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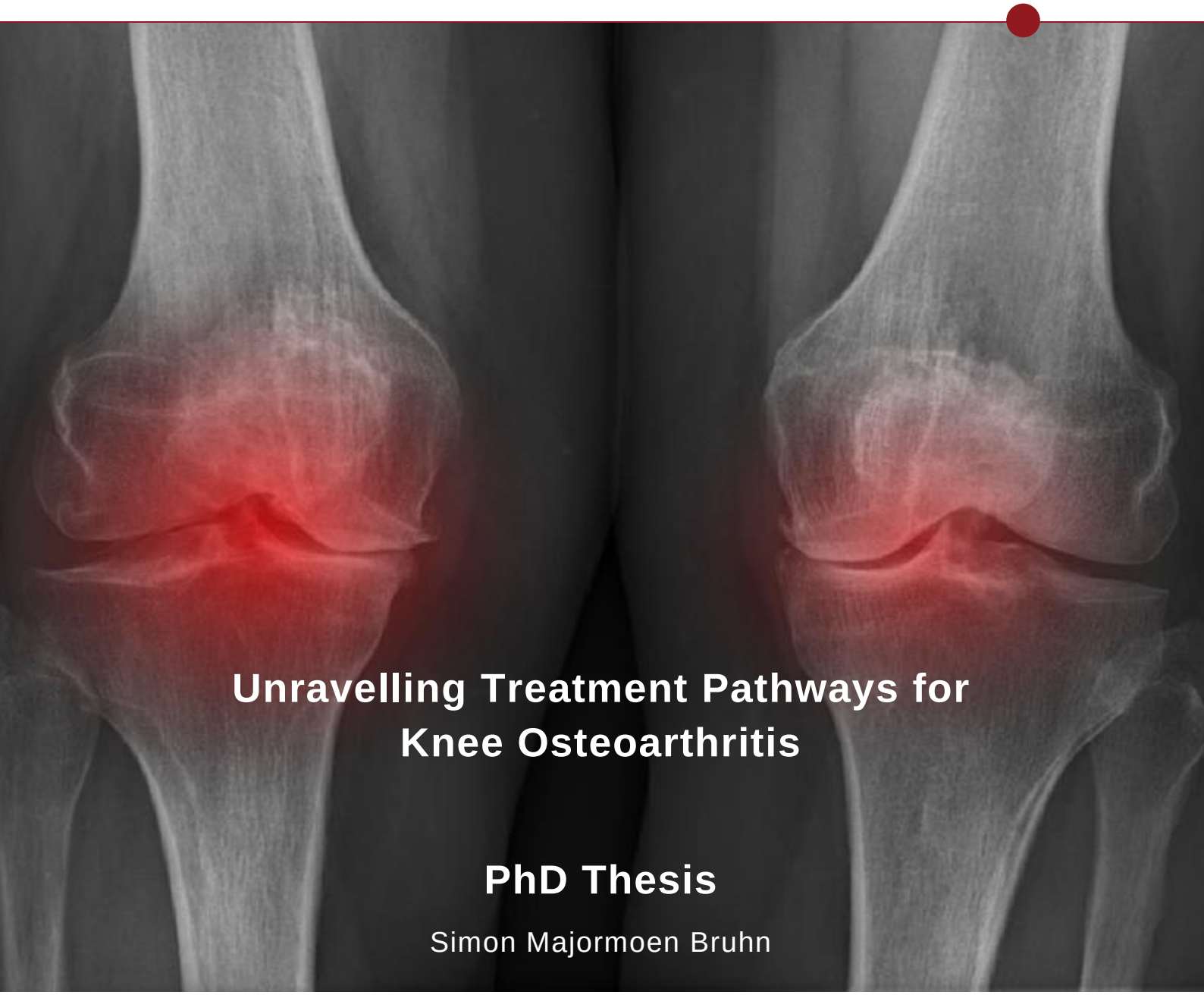

Unravelling Treatment Pathways for Knee Osteoarthritis

PhD Thesis

Simon Majormoen Bruhn

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Preface

This PhD project was carried out at Clinical Orthopaedic Research Hvidovre (CORH) at the Department of Orthopaedic Surgery at Copenhagen University Hospital - Hvidovre from November 2019 to March 2023. The project was part of a larger ongoing research project, the *TREATright* study, which is conducted under the interdisciplinary research collaboration *Clinical Academic Group, Research in Osteoarthritis Denmark (CAG ROAD)* whose overall goal is to improve the quality of life for individuals with osteoarthritis by increasing the focus on prevention and creating better treatments for the patients.

The PhD project includes quantitative data from a cohort of patients referred to an orthopaedic surgeon due to knee osteoarthritis. In addition, qualitative data were included from interviews with patients from the same cohort.

This work was funded by the Copenhagen University Hospital – Hvidovre's local and strategic funds, the Næstved-Slagelse-Ringsted Hospitals' local fund, the Region Zealand Health Science Research Foundation, Helsefonden, Candys Foundation and the Danish Rheumatism Association.

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Thank you to my wife Louise for your great support and for listening when I have been frustrated as well as excited on the PhD journey. Least but not last, I would like to thank our children, Elin and Vilmer, who both came into this world during my enrolment making the ride a little bumpier but at the same time has enriched me with a lot of joy and given me a realisation of what is most important in life.

List of papers

This thesis is based on the following three papers comprising one study protocol and two studies:

Paper I (Study protocol)

Bruhn SM, Ingelsrud LH, Bandholm T, Skou ST, Schrøder HM, Reventlow S, Møller A, Kjellberg J, Kallemose T, Troelsen A.

Disentangling treatment pathways for knee osteoarthritis: a study protocol for the TREATright study including a prospective cohort study, a qualitative study and a cost-effectiveness study.

BMJ Open. 2021;11(7):e048411. doi: 10.1136/bmjopen-2020-048411.

Paper II (Study 1)

Bruhn SM, Skou ST, Harris LK, Bandholm T, Møller A, Schrøder HM, Troelsen A, Ingelsrud LH.

Usage of guideline-adherent core treatments and characteristics of patients undertaking different treatment pathways for knee osteoarthritis: a prospective cohort study.

Submitted to peer-reviewed journal.

Paper III (Study 2)

Bruhn SM, Møller A, Skou ST, Bandholm T, Schrøder HM, Troelsen A, Ingelsrud LH.

Treatment pathways for knee osteoarthritis: a qualitative study exploring patients' perspectives.

Manuscript in preparation.

Abbreviations

ACL	Anterior Cruciate Ligament
ACR	American College of Rheumatology
BMI	Body Mass Index
CI	Confidence Interval
COREQ	Consolidated criteria for Reporting Qualitative research
DKR	Danish Knee Arthroplasty Registry
DREAM	Danish Register for Evaluation of Marginalisation
EQ-5D-3L	3-level version of the European Quality of Life – 5 Dimensions
ICC	Intraclass correlation coefficient
KL	Kellgren and Lawrence
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OKS	Oxford Knee Score
PASS	Patient Acceptable Symptom State
QALYs	Quality-Adjusted Life-Years
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SD	Standard Deviation
STROBE	The Strengthening the Reporting of Observational Studies in Epidemiology
TF	Treatment Failure
TKA	Total Knee Arthroplasty
TREATright	The Right Treatment for the Right Patient at the Right Time
VAS	Visual Analog Scale

English summary

Osteoarthritis (OA) is one of the most frequently reported diseases and, as the knee joint is the most common joint to cause disability, knee OA is a significant economic burden. The condition is characterised by pain and functional limitations often resulting in a decreased quality of life. Different evidence-based clinical guidelines for the management of knee OA exist. There seems to be relative consensus to recommend patient education, exercise, and dietary weight management, if overweight, as non-surgical first-line core treatments. Despite the recommendations it has been reported that compliance with clinical guidelines is poor and that the recommended core treatments for knee OA are underutilised. The overall objectives of this thesis were to unravel the treatment pathways that patients pursue for knee OA, and to explore how patients' perspectives on the treatment pathways can influence their choice of treatment. Three papers constitute this thesis: Paper I (Study protocol): a study protocol for the overarching TREATright study; Paper II (Study 1): a prospective cohort study; and Paper III (Study 2): a qualitative interview study.

The **Study protocol (Paper I)** was developed as an overarching protocol for the TREATright study. In addition to being a study protocol for Study 1 and 2, it also outlines a prediction study aiming to predict good and poor outcomes of different treatment modalities and a cost-effectiveness study aiming to evaluate the cost-effectiveness of different treatment pathways.

In **Study 1 (Paper II)**, we consecutively invited patients, with primary referral to an orthopaedic surgeon due to knee OA. Patients were included during a period of two years from two outpatient clinics in Denmark. Before and six months after the consultation with the orthopaedic surgeon, patients responded to a questionnaire. Through the questionnaire, we collected a wide range of patient self-reported information including patient characteristics and information about which previous treatments they had undertaken for knee OA. In addition to the information collected through the questionnaires, we performed radiographic assessments of the patients' study knee(s) and extracted data from the Danish Knee Arthroplasty Registry (DKR) on the number of patients who had undergone knee arthroplasty since inclusion. We explored the proportion of patients undertaking different treatments and treatment pathways and the characteristics of these patients. Out of 5,251 eligible patients 2,574 were included in the final analyses. Only 23% of the patients had undertaken the recommended combination of core treatments (patient education, exercise, and dietary weight management, if needed) in their entire disease course until six months after the consultation. Patient

characteristics were overall similar for patients who did undertake the recommended core treatments compared to those who did not. We identified 1,143 unique treatment pathways among the 2,574 included patients, with only 7% of the pathways comprising the recommended combination of core treatments. Overall, the findings from Study 1 concludes that the core treatments for knee OA recommended by the clinical guidelines are severely underutilised.

In **Study 2 (Paper III)**, we recruited informants for interviews among the patients included in the cohort in Study 1. The informants were interviewed using a semi-structured approach. Subsequently, we conducted a qualitative content analysis using systematic text condensation and thematization. From the interviews with eight informants, a number of themes emerged that elaborated on the patients' perspectives on treatment pathways for knee OA. Patients' view on their medical condition regarding knee OA and their symptoms influenced which treatments they received or preferred. Worsening of symptoms also led the patients adjust their treatment preferences. Patients' treatment preferences and attitudes towards certain treatment options could be influenced by their expectations of the treatment's effectiveness, accessibility, potential adverse events, and their personal views of their disease as "wear and tear". The patients also had the perception that their trust in the health care provider, how referrals and treatment options were presented to the patients, and the health care providers ability to communicate and educate on different treatments, could impact the treatment pathways. Overall, the findings from Study 2 concludes that patients' preferences for treatment of knee OA are diverse, change over time and are influenced by experiences, expectations, knowledge/understanding of the disease, own resources, and the attitude of health care providers.

In summary, treatment for knee OA is often not in accordance with clinical guidelines. The large variation in patients' treatment pathways is dependent on individual conditions and perspectives, which it is important for health care providers to be aware of in order to take each patients' experiences and preferences into account when considering treatment options and to ensure optimised utilisation of core treatments. This thesis highlights the need for a more structured approach to promote the use of guideline-adherent core treatments. Unravelling the treatment pathways for knee OA hopefully provides a foundation for increasing guideline adherence. Furthermore, the findings of the patients' different perspectives on their treatment pathways contributes to the understanding of which barriers and challenges to address in the daily management of knee OA.

Danish summary (Dansk resumé)

Artrose er en af de hyppigst rapporterede sygdomme, og da knæleddet er det led, der oftest forårsager funktionsnedsættelse, er knæartrose en betydelig økonomisk byrde. Tilstanden er kendetegnet ved smerter og funktionsbegrænsninger, der ofte resulterer i nedsat livskvalitet. Der findes forskellige evidensbaserede kliniske retningslinjer for behandling af knæartrose. Der synes at være relativ enighed om at anbefale patientuddannelse, træning og vægttab, hvis relevant, som ikke-kirurgiske førstevalgs kernebehandlinger. På trods af anbefalingerne, er det blevet rapporteret, at overholdelsen af de kliniske retningslinjer er dårlig, og at de anbefalede kernebehandlinger for knæartrose anvendes for sjældent. De overordnede formål med denne afhandling var at afklare de behandlingsveje, som patienter følger for knæartrose, og at undersøge, hvordan patienters perspektiver på behandlingsvejene kan påvirke deres valg af behandling. Tre manuskripter udgør denne afhandling: Manuskript I (Studieprotokol): en studieprotokol for det overordnede TREATright-studie; Manuskript II (Studie 1): et prospektivt kohorte-studie; og Manuskript III (Studie 2): et kvalitativt interview-studie.

Studieprotokollen (Manuskript I) blev udviklet som en overordnet protokol for TREATright-studiet. Udover at være en studieprotokol for Studie 1 og 2, beskriver den også et prædiktionsstudie, der har til formål at forudsige gode og dårlige resultater af forskellige behandlingsmodaliteter, samt et omkostningseffektivitetsstudie, der har til formål at evaluere omkostningseffektiviteten af forskellige behandlingsveje.

I **Studie 1 (Manuskript II)** inviterede vi konsekutivt patienter, der var henvist til en ortopædkirurg på grund af knæartrose. Patienterne blev inkluderet over en toårig periode fra to ambulante afdelinger i Danmark. Før og seks måneder efter konsultationen med ortopædkirurgen besvarede patienterne et spørgeskema. Ud fra spørgeskemaet indsamlede vi en bred vifte af selvrapporteret information, herunder patientkarakteristika og information om, hvilke tidligere behandlinger de havde gennemgået for knæartrose. Ud over informationen indsamlet gennem spørgeskemaerne vurderede vi røntgenbilleder af patienternes knæ og indsamlede data fra Dansk Knæalloplastik Register (DKR) om antallet af patienter, der havde fået en knæalloplastik siden inklusion. Vi undersøgte andelen af patienter, der gennemgik forskellige behandlinger og behandlingsveje, samt karakteristikaene hos disse patienter. Ud af 5.251 egnede patienter blev 2.574 inkluderet i de endelige analyser. Kun 23% af patienterne havde gennemgået den anbefalede kombination af kernebehandlinger (patientuddannelse, træning og vægttab, hvis relevant) i hele deres sygdomsforløb indtil seks måneder efter konsultationen.

Patientkarakteristika var generelt ens for patienter, der gennemgik de anbefalede kernebehandlinger sammenlignet med dem, der ikke gjorde. Vi identificerede 1.143 unikke behandlingsveje blandt de 2.574 inkluderede patienter, hvoraf kun 7% indeholdt den anbefalede kombination af kernebehandlinger. Generelt konkluderer resultaterne fra Studie 1, at kernebehandlingerne for knæartrose, som anbefales af de kliniske retningslinjer, benyttes alt for sjældent.

I **Studie 2 (Manuskript III)** rekrutterede vi informanter til interviews blandt de patienter, der var inkluderet i kohorten i Studie 1. Informanterne blev interviewet ud fra af en semi-struktureret tilgang. Derefter foretog vi en kvalitativ indholdsanalyse ved hjælp af systematisk tekstkondensering og tematisering. Fra interviewene med otte informanter fremkom en række temaer, der beskriver patienternes perspektiver på behandlingsveje for knæartrose. Patienternes syn på deres egen tilstand i forhold til knæartrose og deres symptomer påvirkede, hvilke behandlinger de modtog eller foretrak. Forværring af symptomer førte også til, at patienterne justerede deres behandlingspræferencer. Patienternes behandlingspræferencer og holdninger til visse behandlingsmuligheder kunne påvirkes af deres forventninger til behandlingens effektivitet, tilgængelighed, potentielle bivirkninger og deres personlige opfattelse af knæartrose som en ”slid-sygdom”. Patienterne opfattede også, at deres tillid til de sundhedsprofessionelle, hvordan henvisninger og behandlingsmuligheder blev præsenteret for patienterne, og de sundhedsprofessionelles evne til at kommunikere og uddanne om forskellige behandlinger, kunne påvirke behandlingsvejene. Overordnet set konkluderede resultaterne fra Studie 2, at patienternes præferencer for behandling af knæartrose er forskellige, ændrer sig over tid og påvirkes af erfaringer, forventninger, viden/forståelse af sygdommen, egne ressourcer og indflydelsen fra de sundhedsprofessionelle.

Sammenfattende er behandling af knæartrose ofte ikke i overensstemmelse med de kliniske retningslinjer. Den store variation i patienternes behandlingsveje afhænger af individuelle forhold og perspektiver, som det er vigtigt for sundhedsprofessionelle at være opmærksomme på for at tage hver patients oplevelser og præferencer i betragtning ved overvejelse af behandlingsmuligheder og for at sikre en optimal anvendelse af kernebehandlingerne. Denne afhandling understreger behovet for en mere struktureret tilgang for at fremme brugen af kernebehandlinger i overensstemmelse med de kliniske retningslinjer. Afklaring af behandlingsvejene for knæartrose skaber forhåbentlig et grundlag for at forbedre overholdelsen af de kliniske retningslinjer. Desuden bidrager resultaterne om patienternes forskellige perspektiver på deres behandlingsveje til forståelsen af, hvilke barrierer og udfordringer, der skal arbejdes med i den daglige håndtering og behandling af knæartrose.

1 Introduction

1.1 Burden of knee osteoarthritis

Osteoarthritis (OA) is one of the most frequently reported diseases in Denmark, only surpassed by allergies[1]. In "The Danish National Health Profile 2021" it is reported that 23% (1,085,000 persons) of the Danish population is affected by OA with an increased prevalence from 20% in 2010[1]. In 2010 the total OA-related financial expenses for the Danish public sector were DKK 11.5 billion (1.5 billion EUR)[2]. Globally, the prevalence of OA more than doubled, from 247 million in 1990 to 528 million in 2019 and was higher for females and increased with age[3,4]. OA most frequently affects the knee joint and is the largest contributor to the burden of disease with 365 million knee OA cases globally and 0.425 million cases in Denmark[3,4]. With the knee joint being the most common joint to cause disability, knee OA is a significant economic burden to society[5]. The burden may become even higher in the future as the prevalence of OA is anticipated to increase due to, e.g., population growth, aging, and rising obesity rates[3–5].

1.2 Knee osteoarthritis: a degenerative joint disease

OA is a multifactorial degenerative joint disease affecting the entire joint and is influenced by both mechanical, inflammatory, genetic, and metabolic factors[6–8]. OA most commonly affects the knees, hips, and hands and involves the articular cartilage and the subchondral bone as well as the joint capsule, synovial membrane, ligaments, and periarticular muscles[6,9]. Among the joint damages are loss of cartilage, formation of osteophytes, structural changes in the subchondral bone, thickening of the joint capsule, and some degree of inflammation[6,7]. Thus, OA is a complex disease and should not only be perceived as a passive degenerative or "wear and tear" disease, but rather as an active process caused by a discrepancy between the damage and regeneration of the joint[6,10,11]. This can also be underlined by a section of the Osteoarthritis Research Society International (OARSI) definition of OA: "*The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness.*"[12].

1.3 Risk factors

There are several risk factors for OA. Some of these are relevant to mention, as this project described a number of characteristics of patients with knee OA undertaking different treatments. One of the most evident risk factors might be aging[13]. Age-related biological changes in the joint and increasing exposure to multiple risk factors may contribute to the increased incidence of OA with age[14]. The age-related loss of muscle mass, deterioration of cartilage, and a reduced ability to respond adequately to joint damage and cartilage degeneration may be some of the underlying risk factors[15,16].

Furthermore, being female is a risk factor and is associated with a more severe and higher prevalence of OA[17]. The reasons for the differences between sexes are not clear but may be explained by muscle and bone strength, alignment, and the volume of cartilage[15,18].

A high body mass index (BMI) is strongly associated with OA, especially with knee OA[19–21]. Obesity (BMI $\geq$ 30 kg/m^2) is considered a substantial risk factor, while overweight (BMI $\geq$ 25 kg/m^2) is less associated with OA but still considered a risk factor[22]. Several studies have found a dose-response relationship between body weight and the risk of knee OA demonstrating a higher risk of knee OA with increased BMI, and a lower risk with a reduction in weight[20,23–26]. Obesity is also associated with hand OA, suggesting that, together with mechanical loading, metabolic syndrome could be related to OA, and that there may be some systemic inflammation affecting the joints[19,27]. This is supported by findings of an increased risk of metabolic syndrome in patients with OA[28,29].

The biomechanics on a more local joint-level is considered a risk factor for OA. Knee alignment is related to the degradation of the knee with the greatest impact on the compartment which is under the highest joint load[30]. Valgus alignment of the knee increases the joint load and risk of OA progression in the lateral compartment, while varus alignment increases the joint load and risk of OA progression in the medial compartment[31–33]. Furthermore, occupational activities with continued kneeling work and heavy lifting have demonstrated a higher risk of knee OA[34–36]. Some high impact sport activities have been found to be a risk factor for knee OA which may partially be explained by knee injuries within these sports activities[37]. Knee injury is a significant risk factor for knee OA[22]. Injuries such as rupture of the anterior cruciate ligament (ACL) are associated with increased prevalence and early onset of knee OA – especially when menisci, cartilage, bone, or collateral ligaments are involved[38–41].

Although genetic involvement in OA will not be covered in this project, it is worth mentioning as an important possible underlying risk factor. Genetic factors are determining for structural OA and have been found to be related to the pathology and onset of OA and are therefore a possible risk factor[42,43]. However, contradictory findings exist on the contribution of genetic factors on knee OA[42].

1.4 Diagnosis

Different recommendations exist with varying ability to identify clinical knee OA[44]. The criteria often used to diagnose clinical knee OA are those of the National Institute for Health and Care Excellence (NICE)[45], the American College of Rheumatology (ACR)[46], and the European League Against Rheumatism (EULAR)[47].

The NICE criteria suggests that knee OA can be clinically diagnosed when the patient meets the following criteria[45]:

- $\geq$ 45 years of age
- Activity-related pain
- No or only brief morning stiffness

Originally the ACR criteria recommended to use a decision tree describing that patients can be diagnosed with clinical knee OA when having knee pain and in addition having one of the following sets of criteria met[46]:

- Bony enlargement and no crepitus
- Crepitus, morning stiffness $\leq$ 30 min., and $\geq$ 38 years of age
- Crepitus, morning stiffness > 30 min., and bony enlargement

Another way in which the ACR criteria are often applied is that clinical knee OA can be diagnosed when patients have knee pain and, in addition, three or more of the following six criteria are met[46,48]:

- > 50 years of age
- Morning stiffness < 30 min.
- Crepitus
- Bony enlargement
- Bony tenderness
- No palpable warmth

The criteria from EULAR suggests to apply six diagnostic criteria to confirm the clinical diagnosis of knee OA[47]:

Symptomatic criteria:

- Movement-related knee pain
- No or only brief morning stiffness
- Functional limitations

And in addition, one or more clinical criteria:

- Restricted range of motion
- Crepitus
- Bone enlargements

In addition, the EULAR recommendations suggest that the minimum age for being diagnosed with clinical knee OA is limited to ≥ 40 years[47]. An increased number of positive criteria from the EULAR recommendations on diagnosis has been estimated to increase the probability of having radiographic knee OA[47]. However, the value of routinely taken radiographs is questionable[49] and the use of radiographs are not recommended for diagnosing patients with typical presentation of clinical OA in the routine clinical assessment[50].

1.5 Treatment and clinical guidelines

Knee OA is characterised by pain and functional limitations often resulting in a declined quality of life[45]. As knee OA cannot be cured, the treatments should focus on decreasing symptoms, reducing potentially modifiable risk factors, and prevent further functional decrease[6]. There are different evidence-based clinical guidelines for the management of knee OA. We summarised the recommendations for the treatment of knee OA from four clinical guidelines: NICE[45], EULAR[51], OARSI[52], and those from the Danish Health Authority[53].

The recommendations from the NICE guideline have been developed for healthcare in England[45]. As core treatments, NICE recommends information/education, exercise, and weight loss, if overweight[45]. The guideline recommends that patients are informed of the disease and management of knee OA and that patients should be informed of misconceptions regarding the treatment and progression of disease[45]. Exercise should be offered to all patients and include "*general aerobic fitness*" and "*local muscle strengthening*", but it is not defined whether exercise should be supervised or carried out on their own[45]. NICE recommends that patients with a BMI ≥ 25 kg/m² should be offered weight loss[45,54].

The guideline recommends to consider referral to surgery/orthopaedic surgeon "*before there is prolonged and established functional limitation and severe pain*", but that the patient should at least be offered the core treatments before considering surgery[45].

An expert group from 10 European countries developed the EULAR guidelines[51]. They identified 11 recommendations for core management of hip and knee OA including five "*core interventions*" that should be considered for all patients: information and education concerning OA; maintaining of activity; individualised exercise; weight loss, if overweight; and decreasing negative mechanical factors (e.g., using appropriate footwear)[51]. Exercise should be individualised regarding the patient's preferences and is recommended both as individual, group-based, and home-based[51]. There are no explicit recommendations on whether exercise should be supervised, but it is stated that initial supervision is required and that exercise over time should be integrated in the patient's everyday life[51]. EULAR highlights that the recommended treatments should be individualised and undertaken as a group of treatments and not as stand-alone treatments[51].

The clinical guideline from OARSI was developed by an international expert panel with input from a patient panel[52]. The OARSI guideline recommends "*structured land-based exercise with or without dietary weight management*" as core treatment(s) for all patients with knee OA[52]. In addition, education is considered a standard part of the treatment and should be provided on an ongoing basis[52]. The health care providers should initially select the core treatment(s), and if appropriate, additional strong or conditional recommended treatments can be selected[52]. Education should include information on self-management, the progression of OA and the benefits of treatment[52]. The guideline does not specify when dietary weight management is relevant for patients with knee OA, but suggests that it could be relevant for patients with hip OA with a BMI $\geq$ 30 kg/m^2[52].

The clinical guideline from the Danish Health Authority is a national guideline developed by a Danish working group[53]. The guideline recommends patient information and education, exercise, and weight loss, if overweight (BMI $\geq$ 28 kg/m^2) as treatments for knee OA[53]. Patient information and education should include information about knee OA and self-management[53]. The recommended exercise should comprise fitness and/or strength training and it is recommended that home-based and unsupervised exercise is always initiated by a supervised session[53]. The guideline recommends that overweight patients should reduce their body weight by > 5%, and that the weight loss must be maintained to preserve the effect[53].

There seems to be relative consensus on the group of core treatments[55,56]. However, summarising recommendations on supplementary treatments were more challenging as the guidelines have different recommendations and strength of these and are sometimes even contradictory[55,56]. The treatments can be stratified into three classifications (Figure 1)[57]. 1) Core treatments comprising patient education, exercise, and dietary weight management, if overweight, are suggested as non-surgical first-line treatments by national and international clinical guidelines for the management of knee OA[45,51–53]. These treatments are considered to be efficient, safe, and affordable and should be offered to all patients[58]. 2) Supplementary non-surgical treatments should be considered if the first-line core treatments are insufficient to relieve pain and improve functional ability[45,51–53]. 3) Surgical treatment with knee arthroplasty may be appropriate for a few individuals with end-stage radiographically verified OA, when all other suitable non-surgical alternatives have failed to relieve symptoms sufficiently after an appropriate amount of time[6,59].

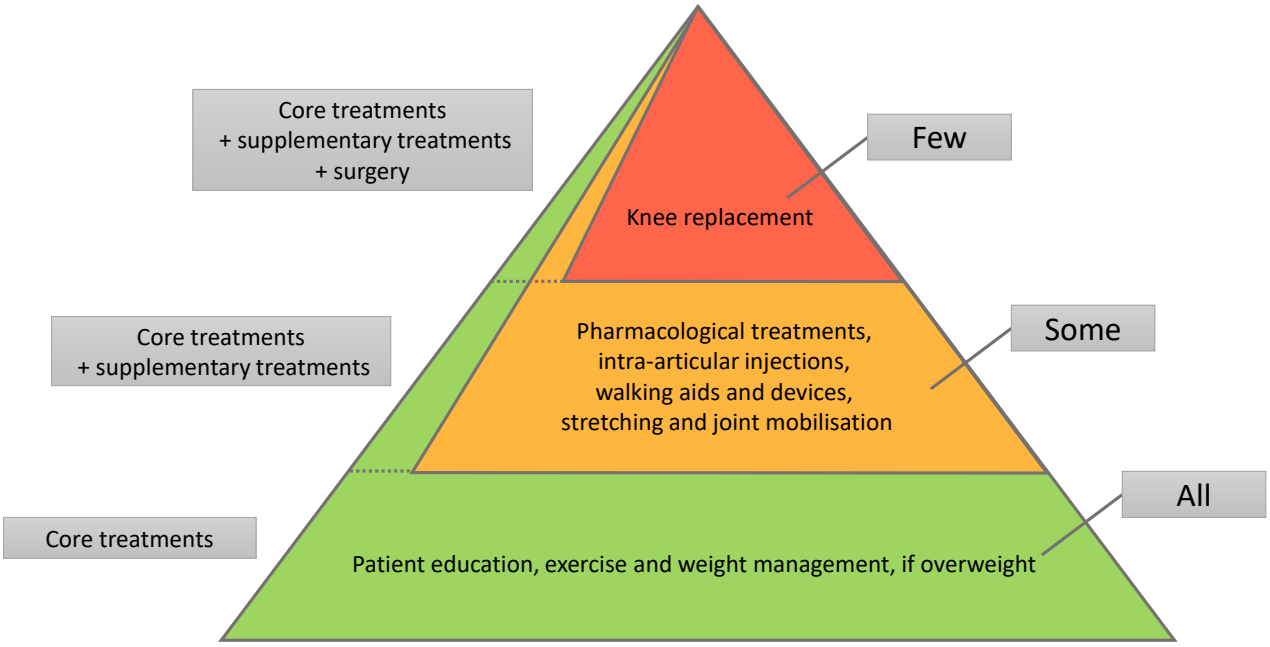

Figure 1 (This figure was created with inspiration from[57]). All patients should be offered the core treatments. Only when core treatments do not result in sufficient pain relief and improvement in functional ability, some patients will need additional supplementary treatments, while only a few will need a knee replacement.

1.5.1 Core treatments

1.5.1.1 Patient education

Patient education should be part of the core treatments and provide patients with information about the disease, potential progression, and how to adapt and live with OA[45,51–53]. Furthermore patient

education should include information about other available treatments and the potential effects of these[45,51–53]. However, patient education by itself has a limited effect on pain and function but has demonstrated to enhance self-efficacy for managing OA and improve treatment adherence when combined with other treatments[60,61]. Such an example is the GLA:D programme (Good Life with osteoArthritis in Denmark) which is an evidence-based program combining education and neuromuscular exercise supervised by physiotherapists[62].

1.5.1.2 Exercise

Exercise is largely recommended as core treatment for OA[45,51–53] and enough evidence has been established to demonstrate a considerable advantage of exercise to reduce pain and improve physical function for patients with knee OA[63–65]. Exercise is often prescribed by health care providers with a functional and neuromuscular aim[62]. A wide range of different exercise modalities are recommended to be effective[45,51–53]. The clinical guidelines primarily recommends exercise supervised by a physiotherapist or similar, and the Osteoarthritis Research Society International (OARSI) specifically recommends "*structured land-based exercise*" as the most effective type of exercise for knee OA[52]. A recent study confirmed the benefit of exercise regarding knee function and pain but found that exercise dose was less important[66], while the timing of physiotherapy initiation has recently shown to be of importance[67]. The total number of sessions with supervised exercise is recommended to be more than 12 and should optimally be carried out three times a week[64,65]. When the supervised sessions come to an end, exercise should be implemented in the patient's everyday life[51]. However, the recommendations on exercise should be adapted to the individual patient with particular attention to the treatment adherence[68].

1.5.1.3 Weight loss and dietary weight management

Weight loss and dietary weight management is recommended as core treatment for OA if overweight or obese[45,51–53]. Studies indicate that weight loss can reduce the mechanical load on knee joints[69,70] and potentially reduce pain and increase physical function in obese patients[71,72]. A weight reduction of more than 5% has been suggested for obese patients to experience a symptomatic relief, while a weight loss of 10% can have moderate to large effects[71]. Weight loss combined with exercise may result in additional pain reduction and improved physical function[73,74], and is considered to be a cost-effective treatment in obese patients with knee OA[75].

1.5.2 Supplementary treatments

In addition to the core treatments, a wide range of other treatments can be considered as supplementary[45,51–53]. If relevant, these should be undertaken in conjunction with the core treatments (Figure 1)[45,51–53,57]. The recommendations of supplementary treatments differ between the guidelines, regarding which treatments are recommended and the strength of these recommendations[55,76]. However, there seems to be relative consensus on recommending, to some extent, pharmacological treatments, intra-articular injections, walking aids and devices, stretching, and joint mobilisation as supplementary treatments for some patients[45,51–53].

1.5.3 Knee replacement surgery

When core treatments and supplementary treatments have been unsuccessful to improve symptoms sufficiently, knee arthroplasty can be considered as an effective and cost-effective treatment for patients with radiographically verified end-stage knee OA[52,77,78]. Patients with definite joint space narrowing and marked bone degeneration will benefit the most from knee arthroplasty[79]. For younger patients it has been suggested that knee arthroplasty surgery might be postponed as the implant, despite excellent long-term survivorship, will nevertheless have a limited survival, and revision surgery has less favourable outcomes[80,81]. For some patients with moderate-to-severe knee OA who are eligible for knee arthroplasty, non-surgical core treatments can postpone or possibly even prevent surgery[82,83]. In addition, patients who are non-surgically treated have a lower risk of serious adverse events[82]. Consequently, regardless of the severity of OA, patients should undertake the full range of non-surgical first-line core treatments prior to knee arthroplasty[6,52,59,65].

1.6 Compliance with clinical guidelines

Studies report that compliance with clinical guidelines is poor and that the recommended first-line core treatments for knee OA are underutilised, despite the evidence[84–90]. Recommended non-pharmacological and non-surgical treatments, including patient education or referral/recommendation to exercise, has been found to be recommended to less than 40% of the patients with OA[85,87]. Others have also reported that only 19% adhered to the clinical guidelines after being recommended non-surgical treatments by an orthopaedic surgeon, with the number being 60% for those patients proceeding to knee replacement surgery[90]. Several barriers for adhering to the clinical guidelines have been reported[91–99]. Having severe radiographical OA or too much pain has

been reported as a barrier for patients to undertake recommended core treatments[94,98]. Patients' perception of knee OA as a "wear and tear" disease seems to lead to a conception that surgery is needed and that exercise can worsen the knee damage[98,99].

Guideline-adherence may also be compromised by health care providers having mistrust in therapeutic exercise and management of dietary guidance[93–96]. A barrier for providing guideline-adherent treatments can also be if the health care provider lacks knowledge of available recommended treatments[93,95,96].

1.7 Why this work is needed

Increasing and optimising the utilisation of guideline-adherent non-surgical core treatments before referring patients to surgery, should be a focus in the management of OA[52,77,100,101]. With the increased future burden of knee OA[3–5] and the underutilisation of recommended core treatments[84–89], despite evidence based clinical guidelines[45,51–53], there is a need for investigating guideline-adherence and current practice. An important foundation to optimise the treatment pathways and increase the use of recommended treatments adhering to clinical guidelines is to unravel existing treatment pathways and describe which patients receive specific treatment modalities (Study 1). Furthermore, to improve understanding of the daily management of patients with knee OA, it will be valuable to clarify the patients' perspectives on treatment pathways for knee OA and the patients' preferences, expectations, and experiences with different treatments (Study 2).

2 Objectives

2.1 General

The overall objectives of this thesis were to unravel the treatment pathways that patients pursue for knee OA, and to explore how patients' perspectives on the treatment pathways can influence their choice of treatment.

2.2 Specific

The specific objectives of the papers included in this thesis were:

Study protocol

To outline a study protocol for studies aiming to:

1. Describe which treatment pathways patients pursue for knee OA during the first two years after consulting an orthopaedic surgeon.
2. Describe the characteristics of patients choosing different treatment pathways.
3. Develop prediction models for good and poor treatment outcomes of different treatment modalities and/or pathways used for knee OA.
4. Evaluate the cost-effectiveness of treatment pathways that adhere to clinical guidelines versus pathways that do not.
5. Describe the patients' perspectives on their treatment pathways for knee OA.

Study 1

1. To investigate the proportion of patients with knee OA undergoing guideline-adherent core treatments until six months after primary referral to an orthopaedic surgeon.
2. To evaluate which specific treatment pathways these patients undertake.
3. To describe the characteristics of patients undertaking different treatment pathways.

Study 2

1. To describe the patients' perspectives on their treatment pathways for knee OA.

3 Methods

3.1 Study design

This project was conducted as part of *The Right Treatment for the Right Patient at the Right Time* (TREATright) study, approved by the Danish Data Protection Agency (Journal no.: AHH-2017-072) and the Danish regional ethical committee (Journal no.: H-17017295). The TREATright study is based on a large cohort of patients with primary referral to an orthopaedic surgeon due to knee OA. The patients were consecutively invited to participate during a period of two years from two outpatient clinics in two different regions of Denmark. The prospective cohort study (Study 1) investigating treatment pathways, reported on the first six months of follow-up from the TREATright study and data were collected from self-reported questionnaires, radiographic assessments, and the Danish Knee Arthroplasty Registry (DKR). Reporting of Study 1 followed The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies[102]. The qualitative study (Study 2) describing the patients' perspectives on their treatment pathways were based on interviews with informants recruited from the TREATright cohort. Reporting of Study 2 followed the Consolidated criteria for Reporting Qualitative research (COREQ)[103]. The Study protocol was developed as an overarching protocol for the TREATright study. In addition to being a study protocol for Study 1 and 2, it also outlines a prediction study aiming to predict good and poor outcomes of different treatment modalities and a cost-effectiveness study aiming to evaluate the cost-effectiveness of different treatment pathways.

3.2 Participants

3.2.1 TREATright cohort (Study 1)

From October 2018 to December 2020, we consecutively included patients who had received primary referrals to an orthopaedic surgeon due to knee OA. Aiming to represent both urban and more rural regions of Denmark, patients were included from the outpatient clinics at the departments of orthopaedic surgery at Copenhagen University Hospital Hvidovre and Næstved Hospital. Using an observational approach, patients were included if their general practitioners diagnosed them with knee OA, regardless of the diagnostic criteria used. The lowest age restriction for being diagnosed with clinical OA has been suggested by EULAR to be ≥ 40 years[47]. Thus, all patients ≥ 40 years who had

been referred with diagnoses like "knee pain" or "knee problems" were also invited to participate, despite the unspecific diagnosis. Previous knee arthroplasty or osteotomy around the study knee, as well as the inability to read and write Danish, were used as exclusion criteria.

3.2.2 Informants for the qualitative study (Study 2)

Informants for interviews were identified using a purposeful sample of informants identified by random sampling from the TREATright cohort (Study 1). There were no exclusion criteria and all patients who were included in the TREATright cohort were eligible. Random samples in groups of five patients were generated. For each random sample we screened the patients' age, sex, which study site they were included from, and whether they had undergone knee arthroplasty. Patients with different characteristics were invited from one random sample before generating the next to reflect the heterogeneity of patients with knee OA. Patients were contacted by phone and invited to participate in an interview. Out of 40 randomly identified patients 13 were contacted; three declined to participate, and two did not show up for the planned interview. The intention was to keep recruiting informants until we reached sufficient information power, i.e., when novel information relevant to the study aim was developed[104]. However, we ended up with the number of recruited informants being decided for pragmatic reasons.

3.3 Procedures

3.3.1 Cohort study (Study 1)

3.3.1.1 Data collection

Approximately two weeks before the consultation with the orthopaedic surgeon, patients were invited to respond to an online questionnaire through a secure e-mail. If the patients did not respond to the questionnaire, we forwarded up to two reminders. For patients who had not yet responded to the questionnaire before their consultation, they were asked to complete it either on paper or a tablet in the outpatient clinic. To prevent apprehension bias, we requested the patients to answer the questionnaire before their consultation with the orthopaedic surgeon. As the study was based on an observational approach, we aimed not to interfere and delay the daily practice in the outpatient clinic due to patient inclusion. Therefore, if the patients had provided information regarding prior treatment for knee OA, they were permitted to complete the questionnaire after their consultation. After

completing the questionnaire, patients whose scheduled consultation was postponed for more than a month were requested to respond to the questionnaire again before the rescheduled consultation. Six months after the patient was included, we sent an online follow-up questionnaire. Paper-based follow-up questionnaires with a pre-paid return envelope were sent to the approximately 15% of patients who did not have a secure e-mail. We accepted a two-month response window, and online reminders were sent after one and two weeks and after five weeks by postal mail. Both at inclusion and at six-month follow-up, responses were deemed complete if the patient had answered the question on previous treatment for knee OA. If the patient had not answered the question about previous treatment, the patient was excluded due to insufficient completion. We used a Research Electronic Data Capture (REDCap) database to collect and store data securely[105]. Follow-up questionnaires were also sent two years after inclusion but results from the two-year follow-up are not part of this thesis.

3.3.1.2 Questionnaires

We collected a wide range of patient self-reported information (Table 1). Some of the variables relevant to Study 1 are described below Table 1.

Table 1 (adapted from Paper I).
Collected variables from the questionnaires at inclusion and at six-month follow-up

Collected outcomes	**Inclusion**	**Six-month follow-up**
Height (cm)	X	
Weight (kg)	X	
PASS (yes/no)		X
Self-reported TF (yes/no)		X
Degree and importance of change in knee-pain and function (ranging from "better, an important improvement" to "worse, an important deterioration")		X
OKS (12 items)	X	X
Residential status (alone/cohabiting)	X	
Level of education (elementary school/high school/vocational education/short-cycle higher education/medium-cycle higher education/long-cycle higher education or more)	X	
Occupation (retired, early retiree or on early retirement/sick leave part time or full time/unemployed/on the labour market or student part time or full time)	X	
Smoking (Yes/No, but I used to/No, never. If Yes: average number of daily cigarettes is recorded)	X	
Comorbidities (list of 15 diseases)	X	
Which knee to be examined by the orthopaedic surgeon (right/left/both)	X	
Duration of knee problems (ranging from 0 months to more than 10 years)	X	

Degree of knee pain (VAS 0 (no pain) – 100 (worst imaginable pain) [100 mm scale])	X	X
Localisation of pain/discomfort elsewhere in the body (marked on a full body pain mannequin)	X	X
Expectations to the following consultation (surgery/injection into the knee joint/training sessions or other treatment/weight loss (if overweight)/treatment for pain/no treatment/other)	X	
Type of health care provider who has examined/treated the knee OA (general practitioner/orthopaedic surgeon/rheumatologist/physiotherapist/occupational therapist/dietitian/osteopath/chiropractor/personal trainer in the gym/alternative therapist (such as massage therapist, healer, Body SDS therapist, reflexologist, acupuncturist or similar)/other/no examination or treatment)	X	X
Number of consultations/treatments for knee OA for each health care provider		X
Previous treatment for knee OA (Table 2)	X	X
OA-QI (15 items)	X	X
Previous knee injury that was examined by a health care provider (none/right knee/left knee/both knees)	X	
Previous joint surgery in lower limb (hip [right/left], knee [right/left], ankle [right/left])	X	
Type of previous joint surgery in lower limb (arthroscopic/open surgery/total or partial replacement)	X	
ASES (11 items)	X	
Self-reported physical activity level (none/30 min./1 hour/2 hours/more than 2 hours)	X	X
Self-reported health condition (EQ-5D-3L) (5 items and EQ-VAS)	X	X
Health care costs (health care provider visits not covered by public health care system)		X
Short term sick leave (<21 days)		X

PASS, Patient Acceptable Symptom State; TF, Treatment Failure; OKS, Oxford Knee Score; VAS, Visual Analogue Scale; SDS, Self-Development's System; OA, osteoarthritis, OA-QI, Osteoarthritis Quality Indicator Questionnaire; ASES, short version of the Arthritis Self-Efficacy Scale; EQ-5D-3L, 3-level version of the European Quality of Life – 5 Dimensions.

At inclusion we used the Oxford Knee Score (OKS) to assess the self-reported function and knee pain ranging from 0 (worst) to 48 (best). The OKS is a questionnaire comprising 12 items with five response options for each item, and has proven sufficient reliability, validity, and responsiveness to be applied in patients with knee OA[106,107]. The degree of knee pain was evaluated using a Visual Analogue Scale (VAS) ranging from 0 (no pain) to 100 (worst imaginable pain) on a 100 mm scale[108]. VAS can be used as a valid and reliable method to measure pain in this study population[109,110]. Patients were also asked which previous treatment(s) they had undertaken for knee OA (Table 2). As physical activity is an important factor influencing the treatment outcomes, the self-reported physical activity level was evaluated as the average amount of time spent on physical activity per week as suggested by the International Consortium for Health Outcomes Measurement (ICHOM)[111]. Self-reported health status on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression was

reported using the 3-level version of the European Quality of Life – 5 Dimensions (EQ-5D-3L) expressed as an index score ranging from –0.624 (worst) to 1 (best)[112].

Some of the same variables that we collected at inclusion were also collected from the six-month follow-up questionnaire (Table 1). In addition, we asked the patients to provide information on the number of specific treatments/consultations since inclusion, the cost per treatment/consultation not covered by the public health care system, and short-term sick leave for patients on the labour market. The information from these questions will contribute to inform the cost-effectiveness study (Study protocol). Furthermore, we asked the patients about their perceived degree and importance of change in their knee problems from inclusion to follow-up using the anchor question: "*How are your knee problems now compared to for 6 months ago, when you first consulted the orthopaedic surgeon?*" Patients answered this question on a 7-level Likert scale ranging from "*Better, an important improvement*" to "*Worse, an important deterioration*"[113,114]. To be used as outcomes in the prediction study (Study protocol), we asked the patients whether they determined their treatment outcome since inclusion as good or poor. A good outcome was defined by a patient acceptable symptom state (PASS) anchor question and a poor outcome by a Treatment Failure (TF) anchor question[115–117]. Patients who responded "*yes*" to the PASS question "*Taking into account all the activities you have during your daily life, your level of pain, and also your functional impairment, do you consider that your current knee state is satisfactory?*", can be categorised as having a good outcome[115]. If the patients responded "*no*" to the PASS question they were asked the TF question "*Would you consider your current state as being so unsatisfactory that you think the treatment has failed?*". Patients who responded "*no*" to the PASS question and "*yes*" to the following TF question, can be categorised as having a poor outcome[115,117]. In addition to the data collected from the six-months follow-up questionnaire, we also collected information on the same variables at two-years follow-up. The two-year follow-up is the primary endpoint in the TREATright study and will be included in future analyses and as additional candidate predictors in the prediction study (Study protocol).

3.3.1.3 Radiographic assessments

In addition to the information collected through the questionnaires, we also assessed radiographs taken in relation to the consultation with the orthopaedic surgeon. We evaluated standing antero-posterior and skyline view radiographs to determine: 1) Kellgren-Lawrence (KL) classification of radiographic OA severity (ranging from 0 (none) to 4 (severe))[118]; 2) OA wear pattern, which was

determined as lateral, medial or bicompartmental; and 3) severe patellofemoral OA. As the radiographic assessments were shared between two investigators, we first evaluated the inter-rater reliabilities using a smaller sample of the radiographs to ensure the inter-rater reliabilities of the radiographic assessments were acceptable. The reliabilities of the assessments were evaluated between the two investigators and an orthopaedic surgeon with many years of radiographic review experience. The inter-rater reliability of the KL classification showed a moderate reliability[119] of 0.566 (95% CI [0.421, 0.695]) using a consistency intraclass correlation coefficient (ICC)[120]. Using Light's kappa[121] we evaluated the inter-rater reliability of the wear pattern to be substantial[122] (0.727) with a percentage agreement of 88%, and the inter-rater reliability of severe patellofemoral wear to be almost perfect[122] (0.846) with a percentage agreement of 93%.

3.3.1.4 Classification of treatments

In the questionnaires, both at inclusion, six-month and two-year follow-up, we asked the patients to indicate which treatments they had received for knee OA. At inclusion, they selected all treatments they had undertaken for knee OA during their entire disease course. At six-month follow-up, they selected which treatments they had undertaken since inclusion and at two-year follow-up they selected the treatments they had undertaken since the six-month follow-up. The patients could select from a list of 19 pre-specified treatments (Table 2). We grouped some of the treatments with common features into 13 treatment categories (Table 2): "1. Information and guidance on living with osteoarthritis" and "2a. Participation in GLA:D" were grouped into "1. Patient education". "2b. Participation in GLA:D", "3. Exercise and gymnastics (strength training, fitness, or other types of exercise) under the supervision of a physiotherapist or similar", "4. Water-based exercise in groups or under supervision", and "5. Exercise on your own (strength training, fitness or other types of exercise)" were grouped into "2. Exercise". "9. Insoles" and "10. Assessment of the need for walking aid (walking stick, crutches, etc.)" were grouped into "6. Walking aids and devices". "15. Acupuncture", "16. Massage", and "17. Ultrasound, laser or other type of electrotherapy" were grouped into "11. Passive treatment". We used a pragmatic approach to identify similarities between the clinical guidelines to group the treatments into four classifications (Table 2): *Guideline-adherent core treatment*: 1. Patient education, 2. Exercise, 3. Dietary weight management, if needed (BMI ≥ 25 or BMI ≥ 30). *Supplements to core treatment*: 4. Pharmacological treatment, 5. Intra-articular injection, 6. Walking aids and devices, 7. Stretching, 8. Joint mobilisation. *End-stage treatment*: 9.

Knee arthroplasty. *Uncertain or not recommended treatment*: 10. Arthroscopic surgery, 11. Passive treatment, 12. Alternative and complementary medicine, 13. No treatment.

We used data from DKR, which has 97% coverage[80,123], to identify the number of patients who had knee arthroplasty since inclusion. If the patients had a knee arthroplasty after being included, they were requested, in the follow-up questionnaires, to indicate any additional treatment they had undertaken prior to surgery, and not to list any postoperative treatment.

Table 2 (Paper I and II).
Pre-defined list of 19 treatments in the questionnaires, grouped into 13 treatment categories and the overall classification of treatments. Patients reported which treatment(s) they had received for knee OA at inclusion, at six-month, and two-year follow-up

Classification of treatments	Treatment categories	Pre-defined list of treatments in the questionnaires
Guideline-adherent core treatment	1. Patient education	1. Information and guidance on living with osteoarthritis
		2a. Participation in GLA:D*
	2. Exercise	2b. Participation in GLA:D*
		3. Exercise and gymnastics (strength training, fitness, or other types of exercise) under the supervision of a physiotherapist or similar
		4. Water-based exercise in groups or under supervision
		5. Exercise on your own (strength training, fitness or other types of exercise)
	3. Dietary weight management, if needed	6. Diet or dietary guidance
Supplements to core treatment	4. Pharmacological treatment	7. Pharmacological treatment (including painkillers)
	5. Intra-articular injection	8. Injection into the knee joint
	6. Walking aids and devices	9. Insoles
		10. Assessment of the need for walking aid (walking stick, crutches, etc.)
	7. Stretching	11. Stretching
	8. Joint mobilisation	12. Other manual therapy
End-stage treatment	9. Knee arthroplasty	13. Total or unicompartmental knee arthroplasty†
Uncertain or not recommended treatment	10. Arthroscopic surgery	14. Arthroscopic surgery
	11. Passive treatment	15. Acupuncture
		16. Massage
		17. Ultrasound, laser or other type of electrotherapy
	12. Alternative and complementary medicine	18. Alternative medicine (such as healing, Body SDS§, craniosacral therapy or similar)
	13. No treatment	19. No treatment

*GLA:D is an evidence-based program that includes education and supervised neuromuscular exercise delivered by certified physiotherapists[62].
†Information on whether the patients had knee arthroplasty was only collected at six-month follow-up.
§ Body SDS is a concept that includes a wide range of therapies (e.g., massage, yoga, talking therapy) delivered by registered alternative therapists.
GLA:D, Good Life with osteoArthritis in Denmark.
SDS, Self-Development's System.

3.3.2 Qualitative study (Study 2)

3.3.2.1 Data collection

A semi-structured interview guide with open-ended questions was developed. The semi-structured approach enabled the interviewer to ask further questions to the informant's responses[124,125]. To ensure all relevant topics were covered, informants were asked to elaborate on their perspectives on different treatments. Probing questions were asked if the answers to the open-ended questions were short of information. The interview guide was developed using data from Study 1, the clinical guidelines on recommended treatments[45,51–53], publications emphasising the underutilisation of these treatments[84–87,97], and potential barriers and facilitators to use the recommended treatments[91–96]. We further developed the interview guide through continuous discussions between members of the study team. The interviews were conducted at Copenhagen University Hospital Hvidovre or Næstved Hospital. To help the informants keep track of their own disease course during the interviews, they were provided with a timeline of a simplified disease course with knee OA (Figure 2). All interviews were audio recorded and transcribed verbatim.

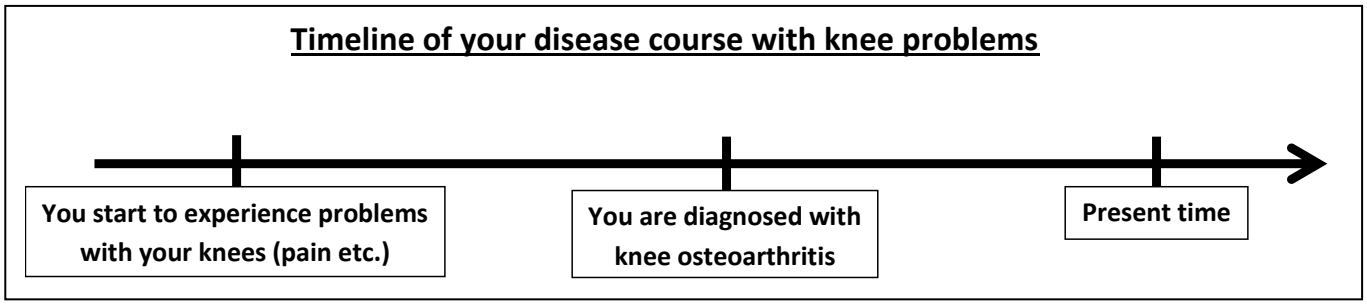

Figure 2 (adapted from Paper III). Timeline of a simplified disease course with knee OA to help informants to keep track of their own disease course during the interview.

3.4 Data analyses

3.4.1 Cohort study (Study 1)

3.4.1.1 Sample size

We used a pragmatic approach based on the number of patients referred with knee OA during a period of two years to estimate the sample size. Each year, a total of approximately 3,000 patients with knee OA are referred to Copenhagen University Hospital Hvidovre and Næstved Hospital. After the first year of inclusion, we reached an inclusion rate of 65% which would result in 3,900 included patients

after two years. With a similar follow-up rate of 65%, we estimated that complete data would be collected from approximately 2,535 patients.

3.4.1.2 Data analysis

The cohort study was a descriptive study exploring the proportion of patients undertaking the recommended combination of guideline-adherent core treatments. Analyses were conducted with both BMI $\geq$ 25 and $\geq$ 30 kg/m², as criteria for when dietary weight management was needed, to accommodate the clinical guidelines' varying definitions of the criterion[45,51–53]. To investigate how that criterion influenced the results, analyses were furthermore conducted without the criterion of dietary weight management. We performed a sensitivity analysis where water-based and unsupervised exercise were not classified as recommended core treatments. A data-driven approach was used to decide how best to describe the treatment pathways that patients had undertaken. Because of the SARS-CoV-2 pandemic, the healthcare facilities in Denmark were inaccessible due to lockdowns for several periods during this study. This prompted us to investigate whether the treatment pathways for patients responding to the six-month follow-up questionnaire before the lockdown differed from those for patients responding after. In the reporting of data, the normal distribution, as indicated by density and quantile-quantile plots, was used to decide whether continuous data should be presented as means or medians. Data management and analyses were conducted using the statistical software program R[126].

3.4.2 Qualitative study (Study 2)

A qualitative content analysis was conducted using systematic text condensation and thematization[127]. Malterud's approach to systematic text condensation involved four phases[127]:

1) Two researchers individually read the transcribed interviews to obtain an overall impression of the material and identify preliminary main themes.

2) The same two researchers individually sorted and coded meaningful units of information related to the preliminary themes.

3) The researchers reviewed and discussed the identified codes and themes to condense and abstract the meaning of the coded units within each theme. In addition, preliminary subthemes

underpinning the main themes were created. The preliminary main themes and subthemes were then reviewed and discussed with a third researcher and were revised several times until consensus was reached.

4) The coded units of meaning within each main theme and subtheme were continuously discussed between the researchers and went through several revisions. The final syntheses within each theme were summarised to reflect the informants' perspectives on the management of knee OA. The most relevant quotations that best described the themes were chosen.

3.4.3 Prediction study (Study protocol)

3.4.3.1 Sample size

There are no clear guidelines on the sample size to develop prognostic prediction models[128]. However, it has been suggested that binary prediction models should have at least 10 outcome events per variable (EPV)[129,130]. Others have suggested at least 20 EPV but that the number of required EPV should be data-driven and take the prevalence of predictors in the study into account[131]. We expected approximately 25% of the patients to respond "*no*" to the PASS question as previously reported in patients undergoing knee replacement surgery[116]. Using an event rate of 25%, at least 20 EPV, and approximately 30 candidate predictors, we will need to include 2,400 patients.

3.4.3.2 Data analysis plan

We intend to use machine learning software packages for the statistical software program R to develop prognostic models[126]. With two primary outcomes, prognostic models for PASS and TF will be developed separately. For the PASS model, the dichotomised dependent variable will be the patients' self-reported assessment of a good treatment outcome, based on whether they responded "*yes*" or "*no*" to the PASS question. The TF model's dichotomised dependent variable will be the patients' self-reported assessment of a poor treatment outcome. If the patient answered "*yes*" to the TF question it will be classified as "TF", and if answering either "*yes*" to the previous PASS question or "*no*" to the following TF question it will classified as "not TF". As independent candidate predictors, we will use data obtained from the questionnaires at inclusion, six-month follow-up, and two-year follow-up (Table 1 [collected variables at the two-year follow-up are not presented in Table

1 but are the same variables as for the six-month follow-up]) together with the radiographic assessments. Several of these variables have been suggested to be relevant predictors associated with the outcome of Total Knee Arthroplasty (TKA)[132,133]. Which variables to include in the predictive models will depend on the predictive performance of the models when in- and excluding these candidate predictors. It is crucial to validate the predictive performance of the final models by developing the model using a development data set and subsequently test the model on a validation data set to assess the predictive performance[128,134–137]. To develop and validate the prediction models, approximately 70% of the data set will be used for development and 30% for internal validation to estimate the predictive performance of the models[128,138]. We will use a data-driven approach to which statistical model to use for model development. The statistical model resulting in the highest predictive performance (i.e., closest to 1.0) will be used. As a general rule, the accuracy of the prediction model can be classified from low (0.50-0.69) to moderate (0.70-0.89) to high (0.90-1.00)[139,140], and an accuracy of 0.70 has been suggested for a machine learning model to be clinically relevant[141].

3.4.4 Cost-effectiveness study (Study protocol)

To compare the cost-effectiveness of treatment pathways adhering to clinical guidelines to pathways that do not, a health economy analysis will be conducted. We will use the EQ-5D-3L to create summary index values based on the Danish value-set, which will be the basis for the outcome[112]. The change in the EQ-5D-3L summary index value between the inclusion and the primary endpoint, i.e., two-year follow-up, will be used to determine quality-adjusted life-years (QALYs). In addition to the patients' self-reported information on self-paid health care costs from the six-month and two-year follow-up questionnaires, we will also collect data from Statistics Denmark. Hospitalisation, visits to health care providers, medication, surgery, and home care services supplied by the municipalities will all be included in the cost of health care during the follow-up period. Information about short-term sick leave, defined as sick leave lasting less than 21 consecutive days, were obtained from the follow-up questionnaires to estimate productivity costs due to short-term sick leave. The Danish Register for Evaluation of Marginalisation (DREAM), which contains weekly data on social transfer payments, will be used to estimate the productivity costs from long-term sick leave[142].

We will calculate an incremental cost-effectiveness ratio (ICER) by dividing the incremental cost by the effectiveness (QALYs)[143]:

$$ICER = \frac{C_a - C_b}{E_a - E_b}$$

where C_a is the cost of non-guideline-adherent treatment pathways, C_b is the cost of guideline-adherent treatment pathways, E_a is the QALYs with non-guideline-adherent treatment pathways, and E_b is the QALYs with guideline-adherent treatment pathways. As there is no recognised willingness-to-pay threshold in Denmark, we will evaluate the ICER against the threshold used by NICE (£20,000–£30,000)[144]. The ICER can be graphically expressed in a cost-effectiveness plane where the cost and effectiveness of non-guideline-adherent treatment pathways and guideline-adherent treatment pathways, respectively, can be plotted (Figure 3)[143].

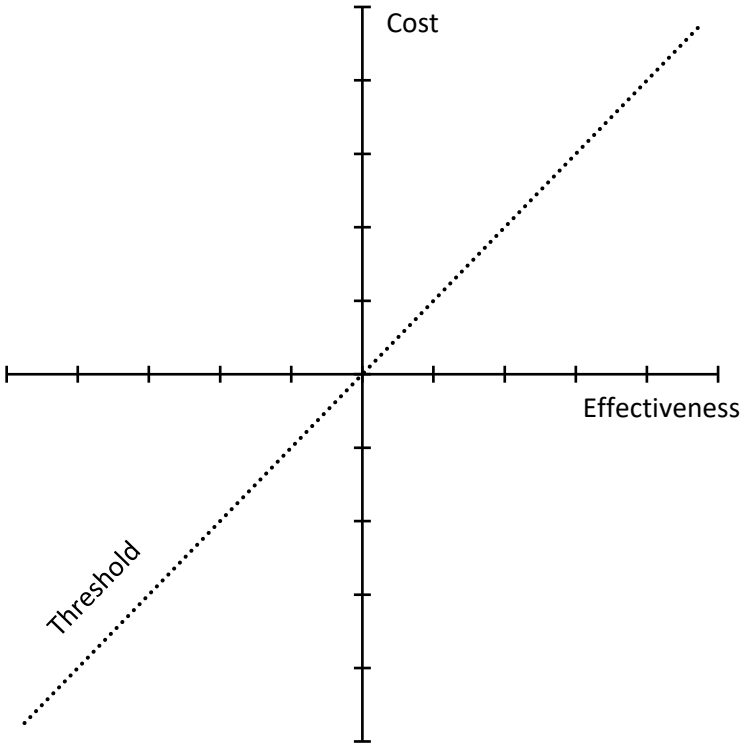

Figure 3. Cost-effectiveness plane where the cost and effectiveness of treatments can be plotted to graphically express the incremental cost-effectiveness ratio (ICER). The slope of the threshold line expresses the willingness-to-pay per unit of QALY.

3.5 Patient involvement

Patients were involved in the planning of the project and ongoing development of the studies to increase the relevancy and importance from the patients' point of view[145,146]. In the initial phase of the project, we discussed the research questions and study objectives with two patients with knee OA. In addition, 11 patients tested the questionnaire before we initiated patient inclusion. Six patients with knee OA were selected to be patient representatives. They were invited to three meetings to discuss the content of the questionnaires and contribute with their opinion on how the project developed. Furthermore, the patient representatives were invited to a meeting to contribute to the development of the interview guide from a patient's point of view.

4 Results

4.1 Cohort study (Study 1)

4.1.1 Patient inclusion

The flow of patients included in the cohort is presented in Figure 4. We invited 6,941 patients to participate based on their primary referral to an orthopaedic surgeon due to knee OA, and 5,251 were deemed eligible. 3,566 (68%) patients responded to the inclusion questionnaire. Out of these patients, 59 had either responded to the questionnaire too soon due to postponed consultation, responded to the questionnaire after the consultation, or had not answered the question about previous treatment for knee OA, and 3,507 (66%) were initially included in the cohort. At six-month follow-up, 2,574 (49%) patients were included in the analyses as they had responded to the questionnaire within the two-month response window and had complete data in terms of answering the question about previous treatment (Figure 4).

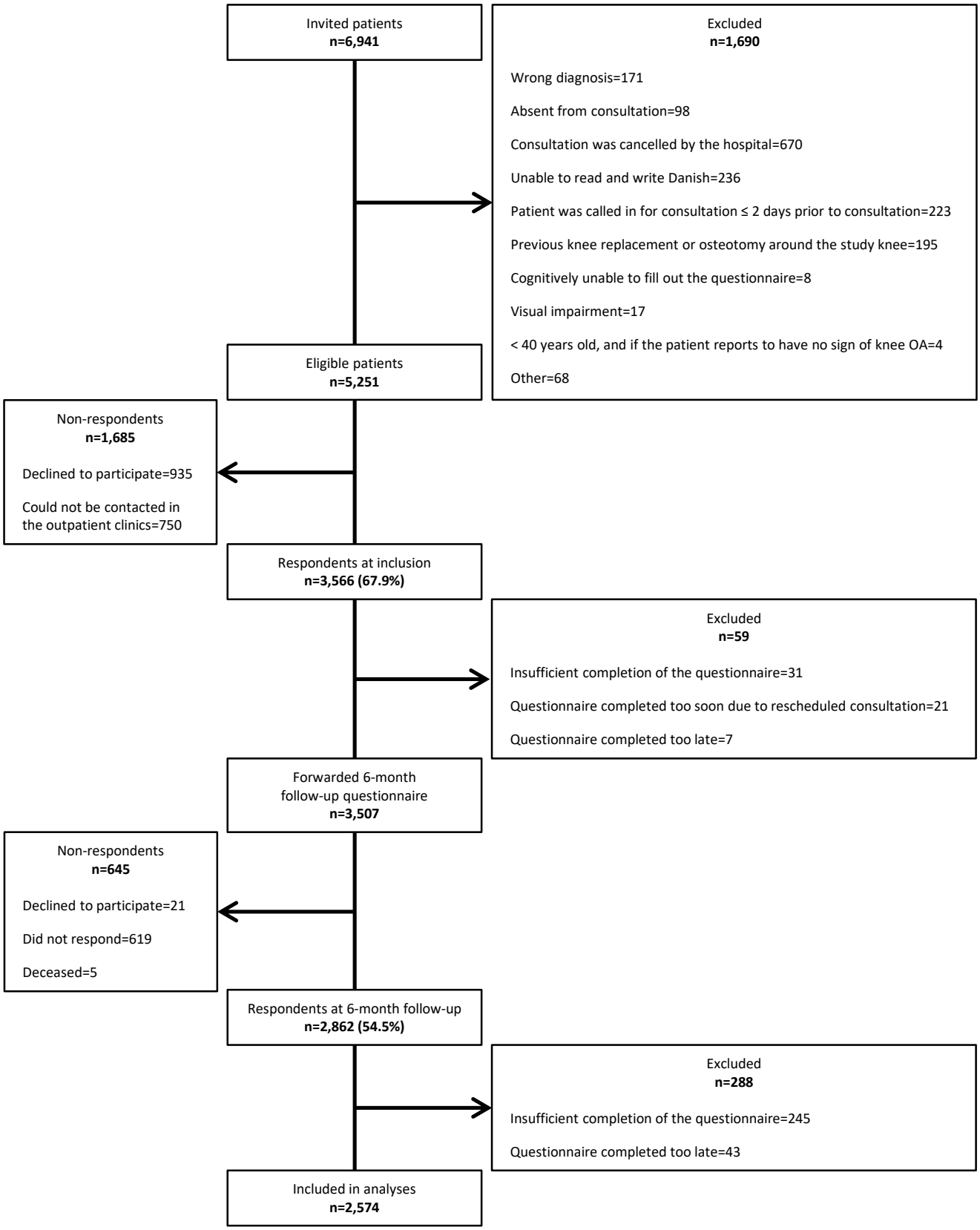

Figure 4 (Paper II). Flowchart of in- and excluded patients and respondents in the TREATright cohort. Non-respondents were patients who declined to participate, were deceased in the follow-up time, or patients who had not responded the inclusion questionnaire and whom the investigators were unable to find in the outpatient clinics. Numbers in parentheses are the response rates for respondents at inclusion and at six-month follow-up, respectively.

4.1.2 Characteristics of included and not included patients

Characteristics of patients with complete data, patients who completed the inclusion questionnaire but not the follow-up questionnaire, and all eligible patients who were not included in the final analyses are presented in Table 3. Patients with complete data had a mean (SD) age of 66.1 (10.1) years, a mean (SD) BMI of 29.5 (5.7) kg/m², and 58% were female. Compared to all eligible patients who were not included, there were no substantial age or gender differences. Patients completing the inclusion questionnaire but not the follow-up questionnaire had similar overall characteristics but were slightly younger with a mean (SD) age of 62.8 (11.4) and fewer were retired (Table 3).

Table 3 (Paper II).
Patient characteristics for included patients, patients who completed the questionnaire at inclusion but did not complete the questionnaire at six-month follow-up, and all eligible patients not included in the final analyses. Values are in percentages (%) with absolute numbers in parentheses unless other is stated

	Patients with complete data included in analyses (n = 2,574)	**Patients not completing the questionnaire at six-month follow-up (n = 933)**	**Eligible patients not included in the final analyses (n =2,677)**
Sex			
Female	58% (1,484)	59% (547)	57% (1,523)
Age, mean (SD)	66.1 (10.1)	62.8 (11.4)	64.4 (12.2)
BMI, mean (SD)	29.5 (5.7)	30.7 (6.2)	
Residential status			
Alone	28% (729)	28% (265)	
Cohabiting	69% (1,766)	63% (588)	
Missing	3% (79)	9% (80)	
Level of education			
Elementary school	16% (407)	16% (153)	
High school	2% (49)	2% (21)	
Vocational education	31% (794)	29% (270)	
Short-cycle higher education	13% (345)	12% (115)	
Medium-cycle higher education	28% (722)	25% (231)	
Long-cycle higher education or more	7% (172)	7% (63)	
Missing	3% (85)	9% (80)	
Occupation			
Retired, early retiree or on early retirement	59% (1,518)	44% (412)	
Sick leave part time or full time	6% (146)	8% (72)	
Unemployed	3% (67)	4% (39)	
On the labour market or student part time or full time	31% (808)	37% (342)	
Missing	3% (82)	9% (81)	
Smoking			
No, never	44% (1,132)	39% (368)	
No, but I used to	42% (1,086)	37% (349)	

Yes	11% (275)	15% (138)
Missing	3% (81)	8% (78)
Comorbidities		
Proportion of patients with comorbidities	76% (1,949)	71% (665)
Self-reported physical activity per week		
None	5% (116)	6% (57)
30 min	10% (265)	11% (102)
1 hour	10% (262)	12% (108)
2 hours	16% (399)	13% (123)
More than 2 hours	57% (1,460)	51% (472)
Missing	3% (72)	8% (71)
VAS knee pain, mean (SD)	63.6 (22.3)	62.9 (23.0)
Duration of knee problems		
0–6 months	15% (397)	17% (157)
7-12 months	13% (338)	13% (123)
1–2 years	17% (434)	16% (150)
3-5 years	20% (503)	18% (169)
6-10 years	14% (355)	11% (103)
> 10 years	20% (517)	22% (201)
Missing	1% (30)	3% (30)
EQ-5D-3L, median (IQR)	0.723 (0.496-0.771)	0.660 (0.356-0.723)
OKS, mean (SD)	23.4 (8.0)	23.1 (8.5)
Radiographical knee OA severity (KL grade)	*	
0	0 (0)	
1	0 (3)	
2	8 (260)	
3	48 (1,527)	
4	41 (1,293)	
Missing	2 (67)	
Severe patellofemoral OA	†	
Yes	2 (50)	
No	10 (315)	
Not assessable	0 (15)	
Tibiofemoral OA wear pattern	*	
Medial	86 (2,700)	
Lateral	11 (343)	
Bicompartmental	1 (40)	
Missing	2 (67)	

BMI, body mass index (kg/m^2); SD, standard deviation; VAS, Visual Analogue Scale (millimetres, 0-100); EQ-5D-3L, 3-level version of the European Quality of Life – 5 Dimensions; OKS, Oxford Knee Score; OA, osteoarthritis; IQR, interquartile range; KL grade, Kellgren and Lawrence classification system.

* Of the 2,574 included patients, 576 had bilateral problems making the total number of examined knees 3,150.

† Of the 3,150 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 380 knees.

4.1.3 Proportion of patients undertaking each specific treatment

From the 19 pre-specified treatments (13 treatment categories) in the questionnaire, the treatments that most patients reported to have undertaken in their entire disease course until six months after consulting an orthopaedic surgeon were: any type of exercise (74% (1,911 patients)), pharmacological treatments (52% (1,329 patients)), and patient education (37% (948 patients)) (Table 4). If we differentiate between the type of exercise, we found that 62% (1,601 patients) reported to have undertaken supervised land-based exercise. 10% (245 patients) reported that they had not received any treatment until six months after the consultation.

Table 4 (Paper II).
Percentage and number of patients reporting to have received each separate treatment before consulting an orthopaedic surgeon, between consultation and six-month follow-up and until six months after the consultation for patients not undergoing knee arthroplasty and until surgery for patients undergoing knee arthroplasty

		Patients reporting to have received each separate treatment (n = 2,574)		
Classification of treatments	**Treatment categories**	**Before consulting an orthopaedic surgeon, % (n)**	**Between consultation and six-month follow-up, % (n)**	**In the entire disease course until six months after consultation, % (n)**
Guideline-adherent core treatment	1. Patient education	23 (580)	23 (604)	37 (948)
	2. Exercise	54 (1,380)	53 (1,361)	74 (1,911)
	3a. Dietary weight management, if needed (BMI ≥ 25)	5 (97)*	3 (57)*	7 (145)*
	3b. Dietary weight management, if needed (BMI ≥ 30)	7 (72)†	4 (48)†	10 (111)†
Supplements to core treatment	4. Pharmacological treatment	44 (1,144)	23 (581)	52 (1,329)
	5. Intra-articular injections	13 (331)	7 (188)	16 (451)
	6. Walking aids and devices	11 (284)	7 (184)	15 (397)
	7. Stretching	6 (146)	4 (100)	9 (230)
	8. Joint mobilisation	2 (61)	2 (40)	4 (94)
End-stage treatment	9. Knee arthroplasty	0 (0)	31 (797)	31 (797)
Uncertain or not recommended treatment	10. Arthroscopic surgery	17 (427)	5 (119)	20 (508)
	11. Passive treatment	18 (456)	10 (244)	22 (574)
	12. Alternative and complementary medicine	4 (89)	2 (48)	5 (116)
	13. No treatment	21 (548)	33 (856)	10 (245)

BMI, body mass index (kg/m²)
*Out of 2,110 patients with BMI ≥ 25
†Out of 1,084 patients with BMI ≥ 30

4.1.4 Proportion of patients undertaking core treatments

The use and combinations of recommended core treatments (exercise, patient education, and dietary weight management) are shown in Figure 5. 37% (951) of the patients had undertaken exercise as the only core treatment, and patient education and dietary weight management was mainly used in

combination with exercise (Figure 5). Before consulting an orthopaedic surgeon, 6% (146) of the patients had undertaken the recommended combination of core treatments (using BMI ≥ 25 as criterion for when dietary weight management was needed). The proportion had increased to 9% (242 patients) at follow-up. When we used BMI ≥ 30 as criterion for when dietary weight management was needed, 14% (362) of the patients had received the recommended combination of core treatments before consultation, which increased to 23% (580 patients) at follow-up. Without the criterion of dietary weight management, the proportion of patients who had undertaken the recommended combination of core treatments was 21% (537 patients) before the consultation and 35% (899 patients) at follow-up. If we, in addition, limited the exercise criterion to supervised land-based exercise, the proportion was 20% (507 patients) before consultation and 33% (861 patients) at follow-up.

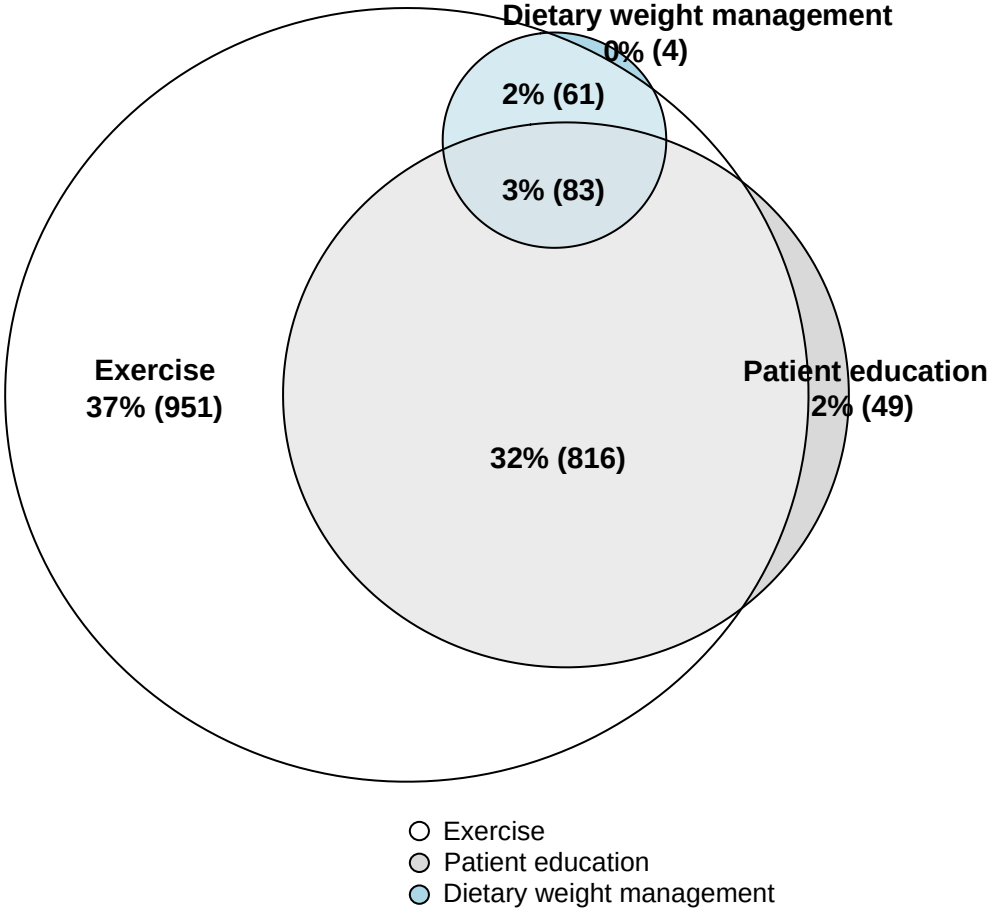

Figure 5 (Paper II). Patients undertaking the recommended core treatments and combinations until six months after consulting an orthopaedic surgeon. Combinations of core treatments are presented as overlapping circles. Percentages are the proportions out of all 2,574 included patients. The number of patients reporting to have received dietary weight management is presented for all patients, disregarding their BMI. However, dietary weight management was only relevant for 2,110 patients with BMI ≥ 25 and for 1,084 patients with BMI ≥ 30 (Table 4).

Patient characteristics were overall similar for patients who received the recommended combination of core treatments and patients who did not (Table 5). However, it seemed that those who had undertaken the recommended core treatments tended to be more often females, retired, had comorbidities, a longer duration of knee problems, and a higher level of education (Table 5).

Table 5 (Paper II).
Patient characteristics for all included patients, patients receiving the recommended combination of guideline-adherent core treatments, and patients who did not. Values are in percentages (%) with absolute numbers in parentheses unless other is stated

	Included patients (n = 2,574)	**Patients receiving the recommended combination of guideline-adherent core treatments (n = 899)**	**Patients not receiving the recommended combination of guideline-adherent core treatments (n = 1,675)**
Sex			
Female	58% (1,484)	65% (581)	54% (903)
Age, mean (SD)	66.1 (10.1)	67.4 (9.2)	65.4 (10.5)
BMI, mean (SD)	29.5 (5.7)	29.5 (5.7)	29.5 (5.7)
Residential status			
Alone	28% (729)	30% (273)	27% (456)
Cohabiting	69% (1,766)	68% (607)	69% (1.159)
Missing	3% (79)	2% (19)	4% (60)
Level of education			
Elementary school	16% (407)	13% (120)	17% (287)
High school	2% (49)	3% (23)	2% (26)
Vocational education	31% (794)	27% (244)	33% (550)
Short-cycle higher education	13% (345)	14% (124)	13% (221)
Medium-cycle higher education	28% (722)	33% (293)	26% (429)
Long-cycle higher education or more	7% (172)	8% (76)	6% (96)
Missing	3% (85)	2% (19)	4% (66)
Occupation			
Retired, early retiree or on early retirement	59% (1,518)	65% (587)	56% (931)
Sick leave part time or full time	6% (146)	5% (45)	6% (101)
Unemployed	3% (67)	3% (25)	3% (42)
On the labour market or student part time or full time	31% (808)	27% (245)	34% (563)
Missing	3% (82)	2% (18)	4% (64)
Smoking			
No, never	44% (1,132)	46% (417)	43% (715)
No, but I used to	42% (1,086)	44% (392)	41% (694)
Yes	11% (275)	8% (71)	12% (204)
Missing	3% (81)	2% (19)	4% (62)
Comorbidities			
Proportion of patients with comorbidities	76% (1,949)	80% (716)	74% (1,233)
Self-reported physical activity per week			
None	5% (116)	4% (35)	5% (81)
30 min	10% (265)	10% (86)	11% (179)
1 hour	10% (262)	9% (85)	11% (177)
2 hours	16% (399)	16% (145)	15% (254)
More than 2 hours	57% (1,460)	59% (533)	55% (927)

Missing	3% (72)	2% (15)	2% (57)
VAS knee pain, mean (SD)	63.7 (22.3)	65.1 (20.3)	62.9 (23.3)
Duration of knee problems			
0–6 months	15% (397)	10% (92)	18% (305)
7-12 months	13% (338)	12% (112)	13% (226)
1–2 years	17% (434)	16% (140)	18% (294)
3-5 years	20% (503)	22% (194)	18% (309)
6-10 years	14% (355)	15% (139)	13% (216)
> 10 years	20% (517)	24% (215)	18% (302)
Missing	1% (30)	1% (7)	1% (23)
EQ-5D-3L, median (IQR)	0.723 (0.496-0.771)	0.708 (0.559-0.723)	0.723 (0.496-0.771)
OKS, mean (SD)	23.4 (8.0)	22.7 (7.5)	23.8 (8.3)
Radiographical knee OA severity (KL grade)	*	§	¶
0	0 (0)	0 (0)	0 (0)
1	0 (3)	0 (2)	0 (1)
2	8 (260)	7 (75)	9 (185)
3	48 (1,527)	47 (540)	49 (987)
4	41 (1,293)	44 (506)	39 (787)
Missing	2 (67)	2 (28)	2 (45)
Severe patellofemoral OA	**†**	‡	#
Yes	13 (50)	2 (23)	1 (27)
No	83 (315)	12 (134)	9 (181)
Not assessable	4 (15)	1 (8)	0 (7)
Tibiofemoral OA wear pattern	*	§	¶
Medial	86 (2,700)	85 (984)	86 (1,716)
Lateral	11 (343)	11 (131)	11 (212)
Bicompartmental	1 (40)	1 (8)	2 (32)
Missing	2 (67)	2 (28)	2 (45)

BMI, body mass index (kg/m²); SD, standard deviation; VAS, Visual Analogue Scale (millimetres, 0-100); EQ-5D-3L, 3-level version of the European Quality of Life – 5 Dimensions; OKS, Oxford Knee Score; OA, osteoarthritis; IQR, interquartile range; KL grade, Kellgren and Lawrence classification system.

* Of the 2,574 included patients, 576 had bilateral problems making the total number of examined knees 3,150.

† Of the 3,150 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 380 knees.

§ Of the 899 patients receiving the recommended combination of guideline-adherent core treatments, 246 had bilateral problems making the total number of examined knees 1,145.

‡ Of the 1,145 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 165 knees.

¶ Of the 1,675 patients not receiving the recommended combination of guideline-adherent core treatments, 330 had bilateral problems making the total number of examined knees 2,005.

Of the 2,005 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 215 knees.

4.1.6 Proportion of surgically treated patients undertaking core treatments

Using data from the DKR, we identified that 31% (797) of the patients had undergone knee arthroplasty from inclusion until they responded to the six-month follow-up questionnaire. With BMI ≥ 25 as the criterion for when dietary weight management was needed, 9% (75) of the patients who had knee arthroplasty had undertaken the recommended combination of core treatments prior to surgery. Using BMI ≥ 30 as the criterion, the proportion was 24% (190 patients), and 37% (297) if we excluded the criterion about dietary weight management. 7% (59) of the patients reported that they had not received any treatment before surgery (Table 6).

Table 6.
Percentage and number of patients reporting to have received each separate treatment until surgery for patients undergoing knee arthroplasty and until six months after the consultation for patients not undergoing knee arthroplasty

		Patients reporting to have received each separate treatment (n = 2,574)	
Classification of treatments	**Treatment categories**	**Patients undergoing knee arthroplasty (n = 797), % (n)**	**Patients not undergoing knee arthroplasty (n = 1,777), % (n)**
Guideline-adherent core treatment	1. Patient education	40 (316)	36 (632)
	2. Exercise	77 (611)	73 (1,300)
	3a. Dietary weight management, if needed (BMI ≥ 25)	7 (47)*	7 (98)§
	3b. Dietary weight management, if needed (BMI ≥ 30)	10 (34)†	10 (77)‡
Supplements to core treatment	4. Pharmacological treatment	61 (484)	48 (845)
	5. Intra-articular injections	17 (132)	18 (319)
	6. Walking aids and devices	18 (144)	14 (253)
	7. Stretching	10 (78)	9 (152)
	8. Joint mobilisation	3 (24)	4 (70)
End-stage treatment	9. Knee arthroplasty	100 (797)	0 (0)
Uncertain or not recommended treatment	10. Arthroscopic surgery	21 (170)	19 (338)
	11. Passive treatment	20 (162)	23 (412)
	12. Alternative and complementary medicine	4 (30)	5 (86)
	13. No treatment	7 (59)	10 (186)

BMI, body mass index (kg/m²)
*Out of 673 patients with BMI ≥ 25
§Out of 1,437 patients with BMI ≥ 25
†Out of 349 patients with BMI ≥ 30
‡Out of 735 patients with BMI ≥ 30

Patient characteristics for those undertaking the recommended treatments and those who did not were also, overall, similar for this subgroup of patients who had knee arthroplasty (Table 7). However, patients undertaking the recommended combination of core treatments before surgery tended to be more often females (63% vs. 53%). It seemed that patients who had not received any treatment prior to surgery were less often retired, had fairly better OKS, shorter duration of knee problems, and lower education levels.

Table 7 (Paper II).
Patient characteristics for patients undergoing knee arthroplasty who received the recommended combination of guideline-adherent core treatments, patients who did not, and patients who did not receive any treatment. Values are in percentages (%) with absolute numbers in parentheses unless other is stated

	Patients undergoing knee arthroplasty receiving the recommended combination of guideline-adherent core treatments (n = 297)	**Patients undergoing knee arthroplasty not receiving the recommended combination of guideline-adherent core treatments (n = 500)**	**Patients undergoing knee arthroplasty not receiving any treatment (n = 59)**
Sex			
Female	63% (186)	53% (265)	36% (21)
Age, mean (SD)	68.8 (8.4)	68.4 (8.8)	69.1 (8.9)
BMI, mean (SD)	29.5 (5.6)	29.9 (5.7)	30.5 (5.6)
Residential status			
Alone	26% (78)	24% (119)	27% (16)
Cohabiting	72% (213)	74% (369)	71% (42)
Missing	2% (6)	2% (12)	2% (1)
Level of education			
Elementary school	9% (27)	16% (78)	19% (11)
High school	3% (9)	2% (9)	0% (0)
Vocational education	34% (101)	36% (179)	53% (31)
Short-cycle higher education	11% (32)	12% (60)	10% (6)
Medium-cycle higher education	34% (100)	26% (129)	14% (8)
Long-cycle higher education or more	7% (22)	6% (30)	3% (2)
Missing	2% (6)	3% (15)	2% (1)
Occupation			
Retired, early retiree or on early retirement	68% (202)	64% (320)	61% (36)
Sick leave part time or full time	6% 18)	6% (29)	5% (3)
Unemployed	2% (7)	2% (9)	2% (1)
On the labour market or student part time or full time	24% (71)	28% (141)	31% (18)
Missing	2% (6)	3% (13)	3% (2)
Smoking			
No, never	46% (143)	45% (227)	39% (23)
No, but I used to	44% (131)	43% (217)	46% (27)
Yes	6% (17)	9% (43)	12% (7)
Missing	2% (6)	3% (13)	3% (2)
Comorbidities			

Proportion of patients with comorbidities	82% (243)	76% (379)	80% (47)
Self-reported physical activity per week			
None	4% (11)	5% (26)	3% (2)
30 min	9% (27)	11% (54)	17% (10)
1 hour	11% (33)	9% (46)	3% (2)
2 hours	19% (56)	16% (78)	22% (13)
More than 2 hours	56% (166)	57% (283)	51% (30)
Missing	1% (4)	3% (13)	3% (2)
VAS knee pain, mean (SD)	70.9 (16.6)	69.9 (18.6)	69.1 (19.9)
Duration of knee problems			
0–6 months	2% (6)	8% (38)	15% (9)
7-12 months	9% (26)	12% (59)	10% (6)
1–2 years	14% (43)	16% (79)	20% (12)
3-5 years	25% (74)	22% (108)	15% (9)
6-10 years	18% (54)	19% (93)	19% (11)
> 10 years	31% (91)	24% (119)	20% (12)
Missing	1% (3)	1% (4)	0% (0)
EQ-5D-3L, median (IQR)	0.658 (0.389-0.723)	0.660 (0.398-0.723)	0.723 (0.618-0.771)
OKS, mean (SD)	20.8 (6.7)	21.3 (6.7)	23.5 (7.0)
Radiographical knee OA severity (KL grade)	*	§	¶
0	0 (0)	0 (0)	0 (0)
1	0 (0)	0 (0)	0 (0)
2	1 (5)	2 (14)	0 (0)
3	31 (121)	31 (194)	20 (14)
4	66 (256)	65 (406)	77 (54)
Missing	2 (7)	1 (7)	3 (2)
Severe patellofemoral OA	†	‡	#
Yes	3 (11)	1 (9)	1 (1)
No	10 (38)	11 (66)	13 (9)
Not assessable	1 (3)	0 (3)	1 (1)
Tibiofemoral OA wear pattern	*	§	¶
Medial	85 (332)	86 (532)	86 (60)
Lateral	13 (50)	12 (72)	9 (6)
Bicompartmental	0 (0)	2 (10)	3 (2)
Missing	2 (7)	1 (7)	3 (2)

BMI, body mass index (kg/m²); SD, standard deviation; VAS, Visual Analogue Scale (millimetres, 0-100); EQ-5D-3L, 3-level version of the European Quality of Life – 5 Dimensions; OKS, Oxford Knee Score; OA, osteoarthritis; IQR, interquartile range; KL grade, Kellgren and Lawrence classification system.

* Of the 297 patients undergoing knee arthroplasty receiving the recommended combination of guideline-adherent core treatments, 92 had bilateral problems making the total number of examined knees 389.

† Of the 389 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 52 knees.

§ Of the 500 patients undergoing knee arthroplasty not receiving the recommended combination of guideline-adherent core treatments, 121 had bilateral problems making the total number of examined knees 621.

‡ Of the 621 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 78 knees.

¶ Of the 59 patients undergoing knee arthroplasty not receiving any treatment, 11 had bilateral problems making the total number of examined knees 70.

Of the 70 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 11 knees.

4.1.5 Impact of the SARS-CoV-2 pandemic on the treatment pathways

We identified 1,140 patients who responded to the six-month follow-up questionnaire before the first national lockdown due to the SARS-CoV-2 pandemic and 1,434 patients responded after. The proportion of patients receiving the recommended combination of core treatments were similar for patients responding to the follow-up questionnaire before and after the lockdown (Table 8). The only substantial difference in which treatments they had undertaken was that 37% (419) of the patients had knee arthroplasty before the lockdown compared to 26% (378) of the patients after.

Table 8 (adapted from Paper II).
Percentage and number of patients (with BMI ≥ 25 and BMI ≥ 30, respectively, as the criteria for when dietary weight management is needed, and when excluding the criterion about dietary weight management) receiving the recommended combination of guideline-adherent core treatments for patients completing the six-month follow-up questionnaire before and after lockdown of the healthcare facilities due to the SARS-CoV-2 pandemic

	Patients completing the six-month follow-up questionnaire before national lockdown (n = 1,140), % (n)	**Patients completing the six-month follow-up questionnaire after national lockdown (n = 1,434), % (n)**
Criterion for when dietary weight management is needed		
BMI ≥ 25	10 (119)	9 (123)
BMI ≥ 30	22 (246)	23 (334)
When excluding the criterion about dietary weight management	35 (398)	35 (501)

BMI, body mass index (kg/m²)

4.1.6 Use of different treatment pathways

Based on the treatments that patients reported to have undertaken before consulting an orthopaedic surgeon and between the consultation and the six-month follow-up, 1,143 unique treatment pathways emerged. The majority (871) of pathways were only pursued by one patient (Figure 6).

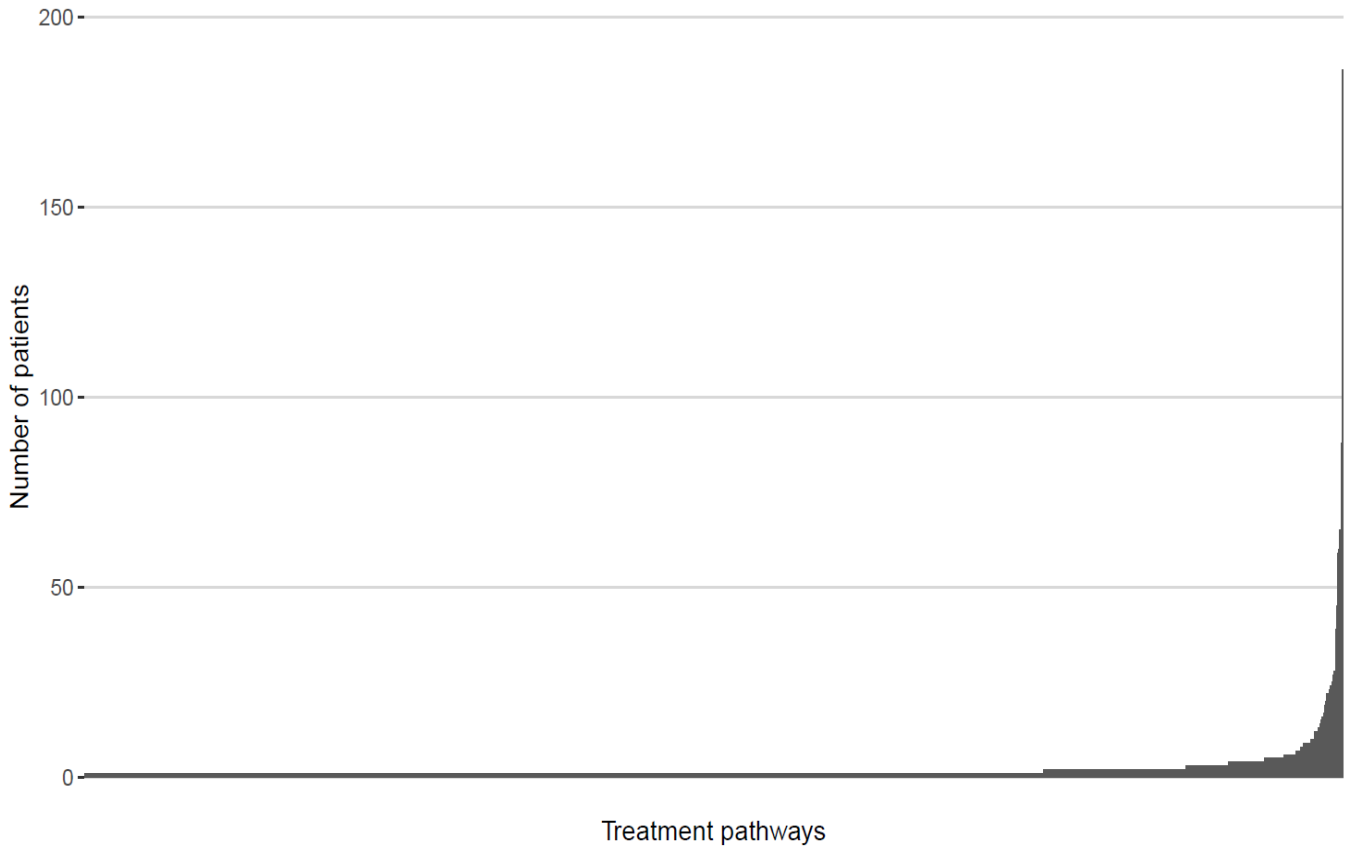

Figure 6. Bar plot comprising 1,143 treatment pathways (bars) and the number of patients undertaking each treatment pathway.

The five most pursued treatment pathways were as follow:

1) 7% (186) of the patients: No treatment before consultation followed by no treatment after.
2) 3% (88) of the patients: No treatment before consultation followed by exercise after.
3) 3% (65) of the patients: Pharmacological treatment before consultation followed by no treatment after.
4) 2% (60) of the patients: Exercise before consultation followed by no treatment after.
5) 2% (59) of the patients: No treatment before consultation followed by no other treatment but knee arthroplasty after.

Exercise was included in 87% (998) of the treatment pathways, and uncertain or not recommended treatments were used in 62% (707) of the pathways. Only 7% (78) of the treatment pathways contained the recommended combination of core treatments, while 10% (111) did not contain any core treatment (Figure 7).

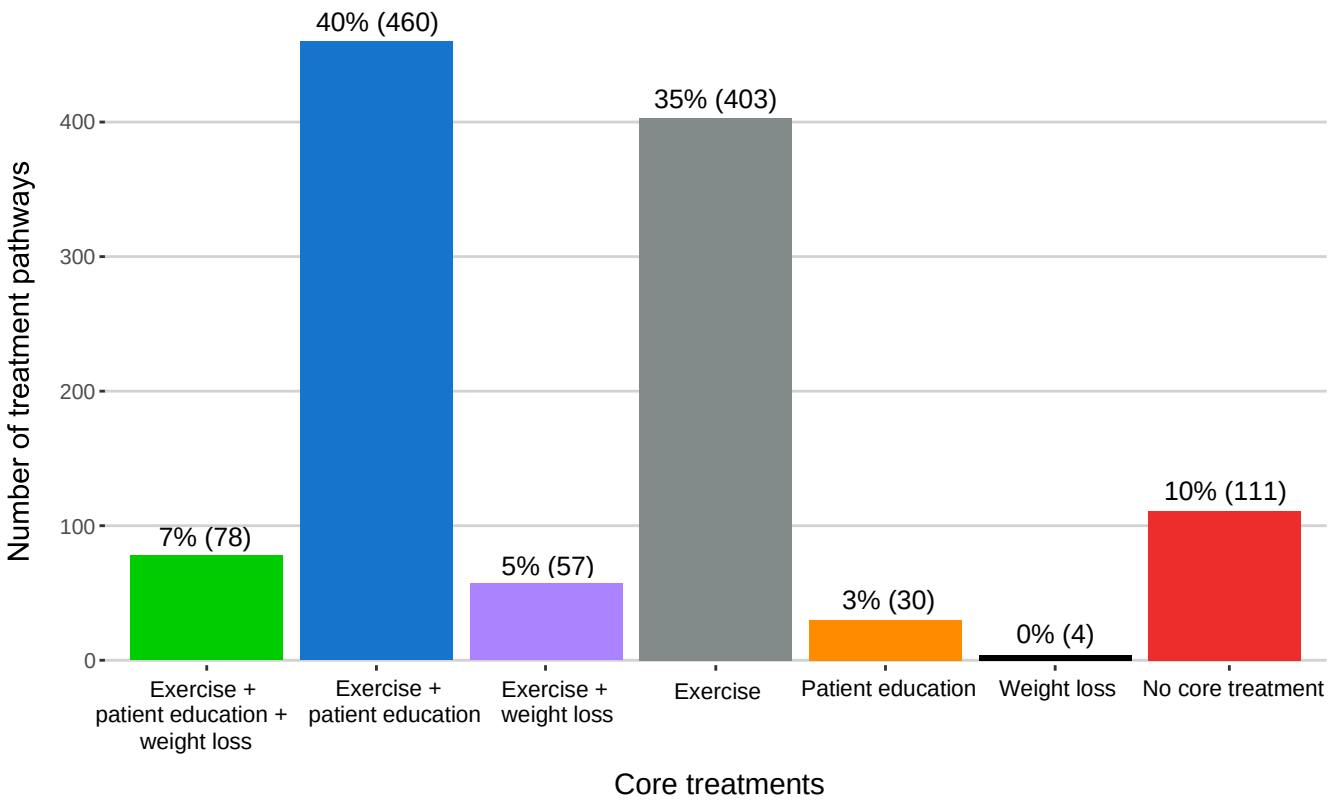

Figure 7 (Paper II). The proportion and number of treatment pathways that includes one core treatment or combination of core treatments.

4.2 Qualitative study (Study 2)

4.2.1 Patient inclusion and characteristics

To recruit informants for the interviews, we generated eight random samples with a total of 40 patients from the TREATright cohort. 13 patients were contacted of whom eight informants were included (Table 9). We included two females and two males from each of the two study sites with ages ranging from 45 to 76 years. Altogether, the informants had undertaken a wide range of treatments for knee OA, and some had undergone knee arthroplasty.

Table 9 (Paper III).
Patient demographics and all the treatments/health care providers that informants reported having pursued.

Informant	Study site	Sex	Age	Knee arthroplasty	Treatments/health care providers
#1	Hospital 1	Male	76	Yes	Acupuncture Glucosamine Pain medication Physiotherapist Osteopathy Chiropractic Crutches Support bandages Zone therapy Rooster comb injection/hyaluronic acid Adrenocorticotropic hormone injections Arthroscopic surgery Knee arthroplasty Re-operation after knee arthroplasty Heat treatment Gait training Rest Laser therapy Unsupervised exercise at home GLA:D* Supervised and unsupervised exercise in fitness centre
#2	Hospital 1	Male	59	Yes	
#3	Hospital 1	Female	70	No	
#4	Hospital 2	Female	45	No	
#5	Hospital 2	Female	76	Yes x 2	
#6	Hospital 2	Male	55	No	
#7	Hospital 2	Male	71	Yes x 2	
#8	Hospital 1	Female	66	Yes x 2 4 re-operations	

*GLA:D is an evidence-based program that includes education and supervised neuromuscular exercise delivered by certified physiotherapists.
GLA:D, Good Life with osteoArthritis in Denmark.

4.2.2 Themes and subthemes

The systematic text condensation and thematization resulted in three main themes and seven associated subthemes (Table 10). The themes elaborate on the patients' perspectives on expectations, experiences, and preferences influencing their treatment pathways.

Table 10 (Paper III).
Themes and subthemes.

Main themes	Subthemes
1. Adaptive treatment preferences	
2. Treatment expectations	1. Own perception of the disease
	2. Treatment effect
	3. Accessibility
	4. Fear of adverse events
3. The health care provider's influence	5. Trust in the health care provider
	6. Ability to communicate and educate
	7. Referral and treatment options

4.2.2.1 Adaptive treatment preferences (Main theme 1)

The patients' view on their medical condition and their symptoms influenced which treatments they received or preferred. Pain and functional limitations influenced the patients' decision on when to pursue a certain treatment. In this context, patients often reflected on when to take pain medication and when to consider surgery.

> "*When it really hurt, I took Ipren (ibuprofen) and Panodil (paracetamol).*" (Informant #2)
>
> And
>
> "*There was no doubt, I was in so much pain. There was no doubt, it was time to go under the knife.*" (Informant #2)

Patients pursued other treatment options if they experienced a worsening of their symptoms or no improvement. Worsening of symptoms often made patients consider injections or surgery. They also

considered specific treatments like pain medication to temporarily alleviate symptoms during periods of severe pain or as preparation for certain activities or situations.

> "*I ended up taking some ibuprofen. When I took one or two of those, for example before I was going to play badminton, I wasn't in pain. Then I could play.*" (Informant #1)

4.2.2.2 Treatment expectations (Main theme 2)

The patients had varying expectations regarding the treatments, which could impact their preferences for specific treatments. The patients' own perceptions of what causes knee OA and how the disease develops, as well as the expected effect of treatments, affected their treatment preferences. Accessibility and fear of potential adverse events from some treatments also had an impact on the patients' preferences.

Own perception of the disease (Subtheme 1)

The patients' own perception of the disease regarding the cause-effect mechanisms and development of the disease influenced their treatment preferences. There was a widespread perception of knee OA as a "wear and tear" disease, and patients often explained how an injury or long-term hard physical work or activity caused their knee OA.

> "*I walk with the tool and jump up as fast as the young people I work with [...] then I can feel, at least my left leg, making trouble [...] So that's how it started to the best of my knowledge.*" (Informant #6)

This made some patients express that the knee had to be restored using surgery, since exercise would not remove what was damaged in the knee.

> "*No, there is nothing that removes the wear and tear. That doesn't exist.*" (Informant #7)
>
> And
>
> *(About GLA:D)* "*It didn't help me, no, it didn't. Because it didn't remove what was worn askew. It just showed something about how fast you could run.*" (Informant #5)

Treatment effect (Subtheme 2)

Having certain expectations for the outcome of different treatments influenced which treatments the patients preferred. The treatment preferences were often affected by others, such as friends, family, acquaintances, or health care providers, but also the patients' experiences with specific treatments. Most often, it was others' positive experiences with treatments that influenced the patients' choice of treatment.

> (About acupuncture) "*It was friends who had said, "you should try it. Because we have such good experience with it".*" (Informant #8)

Some patients described that they discontinued a treatment if they had specific expectations to the effect of the treatment and these expectations were not met.

> "*Well, if it (physiotherapy) had helped, then it would have been great, but in my case [...] it has not had much effect. That's why I'm not going to try it again because I don't think it helps.*" (Informant #3)

Some patients' treatment preferences depended on the expectation that a treatment could postpone or even eliminate the need for surgery.

> "*I expect that the purpose of GLA:D training is that you will be better prepared for surgery, but also that you may be able to completely avoid surgery. I guess that is really the purpose of it.*" (Informant #8)

Accessibility (Subtheme 3)

The patients' expectations of the cost of treatment could influence their choice of treatment. Depending on the expected treatment effect, some patients would not undertake a particular treatment if they perceived the cost to be high and felt that their financial resources were limited. In addition, some patients experienced that they had to discontinue a relevant treatment because of costs and/or financial constraints.

> "*But it (exercise) became minimal because you couldn't afford it when being retired.*" (Informant #7)

Expectations to the availability of the treatment regarding transportation options, distance to the treatment facility, opening hours, or time consumption could influence the treatment choice. For

patients on the labour market, it was a barrier for undertaking certain treatments if the place of treatment was not open outside of normal working hours.

> (About GLA:D) "*Well, I have a job where you are dependent on me being present, so if I have to take an hour off to go to treatment, [...] that has been one of the things that has made me opt out, that I couldn't do that.*" (Informant #8)

Patients' experiences and expectations of a long waiting time for a treatment could be a reason for them to find alternatives to the recommended treatment.

Fear of adverse events (Subtheme 4)

Expectations of adverse events could be a barrier for pursuing certain treatments. Overall, there was an expectation that pain medication and intraarticular injections had side effects and the use of these should be limited.

> "*I can't imagine it's healthy for the body in the long run, stuffing yourself with Panodil (paracetamol) and Ipren (ibuprofen).*" (Informant #2)

Some patients expressed having a fear of adverse events from knee replacement surgery, which could make them postpone surgery.

> *(About fear of surgery)* "*It was because I was afraid I thought: something like that (knee replacement surgery) I don't dare.*" (Informant #5)

The expected positive effect of a treatment may outweigh the side effects, as patients expressed that once the decision to have surgery had been made, potential adverse events were not given much attention.

> "*There was a whole chart that said what could go wrong, but I didn't focus on that.*" (Informant #5)

4.2.2.3 The health care provider's influence (Main theme 3)

Health care providers and the degree to which patients trusted them also had an impact on the patients' perspectives on the treatment pathways. The choice of treatment was also influenced by how the health care providers communicated with their patients and their ability to educate on different treatment options.

Trust in the health care provider (Subtheme 5)

The patients' perceived qualifications and competences of the health care provider could influence the choice of treatment. Patients expressed that they preferred treatments offered by certified health care providers, and that little trust in the health care provider, made them pursue other treatments.

> "*Well, I have the experience that I will go directly to the professionals. Those who have professional skills.*" (Informant #2)

If patients experienced that their general practitioner did not have enough time with the patient at the consultation, or if they did not perceive their general practitioner as an expert, they were less likely to listen to their recommendations.

> "*I probably won't listen so much to the doctor, [...] I don't have much faith in my doctor, [...] they don't have much time to listen to you before you're just sent on your way. They are so busy today.*" (Informant #3)

Conversely, other patients trusted their general practitioner and the healthcare system in general and expressed that the decisions were made in collaboration with the general practitioner.

> *(About the desire for different treatment options)* "*No, I've never actually thought about that because I have faith that the system wants the best for me and that the hospital wants the best for me, so if there was an alternative, well, they would have said so, I think.*" (Informant #4)

The general practitioners' opinions on specific treatments and recommendations had very different influence on the patients' treatment preferences. However, some patients expressed that they were more likely to choose a specific treatment if the general practitioner had a positive attitude towards that treatment.

> "*He said: "without exercise, you will have problems with your knee, you have to do that (exercise), [...] so you have to because it's the only way you can get it back in order, or not in order, but better." So, all that, I certainly intend to start doing.*" (Informant #6)

Ability to communicate and educate (Subtheme 6)

The general practitioners' and other health care providers' ability to communicate and educate influenced whether the patients followed the recommendations and referrals and which treatments they preferred.

> "*But I think the psychological aspect has a lot to say. Trust and communication and credibility, all those things are incredibly important (for the choice of treatment), I think.*" (Informant #8)

Patients expressed that it was important for deciding to undergo a treatment that the health care providers communicated in a language and in a way that made the patient able to understand what the treatment was about.

> *(About communication)* "*It has been great, so there has been, for example, the orthopaedist, if there was something I said: "that I didn't quite understand", well, then he translated it into a language I could understand; more Danish and not Latin. And the same with the physiotherapist and so on. So, if you're just willing to say: "I don't understand that", then I have the understanding that they would very much like to explain it to you in another way. So, I'm satisfied with that. I think there has been good communication, yes.*" (Informant #4)

Referral and treatment options (Subtheme 7)

Some patients expressed that the general practitioner had provided them with a variety of treatment choices. Conversely, others experienced that the general practitioner only presented them for a few or no treatment alternatives, making it difficult to decide which treatment to choose.

> "*It's hard to find the right treatment, isn't it? Of course, it would be nice if the doctor would kind of help.*" (Informant #1)

Patients particularly emphasised that they would like more than one treatment option.

> "*So, when I said: "I don't want surgery", I was given no other option.*" (Informant #2)
>
> And
>
> *(About other treatment options than surgery)* "*No, he didn't talk about anything, no. He only talked about surgery.*" (Informant #5)

5 Discussion

To provide a foundation for optimising treatment pathways, increase appropriate use of clinical guidelines, and improve understanding of the daily management of patients with knee OA, this PhD thesis aimed to unravel the treatment pathways that patients pursue for knee OA and explore how patients' perspectives on the treatment pathways can influence their choice of treatment. Three papers constitute this thesis. Paper I (Study protocol): A study protocol for the overarching TREATright study that also describes a prediction study and a cost-effectiveness study; Paper II (Study 1): a prospective cohort study; and Paper III (Study 2): a qualitative interview study.

5.1 Summary of main findings

Study 1 demonstrated that only 35% of patients with primary referrals to an orthopaedic surgeon due to knee OA had undertaken the recommended combination of the core treatments exercise and patient education in their entire disease course until six months after consulting the orthopaedic surgeon. When considering if patients also had received dietary weight management, if needed, the proportion decreased to 23%. The patient characteristics were overall similar for patients undertaking the recommended core treatments compared to those who did not. We identified 1,143 unique treatment pathways among the 2,574 included patients with only 7% of the pathways comprising the recommended combination of core treatments.

Study 2 identified the patients' perspectives on treatment pathways for knee OA. Patients' view on their medical condition regarding knee OA and their symptoms influenced which treatments they received or preferred. Worsening of symptoms also led the patients adjust their treatment preferences. Patients' treatment preferences and attitudes towards certain treatment options could be influenced by their expectations of the treatment's effectiveness, accessibility, potential adverse events, and their personal views of their disease as "wear and tear". The patients also perceived that their trust in the health care provider, how referrals and treatment options were presented to the patients, and the health care providers ability to communicate and educate on different treatments could impact the treatment pathways.

5.2 Inferior use of guideline-adherent core treatments

Despite the clinical guidelines on the management of knee OA[45,51–53], the descriptive Study 1 found that the recommended core treatments are underutilised. Our findings support the conclusions of previous systematic reviews that found that less than 40% of patients were recommended education, self-management, or exercise[85,87]. As the recommended type of exercise is either not explicitly defined or differs between the clinical guidelines, we presented the proportions of patients who underwent any type of exercise and supervised land-based exercise, respectively. In Study 1, we found that the proportion of patients reporting to have undertaken supervised land-based exercise was 41% before consulting an orthopaedic surgeon, which was similar to the proportion found in the before mentioned systematic reviews[85,87]. However, in our study, a larger proportion of patients reported to have used any type of exercise. At six-month follow-up, we identified that the proportion had increased, both for supervised land-based and any type of exercise, indicating that many patients underwent the first-line core treatment, exercise, for the first time after consulting an orthopaedic surgeon. Even though more patients had received any type of exercise than supervised land-based exercise, the proportion of patients undertaking the combination of exercise, patient education, and dietary weight management (if relevant), was not influenced by how we defined exercise. This suggests that patients who received supervised land-based exercise most often also had undertaken patient education and dietary weight management (if relevant). At six-month follow-up, only 23% had received the recommended combination of core treatments, although this was a larger proportion than previously reported (19%)[90].

In Study 1, we also investigated the usage of different treatments for a subgroup of patients undergoing knee arthroplasty during the first six months after consulting an orthopaedic surgeon (Table 6). The 24% of the patients in this subgroup that underwent the recommended combination of core treatments was a substantially smaller proportion than the 60% previously described in a Canadian study by King et al.[88]. The proportion of patients who received exercise in the study by King et al.[88] was similar to what we have found, but approximately 70% had undergone dietary weight management compared to only 10% in our study, which largely describes the difference.

In general, the guideline-adherence has previously been investigated in different countries and health care sectors using different study designs, and the overall conclusion remains that the recommended core treatments are underutilised[84–89]. In addition to not receiving the recommended core treatments, patients undertake a wide range of treatments, some of which are supplementary, while others are

uncertain or not recommended. As knee OA slowly progresses and symptoms can vary over a long period of time, it is likely that patients pursue many treatments other than the core treatments. However, Study 1 focused on patients referred to an orthopaedic surgeon, which means that many of these individuals have received supplementary, uncertain or not recommended treatments, as first-line treatments[57].

5.3 The influence of patient characteristics on guideline-adherence

In Study 1, we also investigated if there were any differences in patient characteristics for patients undertaking different treatment pathways. Such differences could contribute to understand which patients pursue certain treatment pathways. However, we did not identify substantial differences in characteristics between patients who adhered to the recommended core treatments and those who did not. This finding aligns with a smaller study that also found no distinctions in patient characteristics between patients who adhered to the clinical guidelines and those who did not[89]. However, a Canadian study found that the use of recommended treatments was related to higher education levels and being female[88]. These findings were comparable to the trends from Study 1, but in the Canadian study, the patients who adhered to the recommended treatments were younger[88]. Nevertheless, both our study and the Canadian study showed only minor age differences between those who used core treatments and those who did not, indicating that age is not a significant factor. Men may receive fewer core treatments than women because they are more likely to have knee replacement surgery earlier in the course of disease[147].

5.4 Potential reasons for inferior use of guideline-adherent core treatments

Study 1 provided a descriptive overview of the inferior use of guideline-adherent core treatments. To elaborate on some potential reasons for the inferior use in the context of previous research, Study 2 used a qualitative design. This study design allows an in-depth knowledge of patient's experiences, expectations, and preferences, which, in addition to previous research, may contribute to the broader understanding[148,149].

In study 2, we found that the patients' view on their medical condition and symptoms and an experience of worsening of symptoms influenced their preference for surgery. We identified that patients with functional limitations and severe pain were more likely to consider surgery. As previously described, surgery should not be considered until the core treatments have been

offered[6,45,57,59]. Teo et al. found that pain and functional limitations motivate patients with knee OA to seek physiotherapy[99], even though others have reported that patients who believe they have severe radiographic knee OA or a high level of knee pain may be less likely to receive recommended core treatments[94,98]. This might indicate that patients' treatment preferences are influenced differently by pain and functional limitations depending on their prior experiences with the condition and management of knee OA. Hence, health care providers should take each patients' experiences and preferences into account when considering different treatment options.

The treatment choices can be influenced by the patients' belief that knee OA is a "wear and tear" disease, which may lead some to disregard exercise and favour surgery. The belief that knee OA is caused by "wear and tear" has also been reported by others to result in a perception, that exercise was an insufficient treatment as the cartilage could not be restored, making surgery an inevitable treatment[98,99]. In addition, some patients may have a perception that physiotherapy and exercise in particular can potentially worsen the knee damage and increase pain[98]. These perceptions could partly explain the proportion of patients in Study 1 reporting not to have undertaken exercise or any other treatment in their entire disease course or before surgery. However, it has also been reported that patients with knee OA think that surgery should only be seen as the last option and that consulting a physiotherapist could potentially postpone the need for surgery[94,99]. The interviews in Study 2 also reflected these conflicting attitudes towards exercise, highlighting the importance of educating patients on the beneficial effect of exercise to reduce pain, improve physical function, and delay or even prevent surgery[64,65,82,83].

We also identified in Study 2 that patients' previous experiences and treatment recommendations could influence their perspectives and preferences for certain treatments. The patients expressed that they would recommend treatments to others based on their personal experiences. Patients often opted for treatments they had been recommended by their friends, family members, acquaintances, or health care providers, which is consistent with previous research showing that others can influences the patients to seek nonsurgical treatments[94,99]. However, if people have had positive experiences with surgery, their recommendations may instead become a barrier for the patients to receive the recommended core treatments[94]. The influence of others' recommendations was likely to have affected which treatments the patients had reported to have undertaken in Study 1. Some might have been influenced to undertake the recommended core treatments, while others might have been influenced to undertake supplementary or uncertain treatments on the expense of recommended core

treatments. Consequently, it can be useful to include the patients' next of kin in the discussion of treatment options and potential benefits and outcomes, but also focus on communicate the benefits of recommended core treatments and educate about OA to the wider population.

Some patients in Study 2 expressed that different aspects of accessibility influenced their choice of treatment. While previous studies have reported cost and/or financial constraints as a barrier to choosing the recommended treatments, our study found that the extent to which this influenced the patients' choice of treatment varied largely[91,92,94]. Ackerman et al. emphasised that having health insurance to cover part of the expenditure made it easier for patients to access different treatments[150]. Since the national health security system in Denmark does not usually cover the costs of dietary weight management and exercise, this may have contributed to the inferior use of recommended core treatments reported in Study 1. Study 2 also highlighted that it could be difficult to undertake certain treatments if you were on the labour market and the place of treatment was closed outside normal working hours. Hence, improving patient access to care might be addressed by ensuring financial support as well as more adaptable or longer opening hours at the place of treatment.

Another possible reason, reported in Study 2, for inferior guideline-adherence was the influence by the health care providers, which is likely to have impacted the treatment pathways and which treatments the patients reported to have received in Study 1. Studies have shown that some health care providers are not referring patients to a physiotherapist or dietician due to scepticism about the benefits of dietary weight management and exercise[93,94]. Other barriers to referral to core treatments include general practitioners who prefer surgery or perceive knee OA as an unavoidable process of aging[94,95]. General practitioners have also highlighted the shortage of time with the patient in the consultation as an obstacle to the implementation of clinical guidelines[91,95]. In addition, patients in our study expressed that lack of time with the general practitioner made them less likely to follow their recommendations and that they also found it challenging to choose among treatment options. These findings highlight the need for shared decision-making to optimise the implementation and usage of clinical guidelines, which has also been reported to improve treatment outcomes in patients considering knee replacement[151]. Shared decision-making involves the patients in treatment decisions, allowing them to make informed choices instead of having decisions made for them[152]. As patients' perspectives and treatment preferences can be influenced by their knowledge and information about treatments and knee OA, it would be useful to educate patients as part of the shared decision-making process about the benefits of the core treatments and the disease[98,153]. It would also

be advantageous to educate health care providers about clinical guidelines to increase the use of core treatments[91,95,154], as health care providers' has expressed inadequate knowledge of recommendations as a barrier to refer to recommended treatments[93,95,96].

5.5 Strengths and limitations

For this thesis, different study designs were applied, each of which has its strengths and limitations.

5.5.1 Study 1

The prospective design and large number of consecutively included patients are some of the strengths of the descriptive Study 1. We included patients from two orthopaedic outpatient clinics in two different regions of Denmark to increase the generalisability. Furthermore, the follow-up questionnaire enabled us to explore the changes in proportions undertaking specific treatments from before to after the consultation. All eligible patients were invited to participate if they were referred by their general practitioner to an orthopaedic surgeon due to knee OA, making our findings more representative and clinically relevant. To reflect daily management of knee OA and clinical practice, patients ≥ 40 years with unspecified diagnoses like "knee problems" or "knee pain" were also invited. In this way, we could have included a few patients who did not met the diagnostic criteria for knee OA described in the *Introduction* to this thesis. There was a large number of eligible patients that did not respond to the questionnaires at inclusion or follow-up. Hence, we were only able to include half of the eligible patients in the final analyses, which could have introduced a risk of selection bias[155,156]. The large proportion of patients who were unable to read and write Danish and therefore were excluded could also have contributed to the risk of selection bias and compromised the generalisability of our findings. Additionally, most of the data collected for Study 1 were self-reported, which carries a risk of recall bias[85,157]. The risk of recall bias was particularly present in relation to treatments received before the consultation, since patients were required to report which treatments they had received in their entire knee OA disease course, making the recall period very long[157]. Nevertheless, since there are no registries in Denmark containing exhaustive information on all relevant treatments received for knee OA, we considered our approach to be appropriate. The TREATright cohort consisted of patients referred to an orthopaedic surgeon for assessment for knee replacement surgery, of whom 90% had KL grade ≥ 3. Therefore, one must be aware that the findings from this thesis may be more applicable to patients with more severe knee OA. Nevertheless, the

cohort also comprised patients having mild radiographic OA and patients with an OKS ≥ 30, which indicate that our findings are representative for both patients with mild/moderate and more severe knee OA[116].

5.5.2 Study 2

In order to increase the generalisability of the qualitative Study 2, we recruited informants with a variety of patient characteristics from two hospitals located in both urban and more rural parts of Denmark. The fact that all informants were recruited from the TREATright cohort - patients who had consulted an orthopaedic surgeon and had experience with the progression of the disease and treatment pathways for knee OA - contributed to improve the information power[104]. When having high information power, a smaller sample size might be adequate to provide sufficient information, in contrast to a large sample size with low information power[104]. In the Study protocol, we stated that we planned to recruit informants until sufficient information power was obtained. However, we only recruited eight informants for interview for pragmatic reasons, as data collection took longer than expected. Considering that patients had very different expectations, experiences, and preferences concerning treatment for knee OA, we might have gained an even better understanding of the diversity of patients' perspectives by interviewing more informants. When interpreting the results, it should therefore be considered that the limited number of eight informants may not have been adequate to achieve sufficient information power. In qualitative interview studies, it is important to be aware of the risk of preconception bias, as the investigators' preconceptions might have influenced the analysis and thematization[127]. To address the risk of preconception bias, the study team consisted of investigators with different clinical backgrounds as physical therapist and general practitioner. Throughout the process, we also endeavoured to be aware of our preconceptions and whether they affected the interpretation[127].

6 Conclusions

Until six months after consulting an orthopaedic surgeon, only one in four patients with knee OA had undertaken guideline-adherent treatment pathways. Exercise was the most utilised core treatment and was reported by almost three in four patients. Supervised land-based exercise, which has been suggested as most effective, was undertaken by two in three patients. One in three patients reported to have received patient education, but only one in ten had undertaken dietary weight management, if relevant, making it by far the most underutilised core treatment. Considering that all included patients were at a point in their disease course where they had consulted an orthopaedic surgeon, a large number of patients had not received any treatment. Conversely, uncertain and not recommended treatments were frequently used. We identified a large number of very different treatment pathways, most of which were not guideline-adherent. Overall, the findings from Study 1 concludes that the core treatments for knee OA recommended by the clinical guidelines are severely underutilised.

To provide nuance to the descriptive Study 1, we explored the patients' perspectives on their treatment pathways for knee OA and some possible explanations for the inferior guideline-adherence. Our findings indicate that patients' treatment preferences were adaptive and highly affected by the progression of symptoms and view on their medical condition. Based on their expectations, prior treatment experiences, and perception of the disease, their preferences varied widely. However, the perception of knee OA as a "wear and tear" disease was a general facilitator to consider surgery. Patients had very different perspectives on cost and/or financial constraints, wait times, and distance which influenced their perceptions of the accessibility very differently. Mistrust to the health care providers was a barrier to following their treatment recommendations. Patients expressed that the health care providers themselves influenced the treatment choices and emphasised the importance of effective communication. Overall, the findings from Study 2 concludes that patients' preferences for treatment of knee OA are diverse, change over time and are influenced by experiences, expectations, knowledge/understanding of the disease, own resources, and the influence of health care providers.

In summary, the treatment for knee OA is often not in accordance with clinical guidelines. The large variation in patients' treatment pathways is dependent on individual conditions and perspectives, which it is important for health care providers to be aware of in order to take each patients' experiences and preferences into account when considering treatment options and to ensure optimised utilisation of core treatments.

7 Perspectives and further research

This thesis highlights the need for a more structured approach to promote the use of guideline-adherent core treatments. Unravelling the treatment pathways for knee OA provides a foundation for optimising and increasing the utilisation of recommended guideline-adherent treatments. Furthermore, describing the patients' perspectives on their treatment pathways contributes to the understanding of knee OA management and which barriers and challenges to address.

Enhancing adherence to guidelines is crucial for improving knee OA treatment outcomes[158]. This thesis provides valuable insights into the current usage of treatment, serving as a foundation for improving guideline adherence. Additionally, the patient characteristics and predictive variables identified in our Study 1 can inform the prediction study to identify factors influencing the treatment outcomes. These findings can facilitate tailored treatment approaches for the individual patient and be supportive in the shared decision-making. Furthermore, the cost-effectiveness study will provide information on the costs of guideline-adherent and non-guideline-adherent treatment pathways. Hence, the cost-effectiveness study will offer additional information on which treatment pathways are most cost-effective in terms of treatment costs and expenses related to sick leave.

To examine how treatment pathways can be affected by enhanced patient education about the disease and information on available treatments further research is required. In addition, it is important to focus on improving communication between health care providers and patients to improve shared decision-making and ensure appropriate use of treatments. This highlights the importance of consistency in the recommendations from health care providers and how treatment options are communicated. Future qualitative studies should investigate both patients' and health care providers' perspectives and focus on different health care sectors. Further research is needed to unravel the complexities influencing the shared decision-making and treatment pathways for knee OA[159].

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9 Appendices

Paper I (Study protocol)

Paper II (Study 1)

Paper III (Study 2)

UNIVERSITY OF COPENHAGEN
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Paper I

Disentangling treatment pathways for knee osteoarthritis: A study protocol for the TREATright study including a prospective cohort study, a qualitative study and a cost-effectiveness study

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BMJ Open

Disentangling treatment pathways for knee osteoarthritis: a study protocol for the TREATright study including a prospective cohort study, a qualitative study and a cost-effectiveness study

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ABSTRACT

Introduction Knee osteoarthritis (OA) is associated with chronic knee pain and functional disability that negatively affect the ability to carry out normal daily activities. Patients are offered a large variety of non-surgical treatments, often not in accordance with clinical guidelines. This observational study will provide a comprehensive overview of treatment pathways for knee OA during the first 2 years after consulting an orthopaedic surgeon, including timing and order of treatment modalities, predictors of treatment outcomes, cost-effectiveness of treatment pathways and patients' views on different treatment pathways.

Methods and analysis Patients with primary referrals to an orthopaedic surgeon due to knee OA are consecutively invited to participate and fill out a questionnaire prior to their consultation with an orthopaedic surgeon. Follow-up questionnaires will be obtained at 6 and 24 months after inclusion. Based on a prospective cohort study design, including questionnaires and register data, we will (1) describe treatment pathways for knee OA during the first 2 years after consulting an orthopaedic surgeon; (2) describe the characteristics of patients choosing different treatment pathways; (3) develop predictive models for patient-self-determined classifications of good and poor treatment outcomes; (4) evaluate the cost-effectiveness of treatment pathways that live up to clinical guidelines versus pathways that do not; based on a qualitative study design using semistructured individual interviews, we will (5) describe the patients' perspectives on treatment pathways for knee OA.

Ethics and dissemination The study is approved by the Danish regional ethical committee (journal number H-17017295) and the Danish Data Protection Agency (journal number AHH-2017–072). Data will be anonymised and handled in line with the General Data Protection Regulation and the Danish Data Protection Act. The study results will be submitted to international open-access peer-reviewed journals and disseminated at conferences.

Trial registration number NCT03746184, pre-results.

Strengths and limitations of this study

- This study protocol outlines a multidisciplinary research approach using different methodologies to achieve a comprehensive overview of treatment pathways for knee osteoarthritis (OA) during the first 2 years after consulting an orthopaedic surgeon.
- Patients are consecutively included in the cohort as they are referred to two outpatient clinics (representing both urban and more rural areas) due to knee OA to strengthen the representativeness of the study population.
- The results may be more relevant for patients with more severe knee OA, rather than the whole disease spectrum, since the cohort is composed of patients consulting an orthopaedic surgeon due to their knee OA.
- A pragmatic approach was used to estimate sample size as there were no specific guidelines on sample size estimation for prediction models.
- By using self-reported questionnaires to detail previous treatment, there is a risk of missing data and recall bias.

INTRODUCTION

Knee osteoarthritis (OA) is associated with chronic knee pain and functional disability that negatively affects the ability to carry out regular daily activities.[1] Knee OA is the most common form of arthritis with a prevalence increase of 27.5% worldwide from 2010 to 2019.[2] In 2019, 528 million people were estimated to have OA, and the knee joint is the most common OA site that causes disability.[2] Consequently, knee OA places a major economic burden to the society expected to increase in the future.[3] In order to address the increasing burden, evidence-based and individualised treatment strategies are needed.

Total knee replacement (TKR) is considered cost-effective for end-stage knee OA,[4] but timing is difficult.[5] Skou *et al*'s recent randomised trial has shown that, in patients who are eligible for surgery, TKR, in addition to non-surgical treatment (patient education, neuromuscular exercise, dietary advice, use of insoles and pain medication), was more effective—and with clinically relevant effect sizes—in relieving pain and improving physical function compared with non-surgical treatment alone at 1 year. However, patients treated non-surgically also gained clinically important improvements and had a much lower risk of serious adverse events compared with those who had surgery. Skou *et al*'s findings imply that many patients who are deemed eligible for a TKR can gain substantial improvements with an optimised non-surgical treatment approach.[6]

National and international clinical guidelines on the management of knee OA recommend patient education, exercise and weight loss intervention, if overweight, as core non-surgical treatments for knee OA.[1 7–9] However, several studies have highlighted that compliance with the recommendations is poor,[10–12] and patients are offered a large variety of non-surgical treatments, some in accordance with clinical guidelines and some not.[13] A systematic review showed that only 39% of the patients are offered referral or recommendation to exercise, and 35% are offered education and self-management.[14]

Healthcare practitioners are expected to adhere to clinical guidelines in the shared decision-making process with the patient. Patients have reported that insufficient information about possible treatment options, lack of information on individual consequences of having knee OA, and access to local care can influence the decision-making on different treatments.[15 16] Further, previous research has indicated that patients' decision to undergo TKR is influenced by the interaction between the orthopaedic surgeon and the patient.[17] Challenges with the implementation of clinical guidelines are also a possible factor that may influence which treatments patients are offered.[18 19] The poor compliance with clinical guidelines, including the patients' and clinicians' reported barriers with usage of different treatment modalities, stresses the need to clarify challenges and barriers related to different treatment modalities, and which treatment modalities are applied in which patients, at which stage in their knee OA disease course.

To our knowledge, no previous large-scale studies have provided a comprehensive overview of different treatment pathways or the timing and order, predictors of effect and cost-effectiveness of different treatment options for knee OA, as well as clarifying patients' considerations on different treatments at the point in time when patients consult an orthopaedic surgeon. Such an overview would be helpful in order to design, evaluate and implement individualised treatment strategies.

Objectives

The objectives of this study were

1. To describe which treatment pathways patients pursue for knee OA during the first 2 years after consulting an orthopaedic surgeon.
2. To describe the characteristics of patients choosing different treatment pathways.
3. To develop prediction models for good and poor treatment outcomes of different treatment modalities and/or pathways used for knee OA.
4. To evaluate the cost-effectiveness of treatment pathways that adhere to clinical guidelines versus pathways that do not.
5. To describe the patients' perspectives on their treatment pathways for knee OA.

METHODS AND ANALYSIS

The study will use a prospective cohort study design (objectives 1–4) in which patients are included when consulting an orthopaedic surgeon with follow-ups at 6 and 24 (primary) months after inclusion. A qualitative study design will be used for objective 5. The study was prospectively registered with ClinicalTrials.gov. Since registration, the most significant edits to the registration and protocol (current protocol V.2.0, 21 December 2020) include a specification of primary and secondary outcomes as reflected in the updated registration on clinicaltrials.gov on 8 January 2021. Reporting of the study will follow the The Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines for observational studies.[20] Also the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guidelines[21] for objective 3, the Consolidated Health Economic Evaluation Reporting Standards statement[22] for objective 4, and the Consolidated criteria for Reporting Qualitative research[23] for objective 5 will be followed to facilitate subsequent reporting.[24]

Prospective cohort study

Participants

For the prospective cohort study (objectives 1–4), patients with primary referrals to an orthopaedic surgeon due to unilateral or bilateral knee OA are consecutively invited to participate. A pragmatic approach to inclusion based on the general practitioners' diagnosis of knee OA is applied, irrespective of which diagnostic criteria the general practitioners use. Additionally, patients referred with unspecified diagnoses such as 'knee pain' or 'knee problems' will be invited if their age is ≥40 years, as this is the lowest age limit proposed by international recommendations for clinical OA criteria.[25] Patients are included from the outpatient clinics at the departments of orthopaedic surgery at Copenhagen University Hospital Hvidovre and Næstved Hospital in Denmark (representing both urban and more rural areas). Patient enrolment was initiated in October 2018 and was completed ultimo December 2020. Data collection is ongoing with an expected completion of follow-up in December 2022 (figure 1). Exclusion criteria are previous total or unicompartmental knee

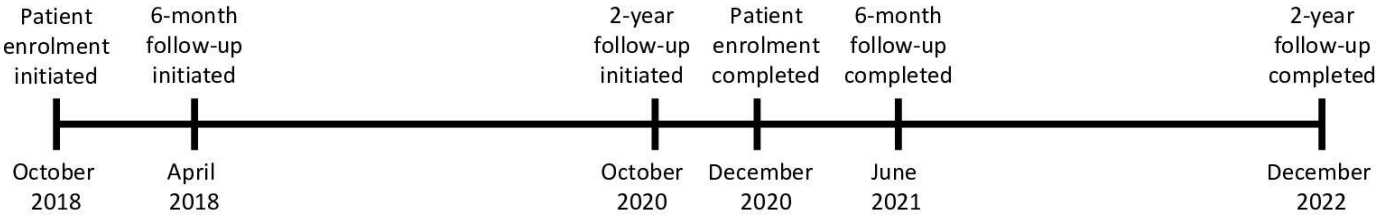

Figure 1 Timeline for data collection for the prospective cohort study.

replacement or osteotomy around the study knee, and inability to read and write Danish.

Procedure

At inclusion, patients with primary referrals to an orthopaedic surgeon due to knee OA are identified from lists of patients referred to the hospital and contacted by a member of the research team through a secure email, with information about the study, an invitation to participate and a link to a patient self-reported questionnaire within 3 days–2 weeks before the consultation with the orthopaedic surgeon. Patients who have not responded at the day of their consultation are asked by a member of the research team to fill out the questionnaire on an iPad or a paper-based questionnaire in the waiting room, prior to their consultation with the orthopaedic surgeon. Patient consent is collected electronically through their response to the questionnaire that also marks the enrolment in the study. At 6 months and 2 years after inclusion, links to the questionnaire will be sent electronically. For patients who do not have secure email (approximately 15% based on actual numbers from the cohort so far), paper versions of the questionnaire and a prepaid return envelope will be sent by post. Two reminders are sent after 1 week and additionally 2 weeks for electronic and 5 weeks for paper-based questionnaires.

In Denmark, patients with knee OA initially visit their general practitioner who may option to refer to an orthopaedic surgeon. This study follows a pure observational design, in which patients are invited to share their pursued treatment pathways through questionnaires, in the 2-year period after consulting the orthopaedic surgeon. The study does not interfere with the chosen treatment, and patients will be followed up for 2 years, whether they are offered surgical treatment or not.

Outcomes

Two primary outcomes will be assessed using the patient-self-determined classifications of achieving good or poor treatment outcomes from inclusion to 2-year follow-up defined by a patient acceptable symptom state (PASS) and a treatment failure (TF) anchor question.[26 27] The PASS anchor question was developed for patients with OA and asks, 'Taking into account all the activities you have during your daily life, your level of pain, and also your functional impairment, do you consider that your current knee state is satisfactory? (yes/no)'. Patients responding 'yes' to this question will be categorised as having a good treatment outcome.[26] Patients responding 'no' will be asked the TF anchor question: 'Would you consider your current state as being so unsatisfactory that you think the treatment has failed? (yes/no)'. Patients answering no to the PASS and subsequently answering yes to the TF anchor question will be defined as having a poor treatment outcome. The PASS and TF questions at the 6-month follow-up will act as secondary outcomes. Another secondary outcome will be based on a supplementary anchor question asking about the patients' experienced degree and importance of change in their knee problems: 'How are your knee problems now compared with for 2 years (6 months) ago, when you first consulted the orthopaedic surgeon?' Patients will respond to this question on a seven-level Likert scale ranging from 'better, an important improvement' to 'worse, an important deterioration'.[28 29] Further, the Oxford Knee Score (OKS) at 6 months and 2 years, and the change in OKS over time will act as an additional secondary outcome. The OKS evaluates self-reported knee pain and function on a scale ranging from 0 (worst) to 48 (best), and has presented sufficient validity, reliability and responsiveness characteristics for use in this patient population.[30 31]

Collected outcomes and predictive variables

A number of variables will be collected at inclusion (prior to the consultation with the orthopaedic surgeon) and at 6 month and 2 year follow-ups after the consultation with the orthopaedic surgeon (table 1) to describe different treatment pathways and to identify possible predictive variables for treatment outcome following different treatments.

At inclusion

The patient self-reported questionnaire includes patient demographics, comorbidities, duration of knee problems and other affected joints, and surgical history in the knees, hips or ankles. Knee pain and function will be evaluated with the OKS. Average knee pain during the past week is measured with a Visual Analogue Scale (VAS) (ranging from 0 (no pain) to 100 (worst imaginable pain) (100 mm scale)),[32] which has sufficient validity and reliability characteristics to measure knee pain.[33 34] The patients mark areas where they currently have pain or discomfort on a pain manikin (19 areas), which has been shown to be reliable to assess musculoskeletal pain.[35] Physical activity level can affect the treatment outcome and is reported as the average time spent on physical activity every week, with a non-validated single item question proposed by the International Consortium for Health Outcomes

Table 1 Collected outcomes and predictive variables at inclusion and at 6-month and 2-year follow-ups

Collected outcomes and predictive variables (response categories)	Source of data	Inclusion	6-month follow-up	2-year follow-up
Primary outcomes				
PASS (yes/no)	Patient-reported			X
Self-reported TF (yes/no)	Patient-reported			X
Secondary outcomes				
PASS (yes/no)	Patient-reported		X	
Self-reported TF (yes/no)	Patient-reported		X	
Degree and importance of change in knee pain and function (ranging from 'better, an important improvement' to 'worse, an important deterioration')	Patient-reported		X	X
Oxford Knee Score (12 items)	Patient-reported	X	X	X
Predictive variables				
Biological gender (female/male)	Extracted from personal identification number	X		
Age (years)	Extracted from personal identification number	X		
Height (cm)	Patient-reported	X		
Weight (kg)	Patient-reported	X		
Body Mass Index (kg/m^2)	Calculated	X		
Residential status (alone/cohabiting)	Patient-reported	X		
Level of education (elementary school/high school/ vocational education/short-cycle higher education/medium-cycle higher education/long-cycle higher education or more)	Patient-reported	X		
Occupation (retired, early retiree or on early retirement/ sick leave part time or full time/unemployed/on the labour market or student part time or full time)	Patient-reported	X		
Smoking (yes/no, but I used to/no never; if yes: average number of daily cigarettes is recorded)	Patient-reported	X		
Comorbidities (list of 15 diseases)	Patient-reported	X		
Which knee to be examined by the orthopaedic surgeon (right/left/both)	Patient-reported	X		
Duration of knee problems (ranging from 0 months to more than 10 years)	Patient-reported	X		
Degree of knee pain (Visual Analogue Scale 0 (no pain)–100 (worst imaginable pain (100 mm scale))	Patient-reported	X	X	X
Localisation of pain/discomfort elsewhere in the body (marked on a full body pain mannequin)	Patient-reported	X	X	X
Expectations to the following treatment (surgery/injection into the knee joint/training sessions or other treatment/ weight loss (if overweight)/treatment for pain/no treatment/ other)	Patient-reported	X		
Type of healthcare provider who has examined/treated the knee OA (general practitioner/orthopaedic surgeon/ rheumatologist/physiotherapist/occupational therapist/ dietitian/osteopath/chiropractor/personal trainer in the gym/ alternative therapist (such as massage therapist, healer, body self-development system therapist, reflexologist, acupuncturist or similar)/other/no examination or treatment)	Patient-reported	X	X	X
Number of consultations/treatments for knee OA for each healthcare provider	Patient-reported		X	X

Continued

Table 1 Continued

Collected outcomes and predictive variables (response categories)	Source of data	Inclusion	6-month follow-up	2-year follow-up
Treatment for knee OA (table 2)	Patient-reported	X	X	X
Osteoarthritis Quality Indicator Questionnaire (15 items)	Patient-reported	X	X	X
Previous knee injury that was examined by a healthcare provider (none/right knee/left knee/both knees)	Patient-reported	X		
Previous joint surgery in lower limb (hip(right/left), knee(right/left) or ankle(right/left))	Patient-reported	X		
Type of previous joint surgery in lower limb (arthroscopic/open surgery/total or partial replacement)	Patient-reported	X		
Short version of the Arthritis Self-efficacy Scale (11 items)	Patient-reported	X		
Self-reported physical activity level (none/30 min/1 hour/2 hours/more than 2 hours)	Patient-reported	X	X	X
Self-reported health condition (3-level version of the European Quality of Life - 5 Dimensions (EQ-5D-3L)) (five items and European Quality of Life Visual Analogue Scale (EQ-VAS))	Patient-reported	X	X	X
Radiographical knee OA severity (grade 0, none–4, severe)	Radiographical assessment	X		
Knee alignment (anatomical tibiofemoral axis)	Radiographical assessment	X		
Knee OA wear pattern (patellofemoral/lateral/medial/involving two to three compartments)	Radiographical assessment	X		
Type of knee replacement surgery for patients who are surgically treated (total/unicompartmental knee replacement)	National Patient Register		X	X
Information for the cost-effectiveness study				
Healthcare costs (hospitalisation, surgery, medication, primary and secondary healthcare provider visits and home-help services)	Statistics Denmark		X	X
Healthcare costs (healthcare provider visits not covered by public healthcare system)	Patient-reported		X	X
Short-term sick leave (<21 days)	Patient-reported		X	X
Long-term sick leave (≥21 days)	Statistics Denmark		X	X

OA, osteoarthritis; PASS, patient acceptable symptom state; TF, treatment failure.

Measurement.[36] The quality of previous treatment for knee OA is assessed with the revised version of the patient self-reported Osteoarthritis Quality Indicator Questionnaire (OA-QI) that had improved validity, reliability and responsiveness.[37] The OA-QI consists of 16 items but only 15 for this study as one question concerning referral for assessment for operation has been excluded from the questionnaire. Further questions elaborate on the previous treatment used for knee OA, including type of healthcare provider consulted. Furthermore, the patients will be asked about their expectations to the treatment they are about to undergo, and their perceived self-efficacy will be evaluated using the 11-item version of the Arthritis Self-efficacy Scale (ASES) that subscales pain and other symptoms.[38] The currently not validity tested Danish version of ASES was chosen for lack of better alternatives to capture self-efficacy.[39] Finally, the 3-level version of the European Quality of Life - 5 Dimensions (EQ-5D-3L) measures the patients' self-reported health status on the five domains mobility, self-care, usual activities, pain/discomfort, anxiety/depression and an additional European Quality of Life Visual Analogue Scale (EQ-VAS) of current self-reported overall health status (ranging from 0 (worst) to 100 (best)).[40]

Standing anteroposterior and lateral short filmed knee radiographs are routinely taken prior to the primary consultation with the orthopaedic surgeon. Radiographical evaluations include (1) the Kellgren-Lawrence classification of radiographical OA severity (five grades ranging from 0 (none) to 4 (severe))[41]; (2) knee alignment, measured as the anatomical tibiofemoral axis[42]; (3) the OA wear pattern, which will be recorded as patellofemoral, lateral or medial, or involving two to three compartments. Radiographical analyses will be performed by

SMB, supervised by LHI (>5 years radiographical review experience) and AT (orthopaedic surgeon).

At follow-up

Additionally, at the 6-month and 2-year follow-ups after the consultation with the orthopaedic surgeon, the type of knee replacement will be extracted from the National Patient Register for patients who are surgically treated and will be registered as a total or unicompartmental knee replacement. Patients are asked about the type of healthcare provider who has examined/treated the knee OA since inclusion and the type of treatment for knee OA received since last questionnaire. Patients who are surgically treated since inclusion will be asked to answer which other treatment modalities they have undergone until surgery. In addition, the follow-up questionnaire includes information on the number of consultations/treatments and the cost per treatment for treatment modalities that are not covered by the national health security system. Finally, for patients who are active on the labour market, details about short-term sick leave are asked for.

Sample size

The sample size for the cohort is based on a pragmatic approach based on the number of primary referrals from patients with knee OA during a 2 year inclusion period. Taken together, Copenhagen University Hospital Hvidovre and Næstved Hospital receive primary referrals from approximately 3000 patients with knee OA per year. With a 2-year period and an expected inclusion rate of 65% (based on the first year of inclusion), we expect to include 3900 patients. With an expected 65% follow-up rate, full data will be obtained from approximately 2535 patients at 2-year follow-up.

Our sample size considerations are based on objective 3, to develop a prognostic prediction model. Although there are no specific guidelines on adequate sample size to develop a prognostic prediction model,[43] for binary prediction models, at least 10 outcome events per variable (EPVs) has been suggested as a rule of thumb.[44 45] It has also been suggested that at least 20 EPVs are required for models that include low-prevalence binary predictors; however, it is recommended that the rule of thumb of EPV should be data driven.[46] An expected event rate of approximately 25% of patients responding no to the PASS will be used, which is the previously found proportion in patients undergoing primary TKR.[27] With a minimum of 20 EPVs and approximately 30 predictor variables, a total number of 2400 patients would be required. Decreasing to a minimum of 10 EPV would require 1200 patients.

Data analysis plan

A flowchart of patients will be presented, including the number of patients excluded and unwilling to participate, stating the reasons for exclusion or missing data. Furthermore, a table of key patient characteristics will be outlined. Multiple and single imputation will be used to handle missing data.

Data analysis plan for the descriptive studies

The first descriptive study (objective 1) will present the treatment pathways that patients with primary referrals to an orthopaedic surgeon due to knee OA pursue during the 2-year follow-up period, or until surgery for those undergoing knee arthroplasty. Patients select which treatments they have received for knee OA from a predefined list of 18 treatments in the questionnaire at inclusion (prior to the consultation with the orthopaedic surgeon), and at 6-month and 2-year follow-ups after the consultation with the orthopaedic surgeon. These treatments will be grouped into 13 treatment categories (table 2). Based on national and international clinical guidelines, the treatments will be classified into (1) core treatment (education/self-management, exercise, weight loss, if needed (patients with Body Mass Index (BMI)≥25[47]), and participation in Good Life with osteoArthritis in Denmark[48]); (2) supplements to core treatment (pharmacological treatments, intra-articular injections, walking aids and devices, stretching and joint mobilisation); (3) end-stage treatment (total or unicompartmental knee arthroplasty); and (4) uncertain or not recommended treatment (arthroscopic surgery, passive treatment and complementary medicine) (table 2).[1 7–9 49] As the questionnaires do not contain other questions about weight loss intervention than diet or dietary guidance, we will additionally also classify the combination of the treatment categories education/self-management and exercise as (1) core treatment. A sensitivity analysis will be performed to investigate subgroups of exercise (supervised, unsupervised and water-based). The order of undertaken treatment will be defined based on response to three questionnaires: (1) treatment up until inclusion (before consultation with the orthopaedic surgeon), (2) treatment from inclusion until 6 months of follow-up and (3) treatments from 6 months of follow-up until to 2 year follow-up. Results will be presented as the percentages of patients undertaking different treatment pathways. The total number of possible treatment pathways based on the 13 treatment categories and three questionnaire time points is too high to enable a description of all pathways. Therefore, we will present the most common pathways using a data-driven approach that best describes the distribution of data. Additionally, we will also describe the proportion of patients pursuing treatment pathways that live up to clinical guidelines, that is, (1) core treatment, (2) core treatment followed by or in combination with any supplemental treatment, (3) core treatment followed by knee replacement and (4) core treatment followed by or in combination with any supplemental or other treatment followed by knee replacement. We anticipate that some patients will receive treatment in line with clinical guidelines but occasionally seek non-guideline-adherent treatments in addition. We believe the most important aspect is whether or not the recommended core treatments have been used. We have therefore chosen to classify treatment pathways as adherent to

Table 2 Predefined list of 18 treatments in the questionnaires, grouped into 13 treatment categories and the overall classification of treatments

Classification of treatments	Treatment categories	Predefined list of treatments in the questionnaire
Core treatment	1. Education/self-management.	1. Information and guidance on living with OA.
	2. Exercise.	2. Exercise and gymnastics (strength training, fitness or other type of exercise) under the supervision of a physiotherapist or similar.
		3. Water-based exercise in groups or under supervision.
		4. Exercise on your own (strength training, fitness or other type of exercise).
	3. Weight loss, if needed.	5. Diet or dietary guidance.
	4. GLA:D.*	6. Participation in GLA:D.*
Supplements to core treatment	5. Pharmacological treatment.	7. Pharmacological treatment (including painkillers).
	6. Intra-articular injections.	8. Injection into the knee joint.
	7. Walking aids and devices.	9. Insoles.
		10. Assessment of the need for walking aid (walking stick, crutches, etc).
	8. Stretching.	11. Stretching.
	9. Joint mobilisation.	12. Other manual therapy.
End-stage treatment	10. Total or unicompartmental knee arthroplasty.†	13. Knee arthroplasty.
Uncertain or not recommended treatment	11. Arthroscopic surgery.	14. Arthroscopic surgery.
	12. Passive treatment.	15. Acupuncture.
		16. Massage.
		17. Ultrasound, laser or other type of electrotherapy.
	13. Complementary medicine.	18. Complementary medicine (such as healing, body self-development system, craniosacral therapy or similar).

Patients select which treatments they have received for knee OA at inclusion and at 6-month and 2-year follow-ups.
*GLA:D is an evidence-based programme that includes education and supervised neuromuscular exercise delivered by certified physiotherapists.
†Type of knee arthroplasty will be extracted from the National Patient Register.
GLA:D, Good Life with osteoArthritis in Denmark; OA, osteoarthritis.

clinical guidelines, as long as the patients have received the core treatments, disregarding any additional non-recommended treatments used.

The second descriptive study (objective 2) will focus on the demographic, functional and radiological characteristics (table 1) in patients choosing the different treatment pathways. For each treatment pathway identified in the first descriptive study, patient characteristics will be presented descriptively. Depending on the identified treatment pathways it may also be relevant to explore and present patient characteristics for selected treatment modalities. Investigating the relationship between patient characteristics and the treatment pursued will help clarify whether patients with certain characteristics are more likely to pursue certain treatment pathways.

Data analysis plan for the prediction study

Through the prediction study (objective 3), we will investigate what predicts good and poor outcomes of available treatment modalities. Prognostic models will be developed using machine learning software packages for the statistical software program R.[50] Two separate prognostic models will be developed—one model for the PASS and one for the TF outcome.

The patients' self-determined classifications of good treatment outcomes, defined as answering yes or no to the PASS question will be the dichotomised dependent variable. Likewise, for the TF model, the dependent variable will be the patients' self-determined classifications of poor treatment outcomes dichotomised into 'TF', if answering yes to the TF question, or 'not TF' if answering either yes to the PASS question or no to the

subsequent TF question. Collected possible predictive variables (table 1), along with the 13 different categories of treatments that patients have received (table 2) at the three different time points, will be included as independent predictive variables. Variables such as BMI, preoperative OKS, physical function and prior knee arthroscopy have previously been shown to be clinically and statistically relevant predictive variables associated with treatment outcome after primary TKR.[51 52] To identify which variables to include in the final model, models with and without specific variables will be compared with evaluate the possible loss in accuracy when excluding these variable.

To develop and determine which machine learning model to use, different models will be compared, for example, neural network and random forest. We intend to split collected data into two data sets so that approximately 70% of the total data can be used for developing/training the prediction models and approximately 30% of the total data can be used for validating/testing the models' actual predictive performance.[43 53] The decision on which statistical model to use depends on the distribution of data and which machine learning model showing the best predictive performance (mean accuracy) closest to 1.00 (100%). Validating the predictive performance of the best model is important[21] and is done by using the model on the validating data set for the purpose of evaluating the actual predictive performance estimated based on the development data set.[54–57] Different metrics will be used to evaluate the predictive performance and as a rule of thumb the accuracy of the model can be ranked from high (0.90 to 1.00) to moderate (0.70 to 0.89) to low (0.50 to 0.69),[58 59] with 0.70 previously used as cut-off for a clinically relevant model.[60]

Qualitative study

We will conduct a qualitative study (objective 5) focusing on the patients' perspectives on the choices and experiences of treatment for knee OA. The qualitative study will ensure a better understanding of current practices, needs and challenges in the daily management of patients with knee OA, seen from the patient's point of view. We expect that patient characteristics in terms of for example, gender, age, BMI, function, OA severity, length of symptoms, received treatments, other comorbidities and connection to the labour market of patients included in the prospective cohort study will vary largely. Therefore, we will strive to include patients with a wide range of these patient characteristics for the qualitative study to better reflect the views of the general population with knee OA. Patients eligible for the qualitative study are selected by a screening of questionnaires from patients included in the TREATright study in both Copenhagen University Hospital Hvidovre and Næstved Hospital. Patients will be recruited from Copenhagen University Hospital Hvidovre and Næstved Hospital and individual interviews will be performed. Approximately 20 patients will be recruited, but the actual number of patients recruited for the qualitative study will depend on information power.[61] The number of patients needed will be evaluated continuously and recruitment will end when sufficient information power is obtained[61] to avoid recruiting too few or too many patients.[62 63] Sufficient information power is influenced by the study aim, sample specificity, use of established theory, quality of dialogue and analysis strategy, and can be considered adequate when new knowledge has been developed with reference to the objectives of the study.[61]

The interviews with patients will be performed as semi-structured interviews, and an interview guide will be prepared prior to the interviews.[64] The interview guide will include themes such as patients' experiences of knee OA, choices and treatment experiences, both in relation to the experience of the effect and when in the course they have received treatment, where and how, as well as experiences with the organisation around their treatment. In addition, the interview guide will be informed by experiences from the survey and descriptive studies. Furthermore, the TREATright patient representatives (see the Patient and public involvement section) will be invited to comment on the guide and to contribute with their perspectives on important and essential questions to be covered. Subsequently, the interview guide will be tested in a couple of pilot interviews on relevant patients after which the interview guide will be adjusted. The interviews will take approximately 1 hour and will take place at Copenhagen University Hospital Hvidovre and Næstved Hospital or, if possible, at the patients' own residence.

All interviews will be recorded and subsequently transcribed for further analysis. A qualitative content analysis involving a systematic text condensation and thematisation will be performed by SMB, in collaboration with AM and SR.[65 66] The analysis will follow the following stages: reading all the material to get an overall impression, identifying units of meaning, representing different aspects of the patients' perspectives and coding for these, condensing and abstracting the meaning within each of the coded groups, and summarising the content of each code group to generalised descriptions reflecting the most important experiences of the patients.[65] Principles for the coding and the choice of themes and categories will be discussed continually in the research team. Furthermore, the analysis will be presented for and discussed with patient representatives.

Cost-effectiveness study

A health economy analysis will be performed to evaluate the cost-effectiveness of treatment pathways that live up to clinical guidelines versus pathways that do not (as outlined under the descriptive studies). The outcome will be based on the EQ-5D-3L, which will be used to derive summary index values based on the Danish value set.[40] Quality-adjusted life years (QALYs) for the cost utility analysis will be calculated using change in EQ-5D-3L summary index value from baseline to 2-year follow-up.

Information on healthcare costs and non-health care costs will be collected from Statistics Denmark, and additionally from the 6-month and 2-year follow-up questionnaires (table 1). Healthcare costs in the follow-up period include hospitalisation, surgery, medication, primary and secondary health provider visits, and home help services provided by the municipalities. Productivity costs estimated from weekly data on long-term sickness absence will be obtained from the National Register on Social Transfer Payments (the DREAM registry) and short-term sick leave (defined as sick leave less than 21 continuous days), will be asked for in the follow-up questionnaires, as well as cost for treatment that is not covered by the public health insurance system. For the purpose of collecting more accurate data and to reduce recall bias, the primary source of data is registry based. Only information on short-term sick leave and cost for treatment that is not covered by the public health insurance system are patient reported.

An incremental cost-effectiveness ratio (ICER) will be calculated by dividing the incremental cost by the QALYs gained. In Denmark, there is no officially accepted and recognised willingness-to-pay threshold. Therefore, the ICER will be compared with threshold applied by NICE (£20 000–£30 000).[67]

Patient and public involvement

To ensure study importance, relevancy and research usefulness from an end-user perspective, patients are involved in the research planning and continuous development of the project.[68 69] The study aims and research questions were discussed with two patients with knee OA. Furthermore, initial pretesting of the questionnaire was performed on 11 patients. Further, six patients with knee OA were appointed as TREAT-right patient representatives and are invited to the study site at Copenhagen University Hospital Hvidovre two to three times a year to be involved in the process of developing the questionnaires and the interview guide and share their views on the research development and results, and contribute with their ideas on how to disseminate the results to people with knee OA.

ETHICS AND DISSEMINATION

We received a waiver (journal number: H-17017295) from the Danish regional ethical committee. Approval from the Danish Data Protection Agency to handle patient-sensitive information from both study sites was acquired (journal number: AHH-2017–072). All data will be handled in line with the General Data Protection Regulation and the Danish Data Protection Act. Data will be collected electronically through a REDCap database that ensures secure data storage. Paper-based questionnaires and other data will be securely stored in a locked cabinet. After data entry into the REDCap database, paper-based questionnaires will be shredded. Patients will be asked for permission to extract data from their medical records. For statistical data processing, only anonymised data will be extracted. After study completion, all data will be anonymised.

To ensure all relevant stakeholders are informed, we will strive for a wide distribution of the results through different news and social media, conferences and workshops. The results will be submitted to international open-access peer-reviewed journals.

DISCUSSION

This study will provide an overview of treatment pathways used for knee OA in a 2-year time period after consulting an orthopaedic surgeon. The strength of this study is that patients are included consecutively from two large centres that represent both rural and urban areas of Denmark, increasing the representativeness of the study population. Although clinical care pathways for knee OA may vary largely between countries, we believe that our results will be of value also to other countries and healthcare systems.

This study will face a number of limitations. Although study invitation is based on referral from the general practitioners due to knee OA, we also include patients with unspecified diagnoses such as knee pain or knee problems if their age is ≥40 years, which introduces a risk of including a small number of patients that do not fit the diagnostic criteria for knee OA.

As part of this study is conducted as a prospective cohort study using self-reported questionnaires including retrospective information of previous treatment, there is a risk of recall bias.[70] Although we risk patients not reporting accurate detail on treatments received, the self-report approach is the only possibility to collect this detailed information. Particularly for the cost-effectiveness analyses, considering that the primary source of data is collected through national registries with a high quality and completeness,[71] we do not believe that the risk of bias is substantial. Only the information on short-term sick leave and cost for treatment that is not covered by the public health insurance system is self-reported.

Furthermore, when collecting possible predictive variables through self-reported questionnaires, we risk missing data. Therefore, for the predictive study, multiple and single imputation will be used.

Lastly, defining treatment pathways for the descriptive and cost-effectiveness studies that adhere to and do not adhere to clinical guidelines is challenging since clinical guideline recommendations are not always consistent.[1 7–9] We have therefore used a pragmatic approach based on drawing similarities between the different clinical guidelines. In addition, the classification is made based on the self-reported treatments that the patients have received limited to a level of detail that the patients can understand and thus answer in a meaningful way.

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UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

Paper II

Usage of guideline-adherent core treatments and characteristics of patients undertaking different treatment pathways for knee osteoarthritis: a prospective cohort study

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Title page

Title

Usage of guideline-adherent core treatments and characteristics of patients undertaking different treatment pathways for knee osteoarthritis: a prospective cohort study

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Running title

Treatments used for knee osteoarthritis

Abstract

Objective

To describe 1) the proportion of patients with knee osteoarthritis (OA) undergoing guideline-adherent core treatments until six months after primary referral to an orthopaedic surgeon, 2) which specific treatment pathways these patients undertake and 3) the characteristics of patients choosing different treatment pathways.

Design

This prospective cohort study consecutively invited patients referred to an orthopaedic surgeon due to knee OA at two Danish hospitals from October 2018 to December 2020. Before and six months after consulting the surgeon, patients answered a questionnaire reporting which treatments they had received for knee OA. The proportion receiving the combination of guideline-adherent treatments (i.e., exercise, education, and dietary weight management if needed) was determined. We evaluated the specific treatment usage before and until six months after the consultation and investigated characteristics of patients undertaking different pathways.

Results

Out of 5,251 eligible patients, 2,574 (49%) had complete data and were included in analyses. 23% received guideline-adherent treatments, 10% had no treatment. Patients underwent 1,143 unique treatment pathways, 62% including treatments not recommended/recommended against. Those who underwent guideline-adherent pathways had similar characteristics to those who did not but tended to be females, retired, had longer-lasting knee problems, have comorbidities, and higher education levels.

Conclusions

Only one in four patients with knee OA received treatment adhering to clinical guidelines before and six months after consulting the surgeon. Patients used many different treatment pathways. There is a need for a structured effort to increase the use of guideline-adherent core treatments.

Trial Identifiers

Registration: NCT03746184, Protocol: PMID: 34233992

Keywords

Knee osteoarthritis; clinical guidelines; patient education; exercise; core treatments; knee arthroplasty

Introduction

International clinical guidelines on the management of knee osteoarthritis (OA) recommend patient education, exercise and dietary weight management, if overweight, as non-surgical first-line core treatments[1–4]. These treatments are considered to be effective, safe, and of low-cost[5]. When non-surgical first-line core treatments do not result in sufficient pain relief and improvement in functional ability, additional non-surgical treatment should be provided, while surgical treatment with knee arthroplasty may be relevant for some patients with end-stage radiographically verified OA[6]. Knee arthroplasty is considered to be an effective but costly treatment for end-stage knee OA[2,7]. However, even in patients with moderate-to-severe knee OA, eligible for knee arthroplasty, the non-surgical core treatment can be effective and can delay or potentially even prevent surgery[8,9]. Therefore, patients should undergo the full range of non-surgical first-line core treatments in primary care, regardless of OA severity, before consulting an orthopaedic surgeon[2,10]. Despite of the evidence and recommendations, studies report that compliance is inadequate and that these treatments are underutilised[11–15]. This evidence-to-practice gap in the treatment of OA might be reduced by optimising and increasing the utilisation of evidence-based non-surgical core treatments for knee OA before referral to surgery[2,7,16,17].

Unravelling current treatment pathways and clarifying which patients undergo certain treatment modalities before and after consulting an orthopaedic surgeon would be an important platform to optimise and adapt treatment pathways to increase utilisation of guideline-adherent treatment. Therefore, we aimed to describe 1) the proportion of patients undergoing the recommended combination of guideline-adherent core treatments, 2) which treatment pathways these patients undertake and 3) the characteristics of patients undertaking different treatment pathways before and until six months after primary referral to an orthopaedic surgeon.

Methods

This prospective cohort study was pre-registered with ClinicalTrials.gov (NCT03746184). Reporting of the study follows The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies[18]. In addition, this study reports on the first six months of follow-up of a longer-term prospective cohort study and pertains to the protocol objectives 1 and 2[19]. The study was approved by the Danish regional ethical committee (Journal no.: H-17017295) and the Danish Data Protection Agency (Journal no.: AHH-2017-072).

Participants

Patients with primary referrals to an orthopaedic surgeon due to knee OA were consecutively invited from October 2018 to December 2020. Patients were included from Copenhagen University Hospital Hvidovre and Næstved Hospital in Denmark (representing both urban and more rural areas) from the outpatient clinics at the departments of orthopaedic surgery. Patients were included based on the general practitioners' diagnosis of knee OA, irrespective of which diagnostic criteria that were used. Patients referred with unspecified diagnoses such as "knee problems" or "knee pain" were invited if their age was ≥ 40 years, as this is the lowest age limit proposed by international recommendations for clinical OA criteria[3]. Exclusion criteria were previous knee replacement or osteotomy around the study knee and inability to read and write Danish.

Procedure

Through a secure e-mail, patients were invited to participate and answer an online questionnaire (supplementary Table S1) approximately two weeks before the consultation with the orthopaedic surgeon. We sent up to two reminders. Patients who had not responded at the day of consultation were asked to fill out the questionnaire on a tablet or a paper-based questionnaire in the outpatient clinic. Questionnaire

responses were collected prior to their consultation with the orthopaedic surgeon to avoid apprehension bias. To avoid introducing delays in the clinic due to study participation, patients were allowed to complete the questionnaire after their consultation if they had responded to questions about prior treatment for knee OA (supplementary Table S1). Patients who had their planned consultation moved to more than one month after responding to the questionnaire were asked to complete the questionnaire again before the new consultation. Six months after inclusion, we sent an online link to a follow-up questionnaire (supplementary Table S1). To the approximately 15% of patients who did not have a secure e-mail, we sent paper-based questionnaires with a pre-paid return envelope. Reminders were sent electronically after one and two weeks and by post after five weeks, and a 2-month response window was accepted. Data were collected electronically through a secure Research Electronic Data Capture (REDCap) database[20].

OA treatment usage

Patients reported which treatments they had received at any point in time for knee OA from a predefined list of 19 treatments (Table 1). After six months, patients reported from the same list which treatments they had received since the consultation. The number of patients undergoing knee arthroplasty during the six-month follow-up period was extracted from the Danish Knee Arthroplasty Registry (DKR) with 97% coverage[21,22]. Patients who had a knee arthroplasty since inclusion were specifically asked for which other treatment modalities they had used up until their surgery and not to include any postoperative rehabilitation. Some of the 19 individual treatments with common features were grouped, which resulted in 13 treatment categories (Table 1): “Information and guidance on living with osteoarthritis” and “participation in GLA:D” (Good Life with osteoArthritis in Denmark, is an evidence-based program that includes education and supervised neuromuscular exercise delivered by certified physiotherapists[23]) were grouped into “patient education”. “Exercise and gymnastics (strength training, fitness, or other type of exercise) under the supervision of a physiotherapist or similar”, “water-based exercise in groups or under supervision”, “exercise on your own (strength training, fitness or other type of exercise)” and “participation

in GLA:D" were grouped into "exercise". "Insoles" and "assessment of the need for walking aid (walking stick, crutches, etc.)" were grouped into "walking aids and devices". Finally, "acupuncture", "massage", and "ultrasound, laser or other type of electrotherapy" were grouped into "passive treatment". Based on national and international clinical guidelines on the management of knee OA[1–4], we used a pragmatic approach to finding similarities between the guidelines to classify treatments as being 1) core treatment (patient education, exercise, dietary weight management, if needed [patients with body mass index (BMI) ≥ 25 or BMI ≥ 30]), 2) supplements to core treatment (pharmacological treatments, intra-articular injections, walking aids and devices, stretching and joint mobilisation), 3) end-stage treatment (knee arthroplasty), and 4) uncertain or not recommended treatment (arthroscopic surgery, passive treatment, alternative and complementary medicine, no treatment) (Table 1).

Table 1.
Pre-defined list of 19 treatments in the questionnaires, grouped into 13 treatment categories and the overall classification of treatments. Patients reported which treatment(s) they had received for knee OA at inclusion and at six-month follow-up

Classification of treatments	Treatment categories	Pre-defined list of treatments in the questionnaire
Guideline-adherent core treatment	1. Patient education	1. Information and guidance on living with osteoarthritis
		2a. Participation in GLA:D*
	2. Exercise	2b. Participation in GLA:D*
		3. Exercise and gymnastics (strength training, fitness, or other type of exercise) under the supervision of a physiotherapist or similar
		4. Water-based exercise in groups or under supervision
		5. Exercise on your own (strength training, fitness or other type of exercise)
	3. Dietary weight management, if needed	6. Diet or dietary guidance
Supplements to core treatment	4. Pharmacological treatment	7. Pharmacological treatment (including painkillers)
	5. Intra-articular injections	8. Injection into the knee joint
	6. Walking aids and devices	9. Insoles
		10. Assessment of the need for walking aid (walking stick, crutches, etc.)
	7. Stretching	11. Stretching
	8. Joint mobilisation	12. Other manual therapy
End-stage treatment	9. Knee arthroplasty	13. Total or unicompartmental knee arthroplasty†
Uncertain or not recommended treatment	10. Arthroscopic surgery	14. Arthroscopic surgery
	11. Passive treatment	15. Acupuncture
		16. Massage
		17. Ultrasound, laser or other type of electrotherapy
	12. Alternative and complementary medicine	18. Alternative medicine (such as healing, Body SDS§, craniosacral therapy or similar)
	13. No treatment	19. No treatment

*GLA:D is an evidence-based program that includes education and supervised neuromuscular exercise delivered by certified physiotherapists[23].
†Information on whether the patients had knee arthroplasty was only collected at six-month follow-up.
§ Body SDS is a concept that includes a wide range of therapies (e.g., massage, yoga, talking therapy) delivered by registered alternative therapists.
GLA:D, Good Life with osteoArthritis in Denmark.
SDS, Self-Development's System.

163

164 *Patient characteristics, pain levels, functional limitations, and general health status*

165 Patients reported demographics, BMI, comorbidities, physical activity, and duration of knee problems
166 (supplementary Table S1). Furthermore, we evaluated the average knee pain during the past week with a
167 Visual Analogue Scale (VAS) (ranging from 0 (no pain) – 100 (worst imaginable pain) [100 mm scale])[24],
168 which is valid and reliable to measure pain in patients with knee OA and knee pain[25,26]. The EQ-5D-3L
169 measures the patients' self-reported health status on mobility, self-care, usual activities, pain/discomfort,
170 and anxiety/depression and is expressed as an index score (ranging from –0.624 (worst) to 1 (best))[27]. The

Oxford Knee Score (OKS) evaluates self-reported knee pain and function ranging from 0 (worst) to 48 (best). It has sufficient validity, reliability, and responsiveness to be used in this group of patients[28,29].

Routinely obtained standing antero-posterior, lateral and skyline view radiographs were evaluated by one of two assessors to evaluate 1) the Kellgren-Lawrence (KL) classification of radiographic OA severity (ranging from 0 (none) to 4 (severe))[30]; 2) the OA wear pattern, evaluated as lateral or medial, bicompartmental and/or severe patellofemoral for patients having a skyline view taken. The inter-rater reliabilities of the radiographic assessments were acceptable (supplement 2).

Data analyses

The sample size estimations indicated that 2,400 patients were needed for a planned prediction study [19]. Data were analysed descriptively. The proportion of patients undergoing the recommended combination of guideline-adherent core treatments was calculated. As the definition of when dietary weight management would be needed varies among the clinical guidelines, we performed analyses using both BMI ≥ 25 and ≥ 30 kg/m² as criteria[1–4]. In addition, analyses were performed where the criterion of dietary weight management was excluded to explore the influence of that criterion. Furthermore, a sensitivity analysis was performed where unsupervised and water-based exercise were not considered as core exercise treatments. The number of treatment pathways to present depended on a data-driven approach that best described the distribution of data. Due to the SARS-CoV-2 pandemic the healthcare facilities in Denmark were not accessible for several periods from March 14, 2020. Therefore, it seemed relevant to explore if there were differences in the treatments received in patients who responded to the six-month follow-up questionnaire before March 14, 2020, compared to patients who responded after. Whether continuous data should be presented as means or medians was determined by the normal distribution assessed with density and quantile-quantile plots. We used the statistical software program R for data management and analyses[31].

Patient involvement

To ensure study importance and relevancy from an end-user perspective, patients were involved in the planning and continuous development of the project[32,33]. We established research priorities in OA based on a survey in almost 500 people with OA and "treatment" was one of the identified important research topics[33]. In addition, the aims, and research questions of the study, were discussed with two patients with knee OA. A total of 11 patients contributed with initial pre-testing of the questionnaire. Furthermore, six patients with knee OA were appointed as patient representatives and were invited to three meetings to help develop the questionnaires and share their views on the study progress.

Results

Out of the 5,251 eligible patients, 3,507 (66%) were included in the cohort. At six-month follow-up, 2,574 (49%) had answered the questionnaire within the prescribed period, had complete data, and were included in the analyses (Figure 1).

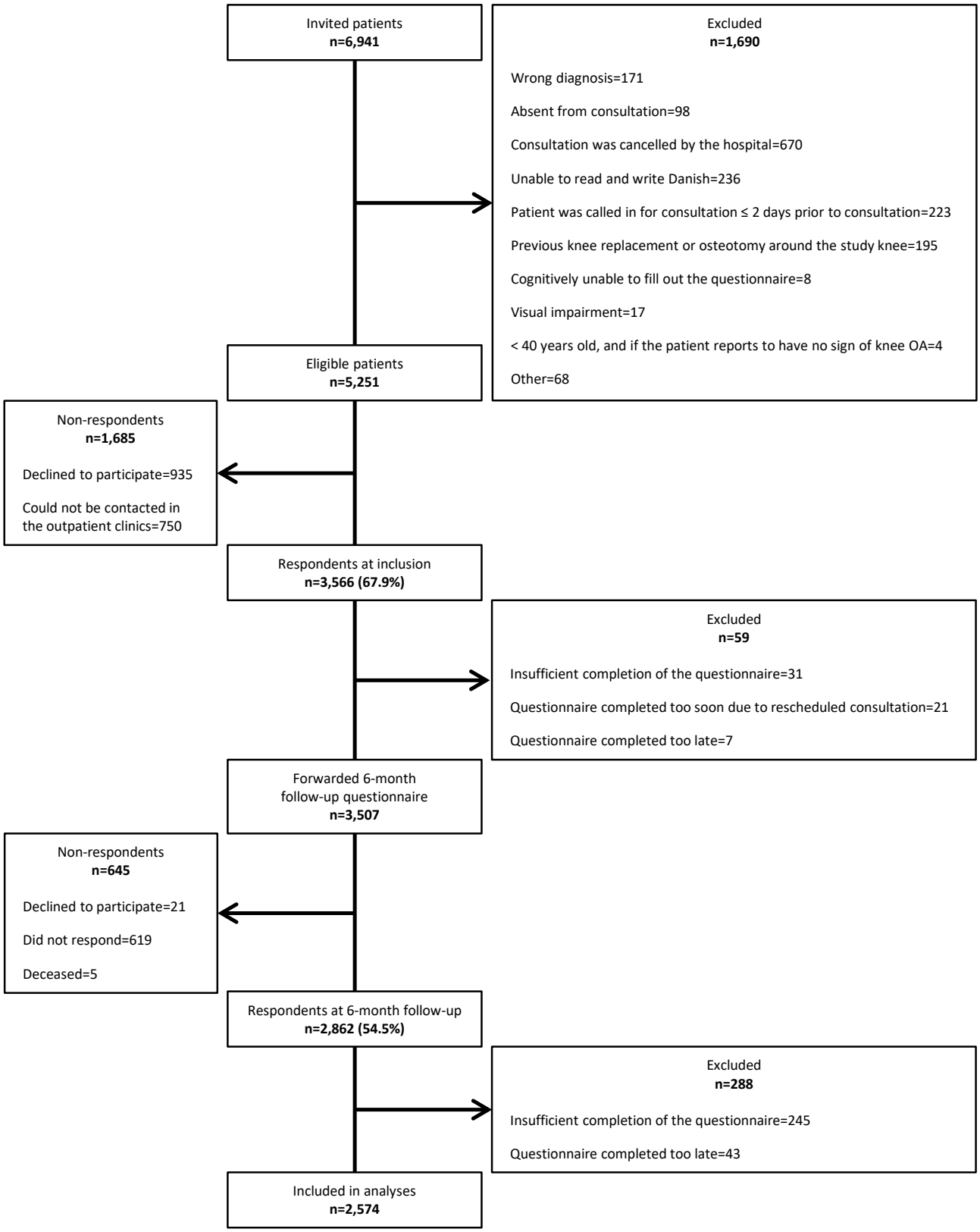

Figure 1. Flowchart for patient inclusion and exclusion, non-respondents, reasons for exclusion and dropout and the number of respondents included in the analyses. Non-respondents were either patients who did not wish to participate in the study or were deceased in the follow-up time. In addition, non-respondents were patients who did not respond to our requests to answer the questionnaires and whom we could not contact in the outpatient clinics. Numbers in parentheses show the response rate for respondents at inclusion and at six-month follow-up, respectively.

Characteristics of patients who were and were not included in the final analyses

The 2,574 respondents who had complete data and were included in the analyses had a mean (SD) age of 66.1 (10.1) years, a mean (SD) BMI of 29.5 (5.7) kg/m² and 58% were female (Table 2). Compared to the information available for the 2,677 eligible patients who did not participate in the study, there were no substantial age or gender differences (supplementary Table S2). In comparison to participants with complete data, participants who did not respond to the six-month questionnaire had overall similar characteristics but were slightly younger (mean (SD) age was 62.8 (11.4) vs. 66.1 (10.1)), and a smaller proportion was retired (44% vs. 59%) (supplementary Table S2).

Table 2.
Patient characteristics for all included patients, patients receiving the recommended combination of guideline-adherent core treatments and patients who did not. Values are in percentages (%) with absolute numbers in parentheses unless other is stated

	Included patients (n = 2,574)	**Patients receiving the recommended combination of guideline-adherent core treatments (n = 899)**	**Patients not receiving the recommended combination of guideline-adherent core treatments (n = 1,675)**
Sex			
Female	58% (1,484)	65% (581)	54% (903)
Age, mean (SD)	66.1 (10.1)	67.4 (9.2)	65.4 (10.5)
BMI, mean (SD)	29.5 (5.7)	29.5 (5.7)	29.5 (5.7)
Residential status			
Alone	28% (729)	30% (273)	27% (456)
Cohabiting	69% (1,766)	68% (607)	69% (1.159)
Missing	3% (79)	2% (19)	4% (60)
Level of education			
Elementary school	16% (407)	13% (120)	17% (287)
High school	2% (49)	3% (23)	2% (26)
Vocational education	31% (794)	27% (244)	33% (550)
Short-cycle higher education	13% (345)	14% (124)	13% (221)
Medium-cycle higher education	28% (722)	33% (293)	26% (429)
Long-cycle higher education or more	7% (172)	8% (76)	6% (96)
Missing	3% (85)	2% (19)	4% (66)
Occupation			
Retired, early retiree or on early retirement	59% (1,518)	65% (587)	56% (931)
Sick leave part time or full time	6% (146)	5% (45)	6% (101)
Unemployed	3% (67)	3% (25)	3% (42)
On the labour market or student part time or full time	31% (808)	27% (245)	34% (563)
Missing	3% (82)	2% (18)	4% (64)
Smoking			
No, never	44% (1,132)	46% (417)	43% (715)
No, but I used to	42% (1,086)	44% (392)	41% (694)
Yes	11% (275)	8% (71)	12% (204)

Missing	3% (81)	2% (19)	4% (62)
Comorbidities			
Proportion of patients with comorbidities	76% (1,949)	80% (716)	74% (1,233)
Self-reported physical activity per week			
None	5% (116)	4% (35)	5% (81)
30 min	10% (265)	10% (86)	11% (179)
1 hour	10% (262)	9% (85)	11% (177)
2 hours	16% (399)	16% (145)	15% (254)
More than 2 hours	57% (1,460)	59% (533)	55% (927)
Missing	3% (72)	2% (15)	2% (57)
VAS knee pain, mean (SD)	63.7 (22.3)	65.1 (20.3)	62.9 (23.3)
Duration of knee problems			
0–6 months	15% (397)	10% (92)	18% (305)
7-12 months	13% (338)	12% (112)	13% (226)
1–2 years	17% (434)	16% (140)	18% (294)
3-5 years	20% (503)	22% (194)	18% (309)
6-10 years	14% (355)	15% (139)	13% (216)
> 10 years	20% (517)	24% (215)	18% (302)
Missing	1% (30)	1% (7)	1% (23)
EQ-5D-3L, median (IQR)	0.723 (0.496-0.771)	0.708 (0.559-0.723)	0.723 (0.496-0.771)
OKS, mean (SD)	23.4 (8.0)	22.7 (7.5)	23.8 (8.3)
Radiographical knee OA severity (KL grade)	*	§	¶
0	0 (0)	0 (0)	0 (0)
1	0 (3)	0 (2)	0 (1)
2	8 (260)	7 (75)	9 (185)
3	48 (1,527)	47 (540)	49 (987)
4	41 (1,293)	44 (506)	39 (787)
Missing	2 (67)	2 (28)	2 (45)
Severe patellofemoral OA	†	‡	#
Yes	13 (50)	2 (23)	1 (27)
No	83 (315)	12 (134)	9 (181)
Not assessable	4 (15)	1 (8)	0 (7)
Tibiofemoral OA wear pattern	*	§	¶
Medial	86 (2,700)	85 (984)	86 (1,716)
Lateral	11 (343)	11 (131)	11 (212)
Bicompartmental	1 (40)	1 (8)	2 (32)
Missing	2 (67)	2 (28)	2 (45)

BMI, body mass index (kg/m²); SD, standard deviation; VAS, Visual Analogue Scale (millimetres, 0-100); EQ-5D-3L, 3-level version of the European Quality of Life – 5 Dimensions; OKS, Oxford Knee Score; OA, osteoarthritis; IQR, interquartile range; KL grade, Kellgren and Lawrence classification system.

* Of the 2,574 included patients, 576 had bilateral problems making the total number of examined knees 3,150.

† Of the 3,150 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 380 knees.

§ Of the 899 patients receiving the recommended combination of guideline-adherent core treatments, 246 had bilateral problems making the total number of examined knees 1,145.

‡ Of the 1,145 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 165 knees.

¶ Of the 1,675 patients not receiving the recommended combination of guideline-adherent core treatments, 330 had bilateral problems making the total number of examined knees 2,005.

Of the 2,005 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 215 knees.

Patients undergoing guideline-adherent core treatments

Of the three core treatments, exercise was the most utilised and patients who had reported education or dietary weight management had most often also reported exercise (Figure 2). The proportion of patients receiving the recommended combination of guideline-adherent core treatments before the consultation with an orthopaedic surgeon (with BMI ≥ 25 as the criterion for whether dietary weight management was needed) was 6% (146 patients). When increasing the criterion for whether dietary weight management was needed to BMI ≥ 30, the proportion was 14% (362 patients). At six months after the consultation, the proportion increased to 9% (242 patients) using BMI ≥ 25 as the criterion and 23% (580 patients) using BMI ≥ 30. If excluding the criterion about dietary weight management, 21% (537 patients) reported to have received both patient education and exercise before the consultation. This proportion increased to 35% (899 patients) six months after the consultation. When additionally restricting the exercise criterion to supervised land-based exercise, the proportion was 20% (507 patients) before, increasing to 33% (861 patients) after six months.

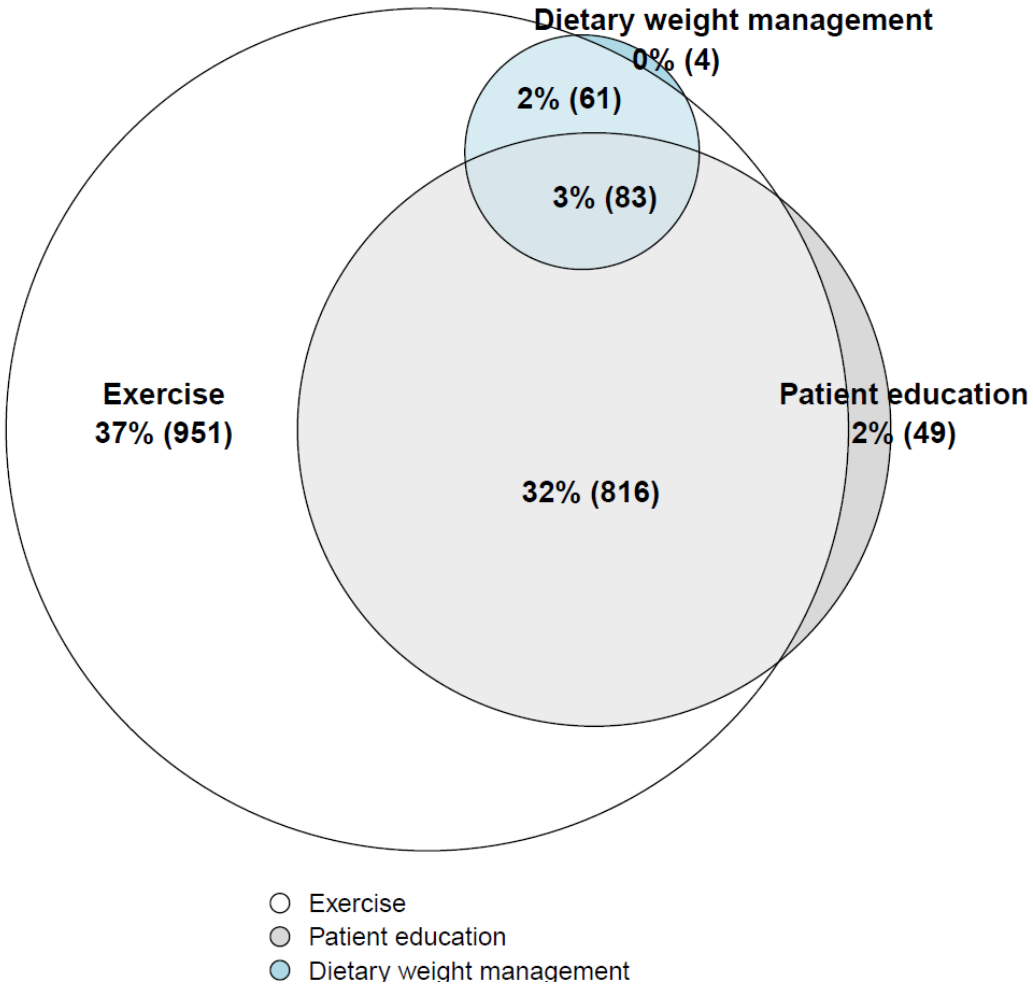

Figure 2. Number of patients receiving the guideline-adherent core treatments and combinations until six months after the consultation. Combinations of core treatments are illustrated as one or more circles overlapping another. Percentages represents the proportions out of all 2,574 included patients. The number of patients reporting to have received dietary weight management is displayed for all, disregarding their BMI. It should be noticed that dietary weight management was only relevant for 2,110 patients with BMI ≥ 25 and for 1,084 patients with BMI ≥ 30 (Table 3).

Exercise, pharmacological treatments, and patient education were the single most utilised treatments both before and in the following six months after the consultation. The proportion of patients reporting to have received any type of exercise was 54% (1,380) before the consultation, increasing to 74% (1,911) until six months after. Supervised land-based exercise was reported by 41% (1,054 patients) before the consultation, increasing to 62% (1,601) until six months after. Pharmacological treatments were received by 44% (1,144) of the patients before the consultation, increasing to 52% (1,329) until six months after, and patient education by 23% (580) before the consultation, increasing to 37% (948) until six months after

252 (Table 3). The proportion of patients who had not received any treatment for knee OA decreased from 21%

253 (548) before the consultation to 10% (245) six months after.

Table 3.
Percentage and number of patients reporting to have received each separate treatment before consulting an orthopaedic surgeon, between consultation and six-month follow-up and until six months after the consultation for patients not undergoing knee arthroplasty and until surgery for patients undergoing knee arthroplasty

		Patients reporting to have received each separate treatment (n = 2,574)		
Classification of treatments	**Treatment categories**	**Before consulting an orthopaedic surgeon, % (n)**	**Between consultation and six-month follow-up, % (n)**	**In the entire disease course until six months after consultation, % (n)**
Guideline-adherent core treatment	1. Patient education	23 (580)	23 (604)	37 (948)
	2. Exercise	54 (1,380)	53 (1,361)	74 (1,911)
	3a. Dietary weight management, if needed (BMI ≥ 25)	5 (97)*	3 (57)*	7 (145)*
	3b. Dietary weight management, if needed (BMI ≥ 30)	7 (72)†	4 (48)†	10 (111)†
Supplements to core treatment	4. Pharmacological treatment	44 (1,144)	23 (581)	52 (1,329)
	5. Intra-articular injections	13 (331)	7 (188)	16 (451)
	6. Walking aids and devices	11 (284)	7 (184)	15 (397)
	7. Stretching	6 (146)	4 (100)	9 (230)
	8. Joint mobilisation	2 (61)	2 (40)	4 (94)
End-stage treatment	9. Knee arthroplasty	0 (0)	31 (797)	31 (797)
Uncertain or not recommended treatment	10. Arthroscopic surgery	17 (427)	5 (119)	20 (508)
	11. Passive treatment	18 (456)	10 (244)	22 (574)
	12. Alternative and complementary medicine	4 (89)	2 (48)	5 (116)
	13. No treatment	21 (548)	33 (856)	10 (245)

BMI, body mass index (kg/m²)
*Out of 2,110 patients with BMI ≥ 25
†Out of 1,084 patients with BMI ≥ 30

254

255 In general, patients receiving the recommended combination of core treatments had largely similar

256 characteristics to those who did not (Table 2). However, patients receiving core treatments tended to be

257 females (65% vs. 54%), with a higher level of education, a longer duration of knee problems, more often

258 retired, and have comorbidities (Table 2).

259 The proportion of patients who received the recommended combination of guideline-adherent core

260 treatments were similar for patients completing the six-month follow-up questionnaire before and after

261 the first national lockdown due to the SARS-CoV-2 pandemic (supplementary Table S3). The proportion of

patients who had knee arthroplasty was larger for patients responding before the lockdown (supplementary Table S4).

Treatment prior to knee arthroplasty

During the six months after consulting an orthopaedic surgeon, 31% (797 out of 2,574) patients had a knee arthroplasty. Out of these, 9% (75) had received the recommended combination of core treatments before surgery, with BMI ≥ 25 as the criterion for when dietary weight management was needed. With BMI ≥ 30 as the criterion, the proportion was 24% (190 patients). If excluding the criterion about dietary weight management, 37% (297) had received the core treatments (patient education and exercise) before surgery. There were 7% (59) of the patients who did not receive any treatment prior to surgery. For those undergoing knee arthroplasty, any type of exercise, pharmacological treatments, and patient education were still the most utilised treatments until surgery, with the proportion of patients reporting to have received these treatments being 77% (611), 61% (484), and 40% (316), respectively (Table 4).

Table 4.
Percentage and number of patients reporting to have received each separate treatment until surgery for patients undergoing knee arthroplasty and until six months after the consultation for patients not undergoing knee arthroplasty

		Patients reporting to have received each separate treatment (n = 2,574)	
Classification of treatments	**Treatment categories**	**Patients undergoing knee arthroplasty (n = 797), % (n)**	**Patients not undergoing knee arthroplasty (n = 1,777), % (n)**
Guideline-adherent core treatment	1. Patient education	40 (316)	36 (632)
	2. Exercise	77 (611)	73 (1,300)
	3a. Dietary weight management, if needed (BMI ≥ 25)	7 (47)*	7 (98)§
	3b. Dietary weight management, if needed (BMI ≥ 30)	10 (34)†	10 (77)‡
Supplements to core treatment	4. Pharmacological treatment	61 (484)	48 (845)
	5. Intra-articular injections	17 (132)	18 (319)
	6. Walking aids and devices	18 (144)	14 (253)
	7. Stretching	10 (78)	9 (152)
	8. Joint mobilisation	3 (24)	4 (70)
End-stage treatment	9. Knee arthroplasty	100 (797)	0 (0)
Uncertain or not recommended treatment	10. Arthroscopic surgery	21 (170)	19 (338)
	11. Passive treatment	20 (162)	23 (412)
	12. Alternative and complementary medicine	4 (30)	5 (86)
	13. No treatment	7 (59)	10 (186)

BMI, body mass index (kg/m²)
*Out of 673 patients with BMI ≥ 25
§Out of 1,437 patients with BMI ≥ 25
†Out of 349 patients with BMI ≥ 30
‡Out of 735 patients with BMI ≥ 30

Among the 297 patients receiving the recommended core treatment combination before surgery, the proportion of females was larger (63% women) compared to the 500 patients who did not (53% women) and the 59 patients who did not receive any treatment (36% women) (supplementary Table S5). Other patient characteristics were largely comparable, but those not receiving any treatment tended to, have lower education levels, slightly better OKS, shorter duration of knee problems and fewer were retired (supplementary Table S5).

Usage of combinations of different treatments

From all possible combinations of the 13 treatment categories, the five most common treatment pathways for knee OA were: 1) No treatment initially followed by no treatment after consultation: 7% (186) of the patients, 2) no treatment initially followed by exercise after consultation: 3% (88) of the patients, 3) pharmacological treatment initially, followed by no treatment after consultation: 3% (65) of the patients, 4) exercise initially followed by no treatment after consultation: 2% (60) of the patients, 5) no treatment initially followed by no other treatment but knee arthroplasty after consultation: 2% (59) of the patients. The total number of unique pathways was 1,143, and 871 pathways were pursued by only one patient. Treatments that were not recommended or recommended against were included in 62% (707) of the pathways. Exercise was included in most pathways (87% (998)), 7% (78) of the 1,143 treatment pathways comprised the recommended combination of core treatments, and 10% (111) of the treatment pathways did not contain any core treatment (Figure 3).

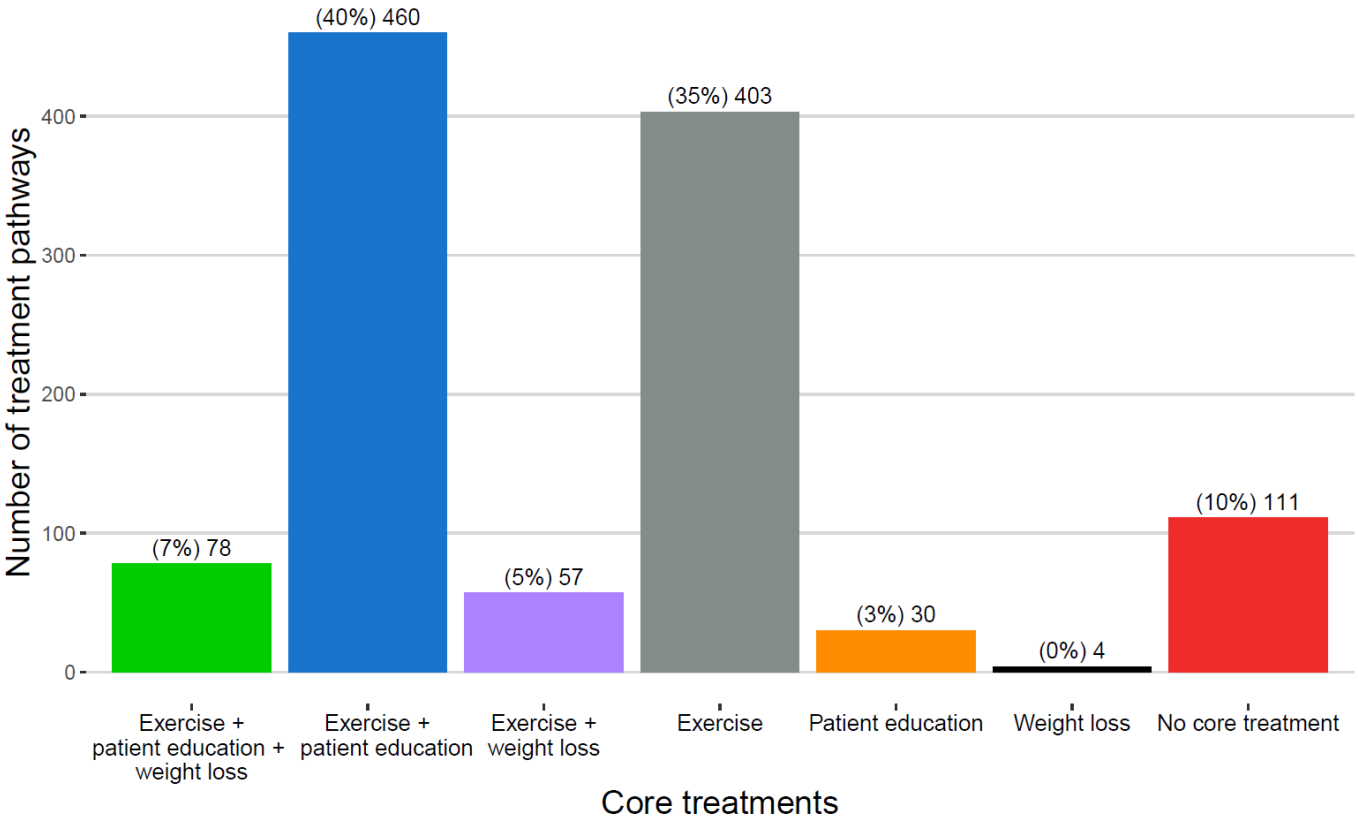

Figure 3. The number of treatment pathways comprising one or more core treatments.

Discussion

We prospectively followed a cohort of 2,574 patients with knee OA in six months from their first consultation with an orthopaedic surgeon. We found that only 35% of these patients had received the recommended combination of guideline-adherent core treatments exercise and patient education, while that proportion decreased to 23% when also considering if dietary guidance was received if needed. Patients who had received core treatments had largely similar characteristics to those who did not undertake core treatments but tended to be females, with a longer duration of knee problems, a higher education level, more often retired, and have comorbidities. Additionally, describing the most common combinations of individual treatments was challenged by the finding that the 2,574 included patients comprised 1,143 unique treatment pathways, suggesting no consistent and systematic use of specific treatment pathways. Only 7% (78) of the pathways included the recommended combination of guideline-adherent core treatments and 62% (707) included treatments that were not recommended or recommended against.

The inferior use of guideline-adherent core treatments for knee OA has been repeatedly shown in studies from several countries. Our results confirm the findings from two systematic reviews showing that, overall, non-drug and non-operative OA treatment, including education and self-management or referral or recommendation to exercise, was recommended to fewer than 40% of the patients[12,15]. The proportion of patients reporting to have used any type of exercise was higher in our study, but we found a similar proportion reporting land-based supervised exercise before consultation (41%), and that proportion increased until the six-month follow-up. The proportion of patients undertaking the recommended combination of core treatments was not impacted by the exercise criterion, indicating that most patients receiving supervised land-based exercise also received patient education and dietary weight management, if needed. Despite differences in study design and healthcare settings, all previous studies conclude that recommended treatments for knee OA are underutilised[11,12,14,15,34,35]. Another finding from our study was

that only 23% of the patients underwent the recommended combination of core treatments until six months after consulting the orthopaedic surgeon. In Canada, guideline-adherence was found in 19% of patients being recommended non-surgical treatment by an orthopaedic surgeon[36]. Additionally, we found that in those proceeding to knee arthroplasty, the proportion was 24%, which was considerably lower than in Canada, where 60% were found to have used recommended core treatments before surgery[34]. Differences in core treatment definitions can possibly explain some of the discrepancy since the proportion reporting to have undergone exercise was similar across studies, but in the Canadian study, almost 70% had reported to have tried dietary weight management. Our dietary weight management criterion was stricter as we had asked patients whether they had received a diet or dietary weight management with a dietician. As the costs for dietary treatment and most often exercise are not covered by the national health security system in Denmark, there may have been a financial barrier for undertaking dietary weight management and exercise[37,38]. Altogether, patients with knee OA undertake a large variety of treatments, often not in accordance with clinical guidelines. Since knee OA develops gradually and symptoms may fluctuate over many years, patients might seek different treatments themselves without involving the public healthcare system. However, our study included patients referred to evaluate the need for surgery, meaning that many patients were offered other treatments than the guideline-adherent core treatments, also as first-line treatments[39].

Patients undertaking core treatments had largely similar characteristics to those who did not. Our findings were similar to a smaller cohort of 195 patients from the Netherlands, where no differences in patient characteristics were found for those complying with guidelines and not[35]. However, a Canadian study reported that being female and having a higher level of education was associated with using recommended treatments, which were similar to the tendencies described in our study, but in contrast to our findings, patients undertaking the recommended treatments were younger[34]. The mean age differences between core treatment users and non-users were only two and four years in our and the Canadian study,

respectively, suggesting that the impact of age is negligible. A potential reason why men use less core treatments is that they are more likely to undergo knee arthroplasty earlier in their course of disease[40].

There may be several barriers influencing which treatments the patients undergo. A barrier for healthcare providers to refer to physiotherapy could be the belief that patients will be offered non-evidence treatments and the misbelief that the effect of therapeutic exercise is questionable[41–44]. Healthcare providers' mistrust in the management of dietary guidance was also pointed at as a possible barrier for receiving recommended treatment for knee OA[41,44]. Additional barriers may be the healthcare provider's insufficient knowledge of available recommended treatment or if knee OA is simply perceived as a normal procedure of aging[41,43,44]. Patients have also reported several potential barriers for use of recommended treatment, such as having too much pain or too severe radiographical OA[42]. If individuals in the patients' environment have had positive experiences with surgery, or if the general practitioner has a preference for surgical treatment, it could also be barriers for receiving recommended treatment[42]. Understanding what influences which treatments the patients undergo for knee OA is complex and further research is needed in this area.

Strengths and limitations

Strengths of this study include the large number of participants and the prospective design with a follow-up questionnaire to obtain information on treatments received both before and after the consultation, which also makes it possible to explore changes in treatment pathways after seeing the surgeon. Patients were recruited from two high-volume orthopaedic departments in different parts of Denmark, which increases the generalisability of our findings. When consecutively inviting all patients referred by the general practitioner to an orthopaedic surgeon due to diagnosed knee OA or symptoms associated with knee OA it reflects the actual clinical practice, hence making the study results more representative and clinically relevant. Despite the effort to consecutively include the eligible patients, we were only able to include half

of the eligible patients in the final analyses, which might have led to a risk of selection bias[45,46]. Patients who were not included in the final analyses were, on average, younger and a smaller proportion were retired. Especially patients who were retired tended to receive the core treatments, meaning that the proportion of patients who received the core treatments could potentially have been even smaller if the response rate had been higher. In addition, a relatively large proportion were excluded because they were unable to read and write Danish, limiting the generalisability of our results. Furthermore, recall bias may potentially impact our findings since data were mainly self-reported[12,47]. Recall bias may especially have impacted on reported treatment until the first consultation, since we asked for any treatment used during the whole knee OA disease course[47]. However, no registries in Denmark contain information about all relevant treatment usage for knee OA. The results of this study may be more relevant for patients with a more severe degree of knee OA because the study cohort is based on patients referred to an orthopaedic surgeon for assessment for knee replacement surgery, and more than 90% had KL grade ≥ 3. However, our cohort was also comprised of patients with mild radiographic OA (KL grade 1 or 2) in 8%, and 22% had an OKS ≥ 30, corresponding to the threshold indicating satisfactory symptom-levels after surgery, suggesting that the study results are representative for the target population with both a mild/moderate and more severe degree of knee OA[48].

Perspectives

Improving guideline adherence is important to optimise the treatment of knee OA[49]. Our findings provide a foundation for advancing guideline adherence by describing current treatment usage and clarifying treatment pathways. Information provided by this study about patient characteristics and other possible predictive variables can be used in future studies investigating determinants of outcomes of available treatments. Such initiatives can be useful to target treatment to the individual patient and aid with shared decision making.

Conclusion

Only one in four patients with knee OA underwent treatment pathways in accordance with clinical guidelines until six months after consulting an orthopaedic surgeon or until surgery for those undergoing knee arthroplasty. All types of exercise were reported by almost three in four patients, while supervised land-based exercise was reported by less than two in three. Patient education was reported by slightly more than one in three patients, and dietary weight management was only reported by one in ten of those for whom it was relevant. Our results highlight that the recommended core treatments are severely underutilised before surgery. In addition, the proportion of patients receiving no treatments or treatment that were not recommended or recommended against, and the large number of different treatment pathways, suggests a need for a more structured effort to increase the use of guideline-adherent core treatments.

Author contributions

Study conception and design: SMB, STS, TB, AM, HMS, AT and LHI.

Interpretation of data, critical revision for important intellectual content and final approval of the article: SMB, STS, LKH, TB, AM, HMS, AT and LHI.

Acquisition of data: SMB, LKH and LHI.

Analysis of data and drafting of the manuscript: SMB and LHI.

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Conflict of interest

STS is associate editor of JOSPT, has received personal fees from Munksgaard, TrustMe-Ed and Nestlé Health Science, outside the submitted work, and is co-founder of GLA:D®, a not-for profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

Role of the funding source

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Supplementary

Supplement 1

Collected outcomes from the questionnaires at inclusion and at six-month follow-up

Table S1.
Collected outcomes from the questionnaires at inclusion and at six-month follow-up

Collected outcomes	Inclusion	Six-month follow-up
Height (cm)	X	
Weight (kg)	X	
PASS (yes/no)		X
Self-reported TF (yes/no)		X
Degree and importance of change in knee-pain and function (ranging from "better, an important improvement" to "worse, an important deterioration")		X
OKS (12 items)	X	X
Residential status (alone/cohabiting)	X	
Level of education (elementary school/high school/vocational education/short-cycle higher education/medium-cycle higher education/long-cycle higher education or more)	X	
Occupation (retired, early retiree or on early retirement/sick leave part time or full time/unemployed/on the labour market or student part time or full time)	X	
Smoking (Yes/No, but I used to/No never. If Yes: average number of daily cigarettes is recorded)	X	
Comorbidities (list of 15 diseases)	X	
Which knee to be examined by the orthopaedic surgeon (right/left/both)	X	
Duration of knee problems (ranging from 0 months to more than 10 years)	X	
Degree of knee pain (VAS 0 (no pain) – 100 (worst imaginable pain [100 mm scale])	X	X
Localisation of pain/discomfort elsewhere in the body (marked on a full body pain mannequin)	X	X
Expectations to the following consultation (surgery/injection into the knee joint/training sessions or other treatment/weight loss (if overweight)/treatment for pain/no treatment/other)	X	
Type of health care provider who has examined/treated the knee OA (general practitioner/orthopaedic surgeon/rheumatologist/physiotherapist/occupational therapist/dietitian/osteopath/chiropractor/personal trainer in the gym/alternative therapist (such as massage therapist, healer, Body SDS therapist, reflexologist, acupuncturist or similar)/other/no examination or treatment)	X	X
Number of consultations/treatments for knee OA for each health care provider		X
Previous treatment for knee OA (Table 1)	X	X
OA-QI (15 items)	X	X

Previous knee injury that was examined by a health care provider (none/right knee/left knee/both knees)	X		
Previous joint surgery in lower limb (hip [right/left], knee [right/left], ankle [right/left])	X		
Type of previous joint surgery in lower limb (arthroscopic/open surgery/total or partial replacement)	X		
ASES (11 items)	X		
Self-reported physical activity level (none/30 min./1 hour/2 hours/more than 2 hours)	X		X
Self-reported health condition (EQ-5D-3L) (5 items and EQ-VAS)	X		X
Health care costs (health care provider visits not covered by public health care system)			X
Short term sick leave (<21 days)			X

PASS, Patient Acceptable Symptom State; TF, Treatment Failure; OKS, Oxford Knee Score; VAS, Visual Analogue Scale; SDS, Self-Development's System; OA, osteoarthritis, OA-QI, Osteoarthritis Quality Indicator Questionnaire; ASES, short version of the Arthritis Self-Efficacy Scale; EQ-5D-3L, 3-level version of the European Quality of Life – 5 Dimensions.

Supplement 2

Inter-rater reliability of radiographic assessments

Radiographic analyses were performed by SMB and LKH supervised by LHI (>5 years radiographic review experience), HMS (orthopaedic surgeon) and AT (orthopaedic surgeon). First, we agreed on consensus on how to assess the radiographs, and subsequently the reliabilities of the radiographic assessments in this study were evaluated between the assessments of SMB and LKH compared to those of HMS. The inter-rater reliability of the wear pattern was evaluated using Light's kappa[S1] showing substantial reliability[S2] of 0.727 and a percentage agreement of 88% and the assessment of severe patellofemoral wear showed an almost perfect reliability[S2] of 0.846 and a percentage agreement of 93%. Assessment of the Kellgren-Lawrence grade showed a moderate reliability[S3] of 0.566 (95% CI [0.421, 0.695]) using a two-way consistency intraclass correlation coefficient (ICC)[S4].

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Supplement 3

Patient characteristics for patients not included in the final analyses

Table S2.
Patient characteristics for included patients, patients who completed the questionnaire at inclusion but did not complete the questionnaire at six-month follow-up, and all eligible patients not included in the final analyses. Values are in percentages (%) with absolute numbers in parentheses unless other is stated

	Patients with complete data included in analyses (n = 2,574)	**Patients not completing the questionnaire at six-month follow-up (n = 933)**	**Eligible patients not included in the final analyses (n =2,677)**
Sex			
Female	58% (1,484)	59% (547)	57% (1,523)
Age, mean (SD)	66.1 (10.1)	62.8 (11.4)	64.4 (12.2)
BMI, mean (SD)	29.5 (5.7)	30.7 (6.2)	
Residential status			
Alone	28% (729)	28% (265)	
Cohabiting	69% (1,766)	63% (588)	
Missing	3% (79)	9% (80)	
Level of education			
Elementary school	16% (407)	16% (153)	
High school	2% (49)	2% (21)	
Vocational education	31% (794)	29% (270)	
Short-cycle higher education	13% (345)	12% (115)	
Medium-cycle higher education	28% (722)	25% (231)	
Long-cycle higher education or more	7% (172)	7% (63)	
Missing	3% (85)	9% (80)	
Occupation			
Retired, early retiree or on early retirement	59% (1,518)	44% (412)	
Sick leave part time or full time	6% (146)	8% (72)	
Unemployed	3% (67)	4% (39)	
On the labour market or student part time or full time	31% (808)	37% (342)	
Missing	3% (82)	9% (81)	
Smoking			
No, never	44% (1,132)	39% (368)	
No, but I used to	42% (1,086)	37% (349)	
Yes	11% (275)	15% (138)	
Missing	3% (81)	8% (78)	
Comorbidities			
Proportion of patients with comorbidities	76% (1,949)	71% (665)	
Self-reported physical activity per week			
None	5% (116)	6% (57)	
30 min	10% (265)	11% (102)	
1 hour	10% (262)	12% (108)	
2 hours	16% (399)	13% (123)	
More than 2 hours	57% (1,460)	51% (472)	
Missing	3% (72)	8% (71)	

VAS knee pain, mean (SD)	63.6 (22.3)	62.9 (23.0)
Duration of knee problems		
0–6 months	15% (397)	17% (157)
7-12 months	13% (338)	13% (123)
1–2 years	17% (434)	16% (150)
3-5 years	20% (503)	18% (169)
6-10 years	14% (355)	11% (103)
> 10 years	20% (517)	22% (201)
Missing	1% (30)	3% (30)
EQ-5D-3L, median (IQR)	0.723 (0.496-0.771)	0.660 (0.356-0.723)
OKS, mean (SD)	23.4 (8.0)	23.1 (8.5)
Radiographical knee OA severity (KL grade)	*	
0	0 (0)	
1	0 (3)	
2	8 (260)	
3	48 (1,527)	
4	41 (1,293)	
Missing	2 (67)	
Severe patellofemoral OA	†	
Yes	2 (50)	
No	10 (315)	
Not assessable	0 (15)	
Tibiofemoral OA wear pattern	*	
Medial	86 (2,700)	
Lateral	11 (343)	
Bicompartmental	1 (40)	
Missing	2 (67)	

BMI, body mass index (kg/m²); SD, standard deviation; VAS, Visual Analogue Scale (millimetres, 0-100); EQ-5D-3L, 3-level version of the European Quality of Life – 5 Dimensions; OKS, Oxford Knee Score; OA, osteoarthritis; IQR, interquartile range; KL grade, Kellgren and Lawrence classification system.

* Of the 2,574 included patients, 576 had bilateral problems making the total number of examined knees 3,150.

† Of the 3,150 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 380 knees.

Supplement 4

Treatments received in patients completing the six-month follow-up questionnaire before and after lockdown of the health care facilities due to the SARS-CoV-2 pandemic

There were 1,140 patients who responded to the six-month follow-up questionnaire before the first national lockdown due to the SARS-CoV-2 pandemic and 1,434 patients responded after. The proportion of patients who received the recommended combination of guideline-adherent core treatments differed by only up to one percentage point before and after lockdown (supplementary Table S3). The treatments that

Table S3.
Percentage and number of patients (with BMI ≥ 25 and BMI ≥ 30, respectively, as the criteria for when dietary weight management is needed, and when excluding the criterion about dietary weight management) receiving the recommended combination of guideline-adherent core treatments for patients completing the six-month follow-up questionnaire before and after lockdown of the health care facilities due to the SARS-CoV-2 pandemic

	Patients receiving the recommended combination of guideline-adherent core treatments (n = 2,574)	
Criterion for when dietary weight management is needed	**Patients completing the six-month follow-up questionnaire before national lockdown (n = 1,140), % (n)**	**Patients completing the six-month follow-up questionnaire after national lockdown (n = 1,434), % (n)**
Dietary weight management, if needed (BMI ≥ 25)	10 (119)	9 (123)
Dietary weight management, if needed (BMI ≥ 30)	22 (246)	23 (334)
When excluding the criterion about dietary weight management	35 (398)	35 (501)

BMI, body mass index (kg/m²)

patients received before and after the national lockdown were similar, with the exception that the proportion of patients who reported to have received dietary weight management was slightly larger before the lockdown compared to after (8% vs. 6% [for patients with BMI ≥25] and 12% vs. 9% [for patients with BMI ≥30]) (supplementary Table S4). Additionally, the proportion of patients who had knee arthroplasty was larger before the lockdown (37% vs. 26%) (supplementary Table S4).

Table S4.
Percentage and number of patients reporting to have received each separate treatment until surgery for patients undergoing knee arthroplasty and until six months after the consultation, for patients completing the six-month follow-up questionnaire before and after lockdown of the health care facilities due to the SARS-CoV-2 pandemic

		Patients reporting to have received each separate treatment (n = 2,574)	
Classification of treatments	**Treatment categories**	**Patients completing the six-month follow-up questionnaire before national lockdown (n = 1,140), % (n)**	**Patients completing the six-month follow-up questionnaire after national lockdown (n = 1,434), % (n)**
Guideline-adherent core treatment	1. Patient education	37 (419)	37 (529)
	2. Exercise	73 (832)	75 (1,079)
	3a. Dietary weight management, if needed (BMI ≥ 25)	8 (74)*	6 (71)§
	3b. Dietary weight management, if needed (BMI ≥ 30)	12 (60)†	9 (51)‡
Supplements to core treatment	4. Pharmacological treatment	49 (558)	54 (771)
	5. Intra-articular injections	16 (179)	19 (272)
	6. Walking aids and devices	14 (163)	16 (234)
	7. Stretching	9 (101)	9 (129)
	8. Joint mobilisation	3 (37)	4 (57)
End-stage treatment	9. Knee arthroplasty	37 (419)	26 (378)
Uncertain or not recommended treatment	10. Arthroscopic surgery	18 (210)	21 (298)
	11. Passive treatment	22 (248)	23 (326)
	12. Alternative and complementary medicine	4 (47)	5 (69)
	13. No treatment	11 (124)	8 (121)

BMI, body mass index (kg/m^2)
*Out of 929 patients with BMI ≥ 25
§Out of 1,181 patients with BMI ≥ 25
†Out of 500 patients with BMI ≥ 30
‡Out of 584 patients with BMI ≥ 30

Supplement 5

Patient characteristics for patients undergoing knee arthroplasty

Table S5.
Patient characteristics for patients undergoing knee arthroplasty who received the recommended combination of guideline-adherent core treatments, patients who did not and patients who did not receive any treatment. Values are in percentages (%) with absolute numbers in parentheses unless other is stated

	Patients undergoing knee arthroplasty receiving the recommended combination of guideline-adherent core treatments (n = 297)	**Patients undergoing knee arthroplasty not receiving the recommended combination of guideline-adherent core treatments (n = 500)**	**Patients undergoing knee arthroplasty not receiving any treatment (n = 59)**
Sex			
Female	63% (186)	53% (265)	36% (21)
Age, mean (SD)	68.8 (8.4)	68.4 (8.8)	69.1 (8.9)
BMI, mean (SD)	29.5 (5.6)	29.9 (5.7)	30.5 (5.6)
Residential status			
Alone	26% (78)	24% (119)	27% (16)
Cohabiting	72% (213)	74% (369)	71% (42)
Missing	2% (6)	2% (12)	2% (1)
Level of education			
Elementary school	9% (27)	16% (78)	19% (11)
High school	3% (9)	2% (9)	0% (0)
Vocational education	34% (101)	36% (179)	53% (31)
Short-cycle higher education	11% (32)	12% (60)	10% (6)
Medium-cycle higher education	34% (100)	26% (129)	14% (8)
Long-cycle higher education or more	7% (22)	6% (30)	3% (2)
Missing	2% (6)	3% (15)	2% (1)
Occupation			
Retired, early retiree or on early retirement	68% (202)	64% (320)	61% (36)
Sick leave part time or full time	6% 18)	6% (29)	5% (3)
Unemployed	2% (7)	2% (9)	2% (1)
On the labour market or student part time or full time	24% (71)	28% (141)	31% (18)
Missing	2% (6)	3% (13)	3% (2)
Smoking			
No, never	46% (143)	45% (227)	39% (23)
No, but I used to	44% (131)	43% (217)	46% (27)
Yes	6% (17)	9% (43)	12% (7)
Missing	2% (6)	3% (13)	3% (2)
Comorbidities			
Proportion of patients with comorbidities	82% (243)	76% (379)	80% (47)
Self-reported physical activity per week			
None	4% (11)	5% (26)	3% (2)
30 min	9% (27)	11% (54)	17% (10)
1 hour	11% (33)	9% (46)	3% (2)
2 hours	19% (56)	16% (78)	22% (13)
More than 2 hours	56% (166)	57% (283)	51% (30)

Missing	1% (4)	3% (13)	3% (2)
VAS knee pain, mean (SD)	70.9 (16.6)	69.9 (18.6)	69.1 (19.9)
Duration of knee problems			
0–6 months	2% (6)	8% (38)	15% (9)
7-12 months	9% (26)	12% (59)	10% (6)
1–2 years	14% (43)	16% (79)	20% (12)
3-5 years	25% (74)	22% (108)	15% (9)
6-10 years	18% (54)	19% (93)	19% (11)
> 10 years	31% (91)	24% (119)	20% (12)
Missing	1% (3)	1% (4)	0% (0)
EQ-5D-3L, median (IQR)	0.658 (0.389-0.723)	0.660 (0.398-0.723)	0.723 (0.618-0.771)
OKS, mean (SD)	20.8 (6.7)	21.3 (6.7)	23.5 (7.0)
Radiographical knee OA severity (KL grade)	*	§	¶
0	0 (0)	0 (0)	0 (0)
1	0 (0)	0 (0)	0 (0)
2	1 (5)	2 (14)	0 (0)
3	31 (121)	31 (194)	20 (14)
4	66 (256)	65 (406)	77 (54)
Missing	2 (7)	1 (7)	3 (2)
Severe patellofemoral OA	†	‡	#
Yes	3 (11)	1 (9)	1 (1)
No	10 (38)	11 (66)	13 (9)
Not assessable	1 (3)	0 (3)	1 (1)
Tibiofemoral OA wear pattern	*	§	¶
Medial	85 (332)	86 (532)	86 (60)
Lateral	13 (50)	12 (72)	9 (6)
Bicompartmental	0 (0)	2 (10)	3 (2)
Missing	2 (7)	1 (7)	3 (2)

BMI, body mass index (kg/m²); SD, standard deviation; VAS, Visual Analogue Scale (millimetres, 0-100); EQ-5D-3L, 3-level version of the European Quality of Life – 5 Dimensions; OKS, Oxford Knee Score; OA, osteoarthritis; IQR, interquartile range; KL grade, Kellgren and Lawrence classification system.

* Of the 297 patients undergoing knee arthroplasty receiving the recommended combination of guideline-adherent core treatments, 92 had bilateral problems making the total number of examined knees 389.

† Of the 389 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 52 knees.

§ Of the 500 patients undergoing knee arthroplasty not receiving the recommended combination of guideline-adherent core treatments, 121 had bilateral problems making the total number of examined knees 621.

‡ Of the 621 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 78 knees.

¶ Of the 59 patients undergoing knee arthroplasty not receiving any treatment, 11 had bilateral problems making the total number of examined knees 70.

Of the 70 examined knees, skyline radiographs to assess severe patellofemoral OA were available for 11 knees.

UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

Paper III

Treatment pathways for knee osteoarthritis: a qualitative study exploring patients' perspectives

Manuscript in preparation.

Title page

Title

Treatment pathways for knee osteoarthritis: a qualitative study exploring patients' perspectives

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Abstract

Introduction

Knee osteoarthritis (OA) is a highly prevalent disease and a major global economic burden causing pain and disability. Despite clinical guidelines on the management of knee OA, patients undertake treatment pathways not adhering to the recommendations. This study explored patients' preferences and experiences with different treatments and will contribute to the understanding of current practices, challenges, and needs in the daily management of patients with knee OA, seen from the patient's point of view. Therefore, this study aimed to explore the patients' perspectives on the treatment pathways for knee OA.

Methods

This qualitative study was based on individual semi-structured interviews. All patients were included from a cohort comprising patients with primary referral to an orthopaedic surgeon due to knee OA at two Danish hospitals. Interviews were transcribed verbatim, and three investigators independently performed a qualitative content analysis based on systematic text condensation and thematization. Meaningful units were identified, coded, and organised in main and subthemes.

Results

Interviews with eight informants identified three main themes and seven subthemes to influence the patients' perspectives on treatment pathways: 1. Adaptive treatment preferences, 2. Treatment expectations (own perception of the disease; treatment effect; accessibility; fear of adverse events), and 3. The health care provider's influence (trust in the health care provider; ability to communicate and educate; referral and treatment options).

Conclusion

Several factors influenced the patients' perspectives on the treatment pathways for knee OA. Treatment preferences were adaptive and depended on the patients' judgement of their medical condition and varied largely due to different expectations and experiences with treatments. The patients' own perceptions of the disease influenced which treatments they preferred, and they emphasised their health care providers' influence on their choice of treatment. This highlights the importance of improved patient education and communication between health care providers and their patients to improve shared decision making and ensure appropriate use of treatments.

Introduction

Knee osteoarthritis (OA) is a highly prevalent disease and a major global economic burden[1,2]. It is a multifactorial degenerative joint disease causing pain and disability[3]. Clinical guidelines recommend education, exercise, and dietary weight management (if overweight) as safe, efficient, and affordable first-line core treatments[4–8]. Surgery, i.e., knee arthroplasty, is advocated for patients with severe knee OA when the core treatments have failed[3,9]. Despite the recommendations, research has emphasised evidence-to-practice gaps resulting in treatment pathways not adhering to clinical guidelines[10–14]. Some possible reasons for these gaps have been reported[15–20], showing that general practitioners mistrusting the quality of care can be a barrier to referral to physiotherapists or dieticians[17,18]. The health care provider's insufficient knowledge of available recommended treatments[17,19,20], and the lack of time in the consultation have also been noted as barriers to implementing clinical guidelines[15,19]. Previous studies investigating the patients' points of view have highlighted severe pain and radiographical OA as barriers to undertake guideline-adherent core treatments[18,21]. In addition, the belief that knee OA is a "wear and tear" disease seems to facilitate the perception that surgery is inevitable as patients are concerned that exercise cannot regenerate the knee cartilage but rather worsen the knee damage[21,22]. These previous studies were restricted to either primary or secondary care and mainly focused on barriers and facilitators for a specific OA treatment modality. There is a need for a comprehensive insight into the patients' perspectives on the choice of treatment in their treatment pathways comprising all healthcare sectors and treatment modalities in their entire disease course. Interviewing patients with knee OA about their preferences and experiences with different treatments will contribute to the understanding of current practices, challenges, and needs in the daily management of patients with knee OA, seen from the patient's point of view. Therefore, the aim of this study was to explore the patients' perspectives on the treatment pathways for knee OA.

Methods

Design

This qualitative study was based on individual semi-structured interviews with patients with knee OA to investigate the patients' perspectives on their treatment pathways for knee OA. The study was carried out as part of the research project, the *TREATright* study, which was pre-registered with ClinicalTrials.gov (NCT03746184) and approved by the Danish regional ethical committee (Journal no.: H-17017295) and the Danish Data Protection Agency (Journal no.: AHH-2017-072)[23]. The project comprises a large cohort of patients with primary referral to an orthopaedic surgeon due to knee OA invited consecutively during a two-year period from two outpatient clinics in two different regions of Denmark[23]. The project aims to investigate which treatments the patients undertake for knee OA and to what extent these adhere to clinical guidelines. Informants for this qualitative study were recruited from the *TREATright* cohort to obtain additional information about patients' perspectives on the choices and experiences with treatment for knee OA. In the reporting of this study the Consolidated criteria for Reporting Qualitative research (COREQ) was followed[24].

Participants

A purposeful sample of informants were identified using a two-step approach, firstly by random sampling from the *TREATright* cohort. All patients included in the *TREATright* study were eligible, and there were no exclusion criteria. To reflect the heterogeneity of individuals with knee OA, we generated random samples in blocks of five patients. Secondly, for each random sample, we screened the patients' characteristics regarding age, sex, whether they had undergone knee arthroplasty, and from which study site they were included. We invited patients with diverse demographics from one random sample before generating the next. In this way, we strived to recruit randomly selected informants reflecting diverse demographics to

increase the generalisability of our findings. Informants were contacted by phone by SMB and invited to participate in the study. A total of 13 out of 40 randomly identified patients were invited, of whom three declined to participate and two did not show up at the scheduled time of interview. The number of informants to recruit was continuously evaluated. We intended to recruit informants until information power was deemed to be sufficient depending on when we found that new information relevant to the study aim had been developed[25]. However, the inclusion of informants was finalised for pragmatic reasons.

Interview

We developed a semi-structured interview guide with open-ended questions allowing the interviewer to come up with new questions based on the responses from the informant[26,27]. If the open-ended questions lacked information, probing questions were asked. The interview guide was developed based on information from an ongoing questionnaire-based study within the TREATright study describing the treatment pathways patients undertake for knee OA. Furthermore, the interview guide was informed by clinical guidelines on the management of knee OA[4–7] and previous publications describing the underutilisation of recommended treatments[10–13,28] and potential barriers for use of recommended treatment[15–20]. The interview guide was initially drafted by SMB and AM and was further developed and revised through discussions and feedback from LHI and STS. Six patients with knee OA, participating as patient representatives in the TREATright study, were invited to a meeting with SMB and AM at one of the study sites to participate in the development of the interview guide and to address important topics to be included. In the resulting version of the interview guide, the first questions prompted the patients to freely talk about their disease course with knee OA. As the interview progressed, the patients were asked to elaborate on the specific treatments they had undertaken and to describe their perspectives on these treatments, to ensure that all important topics were discussed. After the first interview, we made minor adjustments to the interview guide to optimise the following interviews.

The interviews were performed by SMB and took place in a meeting room at one of the two study sites depending on which hospital the informant was included from. In the beginning of the interviews, the informants were provided with a timeline of a generalised disease course with knee OA (from onset of knee problems, pain, and disability, to receiving diagnosis, and until the present time) to help them keep track of their own disease course during the interview (Appendix 1). The interviews lasted approximately one hour and were audio recorded and subsequently transcribed verbatim, anonymised, and securely stored.

Data analysis

SMB, AM, and LHI performed a qualitative content analysis based on systematic text condensation (STC) and thematization[29]. The analysis followed four steps[29]. 1) SMB and AM individually read the transcribed interviews, whereby an overall impression of the material was formed, and preliminary themes were identified. 2) SMB and AM individually identified, sorted, and coded units of meaning, according to the preliminary themes. 3) SMB and AM re-read and discussed the identified codes and themes to condense and abstract the meaning of the coded units within each theme. In this step, preliminary subthemes were also formed. Subsequently the preliminary themes and subthemes were further reviewed and discussed with LHI, and themes were then revised several times before consensus was reached. 4) With continuous revisions and discussions between SMB, AM and LHI, the meaning of coded units within each theme and subtheme were summarised to form the final syntheses within each theme describing the informants' perspectives on the management of knee OA. Quotations best illustrating the descriptions were selected.

Results

Through the recruitment process, eight random samples were generated, and we recruited a total of eight informants (Table 1).

Table 1.
Patient demographics and all the treatments/health care providers that informants reported having pursued.

Informant	Study site	Sex	Age	Knee arthroplasty	Treatments/health care providers
#1	Hospital 1	Male	76	Yes	Acupuncture Glucosamine Pain medication Physiotherapist Osteopathy Chiropractic Crutches Support bandages Zone therapy Rooster comb injection/hyaluronic acid Adrenocorticotropic hormone injections Arthroscopic surgery Knee arthroplasty Re-operation after knee arthroplasty Heat treatment Gait training Rest Laser therapy Unsupervised exercise at home GLA:D* Supervised and unsupervised exercise in fitness centre
#2	Hospital 1	Male	59	Yes	
#3	Hospital 1	Female	70	No	
#4	Hospital 2	Female	45	No	
#5	Hospital 2	Female	76	Yes x 2	
#6	Hospital 2	Male	55	No	
#7	Hospital 2	Male	71	Yes x 2	
#8	Hospital 1	Female	66	Yes x 2 4 re-operations	

*GLA:D is an evidence-based program that includes education and supervised neuromuscular exercise delivered by certified physiotherapists.
GLA:D, Good Life with osteoArthritis in Denmark.

155

156 The thematic analysis yielded three main themes concerning the patients' perspectives on experiences and
157 choices of treatment for knee OA (Table 2). Theme 2 was underpinned by four subthemes and Theme 3 was
158 supported by three subthemes (Table 2).

Table 2.
Themes and subthemes.

Themes	Subthemes
1. Adaptive treatment preferences	
2. Treatment expectations	1. Own perception of the disease
	2. Treatment effect
	3. Accessibility
	4. Fear of adverse events
3. The health care provider's influence	5. Trust in the health care provider
	6. Ability to communicate and educate
	7. Referral and treatment options

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Theme 1: Adaptive treatment preferences

From all interviews, we identified that the patients' judgement of their medical condition or worsening of symptoms impacted on which treatments they preferred or received. Functional limitations or pain could determine if a patient chose a treatment at a given time, especially when deciding to take pain medication or whether they found it relevant to consider surgery.

> *"When it really hurt, I took Ipren (ibuprofen) and Panodil (paracetamol)."* (Informant #2)

And

> *"There was no doubt, I was in so much pain. There was no doubt, it was time to go under the knife."* (Informant #2)

Experiencing worsening of symptoms or lack of improvement motivated other treatment options. Patients often focused on symptom worsening as facilitator for considering injections or surgery. They might also choose certain treatments such as pain medication as symptom-relieving temporary solutions on days/times when they experienced severe pain or as preparation for specific activities or situations.

> *"I ended up taking some ibuprofen. When I took one or two of those, for example before I was going to play badminton, I wasn't in pain. Then I could play."* (Informant #1)

One patient especially expressed to consider undergoing surgery in the future as a more permanent solution if the pain level no longer felt manageable.

> *"It must be in the extreme consequence that you treat the leg by giving me a new knee, that's clear. The one I have now has to last as long as possible, unless I get a lot of pain."* (Informant #6)

Theme 2: Treatment expectations

Patients expressed different expectations to different treatments, which could influence their preferences for specific treatment modalities. These preferences were affected by patients' own perceptions of the disease, expectations to the treatment effect, expectations to the accessibility, and their fear of adverse events related to some treatments.

Subtheme 1: Own perception of the disease

Patients' perceptions of the cause-effect mechanisms and development of the disease influenced which treatments they expected to be relevant and worth undertaking. A common belief was that knee OA is a "wear and tear" disease. Some patients explained that their OA was initiated acutely from an injury, while others believed it was a result of long-term hard physical work or activity.

> *"I walk with the tool and jump up as fast as the young people I work with [...] then I can feel, at least my left leg, making trouble [...] So that's how it started to the best of my knowledge."* (Informant #6)

With the believe of knee OA being a "wear and tear" disease, some patients expected that the only relevant treatment would involve restoring the knee and removing any possible mechanical wear in the knee.

> *"No, there is nothing that removes the wear and tear. That doesn't exist."* (Informant #7)

In addition, since the joint damage cannot be regenerated with exercise, they believed surgery was necessary.

> *(About GLA:D) "It didn't help me, no, it didn't. Because it didn't remove what was worn askew. It just showed something about how fast you could run."* (Informant #5)

Subtheme 2: Treatment effect

Expectations for the outcome of a treatment influenced the treatment choice. Some patients had very specific expectations; others had none. Patients' expectations could be influenced by experiences and recommendations from others, such as family, friends, acquaintances, or health care providers, as well as their own experiences with certain treatments. It was primarily recommendations from others who had positive experiences with a treatment that made them choose a specific treatment.

> (About acupuncture) *"It was friends who had said, "you should try it. Because we have such good experience with it".* (Informant #8)

Some patients experienced good effects from specific treatments, while others did not experience any real effect of the treatment or did not have their expectations met. If a patient had very high expectations to the effect of a specific treatment, it could be difficult to meet these. Some patients described that they discontinued a treatment if their expectations to the treatment effect were not met.

> *"Well, if it (physiotherapy) had helped, then it would have been great, but in my case [...] it has not had much effect. That's why I'm not going to try it again because I don't think it helps."* (Informant #3)

However, some would not undertake specific treatments, if they did not expect that they were effective. For some patients, the choice of treatment might have depended on the expectation of the treatment to either postpone or eliminate the need for another treatment, such as surgery.

> *"I expect that the purpose of GLA:D training is that you will be better prepared for surgery, but also that you may be able to completely avoid surgery. I guess that is really the purpose of it."* (Informant #8)

Subtheme 3: Accessibility

Expectations of the cost of treatment and personal financial situation could also play a role in choosing certain treatments. The patients' expectations for treatment accessibility were based on information from other people's experiences with specific treatments as well as the patients' own experiences, or information they had received or sought about specific treatments.

> *"So 1,500 DKK (200 EUR), if it (rooster comb injections) could alleviate or help, that was cheap enough, wasn't it? [...] didn't give any guarantee that it would help, but there have been some experiences that it could help a little, and then I thought that if that's all it takes, then just let me try."* (Informant #1)

The importance of cost was relative to the patient's own financial situation and expectations of the treatment effect and could be experienced very differently. If the cost was perceived as high, while the patient also evaluated that he/she had limited financial resources, it might mean that the given treatment was not chosen, depending on the expected treatment effect. For some patients, costs/financial situation was a deciding factor when choosing certain treatments, while for others, it was not.

> *"But it (exercise) became minimal because you couldn't afford it when being retired."* (Informant #7)

However, many patients emphasised that they believed that exercise as treatment should be fully funded in the health care system. However, they also expressed that they were willing to pay for any treatment if it was deemed relevant and there was an expectation of a good effect. On the other hand, some patients experienced having to discontinue a relevant treatment due to financial constraints/costs.

> (About self-payment for GLA:D) *"It was also acceptable, but the GLA:D exercise should have been free. I know several people who have had new knees, but not so many who have been to GLA:D training."* (Informant #5)

The decision to choose or reject a certain treatment could depend on expectations or experiences regarding the availability of the treatment. Some had specific expectations regarding the distance to the treatment facility, transportation options, time consumption or opening hours, which could influence the choice of treatment.

> (About GLA:D) *"Well, I have a job where you are dependent on me being present, so if I have to take an hour off to go to treatment, [...] that has been one of the things that has made me opt out, that I couldn't do that.* (Informant #8)

For other patients, the availability was not perceived as a barrier.

Regarding exercise as treatment, some patients described that they preferred not to exercise in a group, as it was important for them to be able to come whenever they wanted without having to be dependent on meeting for exercise at a certain time and using too much time.

> (About group-based exercise) *"No, not those fixed times, this, and that, no, I can't do that. I can't do that. [...] To come when I want."* (Informant #2)

Flexibility might be particularly important for those still on the labour market. Therefore, it could also be experienced as a barrier if the place of treatment was not open outside of normal working hours.

> *"Yes, because you can also say that it can be really difficult to do your full-time job if you have to go to treatments and have to go to exercise and so on."* (Informant #8)

It did not seem that a long distance to the treatment facility was perceived as a major barrier, but it was also mentioned that self-training at home was an easy and good solution, as you did not have to leave your home.

> (About exercise and home-based exercise) "*Well, the advantage is that you don't have to go out the door, you don't have to go to that place, but in my case, it wasn't a problem, it was almost nearby.*" (Informant #6)

Patients' expectations and experiences regarding the schedule and waiting time for a treatment could have an impact on whether a patient would undertake a certain treatment or an alternative. If there was an expectation or experience of a long waitlist, could encourage patients to find alternatives to the recommended treatment. If patients had expected a long wait, but experienced the opposite, they were pleasantly surprised and maybe more likely to prefer or recommend this treatment in the future.

> *"It actually went really fast, the process actually went really fast. From the time I contacted my doctor until I actually started seeing a physiotherapist, well, I don't think it took even a month actually. [...] and maybe that's also why it hasn't gotten as bad as it could have been, for example."* (Informant #4)

Subtheme 4: Fear of adverse events

Patients' expectations of side effects could prevent them from pursuing certain treatments. These expectations were sometimes based on others' (friends, acquaintances, family, healthcare providers) experiences with side effects from certain treatments, or on their own expectations and experiences with side effects. These expectations could influence whether they continued with a treatment, would undertake it again later, or recommend it to others. Other patients did not expect any side effects from certain treatments and were more likely to choose these again. Patients perceived the side effects to have varying degrees of importance, with some considered significant and others insignificant.

There was a widespread expectation that pain medication had side effects and its use should be limited, but some patients reported that they had not experienced such side effects. The same applied for injections, such as corticosteroid or hyaluronic acid.

> *"I can't imagine it's healthy for the body in the long run, stuffing yourself with Panodil (paracetamol) and Ipren (ibuprofen)."* (Informant #2)

However, one patient mentioned that adverse events could occur with some treatments, but that it was not particularly important, as all treatments may have side effects.

> *"He (the general practitioner) also told me that it can be hard on the body to get this blockade, so I was prepared for that. And I feel like, well, okay, there are side effects with everything, that's how it is."* (Informant #4)

Perhaps the perceived positive effect of a treatment outweighs the side effects. Some patients reported being afraid of complications to knee replacement surgery, which made them postpone it. Such complications included a fear of having a stiff knee, that the new knee would not last very long, or a general fear of surgery.

> *(About fear of surgery) "It was because I was afraid I thought: something like that (knee replacement surgery) I don't dare."* (Informant #5)

However, once the decision to have surgery had been made, possible side effects were not given much importance. Some patients would still have surgery, despite expecting side effects or fearing the procedure.

> *"There was a whole chart that said what could go wrong, but I didn't focus on that."* (Informant #5)

Theme 3: The health care provider's influence

The patients' perspectives on the treatment pathways for knee OA were also influenced by the health care providers and to what extent the patients had trust in them. The health care providers ability to communicate with their patients and educate on different treatments could impact the choice of treatment.

Subtheme 5: Trust in the health care provider

Patients preferred treatment offered by certified health care providers. The perceived competence and qualifications of the health care provider could have a significant impact on the choice of treatment. Patients expressed that a high level of trust and confidence in the professional's competences and qualifications, made them more willing to undergo treatment offered by that health care provider or to follow their recommendations and referrals. One patient highlighted that exercise therapy offered by physiotherapists was preferred over engaging a personal trainer. In addition, it was mentioned that little trust and confidence in the health care provider, made them look for other professionals or treatments.

> *"Well, I have the experience that I will go directly to the professionals. Those who have professional skills."* (Informant #2)

Some patients reported that they were less likely to listen to their general practitioner's recommendations, as they did not perceive their general practitioner as an expert, or because the general practitioner did not have enough time with the patient.

> *"I probably won't listen so much to the doctor, [...] I don't have much faith in my doctor, [...] they don't have much time to listen to you before you're just sent on your way. They are so busy today."* (Informant #3)

However, others expressed that the decision was made in collaboration with the general practitioner, and that they trusted their general practitioner's competences and suggestions for treatment. Furthermore, it was mentioned that there was an expectation, that the health care system would always offer what was best for the patient, so that you could trust the treatment suggestions given.

> *(About the desire for different treatment options) "No, I've never actually thought about that because I have faith that the system wants the best for me and that the hospital wants the best for me, so if there was an alternative, well, they would have said so, I think.* (Informant #4)

Additionally, the general practitioner's attitude and recommendation could impact which treatments the patients ended up receiving. Some patients indicated that if the general practitioner had a positive attitude towards a treatment, the patient would more likely choose that specific treatment. However, we observed large differences in the impact that the general practitioner's opinion and recommendation had on the patient's further course of treatment.

> *"He said: "without exercise, you will have problems with your knee, you have to do that (exercise), [...] so you have to because it's the only way you can get it back in order, or not in order, but better". So, all that, I certainly intend to start doing."* (Informant #6)

Some patients described that they investigated the different treatment options themselves and came with demands to their general practitioner, who has a function as gatekeeper in the Danish health care system, about which treatment they wanted a referral to. Thus, there were patients who may have trusted their own preferences for a treatment more than the health care providers' knowledge and competences, and therefore chose treatment on their own.

> *"I knew that you had to go through GLA:D exercise and all that, [...] but I have talked myself out of the fact that it may not have been so relevant for me, I didn't feel that. [...] So, I think I have skipped some of that because I have been so active myself."* (Informant #8)

Subtheme 6: Ability to communicate and educate

Some patients experienced that the health care provider's ability to communicate could impact the choice of treatment.

> *"But I think the psychological aspect has a lot to say. Trust and communication and credibility, all those things are incredibly important (for the choice of treatment), I think."* (Informant #8)

The general practitioner's ability to communicate and educate affected whether the patient followed the general practitioner's recommendations or referrals. Furthermore, other health care providers' ability to communicate could also affect whether the patient continued with a treatment or would pursue and recommend it in the future. Conversely, patients would seek other treatments instead if they experienced poor and inadequate communication. It was particularly emphasised that the health care provider should communicate in a language and in a way that made the patient understand what the treatment entails.

> *(About communication) "It has been great, so there has been, for example, the orthopaedist, if there was something I said: "that I didn't quite understand", well, then he translated it into a language I could understand; more Danish and not Latin. And the same with the physiotherapist and so on. So, if you're just willing to say: "I don't understand that", then I have the understanding that they would very much like to explain it to you in another way. So, I'm satisfied with that. I think there has been good communication, yes."* (Informant #4)

Subtheme 7: Referral and treatment options

Patients experienced large differences in whether a general practitioner had referred them to specific treatments or not. Some patients experienced that the general practitioner had presented many treatment options for them, while others experienced having only a few or no alternatives presented. If a patient experienced their general practitioner not presenting any treatment options, it was difficult for the patient to decide which treatment to undertake.

> *"It's hard to find the right treatment, isn't it? Of course, it would be nice if the doctor would kind of help."* (Informant #1)

Two patients expressed a desire for their general practitioner to offer them treatment alternatives, instead of only one treatment option. In the interviews, patients reflected on the lack of other treatment options, e.g., when offered surgery as the only treatment.

“So, when I said: "I don’t want surgery", I was given no other option.” (Informant #2)

And

(About other treatment options than surgery) "No, he didn't talk about anything, no. He only talked about surgery. (Informant #5)

Discussion

Based on interviews with eight patients with knee OA, we found information about the patients’ perspectives on treatment for knee OA and identified three main themes. Theme 1 describes that patients’ treatment preferences were adaptive and depended on the patients’ judgement of their medical condition or worsening of symptoms. Theme 2 illustrates that patients' expectations of specific treatments, including its effectiveness, accessibility and related adverse events could influence their treatment preferences, although patients’ expectations, experiences and preferences varied greatly. Additionally, patients’ own perception of the disease sometimes impacted their perspectives of certain treatment opportunities. Theme 3 showed that the health care providers could impact the treatment pathways. To which degree the patients felt that their treatment was impacted by their healthcare provider was influenced by their trust in the health care provider, how referrals and treatment options were presented to the patients, and the health care providers ability to communicate and educate on different treatments.

The patients’ judgement of their medical condition or worsening of symptoms influenced their decisions on when to take pain medication or when to consider surgery. Surgery should be considered the end-stage treatment when all other recommended core treatments have been undertaken with inadequate effect[3,9,30]. In this study, we found that a facilitator for considering surgery were functional limitations and

414 severe pain. Previous research has also reported that pain and functional limitations in patients with knee
415 OA are facilitators for seeking physiotherapy care[22]. In contrast, a perception of having severe knee OA or
416 too much pain, has been reported as a barrier for undertaking recommended core treatments[18,21]. This
417 discrepancy could indicate that pain and functional limitations affect the patients' treatment preferences
418 differently due to the large differences in patients' previous experiences with their disease and
419 treatment and thereby their expectations. Health care providers should therefore focus on including the
420 individual patient's preferences in relation to the clinical guidelines.

421 Patients' beliefs of knee OA as a "wear and tear" disease impacted their perception of treatment
422 opportunities and led some patients to disregard exercise and prefer surgery to restore their knees. Similar
423 to our findings, it was also previously reported that patients believe that knee OA is caused by "wear and
424 tear" and therefore surgery was inevitable as exercise could not regenerate the cartilage in the knee[21,22]. It
425 was, however, also found that patients with knee OA believed that seeing a physiotherapist could delay the
426 need for surgery[22] and that they considered that surgery should be the last treatment option[18]. In contrast,
427 patients may also believe that exercise and physiotherapy would cause further knee damage and increase
428 pain[21]. These contrasting attitudes towards exercise as active treatment for knee OA were also reflected in
429 our interviews. These findings point at the need to educate patients about the existing evidence that
430 exercise can in fact decrease pain, increase physical function[31], and delay or potentially even prevent
431 surgery in patients with moderate-to-severe knee OA[32–34].

432 We found that patients' expectations to specific treatments and their effect can be influenced by
433 experiences and recommendations from others. Furthermore, our informants also expressed that they
434 would also recommend or discourage specific treatments to others based on their own experiences. Some
435 patients pursued specific recommended treatments if these treatments had been recommended by
436 friends, acquaintances, family, or healthcare providers. This finding is similar to those from other studies
437 reporting that friends and people in the patients' environment can facilitate the use of nonsurgical

treatments in patients with knee OA[18,22]. Conversely, it has also been reported that recommendations from others can be a barrier for undertaking the recommended core treatments if people in the patients' environment have positive experiences with surgery[18]. Therefore, it may be advantageous also to include patients' next of kin when discussing treatment alternatives. The findings also point at a general societal need to increase awareness about the OA disease and the benefits of undertaking recommended core treatments.

Accessibility of treatment may influence the treatment pathways. In Denmark, the recommended core treatments are not covered by the national health security system. In this study we found that some patients expressed the costs of the treatments to be a barrier for undertaking recommended treatment, which has also been reported in other studies[15,16,18]. Conversely, having a health insurance to pay some of the costs has been reported as a facilitator for accessing care for knee OA[35]. If the place of treatment was not open outside of normal working hours, some patients also reported that being on the labour market was a barrier which has also been previously reported [35]. Therefore, it seems that some degree of financial support as well as flexible or extended opening hours at the place of treatment should be prioritised to ensure that patients have better access to care.

The fact that health care providers play a major role in the referral and management of knee OA and thereby influence the patients' treatment pathways was obvious from our findings. Others have reported that some health care providers hesitate to refer the patients to a physiotherapist or dietician as they may question the effect of therapeutic exercise and dietary weight management[17,18], or if knee OA is simply perceived as an inevitable procedure of aging[19]. It was also reported that general practitioners with preferences for surgery can be a barrier for patients to undertake non-surgical treatments[18]. In addition, general practitioners have also expressed that lack of time is a barrier to their ability to implement the clinical guidelines[15,19]. Patients from our study likewise emphasised that if the general practitioner did not spend enough time with them, or if they felt a poor level of communication, then they were less likely to

462 listen to their general practitioner's recommendations. In addition, our informants highlighted that it could
463 be difficult for to decide which treatment to undertake, and sometimes lacked information about
464 treatment alternatives. These findings call for a stronger emphasis on shared decision making. Shared
465 decision making has been shown to be associated with better outcomes in patients with knee OA
466 considering knee replacement[36]. The shared decision making process ensures that the decisions about
467 treatment options are taken with the patients rather than for the patients, aiding the patients to make
468 informed decisions[37]. Knowledge and information about the disease and treatment of knee OA may also
469 influence the patients' perspectives and treatment preferences[21,38]. Hence, more education of patients
470 about the disease and benefit of using core treatments would be advantageous and should be considered
471 in the shared decision making. Furthermore, health care provider's insufficient knowledge of available
472 recommended treatments has been reported as a barrier for referring to these treatments[17,19,20]. To
473 increase awareness and usage of recommended guideline-adherent treatments there might be a need for
474 more information to the health care providers about these treatments[15,19,39].

475

476 ## Strengths and limitations

477 To strengthen the reporting of this study, we used the Consolidated criteria for Reporting Qualitative
478 research (COREQ)[24]. One of the strengths in this study is that we recruited informants with different patient
479 characteristics from two Hospitals in two different regions of Denmark, representing both urban and more
480 rural areas, to increase the generalisability of the study. All informants were recruited from the *TREATright*
481 cohort, meaning they were all patients who had consulted an orthopaedic surgeon and had some experience
482 with the disease course and treatment options for knee OA. This contributed to increase the information
483 power in the interviews[25]. With high information power in the interviews, data from a small sample size might
484 have been sufficient to provide a rich material as opposed to a large sample size with low information
485 power[25]. Although, we intended to recruit informants until information power was reached, we interviewed

a limited number of eight patients for pragmatic reasons. The interviews revealed a remarkable and large variety in patients' preferences, experiences, and expectations regarding treatment pathways. However, the inclusion of additional informants could have provided greater insight into the variety of patients' perspectives. Hence, eight informants might not have been sufficient to obtain adequate information power, which should be considered in the interpretation of this study. Our preconceptions could potentially have influenced the analysis and thematization. Therefore, we considered it an advantage that the analysis was conducted by investigators with different clinical backgrounds as physical therapist and general practitioner. To reduce the risk of preconception bias we also strived to be conscious of our own preconceptions and constantly be aware of whether this influenced the interpretation[29].

Conclusion

We found several factors influencing the treatment pathways for knee OA from the patients' point of view. The findings highlight that treatment preferences were adaptive and depended on the patients' judgement of their medical condition or worsening of symptoms. Furthermore, patients' treatment preferences varied largely due to different expectations and experiences with treatments and that their own perceptions of the disease influenced which treatments they preferred. The role of treatment accessibility in terms of cost, wait-lists, and distance differed among patients. Finally, patients emphasised their health care providers influence on their choice of treatment and stressed the importance of good communication.

Future work is needed to explore how improved patient education about the disease and information on treatment options can influence treatment pathways. Furthermore, the focus should be on improved communication between health care providers, especially the general practitioners, and their patients to improve shared decision making and ensure appropriate use of treatments. This also implies a need for alignment in the health care providers' recommendations and consistency in how treatment options are presented.

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Appendix 1

Timeline of a generalised disease course with knee osteoarthritis