guarantee that the instrument works in different populations and KOA stages.

The analyses of the existing KOA-related questionnaires reinforce the idea that, for a pre-screening questionnaire to have a consistent association with KOA, scores should include multidisciplinary factors such as the presence of signs and symptoms, physical function and risk factors. Considering that established KOA is an incurable condition, the identification of modifiable risk factors is essential to prevent incidence and progression of the disease.

The literature identifies the following risk factors as important conditions for KOA screening: external risk factors such as past sports participation, injuries, surgical interventions in the lower limbs, occupation, physical demands and lower limb strength and biological risk factors such as BMI, menopause and gender[2, 8, 11, 12, 22-25]. Among these risk factors, only BMI and strength are modifiable with lifestyle changes.

In the predictive models presented by Zhang et al. (2011)[25], age, sex, BMI, occupation, family, and knee injuries were risk factors related to KOA incidence (AUC of ROC curve ranged from 0.55 to 0.81), and age, sex, knee injuries and sports were the risk factors related to KOA progression (AUC of ROC curve ranged from 0.45-0.82).

With regard to self-reported questionnaires, it is important to verify that they are user-friendly. Therefore, they should not be too long and should not have too many issues that may not be easily understood. In addition, the questions should be simple and clear: participants should be able to answer the questions without the assistance of a specialist or expert.

The aim of this study was to develop a KOA instrument that is useful for KOA screening and for health and exercise professionals so that imaging and other expensive resources are not needed. Thus, the specific objectives of this study were to develop a KOA screening questionnaire, to create consensus criteria for early KOA diagnosis and to develop a scoring system for accurate KOA diagnosis.

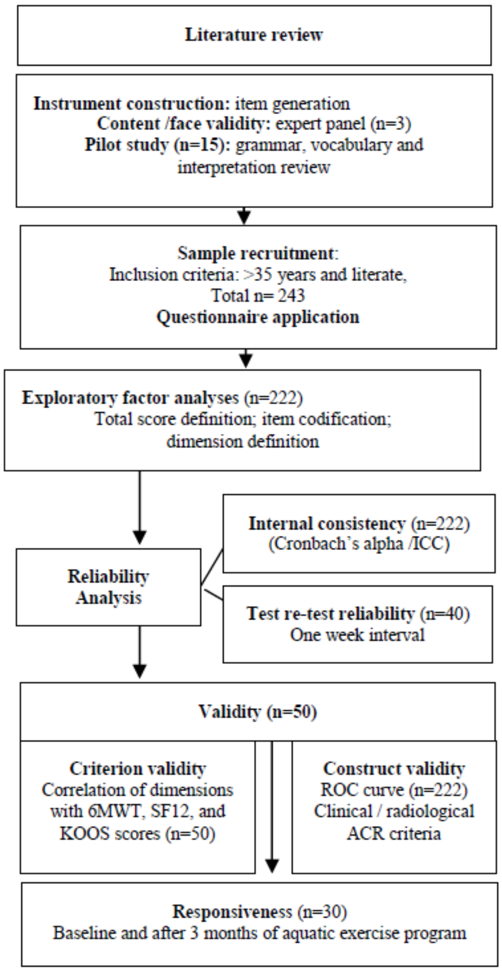
2. Study design and setting

This study comprised five phases: content validity, reliability, criterion validity, construct validity and responsiveness: content validity, reliability (internal consistency and reproducibility), criterion validity, construct validity and responsiveness (Fig 1). The study is part of the PICO project (Intervention Program Against Osteoarthritis, Clinical Trial Registration: NCT01832545), which was approved by the Ethical Committee of the Faculty of Human Kinetics at the University of Lisbon and was already published[26].

2.1. Sample

The subjects were recruited through newspaper announcements and community centers. To detect KOA in progress (KL ≥1 grade)[25], the inclusion criteria were an age ≥ 35 years and the ability to read and write. Although the ACR clinical criteria for the KOA diagnosis include an age limit of ≥50 years old, because of the increase in other risk factors, such as obesity, recent studies have reported KOA at early ages[7, 27]. Thus, the age inclusion criterion of ≥35 years was established to guarantee the ability of the KOPS to detect KOA in a broader age group.

The exclusion criterion was any cognitive/mental impairment that could compromise the understanding of the questionnaire or the quality of self-reported information. A total of 243 volunteers signed the informed consent form and were included in different phases of the validation process.



Abbreviations: ICC = Intra Class Coefficient; KOOS = knee injury and osteoarthritis outcome score; SF12= Health Survey; 6MWT= six minutes walking test

Fig 1. Flow chart of the KOPS construction and validation process

2.2. Procedures and statistical analyses

Instrument development and content validity

The KOPS development and item selection followed a structured process which was supported by an exhaustive literature review, the ACR and EULAR criteria for KOA [6, 7], the validation process for published screening questionnaires[22-24] and the analyses of the WOMAC[13] and the KOOS[15]. The items selection was critically defined by panel of experts, namely two rheumatologists, one physiotherapist, one epidemiologist and one sports science specialist.

So, the first version of the questionnaire included demographics and 13 questions organized into three sections: risk factors (female sex, age, body mass index, lower limb injuries, sports activity and working posture), signs and symptoms (stiffness, crepitus, restricted movement, pain and deformity) and physical function. During this phase, two similar questions about pain intensity were included to determine which pain scale was more accurate: one scale was the 0–10 pain intensity (NRS), and the other was the visual analogue scale (VAS).

This version was tested by performing a pilot study with 15 participants and by consulting the mentioned expert panel. Self-reported answers were confirmed in an interview to verify the Portuguese grammar and semantics, to check the clarity and relevance of the questions, to assure that all essential concepts were included correctly and to guarantee that all of the items related to the objectives were appropriate and comprehensible.

Once the final version was produced, the load for each item was determined to construct a total score to measure the latent variable. To avoid an overload of some items, the discrete variables (age, BMI and the amount of years in sports) were transformed into ordinal variables. Age (years) was categorized into seven intervals ($\leq 39 = 0$; 40-49 = 1; 50-59 = 2; 60-69 = 3; 70-79 = 4; 80-89 = 5; $\geq 90 = 6$); BMI was categorized into 6 intervals (underweight = 1; healthy = 2; overweight = 3; grade 1 obesity = 4; grade 2 obesity = 5 and grade 3 obesity = 6)[28]; and sports volume (years X weekly frequency of sports activity) was categorized into 7 intervals (0 = no sports; 1 = 1-15; 2 = 16-29; 3 = 30-44; 4 = 45-59; 5 = 60-74; 6 = 75-89; $7 \geq 90$ points).

An exploratory factor analysis was used to verify the item-content agreement[29]. The sampling adequacy for factorial analyses was verified using the Kaiser-Meyer-Olkin test (KMO) [30], and sphericity was determined using Bartlett's test[31]. A principal component analysis with varimax rotation was used.

Reliability and validity

The reliability of the KOPS was verified by assessing the internal consistency (IC) (n= 222) with two techniques:

a) Cronbach's alpha coefficient. Reliability is considered acceptable for group comparisons when Cronbach's alpha exceeds 0.8 [32]. Item-total correlations were applied between item scores and the total KOPS score, and correlations ≤ 0.4 were rejected [33].

b) The Intraclass Correlation Coefficient (ICC) was used to measure inter-rater reliability. When the correlations were ≥ 0.90, items were considered redundant and were removed from the questionnaire[32, 34].

Reproducibility

Reproducibility was verified in a test-retest study in which 40 individuals completed the questionnaire at two moments within a one-week interval. The reproducibility of the total KOPS score and the six components were compared by calculating the ICC[35].

Criteria and construct validity

The convergent criterion validity was assessed by comparing the KOPS components' scores with the SF-12v2 Health Survey [Mental Component (MCS) and Physical Component (PCS) scores] 36 and the KOOS questionnaire15. In addition, Spearman's Coefficient (Rho) was used to analyze the correlation between the KOPS and the 6MWT37. Fifty participants were included in this process.

For construct validity, the sensitivity and specificity of the KOPS were verified by assessing the ROC curve. The following questions were analyzed: (1) Do the participants who self-reported a high score potentially have knee OA? (2) Is the KOPS a good instrument for diagnosing KOA? (3) Is there a cut-off KOPS score that indicates the presence of KOA?

For this study, 222 individuals (69 with clinical and radiological diagnosis of KOA) were recruited across the PICO project[26]. The KOPS scores were compared with the ACR clinical and radiological diagnosis[6]. In addition, the ROC curve was used to find the cut-off KOPS score with the best sensitivity and specificity for diagnosing KOA. The confidence interval for the AUC was established at 95% [38].

Responsiveness

Even though the KOPS questionnaire was created to be a screening instrument, its responsiveness was analyzed to verify whether it could be used for longitudinal studies.

The capacity to detect clinically important changes over 3 months of the aquatic Intervention Program Against Osteoarthritis (PICO) was analyzed by determining the pooled effect size (ES), Cohen's d. The KOPS scores of 30 obese patients with KOA were compared. The significance level was set at $P < 0.05$[39].

The data analysis was carried out using the statistical program IBM SPSS Statistics 21, and the Receiver Operating Characteristic (ROC) curve analysis and ES analysis were performed using Med Calc software.

3. Results

The sociodemographic characteristics and working conditions of the participants who were included in the validation process are shown in Table 1.

Table 1. Sample characteristics at different phases of the validation process.

Variables	Content validity (n=222) mean(SD);median	Reliability (n=40) mean(SD);median	Construct validity (n=50) mean(SD);median
Age (yrs)	53.3(11.6); 53.5	52.1(8.7); 50.5	55.4(6.1); 56
Body Mass (Kg)	79.3(17.6); 79	68.6(15.4); 65	91.4(13.4); 91
Height (m)	1.63(0.09); 1.62	1.61(0.08); 1.60	1.60(0.1); 1.60
BMI (Kg/m^2)	29.7(6.1); 29.2	26.5(5.5); 24.6	35.6(5.1); 33.4
	n (%)	*n* (%)	*n* (%)
Sex			
Female	167 (75.2)	33 (82.5)	35(71.4)
Male	55(24.8)	7(17.5)	14(28.6)
Age Group (years)			
≤39	36 (16.2)	1 (2.5)	0
40-49	72(32.4)	17(42.5)	9(18.4)
50-59	62(27.9)	16(40)	26(52.0)
60-69	34 (15.3)	5 (12.5)	15(30.0)
>69	18 (8.1)	1(2.5)	0
Job Posture			
Standing position	105(57.1)	16(45.7)	44(89.8)
Sitting position	108(58.7)	21(60)	30(68.2)
Squatting position	40(21.7)	1(2.9)	6(13.6)
Educational Level			
Reading/writing	2(0.9)	0	0
Elementary school	31(14.0)	6(15.8)	6(12.0)
High school grade 9-12	34(15.4)	4(10.5)	8(16.0)
High school graduate	53(24.0)	10(26.3)	13(26.0)
College	101(45.7)	18(47.4)	23(46.0)

Abbreviations: BMI =body mass index; SD = standard deviation

KOPS characterization

After the pilot study, the main changes adopted in the instrument were as follows: 1) introduction of a new risk factor: Sports Volume; 2) separation of the stiffness question in two questions: morning stiffness and position stiffness; 3) development of a filter to organize the order of the questions and facilitate understanding; and 4) removal of the Likert scales associated with stiffness, creaking, swelling and functional limitations because the experts concluded that this information was more important for assessing functional status than for identifying KOA. In the response options, the term "sometimes" was included to facilitate the respondent's task (for codification, it was counted as a "yes"). For the knee pain questions, the NRS was maintained to obtain additional information about pain intensity, which is considered the main symptom and a cause of lower levels of physical activity.

The final version of the KOPS was a self-report questionnaire composed of closed-ended questions with nominal and ordinal response options. The first part includes sociodemographic information, the second part has risk factor information, the third part is about signs and symptoms and the last part has additional information related to mobility, exercise and clinical supervision. The KOPS takes approximately 9±4 minutes to fill out.

3.1. Factorial Analyses

A total of 10 items were eliminated because they did not contribute to a simple factor structure and failed to meet the minimum criterion of having a primary factor loading of 0.4 or higher[29]. The KMO measure of sampling adequacy was good (0.774, above the commonly recommended value of 0.6)[30]. Bartlett's test of sphericity was significant (χ^2 (153) = 492.84, $P < 0.001$).

Factorial analyses were performed for 3, 4, 5, 6 and 7 components. The best loadings were found for 6 components organized in two dimensions: symptoms (49.1% of variance) and risk factors (18.5% of variance). The factor-loading matrix for this final solution is presented in Table 2.

Table 2. Confirmatory factor analyses: Components' loading for rotated component matrix.

	Dimensions	
Components	**Symptoms**	**Risk factors**
Pain on function	0.849	0.095
Signs/others symptoms	0.817	0.065
Pain intensity (last month)	0.861	0.002
Pain intensity (last year)	0.857	0.011
Biological risk	0.274	0.671
External risk	0.174	0.816
% of variance explained	49.10	18.50

How is the KOPS scored? (Table 3)

The maximum value that could be scored on the KOPS is 54; as the value increases from zero, there is a greater possibility of having knee OA.

Functional pain and the Signs and Other symptom components were scored from 0-1, with one representing a positive answer; both pain components were scored from 0-10.

In the biological risk component, age was scored from 0-6, menopause was scored from 0-1 (with one representing being in menopause) and BMI was scored from 0-6. Finally, the external risk component, lower body injury and job posture were scored from 0-1, and sports volume was scored from 0-7.

Table 3. Dimensions, components, items and maximal scores of the KOPS questionnaire.

Dimensions (2)	Components (6)	Items (18)	Score
Symptom	Functional Pain (FP)		4
		Walking pain	1
		Standing position	1
		Stepping pain	1
		Chair pain	1
	Pain intensity - month (MP)	Last month	10
	Pain intensity-year (YP)	Last year	10
	Signs/others symptoms (SOS)		6
		Morning stiffness	1
		Position stiffness	1
		Swelling	1
		Creaking	1
		Knee extension	1
		Deformity	1
Risk factors	Biological risk (BR)		13
		Age interval	6
		Menopause	1
		BMI classification	6
	External risk (ER)		11
		Lower limb injury	1
		Job posture: stand position	1
		Job posture: sitting position	1
		Job posture: squat position	1
		Sports volume	7
KOPS total score			**54**

3.2. Reliability

The mean KOPS score for the 222 participants in the reliability study was 16.2, ranging from 4-38. The descriptive statistics (mean; SD) for each component were as follows: Functional Pain (1.4; 1.5), Pain intensity/month (2.2; 3.0), Pain Intensity/year (3.0; 3.1), Signs/other symptoms (2.0; 1.8), Biological risk (2.2; 1.7) and External risk (2.2; 1.7).

The internal consistency (IC) analysis revealed acceptable reliability of the KOPS score with a Cronbach's alpha of 0.747 and a satisfactory ICC (an average of 0.646). The reproducibility results are expressed in Table 4. The results for the test-retest over a one-week interval for each component ranged from 0.895-0.992 for the ICC and from 0.894 to 0.979 for Cronbach's alpha.

Table 4. ICC and Cronbach's alpha for reproducibility analyses of each component

Components	**ICC**	**Cronbach's Alpha**
Functional pain	0.895	0.894
Pain last month	0.967	0.970
Pain last year	0.965	0.970
Signs/other symptoms	0.925	0.923
Biological risk	0.992	0.992
External risk	0.904	0.903
KOPS total score	**0.977**	**0.979**

3.3. Criteria and construct validity

The associations between the KOPS score and the KOOS, the SF-12 and the results from the 6MWT were investigated by calculating the Spearman Coefficient (Table 5). The total KOPS score showed a moderate negative correlation with the SF-12 PCS (r =-0.443; *P* = 0.001) and all of the KOOS dimensions except KOOS Pain, which had a strong association (r = - 0.717; *P* = 0.000). The SF-12 MCS did not show a significant correlation with KOPS. Among the risk factors, only the biological risk component showed a significant association with the gold standard instruments (i.e., the 6MWT and the SF12 PCS).

Table 5. Spearman's correlation coefficients (KOPS is 0–54 points, best to worst; SF-12 is 0–100 points, worst to best; KOOS is 0-100 points, worst to best).

KOPS Components	SF-12 PCS	SF-12 MCS	6MWT	KOOS Pain	KOOS Symptoms	KOOS ADL	KOOS Sport/Rec	KOOS QOL
KOPS signs/ other symptom	-0.201	-0.247	-0.488 [b]	-0.564 [b]	-0.617 [b]	-0.413 [a]	-0.344 [a]	-0.295 [a]
KOPS biological risk	-0.417 [a]	-0.030	-0.423 [a]	-0.163	-0.242	-0.301 [a]	-0.048	-0.157
KOPS external risk	0.140	-0.208	0.157	-0.108	-0.144	0.040	-0.084	-0.255
KOPS month pain	-0.457 [b]	-0.125	-0.284 [a]	-0.623 [b]	-0.505 [b]	-0.363 [a]	-0.470 [b]	-0.605 [b]
KOPS year pain	-0.381 [a]	-0.190	-0.380 [a]	-0.633 [b]	-0.481 [b]	-0.368 [a]	-0.466 [b]	-0.597 [b]
KOPS functional pain	-0.413 [a]	-0.020	-0.109	-0.310 [a]	-0.321 [a]	-0.272	-0.293 [a]	-0.390 [a]
KOPS Total	-0.443 [a]	-0.239	-0.415 [a]	-0.717 [b]	-0.615 [b]	-0.454 [b]	-0.500 [b]	-0.662 [b]

Abbreviations: 6MWT, six-minute walking test; PCS, physical component score; MCS, mental component score.

a level of significance p <0.05.
b level of significance p <0.001.

An ROC curve analysis was performed to evaluate the sensitivity and the specificity of the KOPS in comparison with ACR clinical and radiological criteria for KOA diagnosis. The ROC curve revealed a KOPS score of 16 with sensitivity of 86.96, specificity of 75.82 and an AUC of 0.880 ($P < 0.001$).

3.4. Responsiveness

In general, the pooled ES (Cohen's *d*) demonstrated the ability of the KOPS to detect changes after 3 months of an aquatic exercise program for 30 obese adults with KOA. Better ES were observed for the total score ($d = 0.349$) and for 3 components: signs/other symptoms ($d = 0.483$), knee pain in the past month ($d = 0.657$) and functional pain ($d = 0.318$). Less responsiveness was found for biological and external risk components ($d = 0.076$ and $d = 0.000$, respectively) and for knee pain in the past year ($d = 0.174$).

4. Discussion

The major strength of our study was that we designed a KOA screening questionnaire with a complete validation process, including assessments of reproducibility and responsiveness, two important steps that are sometimes not completed because they require more complex procedures.

KOPS was developed for use in KOA screening situations before radiologic diagnostic tests. The KOPS proved to be user-friendly and quick to complete. Furthermore, it did not require specialist supervision, unlike APLAR-COPCORD English questionnaire[23],, which will facilitate its use by exercise instructors, physicians, nurses and other professionals.

In contrast with the KHOA-SQ validation[22], the KOPS has more questions (24 vs 11), but it is more inclusive and applicable to a larger age group (≥35 yrs). It also includes a risk factor dimension, which is an important aspect. Although the sample size for the validation process was smaller than for the KHOA (222 vs 7577), the KOPS had a sample with diverse characteristics, thus supporting the use of the KOPS in different populations.

In comparison with other questionnaires[13, 15, 23, 24], the KOPS is innovative because it includes KOA risk factors in the total score, which may explain the good validity and reliability results obtained in the present study. The factorial analyses revealed a good balance among the loads of the components, and both dimensions explained 67.6% of the variance, which is close to the desired variance in this type of validation process (70%). The ICC and Cronbach's alpha (0.646 and 0.747, respectively) values were comparable to the values obtained in the validation of the KOOS and the WOMAC, two reputable questionnaires.

The questionnaire showed good reproducibility. The high ICC values shown in Table 4 were expected for all signs, symptoms and risk factors except for components related to pain, which typically show greater variability in self-reported conditions. These results can be explained because the questions about other symptoms referred to the last month and the year before, which does not allow for substantial variation in a week. It is important to note that most of the risk factors included in the KOPS items are not modifiable factors.

In comparison with the pre-defined gold standard (KOOS, SF12 and the functional test (6MWT), the KOPS demonstrated good criterion validity. Higher correlations were found between the total KOPS score and the KOOS than between the KOPS and the SF12, mainly for pain, other symptoms and quality of life. These results could be explained by the fact that the KOOS is a specific tool for KOA, whereas the SF12 involves general physical and mental health outcomes. As in the KOOS validation, (when compared with the SF-36), better associations was found between the KOPS and the SF-12 physical component than the mental component. The lower correlation between external risk on the KOPS and the SF12- PCS was expected because they are independent variables: sports participation, surgery and jobs performed in the past might not have any direct relationship with physical function in the present. In addition, our data indicate that the biological risk factors for KOA (BMI and age) are inversely associated with the SF-12 physical function component.

Regarding the ability of the KOPS to assess physical function related to KOA symptoms, beyond the comparison with the SF12, the 6MWT was chosen because it is a valid and direct measure that provides a real asset for assessing the convergent validity of the KOPS. An inverse correlation ranging from 0.4 to 0.5 ($P < 0.05$) was found when the results of the 6MWT were compared with the KOPS total score, with signs/others symptoms and biological risk components. The two first correlations were expected because KOA symptoms compromise the ability to walk. The correlation between 6MWT and biological risk factors is interesting and can be explained by BMI and age.

One advantage of this study is that it was possible to verify the construct validity by comparing the KOPS score with the radiological diagnosis only and with the ACR's clinical and radiological criteria for KOA. Although there is much discussion in the medical community about what is considered the gold standard, the ACR criteria still provide a conservative and valid reference. Therefore, the hypothesis formulated in this process was confirmed: both areas under the ROC curve were above 0.850, higher than the predictive models presented by Zhang et al. (2011)[25] and similar to the AUC for the Thai-HOA-SQ[24]. Regarding sensitivity and specificity, the KOPS values for clinical and radiological diagnosis had a higher sensitivity and slightly lower specificity compared to the Thai-KOA-SQ (79.2%; 78.4%), a lower sensitivity (87.0 vs 94.5%) and a much higher specificity (75.8 vs 43.8%) in comparison with the KHOA-SQ. The lower sensitivity could be related to the smaller sample size in our study. These results clearly show that the total KOPS score can distinguish individuals with KOA from others without KOA, indicating that this instrument has valid constructs.

The suggested threshold value with the highest specificity/sensitivity is 16, which means that participants with a KOPS score ≥16 had a greater probability of KOA, the latent variable. The inclusion of risk factors, according to the EULAR recommendations[7], might have contributed to the strong specificity for detecting the presence of KOA, mainly in special populations that often have other comorbidities.

The ES for responsiveness revealed medium sensitivity for change in some components, mainly the short-term modifiable components such as pain in the last month, functional pain and other symptoms. External risk factors such as surgery, sports or occupational activity in the past are not modifiable risks, so no changes were expected. Likewise, self-reported pain in the past year was not expected to change after the 3-month intervention because the reported pain was in the last year and not in the present. The KOPS detected improvements from the exercise intervention in self-reported pain in the last month and in other symptoms such as stiffness, swelling and functionality. Unlike the KOOS [19], the total KOPS score has a weak sensitivity to change, which can be explained because the former was created to measure treatment outcomes and the latter was created for screening, with many components related to unchangeable outcomes.

5. Conclusion

In summary, the present study confirms the utility and accuracy of the KOPS questionnaire for KOA screening in epidemiological studies and for exercise and health professionals who need to screen KOA for their intervention, specifically for exercise prescriptions.

The KOPS was constructed and validated for a Portuguese population. Given the good results, the authors agree that the KOPS can be a very useful instrument and that future studies validate the instrument in English. In addition, a larger sample size in the validation process will enable the use of the KOPS for different populations.

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Conflict of interest statement

The authors declare no commercial relationships or conflicts of interest.

Authors' Contributions

Flávia Yázigi and Filomena Carnide worked on the design, analysis and interpretation, drafting and revision and approved the final version. Margarida Espanha contributed to the design, patient recruitment and revision and gave final approval.

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