Searching for subgroups of patients benefitting most from meniscal surgery – *do they exist?*

PhD thesis

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Colophon

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Preface

This thesis was completed at the Research Unit for Musculoskeletal Function and Physiotherapy at Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark. The sole supervisor was Associate Professor Jonas B. Thorlund (University of Southern Denmark).

The thesis includes data on 641 patients who had a verified meniscal tear at knee arthroscopy and 176 patients who had knee arthroscopy on suspicion of a meniscal tear but where no meniscal tear was identified. Patients had surgery at either Odense University Hospital (Odense or Svendborg) or Lillebaelt Hospital (Kolding or Vejle) in the Region of Southern Denmark between February 1, 2013 and January 31, 2015.

The single studies that the thesis comprises were conducted in collaboration with the Research Institute for Primary Care & Health Sciences, Keele University, Keele, United Kingdom, the Clinical Epidemiology Unit, Lund University, Lund, Sweden, Department of Orthopaedics and Traumatology, Odense University Hospital, Odense, Denmark, and Department of Orthopaedics, Lillebaelt Hospital, Kolding and Vejle, Denmark.

The PhD project was funded by the Independent Research Fund Denmark | Medical Sciences, and the Region of Southern Denmark.

List of papers

This thesis is comprised of the following four papers. The papers will be referred to by their roman numerals throughout the thesis.

I. **Pihl K**, Turkiewicz A, Englund M, Lohmander LS, Jorgensen U, Nissen N, Schjerning J, Thorlund JB. Association of specific meniscal pathologies and other structural pathologies with self-reported mechanical symptoms: A cross-sectional study of 566 patients undergoing meniscal surgery. *J Sci Med Sport* 2019;22:151-57.

II. Thorlund JB, **Pihl K**, Nissen N, Jorgensen U, Fristed JV, Lohmander LS, Englund M. Conundrum of mechanical knee symptoms: signifying feature of a meniscal tear? *Br J Sports Med* 2019;53:299-303.

III. **Pihl K**, Turkiewicz A, Englund M, Lohmander LS, Jorgensen U, Nissen N, Schjerning J, Thorlund JB. Change in patient-reported outcomes in patients with and without mechanical symptoms undergoing arthroscopic meniscal surgery: A prospective cohort study. *Osteoarthritis Cartilage* 2018;26:1008-16.

IV. **Pihl K**, Ensor J, Peat G, Englund M, Lohmander LS, Jorgensen U, Nissen N, Fristed JV, Thorlund JB. Wild-goose chase, no predictable patient subgroups who benefit from meniscal surgery: patient-reported outcomes of 641 patients 1 year after surgery. *Br J Sports Med* Epub ahead of print: 2019 Jun 11.

Thesis at a glance

Paper	I & II	III	IV
Aim	To investigate if specific meniscal pathology (i.e. tear type, location, etc.) and other concurrent structural pathologies [I] and having a meniscal tear [II] are associated with self-reported preoperative mechanical symptoms.	To compare change in patient-reported outcomes from before to 52 weeks after arthroscopic meniscal surgery between patients *with* and *without* preoperative mechanical symptoms.	To develop a prognostic model for predicting patients' change in self-reported outcomes from before to 52 weeks after arthroscopic meniscal surgery.
Design	Cross-sectional studies.	Prospective cohort study.	Prognostic model study using cohort data.
Participants	566 patients having meniscal surgery [I]. 817 patients having knee arthroscopy for suspicion of a meniscal tear (641 with, and 176 patients without a meniscal tear) [II].	150 patients aged ≤40 years and 491 patients aged >40 years with and without preoperative mechanical symptoms.	641 patients having meniscal surgery.
Methods	Surgery data assessed using a modified ISAKOS form. Mechanical symptoms assessed using two single items from the KOOS symptom subscale.	$KOOS_4$ assessed before surgery and at 12 and 52 weeks after surgery. Mechanical symptoms assessed using a single item from the KOOS symptom subscale.	Patient-reported prognostic factors collected prior to surgery. $KOOS_4$ assessed before surgery and at 12 and 52 weeks after surgery.
Conclusions	Limited associations were found between specific meniscal pathology and other concurrent structural pathologies with mechanical symptoms [I]. Mechanical symptoms were not more frequent in patients with an identified meniscal tear than in patients with other knee problems [II].	Younger patients *with* mechanical symptoms experience greater improvement after meniscal surgery than younger patients *without* mechanical symptoms. No difference was observed between older patients with and without such symptoms.	A combination of a large number of clinically important preoperative factors poorly predicts change in patient-reported outcome after meniscal surgery and was unable to accurately identify patients having a particular outcome.

ISAKOS: International Society of Arthroscopy, Knee Surgery and Orthopedic Sports Medicine classification of meniscal tears; $KOOS_4$: An aggregated score of four of the five subscales (i.e. pain, symptoms, sport and recreational activities, and knee-related quality of life, excluding activity of daily living) from the Knee injury and Osteoarthritis Outcome Score (KOOS).

Description of contributions

Paper I	
Study design	Kenneth Pihl, Aleksandra Turkiewicz, Martin Englund, L. Stefan Lohmander, Jonas B. Thorlund
Data collection	Kenneth Pihl, Uffe Jørgensen, Nis Nissen, Jeppe Schjerning
Data analysis and interpretation	Kenneth Pihl, Jonas B. Thorlund
Manuscript writing	Kenneth Pihl
Manuscript revision	Kenneth Pihl, Aleksandra Turkiewicz, Martin Englund, L. Stefan Lohmander, Uffe Jørgensen, Nis Nissen, Jeppe Schjerning, Jonas B. Thorlund
Paper II	
Study design	Jonas B. Thorlund, Kenneth Pihl, L. Stefan Lohmander, Martin Englund
Data collection	Kenneth Pihl, Uffe Jørgensen, Nis Nissen, Jakob V. Fristed
Data analysis and interpretation	Jonas B. Thorlund, Kenneth Pihl, L. Stefan Lohmander, Martin Englund
Manuscript writing	Jonas B. Thorlund
Manuscript revision	Jonas B. Thorlund, Kenneth Pihl, Nis Nissen, Uffe Jørgensen, Jakob V. Fristed, L. Stefan Lohmander, Martin Englund
Paper III	
Study design	Kenneth Pihl, Aleksandra Turkiewicz, Martin Englund, L. Stefan Lohmander, Jonas B. Thorlund
Data collection	Uffe Jørgensen, Nis Nissen, Jeppe Schjerning
Data analysis and interpretation	Kenneth Pihl, Jonas B. Thorlund
Manuscript writing	Kenneth Pihl
Manuscript revision	Kenneth Pihl, Aleksandra Turkiewicz, Martin Englund, L. Stefan Lohmander, Uffe Jørgensen, Nis Nissen, Jeppe Schjerning, Jonas B. Thorlund
Paper IV	
Study design	Kenneth Pihl, Joie Ensor, George Peat, Martin Englund, L. Stefan Lohmander, Jonas B. Thorlund
Data collection	Uffe Jørgensen, Nis Nissen, Jakob V. Fristed
Data analysis and interpretation	Kenneth Pihl, Joie Ensor, George Peat, Martin Englund, L. Stefan Lohmander, Jonas B. Thorlund
Manuscript writing	Kenneth Pihl
Manuscript revision	Kenneth Pihl, Joie Ensor, George Peat, Martin Englund, L. Stefan Lohmander, Uffe Jørgensen, Nis Nissen, Jakob V. Fristed, Jonas B. Thorlund

List of tables and figures

Abbreviations

ACL	Anterior Cruciate Ligament
ADL	Activities of Daily Living
APM	Arthroscopic Partial Meniscectomy
BMI	Body Mass Index
CI	Confidence Interval
DNPR	Danish National Patient Register
ICRS	International Cartilage Repair System
IQR	Interquartile Range
ISAKOS	International Society of Arthroscopy, Knee surgery and Orthopedic Sports medicine
KACS	Knee Arthroscopy Cohort Southern Denmark
KOOS	Knee injury and Osteoarthritis Outcome Score
MRI	Magnetic Resonance Imaging
N	Number
OA	Osteoarthritis
PCL	Posterior Cruciate Ligament
PR	Prevalence Ratio
QoL	Quality of Life
RCT	Randomised Controlled Trial
REML	Restricted Maximum Likelihood
RR	Risk Ratio
SD	Standard Deviation
SF-36	Short Form 36-item
Sport/Rec	Sport and Recreation function
VIF	Variance Inflation Factor

Introduction

Scope of the problem

Arthroscopic knee surgery for a meniscal tear is one of the most common orthopaedic surgical procedures in the western world[1 2]. During the first decade of the millennium there was a dramatic increase in meniscal surgeries performed in Denmark with nearly a two-fold increase of procedures from 8.750 in 2000 to 17.368 in 2011[3] (Figure 1). Similar trends were reported in the United States and United Kingdom[4 5]. Common for all three countries was that the large increase in meniscal surgery was almost entirely constituted by an increase in procedures among middle-aged and older individuals who form about 3 out of 4 procedures[3].

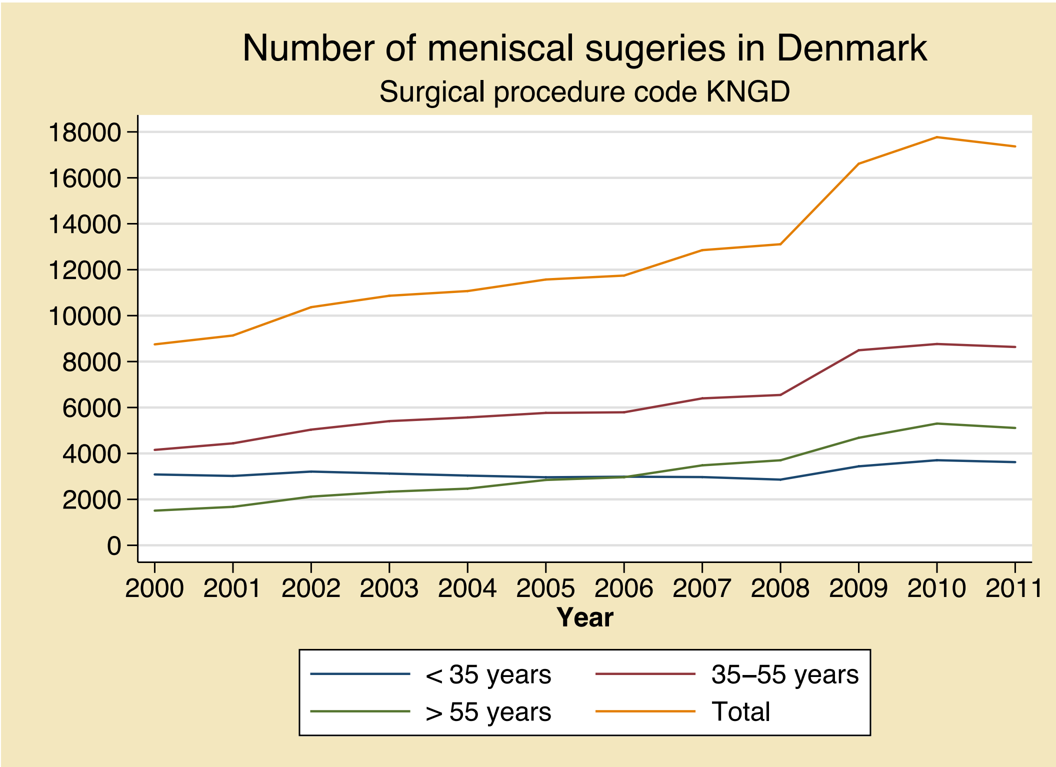

Figure 1. Number of meniscal surgeries performed in Denmark from year 2000 to 2011[3].

Throughout the same period, the effect of meniscal surgery has been heavily questioned by numerous randomised controlled trials (RCT). Already in 2002, Moseley *et al*. found in their pioneering randomised placebo-controlled trial that arthroscopic debridement or lavage were not superior to sham surgery in patients with knee osteoarthritis (OA)[6]. Since then at least eight large RCTs investigating the effect of arthroscopic partial meniscectomy (APM) have been published[7-14]. Patients in these trials were on average middle-aged and older and had a degenerative meniscal tear with and without a diagnosis of knee OA. Seven of the trials did not find APM superior for patient-reported pain or function compared to sham surgery or in addition to exercise therapy[7-11 13], nor that exercise therapy was inferior to APM[14]. Only one trial reported better effect of surgery on patient-reported pain compared to exercise therapy[12], however this difference was absent three years after surgery[15].

Although APM generally is considered a low risk procedure, rare but serious adverse events, including pulmonary embolism, infections, and death, have been reported[16-18]. Furthermore, APM seems to increase the risk of worsening of cartilage damage as compared to knees with meniscal tears left in situ[19].

Despite the substantial amount of trials consistently reporting that the effect of APM is trivial at best, the use of APM has been widely debated[20-23]. In particular, critics of the trials have argued that patients included in RCTs are narrowly selected and may not reflect daily clinical practice, and that specific subgroups of patients benefitting from the procedure do exist[24 25]. However, evidence to support who these subgroups are is sparse.

The menisci

The knee menisci are two discs of fibrocartilage that are situated between the articular surfaces of femur and tibia in the medial and lateral compartment of the knee joint. Seen from above, the menisci are semi-lunar shaped structures with anterior and posterior horns that are attached to the intercondylar part of tibia (Figure 2). From a transverse plane the menisci are wedge shaped. The medial meniscus covers about 50% of the medial tibial articular surface and is attached to the medial collateral ligament. In contrast, the lateral meniscus covers 70% of the tibial articular surface and is not attached to the lateral collateral ligament, making it more mobile than the medial meniscus[26]. The meniscal matrix mainly consists of Type I collagen, which is arranged in a circumferential pattern[27]. Only up to 30% of the menisci's periphery width is vascularised (i.e. red zone) while the inner two-thirds of the menisci is avascular (i.e. white zone)[28]. The menisci are primarily innervated in the peripheral vascular zone where the nerve fibres follow the blood vessels[29].

The main functions of the menisci are shock absorption and to distribute joint load over a larger area of articular cartilage during movement and joint loading[30]. Secondary, the menisci contribute to knee joint stability, proprioception and lubrication[27], thus damage to the menisci may have detrimental effects on knee joint function.

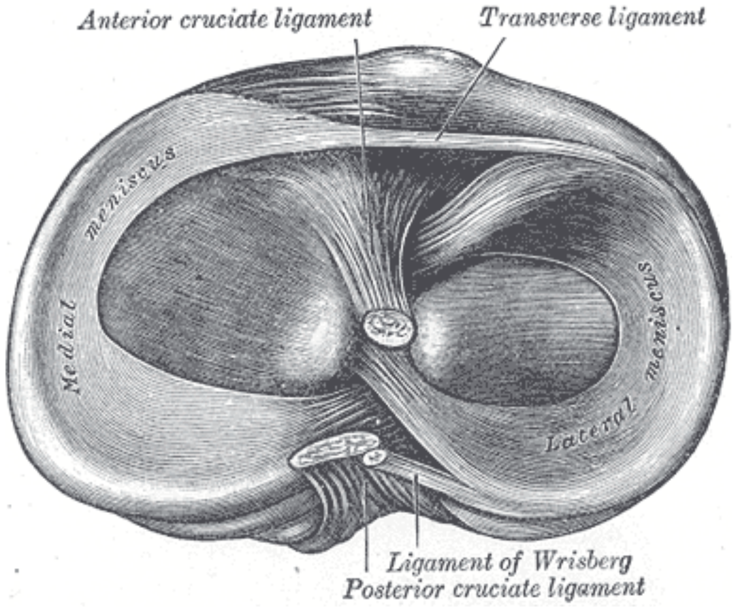

Figure 2. The medial and lateral meniscus as seen from above. The image is derived from Gray's Anatomy of the Human Body 20th edition (ed. Lewis W. H.; Lea & Febiger, USA, 1918)[31].

Meniscus tears

Meniscus tears are typically categorised as either traumatic (i.e. sports injury) or degenerative (i.e. non-traumatic)[32]. Traumatic tears are usually observed in younger individuals with an otherwise healthy meniscus and is often related to a sports trauma. The injury is typically a consequence of internal femur rotation as the knee moved from a flexed to a more extended position whereby the meniscus is split vertically and parallel to the circumferential collagen fibers. Such tears are often referred to as a longitudinal-vertical or bucket handle tears (Figure 3) and is more common in younger individuals than middle-aged older persons[32 33]. In Denmark, the incidence of meniscal tears have been reported to be about 70 per 100.000 persons in emergency departments[34].

Contrary to traumatic meniscal tears, degenerative tears are mainly seen in middle-aged and older individuals and are associated with osteoarthritis[35]. Such tears are typically described as complex (i.e. two or more tear types) or horizontal tears[32 33 35] (Figure 3) and are very common among middle-aged and older persons, also in asymptomatic individuals, and the prevalence increases with age[35 36]. The aetiology of degenerative tears is not fully understood, but they have been suggested to represent early stages of OA[37].

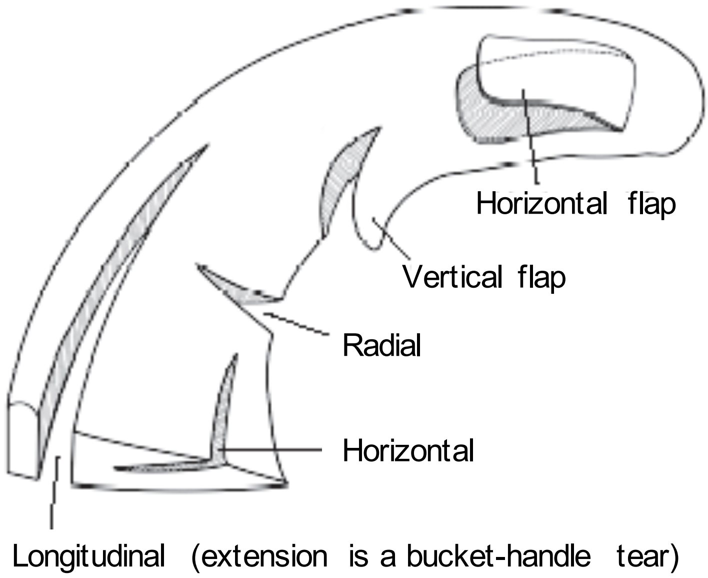

Figure 3. Types of meniscus tears. Image derived from the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS) classification of meniscal tears[38].

Indications for meniscal surgery

Symptoms such as knee pain, giving way and mechanical symptoms (i.e. the sensation of knee catching and/or locking) are often considered related to a meniscal injury[39 40]. Yet, no clear consensus exists for when arthroscopic meniscal surgery is in fact indicated[41]. Although meniscal surgery nowadays is not recommended in most patients with a degenerative meniscal tear[42], presence of mechanical symptoms is often argued as a pivotal indication[24 25], and guidelines still leave an option for surgery for these patients[43 44]. In fact, a recent consensus statement categorised a meniscal tear with concomitant mechanical symptoms as highly suggestive of a surgical treatable meniscal lesion[45]. Previous RCTs did not exclusively include patients with such symptoms[6-14], and five of the RCTs even excluded patients with a chronically locked knee[10-14], despite that these patients may constitute a subgroup having a particular favourable outcome of meniscal surgery.

Mechanical symptoms

The assumption that patients with mechanical symptoms constitute a subgroup that particularly benefit from meniscal surgery relies on the common tenet that such symptoms are caused by meniscal tissue being trapped between articular surfaces and needs to be removed or trimmed to resolve symptoms. Previous studies have reported prevalence estimates of mechanical symptoms between 47% and 64% in middle-aged and older patients with degenerative meniscal tears[46 47], confirming that they are common symptoms, however also suggesting that not all tears may cause mechanical symptoms.

Indeed, meniscal tears can be displaceable[48], and certain types of meniscal tears are considered unstable and more prone to cause mechanical symptoms than others[49]. Especially longitudinal-vertical tears may twist within the joint (i.e. bucket-handle tear) and cause mechanical symptoms, but also vertical flap tears are believed to cause such symptoms[49]. In contrast, degenerative tears such as horizontal cleavage tears are regarded as stable and less likely to result in mechanical symptoms[49]. However, the idea that some tears are more prone to cause mechanical symptoms than others remains unproven.

Meniscal tears often present in combination with other knee pathologies that have been reported to be associated with knee symptoms, including mechanical symptoms[46 50]. These pathologies include synovial inflammation, cartilage lesions and OA[36 51]. As a consequence, it is possible that other knee pathologies than the meniscal tear per se cause mechanical symptoms, and that mechanical symptoms may not be a signifying feature of meniscal tears.

Adding further to the controversy, a secondary analysis of a placebo-controlled trial failed to show better effect of APM in relieving mechanical symptoms compared with sham surgery for middle-aged and older patients with degenerative meniscal tears[47]. Also, a two-year follow-up of the same trial showed no difference in improvement in patient-reported outcomes in a subgroup of patients with preoperative mechanical symptoms[52]. Lastly, data from an observational cohort suggests no difference in improvement in patient-reported outcomes between patients with degenerative meniscal tears with and without preoperative mechanical symptoms[46].

Taken together, solid evidence is lacking supporting that meniscal tears are the cause of mechanical symptoms and that patients with such symptoms constitute a subgroup particularly benefitting of meniscal surgery. Only a negligible proportion of patients in previous studies was younger than 40 years. As previously described, these patients more often have a meniscal tear in an otherwise healthy knee and tear types that are believed to be the main cause of mechanical symptoms. Thus, it is plausible that young patients with mechanical symptoms may constitute a subgroup that have a particular favourable outcome after meniscal surgery. However, this has yet to be confirmed.

Identifying patients improving most

To limit the number of ineffective surgical procedures and unnecessary risk exposure to patients there is a need for improving the preoperative selection of those patients likely to benefit most from meniscal surgery.

Besides from mechanical symptoms, other factors have been argued as important for the outcome after meniscal surgery. For instance, patients with traumatic tears are also considered a group benefitting from surgery[24 25], but were excluded from the RCTs[6-14]. A recent systematic review identified a number of factors, including sex, overall physical status, symptom duration, etc. that were associated with the outcome after meniscal surgery[53]. The direction of associations was conflicting between included studies[53], thus no single factor appeared able to accurately identify subgroups of patients benefitting from APM. However, the combined prognostic ability of factors has not yet been evaluated.

Prognosis research is an important tool in the era of personalised medicine that aim to predict the prognosis for an individual patient[54]. Presuming that subgroups of patients having a particular favourable outcome after meniscal surgery exist, it should be possible to identify them by combining the most logical prognostic factors in a prognostic model using a large clinical cohort of patients having meniscal surgery. Such a model would be valuable for evidence-based selection of patients for meniscal surgery and assist clinicians and patients in the shared decision-making process of discussing benefits, harms, and patients' expectations of surgery.

Aims of the thesis

The general aims of this thesis were to identify which patients that might benefit most from arthroscopic meniscal surgery and add to the understanding of the relationship between meniscal tears and mechanical symptoms.

Specific aims

- To investigate if any specific meniscal pathology or other concurrent structural knee pathologies were associated with the presence of mechanical symptoms (paper I).

- To investigate if mechanical symptoms were more prevalent among patients with a meniscal tear compared to patients with no meniscal tear (paper II).

- To investigate if patients with preoperative mechanical symptoms experience larger improvements in patient-reported outcomes from before arthroscopic meniscal surgery to 52-weeks after surgery than patients without preoperative mechanical symptoms (paper III).

- To develop and internally validate a prognostic model for predicting change in patient-reported outcomes from before to 52-weeks after arthroscopic meniscal surgery (paper IV).

Methods

Study designs

Different study designs were used for the specific aims. The two studies investigating the relationship between meniscal tears and mechanical symptoms (paper I and II) used a cross-sectional study design, whereas the studies that investigated the patient-reported outcome after meniscal surgery (paper III and IV) were prospective longitudinal studies (Figure 4).

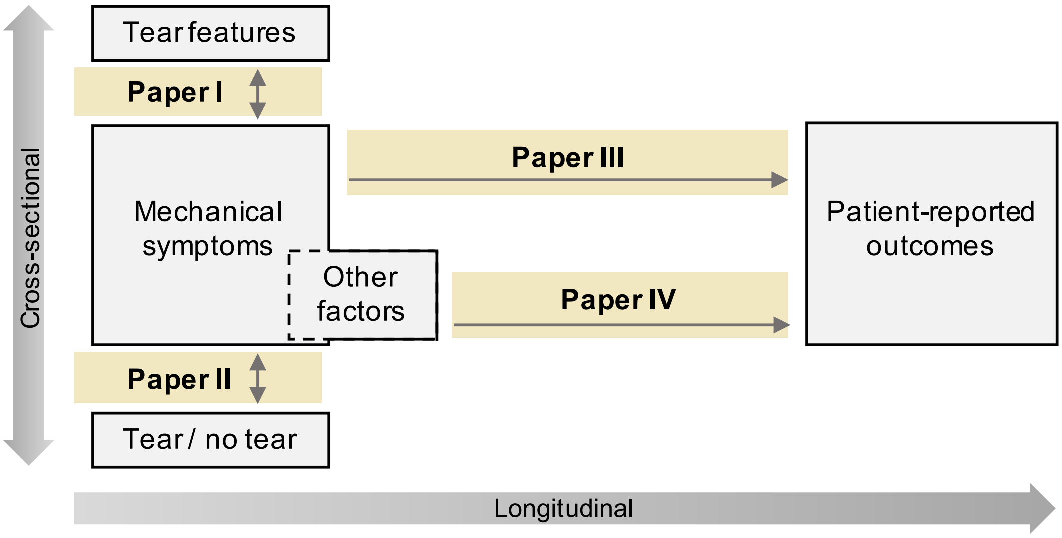

Figure 4. Overview of study designs used in the papers included in this thesis.

Data source and participants

All four papers in this thesis used data from the Knee Arthroscopy Cohort Southern Denmark (KACS)[55]. KACS is a prospective cohort study that follows patients having had knee arthroscopy for a meniscal tear. Participants in KACS were consecutively recruited from four public hospitals in the Region of Southern Denmark when assigned for knee arthroscopy by an orthopaedic surgeon on suspicion of a meniscal tear (based on clinical examination, history of injury, and magnetic resonance imaging (MRI) if considered necessary). The recruitment period was between February 1st, 2013 to January 31st, 2014, and for one of the initial four hospitals also between February 1st, 2014 to January 31st, 2015. A total of 641 patients were included in the KACS cohort at baseline of which 88% had complete follow-up data at 52-weeks after surgery. A detailed overview of the recruitment flow and number of patients included in each paper is shown in Figure 5. The specific in- and exclusion criteria for the single papers of this thesis are listed in Table 1.

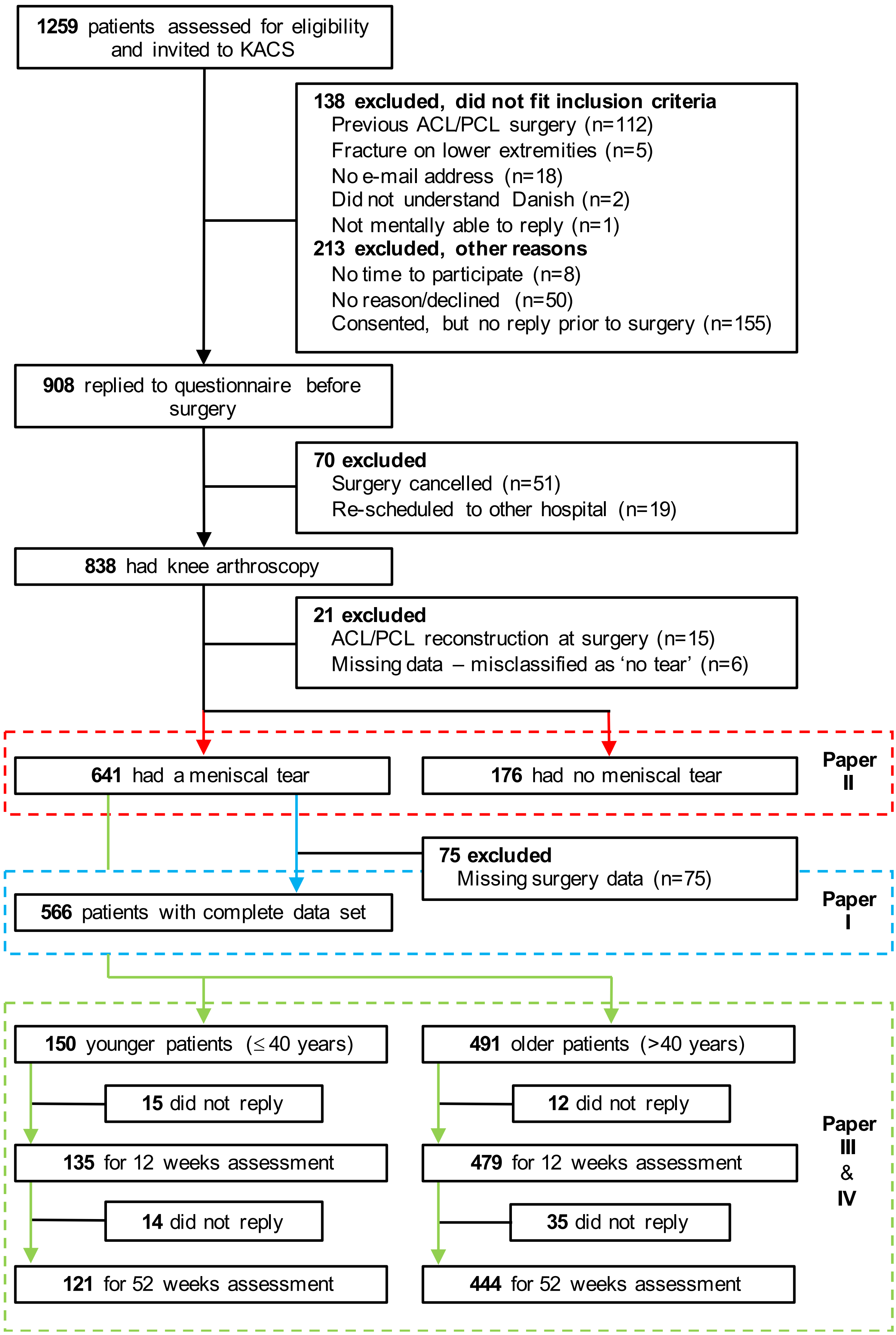

Figure 5. Flowchart of included patients in each paper. KACS: Knee Arthroscopy Cohort Southern Denmark.

Table 1. Overview of in- and exclusion criteria for each paper in this thesis.

	Paper I	Paper II	Paper III	Paper IV
Inclusion criteria				
• ≥18 years of age	X	X	X	X
• Read and understand Danish	X	X	X	X
• Have an e-mail address	X	X	X	X
Exclusion criteria				
• No meniscal tear at surgery	X		X	X
• Previous or planned ACL or PCL reconstruction in either knee	X	X	X	X
• Fracture(s) in lower extremities ≤6 months before recruitment	X	X	X	X
• Inability to reply to questionnaire because of mental impairment	X	X	X	X
• Missing surgery data	X			

ACL: Anterior cruciate ligament; PCL: Posterior cruciate ligament.

All study participants provided written informed consent to participate in KACS. The Regional Scientific Ethics Committee of Southern Denmark waived the need for ethical approval as no ethics approval is needed for questionnaire-based studies in Denmark. Patient characteristics, symptoms, and patient-reported outcomes were self-reported by participants using email-based questionnaires sent out within two prior to surgery (median 7 days, interquartile range 3-10 days), and again at 12 and 52-weeks after surgery. Surgery data were recorded at surgery by the operating surgeon (Figure 6).

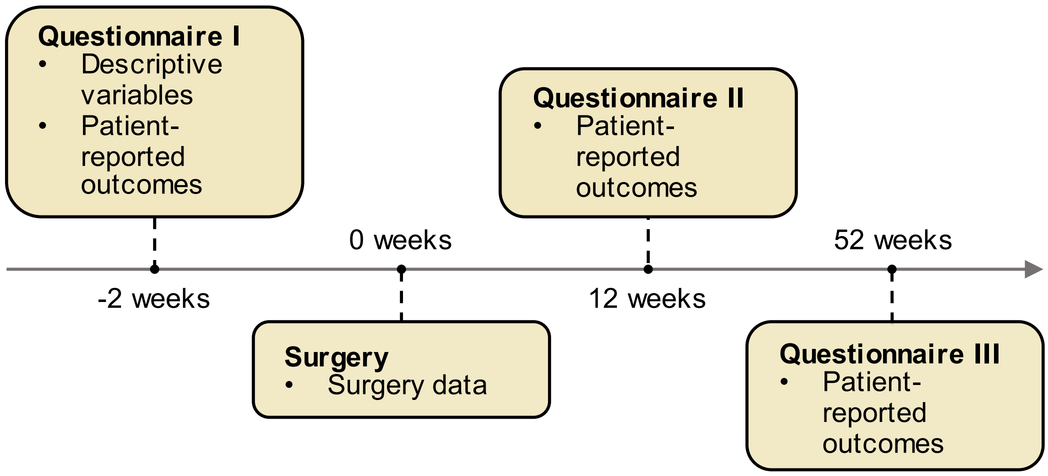

Figure 6. Overview of data collection in KACS.

Descriptive variables

Patient demographics

Level of education was assessed using the question: 'What education do you have (indicate the highest)?' with eight response options ranging from 'elementary school' to 'PhD'.

Physical activity at leisure time and work was assessed using two questions, respectively: 'To what extent did you participate in leisure activities before your knee problems' with seven response options ranging from 'no household work' to 'sport at competitive level', and 'Describe your physical activity at work (even work at home, sick leave at home and studying, for instance at a university)?' with four response options going from 'very light (mainly desk work)' to 'hard (heavy industrial, farmer, etc.)'[56].

Medical history

Patients were asked to indicate if having had previous surgery for a meniscal tear in the index knee, and if they suffered from back problems. Both questions had the binary response option 'yes/no'.

Knee instability was assessed with the question: 'Within the last three months, how much have the experience of your knee giving away or being unstable affected your daily activity level?' with six response options ranging from 'knee not unstable' to 'unstable, preventing all activities'[57].

To what extent the patients felt sad was assessed using a single item from the Short Form (SF) 36-item mental health subscale: 'How much of the time during the past four weeks have you felt downhearted and blue?' with six response options ranging from 'none of the time' to 'all of the time'[58].

In addition, patients indicated their knee alignment by completing the question: 'Which picture best describes the current angle of your leg?" with five response options ranging from 'pronounced varus' to pronounced 'valgus'[59].

Symptom onset and duration of symptoms

Onset of symptoms was assessed using the question: 'How did the knee pain/problems for which you are now having surgery develop? (choose the answer that best matches your situation)´ with the response options 'the pain/problems have slowly developed over time´, 'as a result of a specific incident (i.e. kneeling, sliding, and/or twisting of the knee or the like)', and 'as a result of a violent incident (i.e. during sports, a crash, or collision or the like)'.

Duration of symptoms was assessed with the question: 'How long have you had your knee pain/problems for which you are now having surgery?' with five response options ranging from '0-3 months' to 'more than 24 months'.

Outcomes

The outcome measurement tool was the Knee injury and Osteoarthritis Outcome Score (KOOS), which is a knee specific patient-reported outcome that consist of five subscales: pain, symptoms, activities of daily living (ADL), sport and recreation function (Sport/Rec), and knee-related quality of life (QoL). Each subscale ranges from 0 to 100 (0 representing extreme knee problems and 100 representing no knee problems)[60]. The KOOS has been validated in patients having arthroscopic meniscal surgery[60-62] and has shown to perform well in the continuum from early signs of knee OA to knee arthroplasty[63]. A change of 8-12 points on a KOOS subscale is typically considered to be the minimal clinically relevant change[62 64].

$KOOS_4$

In the two longitudinal studies (paper III and IV) the main outcome measure was the $KOOS_4$, which is the mean aggregated score of four of the five subscales of the KOOS (i.e. pain, symptoms, sport/rec, and QoL) excluding the ADL subscale that has shown ceiling effects in younger and more active populations[65]. $KOOS_4$ has previously been used in randomised trials assessing the effect of knee surgery, including arthroplasty, ACL reconstruction, and APM[13 66 67].

Mechanical symptoms

Patient-reported mechanical symptoms were assessed using two single items from the KOOS symptoms subscale[60]. The sensation of knee catching and/or locking was assessed using the item: ‘Thinking of your knee symptoms during the last week – does your knee catch or lock when moving?’, while patient’s ability to straighten the knee fully (i.e. extension deficit) was assessed with the question: ‘Thinking of your knee symptoms during the last week – can you straighten your knee fully?’. Response options ranged from ‘never’ to ‘always’ on a 5-point Likert scale and patients were categorised as having knee catching and/or locking if not replying ‘never’ and having extension deficit unless replying ‘always’.

In the cross-sectional studies (paper I and II) the two mechanical symptoms items were the outcomes, while they were used as exposures in the longitudinal studies (knee catching and/or locking in paper III, and both items in paper IV).

Surgery data

Details about meniscal pathology and cartilage status were recorded using a modified version of the International Society of Arthroscopy, Knee Surgery and Orthopedic Sports Medicine (ISAKOS) classification of meniscal tears[38], which included the International Cartilage Repair System (ICRS) grading system for scoring cartilage lesions[68]. Additional information on structural knee pathology (i.e. ACL status and presence of synovitis) at arthroscopy was extracted from the patients' surgery reports. As presence of synovitis generally was well described any missing descriptions of synovitis in the surgery reports were considered as no synovitis present. The modified ISAKOS schemes were transferred from paper format to electronic format using automated forms processing[69].

Because participants originally were excluded from KACS if not having a meniscal tear at arthroscopy[55] the modified ISAKOS, including the ICRS, were not completed for these persons. Instead, information about synovitis, cartilage defects, ACL status, and the performed surgical procedure was gathered from surgery reports.

Statistics (paper I-III)

Descriptive statistics are reported as means and standard deviations (SD), median and interquartile range (IQR), or numbers with percentages as appropriate. For all analyses, Stata version 14.2, 15.0, or 15.1 was used.

Paper I and II

Risk and prevalence ratios (RR and PR, respectively) estimated from logistic regression using a method described by Norton *et al.*[70] were used to examine the association between specific meniscal pathology and other structural pathologies with mechanical symptoms (paper I), and having a meniscal tear with mechanical symptoms (paper II). For each mechanical symptom (i.e. dependent variable) a logistic model was fitted.

In paper I, 14 different meniscal pathologies and other structural pathologies (including tear location, tear depth, ACL status, cartilage damage, etc.) were included as independent variables and models were adjusted for age, sex, body mass index (BMI), and if having had previous meniscal surgery on index knee. Categorical and continuous variables were handled as such in the analyses with the exception of the ordinal variables cartilage grade and synovitis, which were handled as continuous.

In paper II, the independent variable was having a verified meniscal tear or not and all models were adjusted for age, sex, and BMI. In addition to the main analyses that included all patients, separate analyses for patients aged 40 years or younger and 41 years or older were also conducted. Furthermore, a subgroup analysis on the association between large longitudinal tears involving at least two of three adjacent meniscal subregions (anterior, body, and posterior horn) with mechanical symptoms were performed.

Sensitivity analyses to assess the robustness of results were conducted using alternative cut-offs for classifying presence of mechanical symptoms (i.e. catching if not replying ‘never’ or ‘rarely’ in paper I, or if replying ‘often’ or ‘always’ in paper II, and inability to straighten knee fully if not replying ‘always’ or ‘often’ in paper I, and replying ‘rarely’ or ‘never’ in paper II).

Before all analyses, independent variables were investigated for collinearity as reflected by the variance inflation factor (VIF). The level of collinearity was not considered a problem if mean VIF was <5 and individual VIFs were ≤10[71]. For all models the underlying assumptions of logistic regression were examined by checking residuals and leverage.

Paper III

The between-group difference in $KOOS_4$ change score from baseline to 52-weeks was analysed using a mixed linear model (restricted maximum likelihood estimation (REML)) with patients nested within surgery site as random effects, and group (mechanical symptoms vs no mechanical symptoms) and time (baseline, 12 and 52-weeks) as fixed effects. All models were adjusted for potential confounding factors, which included age, sex and BMI. The same analysis approach was used for all five KOOS subscales as secondary outcomes. The assumptions for mixed linear models were examined using residual and kernel density plots.

To assess the robustness of results, sensitivity analyses were carried out using an alternative cut-off for classifying patients having mechanical symptoms (i.e. having mechanical symptoms if replying ‘never’ or ‘rarely’). Also, to account for possible ceiling or flooring effects, analyses were repeated using mixed linear tobit regression.

Statistics paper IV

In paper IV the aim was to develop a prognostic model that could predict change in patient-reported outcomes from before to 52-weeks after meniscal surgery and identify patients having a particular favourable outcome. This involved a number of different steps summarised in Figure 7.

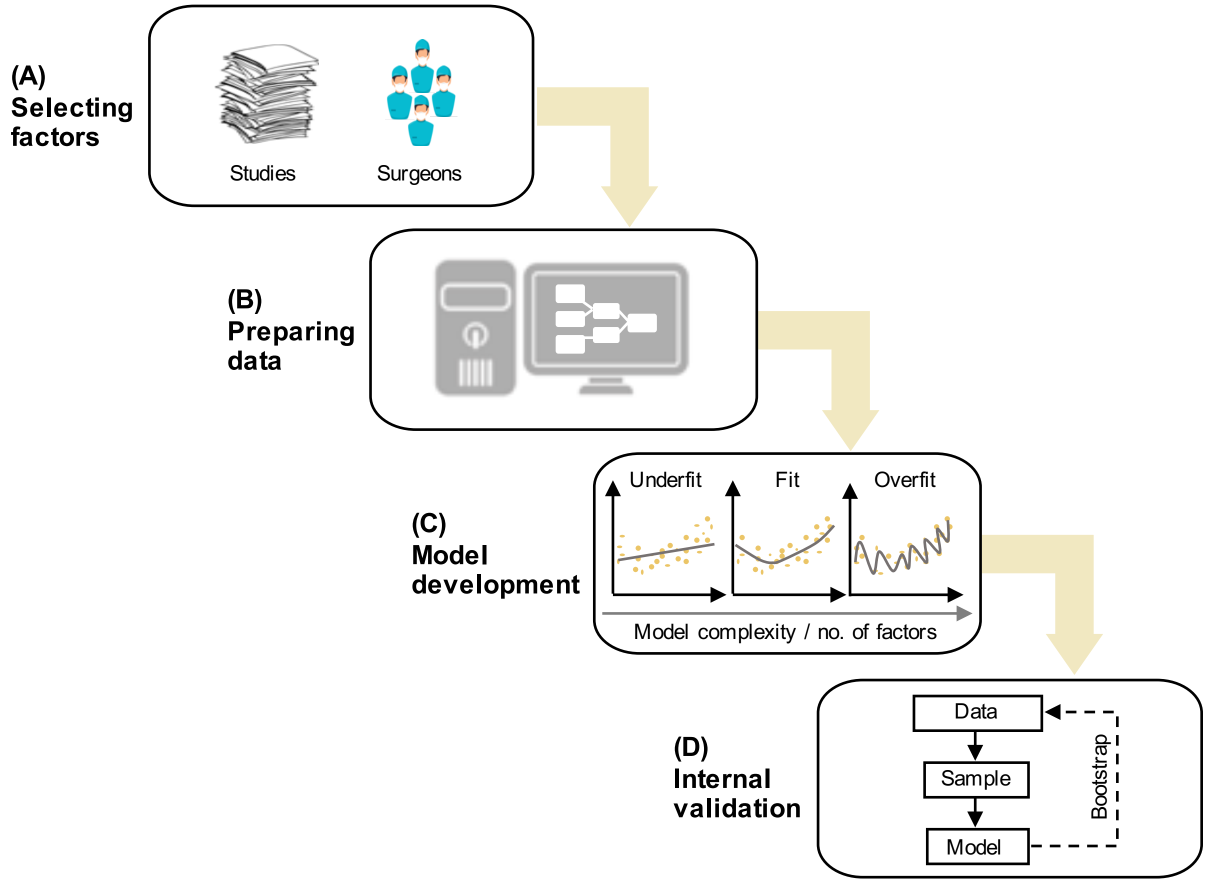

Figure 7. Overview of the steps for developing and internally validating the prognostic model.

Selecting prognostic factors

Among the preoperative factors available in KACS, 26 factors were initially considered for inclusion in the prognostic model. These were identified from published literature suggesting an association with the outcome after meniscal surgery[53 72 73] and/or considered important by orthopaedic surgeons[24 25]. These factors included patient demographics, medical history, knee-related symptoms, etc. Of these, eight factors were omitted with the aim to make the model less complex and more manageable in clinical practice. The omission was based on large correlations with other factors resulting in redundant prognostic information[74] or limited external validity (paper IV's supplementary table 1). Detailed information about the 18 prognostic factors included in the models are available in paper IV's supplementary table 2 and response options are shown in paper IV's table 1 and 2.

Data preparation

Among all patients, the outcome at 52-weeks were missing for 76 (12%) while the number was 29 (19%) among those aged 40 years or younger. Only one patient had missing data in any of the prognostic factors (i.e. previous meniscal surgery). Missing data were imputed using multiple imputation with chained equations[75], under the assumption of data being missing at random[76]. The multiple imputation model included all 18 prognostic factors, the outcome, three interaction terms (i.e. age and knee catching/locking, age and knee extension deficit, and age and symptom onset), and the presurgery and 12-weeks $KOOS_4$ scores as auxiliary variables. Continuous variables (i.e. age, BMI, $KOOS_4$ scores) were kept as linear after multivariable fractional polynomials[77 78] showed no nonlinear relations. A total of 10 and 20 imputed datasets, equal to the proportion of missing data[75], were generated for older and younger patients, respectively, using the 'ice'-package[79] in Stata version 15.1.

As a consequence of categories with sparse data in some categorical factors, and to retain a ratio of ≥20 patients per estimated model parameter[74], categories were collapsed in certain categorical factors. Also, some ordinal categorical factors had categories collapsed if no linearity with the outcome (visually examined using scatter plots), otherwise they were handled as continuous in the models. All continuous factors were modelled as linear as multivariable fractional polynomials did not reveal any nonlinear relations between the factors and the outcome[77 78].

Model development

To predict change in $KOOS_4$ from before to 52-weeks after surgery, multivariable linear regression was used to develop a prognostic model that included all 18 preselected prognostic factors (model I), and for a parsimonious model based on statistical significance (model II). The models were fitted across the imputed datasets and the model coefficients were estimated using Rubin's rules[80]. Three predefined interaction terms (i.e. age and knee catching/locking, age and knee extension deficit, and age and symptom onset) were initially included in the models, but removed, and models refitted, if group significance was $p>0.20$ as tested using multiple Wald test. For the parsimonious model (model II), backward stepwise elimination was performed in the combined imputed datasets. Factors with $p>0.20$ tested with a likelihood-ratio test using the 'mfpmi'-package[81] in Stata version 15.1 were omitted from the model.

Secondary full and parsimonious models for patients aged 40 or younger and patients aged 41 or older, separately, were developed using the same approach. Furthermore, as sensitivity analyses, all models were also developed using only patients with complete data.

Finally, assumptions of linearity, homoscedasticity and normality of residuals were assessed for all models using scatter and Q-Q plots.

The overall predictive performance of all models were examined using the R^2 statistic that measures the proportion of variance explained by the models[82]. Three measures of calibration were used to assess the models' ability to provide unbiased estimates of the predicted outcome[83]: (i) Mean calibration (calibration-in-the-large) measuring the mean difference between observed and predicted outcome (0 indicate no under- or overestimation of predicted outcomes), (ii) weak calibration (calibration slope) reflecting the average strength of predictor effects (1 reflects no under- or overestimation of predictor effects), and (iii) moderate calibration (calibration plot) measuring the agreement between each observed and predicted outcome. The median was used to combine R^2 statistics and calibration slopes across imputed datasets[84], whereas the developed models' calibration-in-the-large and calibration plot were evaluated on patients with complete data.

Internal validation

The bootstrap resampling technique[82] was used to adjust the apparent R^2 for any optimism and estimate an optimism adjusted calibration slope. In 1000 bootstrap samples drawn with replacement from the original sample the entire modelling process was repeated. The models were fitted in each bootstrap replicate and tested on the original data to quantify any optimism in model performances, which was then subtracted from the apparent performances.

Results

Included patients in the KACS cohort were on average middle-aged and slightly overweight (Table 2). Most patients had resection of the meniscus (n=600), 33 had it repaired, while 8 had a combination. Mechanical symptoms in terms of knee caching and/or locking and extension deficit were highly prevalent regardless of age (Table 4), and the most common meniscal tear types were longitudinal-vertical and complex tears among the younger and older patients, respectively (paper III's table I).

Table 2. Baseline patient characteristics.

	Patients *with* a meniscal tear			Patients *without* a meniscal tear
Variables	All (n=641)	≤40 years (n=150)	>40 years (n=491)	All (n=176)
Age, years (SD)	48.7 (13)	30.6 (7)	54.2 (9)	41.6 (13)
Sex, female, n (%)	280 (44)	50 (33)	230 (47)	116 (66)
BMI, kg/m^2 (SD)	27.3 (4.4)	26.4 (4.2)	27.5 (4.5)	26.9 (5.2)
Duration of knee symptoms, n (%)				
0-3 months	129 (20)	41 (27)	88 (18)	35 (20)
4-6 months	181 (28)	24 (16)	157 (32)	42 (24)
7-12 months	135 (21)	31 (21)	104 (21)	24 (14)
13-24 months	94 (15)	20 (13)	74 (15)	31 (18)
More than 24 months	102 (16)	34 (23)	68 (14)	42 (24)
Knee symptom onset, n (%)				
Slowly evolved	208 (32)	29 (19)	179 (36)	66 (38)
Semi traumatic	260 (41)	51 (34)	209 (43)	53 (30)
Traumatic	173 (27)	70 (47)	103 (21)	57 (32)
KOOS, mean (SD)				
$KOOS_4$	45.7 (15.3)	47.7 (16.8)	45.1 (14.8)	43.2 (17.3)
Pain	54.9 (18.5)	58.9 (20.2)	53.6 (17.8)	52.3 (18.9)
Symptoms	60.0 (18.6)	60.6 (19.2)	59.8 (18.4)	56.0 (21.6)
ADL	63.7 (19.5)	69.8 (19.6)	61.8 (19.0)	61.7 (20.5)
Sport/Rec	26.3 (21.9)	31.1 (23.3)	24.9 (21.3)	24.0 (24.0)
QoL	41.6 (15.4)	40.2 (16.1)	42.0 (15.2)	40.1 (16.1)

n: number; SD: Standard deviation; BMI: body mass index; KOOS: Knee injury and Osteoarthritis Outcome Score; ADL: activities of daily living; Sport/rec: sport and recreational activities; QOL: knee-related quality of life.

Mechanical symptoms

Paper I

Most of the 14 specific meniscal tear features and other concurrent structural knee pathologies were not associated with presence of mechanical symptoms of any kind, with RRs close to 1.00 (Table 3). For knee catching and/or locking, only meniscal tears not solely involving the posterior or posterior-mid part of the meniscus were associated with such symptoms, although only tears involving both the posterior and anterior part (24/566 (4%)) were statistically significant (RR 1.49 [95%CI 1.15 to 1.93]). However, sensitivity analyses supported an association between other tears not solely involving the posterior part with catching and/or locking (paper I's supplementary table 2).

Meniscal tears in both menisci simultaneously (49/566 (9%)) and unstable meniscal tears (i.e. longitudinal-vertical and vertical flap tears) (292/566 (52%)) were associated with extension deficit (RR 1.32 [95%CI 1.01 to 1.73], and RR 1.23 [95%CI 1.02 to 1.49], respectively) (Table 3). The latter association, however, were absent in sensitivity analyses (RR 1.06 [95%CI 0.79 to 1.44]). The pathologies strongest associated with extension deficit were partial and complete ACL rupture (29/566 (5%) and 37/566 (7%), respectively) (Table 3), which was consistent in sensitivity analyses (paper I's supplementary table 2).

Table 3. Results from logistic regression for association between meniscal pathology and other concurrent structural knee pathologies with presence of mechanical symptoms of the knee.

Variables	Catching/locking (n=566) Adjusted* RR (95% CI)	Extension deficit (n=566) Adjusted* RR (95% CI)
Tear location (ref: medial, n=420)		
Lateral, n=97	1.00 (0.78-1.27)	1.04 (0.79-1.38)
Both, n=49	0.91 (0.67-1.24)	1.32 (1.01-1.73)
Tear depth (ref: partial, n=225)		
Complete, n=341	0.90 (0.76-1.06)	0.98 (0.81-1.19)
Tear pattern (ref: stable, n=274)		
Unstable†, n=292	1.04 (0.88-1.22)	1.23 (1.02-1.49)
Meniscal tissue quality (ref: non-degenerative, n=232)		
Degenerative, n=318	1.04 (0.85-1.27)	1.22 (0.97-1.54)
Undetermined, n=16	0.57 (0.27-1.21)	1.14 (0.67-1.95)
Length of tear, cm	1.00 (0.91-1.11)	0.97 (0.87-1.08)
Circumferential location (ref: white zone, n=473)		
Red zone‡, n=93	1.02 (0.85-1.21)	1.07 (0.88-1.31)
Radial location (ref: posterior/posterior-mid body, n=469)		
Mid body, n=50	1.18 (0.92-1.52)	1.07 (0.78-1.47)
Anterior/Anterior-mid body, n=25	1.31 (0.95-1.79)	1.26 (0.85-1.86)
All/Posterior+anterior, n=22	1.49 (1.15-1.93)	1.23 (0.81-1.85)
Synovitis, n=211	0.96 (0.90-1.02)	1.06 (0.97-1.16)
ACL status (ref: intact, n=500)		
Partial rupture (non-reconstructed), n=29	0.82 (0.51-1.30)	1.83 (1.47-2.28)
Total rupture (non-reconstructed), n=37	0.97 (0.66-1.44)	1.44 (1.05-1.98)
Plica, n=234	0.87 (0.73-1.02)	1.00 (0.83-1.20)
Knee joint laxity, n=73	0.98 (0.73-1.33)	0.74 (0.49-1.12)
Medial cartilage grade	1.09 (0.99-1.21)	1.03 (0.93-1.15)
Lateral cartilage grade	0.98 (0.88-1.08)	0.93 (0.83-1.04)
Patellofemoral cartilage grade	0.96 (0.88-1.04)	1.00 (0.90-1.11)

n: number; RR: risk ratio; CI: confidence interval; ACL: anterior cruciate ligament. *Adjusted for age, sex, BMI, and previous surgery to the meniscus on the index knee. †Longitudinal-vertical or vertical flap tear. ‡Zone 3 on ISAKOS form.

Paper II

Both knee catching and/or locking and extension deficit were common symptoms in patients with and without a meniscal tear and were not more prevalent among those with a meniscal tear (PR 0.89 [95%CI 0.77 to 1.03] for catching/locking and PR 1.02 [95%CI 0.84 to 1.23] for extension deficit) (Table 4). Results were the same in the analyses for young and older patients separately, although there was a signal of extension deficit being more prevalent in patients with meniscal tears among younger patients, but this was absent in the sensitivity analyses (paper II's table 2 and supplementary table 2). Only in a subgroup of patients with a large longitudinal meniscal tear extension deficit was more prevalent than in patients with no tear (Table 4). Among those patients with no meniscal tear at arthroscopy, the most performed surgical procedures were synovectomy (83/176 (47%)), debridement (72/176 (41%)), and diagnostic arthroscopy alone (46/176 (26%)) (paper II's supplementary table 1).

Table 4. Prevalence of mechanical knee symptoms according to presence or absence of a meniscal tear and the presence or absence of a large longitudinal tear* at surgery.

	Symptom present		Prevalence ratio†
	Yes, n (%)	No, n (%)	Adjusted (95% CI)‡
Catching or locking			
All patients (n=817)			
Meniscal tear present	340 (53)	301 (47)	0.89 (0.77 to 1.03)
No meniscal tear	112 (64)	64 (36)	
All patients (n=216)			
Large longitudinal tear	24 (60)	16 (40)	0.98 (0.75 to 1.28)
No meniscal tear	112 (64)	64 (36)	
Extension deficit			
All patients (n=817)			
Meniscal tear present	292 (46)	349 (54)	1.02 (0.84 to 1.23)
No meniscal tear	88 (50)	88 (50)	
All patients (n=216)			
Large longitudinal tear	30 (75)	10 (25)	1.55 (1.24 to 1.94)
No meniscal tear	88 (50)	88 (50)	

n: number; CI: confidence interval. *Large longitudinal tear was defined a complete longitudinal-vertical tear (i.e. extending all the way through the meniscus tissue parallel to the circumferentially-oriented collagen fibers) involving at least two regions of the meniscus (i.e. posterior horn + body, anterior horn + body or entire meniscus), as reported by the surgeon at arthroscopy. †The prevalence ratio was calculated as the proportion of patients with mechanical symptoms among those *with* a meniscal tear divided by the corresponding proportion among patients *without* a meniscal tear. ‡Adjusted for age, sex and BMI.

Paper III

Patients with preoperative mechanical symptoms had on average worse $KOOS_4$ scores before surgery than patients without such symptoms (Figure 8). However, for younger patients this difference was nearly absent at 52-weeks as those with mechanical symptoms improved more from before surgery to 52-weeks after surgery than patients without mechanical symptoms (adjusted mean difference 10.5 [95%CI 4.4 to 16.6]). This was consistent in all KOOS subscales (paper III's table II). Among older patients, essentially no difference in improvement was observed between those with and without mechanical symptoms (adjusted mean difference 0.7 [95%CI -2.6 to 3.9]). Sensitivity analyses did not change the results much (paper III's supplementary tables IV to VII).

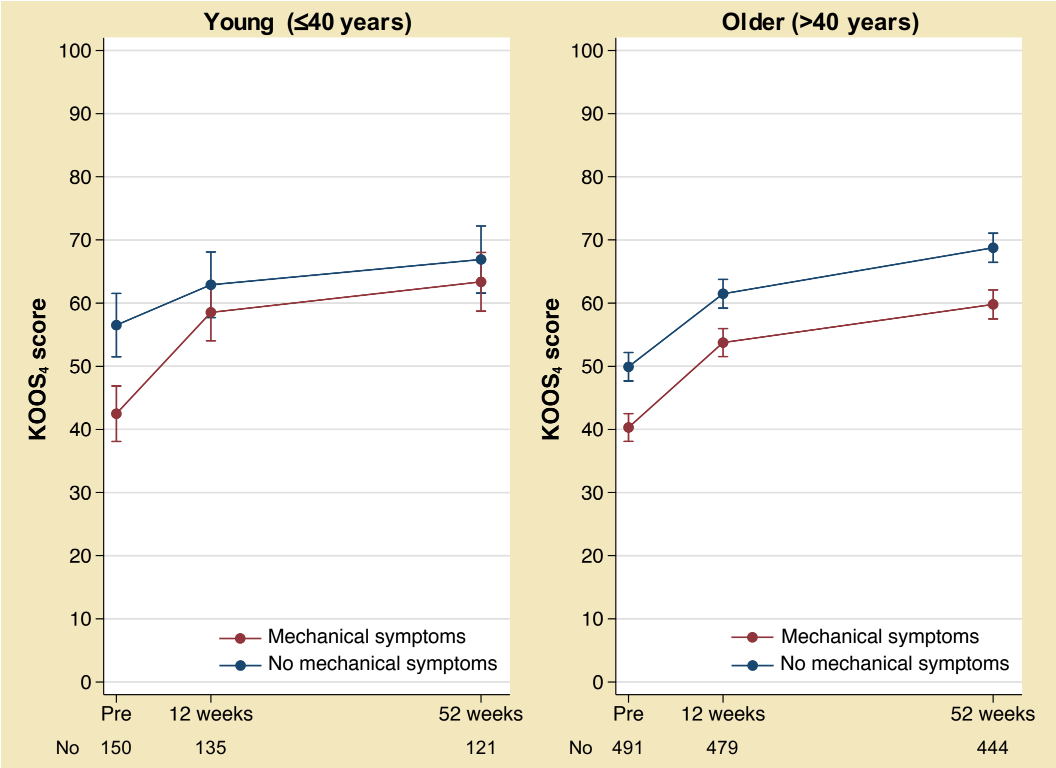

Figure 8. Mean $KOOS_4$ scores for younger and older patients, respectively, with and without mechanical symptoms prior to surgery (complete data available in paper III's supplementary tables II and III). Data are from models adjusted for age, sex and BMI. Bars indicate 95% confidence intervals.

Prognostic models

Paper IV

The average improvement in $KOOS_4$ from before to 52-weeks after surgery was 18.6 (SD 20) for the full cohort, 16.2 (SD 20) and 19.2 (SD 20) for the young and older patients, respectively.

For the main models, the statistically strongest prognostic factors were previous meniscal surgery and knee-related symptoms, and only 9 of the initial 18 factors were retained in the parsimonious model (paper IV's table 3). The secondary models that included younger or older patients separately did not deviate much from these models (paper IV's table 4).

The models' apparent R^2 ranged from 0.13 to 0.42, however were considerably lower after adjustment for optimism (optimism adjusted R^2 0.04 to 0.10). All models had poor weak and moderate calibration as all models systematically overestimated predicted outcomes (i.e. calibration slope <1) and showed little agreement between observed and predicted $KOOS_4$ change scores (Figure 9). Similar results were observed in the sensitivity analyses (paper IV's supplementary table 6 and 7 and figure 1).

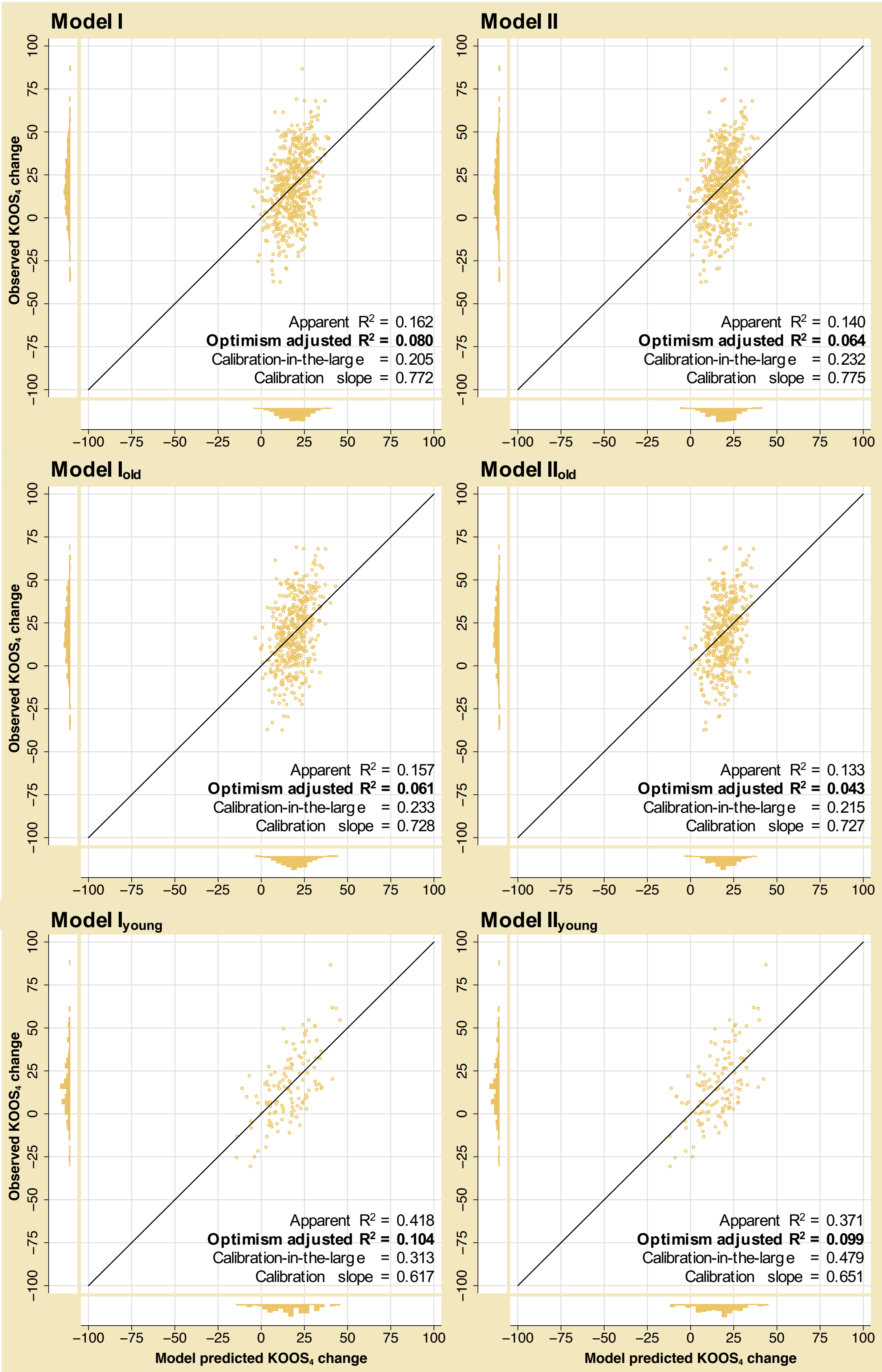

Figure 9. Calibration plots comparing the distribution of observed and model predicted $KOOS_4$ change scores, respectively, and performance measures for all models. A well-calibrated model would be indicated by all predicted values being close to the black identity line.

Discussion

The effectiveness of APM has been questioned in a number of recent randomised trials[6-14]. Still, meniscal surgery is widely performed[1 2], partly based on the assumption that subgroups of patients, including patients with mechanical symptoms, that especially benefit from the procedure exists[24 25]. In this thesis, the aim was to investigate that assumption. In a large clinical cohort of patients undergoing arthroscopic meniscal surgery it was investigated if mechanical symptoms were specific for meniscal tears or certain tear types (paper I and II), and if subgroups with certain characteristics having a particular favourable outcome after meniscal surgery could be identified (paper III and IV).

Main findings

The results showed that mechanical symptoms are common in patients with knee problems undergoing knee arthroscopy irrespective of having a verified meniscal tear (paper II), and that only few, but rare, characteristics of a meniscal tear are associated with the presence of such symptoms (paper I). Younger patients with mechanical symptoms may represent a subgroup benefitting from meniscal surgery (paper III), however the presence of mechanical symptoms in combination with numerous other clinically important factors failed to accurately predict the outcome after meniscal surgery and identify those patients having the most favourable outcome (paper IV).

Mechanical symptoms – features of meniscal tears?

Catching and/or locking symptoms

Mechanical symptoms are often considered a sign of injury to the meniscus and have typically been described as catching and/or locking symptoms[24 25 43 44]. Such symptoms are thought to occur as a result of part of the damaged meniscus getting stuck between the femoral and tibial articular surfaces[48 49]. Indeed, knee catching and/or locking are common in patients with a meniscal tear, with about half of patients reporting such symptoms in this thesis, which is similar to the prevalence found in other cohorts (47% and 64%), despite the use of another questionnaire to assess these symptoms[46 52].

However, in this thesis it was found that knee catching and/or locking were equally prevalent regardless of presence of a verified meniscal tear in patients undergoing arthroscopic knee surgery on suspicion of a meniscal tear (paper II). This was observed even among younger patients only (≤40 years), despite that the tear types believed to be the main cause of catching and/or locking are more common in these patients[33 49]. Of course, other structures such as rupture to the ACL, synovitis and cartilage defects may also cause catching and/or locking[36 51]. However, in the present cohort these pathologies were generally less common in those without a meniscal tear than those with a tear. Furthermore, 1 of 4 patients without a meniscal tear only received diagnostic arthroscopy without any pathology identified. Taken together, this makes it less likely that the high prevalence of catching and/or locking among those patients without a meniscal tear is explained by other structural pathologies and questions the relationship between structural changes and patient-reported knee catching and/or locking.

The lacking relationship between structural changes and patient-reported catching and/or locking is supported by the results of paper I in this thesis. Here it was found that 13 out of 14 different meniscal characteristics and other structural pathologies were not associated with catching and/or locking symptoms, and the assumption of specific tear types being unstable and likely to cause such symptoms[49] was not supported. This finding is in line with a previous study that involved 227 knees[85], but contrary to another study in which flap tears were associated with such symptoms[86]. However, that study was a small case-series of 8 meniscal tears and did not adjust for other knee structures. The only specific meniscal pathology associated with catching and/or locking in this thesis were tears not solely involving the posterior or posterior-mid body of the meniscus. The strength of the association was not consistent in the main and sensitivity analyses and the association is only partly supported in the literature. One case-series also reported catching more frequent in patients with a tear located in the middle part than the posterior alone[86]. In contrast, a cross-sectional study of 227 knees failed to observe any difference in prevalence of such symptoms between tears located in different parts of the meniscus[85].

Extension deficit

This thesis also included the inability to straighten the knee fully (i.e. extension deficit) as a mechanical symptom, although less commonly described as such in patients with meniscal tears. Similar to catching and/or locking symptoms, extension deficit was a common symptom irrespective of having a meniscal tear or not and reported by half of patients. However, contrary to catching and/or locking, extension deficit was more prevalent in a subgroup of patients having large longitudinal tears compared to patients with no meniscal tear (paper II). This association was partly supported in paper I where unstable tears (i.e. longitudinal-vertical and vertical flap tears) were associated with higher risk of extension deficit in the main analysis but not in the sensitivity analysis. The reason for this discrepancy might be the different definitions of tears used in paper I and II. In paper I, unstable tears included all longitudinal-vertical and vertical flap tears, whereas paper II in the subgroup analysis only included large longitudinal-vertical tears (i.e. tears involving at least two adjacent parts of the meniscus). Also having a meniscal tear in both knee joint compartments simultaneously and a partial or total ACL rupture were associated with extension deficit.

Compared to knee catching and/or locking symptoms, extension deficit is less commonly described as an indication for meniscal surgery[24 25 43 44]. Nevertheless, the results of this thesis suggest that extension deficit is more related to meniscal pathology than knee catching and/or locking symptoms. The results also support that some tear types such as large longitudinal tears might cause mechanical symptoms, but a different kind than the one normally described. Notably, however, structures found associated with any kind of mechanical symptoms were rare findings compared with the frequency of such symptoms. Thus, only a minority of mechanical symptom cases may be explained by presence of specific meniscal pathology, indicating that such symptoms are non-specific and common among patients with knee problems. The concept that knee symptoms originate from a meniscal tear has furthermore been challenged by Tornbjerg *et al*., who failed to find any associations between specific meniscal pathology and symptoms, including pain and physical impairments[87], and by the fact that meniscal tears on MRI are common findings in asymptomatic middle-aged and older persons[35].

Subgroups of patients benefitting from APM – do they exist?

Mechanical symptoms

Recent surgical guidelines and consensus statements still argue that patients with meniscal tears and concomitant mechanical symptoms represent a distinct subgroup that benefits from arthroscopic meniscal surgery[43-45]. This relies on the biomechanical rationale that meniscal tissue can get stuck between articular surfaces and needs to be physically (i.e. surgically) removed to alleviate symptoms[49]. However, this has recently been challenged by a secondary analysis of a randomised trial including patients with degenerative meniscal tears that showed no difference in improvement between APM and sham surgery in a subgroup of patients with mechanical symptoms [52]. Additionally, a cohort study that included 900 middle-aged and older patients with degenerative meniscal tears found those with and without preoperative mechanical symptoms to have similar improvements after surgery[46]. The results of this thesis are generally in line with these studies, as no difference in improvement was observed between patients with and without mechanical symptoms among middle-aged and older patients (paper III). In contrast, younger patients with preoperative mechanical symptoms in terms of knee catching and/or locking had on average clinically important larger improvement in $KOOS_4$ at 52-weeks after surgery than young patients without such symptoms. Still, although all groups improved, $KOOS_4$ scores did not reach population-based KOOS scores from Sweden on individuals aged 18-34, 35-54, and 55-74 years[88]. The results contradict that patients with mechanical symptoms among middle-aged and older patients should represent a subgroup particularly benefitting from meniscal surgery. In contrast, a subgroup benefitting from meniscal surgery may be younger patients with mechanical symptoms. However, the observed improvements varied considerably within these patients, thus such symptoms alone are unlikely to accurately identify patients that will benefit from meniscal surgery.

Combination of factors

Besides mechanical symptoms, a number of other factors are also considered important for the outcome after meniscal surgery[24 25 53], but are unlikely to independently identify patients having a certain outcome[53]. Therefore, this thesis developed prognostic models combining the additive prognostic performance of a number of factors considered clinically important[24 25 53] (paper IV). Yet, all models failed to accurately predict and identify patients having a particular outcome after surgery. The majority of patients used for the development of the models were middle-aged and older, which reflects current clinical practice[1 3]. In all models, knee-related symptoms were the statistically strongest individual prognostic factors, however the combined prognostic performance differed substantially between models. In the models that mainly included older patients the prognostic performance was poor, while the models that only included younger patients had promising apparent prognostic performance.

The observed differences between younger and older patients, are likely a consequence of difference in pathology. In older patients, meniscal tears are typically degenerative and associated with OA[32 33]. This was also true in the present cohort, where the majority of middle-aged and older patients had a degenerative meniscal tear and nearly half had severe cartilage defects (i.e. ICRS grade 3 or higher) in at least one knee joint compartment (paper III' table I) indicative of early or more pronounced stages of OA[89]. The symptoms are therefore likely to be a result of the multiple and complex processes of OA rather than the meniscal tear[36]. This may explain the poor ability of knee symptoms, including mechanical symptoms, to accurately predict the outcome after a treatment that targets the meniscal tear in middle-aged and older patients. In contrast, younger patients more often have a non-degenerative tear in an otherwise healthy knee joint and a larger proportion of tear types considered the cause of mechanical symptoms[32 33]. This fits well with what was seen in the present thesis and makes it more likely that symptoms in fact origin from the meniscal tear or is a consequence of loss of meniscus function. Thus, in younger patients the connection between knee symptoms and meniscal tears is more likely to exist and might explain the better apparent prognostic performance and ability to identify patients having a particular outcome after meniscal surgery. Importantly however, the prognostic performance of the models that included younger patients alone was severely over optimistic due to the small sample size used, thus the results of these models should be considered explorative.

Some other studies have investigated if APM was more effective in specific subgroups such as patients with traumatic meniscal tears or preoperative mechanical symptoms, but were unsuccessful in finding any additional benefit of APM for these patients[12 52 90]. Different from those studies, this thesis added several other clinical factors and combined their prognostic ability using data from a large clinical cohort that included a heterogeneous population in which the average improvement after meniscal surgery was similar to the improvements observed in previous RCTs[16 91 92]. Overall, the results of this thesis do not support the existence of certain subgroups of patient having specific characteristics among middle-aged and older patients that particularly benefit from meniscal surgery. Thus, the observed variations in improvement observed in this thesis and the surgical arms of previous RCTs[16 91] may just reflect random variation, and not a sign of the existence of certain subgroups having a particular favourable outcome after meniscal surgery.

Limitations

This thesis is based on observational data, thus no firm conclusions can be drawn regarding any causality between meniscal tears and mechanical symptoms, nor if mechanical symptoms cause greater improvement after meniscal surgery as seen for younger patients, or is just a result of greater room for improvement or regression to the mean[93]. The latter goes for any of the included prognostic factors as well, however is of less importance when developing a prognostic model where the aim is to predict and not explain the outcome[54].

Presence of mechanical symptoms was defined using two single items from the KOOS symptom subscale, which is a validated knee specific patient-reported outcome[60 61]. Still, presence or absence of symptoms was based on an arbitrary cut-point that may have affected associations, however most results did not change much in sensitivity analyses using alternative cut-points. In addition, the definition of mechanical symptoms in the literature is rather vague[43], and ‘locking’ may be comprehended differently between and within patients and clinicians as either “true locking” (i.e. mechanical symptoms/structural cause) or “pseudo-locking” (i.e. muscle spasm/functional cause)[94]. However, this likely reflects the non-standardised use of such terms in clinical practice. Finally, given that extension deficit seemed more associated with meniscal tears than catching and/or locking symptoms (paper I and II), the use of this term as the exposure in paper III could potentially have yielded different results. Still, it was included in the prognostic models, which performed poorly anyhow.

Although validated methods were used to collect information about knee pathology[38 68], misclassification of these may still have occurred. In particular for patients not having a meniscal tear for whom surgery data were collected in a less standardised way. Also, the classification of meniscal tears into stable or unstable tears as defined by Mordecai *et al.*[49] may potentially have affected any association in paper I, as some complex tears may also be unstable. These could not be distinguished between in this thesis.

A large number of different factors believed to be important for the outcome after meniscal surgery was included in the prognostic models (paper IV)[53 72]. Yet, some factors might have been missed. Perhaps most importantly, information from preoperative MRI was not available in the KACS cohort, thus information about presence of specific meniscal pathology was not included in the models. This could have had an impact on the models' prognostic performance for especially the younger patients in which meniscal pathology theoretically and based on the results from paper I and II may be important. For older patients, however, MRI is generally not recommended due to limited clinical relevance as meniscal tears are frequent incidental findings on MRI in asymptomatic patients[35]. Of other factors missing are radiographic knee OA and workers compensation, which have been associated with the outcome after meniscal surgery[53 72 95], but these were unavailable in KACS. If any missing factors should improve the models substantially, they would need to be strongly associated with the outcome and weakly associated with already included prognostic factors[82]. That makes it less likely that any missing factors potentially would have a considerable impact on the models' performances.

All prognostic models, except those solely including younger patients, had sample sizes sufficient to maintain a ratio of 15-20 patients per model parameter as recommended at the time models were developed[74]. Yet, all models were severely overfitted as illustrated by the large degree of optimism and overestimation of predictor effects (i.e. calibration slope considerably lower than 1). Based on calculations from a recent guideline for the required minimum sample size, the necessary total number of patients for the full model (including all patients) are 1329 to avoid overestimation and optimism[96]. Importantly however, a sufficient sample size will mainly reduce the optimism in models, but not increase the apparent performance[82]. Thus, it is unlikely that the models would perform better despite larger sample sizes.

The external validity of this thesis is believed to be high as demographics in terms of age and sex of included patients are similar to what has previously been reported for patients undergoing arthroscopic meniscal surgery in Denmark[3] and the United States[97].

Clinical and research implications

The results of this thesis contradict the common tenet that mechanical symptoms are a signifying feature of a meniscal tear, but rather symptoms that appear in patients with knee problems in general. Thus, clinicians should be cautious to conclude that patient-reported mechanical symptoms, even in the presence of an MRI verified meniscal tear, is attributable to that tear. Only for a small minority of mainly younger patients who have a large longitudinal tear, the symptoms might be caused by the meniscal tear and warrant surgery. However, RCTs that include younger patients with meniscal tears are needed to confirm if younger patients in general, or those with mechanical symptoms represent subgroups that benefit from meniscal surgery.

For middle-aged and older patients this thesis provides no evidence of the existence of presumed subgroups of patients having a particular favourable outcome after APM. This despite that a large number of factors regarded as clinically important for the outcome after meniscal surgery were considered in a prognostic model. Arguably, there might still be some patients with meniscal tears where APM is more effective than other treatments, for instance in patients with a chronically locked knee. However, such symptoms are rare in the clinic. Consequently, although the number of arthroscopic meniscal procedures in Denmark has declined in recent years (Figure 10), the amount of surgeries on middle-aged and older patients is still high considering the likely small proportion that may actually benefit from the procedure.

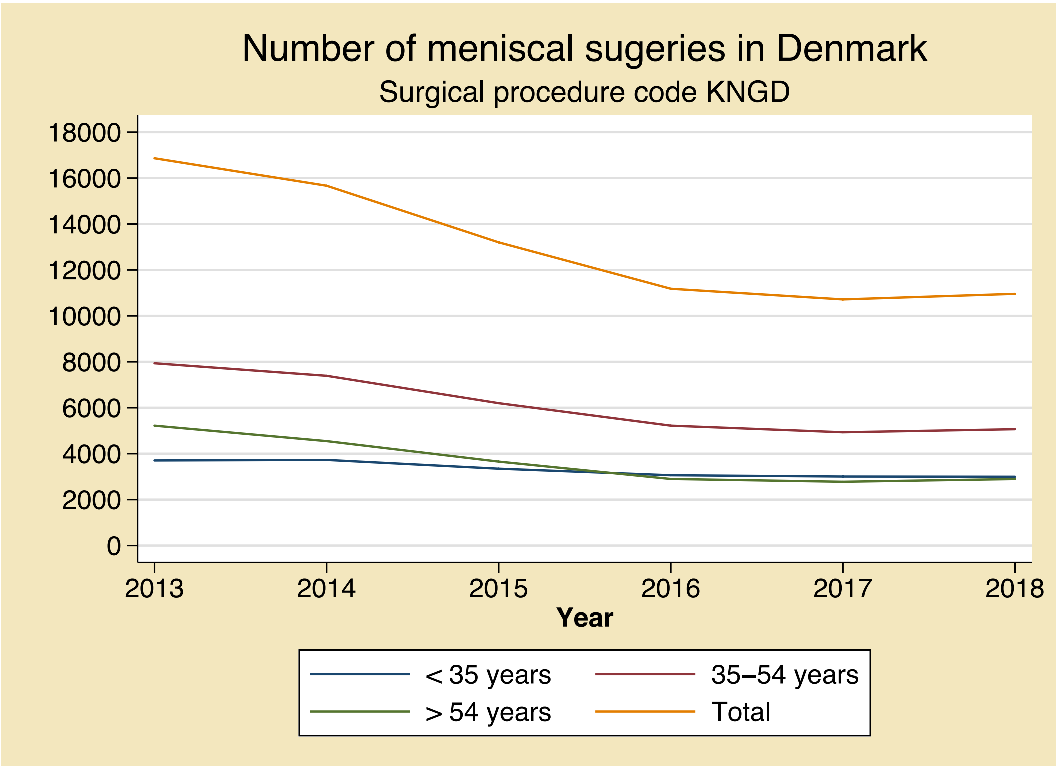

Figure 10. Number of meniscal surgeries performed in Denmark from year 2013 to 2018. Data from the Danish National Patient Register (DNPR).

Conclusion

This thesis investigated the relationship between mechanical symptoms and meniscal tears and if subgroups of patients with certain characteristics benefitting most from meniscal surgery could be identified. The results showed that mechanical symptoms are not specific for meniscal tears or tears with certain characteristics, but a common symptom in patients with knee problems. Furthermore, although younger patients with mechanical symptoms experience larger improvements after surgery, the combination of a number of factors considered important for the outcome after meniscal surgery could not accurately predict change in patient-reported outcomes and identify patients improving most after meniscal surgery. Overall, the results question the importance of mechanical symptoms as an indication for surgery in the majority of patients with meniscal tears and that subgroups with certain characteristics among middle-aged and older patients having a particularly favourable outcome after meniscal surgery exists.

Summary

A series of high-quality randomised controlled trials have failed to find any additional effect of arthroscopic partial meniscectomy (APM) compared to placebo surgery or in addition to exercise therapy for patients with degenerative meniscal tears. Still, meniscal surgery is widely performed, partly because certain subgroups of patients having a particular favourable outcome after APM are presumed to exist. Evidence of what constitutes such subgroups is sparse, although a number of different factors, including presence of mechanical symptoms (i.e. the sensation of catching and/or locking of the knee), are argued as important for the outcome after meniscal surgery.

The aims of this thesis were to identify which patients that might benefit most from arthroscopic meniscal surgery, and investigate the common, however unproven tenet that mechanical symptoms are signifying symptoms for meniscal tears. For this, data from a large prospective cohort of patients having knee arthroscopy on the suspicion of a meniscal tear were used.

In paper I, out of fourteen different characteristics of a meniscal tear and other concurrent structural pathologies, only few and rare pathologies were slightly associated with self-reported mechanical symptoms.

In paper II, mechanical symptoms were equally prevalent in patients undergoing knee arthroscopy regardless if having a verified meniscal tear at arthroscopy.

In paper III, younger patients with preoperative mechanical symptoms had clinically important larger improvements than those without such symptoms. This was not found among older patients.

In paper IV, despite combining 18 factors considered clinically important for the outcome after meniscal surgery in a prognostic model, the outcome after meniscal surgery could not be accurately predicted.

The findings question the clinical importance of mechanical knee symptoms as an indication for meniscal surgery. Although younger patients with mechanical symptoms had larger improvement after surgery, the prognostic model was unable to accurately predict outcome after meniscal surgery and identify patients having a particular outcome. This largely bust the myths of existing subgroups with certain characteristics having a particularly favourable outcome after meniscal surgery.

Dansk resumé (Danish summary)

Studier har gentagne vist, at meniskkirurgi ikke har større effekt end placebokirurgi og ikke-kirurgiske behandlinger, herunder træningsterapi, for patienter med degenerative meniskskader. Alligevel er meniskkirurgi fortsat en af de hyppigst udførte ortopædkirurgiske behandlinger. En del af årsagen er en stærk tro på, at der findes specifikke undergrupper af patienter, som har særlig effekt af kirurgi. Viden om hvad der karakteriserer disse patienter, er dog mangelfuld. Forskellige faktorer antages at have betydning for effekten af meniskkirurgi, herunder såkaldte mekaniske symptomer defineret som at knæet låser eller hager sig fast, men dette mangler at blive bevist.

Formålet med denne afhandling var at identificere hvilke patienter, der har størst effekt af meniskkirurgi, samt undersøge den almene, dog udokumenterede teori, at mekaniske symptomer er specifikke for meniskskader. Til dette blev brugt data fra en stor prospektiv kohorte af patienter, der undergik kikkertkirurgi som følge af mistanke om meniskskade.

I artikel I blev fundet at ud af 14 forskellige specifikke karakteristika ved meniskskader og andre samtidige knæskader, var kun enkelte og sjældne karakteristika svagt associerede med selvrapporterede mekaniske symptomer.

I artikel II blev det fundet at mekaniske symptomer hos patienter, der fik kikkertkirurgi, var lige hyppigt optrædende ligegyldigt om de havde en meniskskade eller ej.

I artikel III sås det, at yngre patienter med præoperative mekaniske symptomer forbedrede sig klinisk relevant mere efter meniskkirurgi end patienter uden sådanne symptomer. En sådan forskel blev ikke fundet hos ældre patienter.

I artikel IV blev 18 faktorer, der betragtes at være vigtige for udfaldet af meniskkirurgi, kombineret i en prognostisk model. Alligevel kunne udfaldet efter meniskkirurgi ikke forudsiges i tilstrækkelig grad.

Resultaterne betvivler den kliniske værdi af mekaniske knæsymptomer som indikation for meniskkirurgi. Trods yngre patienter med sådanne symptomer havde større forbedring efter kirurgi, blev dette ikke afspejlet i den prognostiske model, som ikke kunne forudsige udfaldet efter kirurgi og identificere patienter med særlig effekt af meniskkirurgi. Samlet underbygger fundene ikke, at der skulle findes bestemte grupper med specifikke karakteristika, som har særlig favorabel nytte af meniskkirurgi.

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Appendices

Paper I

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Paper II

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Paper III

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