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Literature review of risk factors, evaluation instruments, and care and service interventions for knee osteoarthritis

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Occupational Rehabilitation

Studies and Research Projects

REPORT **R-892**

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PEER REVIEW

In compliance with IRSST policy, the research results published in this document have been peer-reviewed.

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SUMMARY

Osteoarthritis is a chronic disease characterized by progressive degeneration of the cartilage and subchondral bone and resulting in pain, functional limitations and long-term disability. The weight-bearing joints are especially vulnerable to the disease, but knee osteoarthritis (OA) is more likely to cause functional disabilities. Although the disease is found mainly in people aged 65 and over, the Public Health Agency of Canada estimates that the prevalence of knee OA in people aged 55 to 64 will be 66% by 2026. This anticipated rise in prevalence is a serious concern given that osteoarthritis is one of the chronic diseases that incur the greatest use of health care services. Knee OA has many adverse social and economic impacts. These data highlight the importance of proposing more efficient knee OA management across the care and services continuum (prevention-treatment-rehabilitation).

In current evidence-based practice trends, clinicians and managers are increasingly required to consult the scientific literature in order to propose better interventions to clients. This disease has been the subject of a considerable number of publications in a variety of research areas. It has become difficult for people who provide care and services to knee OA patients to make sense of such an abundance of information, let alone use it effectively.

The general objective of this project was to produce a synthesis of knowledge on risk factors and evaluation instruments for knee OA and on care and service interventions for people with the disease. The first specific objective was to produce a synthesis of scientific evidence on all risk factors associated with the onset and progression of knee OA. The second specific objective was to identify the evaluation instruments used during the rehabilitation of knee OA patients and to analyze their relevance and psychometric properties. The third specific objective was to produce a synthesis of the scientific evidence available on intervention options offered to knee OA patients.

The approach used was a systematic or critical review of the scientific literature. Research strategies were adopted for each specific objective in order to identify the relevant literature in various electronic databases (MEDLINE, SCOPUS, AMED, etc.). Manual searches were also performed. Lastly, a synthesis of the best evidence was prepared on the basis of high-quality studies (specific objectives 1 and 3) and of all the studies we considered to be of interest (objective 2); it is presented in this report. Summary tables of the detailed results are found in a separate document (available on the REPAR/FRQS site at http://repar.ca/Admin/Files/images/ANNEXES_v13_mai_2014.pdf).

For specific objective 1, it was determined that advancing age, being female, obesity, and high body mass index (BMI), performing work in kneeling or squatting positions and handling heavy loads, high-intensity physical activities performed over a long period, and high bone mineral density are the most significant risk factors for knee OA. The strength of evidence for these risk factors ranges from moderate to strong. Considerable inter-study heterogeneity was found in the characterization of exposure.

For objective 2, the criterion validity of a clinical measure of knee alignment using an inclinometer was demonstrated. The pain subscales of most of the algofunctional questionnaires have good validity and good reliability. However, some instruments, like the Intermittent and Constant Osteoarthritis Pain (ICOAP), are useful for assessing more specific aspects such as intermittent and constant pain. For joint and muscle function, Cyriax's concept of capsular pattern has not been validated, whereas methods for measuring the isometric and isokinetic muscle strength of knee OA patients are reliable. The results of our study confirm the robustness of the psychometric properties (which range from good to excellent) of several instruments used to assess the Activity and/or Participation components, specifically the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Oxford Knee Score (OKS), Patient Function Numerical Rating Scale (NRS) and Lequesne Algofunctional Index (LAI). Lastly, the Work Limitations Questionnaire (WLQ) scores well for internal consistency and content and construct validity in measuring the effects of knee OA on work performance. However, the WLQ is less responsive to change than the Work Instability Scale for Rheumatoid Arthritis (RA-WIS).

Regarding specific objective 3, physical exercise has been shown to be as much as moderately effective; it must be practiced regularly to maintain its positive effect on pain and function. Hyaluronic acid injections are only marginally effective in alleviating pain: their action is neither immediate nor lasting. Non-steroidal anti-inflammatories (NSAIDs) have good analgesic effects, but also significant side effects. As for supplements, electrical stimulation therapy, acupuncture, heat, cold, orthoses and laser therapy, evidence of their effectiveness is often conflicting or based on poor-quality or non-homogeneous studies.

In conclusion, our findings for objective 1 are consistent overall with those reached by authors of previously published systematic reviews and meta-analyses. However, the scientific evidence would probably have been stronger for certain risk factors if the methods of characterizing exposure had been more homogeneous. Likewise, the role of several risk factors could have been clarified if more high-quality observational studies had been found on these subjects. Although as a whole we were able to develop a fairly comprehensive profile of factors associated with the onset of knee OA, the same cannot be said for progression-related factors. More cohort studies would have been required for us to do so.

For objective 2, we found great interest in cross-cultural validation of algofunctional questionnaires and in validation studies of measurement tools that produce an aggregate score derived from the sum of scores on several dimensions or categories of the International Classification of Functioning, Disability and Health (ICF). Although most of these tools are valid and reliable, several are generic. This points to a need for development or validation of tools that are more effective in measuring each ICF category, particularly the Activities and Participation components.

One finding emerges for objective 3: at present, there is no miracle treatment or therapy for people suffering from knee OA. Exercise is most definitely recommended and must be practiced regularly to maintain its positive effects. Hyaluronic acid injections are effective, but they have neither immediate nor lasting action. NSAIDs are highly effective painkillers but are only short-term solutions and have significant side effects. Accordingly, different treatment options should

be considered for effective management of knee OA. This is consistent with points raised in many practice guides based on literature reviews.

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1. INTRODUCTION/PROBLEM

Osteoarthritis is a chronic disease characterized by progressive degeneration of cartilage and subchondral bone, resulting in pain, functional limitations, and long-term disabilities.[1,2] Weight-bearing joints are especially vulnerable to the disease, but knee osteoarthritis (knee OA) is more likely to cause functional disabilities.[3] More than three million Canadians have knee OA.[4] In Québec, of the people who claim to suffer from knee OA, 53.2% report the presence of symptoms in their knees.[5] Although the disease is found mainly in individuals aged 65 and up, the Public Health Agency of Canada estimates that the prevalence of knee OA in people aged 55 to 64 will be 66% by 2026.[6] This anticipated growth in prevalence is a serious concern given that osteoarthritis is one of the chronic diseases that incur the greatest use of health care services.[7] In Canada, the costs associated with osteoarthritis are in the order of CAD$3.26 million.[8] Studies conducted in various countries report that the cost of osteoarthritis represents from 0.4 to 2.8% of the gross national product.[8-10] The economic burden of the disease stems mainly from the resulting functional and work-related disabilities. In people aged 65 and over, the risk of reduced mobility (defined as difficulty walking or negotiating stairs) is higher among individuals with osteoarthritis than among those with any other disease.[1,2] Leigh et al. estimate that in the younger population, nearly 15% of the economic price of knee or hip OA is attributable to work absenteeism, making this disease more costly, in terms of work disability, than either respiratory or neurological diseases.[11] Moreover, the economic burden of knee OA in the workplace risks growing heavier due to the increasing number of arthroplasties that will be performed in the years ahead. Nearly 95% of the knee arthroplasties performed from 2009 to 2010 followed a diagnosis of degenerative osteoarthritis.[12] The total number of knee arthroplasties for 2008 and 2009 represented a 139% increase over that for the previous decade. Knee OA saw its biggest increase among 45- to 54-year olds, with numbers doubling in the past ten years irrespective of gender. This is an alarming fact given that in 2011, this age group represented 42.4% of the working-age population in Canada. Knee OA can therefore no longer be regarded as a disease limited to the elderly and retired.

These data highlight the prime importance of proposing more efficient management of knee OA across the care and services continuum (prevention-treatment-rehabilitation). National[13] and international[14,15] public health agencies and organizations have in fact made this a priority. In current evidence-based practice trends, clinicians and managers are increasingly required to consult the scientific literature in order to propose the best interventions to their clients. This disease has given rise to a considerable number of publications in a variety of research areas. It has become difficult for people who provide care and services to knee OA patients to navigate through such an abundance of information, let alone to use it effectively. Our knowledge of the field leads us to believe that to date certain aspects of the problem are still little documented. This research report therefore presents the results of an exhaustive inventory of existing scientific documentation on the problem of knee OA. The report is divided into three main sections, each pertaining to a specific objective.

The first section discusses the risk factors for knee OA. Their identification has given rise to numerous observational studies on a variety of risk factors, some systemic in origin and others related to joint structures and function or to activities and lifestyle habits. Job-related risk factors

fall into the last category. Most of the authors of these studies have focused on exposure to a specific factor, and the knowledge acquired about the majority of factors has rarely been the subject of high-quality synthesis work. We believe that by establishing the strength of evidence available for all risk factors for the onset and progression of the disease and compiling it within a single document, the individuals who work with these clients will be able to make better use of this knowledge. Among other things, they will be able to identify the modifiable factors on which they could conceivably act in order to take measures aimed at preventing the disease and the resulting disabilities.

The second section examines the instruments developed to assess the health status of individuals with knee OA. The word *health* must be understood here in its broadest sense, as defined by the World Health Organization (WHO): "*Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*."[16] Pain and functional limitations are clearly clinical characteristics that have a substantial negative impact on the health of individuals with knee OA. Numerous algofunctional questionnaires have therefore been developed to measure them. Yet other dimensions of health such as organic or affective functions, alterations in the structures that make up the knee, limitations in social participation, or environment-related factors, also impede a person's well-being.[17] To gain a better understanding of the impact of knee OA on a person's health, instruments must be available for evaluating all dimensions of that person's health. These instruments must also be valid, responsive, and reliable for the purpose of evaluating the effectiveness of interventions. An inventory of knowledge on evaluation instruments, tests, and protocols used in rehabilitation will reveal any gaps that exist in this important component of managing individuals with knee OA. This review will also provide clinicians with better guidelines for choosing which instruments to use to evaluate their clients with knee OA.

The third section presents a synthesis of the scientific evidence on interventions. To date, there is no curative treatment for knee OA, apart from joint replacement surgery. The approaches taken are aimed primarily at reducing pain, improving function and increasing quality of life for the individuals affected. Many varied interventions are used to treat individuals with knee OA, and their efficacy has been the focus of many studies. These interventions fall into three general categories: (1) non-pharmacological approaches (e.g. rehabilitation programs, exercise classes), (2) pharmacological approaches (e.g. anti-inflammatories, analgesics, corticosteroids), and (3) surgical approaches (e.g. joint debridement, arthroplasty). A readily accessible synthesis document on this subject should facilitate clinicians' use of evidence-based data in their practices.

2. OBJECTIVES

The **general objective** of this project was to produce a synthesis of the knowledge available on risk factors for knee OA and on the evaluation instruments and care and service interventions used with this clientele.

Specific objective 1:

To produce a synthesis of the scientific evidence on all risk factors associated with the onset and progression of knee OA.

Specific objective 2:

To identify the evaluation instruments used in the rehabilitation of individuals with knee OA, and document them in terms of their pertinence and psychometric properties.

Specific objective 3:

To produce a synthesis of the scientific evidence available on the interventions offered to individuals with knee OA.

3. METHOD

3.1 Search Strategy

To identify the scientific literature likely to be pertinent, the following electronic databases were queried: MEDLINE, EMBASE, CINAHL, AMED, HEALTHSTAR, MANTIS, SCOPUS, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and ACP Journal Club. For objectives 1 and 3, the databases were queried from the date of their creation to June 2011 inclusive. For objective 2, they were queried from the date of their creation to June 2012. The databases had initially been consulted up to June 2011 for our three research objectives. However, a year later, we decided to re-think our search strategy for objective 2 because we no longer deemed it appropriate. This explains why the time span over which the databases were consulted differs according to the objective.

To structure the document search for objective 2, we opted to base ourselves on the International Classification of Functioning, Disability, and Health (ICF).[18] Adopted in 2001 by the WHO, the ICF is a conceptual framework that presents a standardized terminology and classification of the consequences of diseases. It allows the individual to be situated in his[1] particular context and to understand how certain external factors interact with each other and with the physical, social, and mental consequences of the disease. The person's health status is described in terms of the following components: Body Functions, Body Structures, Activities and Participation, and Environmental Factors. Each of these components in turn has several categories. The ICF was used by Xie et al.[17] to describe knee OA; these authors also identified the categories for which the disease could have consequences. Our review concerns the following components: Body Structures, Body Functions, and Activities and Participation (see Figure 1). According to this model, *body structures* designate body parts, such as organs, limbs, and their components; *body functions* refer to physiological functions of organic systems (including psychological functions); *activity* implies the performance of a task or an action by a person, and *participation* designates the involvement of a person in a real-life situation.[18]

For each of the three objectives, searches were performed simultaneously for titles, abstracts, and key words by combining sets of expressions and terms (see Appendix A). The references obtained from each of the databases were imported into EndNote software and duplications were eliminated. To complement the electronic searches, the lists of references provided in the systematic reviews and meta-analyses obtained were scanned to identify any documents that might have escaped notice. The grey literature was covered by means of SCOPUS, which indexes publications such as *The Grey Journal*.

Many key words were used in connection with knee OA (see Appendix A). While their variable precision meant that we ended up with a large number of articles potentially of interest, this probably minimized the losses of information associated with very narrow search strategies.

[1] The masculine form is used in this text with no gender discrimination intended and solely in the interests of readability.

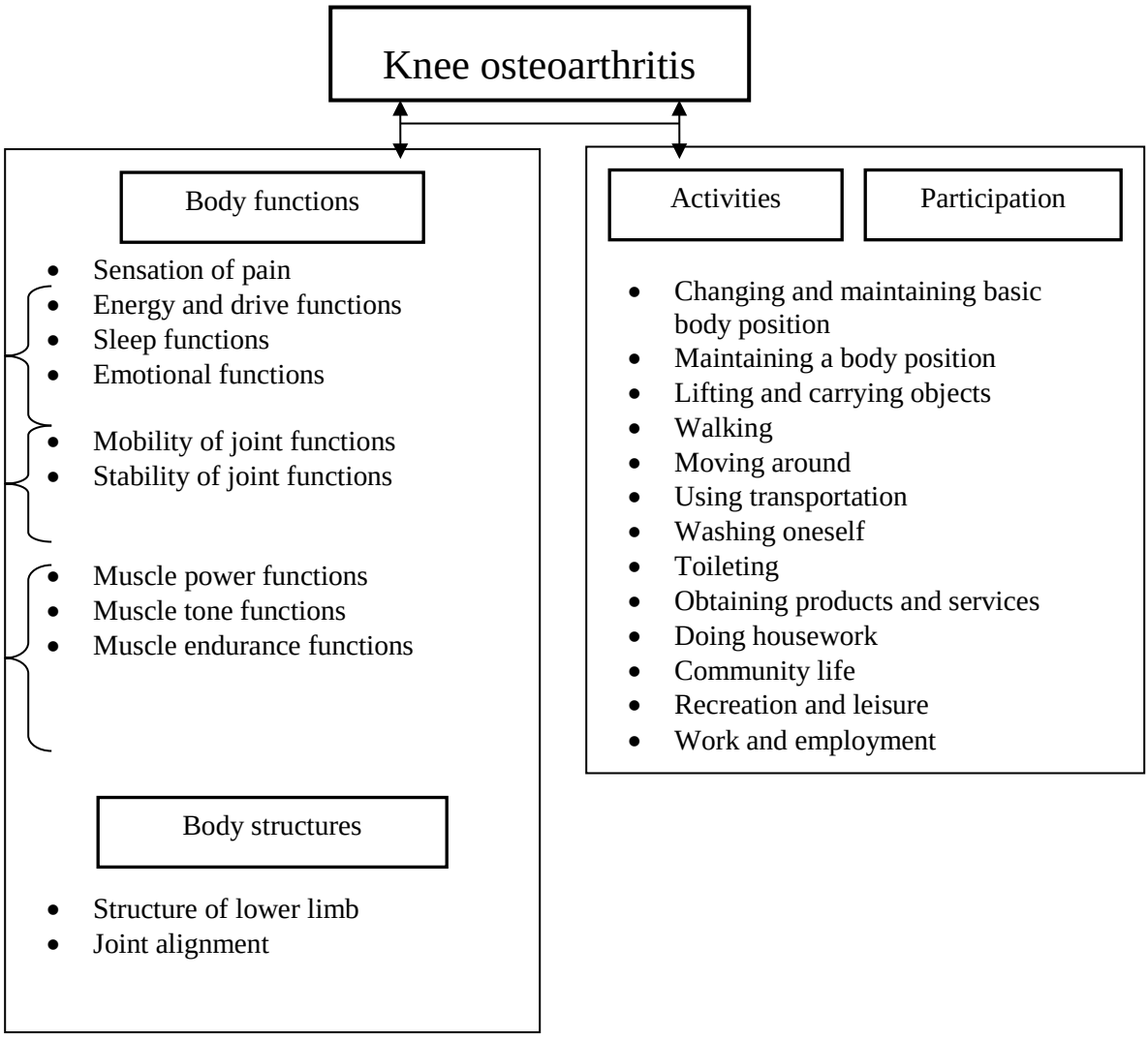

Figure 1: ICF components and categories used for this study

3.2 Selecting the Studies

Two independent reviewers were assigned the task of selecting the studies. One of them, who was also the project coordinator, benefitted from a two-day training session offered by a group from The Cochrane Collaboration at McMaster University. The other reviewer did training through a webinar, in addition to having access to all documentation received by the coordinator during training.

The titles of the potentially pertinent references were read and then classified in three categories entitled “Accept,” “Uncertain,” and “Reject,” depending on their probable fit with the research objectives. The abstracts for references whose titles had been classified in the “Accept” or

"Uncertain" categories by both reviewers were obtained so they could be read and classified. The same process was repeated for the complete articles and when selecting the articles to be included in the systematic review. Inter-reviewer agreement was good throughout the selection process. In the case of disagreement, the two reviewers sought to reach a consensus, and where that was impossible, the principal investigator was asked to make the decision.

Inclusion and exclusion criteria were defined at the outset and guided the choices of publications (see tables 1, 2 and 3). Overall, the two reviewers made similar choices. However, for risk factors, it was decided that the description of knee OA had to be based on recognized and frequently used measures: the Kellgren-Lawrence (KL) Grading Scale for the radiological assessment of knee OA[19] and the criteria of the American College of Rheumatology (ACR) for symptomatic knee OA.[20]

Table 1: Inclusion and exclusion criteria – Risk factors

Inclusion criteria:
- English- and French-language publications
- Cross-sectional studies, case-control studies, cohort studies
- Analytical studies
- Studies of adult subjects
- Radiographic knee OA characterized by a KL grade ≥ 2: osteophytes and well-defined joint space narrowing (gold standard)
- Symptomatic knee OA characterized by the criteria of the American College of Rheumatology (ACR): age ≥ 50, morning stiffness of less than 30 minutes, crepitus, bony tenderness, bone enlargement, and/or absence of palpable heat (gold standard)
- Appearance of radiographic knee OA: moving from a KL grade of 0 or 1 at baseline, to a grade of 2 or more at any of the follow-ups
- Progression of radiographic knee OA: moving from a KL grade of at least 2 to a grade of 3 or 4 at any of the follow-ups, having undergone knee replacement in the meantime or being on a waiting list for one
- Appearance of symptomatic knee OA: moving from asymptomatic knee OA at baseline, to symptomatic knee OA at any of the follow-ups
- Studies of patients on a waiting list for knee arthroplasty or having undergone this surgery due to OA were also included, as they involved severe knee OA

Exclusion criteria:
- Publications in languages other than English or French
- Systematic reviews and meta-analyses, opinion pieces, editorials, commentaries and literature reviews
- Descriptive studies
- Studies on children or adolescents
- Studies focusing solely on the presence or progression of a so-called characteristic radiographic manifestation of knee OA
- Self-reported measurements (even if a physician issued the diagnosis in the past) or symptomatic aspects examined in isolation (stiffness, pain, limitations in everyday activities, etc.)

Table 2: Inclusion and exclusion criteria – Evaluation instruments

Inclusion criteria: - English- and French-language publications - Studies of psychometric properties - Studies conducted on living, adult human subjects **Exclusion criteria:** - Publications in languages other than English or French - Opinion pieces, editorials, and commentaries - Studies presenting undifferentiated results for different populations (e.g. rheumatoid arthritis and osteoarthritis, knee and hip OA, OA and meniscus or ligament injuries) - Studies not differentiating the results for individuals in the pre-operative and post-operative phases or focussing solely on individuals in the post-operative phase

Table 3: Inclusion and exclusion criteria – Interventions

Inclusion criteria: - English- and French-language publications - Systematic reviews and meta-analyses - Controlled trials published between 2009 and 2011 inclusively, i.e. those least likely to have been included in the systematic reviews and meta-analyses that we selected - Studies conducted on living, adult human subjects **Exclusion criteria:** - Publications in languages other than English or French - Opinion pieces, editorials, commentaries, and literature reviews. Trials without control groups - Studies conducted on children or adolescents

3.3 Evaluating Data Quality and Extraction

The task of assessing the quality of the selected studies was given to the same two independent reviewers who had selected the studies. Here again, in cases of disagreement, the two reviewers aimed to achieve consensus, and where impossible, the principal investigator made the final judgment as to the quality. The instruments used for this task varied, depending on the type of study design (see Appendix E).

For risk factors

The instrument selected to assess the quality of the cohort and case-control studies was a list of assessment criteria proposed by Lievense et al.[21] It included a set of standardized item-related criteria for assessing observational studies and was used by these authors in a systematic review on the influence of work on the onset of hip osteoarthritis. Most of the items concern validity/precision while a few concern the informative nature of the article. Since that time, this list of criteria has been used by authors examining risk factors for knee OA.[22-24] Moreover, while some authors have used this list to evaluate the quality of cross-sectional studies,[24] we chose not to do so because the strength of scientific evidence from cohort and case-control studies is already considered superior to that from cross-sectional studies. We nonetheless examined these

cross-sectional studies because cohort and case-control studies are virtually non-existent for certain risk factors.

The list proposed by Lievense et al.[21] comprises 19 items, three of which apply only to cohort studies and another three of which apply only to case-control studies. One point was awarded for each item-related criterion met. The total number of points was then tallied and divided by 16, or the maximum possible score; the net result was a quality score. A study that obtained a quality score of more than 60% was deemed to be of high quality.

For evaluation instruments

The instrument used for this purpose was an in-house questionnaire comprising 17 items, 13 of which come from the instrument developed by Brink et al.[25] to assess the quality of reliability and validity studies. The other four items were added to assess the quality of studies focussing on responsiveness to change. Each item had to be rated "yes" or "no" or "not applicable (N/A)". No total score was calculated. Using this list of items, we were able to determine, on the basis of the decision-making rules presented in Appendix E, whether the methodology of a given study was excellent, good, or poor. This step served to eliminate studies deemed to be poor, and proved necessary for making a critical appraisal of the documents retained.

For interventions

To assess the quality of the systematic reviews, meta-analyses, and controlled trials, we opted to use the revised instrument Assessing Methodological Quality of Systematic Reviews (R-AMSTAR), developed by Kung et al.[26] based on work done by Shea et al.[27] This instrument comprises 11 items, each with between three and five criteria. A mark was awarded for each item, depending on the number of criteria met. The marks were then added up to obtain a total score ranging from 11 to 44. A quality score greater than 60% indicated that a given systematic review or meta-analysis was of high quality.

To assess the quality of the controlled trials, the Jadad score[28] is very often used. However, it is criticized for being overly simplistic, for over-emphasizing blinding, and for yielding results that are not easily reproducible.[29] Mention is sometimes made of the Consolidated Standards of Reporting Trials (CONSORT[30]), but these are used more to appraise the quality of reporting of research data. In other words, they serve as a kind of checklist for ensuring that nothing is forgotten when writing an article. We therefore opted instead for The Cochrane Collaboration's Tool for Assessing Risk of Bias.[31] It is more complete than the Jadad score because it looks at a number of criteria: practices planned for distributing participants in trial groups, blinded trials (participants, person who measures the primary variable, person who gives the treatment), intention-to-treat (ITT) analysis, etc. Moreover, it leaves room for adding criteria to be assessed, depending on the researchers' needs. In our case, we added the aspects "comparable experimental and control groups" and "conflicts of interest." Lastly, this instrument takes a more qualitative approach (low risk, uncertain risk, high risk), which does not, however, prevent the tallying of the number of "low risk" mentions to appraise the quality of a trial. We determined that a study earning five or more "low risk" mentions out of a total possible of eight was of high quality.

Data extraction was performed simultaneously with quality assessment by one of the two reviewers. The variables retained concerned, among other things, the study populations (distribution by gender, age, and origin), the ways in which knee OA was characterized, adjustment or control variables, outcomes, and the main conclusions to be retained. The quality scores were also included. The research coordinator was responsible for data entry. In cases of uncertainty about the data to be selected, the principal investigator made the decision.

3.4 Synthesizing the Best Scientific Evidence

For risk factors

Given that the selected observational studies were often heterogeneous in their characterization of exposure to risk factors, we did not perform meta-analyses, opting instead to synthesize the best scientific evidence. The studies were thus divided into sub-groups according to design: the cohort studies were regarded as offering the most solid evidence, followed by the case-control studies and then the cross-sectional studies.

The evidence for a given risk factor was then established based on high-quality studies only (score > 60%), in keeping with the recommendations made by van Tulder et al.[32] The "+" notation was our initiative.

1) Solid evidence is provided by convergent results in several high-quality cohort studies. **++++**
2) Moderate evidence is provided by convergent results in: a) one high-quality cohort study and at least two high-quality case-control studies; b) at least three high-quality case-control studies. **+++**
3) Limited evidence is provided by similar results in: a) one cohort study; b) at least two case-control studies; c) most of the cross-sectional studies. **++**
4) Conflicting evidence is provided by results pointing in opposite directions (< 75% of the studies reported similar results). **+**
5) No evidence is provided if an insufficient number of studies or no study could be found. **-**

For evaluation instruments

A systematic review by Dobson et al.[33] served as the basis for this synthesis. The values of the results they documented were taken from their adaptation of work by Terwee et al.[34] Only elements taken from the Brink et al.[25] assessment of the instrument's quality were added in our literature review. The evidence was then categorized as strong, moderate, or weak/conflicting.

For interventions

Given the abundant scientific literature on interventions, only high-quality systematic reviews, meta-analyses, and controlled trials are discussed in the "Results" section. Even if we would have

liked to establish the strength of the evidence using a checklist such as that proposed by Harbour et al.[35], we would have been left with strong evidence for each type of intervention.

Instead, we opted to determine levels of effectiveness. For any given intervention, these levels were established first on the basis of systematic reviews and meta-analyses, and then on the basis of controlled trials. The trials cast light on the most recent data for any given intervention, but have less weight in terms of determining level of effectiveness. The assessment of the evidence is thus more qualitative than for objective 1 concerning risk factors for knee OA.

The notation used for levels of effectiveness is similar to that used for objective 1:

1) High level of effectiveness : ★★★★
2) Moderate level of effectiveness: ★★★
3) Low level of effectiveness: ★★
4) Conflicting levels of effectiveness or too much inter-study heterogeneity to determine a level of effectiveness ★
5) Zero level of effectiveness. ☆

The research coordinator and the principal investigator worked together to analyze the data.

4. RESULTS

4.1 Risk Factors for Knee OA

Our searches yielded 4,227 potentially pertinent references. Once the selection process was completed, 177 documents were selected for our review (see Appendix B).

4.1.1 Risk factors related to lifestyle habits and sociodemographic characteristics

4.1.1.1 Age

+++

Fourteen articles on the link between age and knee OA were retained. Of this number, two were cohort studies: one obtained a quality score higher than 60 %[36], while the other obtained a lower score.[37] Of the four case-control studies retained, three were of high quality [38-40] and one was of poorer quality[41]. Eight cross-sectional studies completed our research corpus.[42-49]

As all the studies revealed an association between advancing age and knee OA, we can affirm that age represents a significant risk factor for the disease, in both its radiographic and symptomatic forms. The evidence was moderate, given the few quality cohort studies identified on this subject. However, it is difficult to specify as of what age exactly and to what degree the risk for knee OA increases, because the characterization of exposure varied from one study to the other. The link between advancing age and the progression of knee OA appears not to have been studied per se.

4.1.1.2 Gender

+++

Thirteen articles on the link between gender and knee OA were retained. This number included three cohort studies, one deemed to be of high quality[36] and two of poorer quality.[37,50] Two case-control studies, both of high quality, were retained.[39,40] Eight cross-sectional studies were also retained.[42-45,47-49,51]

With one cohort and two case-control studies all of high quality and reaching the same conclusions, it is safe to say that we have moderate evidence to the effect that being a woman represents a higher risk for knee OA. The cross-sectional studies concur on this. In fact, regardless of how the knee OA was characterized (radiographic, radiographic with symptoms, or

symptomatic), the authors always concluded that women were at greater risk for knee OA than men. However, we could not reach any conclusion regarding the association between gender and the progression of knee OA, as this factor was the subject of little study.

4.1.1.3 Weight and obesity

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We retained 47 articles of interest on the risk factors for knee OA associated with weight or obesity. Of these articles, 12 were cohort studies: nine obtained a quality score higher than 60%[36,52-59] and three a score equal to or less than 60%. [37,50,60] Seventeen studies were case-control studies, 13 of which obtained a quality score higher than 60%[38-40,61-70] and four a score lower than this percentage.[41,71-73] Lastly, we documented 18 pertinent cross-sectional studies.[42-47,49,51,74-83]

Given the large number of high-quality cohort and case-control studies with convergent results, we can affirm that solid evidence exists to the effect that excess weight and obesity constitute risk factors for knee OA, even for severe knee OA requiring arthroplasty. The BMI is without question the most widely used measurement for differentiating individuals at the highest risk from those at less risk. While a person's BMI can help predict the onset of knee OA, we do not have enough evidence to suggest that a BMI above normal or high increases the risk of the disease's progression.

4.1.1.4 Occupational factors

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Twenty-six articles on occupational/work-related risk factors were retained. They included two cohort studies, both of high quality.[84,85] Fourteen case-control studies were also retained: nine obtained a quality score higher than 60%[38,64,65,68,86-90] and five a score lower than 60%.[41,71-73,91] In addition, ten cross-sectional studies were retained.[42-44,46-48,51,92-94]

The two quality cohort studies with long follow-ups did not characterize exposure in the same way: one looked at work postures or specific tasks while the other examined groups of skilled tradesmen in the construction industry. While the descriptions were not identical, we can reasonably postulate that workers in the construction industry are frequently exposed to postures or tasks involving the knees, thereby making a comparison between the two studies possible. Hence, in jobs that involve using the knees and/or lifting or carrying heavy objects, risk for knee OA appears to be two to three times higher than in sedentary jobs.

Regarding the case-control studies, the issue of the characterization of exposure arose again. Here too, the results were expressed in terms of specific tasks, job categories, or occupational groups. Even so, the studies remained somewhat comparable. Risk for knee OA appears to be two to three times higher for a "physically demanding" job than for a lighter or sedentary type of job.

Moreover, in two studies, the interaction between the work-related risk factors and an above-normal BMI appeared to put the person at higher risk for knee OA.[38,88]

As a whole, the retained cross-sectional studies corroborated the results of the cohort and case-control studies. When this was not the case, it was essentially attributable to a less precise or detailed categorization of exposure. This situation can be explained by the fact that the authors examined different risk factors within the same study, one of which was work-related risk factors.

Given the similar results we found in more than one high-quality cohort study – even they do not all characterize exposure in the same way – and several case-control studies, we can say that there is solid evidence that work in which the knees are frequently used and/or rather heavy objects have to be lifted or carried puts the person at higher risk for knee OA, possible even severe knee OA.

4.1.1.5 Physical and recreational activities

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Thirteen articles on risk factors for knee OA related to physical and recreational activities were retained. These included five cohort studies, all of high quality[57,95-98], and seven case-control studies. Five of these obtained a quality score above 60%[38,89,99-101], while two obtained a lower score[72,73]. Only one cross-sectional study was retained.[47]

While the characterization of exposure varied greatly from one cohort study to the other (sports and recreational activities, frequency measures and reference period), it is clear that the practice of physical and recreational activities of low to moderate intensity does not significantly increase the risk of onset of knee OA and possibly of its progression. On the other hand, vigorous activities such as running, track and field, or competitive cross-country skiing could put those who practice these sports at higher risk for knee OA in the long term. In fact, of the five cohort studies, the Felson et al.[98] study was the only one that did not show an association between more intense physical activities and higher risk for knee OA. Also, while some authors asserted that the most physically active overweight or obese individuals are at higher risk for the onset or progression of knee OA[96], others found no statistically significant interaction in this regard.[98]

The authors of the case-control studies tried in various ways to establish a cumulative measure of exposure to physical and/or recreational activities over a lifetime. As was the case in the cohort studies, moderate exposure would appear not to increase risk for knee OA – regardless of how the disease is characterized – and, in fact, may even reduce it[100]. Furthermore, certain sports practiced intensively over a number of years could lead to a higher risk for the disease: cross-country skiing, soccer, hockey, ball sports, and cycling[38,89,101]. It is important to point out the variability in the characterization of exposure.

With this number of quality cohort and case-control studies reaching the same findings, it is safe to say that solid evidence exists to the effect that physical activity practiced at high intensity over

a relatively long period of time puts the person at higher risk for knee OA. This is not the case for physical and recreational activities of moderate or low intensity. However, given the inter-study variability in terms of characterization of exposure, it is impossible at this time to identify with certainty the sports posing this risk, and equally inappropriate to attempt to quantify the magnitude of risk.

4.1.1.6 Smoking

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Thirteen articles of interest looked at smoking as a possible risk factor for knee OA. Of these, two were cohort studies. One obtained a high-quality score[102], and the other a poorer score.[37] Three case-control studies were deemed to be of interest: two obtained a quality score higher than 60%[38,39], while the third scored lower.[68] Eight cross-sectional studies completed our research corpus.[42-44,48,51,77,83,103]

To date, we find conflicting evidence regarding an association between knee OA and smoking: sometimes it is regarded as a risk factor, and at other times, as a protective factor against the disease. More quality observational studies are needed to resolve this issue. Furthermore, the characterization of exposure varied from one study to the other, which may have influenced the verdict presented here.

4.1.1.7 Diet

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A total of eight articles on risk factors for knee OA related to dietary intake/nutrient consumption were selected. This number included four high-quality cohort studies[104,105 106,107], two case-control studies (one of high quality[108] and the other of poorer quality[41]), and two cross-sectional studies[45,109].

Eating habits and nutrient intake could have an impact on risk for knee OA, but the evidence was deemed insufficient to make any assertion whatsoever regarding any specific dietary factor (e.g. red meat, legumes, antioxidants and vitamins D and K).

4.1.1.8 Other

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A handful of observational studies of interest concerning ethnicity[46,50], level of education[50,110], alcohol consumption[43] and the wearing of high-heeled shoes[68] as potential risk factors for knee

OA were documented, but to date the evidence remains insufficient to reach any conclusions in their regard. Other high-quality studies are needed.

4.1.2 Biological and physiological risk factors

4.1.2.1 Hormones and reproductive history

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A total of nine articles on risk factors for knee OA related to hormones or reproductive history were selected. These included five cohort studies (three of high quality[111-113] and two of poorer quality[114,115]), one case-control study of high quality[116], and three cross-sectional studies.[80,117,118]

Conflicting evidence emerged from our examination of the literature on hormone replacement therapy: some authors assert that it is a risk factor for knee OA, while others state that it is a protective factor. Regarding the other factors in this category (number of pregnancies, age at time of menopause, etc.), trends were noted, but the evidence was deemed insufficient to conclude that any particular factor was associated or not with the onset or progression of knee OA.

4.1.2.2 Metabolic syndrome and other diseases

–

Seven articles on risk factors for knee OA related to metabolic syndrome or the presence of other diseases were deemed to be of interest. These included two case-control studies of high quality[39,62] and five cross-sectional studies.[80,83,119-121]

Here too we found insufficient evidence to assert that either metabolic syndrome or the presence of other diseases (such as hypertension or diabetes) puts the person at higher risk for knee OA. The characterization of exposure also varied greatly from one study to the other.

4.1.2.3 Biochemical factors

+ / –

Eight articles on biochemical risk factors for knee OA met our inclusion criteria. These included four high-quality cohort studies[122-125], one high-quality case-control study[126] and three cross-sectional studies.[127-129]

Given that a number of risk factors were grouped in the “biochemical” category and that few studies dealt with all of the factors, it is more difficult to summarize the evidence. While high urinary concentration of CTX-II was associated with higher risk for radiographic knee OA in one

cohort study, one case-control study, and one cross-sectional study, the evidence is nonetheless limited.

Other high-quality studies on the other risk factors (concentration of cell adhesion molecules, blood concentration of homocysteine, etc.) are needed because there is less scientific literature available on them.

4.1.2.4 Bone mineral density

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A total of five articles on risk factors for OA related to bone mineral density met our inclusion criteria. These included four cohort studies: three were deemed to be of high quality[36,130,131] and one of poor quality.[37] One cross-sectional study completed our research corpus for this factor.[80]

Based on the quality studies retained, there is solid evidence that an association exists between a high bone mineral density and the onset of radiographic knee OA. However, the same cannot be said about its association with the disease progression because there are too few studies on this subject to date.

4.1.2.5 Hand osteoarthritis, NSAIDs, and Heberden's nodes

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A handful of observational studies of interest on hand osteoarthritis[132], the taking of nonsteroidal anti-inflammatory drugs (NSAIDs)[133], and Heberden's nodes[37,70] as potential risk factors for knee OA were documented, but as yet there is insufficient evidence to make any assertions in their regard. Additional high-quality studies are needed.

4.1.3 Risk factors related to joint structures and functions

4.1.3.1 Injuries and history of injury

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Thirteen articles on risk factors for knee OA related to injuries or history of injury were retained. These included three cohort studies, one deemed of high quality[57] and the other two of poorer quality.[50,134] They also included eight case-control studies, five of them deemed to be of high quality[39,64,65,70,135] and the remaining three of poorer quality.[41,72,73] Two cross-sectional studies were also of interest.[47,80]

Given that we had one quality cohort study and one quality case-control study, we can affirm that there is moderate evidence to the effect that a history of knee injuries puts a person at higher risk for knee OA. However, as the authors of the studies on the subject opted for a vague characterization of exposure, we know little about the nature and severity of the injuries that pose a higher risk.

4.1.3.2 History of surgery

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Only two articles on risk factors for knee OA related to a history of surgery were retained. They included one cohort study[136] and one case-control study, both of high quality.[70]

Given the few quality observational studies we found on this subject, the scientific evidence is deemed insufficient to assert that an association exists between a history of surgery and risk for the onset of knee OA. Additional quality studies are needed for the various types of surgical interventions performed on the knee.

4.1.3.3 Alignment

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Six articles examining the association between alignment and risk for knee OA were deemed of interest. They included two cohort studies[137,138] and three case-control studies of high quality[39,139,140], as well as one cross-sectional study.[141]

In light of the results obtained, we can say that moderate evidence exists to the effect that risk for knee OA is higher in persons with varus knee alignment. However, the evidence of an association between valgus knee alignment and increased risk for knee OA is limited. In both cases, it is difficult to calculate an overall odds ratio at this point in time, partly due to the differing ways in which alignment was measured from one study to the other.

Moreover, there is insufficient evidence to associate poor alignment with the progression of the disease.

4.1.3.4 Height

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We documented five articles on height-related risk factors for knee OA. All of them met our inclusion criteria. They included one quality cohort study[56], two case-control studies (one of high quality[40] and the other of poorer quality[72]), as well as two cross-sectional studies.[142,143]

We find conflicting evidence as to whether taller individuals are at higher risk for knee OA. Other studies are needed to obtain a clearer picture of the situation in this regard.

4.1.3.5 Quadriceps strength

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We retained four articles of interest on quadriceps strength as a potential risk factor for knee OA. They included three high-quality cohort studies[136,144,145] and one cross-sectional study.[146]

To date, the evidence is too limited to assert that greater quadriceps strength guarantees a lower risk for knee OA. The evidence would have been stronger if the characterization of exposure had been more homogenous.

4.1.3.6 Lesions and oedema of the bone marrow

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Three articles on lesions and oedema of the bone marrow as a potential risk factor for knee OA were retained. They included two cohort studies (one of high quality[147] and the other of poorer quality[134]) and one cross-sectional study.[148]

There is limited evidence to show that oedema of the bone marrow is associated with the progression of severe knee OA toward arthroplasty.

Evidence is also insufficient to assert that bone marrow lesions increase risk for knee OA.

4.1.3.7 Other

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Few observational studies of interest on lower limb length inequality[149-151] and proprioception[144] as potential risk factors for knee OA were documented. The evidence is insufficient to allow for any assertions in their regard. More high-quality studies are needed.

4.2 Evaluation Instruments

The instruments of interest documented for each ICF component (see Appendix C) that we retained are presented in the following pages.

4.2.1 Instruments for "Body Structures" component

4.2.1.1 Lower limb alignment

One article on the clinical measurement of lower limb alignment was documented. The Hinman et al.[152] studied the association between the measure of the lower-limb mechanical axis of the knee based on a complete radiograph of the lower limb (the gold standard) and various other parameters, some evaluated clinically: the anatomic axis measured by radiograph, visual observation of the lower limbs, distance between medial knee joint lines or between medial malleoli measured using a caliper, distance between a plumb line and medial knee joint line or medial malleolus measured using a caliper, tibial alignment measured using a gravity inclinometer, and lower-limb alignment measured using a goniometer. The highest Pearson's correlation coefficients were observed for the anatomic axis measure (r = 0.88) followed by the tibial alignment measured using an inclinometer (r = 0.80). The measures obtained with a caliper and those taken using a plumb line showed strong correlations (r = 0.76 and 0.71 respectively). Low correlation was observed with visual observation (r = -0.52). Given its strong correlation with the mechanical axis and its ease of use, the authors recommend the inclinometer method for the clinical evaluation of knee alignment in people suffering from knee OA.

4.2.2 Instruments for "Body Functions" component

4.2.2.1 Pain

4.2.2.1.1 Intermittent and Constant Osteoarthritis Pain (ICOAP)

Bond et al.[153] reported a strong correlation between the ICOAP and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale (Pearson's r = 0.81), and moderate responsiveness to change (ESs from 0.46 to 0.54). The authors mentioned that the ICOAP is best used together with the WOMAC pain subscale in order to obtain a more multi-dimensional evaluation of pain. The study conducted by Ruyssen-Witrand et al.[154] supports the internal consistency of the instrument (Cronbach's alpha of 0.84 for items in the "intermittent pain" dimension and of 0.80 for those in the "constant pain" dimension. However, again according to these authors, the correlation with the WOMAC pain subscale, the pain scale of the Lequesne Algofunctional Index (LAI), and the Numeric Pain Scale is moderate (r of 0.48 to 0.60). The instrument's test-retest reliability is moderate to good (ICC = 0.65) and slightly higher for the evaluation of constant pain compared to that of intermittent pain. Responsiveness to change is moderate to good (SRM = 0.62). The instrument has been translated into Portuguese, and this version is valid and reliable (r = 0.81; ICC = 0.85).

4.2.2.1.2 Knee Injury and Osteoarthritis Outcome Score (KOOS) and KOOS-Physical Scale (KOOS-PS)

The KOOS and KOOS-PS, which evaluate different dimensions of health including function and pain, have been the subject of several studies. However, while two articles were found on the validation of the Physical Scale (PS) version for evaluating pain, there was no article found on the validation of the complete version of the instrument (KOOS) as an instrument for measuring pain. Thus, for the KOOS-PS, validity values (for the items measuring pain) ranging between 0.55 and 0.61, reliability values (ICC = 0.89), and responsiveness to change values (ESs = 0.45-0.54) were obtained.[153,154] The other documented studies involved transcultural validation (French, Dutch, Turkish, and Chinese).[155-158] Weak to moderate validity values (Spearman's correlation coefficient ranging from 0.366 to 0.61) were obtained in this regard. In all cases, internal consistency values were high (Cronbach's alpha between 0.65 and 0.94), as were the test-retest reliability values (ICCs ranging from 0.80 to 0.87). Only one study, that of Ornetti et al.,[156] documented the responsiveness to change of the French version of the KOOS-PS. It reported moderate indices (ES = 0.51; SRM = 0.80). Only the De Groot et al.[155] study included the specific feature of evaluating the validity and reliability of the Dutch adaptation of the KOOS in light of the knee OA severity levels in the study participants. Good validity (r = 0.63 and 0.69, when correlated with the Short-Form Health Survey (SF-36) (pain) and the Visual Analogue Scale for Pain (VAS PAIN) respectively) and good reliability (ICC = 0.87) were observed for participants with moderate knee OA compared to those with mild or severe knee OA. Lastly, one study documented the validity of the computerized version of the KOOS. For the "pain"

dimension, minimal differences were reported between the paper version and the computerized version (mean difference = -1.5 [-3.8; 0.7]), rendering the use of this version appropriate according to the authors. Moreover, the test-retest reliability values were high (ICC = 0.98).[159]

4.2.2.1.3 Oxford Knee Score (OKS)

The OKS evaluates level of function as well as pain; the specific results for pain are presented in this section. Three studies were documented. According to Xie et al.[160] and Naal et al.[161], the OKS is a valid instrument for evaluating pain when compared to the Short-Form Health Survey (SF-6D) and Euro Quality of Life-5D (EQ-5D) (values of p = 0.51 and 0.82 respectively) or even to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale (p = 0.71). Ko et al.[162] demonstrated by means of a Rasch model, a misfit of the "night pain" item (infit and outfit mean-square (MNSQ) = 1.55 and 2.16).

4.2.2.1.4 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Twenty articles on the WOMAC were included. Of these, only two studied the validity of the original version. With regard to the pain scale, the instrument shows excellent internal consistency (Cronbach's alpha = 0.78-0.89) and moderate to strong validity when correlated with the SF-36 Bodily Pain Scale, the VAS Pain, or the evaluation of pain using the Lequesne Algofunctional Index (r = 0.59; r = 0.46; r = 0.66, respectively). It also showed high test-retest validity (ICCs = 0.80-0.98).[163,164] Responsiveness to change was examined in only one study. According to Angst et al.,[165] the most responsive scale of the instrument is the pain scale (ES = 0.566; SRM = 0.743). Lastly, the transcultural validation studies shows that for the Chinese, Finnish, Moroccan, Thai, Turkish, Arabic, Italian, Canadian French, Spanish, Korean, Hebrew, and Swedish versions, the reported validity indices ranged from poor to good (r = 0.37 to 0.71).[166-175]

Substantially different versions of the instrument have also been developed. A factorial version evaluating pain perceived during certain functional tasks was documented. The validity of the instrument when administered prior to an intervention would appear to be better than when administered post-intervention (Spearman's correlation coefficient ranging from 0.62 to 0.68 pre-intervention and from 0.20 to 0.52 post-intervention). However, responsiveness to change was lower than that of the pain scale of the original version of the WOMAC (ES = 0.31-0.65 compared to 0.52).[176]

Another study compared the validity of the VAS version to that of the categorical scaled version (CT).[177] The validity indices for both versions were similar and poor (Pearson's correlation coefficients with the Lequesne index, pain dimension = 0.38 for the VAS version compared to 0.31 for the CT version). The values for internal consistency (Cronbach's alpha = 0.71-0.91 for the VAS and 0.76-0.79 for the CT), for test-retest reliability (ICCs = 0.71 for the VAS and 0.55 for the CT), and for responsiveness to change (VAS = 26.82/20.82 $p < 0.0001$ and CT = 10.38/18.60 $p = 0.003$) were good.

Another study documented the differences between the telephone administration and self-administration of the instrument. The mean difference between the two methods was roughly 0.09.[178]

Lastly, Bellamy et al.[179] looked at the psychometric properties of the computerized version of the WOMAC. The authors observed that the pain scale scores were significantly higher with the paper version than with the computerized version ($p = 0.04$). The reliability of the computerized version was high (ICC = 0.89).

4.2.2.1.5 Arthritis Impact Measurement Scale (AIMS2)

While it was actually developed for assessing quality of life, this instrument also includes a few items on pain. Three studies documented the psychometric properties of translated and adapted versions of the instrument. The validity of the Persian, Turkish, and Italian versions of the AIMS2 was good (with Pearson's correlation coefficient ranging from 0.14 to 0.57, and Cronbach's alpha from 0.76 to 0.83). The test-retest reliability of these versions varied from good to excellent, with ICCs ranging from 0.85-0.94.[180-182]

4.2.2.1.6 Lequesne Algofunctional Index (LAI)

The LAI includes five pain-related items. We documented seven studies that sought to validate this instrument as a means for measuring this health component. Only one study endeavoured to validate the original version of the instrument. Stucki et al.[164] reported that the instrument had good validity for evaluating pain (internal consistency: Cronbach's alpha = 0.55; Spearman's correlation coefficient when correlated with the WOMAC pain subscale = 0.66; test-retest reliability: ICC = 0.87).

Faucher et al. (2003) studied the validity and test-retest reliability of a modified version of this instrument that excluded the items not representative of pain. The validity and test-retest reliability indices obtained were similar to those obtained in the Stucki et al. study (1998) (Spearman's correlation coefficient with the WOMAC pain subscale = 0.56; with the VAS Pain scale = 0.46; and ICCs = 0.65-0.86).[183]

The other studies assessed the validity of adapted and translated versions. The Turkish, Chinese, Arabic, Canadian French, and Korean versions demonstrated validity indices ranging from poor to good (Spearman's correlation coefficient = 0.32-0.63). The reliability indices, however, ran from good to excellent (ICCs = 0.61-0.86; internal consistency: Cronbach's alpha = 0.44-0.71).[163,166,168,184,185]

4.2.2.1.7 Joint-Specific Multidimensional Assessment of Pain (J-MAP)

Assessing the effect of interaction among the psychological (Pain Affect) and physiological components (Pain Sensory) on the presence of pain, the J-MAP was found to be the subject of one study. O'Malley et al.[186] found this instrument to be valid, reliable, and responsive to change. A validity score was obtained by correlating the instrument with the AIMS (pain items) and with the SF-36 (pain component). A correlation (Spearman's coefficient) ranging from good to

moderate was obtained ("physiological" dimension: r = 0.49-0.63; "psychological" dimension: r = 0.56-0.59). The instrument showed good reliability (ICCs = 0.86-0.90), with the "pain sensory" dimension showing slightly greater reliability. Good responsiveness to change was observed (ES = 0.65-0.66) and the study also identified minimal clinically important differences (MCID = 6.8-10.2).

4.2.2.1.8 Visual Analogue Scale (VAS) and the Modified Verbal Rating Scale (MVRS)

Only one study investigated the psychometric properties of evaluating pain using the VAS and the MVRS, although both instruments are frequently used in clinicians' practice. With high validity scores (r = 0.892-0.922) and high intra- and inter-reviewer reliability scores (r = 0.892-0.920 and r = 0.959-0.909 respectively), the use of these instruments would appear to be recommended.[187]

Another study documented the validity of a computerized version of the VAS. Mean differences of the order of -3.9 (-9.4; 1.6) were obtained between the paper and computerized versions. The test-retest reliability of the computerized version was excellent (ICC = 0.95).[159]

4.2.2.1.9 Knee Society Clinical Rating System (KSS)

Developed to assess the repercussions of knee pathologies on level of activity, the KSS includes one dimension for evaluating pain. The validity of the instrument's "pain" dimension was good (r = 0.68 when correlated with the WOMAC pain subscale; r = 0.35 when correlated with the pain component of the SF-36), as was responsiveness to change (SRM = 2.1, pre-intervention/post-intervention score = 28.9/13.6).[188]

4.2.2.1.10 Short-Form Health Survey (SF-36)

A computerized version of this instrument was also evaluated by Gudbergsen et al. Minimal differences between the paper and computerized versions were reported (-0.5 (-2.8; 1.9)) and test-retest reliability was excellent (ICC = 0.87).[159] We did not retain any study on the validity of the original version of the instrument for measuring pain in individuals with knee OA.

4.2.2.1.11 Dolorimeter (pressure algometer): pain thresholds

Wessel et al.[189] documented the psychometric properties of the measure of pain tolerance or perception thresholds using a dolorimeter. When compared to the VAS PAIN and to the McGill Pain Questionnaire (MPQ), the instrument's validity for determining pain thresholds was poor to moderate (r = -0.20-0.45). However, its reliability ranged from good to excellent (ICCs = 0.606-0.912).

4.2.2.1.12 Knee Pain Scale (KPS)

Designed to assess pain occurring during functional activities replicated clinically, the KPS was the subject of one study. Rejeski et al.[190] reported that when the results were compared to those on the MPG and other functional measures, the instrument's validity was moderate to good (with values p = 0.455-0.572). High reliability indices were also obtained (ICCs > 0.84; Cronbach's alpha = 0.82-0.86).

4.2.2.1.13 Pain Index of the Knee (PIK)

Measuring pain intensity and impact on movement, this instrument includes ten tasks (active and passive) that the patient must perform (e.g. active knee extension, unipodal stance on the impaired leg, and maximum knee extension). The instrument showed good validity (correlation with the VAS: r = 0.70) and excellent test-retest reliability (Pearson's correlation coefficient = 0.90-0.96).[191]

4.2.2.1.14 PainDETECT

Only one study examined the psychometric properties of the computerized version of this instrument for assessing pain.[159] Differences of the order of -0.3 to 0.1 were obtained by comparing the results to those obtained with the paper version. The test-retest reliability of this version was excellent (ICCs = 0.94-0.99). No study on the psychometric properties of the original version was found.

Table 4: Summary of evaluation instruments and rating scales documented in articles in "Pain" category

First author, year (reference)	Instrument/Rating Scale	Item measured	Property measured*
Bond, 2012[153]	ICOAP KOOS-PS	Pain	V R RC
Gudbersen, 2011[159]	KOOS VAS SF-36 painDETECT	Pain (computerized version of the instruments)	V R
Ruyssen-Witrand, 2011[154]	ICOAP	Pain (intermittent and constant aspects)	V R RC

Xie, 2011[160]	OKS	Pain	V
Basaran, 2010[163]	WOMAC (computerized version) LAI (Turkish version)	Pain	V R
Mousavi, 2009[181]	AIMS2 (Persian version)	Pain	V R
Naal, 2009[161]	OKS	Pain	V
Ko, 2009[162]	OKS	Pain	V
Ornetti, 2009[156]	KOOS-PS (French version)	Pain	V R RC
de Groot, 2008[155]	KOOS (Dutch version)	Pain	V R
Faik, 2008[175]	WOMAC (Moroccan version)	Pain	V R
Soininen, 2008[192]	WOMAC (Finnish version)	Pain	V R RC
Xie, 2008[193]	WOMAC (Chinese version)	Pain	V R
Kuptniratsaikul, 2007[194]	WOMAC (Thai version)	Pain	V R
Paker, 2007[157]	KOOS (Turkish version)	Pain	V R
Xie, 2007 (X)[185]	LAI (Chinese and English versions for individuals living in Singapore)	Pain	V R
Xie, 2006 (X)[158]	KOOS (Chinese and English versions for individuals living in Singapore)	Pain	V R
Angst, 2005[176]	WOMAC (factorial version)	Pain	V RC
Atamaz, 2005 [180]	AIMS2 (Turkish version)	Pain	V R
Tuzun, 2005[173]	WOMAC (Turkish version)	Pain	V RC
Faucher, 2004[169]	WOMAC (modified French version)	Pain	V R
Guermazi, 2004[170]	WOMAC (Arabic version)	Pain	V R
Guermazi, 2004[184]	LAI (Arabic version)	Pain	V R
Villanueva-Torrecillas, 2004[177]	WOMAC (VAS and CT versions)	Pain	V R

			RC
Faucher, 2003[183]	LAI (modified version)	Pain	V R
Olaogun, 2003[187]	VAS MVRS	Pain	V R
O'Malley, 2003[186]	J-MAP	Pain ("physiological" and "psychological")	V R RC
Salaffi, 2003[172]	WOMAC (Italian version)	Pain	V R
Bellamy, 2002[178]	WOMAC (telephone and self-administered versions)	Pain	V
Escobar, 2002[167]	WOMAC (Spanish version)	Pain	RC
Faucher, 2002[168]	WOMAC (Canadian French version) LAI (Canadian French version)	Pain	V R
Angst, 2001[165]	WOMAC	Pain	RC
Bae, 2001[166]	WOMAC (Korean version) LAI (Korean version)	Pain	V R RC
Lingard, 2001[188]	KSS	Pain	V RC
Salaffi, 2000[182]	AIMS2 (Italian version)	Pain	V R
Roos, 1999[171]	WOMAC (Swedish version)	Pain	V R RC
Wigler, 1999[174]	WOMAC (Hebrew version)	Pain	V R
Stucki, 1998[164]	WOMAC LAI	Pain	V R
Bellamy, 1997[179]	WOMAC (computerized version)	Pain	V R
Lewis, 1995[191]	KIP	Pain during active or passive movements	V R
Rejeski, 1995[190]	KPS	Pain during functional activities	V R
Wessel, 1995[189]	Dolorimeter (pressure algometer)	Pain threshold	V R

*V: validity; R: reliability; RC: responsiveness to change

4.2.2.2 Energy-Sleep-Emotions

4.2.2.2.1 Joint-Specific Multidimensional Assessment of Pain (J-MAP)

A study was conducted by O'Malley et al.[186] to determine the validity and responsiveness to change of the J-MAP, a self-administered questionnaire evaluating the affective components of pain in individuals with knee OA. According to the authors, the J-MAP provides a valid measure of the emotional impact of pain on such individuals (correlation coefficient ranging from 0.49 to 0.64) and the instrument is responsive to change (internal responsiveness = 0.65-0.66).

4.2.2.2.2 McGill Pain Questionnaire (MPQ) and Short Pain Inventory (SPI)

Kilminster et al.[195] were the first authors to contrast the MPQ and SPI. In general, the validity was found to be poor to moderate for both instruments (correlation coefficient ranging from 0.317 to 0.405), but their internal consistency was strong (Cronbach's alpha = 0.88 for the SPI; 0.823 for the MPQ (total score)). However, the SPI was found to be superior to the MPQ for evaluating the affective aspect of pain, while the MPQ was better for evaluating the sensory aspect.

4.2.2.3 Joint Function

4.2.2.3.1 Pivot Shift Test: joint stability – ligament integrity

Dodd et al.[196] investigated the validity of the pivot shift test by comparing it to an intraoperative visualization of the anterior cruciate ligament (ACL). The results showed that 100% of the study participants had a negative pivot shift test pre-operatively (indicating ligament integrity). Yet 42 of the 50 study participants had an ACL described as normal in the intraoperative visualization evaluation. The authors reported a specificity value of 1% and a responsiveness of 0%.

4.2.2.3.2 Pendulum test: joint stiffness

Another study, conducted by Burks et al.[197], assessed the validity of a modified pendulum test (using the 3D Vicon movement measurement system) for evaluating joint stiffness. A poor correlation between the stiffness coefficient estimated using the modified pendulum test and the self-report stiffness measure ("Stiffness Subscale" of the WOMAC) (r = 0.36) and non-significant correlations with the total score on the WOMAC were obtained. However, due to substantial methodological shortcomings, the validity of this test was cast into doubt. The statistical analyses were in fact not described. Also, the results of the control group participants were not differentiated from those of the participants with knee OA. The severity of the knee OA was characterized by the WOMAC score. Lastly, other tests assessing joint stiffness objectively were also apparently performed, but were not included in the analyses.

4.2.2.3.3 Active knee repositioning test: proprioception

Proprioception was the subject of only one validity and reliability study involving a population with knee OA. By evaluating equations that calculated active knee repositioning, Marks[198] found that two of these equations could be used to predict the presence of knee OA. Moreover, the fact that only 6.66% of the participants were able to reposition their knees at exactly the same angle as the starting angle demonstrated the prevalence of this problem in individuals with knee OA. Also, the authors found that calculating the mean algebraic error and the total constant error were the best methods for determining which individuals had knee OA. Moderate reliability indices (ICC = 0.47 for the mean algebraic error and ICC = 0.46 for the total constant error) and high validity scores (correlations with the Lequesne index: $r = 0.84$ for the mean algebraic error and $r = 0.91$ for the total constant error) were found for these methods of calculation.

4.2.2.3.4 Cyriax's concept of capsular pattern

The validity and reliability of the evaluation of capsular patterns was the subject of two studies. According to Bijl et al.[199], the evaluation of capsular patterns is not a valid method for differentiating an impaired knee with OA from a healthy knee. In fact, the range of motion values for healthy knees showed no significant difference from those for arthrosic knees. However, the "normal" range of motion values were obtained in the same participants by measuring their "healthy" limb. This limits how these results can be interpreted because the function of the contralateral joint can also be altered.

The results of the study conducted by Hayes et al.[200] were similar. While correlations were established between pain intensity and disease chronicity, and good test-retest reliability scores were obtained (ICCs ranging between 0.71 and 0.99, depending on the movement evaluated), only a few participants with knee OA and who had had symptoms for an average of 83.6 months presented with capsular pattern restrictions.

Table 5: Summary of evaluation instruments and rating scales documented in articles in "Joint Function" category

First author, year (reference)	Instrument/Rating Scale	Item measured	Property measured*
Dodd, 2010[196]	Pivot Shift Test	Ligament integrity (ACL)	V
Burks, 2006[197]	Pendulum test	Joint stiffness	V
Bijl, 1998[199]	Cyriax's concept of capsular pattern	Range of joint motion	V R
Marks, 1994[198]	Active knee repositioning test	Proprioception	R V
Hayes, 1994[200]	Cyriax's concept of capsular pattern	Range of joint motion	V R

*V: validity, R: reliability, RC: responsiveness to change.

4.2.2.4 Muscle function

4.2.2.4.1 Validity of protocols for evaluating muscle strength

The validity of protocols used to evaluate muscle strength in a population with knee OA was assessed in three studies. The first, conducted by Roschel et al.[201], concerned the number of familiarization sessions needed to evaluate maximum muscle strength using the 1-repetition maximum (1-RM) procedure. The results showed that 3.8 sessions were required on average to obtain reliable results and avoid overestimating gains in strength following an intervention.

Hayes et al.[202] measured the association between two commonly used clinical techniques for evaluating muscle strength: hand-held dynamometry and manual muscle testing. The authors concluded that manual muscle testing overestimated muscle strength in individuals with knee OA (Kendall's correlation coefficient = 0.24). Also, dynamometry was found to provide a more objective measure for evaluating strength for higher levels of strength than manual muscle testing. Only hand-held dynamometry was able to detect weakness in the knee extensor muscles. Both intra-reviewer reliability (ICCs = 0.89-0.98) and inter-reviewer reliability (ICC = 0.92) of hand-held dynamometry were found to be excellent.

The third study, carried out by McNair et al.[203], measured the association between prediction equations developed to determine the one-repetition maximum (1-RM) and the 1-RM values obtained by applying the traditional assessment method. Two reinforcement exercises for the knee extensors were studied: the first, an open-chain leg extension exercise, and the second, a closed-chain seated leg press exercise. A strong association was observed between the traditional method of determining the 1-RM and the equations of Brown and Weir[204], Brzycki[205], and Mayhew et al.[206] for the knee extension exercise; and the equations of Adams, Berger, Kemmler et al. and of O'Conner et al. for the seated leg press exercise (CCI between 0.96 and 0.99). The typical error (% coefficient of variation) was 4% for the knee extension exercise and 6% for the seated leg press exercise. The authors mention that the use of these prediction equations would reduce the number of repetitions required, which would in turn reduce the pain bias.

4.2.2.4.2 Indices of strength

Steultjens et al.[207] conducted a study to develop indices of muscle function based on assessment of the strength of 16 lower limb muscles. The authors showed that the strength of the knee muscle strength was the most representative index for quantifying the impact of knee OA on muscle function (Cronbach's alpha values > 0.74).

4.2.2.4.3 Reliability of assessment of isometric muscle strength

Several studies on this subject were documented. Generally speaking, test-retest, intra- and/or inter-reviewer reliability of the assessment of isometric quadriceps strength in individuals with knee OA were found to be good to excellent (ICCs ranging from 0.76 to 0.99).[208-215] However, regardless of the system used to measure strength (Cybex hand-held dynamometer, Kin-Com isokinetic dynamometer, Xtran load cell), measurement error was high (values as high as 36.2%). Koblbauer et al.[208] nonetheless observed that inter-reviewer reliability (ICCs = 0.90- 0.96) was better than intra-reviewer reliability (ICCs = 0.76-0.97). The study by Wessel et al.[214] reported that the assessment of isometric strength would be more reliable if the knee were positioned at a 60° angle of extension. However, these results must be interpreted with caution given the small sample size (n = 17).

4.2.2.4.4 Reliability of assessment of isokinetic muscle strength

Four studies assessing isokinetic muscle strength were retained. The results of these studies converged and showed test-retest reliability varying from good to excellent (ICCs ranging from 0.75 to 0.98).[209,213,215,216] High measurement error was also reported (values approaching 30%). Only one study, that conducted by Germanou et al.[216], investigated the difference in reliability values in a sample of participants with various levels of impairment. The results showed that the reliability of assessment of isokinetic muscle strength was slightly higher in participants with knee OA in the early stages (ICCs = 0.89-0.93) than in those with more advanced knee OA (ICCs = 0.75-0.93).

4.2.2.4.5 Reliability of assessment of muscle activation

Kean et al.[209] investigated the test-retest reliability of a method for assessing quadriceps activation using an electrical nerve stimulator during resisted knee extension. The method was found to have excellent reliability (ICC = 0.93) and a relatively low percentage of error (4.67%). The authors recommended, however, using the instrument solely for research given the lack of scientific knowledge regarding its clinical use. In another study, McCarthy et al.[210] tested the quantification of muscle activation and fatigue using EMG assessment. The reliability and error indices obtained for quadriceps activation were good (ICC = 0.84-0.91; SEM = 3.60-5.77). However, the assessment of muscle fatigue was unreliable, with a wide variation observed in the reliability and error indices (ICCs = 0.04-0.72; SEM = 0.10-0.784).

Table 6: Summary of evaluation instruments and methods documented in articles in "Muscle Function" category

First author, year (reference)	Instrument/Method	Item measured	Property measured*
Roschel, 2011[201]	Assessment of 1-RM	Maximal muscle strength	V
McNair, 2011[203]	Prediction equations for 1-RM	Maximal muscle strength	V
Koblbauer, 2011[208]	Citec hand-held dynamometer type CT 3001	Isometric muscle strength	R
Steultjens, 2011[207]	-	Muscle strength indices	R
Kean, 2010[209]	Isokinetic dynamometer Voluntary muscle activation (electric stimulator)	Isokinetic and isometric muscle strength Muscle activation	R R R
McCarthy, 2008[210]	Biodex isokinetic dynamometer Biodex EMG signal	Isometric muscle strength Maximal muscle strength Muscle activation Muscle fatigue	R R R R
Germanou, 2007[216]	Cybex 6000	Isokinetic muscle strength Maximal muscle power	R R
Fransen, 2003[211]	Xtran Load Cell	Isometric muscle strength	R
Robertson, 1998[212]	Leg Extensor Power (power rig) Kin-Com dynamometer	Isometric muscle strength	R
Madsen, 1996[213]	Cybex 6000 dynamometer	Isometric and isokinetic muscle strength	R R
Wessell, 1996[214]	Kin-Com isokinetic dynamometer	Isometric and isokinetic muscle strength	R R
Madsen, 1995[215]	Cybex II dynamometer	Isometric and isokinetic muscle strength	R R
Hayes, 1992[202]	Hand-held dynamometer Manual muscle testing	Comparison of measurements	V R

*V: validity, R: reliability, RC: responsiveness to change

4.2.3 Instruments for "Activity" component

4.2.3.1 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The WOMAC is, by far, the measurement instrument most often studied and used with this population. Even so, very little information on the psychometric properties of the original version of the instrument is available, with most studies focusing on its transcultural validation.

WOMAC (original version): Due to the poor quality of the study conducted by French et al.[217] (insufficient information on the sample), the Angst et al.[165] study is the only one retained in this systematic review. The results showed that the "Function" subscale of the WOMAC had good responsiveness to change following a rehabilitation program lasting three to four weeks (SRM = 0.638; ES = 0.425). The WOMAC's responsiveness to change was higher than that of the SF-36.

WOMAC-SF: Yang et al.[218] studied the validity of the WOMAC-SF, which is a short version of the instrument. The high correlation indices observed between the WOMAC and the WOMAC-SF (Lin's concordance coefficient correlation: 0.96-0.98), as well as the absence of difference between the two formats of the questionnaire (Bland Altman plot: 0.23 [SD: 5.8]) pointed to their equivalence. The same applied to its responsiveness to change, which was comparable at three and six months (SF: SRM = 0.44-0.56; full version: SRM = 0.51-0.58).

WOMAC (telephone interview): Bellamy et al.[178] showed equivalent results for the telephone-administered version of the WOMAC and the traditionally administered version (paper questionnaire). In fact, agreement between the scores was excellent, with a mean difference for the "Function" subscale of 0.78 and for the total score, of 0.98.

Transcultural validation: Several studies focussed on the transcultural validation of the WOMAC. The Canadian French version demonstrated moderate to good validity and good reliability (validity: r = 0.37-0.72; test-retest reliability: ICCs = 0.74-0.85)[168,169], as did the other translated versions (validity: r = 0.33-0.69; test-retest reliability: ICCs = 0.69-0.98; responsiveness to change (ES: 0.56-1.5; SRM: 0.70-1. 3).[163,166,167,170,173-175,192,193]

4.2.3.2 Lequesne Algofunctional Index (LAI)

Original version: Franchignoni et al.[219] reported poor correlation between the "*pain or discomfort when getting up from sitting without the help of arms*" item (r = 0.28) and the total score for all items. In addition, the Rasch models showed two misfitting items associated with pain: "*pain or discomfort when getting up from sitting without the help of arms"* and "*duration of morning stiffness or pain after getting up*."

LAI-modified: Faucher et al.[183] developed a short version of the instrument. It showed good construct validity (r = 0.75) and excellent test-retest reliability (intervals of 3.04 ± 0.24h; average ICC of 0.95). No ceiling or floor effect was observed.

Transcultural validation: Most of the studies on the transcultural validation of the LAI showed the translated versions to have good psychometric properties (validity: correlation coefficients ranging from 0.37 to 0.80; test-retest reliability: ICCs = 0.61-0.92; responsiveness to change: ES = 0.05).[163,166,184,185]

4.2.3.3 Knee Injury and Osteoarthritis Outcome Score (KOOS)

KOOS-PS: Ruyssen-Witrand et al.[154] demonstrated that the short version of this instrument had good construct validity. Moderate to strong correlations were found between the KOOS-PS and the function subscale of the WOMAC (r = 0.84), the Patient Function Numerical Scale (r = 0.53), and the Lequesne Algofunctional Index (r = 0.66). Lastly, it was found to have moderate responsiveness to change when evaluated at six weeks following a treatment with non-steroidal anti-inflammatories (NSAIDs) (SRM = 0.52)[153], but excellent responsiveness at 12 weeks following knee arthroplasty (SRM = 0.89).[154]

Transcultural validation: The KOOS is available in several languages, including Japanese, Portuguese, German, and French. All versions have good psychometric properties (validity: correlation coefficients = 0.60-0.92; test-retest reliability: ICCs = 0.70-0.92; responsiveness to change: SRM = 0.70-1.21).[155,156,158,220-222]

4.2.3.4 Patient Function Numerical Rating Scale (NRS)

The Patient Function NRS evaluates an individual's perception of his or her level of functioning. The person has to answer the following question: "*What is the degree of difficulty you have experienced for the daily activities during the last 48 hours due to your (knee or hip) OA*?" The results of the study by Ornetti et al.[223] showed good construct validity (strong correlations with the VAS PAIN subscale, with the function subscale of the WOMAC and with the Patient Global Assessment (PGA) (r = 0.666; 0.616 and 0.714 respectively)) and excellent responsiveness to change (SRM = 0.83, ES = 0.89) following a four-week treatment with anti-inflammatories. No floor or ceiling effect was found. However, the test was not able to discriminate between patients on the basis of the radiographic progression in their disease.

4.2.3.5 Oxford Knee Score (OKS)

The three studies on the OKS investigated the instrument's transcultural validation. They showed that the English version, the Cantonese version adapted to the Singapore population, and the Italian version all have good validity (correlation coefficients = 0.49-0.81) and good test-retest reliability (ICCs = 0.66-0.88).[224] [162,225]

4.2.3.6 Osteoarthritis of Knee Hip Quality of Life (OAKHQOL)

Only one article reported on the psychometric properties of this questionnaire.[226] A strong correlation was observed between the "physical activity" dimension of the OAKHQOL and the "physical function" dimension of the SF-36 (r = 0.66). The instrument also showed a strong correlation with the WOMAC (r = 0.88) and the LAI (r = 0.66). Lastly, the questionnaire's responsiveness to change, evaluated at six months and one year, was poor to moderate for the domains related to social activities (SRM = 0.21/0.04) and social support (SRM = 0.28/0.23), but excellent for the other domains (SRM six months = 0.73 to 1.19, SRM on year = 0.58 to 1.10). Of the 46 items in the instrument, 13 had a significant ceiling or floor effect (> 30%).

4.2.3.7 Physical Activity Restrictions (PAR)

Only one study documented the PAR, a functional disability measurement instrument including an evaluation of the performance of various activities of daily living, including walking (evaluated by a six-minute test), climbing stairs, leaning over to pick up an object, sitting down, lifting and carrying loads, and getting into and out of a vehicle. According to Rejeski et al.[190], the instrument had low validity (r = 0.13-0.48), while test-retest reliability was more robust (moderate to high, r = 0.46-0.93).

4.2.3.8 Aggregated Locomotor Function (ALF)

One study investigated the ALF.[227] High intra-class correlation coefficients were reported between each test and the total result (ICCs = 0.98-0.99). Also, the standard errors of measurement were very low (SEM = 0.26-0.87 seconds). The correlation values between the sub-dimensions of the ALF and the reference instruments (the "Function" subscale of the WOMAC and "Physical Function" domain of the SF-36) pointed to moderate to good construct validity (WOMAC: r = 0.57-0.59 and SF-36: r = 0.41-0.53). Responsiveness to change, evaluated 12 months after an exercise program was higher than that of the SF-36 and the WOMAC (ALF: 0.49, WOMAC: 0.39, SF-36: 0.12). Lastly, the smallest detectable difference was 9.5% of the total score.

4.2.3.9 Knee Society Clinical Rating System (knee and function scores)

Lingard et al.[188] studied this instrument's validity and responsiveness to change. Both parts of the questionnaire (Knee Society knee score and Knee Society function score) showed moderate to strong correlations with the corresponding domains of WOMAC (r = 0.58) and of the SF-36 (r = 0.72), which attests to good convergence validity. However, the responsiveness to change of the two parts, evaluated 12 months after total knee replacement, was lower than that of both the WOMAC and the SF-36. Given that the SF-36 and the WOMAC have better psychometric properties and are self-administered, the authors recommended using these questionnaires over the Knee Society Clinical Rating System.

4.2.3.10 Knee Outcome Survey-Activities of Daily Living Scale (KOS-ADLS)

No study examining the psychometric properties of the original version of this questionnaire was found. However, the study conducted by Goncalves et al.[228] supported the validity, reliability, and responsiveness to change of the Portuguese version of the instrument (r = 0.69; ICC = 0.97; ES and SRM = 0.38 and 0.46 respectively).

4.2.3.11 Arthritis Impact Measurement Scales (AIMS2)

Only the Salaffi et al.[182] study investigated the AIMS2. It demonstrated that the Italian version of the instrument has good validity and good reliability (r = 0.35-0.67; ICC = 0.78-0.80). No data on the original version was available.

4.2.3.12 Human Activity Profile (HAP)

Bennell et al.[229] documented the reliability and validity of the two HAP scores: the Maximal Activity Score (MAS), which represents the highest level of cardiorespiratory activity that the individual is able to attain, and the Adjusted Activity Score (AAS), which represents the mean

cardiorespiratory level attained on a daily basis. Both scores had excellent test-retest reliability (intervals of 2 to 7 days, ICC = 0.96 and 0.95 for the MAS and AAS respectively) and a low measurement error (SEM = 3% for both scores). The HAP, particularly the AAS score, discriminated individuals with knee OA. The results showed low or moderate correlations with the generally-used pain and function measurement instruments, such as the WOMAC (MAS: r = 0.23-0.46; AAS: r = 0.39-0.59). Multiple regression analysis explained only 50% of the variance in the HAP scores. The authors suggest that the HAP evaluates another aspect of function, possibly, level of physical activity and energy expenditure. They therefore recommend using it as a complement to the instruments used to evaluate functional activities.

4.2.3.13 Walking Impairment Questionnaire (WIQ)

The WIQ is a questionnaire that was developed to assess walking tolerance in individuals with peripheral artery disease in their lower extremities. Collins et al.[230] studied its reliability and validity for people with knee OA. The results revealed excellent internal consistency (Cronbach's alpha ranging from 0.87 to 0.97) and excellent test-retest reliability at 14-day intervals (ICC ranging from 0.86 to 0.87; mean differences: 2.75 to 6.25 points ($p < 0.05$)). With regard to validity, moderate correlations were found with the 6-minute walk test (6MWT) and with the evaluation of the number of stairs climbed and descended in three minutes (r = 0.50 and 0.56). In addition, the relationship between pain, stiffness, and function as reported by the individual pointed to good construct validity; the more significant the pain, stiffness, and functional decline, the lower the WIQ scores.

4.2.3.14 Short-Form Health Survey (SF-36)

Angst et al.[165] documented the responsiveness to change of the SF-36 and the WOMAC following a three- to four-week rehabilitation program. Generally speaking, the results showed that the SF-36 was responsive to change, but less so than the WOMAC (WOMAC: SRM/ES = 0.628/0.425; SF-36: SRM/ES = 0.249/0.202).

4.2.3.15 Lower Extremity Activity Profile (LEAP)

Finch et al.[231] reported that the LEAP had good internal consistency (Cronbach's alpha ranging from 0.69 to 0.78) and the "Mobility" domain was responsive to change (SEM = 5.0). However, the correlations between the LEAP and clinical measures (e.g. comfortable walking speed and range of joint motion) were poor to moderate.

4.2.3.16 Timed-Up-and-Go Test (TUGT), Timed-Stand Test (TST), Six-Minute Walk Test (6MWT)

The only study that investigated the responsiveness to change of these instruments was one conducted by French et al.[232] Due to methodological weaknesses (lack of information on the

study sample, no hypothesis presented, lack of information that would allow the study to be reproduced, etc.), the results are not presented in this systematic review.

4.2.3.17 Self-Paced Walking Time Measure (SPW)

Two studies carried out by Marks examined the psychometric properties of the SPW.[198,233] The results revealed a strong correlation with the Index of Severity for Knee Disease (ISK), a short version of the LAI (r = 0.65), thus supporting its construct validity.

Table 7: Summary of evaluation instruments and rating scales documented in articles in "Activity" category

First author, year (reference)	Instrument/Rating Scale	Details	Property measured*
Franchignoni 2012[219]	LAI	Original version	Rasch
Bond 2012[153]	KOOS	Short version (KOOS-PS)	RC
Ruyssen-Witrand 2011[154]	KOOS	Short version (KOOS-PS)	R, V, RC
Ornetti 2011[223]	Patient function NRS	Original version	V, RC
Nakamura 2011[222]	KOOS	Japanese version	T (R, V, RC)
French 2011[232]	LAI, WOMAC, 6MWT, TST, TUGT	Original version	RC
Goncalves 2010[221]	KOOS	Portuguese version	T (R, V, RC)
Basaran 2010[163]	WOMAC, LAI	Turkish version	T (R, V, RC)
Ornetti 2009	KOOS	French version (KOOS-PS)	T (R, V, RC)
Ko 2009	OKS	English and Cantonese versions (Singapore)	R, V
Goncalves 2009[220]	KOOS	Portuguese version	T (R, V, RC)
Xie 2008[193]	WOMAC	English and Cantonese versions (Singapore)	T (R, V, RC)
Soininen 2008[192]	WOMAC	Finnish version	T (R, V, RC)
Ornetti 2008[156]	KOOS	French version	T (R, V, RC)
Goncalves 2008[228]	KOS-ADLS	Portuguese version	T (R, V, RC)
Faik, 2008[175]	WOMAC	Moroccan version	T (R, V, RC)
de Groot 2008[155]	KOOS	German version	T (R, V, RC)
Collins 2008[230]	WIQ	Original version	R, V
Yang 2007[218]	WOMAC-SF	Short version	V, RC
Xie 2007[185]	LAI	English and Cantonese versions (Singapore)	T (R, V, RC)
Xie 2007[225]	OKS	English and Cantonese versions (Singapore)	T (R, V)
Xie 2006[158]	KOOS	English and Cantonese versions (Singapore)	T (R, V, RC)
Rat 2006[226]	OAKHQOL	Original version	R, V, RC
Tuzun 2005[173]	WOMAC	Turkish version	T (R, V, RC)
Mc Carthy 2004[227]	ALF	Original version	R, V, RC
Guermazi 2004[170]	WOMAC	Arabic version (Tunisia)	T (R, V)
Guermazi 2004[184]	LAI	Arabic version (Tunisia)	T (R, V, RC)
Faucher 2004[169]	WOMAC	Canadian French version (modified version)	T (R, V)
Bennell 2004[229]	HAP	Original version	R, V
Padua 2003[224]	OKS	Italian version (OKS-12)	T (R, V)
Faucher 2003[183]	LAI	Modified LAI	R, V
Faucher 2002[168]	WOMAC and LAI	Canadian French version	T (R, V)
Escobar 2002[167]	WOMAC	Spanish version	T (R, V, RC)
Bellamy 2002[178]	WOMAC	Telephone interview format	V

		(WOMAC LK 3.0)	
Lingard 2001[188]	Knee Society Clinical Rating System	Original version	V, RC
Bae 2001[166]	WOMAC and LAI	Korean version	T (R, V, RC)
Angst 2001[165]	WOMAC and SF-36	Original version	RC
Salaffi 2000[182]	AIMS	Italian version (AIMS2)	T (V, R)
Wigler 1999[174]	WOMAC	Hebrew version	T (V, R, RC)
Rejeski 1995[190]	PAR	Original version	V, R
Finch 1995[231]	LEAP	Original version	V, RC
Marks 1994[198]	SPW	Original version	V
Marks 1994[233]	SPW	Original version	V

*V: validity, R: reliability, RC: responsiveness to change; T: transcultural validation

4.2.4 Instruments for "Participation" component

4.2.4.1 Difficulties in the Daily Life of Patients with Knee Osteoarthritis Scale (DDLKOS)

This instrument measures the level of difficulty experienced in performing activities of daily living (AVQ). Tanimura et al.[234] reported the instrument as having moderate validity when the results they obtained were compared to those obtained with other measures such as range of joint motion, pain, and weakness (p = 0.45, p = 0.45 and p = 0.44, respectively). However, the instrument's internal consistency indices were high (Cronbach's alpha = 0.89-0.90).

4.2.4.2 World Health Organization Disability Assessment Schedule II (WHODAS-II)

This instrument was developed by the World Health Organization (WHO) for the purpose of assessing participation restrictions. Kutlay et al.[235] obtained moderate validity scores when they studied the instrument's correlation with the WOMAC's function subscale (r = 0.59). The instrument showed excellent test-retest reliability (ICCs = 0.95 (IC 95%: 0.92-0.97) and 0.59 (IC 95%: 0.90-0.95) for the "general participation" and "participation in society" domains respectively. Lastly, the instrument was found to have good internal consistency (Cronbach's alpha ranging from 0.74-0.87).

4.2.4.3 LEAP

Finch et al.[231] reported that the "leisure" and "social participation" domains were responsive to change (SEM = 6.1 for leisure and 6.2 for social participation).

4.2.4.4 ADL Taxonomy

This instrument measures a person's ability to perform 47 tasks normally classified under the heading of activities of daily living (ADLs). Gudbergsen et al.[159] compared the paper and

computerized versions of the instrument. The median difference in values was 0.8, while test-retest reliability was 0.97 (ICC).

4.2.4.5 Work Instability Scale for Rheumatoid Arthritis (RA-WIS)

Tang et al.[236] studied the validity of the RA-WIS in individuals with knee OA. This instrument covers a set of constructs including perception of control over symptoms, performance of work-related tasks, energy at work, time management at work, and psychological distress at work. Overall, the difficulties experienced in relation to these constructs would appear to contribute to a state of instability at work. The authors showed that the RA-WIS has excellent construct validity (χ^2 = 83.2, p = 0.03), strong internal consistency (KR-20 = 0.93) and high responsiveness to change (SRM = 1.05 [deterioration]); -0.78 [improvement]).

4.2.4.6 Work Limitation Questionnaire (WLQ)

Lerner et al.[237] documented the validity of the WLQ, an instrument designed to measure the impact of knee OA on work. Correlations were established with various measures of health status, such as the scores on the WOMAC, the SF-12 (physical component), and the SF-36. The results appear to support the WLQ's construct validity: the instrument appears capable of differentiating people with knee OA from those without. The WLQ was also correlated with measures of health status. Excellent internal consistency scores were also obtained (Cronbach's alpha = 0.93-0.97).

Table 8: Summary of evaluation instruments and rating scales[2] documented in articles in "Participation" category

First author, year (reference)	Instrument/Rating Scale	Details	Property measured*
Xie, 2011[160]	OKS	Participation	V
Tanimura, 2011[234]	DDLKOS	Difficulties experienced in performing activities of daily living (ADLs)	V
Ornetti, 2011[223]	Patient Function NRS	The individual's perception of his or her functional level	V, RC
Kutlay, 2011[235]	WHODAS-II	Participation	V, R
Finch 1995[231]	LEAP	Original version	V, RC
Gudbergsen, 2011[159]	KOOS VAS function subscale SF-36 Physical Activity Scale ADL Taxonomy (computerized versions)	Participation	V, R

[2] Due to the key words used in the search strategy, several instruments/rating scales were identified for both the "Activity" component and the "Participation" component. This factor explains why the number of studies in the flowchart is 52 (Appendix C). It also explains why Table 8 lists more than the five instruments discussed in the section.

French, 2011[232]	LAI WOMAC	Participation	RC
Basaran, 2010[163]	WOMAC LAI	Participation	V, R
Naal, 2009[161]	OKS	Participation	V, R
Mousavi, 2009[181]	AIMS2	Participation	V, R
Goncalves, 2009[220]	KOOS	Portuguese version	V, R, RC
Xie, 2008[193]	WOMAC	English and Chinese versions	V, R
Soininen, 2008[192]	WOMAC	Participation	V, R, RC
Ornetti, 2008[156]	KOOS	French version	V, R, RC
Faik, 2008[175]	WOMAC	Moroccan version	V, R
De Groot, 2008[155]	KOOS	Participation	V, R
Yang, 2007[218]	WOMAC-SF	Participation	V, R RC
Paker, 2007[157]	KOOS	Participation	V, R
Kuptniratsaikul, 2007[194]	WOMAC	Participation	V, R
Xie, 2006[158]	KOOS	English and Chinese versions	V, R
Tuzun, 2005[173]	WOMAC	Participation	V, R, RC
Salaffi, 2005[172]	WOMAC SF-36	Italian versions	V
Atamaz, 2005[180]	AIMS2	Participation	V, R
Angst, 2005[176]	WOMAC factors	Participation	V, RC
Villanueva-Torrecillas, 2004[177]	WOMAC	VAS and CT versions	V, R, RC
Guermazi, 2004[170]	WOMAC	Participation	V, R
Faucher, 2004[169]	WOMAC	Participation	V, R
Bennell, 2004[229]	HAP	MAS AAS	V, R
Salaffi, 2003[172]	WOMAC	Participation	V, R
Padua, 2003[224]	OKS-12	Italian version	V, R
Faucher, 2003[183]	LAI	Participation	V, R
Faucher, 2002[168]	WOMAC LAI	Participation	V, R
Escobar, 2002[167]	WOMAC	Participation	V, R, RC
Bellamy, 2002[178]	WOMAC LK 3.0	Paper version Telephone version	V
Bae, 2001[166]	WOMAC LAI	Participation	V, R, RC
Angst, 2001[165]	WOMAC	Participation	RC
Salaffi, 2000[182]	AIMS2	Participation	V, R
Wigler, 1999[174]	WOMAC	Participation	V, R
Roos, 1999[171]	WOMAC	Participation	V, R RC
Brazier, 1999[238]	WOMAC SF-36 EQ-5D HAQ		V, RC
Stucki, 1998[164]	WOMAC LAI	Participation	V, R
Bellamy, 1997[179]	WOMAC	Computerized version	V, R
Tang, 2010[236]	RA-WIS	Work disability	V, RC
Lerner, 2002[237]	WLQ	Work disability	V, R

* V: validity, R: reliability, RC: responsiveness to change

4.3 Interventions

Our searches yielded 5,126 potentially relevant references. After completing the selection process, we retained 273 documents for our review (see Appendix D, which includes two flowcharts).

4.3.1 Non-pharmacological approaches

4.3.1.1 Exercises

Pain: ★★ – ★★★
Function: ★★

A number of quality systematic reviews and meta-analyses have determined that land-based exercise (such as aquatic exercise) has beneficial impact ranging from low to moderate on the symptoms of knee OA, mainly with respect to pain and function. These effects appear to be felt mostly in the short term[239-242]. In a systematic review specifically on this topic, Pisters et al.[243] demonstrated that solid evidence existed about their long-term ineffectiveness.

Strength training and exercise therapy both appear to have low positive impact in terms of reducing pain and improving function. This impact appears to be moderate when manual passive mobilization is combined with exercises[244]. Added to the results of this review are those from several trials published between 2009 and 2011. The latter demonstrated that knee and hip muscle strengthening exercises, regardless of type, were more beneficial than doing no exercises in terms of reducing the symptoms of knee OA and improving physical performance and range of motion, to name but a few of their benefits.[245-247]

In their systematic review, Lange et al. concluded that resistance training programs improve pain, stiffness, and physical performance scores in a majority of the subjects who do such programs.[248] A recent article[249] demonstrated that the addition of agility and perturbation training techniques to such programs did not really enhance their effectiveness.

Aerobic exercises, regardless of their intensity, appear to reduce pain and improve function, walking ability, and aerobic ability.[250] Moreover, two recent articles[251,252] revealed that high-intensity training does not appear to have more beneficial effects than lower-intensity training.

What emerges from Walsh et al.'s systematic review is that therapies which combine exercises with self-management programs appear to reduce pain and improve function.[253] However, considered separately, both would appear to be almost equally effective in reducing systems of knee OA and improving both physical performance and well-being.[254-256] The beneficial effects may be modest, but are nonetheless important from a clinical standpoint.

The scientific evidence concerning Tai chi is not clear-cut. The authors of one systematic review concluded that it is ineffective in reducing pain, function, and stiffness scores[257], while other

authors reached the opposite conclusion.[258] They nonetheless concurred that the trials on the subject were generally of poor quality and that their results were based on small samples. However, in the two quality articles retained[259,260], the authors concluded that Tai chi was effective in reducing symptoms of knee OA and improving physical performance.

Synthesis

Overall, individuals with knee OA who envisage doing exercise may expect low to moderate beneficial impacts in terms of pain and low beneficial impacts in terms of function. These impacts appear to be felt more in the short term, regardless of the type or intensity of exercise recommended. The authors generally concur that more high-quality trials and homogenous interventions are required to better ascertain the impacts of exercise on knee OA. Other trials should also investigate optimal dose-response relationships.

4.3.1.2 Intra-articular injections

Pain (hyaluronic acid and derivatives): ★ – ★★
Function (hyaluronic acid and derivatives): ★

The authors of six systematic reviews on the efficacy of hyaluronic acid injections[261-266] all found that these injections had beneficial effects in terms of alleviating pain and improving function. While some authors actually take a position by specifying that these effects are small, others are more reticent to reach a conclusion due to major publication biases and the heterogeneity among the studies. Moreover, hyaluronic acid appears to achieve maximum efficacy between the fourth and thirteenth weeks following injection[262,263,265], not to mention the fact that higher-molecular-weight hyaluronic acid has greater efficacy than acid with lower molecular mass.[264] With regard to recent controlled trials, the authors of one concluded that hyaluronic acid injections had greater efficacy than injections of placebo saline solutions in alleviating pain and improving function (regardless of molecular mass)[267], while the authors of another stated the opposite: that hyaluronic acid had no more efficacy than the placebo.[268] Other trials have shown that hyaluronic acid injections have as much, or greater, efficacy than injections of substances such as long-chain polynucleotides or Clodronate.[269-271]

One systematic review looked specifically at the efficacy of Hylan G-F 20.[272] The authors found that a single intra-articular injection of Hylan G-F 20 could significantly reduce pain in the short term and improve function, with fewer side effects than oral NSAIDs. Another systematic review, carried out by Reichenbach et al.,[273] sought to compare the efficacy of intra-articular injections of high-molecular-weight Hylan to that of regular preparations of hyaluronic acid in terms of pain reduction. Both were found to have comparable efficacy, although the relative risk of side effects was approximately twice as high in subjects treated with Hylan. In a more recent trial, Diracoglu et al.[274] were able to demonstrate that injections of Hylan G-F 20 led to a short-term increase in proprioception and isokinetic muscle strength as well as significant improvements in symptoms and function.

While the systematic review by Arroll and Goodyear-Smith[275] on the efficacy of corticosteroid injections established that their beneficial effects on the symptoms of knee OA were felt in both the short and long terms, more recent systematic reviews state that the beneficial effects, essentially regarding pain, are felt for a maximum of one to three weeks.[276-278] Furthermore, it appears that triamcinolone has greater efficacy than the other corticosteroids.[278]

More recent trials have investigated the efficacy of other injectable substances, but it is too early at this stage to draw any firm conclusions because the trials are too few in number.

Synthesis

Overall, our results confirm that injections of hyaluronic acid and its derivatives have beneficial effects on the alleviation of pain caused by knee OA. In half of the studies, the authors concluded that the beneficial effects were small, while in the other half, the authors found it impossible to rule on the level of efficacy because of the heterogeneity among the studies. Beneficial effects were also reported in terms of function, but again, there was too much heterogeneity among the studies to be able to establish the level of efficacy. It should further be noted that the beneficial effects are not immediate and their duration is limited.

4.3.1.3 **Supplements**

Pain and function (glucosamine and chondroitin): ★
Structural progression of knee OA (glucosamine and chondroitin): ★

Several of the selected systematic reviews investigated the efficacy of glucosamine and chondroitin in alleviating the main symptoms of knee OA. While some authors stated that the positive effects of these supplements in terms of pain and function ranged from small to large[279-282], others found that the efficacy of glucosamine and chondroitin was more or less equal to, or no more greater than, that of placebos.[283-285] The authors of one review also found that one particular commercial-brand of glucosamine proved to have efficacy, but not the others.[286] Taking either one of these supplements could nonetheless slow the structural progression of the disease and the narrowing of the joint space.[281,282,286-288] Some authors spoke of minimal to moderate effects, while others preferred not to express an opinion on their impact owing to the heterogeneity among the studies. Regarding the more recent controlled trials, the authors generally talked about the efficacy of glucosamine and chondroitin[289-291]; only one study concluded otherwise.[292]

Systematic reviews of the efficacy of other supplements for alleviating the symptoms of knee OA, i.e. the avocado-soybean unsaponifiables,[293] dimethyl sulfoxide, and methylsulfonylmethane[294,295] and S-Adenosylmethionine[296] were also carried out. Despite a few encouraging results, no firm conclusions were reached due, among other factors, to major publication biases and lack of homogeneity among the studies. Regarding the recent controlled trials, various supplements were tested, and it was not possible to draw clear conclusions regarding any specific one.

Synthesis

As a whole, the cumulative evidence about the efficacy of glucosamine and chondroitin in alleviating the main symptoms of knee OA is conflicting, making it risky to assess their level of efficacy. However, the efficacy of these two supplements in terms of slowing the structural progression of the disease and the narrowing of the joint space appears to be promising. That said, it is not currently possible to define their level of efficacy in specific terms.

There are too few studies on the other supplements to allow for any conclusions in their regard.

4.3.1.4 Electrotherapy and ultrasound

Pain: ★
Function: ★

The authors of two systematic reviews[297,298] showed that ultrasounds were beneficial in reducing the pain associated with knee OA, and possibly in improving function. However, the poor quality of the trials and their heterogeneity prevented the authors from reaching a conclusion regarding the magnitude of the benefits. Apart from that, in one trial,[299] the authors showed that continuous ultrasound rays were as, or almost as, efficacious as pulsed ultrasound waves in attenuating the symptoms of knee OA and increasing walking speed.

Among the systematic reviews that looked at the efficacy of pulsed electromagnetic energy,[300-302] the authors of only one study (in fact, the oldest of the studies) reported a significant reduction in the main symptoms of knee OA. These electromagnetic energy fields may nonetheless have beneficial effects on some clinical variables and on ability to perform activities of daily living.[302] Also, one relatively recent trial[303] found that the combination of pulsed electromagnetic field therapy and so-called conventional treatment had no added value in terms of reducing the symptoms of knee OA.

As for the effects of transcutaneous electrical nerve stimulation, the review produced by Brosseau et al.[304] revealed that it does more to reduce pain and stiffness than simulated stimulation, thus representing an adjunctive treatment worth considering. For their part, Rutjes et al.[305] were unable to confirm that transcutaneous electrostimulation was effective in reducing pain. And one recent trial[306] was unable to show that such a treatment either significantly reduces the symptoms of knee OA or improves physical and mental health.

Synthesis

Overall, the data collected does not confirm that electrotherapy and ultrasound are truly effective in treating knee OA. Moreover, the quality of the trials and heterogeneity among the studies were very often problematic.

4.3.1.5 Acupuncture

Pain: ★
Function: ★

According to the authors of the selected systematic reviews,[307-309] traditional acupuncture appears to significantly reduce the pain attributable to knee OA. However, the results varied from one author to the other, depending on whether the control treatments consisted of simulated acupuncture or simply the fact of being on a waiting list for this type of therapy. Regarding improvement in function, the authors found it difficult to reach a conclusion about the true impacts of acupuncture. It was also difficult for them to establish the efficacy of acupuncture compared to that of conventional approaches to treating knee OA. They further indicated that the controlled trials on the efficacy of acupuncture were very heterogeneous, making it impossible to determine their level of efficacy.

Quality trials have examined the efficacy of pharmacopuncture,[310] electroacupuncture[311], and the acupuncturist's behaviour[312]. However, to date, too few studies have been conducted on these variations to allow for any conclusions in their regard.

Synthesis

Acupuncture appears mainly to be effective in alleviating pain attributable to knee OA, but the level of efficacy is difficult to establish owing to the heterogeneity among the studies.

4.3.1.6 Heat or cold

Main symptoms of knee OA: ★

Warm baths, regardless of type, appear to have short to longer-term beneficial effects in terms of reducing the main symptoms of knee OA and are worth combining with conventional therapy treatments for the disease.[313-316] Hyperthermia may have a positive effect on pain, stiffness, and function, and even on physical performance.[317] Regarding the local application of cold temperatures, ice massages appear to have a positive effect on range of motion, function, and knee strength.[318]

The authors of the systematic reviews stressed the fact that higher-quality, homogeneous studies involving larger study samples are needed to ascertain the level of efficacy of thermotherapy in treating knee OA.

Synthesis

Thermotherapy (heat or cold) appears to be effective in treating knee OA, but it is not possible to determine its level of efficacy owing to the lack of homogeneity among the studies conducted and the small sample sizes.

4.3.1.7 Orthoses

Main symptoms of knee OA: ★

The authors of the three systematic reviews on orthoses concur on one particular point: orthoses are effective in alleviating the main symptoms of knee OA.[319-321] Of these reviews, only one mentions the magnitude of the beneficial effects, which appears to be small. However, opinions are divided about possible functional and structural improvements. The same applies to recent trials on the subject.[322-324] Laterally wedged orthoses do not appear to be more effective than regular orthoses.

The authors of the reviews found the controlled trials on orthoses often to be poor in quality, heterogeneous, and involving too small sample sizes, making it risky to ascertain their level of efficacy.

Synthesis

Orthoses appear to be effective in managing knee OA, but it is impossible to determine the degree of efficacy, largely owing to the lack of homogeneity among the studies and the small sample sizes.

4.3.1.8 Various care approaches

☆

No systematic review on care approaches was found. However, two high-quality trials were identified.[325,326] The proposed approaches consisted of a combination of education, exercises, and individual or group meetings. It is too early to discern trends in their effects given that the control groups differed, as did the outcomes obtained.

4.3.1.9 Laser therapy

Pain: ★

One systematic review showed that laser therapy was beneficial in relieving the pain associated with knee OA.[327] A more recent trial reached the same finding, indicating that this type of therapy appears to reduce sensitivity to pressure while increasing range of motion.

The authors of the systematic review concluded that greater homogeneity among the equipment and interventions used would provide a clearer idea of the magnitude of the effects of laser therapy.

4.3.2 Pharmacological approaches

Pain (acetaminophen and non-steroidal anti-inflammatories [NSAIDs]): ★★ – ★★★

Acetaminophen and NSAIDs taken orally are both effective in reducing pain related to knee OA. However, NSAIDs have greater efficacy.[328-330] The effect sizes vary between 0.20 and 0.33. In a recent controlled trial, Schnitzer et al.[331] also studied the efficacy of NSAIDs in reducing pain. However, NSAID users were found to experience more frequent side effects than acetaminophen users.

NSAIDs have minimal to moderate and only short-term beneficial effects,[332] which peak between the second and fourth weeks after the start of treatment for subjects with moderate to severe pain.[333] Moreover, to date there is no evidence regarding greater efficacy of some NSAIDs over others or regarding the doses to be recommended.[334]

The authors of the only systematic review on topical solutions like diclofenac—a class of NSAIDs—found that they were effective in improving pain, stiffness, and function scores in individuals with knee OA.[335] A relatively recent trial reached the same conclusions.[336] Yet another trial showed that topical diclofenac was as effective as oral diclofenac, but demonstrated greater tolerability.[337]

Other systematic reviews highlighted the short- and longer-term efficacy of diacerein[338] and of opioids[339] in reducing the main symptoms of knee OA. While the undesirable effects of diacerein were found to be less severe than those of NSAIDs, the beneficial effects of opioids were offset by the magnitude of the adverse effects. Apart from that, tramadol was found to have small benefits in terms of pain and function[340] while those of doxycycline were non-existent.[341] A recent controlled trial[342] also confirmed that doxycycline was not effective for reducing symptoms or improving health in subjects with knee OA.

The efficacy of several other medications was assessed in controlled trials, but it is impossible as yet to discern trends for any of them.

Synthesis

As a whole, the results of the systematic reviews presented here were based on high-quality, relatively homogeneous controlled trials, which adds credence to their conclusions. NSAIDs appear to have short-term efficacy in relieving pain associated with knee OA, and a low to moderate level of efficacy. Moreover, NSAIDs tend to have fewer adverse effects when administered transcutaneously than when taken orally.

There was an insufficient number of studies on other pharmacological approaches to point to any firm conclusions.

4.3.3 Surgical approaches

Notation not applicable

Regarding total knee arthroplasty, the results of one systematic review, one meta-analysis, and one controlled trial revealed a similar decrease in pain and improvement in function, whether or not the surgery included patellar resurfacing[343-345] or whether the approach used was mini-subvastus/midvastus or medial parapatellar.[346-348] Trials show that the materials and types of prostheses used appear to give comparable outcomes to those obtained with standard designs,[349,350] but additional high-quality trials are needed before any conclusions can be drawn in this regard. It is also worth noting that knee arthroplasty is as effective in patients under the age of 55 as in those aged 55 or over.[351]

Some authors affirm that the beneficial effects on pain and function are essentially the same, whether the surgery involves total knee arthroplasty, unicompartmental knee arthroplasty, or high tibial osteotomy.[319,352] Some assert, however, that unicompartmental arthroplasty gives better outcomes than upper tibial osteotomy[353]. Still other authors note better outcomes with unicompartmental arthroplasty than with total arthroplasty in terms of improvement in range of knee motion, function, and complication rates.[354]

The authors of two reviews showed that arthroscopic debridement and lavage were not effective in either relieving pain caused by knee OA or improving function.[355,356]

Synthesis

Overall, the data showed that knee arthroplasty performed using the most conventional method was as effective as that performed using “new” approaches or techniques. However, the quality of the trials included in the systematic reviews varied, so caution is required.

5. DISCUSSION

5.1 Risk Factors for Knee OA

5.1.1 Risk factors related to lifestyle habits and sociodemographic characteristics

Age

Based on our systematic review of the literature, we found moderate evidence to the effect that aging is associated with increased risk for knee OA.

The authors of other, previously published systematic reviews or meta-analyses of the association between age and knee OA[22,357,358] also found that increasing age represented a risk factor for knee OA, but did not reach a conclusion about the strength of evidence because of the diverging categorization of age groups. In one of these reviews,[22] the authors looked at the role of the age variable in the risk of progression of knee OA. After examining the relevant literature, they concluded that evidence in this regard was both scarce and conflicting.

Contrary to authors of previously published systematic review or meta-analyses, we are able to asset that there is moderate evidence of the association between aging and increased risk for knee OA. However, further studies on the relationship between age and the progression of knee OA are needed.

Age appears to be regarded as a “self-evident” risk factor for knee OA, i.e. it is more often used as a control variable in multivariate analyses than studied as a risk factor in its own right. In summary, it has been the subject of little study because it seems to be taken for granted. This may explain the moderate strength of evidence for a factor that is nonetheless associated with high risk by default.

Gender

We found moderate evidence to the effect that women are at higher risk for knee OA than men. However, we were unable to establish where there is an association between gender and the progression of knee OA.

The authors of some early systematic reviews and meta-analyses[22,357,359] also drew the conclusion that women ran a significantly higher risk than men of suffering from knee OA or developing the disease, without venturing any assertions about the relationship between gender and the disease progression. Here again, gender appears to be regarded as a self-evident risk factor for knee OA. It is therefore used more often as a control variable in multivariate analyses than studied as a risk factor in its own right, yielding a moderate strength of evidence that may come as somewhat of a surprise.

Weight and obesity

In light of the results obtained, there is solid evidence that obesity and high BMI scores are associated with a higher risk of developing knee OA. BMI is the measurement most often used to distinguish individuals at higher risk from those at lower risk, and it appears to be the measurement to be prioritized over other weight-related measurements (waist, % of body fat, waist-to-hip ratio, etc.).

A few systematic reviews and meta-analyses on weight- or obesity-related risk factors for knee OA have been published in the past. Blagojevic et al.[357] concluded that being overweight or obese, generally measured by means of the BMI, was still associated with increased risk for knee OA. Further to a meta-analysis, the pooled odds ratio for overweight versus normal weight was found to be 2.18 (1.86-2.55) and 2.63 (2.28-3.05) for obesity versus normal weight. These authors reported that substantial scientific evidence of the relationship between BMI and the onset of knee OA. Norman et al.[358] were of the same view. Belo et al.[22] focussed specifically on the progression of knee OA, and concluded that the evidence was conflicting as to the relationship between a high BMI and the disease progression.

Our results therefore concur for the most part with those obtained in the aforementioned studies. However, the relationship between weight and the progression of knee OA will have to be clarified in future work.

Work-related factors

We found solid evidence to the effect that workers who, in their jobs, had to perform tasks requiring significant use of their knees (going up and down stairs, kneeling on hard surfaces, etc.) or lifting heavy loads, were at greater risk of developing knee OA. We reached this finding despite the great heterogeneity among the descriptions of exposure.

Several systematic reviews or meta-analyses on work-related risk factors for knee OA have already been published.[357,358,360-366] Overall, the authors mention evidence ranging from moderate to solid regarding work performed on the knees or crouching and the handling of heavy loads when practiced over long periods of time during a working life. Some authors specify that publication biases and heterogeneity represent major limitations in the studies considered.

In our case, the level of solid evidence attributed to the selected literature concurs with the conclusions drawn in the previously published systematic reviews.

Physical and recreational activities

We determined that physically demanding activities such as running, track and field, or competitive cross-country skiing could, in the long term, put individuals who practice these sports at higher risk for knee OA; the level of evidence to this effect is solid. By contrast, low- or moderate-intensity activities appear not to increase but rather to decrease risk for knee OA.

Systematic reviews and meta-analyses on risk factors related to the practice of physical or recreational activities have been published in the past.[22,357,358,367] Their authors all conclude that there is a high degree of scientific evidence of increased risk for knee OA with intense activities practiced over a long period during a lifetime. On the other hand, the authors report great variability in the measurement of exposure and characterization of knee OA. We drew the same conclusion, despite applying different inclusion and exclusion criteria.

Belo et al.[22] looked at the risk factors for the progression of knee OA and found that the regular practice of physical activities was not associated with disease progression. We were unable to either corroborate or refute this assertion.

Smoking

Conflicting evidence emerged from our examination of the literature on smoking. It was not clear whether the fact of smoking increases or decreases the risk of knee OA. This may, in part, be attributable to the fact that smokers could have different lifestyles than non-smokers (e.g. less participation in intense physical activities).

One meta-analysis has already studied this subject.[357] Recognizing that the results of the different studies (n=18) were conflicting, the authors nonetheless reported smoking as having a small protective effect (pooled odds ratio 0.84 (0.74-0.95)). However, no significant protective effect was found when cohort studies only were analyzed (pooled odds ratio 0.97 (0.88-1.07)).

Diet

To date, it is not possible to establish a clear relationship between diet and risk for knee OA. We found no systematic reviews or meta-analyses on this subject.

Other

Insufficient evidence was found to assert that ethnicity, education, alcohol consumption, and the wearing of high-heeled shoes are associated with knee OA. We found no systematic reviews of meta-analyses studying these factors, which is indicative of the little attention they are given. We cannot therefore compare our results to those of other systematic reviews.

5.1.2 Biological and physiological risk factors

Hormones and reproductive history

In their meta-analyses, Blagojevic et al.[357] obtained conflicting or non-significant results regarding the use of oral contraceptives, the fact of having undergone a hysterectomy, and hormone replacement therapy. Associations between these factors and risk for knee OA have certainly been observed, but the authors deemed that more longitudinal studies are required before a clear verdict can be rendered. Tanamas et al.[24] produced a review specifically on sex hormones and risk for knee OA. They concluded that there was too much heterogeneity among studies as well as insufficient evidence to draw any viable conclusions.

Like Blagojevic et al., we too found that the evidence of an association between hormone replacement therapy and risk for knee OA remains conflicting. In summary, the position taken by these authors concurs with our own, namely, that more high-quality studies are needed to determine the real effect of hormones and reproductive history on risk for knee OA.

Metabolic syndrome and other diseases

Since we found no cohort studies on metabolic syndrome or the presence of other diseases and retained only two case-control studies on the subject, there is insufficient evidence to draw any conclusions regarding any one factor.

Blagojevic et al.[357] looked specifically at hypertension as a possible risk factor for knee OA. In their review, the authors found only observational studies on the subject and the evidence proved to be conflicting. For their part, Norman and Kress[358] reported no significant association between the fact of being diabetic and risk for knee OA.

To date therefore, no systematic review or meta-analysis clearly indicates that the fact of having metabolic syndrome or some other disease produces a higher risk for knee OA, which concurs with our finding.

Biochemical factors

Regarding biochemical risk factors for knee OA (urinary CTX-II concentration, cell adhesion protein concentration, blood homocysteine concentration, etc.), trends were observed, although there was insufficient evidence to reach any conclusions regarding any particular factor. We did not find any systematic reviews or meta-analyses on the subject with which we could compare our results.

Bone mineral density

In light of our results, there appears to be solid evidence that people with high bone mineral density are at higher risk of suffering from knee OA. In our view, lifestyle may play a role in this association. For example, the bones of elite athletes and obese individuals may respond to impacts and mechanical loads by synthesizing more bone, thereby increasing bone mineral density.

The review prepared by Blagojevic et al.[357] considered bone mineral density among the host of risk factors it covered; it was the only review we found on the subject. The authors concluded that a consistent and strong association existed between an increase in bone mineral density and the onset of knee OA. These results concur with our own.

Hand osteoarthritis, taking NSAIDs, Heberden's nodes

To date, there is insufficient evidence to assert that hand osteoarthritis, taking NSAIDs, and Heberden's nodes are associated with knee OA. We found no systematic review or meta-analysis on these subjects, indicating that these factors have attracted little attention. We cannot therefore compare our results to those of other systematic reviews.

5.1.3 Risk factors related to joint structures and functions

Injuries and history of injury

Relevant systematic reviews and meta-analyses have been published on this subject in the past.[22,357,368,369] Blagojevic et al.[357] reported that a history of knee injuries was a major risk factor for knee OA, despite great heterogeneity among the studies. The pooled odds ratio was 3.86 (2.61-5.70). We found moderate evidence to the effect that individuals with a history of knee injuries were at greater risk for knee OA.

The other reviews concentrated on specific injuries (e.g. rupture of the anterior cruciate ligament). Nothing conclusive emerged from the analyses performed. Nor did our own examination of the literature allow us to establish an association between the fact of sustaining a particular type of injury and subsequent risk for knee OA.

Lastly, Belo et al. were the only authors to have investigated the progression of knee OA.[22] Their results pointed to a finding that knee injuries were not associated with the progression of knee OA.

History of surgery

Given the few high-quality observational studies found on the relationship between history of knee surgery and risk for knee OA, we concluded that to date, there was insufficient evidence of an association between the two.

With regard to the systematic reviews already produced, Magnussen et al.[368] observed that people who have undergone partial meniscectomy during reconstruction of their anterior cruciate ligament (ACL) were at significantly greater risk of developing radiographic signs of knee OA than people with normal menisci. However, these authors did not provide any pooled odds ratios. Blagojevic et al.[357] looked at meniscectomy and subsequent risk of knee OA. The authors of the three retained case-control studies found that people who had undergone this intervention were at greater risk for knee OA than those who had not. They found an insufficient number of studies to establish a pooled odds ratio. Lastly, Belo et al.[22] concluded that there was no relationship between the fact of having undergone a meniscectomy and the risk of progression in knee OA. However, the evidence to date is limited in this regard.

Vairo et al.[370] reached the conclusion that the risk for early onset of knee OA in physically active individuals was higher in those who had had ACL reconstruction using the bone-patellar tendon-bone technique than in those whose surgery had involved the semitendinosus and gracilis technique.

In summary, the authors of these systematic reviews were able to identify a specific type of intervention more likely to result in knee OA: meniscectomy. We were unable to do the same based on the literature we had selected.

Alignment

We identified two systematic reviews on alignment. Authors Belo et al.[22] reported limited evidence of an association between valgus or varus knees and the progression of knee OA, whereas Tanamas et al.[23] found that poor alignment constituted an independent factor in the progression of the disease. However, the authors concurred that too few studies had been conducted to conclude that it was also a risk factor for onset of the disease.

Based on our review, we were able to establish that moderate evidence exists to the effect that the risk for knee OA may be higher in individuals with varus knee alignment, and limited evidence for those with valgus alignment. Moreover, there was insufficient evidence to establish a relationship between alignment and the disease's progression. These results therefore concur only partly with those obtained in previously published systematic reviews.

Other

We established that the evidence was conflicting, limited, or insufficient to assert that height, quadriceps strength, injuries, bone marrow oedema, unequal leg length, or proprioception play a significant role in the progression of knee OA. Nor did we find any systematic reviews or meta-

analyses on these risk factors that would have allowed us to corroborate or refute the levels of evidence we found.

5.1.4 Remarks and commentaries

We adopted certain criteria regarding the characterization of knee OA. For radiographic knee OA, studies using the Kellgren-Lawrence (KL) grading scale were the ones we retained. For symptomatic knee OA, we adopted the criteria of the American College of Rheumatology (ACR). Thus, for example, studies that had established the presence of knee OA solely on the word of their participants were not retained. Even though this choice may have slightly altered the results we obtained because they were more restrictive, it allowed us to get around the biases inherent in less precise knee OA characterization measures. Generally speaking, the systematic reviews on risk factors for knee OA are actually very inclusive regarding the definitions of the disease they deem acceptable. This constitutes an original aspect of our research.

Our goal was to produce a synthesis of the scientific literature on all the risk factors associated with the onset and progression of knee OA. While on the whole we were able to provide a relatively exhaustive picture of the factors associated with the onset of the disease, the same cannot be said about the factors related to its progression. In order for us to have done so, we would needed more cohort studies, which are, in our view, the only ones that would have been able to provide us with information in this regard; these studies do follow-ups of their participants.

Increasing age, the fact of being a woman, obesity, high BMI sores, high-intensity physical activities practiced over a long period of time, and high bone mineral density are the biggest risk factors for knee OA. However, the scientific evidence would probably have been stronger for certain risk factors if the ways of characterizing exposure had been more homogeneous. Similarly, the role of a few risk factors might have been clarified if more, high-quality observational studies had been found in their regard.

5.1.5 Recommendations for practice

Health professionals should be in a position to inform their patients or clients about the modifiable risk factors most likely to lead to knee OA. While it is impossible to do anything about age or gender—to name but a few—it is nonetheless possible to inform patients that their excess weight, the tasks they perform at work, or their intensive practice of physical activities put them at higher risk for knee OA.

In the workplace, occupational health and safety professionals should be able to tell employees which tasks are likely, in the long term, to lead to knee OA (repeatedly lifting heavy loads, kneeling frequently, etc.). These professionals should also be able to suggest measures for reducing the risks associated with such tasks.

Given their demonstrated beneficial effects on pain, function, and physical performance, exercises should be prescribed to people with knee OA. It is all the more important that these individuals integrate exercises into their lifestyle because their beneficial effects are felt regardless (or almost regardless) of exercise intensity or type. The choice of exercises to be practiced may therefore depend on the person's capacities and preferences. However, it would appear essential to do the exercises regularly since the benefits are felt in the short-term only. For certain people, professional supervision or education in self-management could promote their adherence. For those people who can allow themselves to do so, exercises ensuring substantial energy expenditure are worthwhile inasmuch as they can lead to weight loss. There is no longer any doubt that obesity or high BMI scores are associated with a higher risk for knee OA.

5.2 Evaluation Instruments

5.2.1 Instruments for "Body Structures" component

5.2.1.1 Lower extremity alignment

The study carried out by Hinman et al.[152] showed that the clinical assessment of knee alignment using the inclinometer method was recommended due to its strong correlation with the measure of the mechanical axis of the knee calculated from a full-leg radiograph. Current knowledge indicates that the association between varus alignment and the progression of knee OA has been clearly established. Clinically feasible and low in cost, this method could help to identify people at risk of developing knee OA or of seeing their disease progress.

5.2.2 Instruments for "Body Functions" component

5.2.2.1 Pain

A number of instruments are used to assess pain in people with knee OA. Most are algofunctional questionnaires that include a "pain" domain. The results show that the majority of these instruments have good validity and good to excellent reliability. More specifically, the ICOAP[154] is an interesting instrument because it covers two dimensions: "intermittent pain" and "constant pain." KOOS-PS would appear to be preferable to the full version of the KOOS[156] for assessing pain. The OKS is valid for assessing pain, but its reliability has yet to be documented in a population with knee OA[161]. The WOMAC pain subscale, the most frequently documented rating scale, is recommendable. This recommendation applies to both the original version and the modified, adapted, and translated versions of the instrument (factorial, VAS, categorical scaled, telephone, and computerized versions).[163-165,177-179] However, the VAS version of the WOMAC subscale should be given preference over the categorical scaled version because of its slightly superior psychometric properties.[177] Also, the telephone-administered WOMAC appears to be a valid and potentially more effective alternative to the paper version of the instrument, and data

processing time would notably be reduced, according to Bellamy et al.[178] We cannot draw any conclusions regarding the psychometric properties of the original version of the AIMS2. The available data concern the adapted and translated versions and suggest that they can be recommended for use.[180-182] The LAI[164,183], the KSS[188] and the J-MAP are also recommended for assessing pain. However, the J-MAP has the particular feature of measuring both the physiological and psychological dimensions of pain[186]. A comparison between the VAS and the Modified Verbal Rating Scale (MVRS), two measurement instruments commonly used by clinicians, shows the VAS to have more robust psychometric properties.[187] While reliable, the assessment of tolerance and pain perception thresholds using a dolorimeter is not recommendable because the validity of this method has not been demonstrated.[189] The KPS[190] and the PIK[191] have the particular feature of measuring the appearance of pain during functional movements or activities of daily living (ADLs), and are recommendable for clinical practice. Use of the computerized version of the painDETECT[159] does not appear to be recommended as the psychometric properties of the English version of the instrument have not yet been documented for a population with knee OA.

These results concur with those presented in the systematic reviews of both Howe et al.[371] and Veenhof et al.[372]. However, Howe's study mentions other pain evaluation instruments. This distinction may be attributable to less restrictive inclusion criteria than those applied in our study, for example, the taking into account of studies on various knee pathologies. Lastly, Veenhof et al. conclude that the WOMAC (VAS version), the SF-36, and the LAI should be used when evaluating individuals with knee OA because they have more robust psychometric properties.

5.2.2.2 Energy-Sleep-Emotions

The results of our study show that for this category of body functions, the psychometric properties are documented for only three instruments: the J-MAP, the SPI, and the MPQ. However, with low to moderate validity, the SPI and MPQ should be used with caution. According to Kilminster et al.[195], the MPQ appears to be rather tedious to administer and score. Of these three instruments, the J-MAP is therefore the one to be favoured for measuring the emotional impact of pain in people with knee OA.

5.2.2.3 Joint function

The Pivot Shift Test appears not to be a valid measure of ACL integrity for individuals with knee OA[196], and the modified pendulum test of Burks et al.[197] should not be used to measure stiffness in osteoarthritic knees. However, the use of equations for predicting active repositioning to measure proprioception appears to be a valid and reliable method[198]. Interestingly, a strong correlation was found between difficulty in repositioning the knee and the presence of a functional limitation. That said, the clinical application of such a method remains debatable. Lastly, Cyriax's concept of capsular pattern, still currently used by clinicians and serving as their basis for issuing a diagnostic impression, should be questioned as it has not been validated.[199,200]

In their systematic review, Howe et al.[371] documented the psychometric properties of the goniometer for evaluating joint mobility in people with various knee pathologies. No result specific to individuals with knee OA was presented.

5.2.2.4 Muscle function

The results of the studies that analyzed the psychometric properties of methods for evaluating the isometric and isokinetic muscle strength of people with knee OA concur, showing that they offer a reliable measure. However, accessibility to isokinetic devices hinders the use of this method of evaluation, not to mention the fact that measurement error appears to be high.[208-216] Knee muscle strength appears to be the most representative index for quantifying the impact of knee OA on muscle function. According to Steultjens et al.[207], the muscle impact of knee OA is not better quantified by adding an evaluation of hip muscle strength. However, this does not mean that clinically the evaluation of hip or ankle muscles is not pertinent. These muscle groups must be evaluated to better understand the impact of their weakness on the performance of functional activities. The use of prediction equations appears to be a valid method for determining the 1-repetition maximum (1-RM).[203] These equations could therefore be useful because the 1-RM procedure is often perceived by clinicians as long and tedious. Lastly, use of a portable hand-held dynamometer is recommended for clinical use.[202]

5.2.3 Instruments for "Activity" component

The documents reviewed for the most part confirmed the robustness of the psychometric properties of several instruments, notably the WOMAC, the OKS, the Patient Function NRS, and the LAI. Adapted, translated, and validated versions of the WOMAC and the LAI are available in several languages so that these instruments can be used around the world. The modified versions of the WOMAC (e.g. WOMAC-SF, telephone interview WOMAC, computerized WOMAC) and of the LAI were found to be valid and equivalent to the original version, which concurs with the results of the previous studies.[372] Validity was primarily studied by assessing the correlations between rating scales of similar constructs. Satisfactory convergent validity was found for the KOOS, Patient Function NRS, OAKHQOL, WIQ, ALF, Knee Society Clinical Rating System, and the SPW. Moreover, the HAP and OAKHQOL appear to have a good capacity for discriminating between individuals based on certain characteristics, specifically, the presence of

knee OA for the HAP, and BMI, age, disease severity, and gender for the OAKHQOL. However, the Patient Function NRS does not appear to discriminate between individuals based on the severity of disease-related radiological changes.

The adapted and modified versions of the WOMAC and the LAI have excellent reliability, as do the HAP, ALF, and WIQ. The HAP and ALF stand out due to their low measurement error. Our results are similar to those reported in another systematic review.[372] However, the authors of that study included several articles that were rejected in our review because the results specific to the knee OA population were not differentiated from those for the hip OA population. Wang et al.[373] also reported, in another literature review on the psychometric properties of instruments evaluating function, that the KOOS, OKS, and KOS-ADLS have good test-retest reliability. However, studies supporting the reliability of the KOOS and the KOS-ADLS have not been carried out specifically with a population suffering from knee OA.[178,218]

Responsiveness to change was deemed good to excellent for most of the function measurement instruments retained in this study: the SF-36, WOMAC, KOOS, OAKHQOL (except for the "Social Activities" and "Social Support" components), ALF, and Knee Society Clinical Rating System. Moreover, the OAKHQOL is not recommended owing to the large number of items with floor and ceiling effects. By contrast, Veenhof et al.[372] were unable to draw any clear conclusion regarding the responsiveness to change of the instruments used to evaluate functional activities. They found the studies included in their systematic review to be of debatable quality. They nonetheless concluded that the WOMAC appears more responsive to change than the SF-36, which concurs with our results.

5.2.4 Instruments for "Participation" component

The instruments we identified as evaluating this ICF component had also been identified as evaluating both pain and functional activities. Thus, nearly 15 instruments including items evaluating the impact of knee OA on participation were found, in addition to two other instruments evaluating work disability. Overall, the studies documenting the psychometric properties of these instruments confirmed good to excellent validity for the WOMAC, OKS, Patient Function NRS, and the LAI, as well as excellent reliability.[160,161,223,238] Use of these instruments is therefore recommended for evaluating participation among people with knee OA. Two other instruments, the DDLKOS and the WHODAS-II, which were developed specifically to assess the "Participation" component of the ICF, were found to have moderate validity.[234,235] The results of our study concur with those reported in the literature review of Veenhof et al.[372] These authors gave their opinion, however, about the superiority of the WOMAC and the LAI: the SF-36 remains a tool of choice in their view.

By doing a bibliographic search, we identified a systematic review on the psychometric properties of instruments measuring work disability in populations with osteoarthritis and rheumatoid arthritis (Beaton et al., 2010). The Work Limitations Questionnaire (WLQ) is without doubt the instrument that comes up most often in the literature, given the number of scientific publications that make reference to it, all pathologies combined[374]. It shows good internal consistency results as well as content and construct validity in terms of measuring the effects of

knee OA[237] on employees' work performance. However, the WLQ had poorer responsiveness to change than other instruments such as the Rheumatoid Arthritis Work Instability Scale (RA-WIS) and the Work Activity Limitation Scale (WALS) in terms of measuring the work effects of arthritis (rheumatoid arthritis or knee OA), whether for changes in work capacities or in work productivity.[375] The WALS appears to have been validated only with a rheumatoid arthritis population. In light of the results of this systematic review and the results of our own study, the RA-WIS appears to be the instrument to use.

5.3 Interventions

5.3.1 Remarks and commentaries

Given the wealth of scientific literature on treatments and therapies for knee OA, we opted to synthesize the results of the systematic reviews, which we then complemented by detailing the results of the most recent controlled trials. While such a practice lends itself poorly to meta-analyses, it nonetheless provides an overview of changes in the conclusions drawn in the reviews as the evidence accumulates with the various trials. In addition, and contrary to other authors, we did not limit ourselves to reviews incorporating only randomized controlled trials with groups receiving a placebo or a simulated intervention. The fact that we made more "flexible" choices distinguishes our approach from more conventional approaches to carrying out systematic reviews on these subjects (e.g. those in The Cochrane Collaboration), while allowing nuances and distinctions to be made, mainly regarding the relative effectiveness of the various treatments.

The scientific literature was also so prolific that only the high-quality studies are presented in the "Results" section of our study, particularly as they served as the basis for our assessment of the level of evidence available. This choice may be debatable, although an examination of poorer-quality studies reveals that the results would not have been essentially any different had they been included in this section. In fact, both the high-quality and poorer-quality studies reached very similar conclusions. However, as far as exercises are concerned, an investigation of poorer-quality studies would have highlighted the range of interventions studied and their effectiveness. Regarding orthoses, a consideration of poorer-quality studies would have made it possible to better determine the magnitude of their beneficial effects in terms of alleviating the symptoms of knee OA.

5.3.2 Recommendations for practice

One major finding emerges from our results: no miracle treatment or therapy exists to date for individuals with knee OA. Injections of hyaluronic acid and its derivatives are definitely useful for alleviating pain attributable to knee OA and warrant being used. However, their beneficial effects are not felt immediately, and patients with severe pain will most likely have to seek options offering faster analgesic effects. NSAIDs offer an interesting option in this regard,

although they are only effective in the short term. Also, they often have significant side effects and must therefore be taken prudently. For more severe cases of knee OA, knee arthroplasty performed using conventional methods appears to be almost as beneficial and sustainable as arthroplasty performed using "new" approaches or techniques.

While very popular, glucosamine and chondroitin—ostensibly the best known supplements among individuals with knee OA—do not offer assured relief from the main symptoms of knee OA. In fact, the data regarding their efficacy is conflicting. What is true, however, is that these two supplements can reduce the structural progression of the disease and at least partly slow down the narrowing of the joint space. Glucosamine and chondroitin should therefore be recommended only on this basis.

Given the generally poor quality of the studies, the conflicting results, and the heterogeneity among the interventions, to date there is no justification for widely recommending electrical stimulation therapy, acupuncture, heat, cold, orthoses, laser therapy, other care approaches, or physiotherapy to individuals with knee OA. At best, a patient who believes he or she might derive benefit from these interventions could try them, as their side effects are not a concern.

In the absence of management initiatives and programs designed specifically for workers, we recommend the most effective of the interventions presented earlier, namely, exercise, hyaluronic acid injections, and NSAIDs. To date, most studies have been conducted on aging subjects, but nothing indicates that they are not also effective in younger subjects who are likely to be in the labour force.

In summary, the proper management of individuals with knee OA must involve giving priority to a combination of interventions when one alone is inadequate, which is probably the case mainly for people in advanced stages of the disease. Special attention must also be paid to the patient's preferences. This concurs with points raised in several practice guides that are based on literature reviews.[376-381]

6. LIMITATIONS OF THE STUDY

Our study had certain limitations. Given the space constraints, we opted to present only those studies deemed to be of high quality in the "Results" section. This is acceptable in that we were able to make our recommendations on the basis of high-quality studies. However, readers wishing to know the results of poorer-quality studies will necessarily have to refer to the appendices presented in *Document II, Tableaux récapitulatifs* (available on the REPAR/FRQS website at http://repar.ca/Admin/Files/images/ANNEXES_v13_mai_2014.pdf). Moreover, the fact that we covered a broad range of risk factors, evaluation instruments, and interventions, combined again with space constraints, means that the reader cannot assess the particular features of each of the selected studies, for example, regarding the populations studied or the characterization of exposure to a risk factor. Again, interested readers will have to refer to the appendices presented in aforementioned *Document II, Tableaux récapitulatifs*.

The fact that data extraction was performed by a single reviewer constitutes another limitation of our study. Our choice to use only one reviewer remains debatable, but was dictated by the vast amount of scientific literature to be processed and the limited resources available to us. However, we had two reviewers carry out the quality evaluation, given that we wanted to make recommendations based on high-quality studies; we considered it important to focus our efforts on differentiating the high-quality from the poorer-quality studies.

We had envisaged carrying out quantitative analyses of the combined results as advocated by The Cochrane Collaboration, but opted instead to remain accessible to a broad-based public by favouring a results presentation that was easier to understand. We did not adopt a "purist" Cochrane approach, in which double-blind randomized studies are paid the most attention. In fact, for objective 1, we retained observational studies. For objective 2, we documented studies with varying designs, and to some extent, did a critical review of them. Lastly, for objective 3, we carried out what we could call a "review of reviews," topped up with more recent controlled trials. While we drew great inspiration from the work of The Cochrane Collaboration, particularly regarding methodological rigour, we are aware that our "adaptations" of the method may appeal less to some members of the scientific community.

7. CONCLUSION

As a whole, we identified great heterogeneity among the methods used to measure exposure to knee OA risk factors. It was therefore impossible for us to establish precise odds ratios. New, high-quality observational studies would no doubt make this possible.

More systematic reviews on genetic risk factors for knee OA should be carried out in order to provide a clear picture of their impact on the onset of the disease. Our lack of expertise in this area prevented us from doing so ourselves, but several studies suggest that such a link warrants investigation.

Unlike risk factors for the onset of knee OA, those associated with the disease's progression have been the subject of little study. Cohort studies for most of the risk factors should be conducted to remedy the lack of knowledge in this regard.

Generally speaking, researchers focus their studies on a very specific risk factor. In future studies, it might be worthwhile for them to examine the impact of the interaction of two or more risk factors. For example, it has been established that obesity or the fact of lifting heavy loads on a regular basis appears to create higher risk for knee OA. It may well be worth investigating whether the fact of being obese and of having to lift heavy loads increases the risk of knee OA, and if so, to what degree. Similarly, it might be enlightening to explore the interaction between obesity and poor alignment.

Lastly, risk factors for work disability in connection with knee OA remain a research topic that warrants investigation as there are virtually no studies on this subject.

We found that health status measurement tools providing an aggregate score based on the sum of scores on several dimensions (or ICF categories) are often used. Also, a number of these tools are generic. While for the most part they are valid and reliable, we conclude that there is a need to develop and validate tools that are more likely to measure each of the ICF categories, particularly for the "Activities" and "Participation" components.

Regarding exercise, hyaluronic acid injections, and NSAIDs, their benefits have been demonstrated in subjects with knee OA, but optimal dose-responses have yet to be determined. More high-quality controlled trials are needed on this subject. Regarding glucosamine and chondroitin, new trials should help determine whether or not these supplements are effective in alleviating the symptoms of knee OA. Lastly, with regard to electrical stimulation therapy, acupuncture, heat, cold, orthoses, laser therapy, other care approaches, and physiotherapy, higher-quality studies involving more homogeneous interventions may reveal conclusive evidence about the pertinence of incorporating them into the treatment of knee OA or not. In any case, efforts to fill in these gaps would allow for more accurate assessment of effect sizes. In the future, it could also be useful to do systematic reviews of the effectiveness of care approaches that combine various treatment modalities, but prior to that, more controlled trials on the subject are needed. While we retained trials of this type in our review, there were too few to allow us to synthesize the literature. In today's context, when the retirement age is tending to be pushed

back, controlled trials on the effectiveness of management initiatives or programs designed specifically for workers with knee OA should be conducted. These trials should include outcome measures related to return to work and job retention. Other controlled trials should also include these measures, but for a worker population having undergone knee arthroplasty.

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APPENDICES

APPENDIX A: SEARCH STRATEGIES: KEY WORDS

Risk factors for knee OA

Terms related to knee OA	*Terms related to risk factors*
1. KNEE OSTEOARTHRITIS/	24. Risk Factors/
2. Gonarthrit$.mp.	25. exp Epidemiology/
3. Gonarthro$.mp.	26. determinant$.mp.
4. (Knee$ adj3 pain$).mp.	27. Prognosis/
5. (Knee$ adj3 ach$).mp.	28. Risk Assessment/
6. (Knee$ adj3 discomfort$).mp.	29. predictive factor$.mp
7. (Cartilage adj3 degradation).mp.	30. 24 or 25 or 26 or 27 or 28 or 29
8. (Cartilage adj3 degeneration).mp.	
9. (Cartilage adj3 destruction).mp.	**Final combination**
10. exp OSTEOARTHRITIS/	31. 23 and 30
11. Osteoarthriti$.mp.	
12. Osteoarthro$.mp.	
13. exp OSTEOPHYTE/	
14. Osteophyte.mp.	
15. Joint space narrowing.mp.	
16. Degenerative joint disease$.mp.	
17. Arthriti$.mp.	
18. Arthrosi$.mp.	
19. exp KNEE/	
20. Knee$.mp.	
21. exp KNEE JOINT/	
22. Knee joint$.mp.	
23. 1 or 2 or 3 or 4 or 5 or 6 or ((7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18) and (19 or 20 or 21 or 22))	

Evaluation instruments

"Joint"

Knee OA	***Psychometric properties***	***Measurement instruments***	***Joint***
1. KNEE OSTEOARTHRITIS/	24. Validation Studies/	41. Questionnaires/	65. (mobility adj4 joint$).mp.
2. Gonarthrit$.mp.	25. (validation adj2 stud$).mp.	42. questionnaire$.mp.	66. joint$ range of motion.mp.
3. Gonarthro$.mp.	26. "Reproducibility of Results"/	43. Exercise Test/	67. "Range of Motion, Articular"/
4. (Knee$ adj3 pain$).mp.	27. (reproducibility adj2 result$).mp.	44. exercise test$.mp.	68. joint$ flexibility.mp.
5. (Knee$ adj3 ach$).mp.	28. "Sensitivity and Specificity"/	45. Physical Examination	69. tightness.mp.
6. (Knee$ adj3 discomfort$).mp.	29. (sensitivity adj2 specificity).mp.	46. physical exam$.mp.	70. heaviness.mp.
7. (Cartilage adj3 degradation).mp.	30. (sensitivity adj2 change).mp.	47. clinical test$.mp.	71. end feel.mp.
8. (Cartilage adj3 degeneration).mp.	31. "Predictive Value of Tests"/	48. (evaluat$ adj2 tool$).mp.	72. (stability adj4 joint$).mp.
9. (Cartilage adj3 destruction).mp.	32. (predictive adj2 value).mp.	49. (screen$ adj2 test$).mp.	73. joint$ instability.mp.
10. exp OSTEOARTHRITIS/	33. reliab$.mp	50. rating scale$.mp.	74. Joint Instability/
11. Osteoarthriti$.mp.	34. valid$.mp.	51. (visual adj1 estimat*).mp.	75. joint$ hypermobility.mp.
12. Osteoarthro$.mp.	35. responsiveness.mp.	52. goniomet$.mp.	76. joint laxity.mp.
13. exp OSTEOPHYTE/	36. (internal adj1 consisten$).mp	53. inclinometer.mp.	77. ligament$.mp.
14. Osteophyte.mp.	37. likelihood ratio.mp.	54. (ligament$ adj3 test$).mp	78. Ligaments/
15. Joint space narrowing.mp.	38. clinimetric propert$.mp.	55. (manual adj3 test$).mp.	
16. Degenerative joint disease$.mp.	39. measurement protocol.mp.	56. (directional adj3 test$).mp.	
17. Arthriti$.mp.		57. (articul$ adj3 evaluat$).mp.	
18. Arthrosi$.mp.		58. ligament$ stability.mp.	
19. exp KNEE/		59. lachman test.mp.	
20. Knee$.mp.		60. anterior drawer test.mp.	
21. exp KNEE JOINT/		61. arthrometer.mp.	
22. Knee joint$.mp.		62. genucom.mp.	
		63. knee laxity test*.mp.	
23. 1 or 2 or 3 or 4 or 5 or 6 or ((7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18) and (19 or 20 or 21 or 22))	40. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	64. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63	79. 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78

"Muscle"

Knee OA	***Psychometric properties***	***Measurement instruments***	***Muscle***
1. KNEE OSTEOARTHRITIS/ 2. Gonarthrit$.mp. 3. Gonarthro$.mp. 4. (Knee$ adj3 pain$).mp. 5. (Knee$ adj3 ach$).mp. 6. (Knee$ adj3 discomfort$).mp. 7. (Cartilage adj3 degradation).mp. 8. (Cartilage adj3 degeneration).mp. 9. (Cartilage adj3 destruction).mp. 10. exp OSTEOARTHRITIS/ 11. Osteoarthriti$.mp. 12. Osteoarthro$.mp. 13. exp OSTEOPHYTE/ 14. Osteophyte.mp. 15. Joint space narrowing.mp. 16. Degenerative joint disease$.mp. 17. Arthriti$.mp. 18. Arthrosi$.mp. 19. exp KNEE/ 20. Knee$.mp. 21. exp KNEE JOINT/ 22. Knee joint$.mp.	24. Validation Studies/ 25. (validation adj2 stud$).mp. 26. "Reproducibility of Results"/ 27. (reproducibility adj2 result$).mp. 28. "Sensitivity and Specificity"/ 29. (sensitivity adj2 specificity).mp. 30. (sensitivity adj2 change).mp. 31. "Predictive Value of Tests"/ 32. (predictive adj2 value).mp. 33. reliab$.mp 34. valid$.mp. 35. responsiveness.mp. 36. (internal adj1 consisten$).mp 37. likelihood ratio.mp. 38. clinimetric propert$.mp. 39. measurement protocol.mp.	41. Questionnaires/ 42. questionnaire$.mp. 43. Exercise Test/ 44. exercise test$.mp. 45. Physical Examination 46. physical exam$.mp. 47. clinical test$.mp. 48. (evaluat$ adj2 tool$).mp. 49. (screen$ adj2 test$).mp. 50. rating scale$.mp. 51. (manual adj3 test$).mp. 52. dynamometry.mp. 53. dynamometer.mp. 54. cybex.mp. 55. biodex.mp. 56. Muscle Strength Dynamometer/	58. (muscle$ adj2 power).mp. 59. (muscle$ adj2 endurance).mp 60. (muscle$ adj2 strength).mp. 61. isokinetic strength.mp. 62. isometric strength.mp. 63. Muscle Strength/ 64. 1rm.mp.
23. 1 or 2 or 3 or 4 or 5 or 6 or ((7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18) and (19 or 20 or 21 or 22))	40. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	57. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56	65. 58 or 59 or 60 or 61 or 62 or 63 or 64

"Activities"

Knee OA	***Psychometric properties***	***Measurement instruments***	***Activities***
1. KNEE OSTEOARTHRITIS/	24. Validation Studies/	41. Questionnaires/	51. body position.mp.
2. Gonarthrit$.mp.	25. (validation adj2 stud$).mp.	42. questionnaire$.mp.	52. lying.mp.
3. Gonarthro$.mp.	26. "Reproducibility of Results"/	43. Exercise Test/	53. squat$.mp.
4. (Knee$ adj3 pain$).mp.	27. (reproducibility adj2 result$).mp.	44. exercise test$.mp.	54. kneel$.mp.
5. (Knee$ adj3 ach$).mp.	28. "Sensitivity and Specificity"/	45. Physical Examination	55. stand$.mp.
6. (Knee$ adj3 discomfort$).mp.	29. (sensitivity adj2 specificity).mp.	46. physical exam$.mp.	56. sit$.mp.
7. (Cartilage adj3 degradation).mp.	30. (sensitivity adj2 change).mp.	47. clinical test$.mp.	57. bend$.mp.
8. (Cartilage adj3 degeneration).mp.	31. "Predictive Value of Tests"/	48. (evaluat$ adj2 tool$).mp.	58. (lift$ adj2 object$).mp
9. (Cartilage adj3 destruction).mp.	32. (predictive adj2 value).mp.	49. (screen$ adj2 test$).mp.	59. (carry$ adj2 object$).mp.
10. exp OSTEOARTHRITIS/	33. reliab$.mp		60. Walking/ or walk$.mp.
11. Osteoarthriti$.mp.	34. valid$.mp.		61. crawl$.mp.
12. Osteoarthro$.mp.	35. responsiveness.mp.		62. climb$.mp.
13. exp OSTEOPHYTE/	36. (internal adj1 consisten$).mp		63. Running/ or run$.mp.
14. Osteophyte.mp.	37. likelihood ratio.mp.		64. jump$.mp.
15. Joint space narrowing.mp.	38. clinimetric propert$.mp.		65. Swimming/ or swim$.mp.
16. Degenerative joint disease$.mp.	39. measurement protocol.mp.		66. mov$.mp.
17. Arthriti$.mp.			
18. Arthrosi$.mp.			
19. exp KNEE/			
20. Knee$.mp.			
21. exp KNEE JOINT/			
22. Knee joint$.mp.			
23. 1 or 2 or 3 or 4 or 5 or 6 or ((7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18) and (19 or 20 or 21 or 22))	40. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	50. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	67. 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66

"Participation"

Knee OA	***Psychometric properties***	***Measurement instruments***	***Participation***
1. KNEE OSTEOARTHRITIS/ 2. Gonarthrit$.mp. 3. Gonarthro$.mp. 4. (Knee$ adj3 pain$).mp. 5. (Knee$ adj3 ach$).mp. 6. (Knee$ adj3 discomfort$).mp. 7. (Cartilage adj3 degradation).mp. 8. (Cartilage adj3 degeneration).mp. 9. (Cartilage adj3 destruction).mp. 10. exp OSTEOARTHRITIS/ 11. Osteoarthriti$.mp. 12. Osteoarthro$.mp. 13. exp OSTEOPHYTE/ 14. Osteophyte.mp. 15. Joint space narrowing.mp. 16. Degenerative joint disease$.mp. 17. Arthriti$.mp. 18. Arthrosi$.mp. 19. exp KNEE/ 20. Knee$.mp. 21. exp KNEE JOINT/ 22. Knee joint$.mp.	24. Validation Studies/ 25. (validation adj2 stud$).mp. 26. "Reproducibility of Results"/ 27. (reproducibility adj2 result$).mp. 28. "Sensitivity and Specificity"/ 29. (sensitivity adj2 specificity).mp. 30. (sensitivity adj2 change).mp. 31. "Predictive Value of Tests"/ 32. (predictive adj2 value).mp. 33. reliab$.mp 34. valid$.mp. 35. responsiveness.mp. 36. (internal adj1 consisten$).mp 37. likelihood ratio.mp. 38. clinimetric propert$.mp. 39. measurement protocol.mp.	41. Questionnaires/ 42. questionnaire$.mp. 43. Exercise Test/ 44. exercise test$.mp. 45. Physical Examination 46. physical exam$.mp. 47. clinical test$.mp. 48. (evaluat$ adj2 tool$).mp. 49. (screen$ adj2 test$).mp.	51. shop$.mp. 52. goods adj4 services.mp. 53. necessit$.mp. 54. play.mp. 55. sport$.mp. or Sports/ 56. art$.mp. or Art/ 57. Culture/ or culture.mp. 58. craft$.mp. 59. hobb$.mp. 60. social$.mp. 61. recreat$.mp. 62. leisure.mp. or Leisure Activities/ 63. associat$.mp. 64. ceremon$.mp. 65. community life.mp. 66. vehicule$.mp. 67. transport$.mp. 68. wash$.mp. 69. urin$.mp. 70. dry$.mp. 71. defecat$.mp. 72. menstrua$.mp. 73. toileting.mp. 74. clean$.mp. 75. cook$.mp. 76. household$.mp. 77. garbage.mp. 78. housework.mp 79. Housekeeping/
23. 1 or 2 or 3 or 4 or 5 or 6 or ((7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18) and (19 or 20 or 21 or 22))	40. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	50. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	80. 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79

"Energy, sleep, emotions"

Knee OA	***Psychometric properties***	***Measurement instruments***	***Energy, sleep, emotions***
1. KNEE OSTEOARTHRITIS/ 2. Gonarthrit$.mp. 3. Gonarthro$.mp. 4. (Knee$ adj3 pain$).mp. 5. (Knee$ adj3 ach$).mp. 6. (Knee$ adj3 discomfort$).mp. 7. (Cartilage adj3 degradation).mp. 8. (Cartilage adj3 degeneration).mp. 9. (Cartilage adj3 destruction).mp. 10. exp OSTEOARTHRITIS/ 11. Osteoarthriti$.mp. 12. Osteoarthro$.mp. 13. exp OSTEOPHYTE/ 14. Osteophyte.mp. 15. Joint space narrowing.mp. 16. Degenerative joint disease$.mp. 17. Arthriti$.mp. 18. Arthrosi$.mp. 19. exp KNEE/ 20. Knee$.mp. 21. exp KNEE JOINT/ 22. Knee joint$.mp.	24. Validation Studies/ 25. (validation adj2 stud$).mp. 26. "Reproducibility of Results"/ 27. (reproducibility adj2 result$).mp. 28. "Sensitivity and Specificity"/ 29. (sensitivity adj2 specificity).mp. 30. (sensitivity adj2 change).mp. 31. "Predictive Value of Tests"/ 32. (predictive adj2 value).mp. 33. reliab$.mp 34. valid$.mp. 35. responsiveness.mp. 36. (internal adj1 consisten$).mp 37. likelihood ratio.mp. 38. clinimetric propert$.mp. 39. measurement protocol.mp.	41. Questionnaires/ 42. questionnaire$.mp. 43. Exercise Test/ 44. exercise test$.mp. 45. Physical Examination 46. physical exam$.mp. 47. clinical test$.mp. 48. (evaluat$ adj2 tool$).mp. 49. (screen$ adj2 test$).mp. 50. rating scale$.mp.	51. energy.mp. 52. motivation.mp. or Motivation/ 53. appetite.mp. or Appetite/ 54. craving.mp. 55. impulse control.mp. 56. drive function$.mp. 57. sleep$.mp. 58. emotion$.mp. or Emotions/
23. 1 or 2 or 3 or 4 or 5 or 6 or ((7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18) and (19 or 20 or 21 or 22))	40. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	51. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50	59. 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58

"Work"

Knee OA	***Psychometric properties***	***Measurement instruments***	***Work***
1. KNEE OSTEOARTHRITIS/ 2. Gonarthrit$.mp. 3. Gonarthro$.mp. 4. (Knee$ adj3 pain$).mp. 5. (Knee$ adj3 ach$).mp. 6. (Knee$ adj3 discomfort$).mp. 7. (Cartilage adj3 degradation).mp. 8. (Cartilage adj3 degeneration).mp. 9. (Cartilage adj3 destruction).mp. 10. exp OSTEOARTHRITIS/ 11. Osteoarthriti$.mp. 12. Osteoarthro$.mp. 13. exp OSTEOPHYTE/ 14. Osteophyte.mp. 15. Joint space narrowing.mp. 16. Degenerative joint disease$.mp. 17. Arthriti$.mp. 18. Arthrosi$.mp. 19. exp KNEE/ 20. Knee$.mp. 21. exp KNEE JOINT/ 22. Knee joint$.mp.	24. Validation Studies/ 25. (validation adj2 stud$).mp. 26. "Reproducibility of Results"/ 27. (reproducibility adj2 result$).mp. 28. "Sensitivity and Specificity"/ 29. (sensitivity adj2 specificity).mp. 30. (sensitivity adj2 change).mp. 31. "Predictive Value of Tests"/ 32. (predictive adj2 value).mp. 33. reliab$.mp 34. valid$.mp. 35. responsiveness.mp. 36. (internal adj1 consisten$).mp 37. likelihood ratio.mp. 38. clinimetric propert$.mp. 39. measurement protocol.mp.	41. Questionnaires/ 42. questionnaire$.mp. 43. Exercise Test/ 44. exercise test$.mp. 45. Physical Examination 46. physical exam$.mp. 47. clinical test$.mp. 48. (evaluat$ adj2 tool$).mp. 49. (screen$ adj2 test$).mp. 50. rating scale$.mp. 51. test$.mp. 52. tool$.mp. 53. instrument$).mp.	55. (work adj2 participation).mp. 56. (work adj2 disability).mp. 57. (work adj2 retention).mp. 58. (occupation$ adj2 retention).mp 59. (occupation$ adj2 disability).mp. 60. (occupation$ adj2 $capacity).mp. 61. (work adj2 $capacity).mp. 62. (work$ adj2 presen$).mp. 63. (occupation$ adj2 presen$).mp 64. (work adj2 absent$).mp. 65. (occupation$ adj2 absent$).mp.
23. 1 or 2 or 3 or 4 or 5 or 6 or ((7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18) and (19 or 20 or 21 or 22))	40. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	54. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53	66. 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65

"Pain"

Knee OA	***Psychometric properties***	***Measurement instruments***	***Pain***
1. KNEE OSTEOARTHRITIS/ 2. Gonarthrit$.mp. 3. Gonarthro$.mp. 4. (Knee$ adj3 pain$).mp. 5. (Knee$ adj3 ach$).mp. 6. (Knee$ adj3 discomfort$).mp. 7. (Cartilage adj3 degradation).mp. 8. (Cartilage adj3 degeneration).mp. 9. (Cartilage adj3 destruction).mp. 10. exp OSTEOARTHRITIS/ 11. Osteoarthriti$.mp. 12. Osteoarthro$.mp. 13. exp OSTEOPHYTE/ 14. Osteophyte.mp. 15. Joint space narrowing.mp. 16. Degenerative joint disease$.mp. 17. Arthriti$.mp. 18. Arthrosi$.mp. 19. exp KNEE/ 20. Knee$.mp. 21. exp KNEE JOINT/ 22. Knee joint$.mp.	24. Validation Studies/ 25. (validation adj2 stud$).mp. 26. "Reproducibility of Results"/ 27. (reproducibility adj2 result$).mp. 28. "Sensitivity and Specificity"/ 29. (sensitivity adj2 specificity).mp. 30. (sensitivity adj2 change).mp. 31. "Predictive Value of Tests"/ 32. (predictive adj2 value).mp. 33. reliab$.mp 34. valid$.mp. 35. responsiveness.mp. 36. (internal adj1 consisten$).mp 37. likelihood ratio.mp. 38. clinimetric propert$.mp. 39. measurement protocol.mp.	41. Questionnaires/ 42. questionnaire$.mp. 43. Exercise Test/ 44. exercise test$.mp. 45. Physical Examination 46. physical exam$.mp. 47. clinical test$.mp. 48. (evaluat$ adj2 tool$).mp. 49. (screen$ adj2 test$).mp. 50. rating scale$.mp. 51. test$.mp. 52. tool$.mp. 53. instrument$).mp.	55. Pain/ 56. pain.mp.
23. 1 or 2 or 3 or 4 or 5 or 6 or ((7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18) and (19 or 20 or 21 or 22))	40. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	54. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53	57. 55 or 56

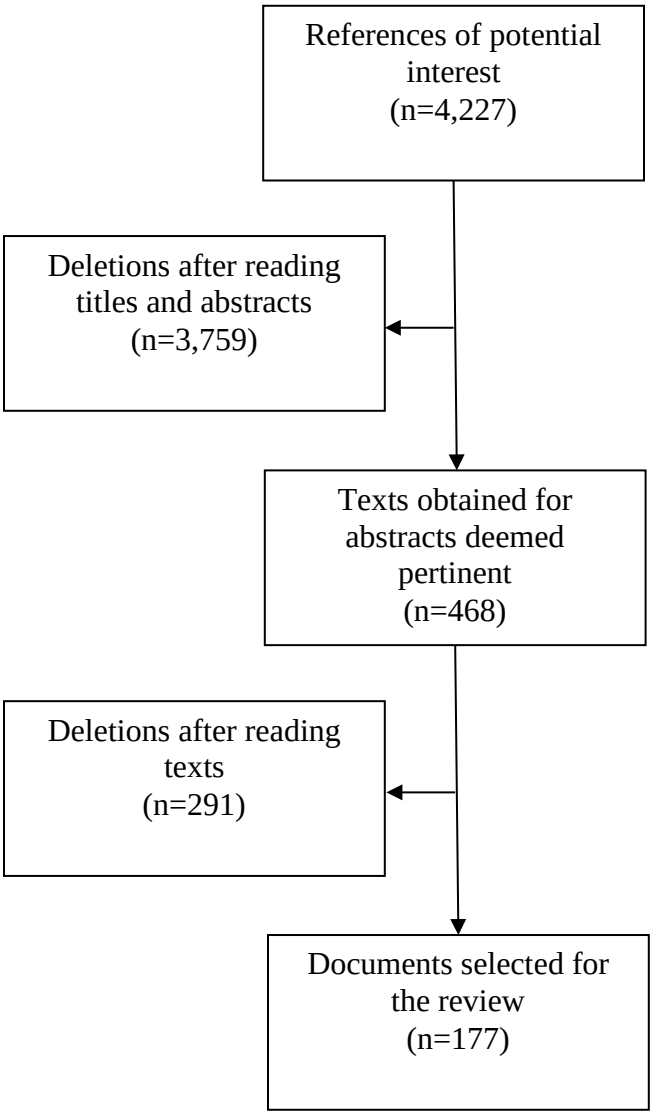
Trials on treatments/therapies

Terms related to knee OA	***Terms related to treatments/therapies***
1. KNEE OSTEOARTHRITIS/	24. exp Rehabilitation/
2. Gonarthrit$.mp.	25. exp Therapeutics/
3. Gonarthro$.mp.	26. exp Disease Management/
4. (Knee$ adj3 pain$).mp.	27. exp Treatment Outcome/
5. (Knee$ adj3 ach$).mp.	28. therap$.ti.
6. (Knee$ adj3 discomfort$).mp.	29. treat$.ti.
7. (Cartilage adj3 degradation).mp.	30. manag$.ti.
8. (Cartilage adj3 degeneration).mp.	31. 24 or 25 or 26 or 27 or 28 or 29 or 30
9. (Cartilage adj3 destruction).mp.	
10. exp OSTEOARTHRITIS/	***Terms related to selected designs***
11. Osteoarthriti$.mp.	32. exp Randomized Controlled Trial/
12. Osteoarthro$.mp.	33. randomized trial$.mp.
13. exp OSTEOPHYTE/	34. exp Clinical Trial/
14. Osteophyte.mp.	35. exp Random Allocation/
15. Joint space narrowing.mp.	36. exp Double-Blind Method/ or double blind.mp.
16. Degenerative joint disease$.mp.	37. exp Single-Blind Method OR single blind.mp.
17. Arthriti$.mp.	38. exp Placebos/ OR placebo$.mp.
18. Arthrosi$.mp.	39. Comparative Study/
19. exp KNEE/	40. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
20. Knee$.mp.	
21. exp KNEE JOINT/	**Final combination**
22. Knee joint$.mp.	41. 23 and 31 and 40
23. 1 or 2 or 3 or 4 or 5 or 6 or ((7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18) and (19 or 20 or 21 or 22))	

Systematic reviews and meta-analyses on interventions

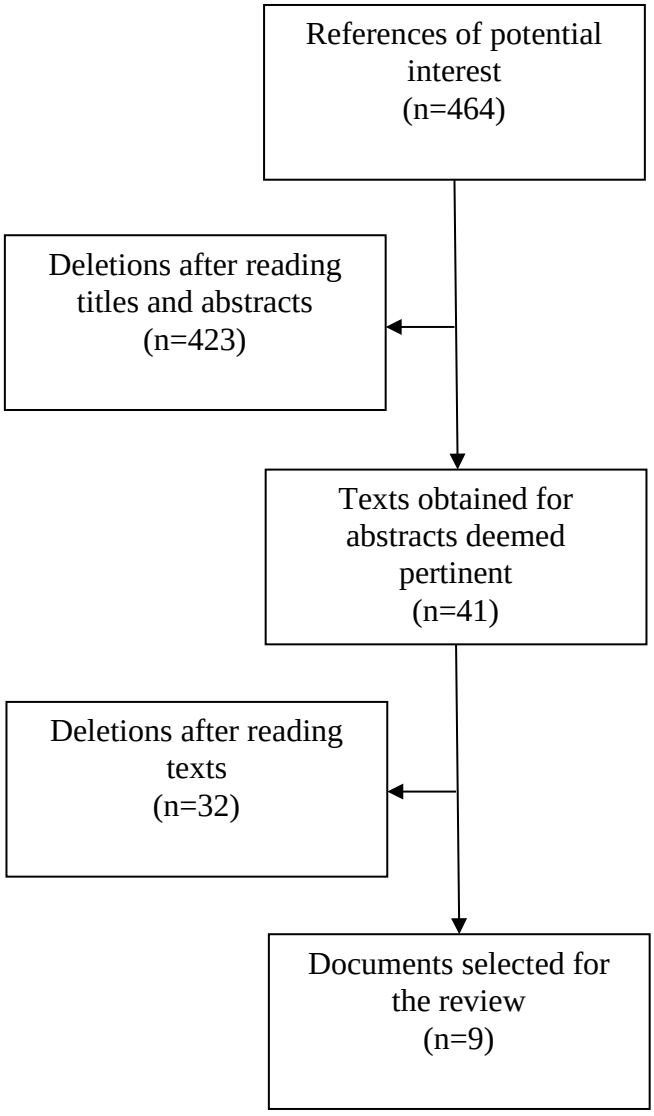
Terms related to knee OA	***Terms related to treatments/therapies***
1. KNEE OSTEOARTHRITIS/	24. exp Rehabilitation/
2. Gonarthrit$.mp.	25. exp Therapeutics/
3. Gonarthro$.mp.	26. exp Disease Management/
4. (Knee$ adj3 pain$).mp.	27. exp Treatment Outcome/
5. (Knee$ adj3 ach$).mp.	28. therap$.ti.
6. (Knee$ adj3 discomfort$).mp.	29. treat$.ti.
7. (Cartilage adj3 degradation).mp.	30. manag$.ti.
8. (Cartilage adj3 degeneration).mp.	31. 24 or 25 or 26 or 27 or 28 or 29 or 30
9. (Cartilage adj3 destruction).mp.	
10. exp OSTEOARTHRITIS/	***Terms related to selected designs***
11. Osteoarthriti$.mp.	32. review$.mp.
12. Osteoarthro$.mp.	33. meta-analysis/
13. exp OSTEOPHYTE/	34. meta-analysis.mp.
14. Osteophyte.mp.	35. 32 or 33 or 34
15. Joint space narrowing.mp.	
16. Degenerative joint disease$.mp.	**Final combination**
17. Arthriti$.mp.	36. 23 and 31 and 35
18. Arthrosi$.mp.	
19. exp KNEE/	
20. Knee$.mp.	
21. exp KNEE JOINT/	
22. Knee joint$.mp.	
23. 1 or 2 or 3 or 4 or 5 or 6 or ((7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18) and (19 or 20 or 21 or 22))	

APPENDIX B: FLOWCHART – RISK FACTORS

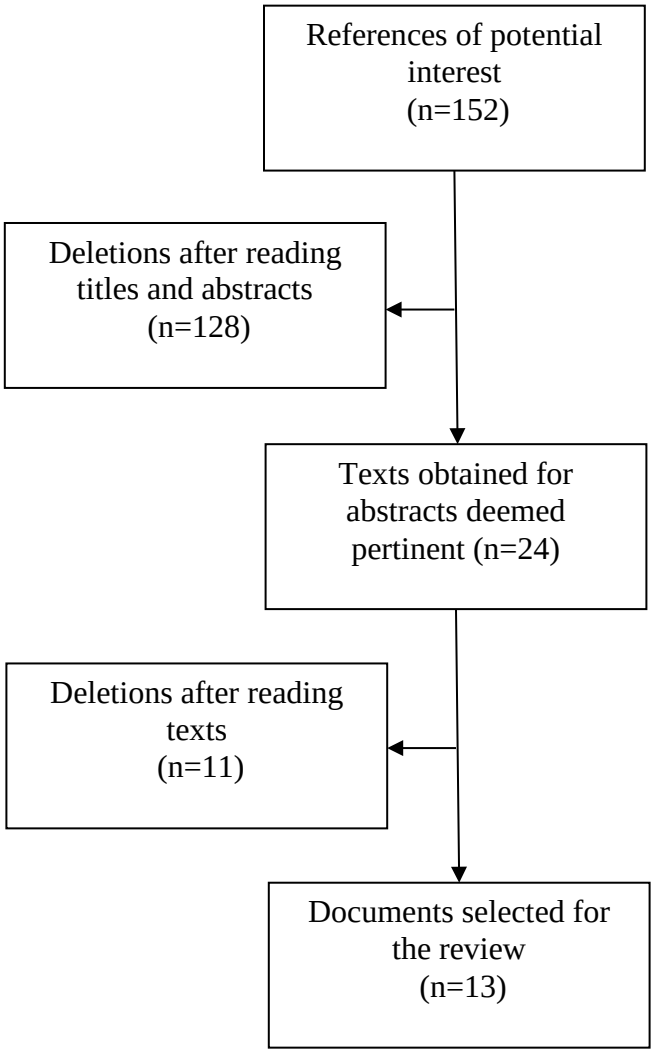


APPENDIX C: FLOWCHARTS – EVALUATION INSTRUMENTS

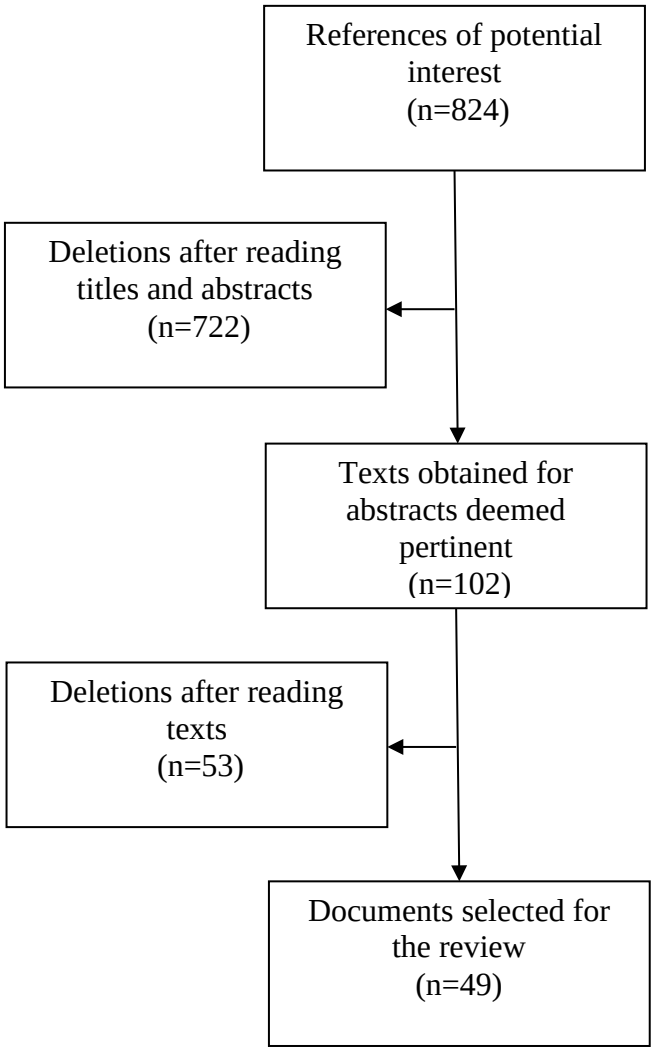
“Joint”



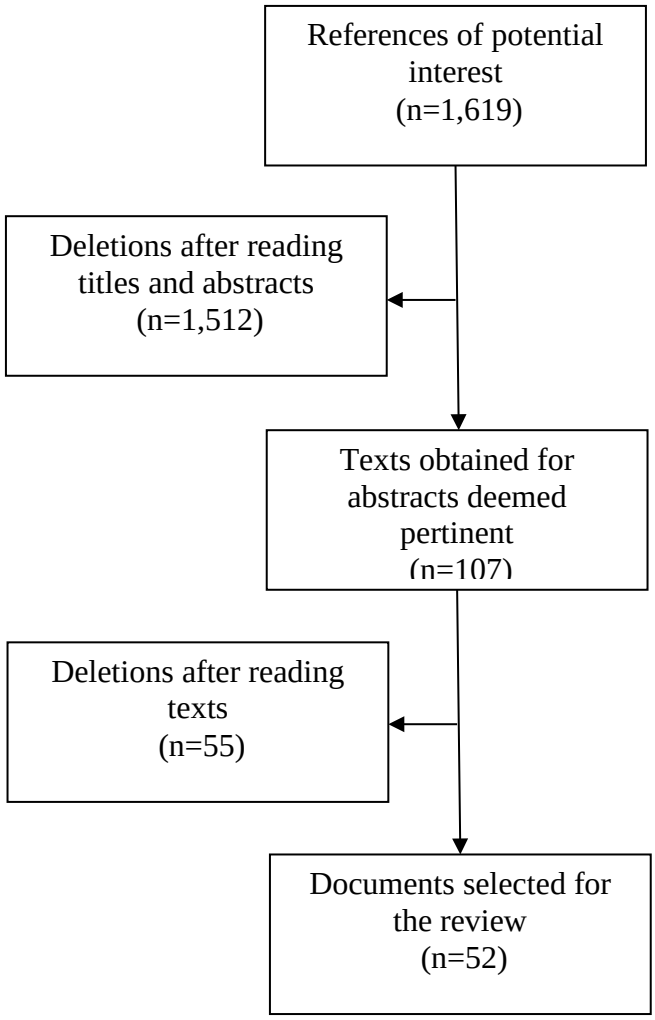
“Muscle”


References of potential interest (n=152)
Deletions after reading titles and abstracts (n=128)
Texts obtained for abstracts deemed pertinent (n=24)
Deletions after reading texts (n=11)
Documents selected for the review (n=13)

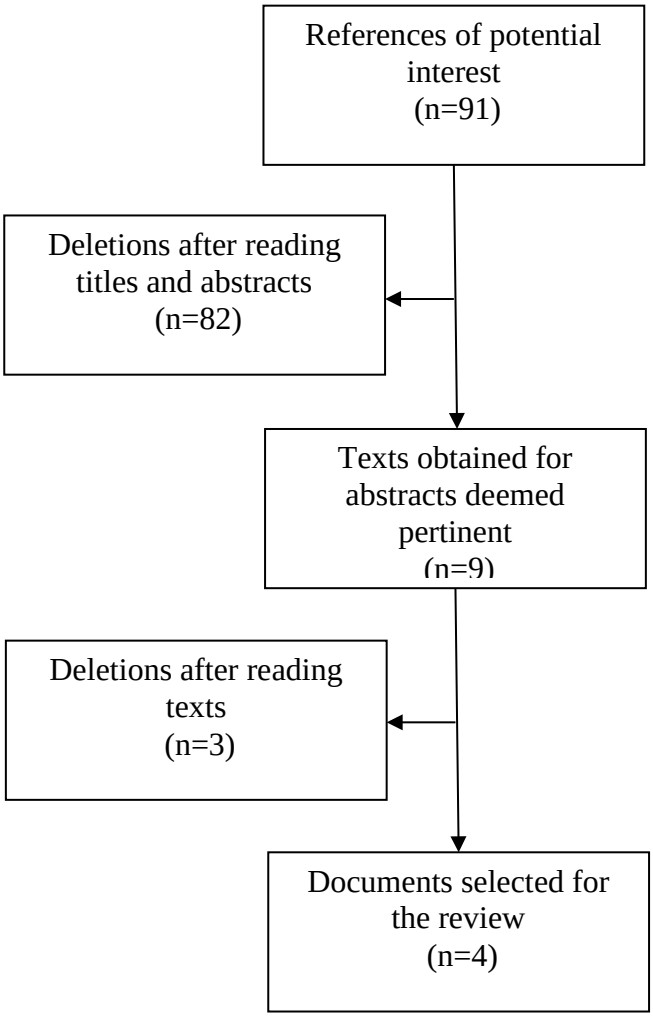
“Activities”


References of potential interest (n=824)
Deletions after reading titles and abstracts (n=722)
Texts obtained for abstracts deemed pertinent (n=102)
Deletions after reading texts (n=53)
Documents selected for the review (n=49)

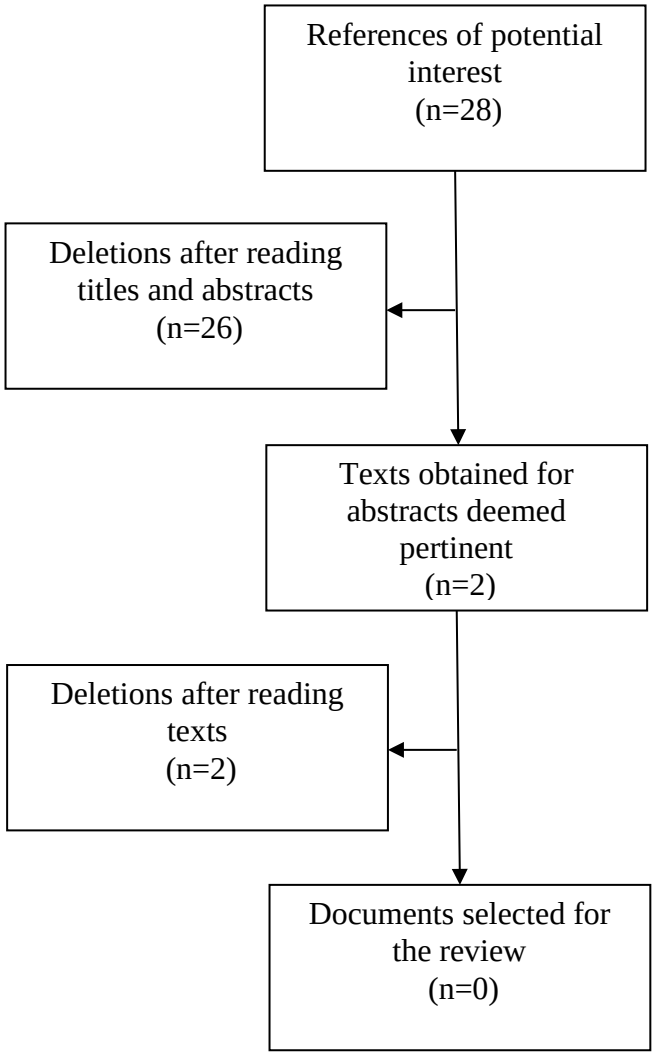
“Participation”



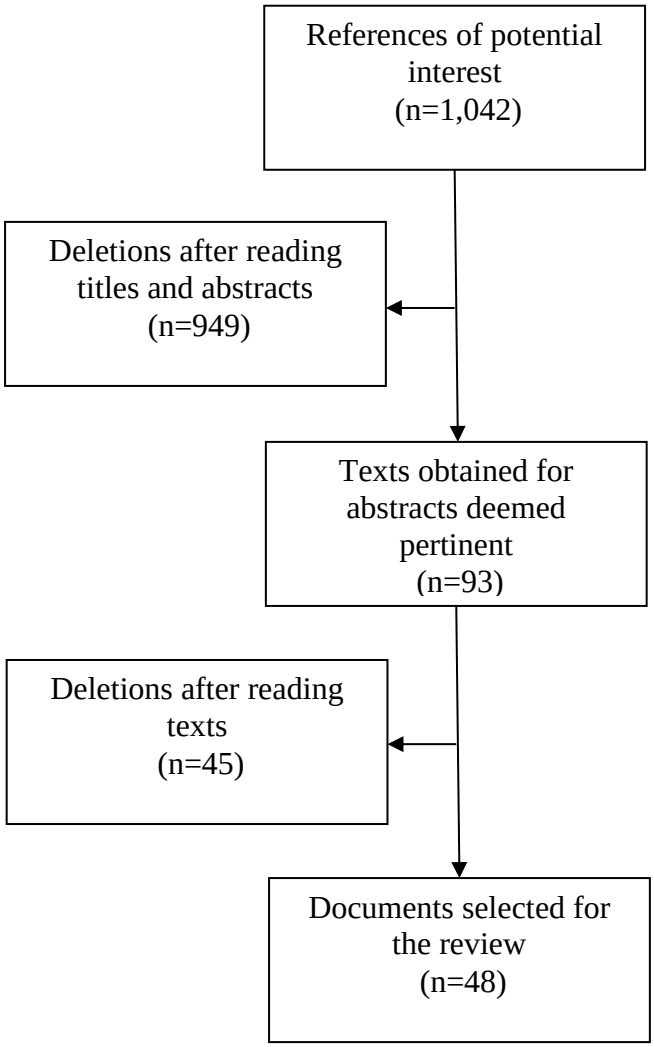
“Energy, sleep, emotions”



“Work”

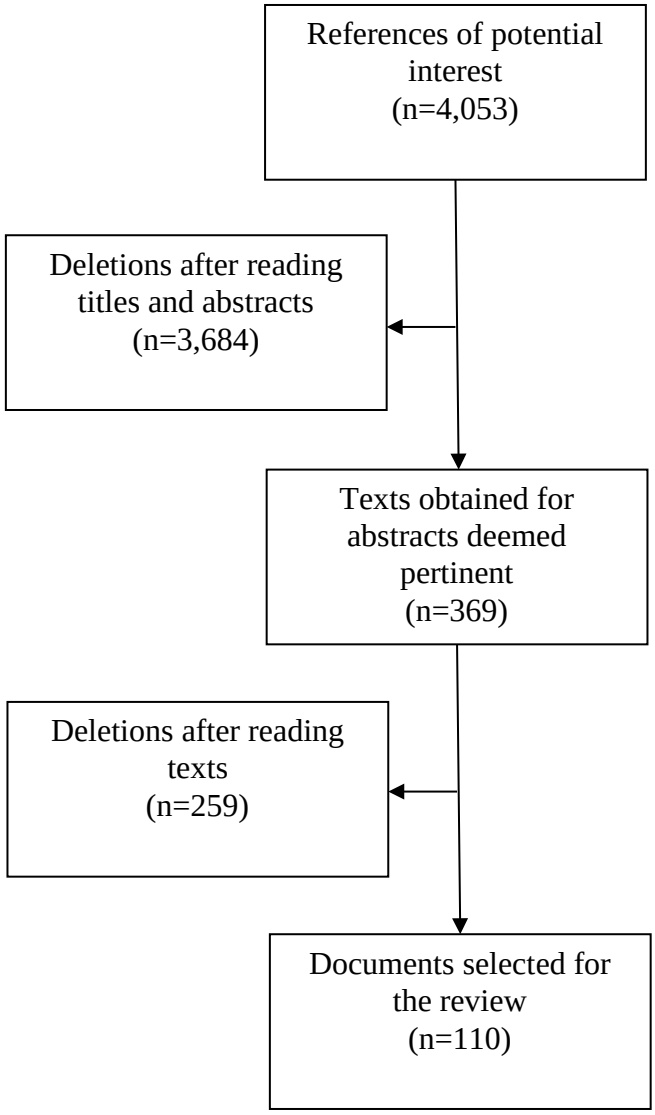

References of potential interest (n=28)
Deletions after reading titles and abstracts (n=26)
Texts obtained for abstracts deemed pertinent (n=2)
Deletions after reading texts (n=2)
Documents selected for the review (n=0)

“Pain”

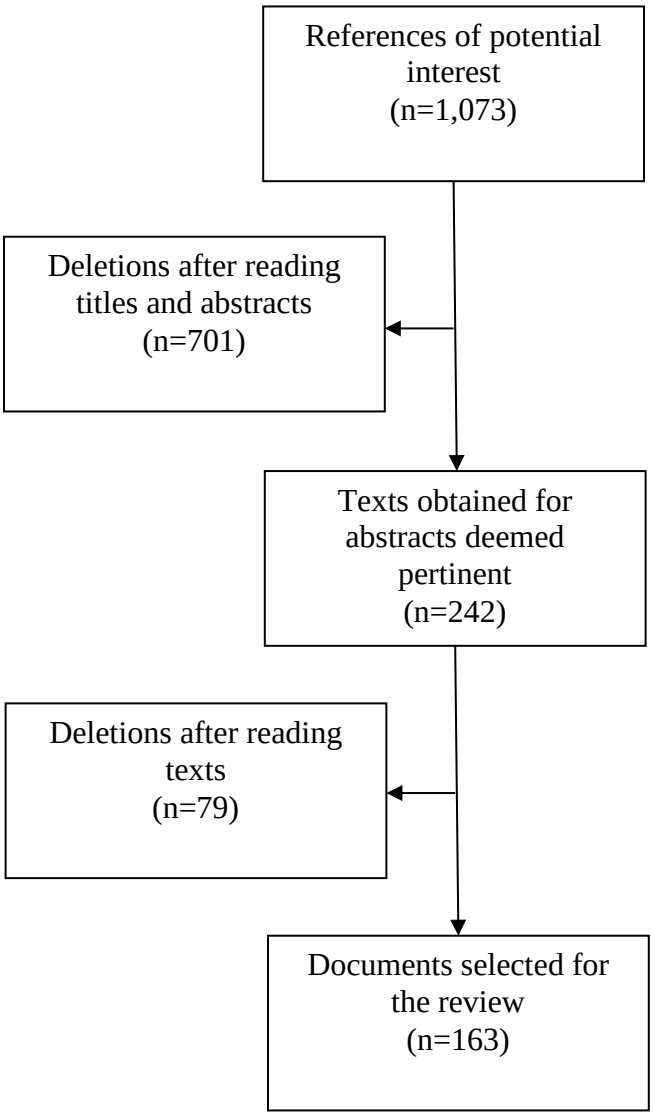

References of potential interest (n=1,042)
Deletions after reading titles and abstracts (n=949)
Texts obtained for abstracts deemed pertinent (n=93)
Deletions after reading texts (n=45)
Documents selected for the review (n=48)

APPENDIX D: FLOWCHARTS – INTERVENTIONS

Systematic reviews and meta-analyses of interventions



Controlled trials on interventions



APPENDIX E: HIGH-QUALITY EVALUATION INSTRUMENTS

Questionnaire 1[3]

Risk factors for knee OA: cohort and case-control studies

Item Criteria	V/I*	CH/CC[T]
Study population		
1 Selection before disease was present or at uniform point	V	CH/CC
2 Cases and controls were drawn from the same population	V	CC
3 Participation rate ≥ 80% for cases/cohort	V	CH/CC
4 Participation rate ≥ 80% for controls	V	CC
5 Sufficient description of baseline characteristics	I	CH/CC
Assessment of risk factor		
6 Exposure assessment was blinded	V	CH/CC
7 Exposure was measured identically in studied population	V	CC
8 Exposure was assessed prior to the outcome	V	CH/CC
Assessment of knee OA		
9 Knee OA was assessed identically in studied population	V	CH/CC
10 Presence of knee OA was assessed reproducibly	V	CH/CC
11 Presence of knee OA was according to valid definitions	V	CH/CC
12 Classification was standardized	I	CH/CC
Study design		
13 Prospective design was used	V	CH/CC
14 Followup time ≥ 3 years	V	CH
15 Withdrawals ≤ 20%	V	CH
16 Information for completers vs withdrawals	I	CH
Analysis and data presentation		
17 Frequency of most important outcomes was given	I	CH/CC
18 Appropriate analysis techniques were used	V	CH/CC
19 Adjusted for at least age and sex	V	CH/CC

* V: criterion on validity/precision; I: criterion on informativeness.

[T] CH: applicable to cohort-designed studies; CT: applicable to case-control studies.

Questionnaire 2[4]

[3] Adapted from Lievense, A., Bierma-Zeinstra, S., Verhagen, A., Verhaar, J. et Koes, B. (2001). Influence of work on the development of osteoarthritis of the hip: a systematic review. The Journal of Rheumatology, 28(11), pp. 2520-2528.

Items used to assess the quality of the studies on the psychometric properties of evaluation instruments

Items

1 If human subjects were used, did the authors provide a detailed description of the subjects to whom they administered the test (index)? (V/R/RC)

2 Did the authors clarify the qualifications or competence of the reviewers who administered the test (index)? (V/R/RC)

3 Was the reference test explained? (V/RC)

4 If inter-reviewer reliability was evaluated, were the reviewers unaware of the findings of the other reviewers?(R)

5 If inter-reviewer reliability was evaluated, were the reviewers unaware of their own previous findings on the evaluation test? (R)

6 Was the order of evaluation varied? (R)

7 If human subjects were used, was the period of time elapsed between the completion of the reference test and of the index test sufficiently short that the condition under study did not change between the two evaluations? (V)

8 Was the stability (or theoretical stability) of the variable under study taken into account when it was decided what period of time should reasonably elapse between repeated measures? (R)

9 Was the reference test independent of the index test? (V)

10 Was the execution of the index test sufficiently well described that it could be replicated?? (V/R)

11 Was the execution of the reference test sufficiently well described that it could be replicated? (V/RC)

12 Were the deletions from the study explained? (V/R/SC)

13 Were the statistical methods appropriate for the aim of the study? (V/R/RC)

Additional items for assessing responsiveness to change

[4] Brink, Y. and Louw, Q. A. (2012). Clinical instruments: reliability and validity critical appraisal. Journal of Evaluation in Clinical Practice, 18(6), pp. 1126-1132.

14 Is the study design longitudinal and does it include at least two measures? Is the time elapsed between the two measures clearly defined and is it long enough to observe a change?

15 Is what happens between the two measurement times in the study (e.g. treatment, absence of treatment) sufficiently well described that the study could be reproduced?

16 Is there a measure which provides assurance that the individuals changed between the various measurement times in the study (e.g. does the reference instrument reveal a significant change between the two measurement times)?

17 Are the hypotheses to be tested clearly stated (direction and magnitude of the correlations to be observed using the reference instrument)?

* V= applies to validation studies
R = applies to reliability studies
RC = applies to responsiveness-to-change studies

System used to assess the QUALITY of the studies:

For all types of publications:

1. To be deemed of excellent quality, the answers to items 1, 10 and 13 must be "yes."

2. To be deemed of good or moderately good quality, the answers to at least two of the aforementioned items must be "yes."

3. To be deemed of poor quality, the answers to the three aforementioned items must be "no."

For the RELIABILITY assessments:

4. To be deemed of excellent quality, the answers to at least four of the six following criteria – 2, 4, 5, 6, 8 and 12 – must be "yes."

5. To be deemed of good or moderately good quality, the answers to two or three of the following six criteria – 2, 4, 5, 6, 8 and 12 – must be "yes."

6. To be deemed of poor quality, the answers to items 8 and 4 and/or 5 must be "no", or the answers to fewer than two of the following criteria – 2, 4, 5, 6, 8 and 12 – must be "yes."

For the VALIDITY assessments, (in addition to criteria 1, 10 and 13, there are six other criteria applicable to validity studies, giving a total of nine criteria applicable to validity studies):

7. To be deemed of excellent quality, the answers to at least four of the six following criteria – 2, 3, 7, 9, 11 and 12 – must be “yes.”
8. To be deemed of good or moderately good quality, the answers to two or three of the six following criteria – 2, 3, 7, 9, 11 and 12 – must be “yes.”
9. To be deemed of poor quality, the answers to item 7 must be “no” or the answers to fewer than two of the following criteria – 2, 3, 7, 9, 11 and 12 – must be “yes.”

Questionnaire 3[5]

a) Controlled trials (in English only)

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed	Attrition bias due to amount, nature or handling of incomplete outcome data.

[5] Higgins, J. P. T. and Altman, D. G. (2008). Assessing Risk of Bias in Included Studies *Cochrane Handbook for Systematic Reviews of Interventions* (pp. 187-241): John Wiley & Sons, Ltd.

	by the review authors.	
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

b) Systematic reviews and meta-analyses (in English only)[6]

Revised Amstar

1. Was an 'a priori' design provided?
If it satisfies 3 of the criteria →4
If it satisfies 2 of the criteria →3
If it satisfies 1 of the criteria →2
If it satisfies 0 of the criteria →1

Criteria:

(A) 'a priori' design
(B) statement of inclusion criteria
(C) PICO/PIPO research question (population, intervention, comparison, prediction, outcome)

[6] Kung, J., Chiappelli, F., Cajulis, O. O., Avezova, R., Kossan, G., Chew, L., et al. (2010). From Systematic Reviews to Clinical Recommendations for Evidence-Based Health Care: Validation of Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) for Grading of Clinical Relevance. Open Dent J, 4, pp. 84-91.

2. Was there duplicate study selection and data extraction?
If it satisfies 3 of the criteria →4
If it satisfies 2 of the criteria →3
If it satisfies 1 of the criteria →2
If it satisfies 0 of the criteria →1
Criteria:

(A)	There should be at least two independent data extractors as stated or implied.
(B)	Statement of recognition or awareness of consensus procedure for disagreements.
(C)	Disagreements among extractors resolved properly as stated or implied

3. Was a comprehensive literature search performed?
If it satisfies 4 or 5 of the criteria → 4
If it satisfies 3 of the criteria → 3
If it satisfies 2 of the criteria →2
If it satisfies 1 or 0 of the criteria → 17
Criteria:

(A)	At least two electronic sources should be searched.
(B)	The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE).
(C)	Key words and/or MESH terms must be stated **AND** where feasible the search strategy outline should be provided such that one can trace the filtering process of the included articles.
(D)	In addition to the electronic databases (PubMed, EMBASE, Medline), all searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.
(E)	Journals were "hand-searched" or "manual searched" (i.e. identifying highly relevant journals and conducting a manual, page-by-page search of their entire contents looking for potentially eligible studies)

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
(Grey literature is literature produced at all levels of government, academia, business and industry in print and electronic f mats, but is not controlled by commercial publishers. Examples can be but not limited to dissertations, conference proceed Here is an extra description of what grey literature is.
If it satisfies 3 of the criteria →4
If it satisfies 2 of the criteria →3
If it satisfies 1 of the criteria →2
If it satisfies 0 of the criteria →1
Criteria:

(A)	The authors should state that they searched for reports regardless of their publication type.
(B)	The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.
(C)	"Non-English papers were translated" or readers sufficiently trained in foreign language
(D)	No language restriction or recognition of non-English articles

5. Was a list of studies (included and excluded) provided?
If it satisfies 4 of the criteria →4
If it satisfies 3 of the criteria →3
If it satisfies 2 of the criteria →2
If it satisfies 1 or 0 of the criteria → 1
Criteria:

(A)	Table/list/or figure of **included** studies, a reference list does not suffice.
(B)	Table/list/figure of **excluded** studies[1] either in the article or in a supplemental source (i.e. online). (Excluded studies refers to those studies seriously considered on the basis of title and/or abstract, but rejected after reading the body of the text)
(C)	Author satisfactorily/sufficiently stated the **reason for exclusion** of the seriously considered studies.
(D)	Reader is able to **retrace** the included **and** the excluded studies anywhere in the article bibliography, reference, or supplemental source

6. Were the characteristics of the included studies provided?

If it satisfies 3 of the criteria →4
If it satisfies 2 of the criteria →3
If it satisfies 1 of the criteria →2
If it satisfies 0 criteria → 1

Criteria:

(A)	In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions **AND** outcomes.
(B)	Provide the ranges of **relevant** characteristics in the studies analyzed (e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.)
(C)	The information provided appears to be complete and accurate (i.e. there is a tolerable range of subjectivity here. Is the reader left wondering? If so, state the needed information and the reasoning).

7. Was the scientific quality of the included studies assessed and documented?

If it satisfies 4 of the criteria →4
If it satisfies 3 of the criteria →3
If it satisfies 2 of the criteria →2
If it satisfies 1 or 0 of the criteria → 1

Criteria:

(A)	'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.
(B)	The scientific quality of the included studies appears to be meaningful.
(C)	Discussion/recognition/awareness of level of evidence
(D)	Quality of evidence should be rated/ranked based on characterized instruments. (Characterized instrument is a created instrument that ranks the level of evidence, e.g. GRADE[Grading of Recommendations Assessment, Development and Evaluation.])

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

If it satisfies 4 of the criteria →4
If it satisfies 3 of the criteria →3
If it satisfies 2 of the criteria →2
If it satisfies 1 or 0 of the criteria → 1

Criteria:

(A)	The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review
(B)	The results of the methodological rigor and scientific quality are **explicitly stated** in formulating recommendations.
(C)	To have conclusions integrated/drives towards a clinical consensus statement
(D)	This clinical consensus statement drives toward revision or confirmation of clinical practice guidelines

9. Were the methods used to combine the findings of studies appropriate?

If it satisfy 4 of the criteria → 4
If it satisfy 3 of the criteria → 3
If it satisfy 2 of the criteria → 2

[1] It is worth to have a brief overview of the excluded studies, since they do present relevant clinical information.

If it satisfy 1 or 0 of the following criteria → 1

Criteria:

(A)	Statement of criteria that were used to decide that the studies analyzed were similar enough to be pooled?
(B)	For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2).
(C)	Is there a recognition of heterogeneity or lack of thereof
(D)	If heterogeneity exists a "random effects model" should be used and/or the rationale (i.e. clinical appropriateness) of combining should be taken into consideration (i.e. is it sensible to combine?), or stated explicitly
(E)	If homogeneity exists, author should state a rationale or a statistical test

10. Was the likelihood of publication bias (a.k.a. "file drawer" effect) assessed?

If it satisfies 3 of the criteria →4
If it satisfies 2 of the criteria →3
If it satisfies 1 of the criteria →2
If it satisfies 0 of the criteria →1

Criteria:

(A)	Recognition of publication bias or file-drawer effect
(B)	An assessment of publication bias should include graphical aids (e.g., funnel plot, other available tests)
(C)	Statistical tests (e.g., Egger regression test).

11. Was the conflict of interest stated?

If it satisfies 3 of the criteria →4
If it satisfies 2 of the criteria →3
If it satisfies 1 of the criteria →2
If it satisfies 0 of the criteria →1

Criteria:

(A)	Statement of sources of support
(B)	No conflict of interest. This is subjective and may require some deduction or searching.
(C)	An awareness/statement of support or conflict of interest in the **primary** inclusion studies