Discussion

The work presented in this thesis was part of an EU initial training network, the KneeMo project, which includes fifteen research fellows at eight host institutions. The overall research theme for the KneeMo project is to move “towards targeted and tailored interventions fore knee osteoarthritis”. Our overarching aim for this specific project within the overall network was to investigate the use of gait retraining for reducing the knee adduction moment (KAM) in people with medial knee osteoarthritis (KOA). We had further three specific aims, which are individually discussed in the following sections of this discussion. The specific aims of this project were:

1. To investigate how different types of feedback can influence changes in the knee joint kinetics while walking in a modified gait pattern.
2. To investigate the feasibility and effects (both short and longer-term) of a six-week gait training program, targeted to train patients with medial KOA to walk in a way which reduces the KAM.
3. To investigate the relationship between the KAM (and changes therein) and the knee contact forces.

The project started with a systematic review to evaluate the effects of different types of feedback delivery (audio, haptic or visual) and the response of people to direct feedback on the KAM itself vs. response to indirect feedback (on a parameter assumed to influence the KAM). Following this, we recruited 40 patients with medial KOA to a single-session study where we assessed the effects of using direct feedback on the KAM with and without specific instructions of which kinematics to modify. This study was used to inform our longitudinal study, in which we assessed the feasibility and effects (both short and longer-term effects) of a toe-in gait retraining program of six weeks on the KAM, knee flexion moment (KFM), knee pain and functional ability. In collaboration with Aalborg University, we investigated the relationship between the KAM and the knee contact forces and the effects of gait modifications on the forces. Finally we investigated the effects of toe-in and toe-out gait modifications on the KAM, knee flexion moment (KFM) and the KAM impulse and the factors influencing these relationships through systematic review of the literature.
Based on the above studies we conclude the following:

1. In healthy controls walking with a modified gait pattern, direct feedback on the KAM tends to produce a larger effect on the KAM than indirect feedback.
2. KOA patients require specific kinematic instructions alongside the direct feedback to consistently reduce the first peak KAM and KAM impulse.
3. After six weeks gait training focusing on walking with toe-in gait, KOA patients are able to reduce the first peak KAM without receiving feedback.
4. Functional ability was also improves after the training program with a trend towards lower knee pain.
5. At three and six-month follow-up measurements, the effect of the training program starts to wash-out although first peak KAM is on average still reduced compared to the baseline measurements.
6. KAM and KFM together provide a reasonable representation of the medial knee contact force (KCF) based on statistical and musculoskeletal modeling, but the effects of the gait modifications on the medial KCF is limited.
7. Toe-in gait reduces first peak KAM and toe-out gait reduces second peak KAM with a linear dose-response relationship between the foot progression angle and the change in KAM (both first and second peak).

In the following sections we firstly discuss the results of the studies in this thesis in relation to our three primary hypotheses, and then present the limitations of this project followed by recommendations for future research, implications for clinical practice and finally our overall conclusions.

1. Hypothesis I: Direct feedback with implicit instruction is more effective for training a modified gait pattern to reduce KAM than direct feedback with explicit instructions on how to modify the kinematics

In part one of this thesis we investigated the effects of different feedback modalities and delivery on the resulting change in KAM during biofeedback gait training. For the purpose of this project we defined direct feedback as feedback on the parameter that we are trying to modify, the KAM, and indirect feedback as feedback on a parameter that has (or is expected to have) an influence on the KAM, such as foot progression angle. Based on our systematic review of the literature (chapter two) of studies using biofeedback to teach gait modifications to reduce the KAM, we found that there was insufficient evidence to support the use of either direct over indirect feedback and that there were a very limited number of studies using direct feedback\(^1\). However, we observed a strong trend towards higher KAM reductions in studies using direct feedback compared to those using indirect feedback. Larger performance gains, both in terms of initial skill acquisition and skill retention, when using direct vs. indirect feedback, which can also be considered as an internal vs. external focus of attention, have repeatedly been shown in sports research\(^2\). This evidence, together with the results from our systematic review provided the motivation for the use of direct KAM feedback in our first experimental study (chapter three)\(^3\). We hypothesised that being able to self-select a gait strategy to reduce the KAM would result in the modified gait pattern being internalised more quickly than an imposed specific kinematic modification. However, we found that patients had substantial difficulty in selecting and maintaining their own gait strategy using this method and required specific kinematic instructions in order to consistently walk with a reduction in the KAM. This may have been influenced by the length of time we allowed for the patients to practice walking with KAM feedback (2 minutes). With additional time, we may expect improved results, as shown by Jackson, et al. (2017)\(^4\) who allowed study participants to walk for 15 minutes with direct feedback.

Direct feedback can be used in combination with implicit instructions (instructions on the end goal) or with explicit instructions (step-by-step focussed kinematic instructions). Explicit instructions are analogous to an internal focus of attention (attention on the body movements producing the effects) while implicit instructions can be considered analogous to an external focus of attention (focus on the effects of the movements)\(^2,5\). When we provided patients with explicit instructions on how to modify their kinematics, together with indirect feedback on a specific parameter, such as foot progression angle, patients were able to walk with a modified gait pattern. When indirect feedback was replaced with direct feedback, patients were generally able to maintain the modified gait pattern and the KAM reduction. Hence, from this study it appears that a combination of direct feedback with explicit instructions is more effective for training the gait modification than direct feedback with implicit instructions.

Regarding the mode of delivery of the feedback, our systematic review found no clear distinction between haptic and visual feedback. Insufficient numbers of studies used audio feedback, thus we were unable to compare this modality. In our experimental study we compared the effects of audio and visual feedback. While the patients' responses (in terms of change in KAM) were similar, patient preference was for visual rather than audio feedback. Haptic feedback, which can be delivered via a discrete wearable sensor, may be the most practical and clinically viable option for long-term training as it leaves the visual and auditory channels free for information processing. However, in the first stage of motor learning (during which the skill is being acquired), visual feedback providing movement guidance may be required,
until such a time that the patient progresses from the first to the second stage of learning, where cognitive demand reduces. A review of the effects of different types of feedback on motor skill learning suggests that the effectiveness of visual feedback may also depend on the complexity of the task. Furthermore, the authors suggest that multi-modal feedback (i.e. audio-visual or visual-haptic) may be more effective than uni-modal testing due to a reduction in the cognitive loading as a result of distributed information processing. To date this theory has not been tested in the field of gait modifications with KOA patients.

Our hypothesis that direct feedback with implicit instructions would be more effective than direct feedback with explicit instructions in producing a KAM reduction was not proven to be true. Through chapters two and three we have provided new contributions to the literature as described above. Nonetheless, further research is still needed to optimise feedback delivery during gait retraining in KOA patients.

2. Hypothesis II: Six week’s gait training would result in short (6 weeks) and longer-term (3 and 6 months) reductions in KAM as well as improvements in pain and function

In part two of this study, we investigated the feasibility and effects of a six-week gait retraining program for reducing the KAM as well as investigating the learning process behind the changes in the gait modifications. Given that patients in our first experimental study (chapter three) did not respond as well as expected to direct feedback with explicit instructions, our longitudinal study was designed to use indirect feedback on the foot progression angle. In the last decade, five studies with KOA patients have presented the immediate-term effects (within-session effects) of changes in the foot progression angle, FPA, (toe-in or toe-out gait) on the KAM.

In our systematic review and meta-analyses in chapter seven, we confirmed the findings of Simic, et al. (2013) and van den Noort, et al. (2013) that toe-in gait tends to reduce the first peak KAM while toe-out gait tends to reduce the second peak. However, the longer-term effects have been largely neglected in the literature, with follow-up limited to one-month post-training. In our longitudinal study (chapter four), we followed up patients at three and six months post-training to obtain an insight into the longer-term changes in the knee moments. While this is a longer period than previously investigated, we acknowledge that six months is still not a long period for someone with a chronic condition. For example, in longitudinal studies investigating changes in cartilage thickness, changes are assessed over several years instead of several months.

2.1 Effects on kinematics and kinetics

After a six-week training program, to walk with toe-in gait, patients were able to reduce the first peak KAM (chapter four). Effects on the KAM were observed when patients walked without feedback (natural walking trial) and increased further when patients were asked to concentrate on their gait pattern (retention trial). We also saw a similar effect regarding the FPA. The KAM impulse, representing the area under the KAM curve was not significantly reduced between week one and week six. The data indicates that the modified gait pattern was not maintained in all patients, leading to a wash-out effect at the three and six-month post-training measurements. This suggests that in order to maintain the effects more frequent training may be needed to maintain the modified gait.

In comparison with data from another toe-in gait retraining study from Shull, et al. (2013), we found a smaller effect on the first peak KAM. However, this is likely explained by the smaller change in FPA in our study compared to the former. A comparison of the data from our study (chapter four) and the data from Shull, et al. (2013) performed their follow-up measurements at one month post-training whereas we followed up at three and six months; hence the data are not perfectly comparable. In both studies, a significant reduction in first peak KAM was observed between the start and end of the training program (between week one and week six). In the study of Shull, et al. (2013) this effect was still evident at one month follow-up. In our study the line between the end of the training period (week six) and the three month follow-up is flat (no difference between week six and three month follow-up data). However using repeated measures ANOVA (for within subject analysis) we did not find any significant difference between the week one and three month follow-up data. The reason for this is the heterogeneity of our study group: we found that while some people maintained the KAM reduction and in some the KAM was even further reduced compared to week six, we also observed that the KAM increased again in some patients. We will address this in more detail in section 2.3 of this discussion. From personal communication with Shull (ISB congress 2017, Brisbane Australia), we learnt that there were also some non-responders in their study. Differences in the methods of the two studies may also have resulted in differences in the results, for example while we used visual feedback during the training, Shull, et al. (2013) used haptic feedback. While a direct comparison of these two feedback modalities has not been undertaken in the context of gait retraining over a longer period, we may suspect that haptic feedback would be more effective in producing a longer-term effect, because it allows for more training opportunities.
2.2 Effects on pain and function

We found significant improvements in the functional ability after the six-week training program. Knee pain reduced in some participants, but increased or remained stable in others, meaning that there was no significant change in this parameter at the group level. While the knee joint moments were the primary outcome measures, it was important for us to measure changes in pain and functional ability since we assumed that a reduction in KAM would lead to a reduction in pain and an improvement in functional ability. Furthermore, the ultimate clinical success of a treatment for KOA patients is likely to be judged on its ability to reduce pain, improve function and delay the need for a knee replacement.

Interventions that target a reduction in KAM, such as gait retraining, unloader braces and lateral wedged insoles often consider changes in pain and function alongside the changes in biomechanical parameters. However, the relationship between knee pain and KAM is also not clearly defined and has been shown to be modified by KOA severity, with a negative relationship between pain and KAM in patients with less severe KOA. The negative relationship in less severe patients is suggested to be a compensatory mechanism to reduce mechanical loads at higher pain intensities. While this theory is supported by studies which show that peak KAM increases with use of pain relief, it may not hold true for longitudinal studies where the intervention aims primarily to reduce the KAM. For example, commonly patients using a knee unloader brace or orthotic wedge with the aim of reducing the KAM also report a reduction in pain. Hence, there is evidence to expect a positive correlation between KAM reduction and pain reduction, even if baseline relationships predict the opposite. Despite this, a recent randomised control trial (RCT) using a lateral wedged insole as the intervention found no relationship between KAM reduction and change in self-reported pain with the majority of the variance in the pain scores explained by baseline pain levels. Given this, future studies in gait retraining (particularly randomised control trials, RCTs) should carefully control for baseline pain levels in the design of the studies.

2.3 Responders and non-responders

In our studies, we defined responders as those achieving a reduction of greater or equal to 10% of the baseline KAM. Nevertheless, a change of less than 10% may still be clinically significant, particularly considering the effect of cumulative loading over a period of a day, a week or a year.

Post-hoc testing of the data from our longitudinal study showed that of the 16 patients who completed all training sessions, 11 were able to reduce the first peak KAM by 10% or more (during normal walking or during retention condition at the end of the training program). We defined these people as responders. At the three-month follow-up, there were eight responders, but only five at the six-month follow-up. The change in the target kinematics (FPA and step width) between the end of the training program and the follow-up measurements was generally small on the group level, particularly during baseline walking. Some subjects walked with more toe-in after the end of the training program whilst others went back to their baseline levels (non-responders). Yet others were able to modify their FPA to some extent but started to walk with other compensations, such that the KAM did not reduce. All patients who were included in our longitudinal study had previously participated in our cross-sectional study from which patients were selected for the training study. Thus, at the outset of the longitudinal study we expected all participants to respond to the intervention (toe-in gait). However, this was somewhat contrary to what we found; not all of the subjects responded as expected. Future studies could also consider responders and non-responders based on the KFM or the KAM impulse, both important parameters in knee joint loading and progression of KOA respectively.

Responders and non-responders might also be defined by the change in pain and/or functional ability with responders defined as people whose change in pain/function equals or exceeds the minimal clinically important difference (MCID). However, since our primary aim was to change the knee kinetics and our secondary...
aim was to reduce pain and improve pain, our study was not designed appropriately to use this definition. It is, however, likely to be the most important parameter in terms of transfer of the intervention to clinical practice and therefore future studies might take this into account during the design of the study. Responders may also be defined based on changes in the radiographic features or changes in cartilage stresses assessed through finite element modelling.

**2.4 Learning and Retention of the Modified Gait Pattern**

In *chapter five*, we present an analysis of the learning effects during the gait retraining program. This is important to consider, as well as the biomechanical effects, in order for gait retraining to become a useful clinical therapy. Our results suggest that while patients could adapt their gait pattern, walking with the modifications required additional cognitive demand to place the foot in the correct position. Walking with an unmodified gait pattern is generally an autonomous process, requiring little or no cognitive effort. Through the gait retraining program, we were unable to modify the gait pattern to this extent, suggesting a lack of slow learning and neuronal reorganisation. To increase the slow learning, additional practice time is required. Informal discussions with clinicians at Reade, Centre for Rheumatology and Rehabilitation, Amsterdam, suggest that one way of achieving this may be to train patients not only to walk with modified gait pattern, but also to stand from a chair and climb stairs with the target modifications, thus incorporating the modification into more activities of daily living. Furthermore, increased training time could be facilitated using a wearable device to provide feedback on the FPA. Haptic feedback is suggested to be more effective in retention of a learnt effect and can be configured to in a small, discrete, wearable sensor for use outside of the lab environment. Finally, continuous real-time feedback may not be required; instead a system which can display (for example via a mobile phone application) the number of on-target steps per day may be sufficient to increase awareness of using the modified gait pattern and therefore to increase compliance. However, this option nevertheless requires that the modifications can be accurately and continuously measured over the course of a day during normal daily activities, which still presents some challenges. We will discuss further wearable technology in section 6.1 of this discussion.

Our data partly support our hypothesis; KAM was significantly reduced after the training program but not at the follow-up measurements. Furthermore, changes in knee pain, perhaps the most important clinical outcome, did not meet statistical significance. Further work is required to investigate how to sustain the initial effects and which patients are likely to be responders.

**3. Hypothesis III: Knee joint forces can be represented by knee joint moments and can be modified by walking with a modified gait pattern**

In part one and two we focus on the changes in KAM and to a lesser extent the KFM, making the main assumption that KAM (and KFM) are representative of the internal knee joint loading. In addition we assumed that the internal knee joint loading and/or KAM are representative of the detrimental biomechanics that lead to cartilage degeneration. In part three, we focus on the internal loading itself, which we assume is a better representation of the detrimental mechanics than the KAM. That there is a relationship between KAM and progression of KOA is generally acknowledged. Despite this, it is argued that KAM is a poor surrogate for the internal joint loading. While the debate around the use of KAM and to a lesser extent KFM as substitutes for medial knee force will undoubtedly continue, through this thesis we have contributed to the knowledge in this area, with the results in *chapter six* showing the relationship between KAM and knee contact force (KCF) based on our experimental data. To summarise, we found that there was a moderate to strong association between the KAM and the medial contact force ($R^2 = 0.597$) at the first peak of the curve and that with the addition of the KFM, more variance was explained (adjusted $R^2 = 0.733$) during normal (unmodified) gait. The unexplained variance ($\sim 30\%$) may be as a result of co-contractions of the knee spanning muscles, which are not represented by the external moments but are represented by the modelled contact forces. Co-contractions may be higher when walking with a novel gait pattern than when walking with a normal gait pattern, for example prolonged activity of both the gastrocnemius and hamstrings during toe-in/wider-steps gait have previously been reported. With time and training, we may expect a reduction in the co-contraction and a reduction in KCF independent of the reduction in KAM. To investigate this further, electromyography (EMG) driven modelling may be required, although this method nonetheless presents some limitations; for example it is limited to measurement of a small sub-set of the superficial muscles.

We used modelling to calculate changes in the knee contact forces with use of gait modifications (toe-in gait and wider steps). For both gait modifications there was no significant effect on the contact force. Koblauch, et al. (2013) also investigated the effects of toe-in gait on the medial contact force and found a large reduction (0.40BW); however, their results are not fully comparable to ours due to the dosage of the intervention (i.e. much larger changes in the FPA in Koblauch, et al. (2013)). This suggests that a much larger change in FPA is needed to reduce the medial contact force. However, in addition to the reduction in medial contact force, they showed significant increases in the forces in the lateral compartment, providing a contra-
indication for this kind of intervention. Ogaya, et al. (2015)\textsuperscript{33} reported that toe-out gait reduced the second peak contact force in healthy controls; however, this work is yet to be replicated in KOA patients.

For comparison, high tibial osteotomy, a surgical procedure used to correct malalignment, reduces the medial knee loading at the first peak by as much as 0.53BW\textsuperscript{44}. Since work in this area is still in its relative infancy, it is not known if similar changes are possible through use of small and sustainable gait modifications or other commonly used non-surgical interventions in KOA patients. With a hard unloader brace, the total knee contact force was reduced by up 0.29BW, but the changes in the medial contact force were not reported\textsuperscript{45}. Gait modification studies in patients with instrumented knee replacements also provide some insight into the changes in contact forces with use of gait modifications\textsuperscript{36-39}. However, these are single subject case studies in subjects with prosthetic knees and therefore the results may not be generalizable to the KOA population.

In our modelling study (chapter six) we used a generic musculoskeletal model that was scaled to fit the patient according to a published scaling algorithm\textsuperscript{39}. In the past years there have been efforts to customise the musculoskeletal model to ultimately improve the prediction capabilities\textsuperscript{40}. In a small study of five subjects with medial KOA and four control subjects, use of the improved subject specific models showed that there was a trend towards reduced KAM impulse and peak KAM in the medial KOA and four control subjects, use of the improved subject specific models. In a small study of five subjects with medial KOA and four control subjects, use of the improved subject specific models showed that there was a trend towards reduced KAM impulse and peak KAM in the KOA subjects with toe-in gait and wide steps gait\textsuperscript{45}. The authors do not present on the comparison of the subject-specific model compared to the standard model we used, thus we cannot speculate on the size of the improvement gained by using the subject specific model.

However, modelling of the normal knee contact forces does not tell the whole story. Recently, the point of contact of the force has also been implicated\textsuperscript{42}. Shear forces which are typically less than 10% of the compressive forces and less often reported, may nonetheless contribute to the detrimental biomechanics\textsuperscript{44}. Further work is required to determine the relative contributions of the compressive and shear forces to the detrimental biomechanics and ultimately to disease progression.

Finite element analysis to evaluate tissue loading using detailed and subject specific modelling is necessary to predict the effects of interventions on the peak contact stress and stress distribution. For example, use of a lateral wedged insole has been shown to reduce the peak contract stress in the femoral cartilage from 2.57MPa to 2.37MPa (5° wedge) and to 2.24MPa (10° wedge)\textsuperscript{44} while in another study use of a 5° wedge increased the 1st peak contact pressure by 17% and the 1st peak contact stress by 71%\textsuperscript{46}. This emphasises that an effective KAM reducing intervention does not necessarily guarantee reduced forces\textsuperscript{46} or contact pressures\textsuperscript{46}.

While subject specific modelling may have an important role to play in terms of evaluating treatment effects, in its current form, it is unlikely to be clinically feasible due to the extra time needed for the data collection and post-processing (specifically for acquisition of MRI or CT images and segmentation of the resulting images) compared to generic modelling. Therefore, the balance between the added value of complex modelling versus the time and monetary investment needed to perform it, should be carefully considered.

A method for real-time modelling of the KCF during gait using EMG driven models has recently been developed and tested in healthy controls\textsuperscript{46, 47}. This may offer a useful assessment tool for obtaining a quick evaluation of the forces during future biomechanical intervention and gait training studies.

Our hypothesis was proved partially correct; we were able to account for over 70% of the variance in the medial knee contact force using the external joint moments. Despite this, reduction in the KAM during modified gait walking did not translate to reductions in the knee contact force.

4. Measurement considerations
4.1 Gait Measurements

Gait analysis is subject to several sources of error which contribute to inaccuracies in the results, for example marker placement errors, skin movement artefacts and calibration errors. We took steps to minimise the errors in our measurements (e.g. using a UV pen to mark the positions of the markers), but nonetheless the measurements are unlikely to be completely error free. Soft tissue artefacts as a result of skin based surface markers affect both the knee kinematics and the calculated knee moments. In a test-retest reliability study of 31 patients with medial KOA measured greater than 24 hours and less than one week apart, Birmingham, et al. (2007)\textsuperscript{47} found that the limits of agreement between the two measurements for the KAM were approximately ±1.0% BW*Ht. At the 95% confidence interval level, they reported that the measurement error could be as high as 0.7% BW*Ht with minimally detectable change of ±1.0% BW*Ht. In our review in chapter seven only 5 studies reported changes of greater than 0.7%BW*Ht in the first peak KAM\textsuperscript{12, 32, 48-50} and 7 in the second peak KAM\textsuperscript{8, 10, 12, 32, 33, 51, 52} and only 4 studies\textsuperscript{12, 32, 49, 51} reported reductions in the KAM of greater than 1.0%BW*Ht. Therefore, our results should be evaluated with consideration for potential measurement errors.

Use of dual-plane fluoroscopy can reduce these measurement errors by measuring the actual movement of the bones\textsuperscript{12, 51}, rather than measuring the position of the skin mounted marker and making rigid body assumptions. At present this is not a clinically feasible option and is limited to a small number of research labs (e.g. Cardiff University, UK, University of Melbourne, Australia, ETH (Eidgenössische...
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Technische Hochschule), Zurich, Switzerland and Harvard Medical School, America among others). While this technique provides a high level of accuracy, it relies on the use of ionising radiation to form the required images, albeit low dose radiation. This, coupled with significant processing times and costly MRI or CT procedures (required for reconstructing the bone geometry), means it is unlikely to become a standard clinical tool. However, there is huge potential for fluoroscopy to be used in research applications, particularly for applications where higher accuracy than can be achieved using optical tracking is desirable, for example as input data for complex, patient specific musculoskeletal modelling and finite element modelling of the knee cartilage. This could help to further our understanding of the specific mechanics and allowed patients to decide which shoes they wanted to wear (most chose to wear comfortable sport shoes/ trainers). Patients wore the same shoes during each training session and at the follow-up measurements. Since our comparisons were within-subject, we do not expect that the choice of shoe had a confounding effect on our results. Indeed, the use of own shoes, may be beneficial in transferring the learnt gait modification from the lab to the home environment.

4.2 Pain and Function Measurements

To evaluate changes in the patient reported outcome measures (including knee pain), we used the WOMAC questionnaire, which is a validated instrument for assessing changes in pain, functional ability and joint stiffness in knee (and hip) OA patients. Besides the WOMAC questionnaire which was used at the beginning and end of the training we assessed weekly changes in baseline pain using an NRS scale. Nevertheless, we found that this scale was insensitive to changes in the pain as a result of walking with the modified gait pattern; changes that came to light through anecdotal evidence.

Pain, and the assessment thereof, is a complex issue. In KOA the genesis of pain is complex. Both the central nervous system and the peripheral system are considered to be involved in chronic pain experienced by people with KOA. The
link between pain and biomechanical parameters and radiographic KOA severity is also complex. That clinical symptoms are not well correlated with KOA severity is well known, but there are no well accepted explanations for this phenomenon.

One study of 108 patients in three sub-groups (symptomatic KOA with KL grade 2, asymptomatic KOA with KL grade 2 and asymptomatic KOA with KL grade 0-1) found that both peak KAM and KAM impulse were higher in the symptomatic KOA group than in both asymptomatic groups, suggesting that there may be a causative relationship between increased loading (higher KAM) and increased knee pain, but not between increased loading and radiographic severity.

5. Limitations of the project

As in any scientific work, we must acknowledge some limitations of this project as a whole, in addition to the limitations described in each individual chapter. One of the biggest limitations was the lack of statistical power especially in our longitudinal study, which means we must be cautious about over-interpretation of the data. Secondly, as previously described we must be aware of potential errors associated with the data collection and the calculation of the KAM. These errors will also manifest in errors in the calculated knee contact forces. Thirdly, all training sessions were conducted in a tightly controlled lab environment that does not represent the normal environment. Next to these limitations, we can consider, that limitations in the study design (lack of control group, length of follow-up) meant that we were unable to assess whether the gait modifications had any effect within the joint (e.g. through measurement of radiographic changes).

Furthermore, the people who participated in our study were people who were motivated to do something to limit the progression of their KOA. This means that the people included in our study had lower BMI (25.4 ±2.6), and were more motivated to exercise than may be expected in normal KOA population. Since higher BMI is associated KOA progression, this may constitute a recruitment bias in our study and limit the generalizability of our findings to the wider KOA population. While people included in our study had lower BMI (25.4 ±2.6), and were more motivated to do something to limit the progression of their KOA. This means that the people included in our study had lower BMI (25.4 ±2.6), and were more motivated to exercise than may be expected in normal KOA population. Since higher BMI is associated KOA progression, this may constitute a recruitment bias in our study.

5. Limitations of the project

6. Future research directions

6.1 Taking the measurements out of the gait lab

To date, most studies in the field of gait retraining have been conducted in gait laboratories in university or hospital settings, where the researchers can carefully control the environment. Outside of this setting, the real world presents many additional challenges (think for example of walking along a busy shopping street or along an uneven path). For gait retraining to be a clinically useful tool, solutions are needed for firstly measuring relevant features of the gait pattern outside of the lab and secondly for providing feedback (training) outside of the lab. Anecdotal evidence from patients during the training sessions, suggested that a home training device would be very useful. Furthermore, the results presented in chapter five suggest that it may be necessary to increase practice time and slow-learning and hence allow patients to incorporate the gait modifications into their everyday gait pattern without increasing cognitive demand. In recent years there has been a huge rise in the use of commercial wearable technology (e.g. for monitoring daily activity levels sports performance, sleep or heart rate etc.). However, wearable sensors for gait analysis are less common. A review of the literature published in 2014, found that wearable sensors had been used in nine studies with KOA patients; with the majority of the studies in the review investigating use of inertial measurement units (IMUs). When including healthy controls, the knee kinematics had been reported in 36 studies and used for feedback applications in four studies. Nevertheless, most studies were undertaken in laboratory settings and not in the real environment which may present greater challenges.

Important developments have been made in this area in recent years, such as the invent of a smart shoe that can monitor a person's foot progression angle in real-time outside of the lab using a small sensor embedded in the sole of the shoe. A recent study found that both peak KAM and KAM impulse were higher in the symptomatic KOA group than in both asymptomatic groups, suggesting that there may be a causative relationship between increased loading (higher KAM) and increased knee pain, but not between increased loading and radiographic severity.

6.1 Taking the measurements out of the gait lab

6.2 Using a mobile application

Developed to allow real-time pain assessment in patients with rheumatoid arthritis (Track + React), which allows patients to log their pain in addition to medication use, fitness, nutrition, and sleep. This may provide a means of tracking pain and relating the effects of using the modified gait pattern to immediate changes in pain. However, to the best of our knowledge there has been no validation of this app to date.

Finally, we may consider that the dosage of the modification applied in this study was too small to produce a clinically meaningful effect, although with a higher dosage we would expect reduced compliance and possibly reduced walking speed and additional unwanted compensations in the kinematic chain.
development from Xu, et al. (2017) that combines a discreet haptic feedback device (vibration) with IMU sensors has the potential to advance the field significantly by providing a practical and simple wearable device for home training. In short, the system uses a single sensor placed on the dorsal side of the foot and two feedback units placed on the medial and lateral sides of the shank. Vibro-tactile feedback is provided when the FPA exceeds pre-set limits, with the medial and lateral units responding to the upper and lower limits independently. In feasibility tests with 6 healthy older adults, a significant change in FPA was observed when using the feedback system to modify the FPA. Furthermore, participants were able to walk with more than 65% steps inside the pre-set limits for FPA.

Nonetheless, there remain obstacles to overcome. For example, while the smart shoe demonstrated impressive performance under lab conditions, testing in the real-world has yet to be published and is likely to reveal difficulties in the ability to track the FPA when the heading direction (walking direction) is constantly changing. In addition, this type of sensor is dependent on magnetic field measurements and therefore is likely to be sensitive to disturbances in the magnetic field when used outside of the laboratory environment. Furthermore, while monitoring the FPA may indeed be useful, it is still one step removed from monitoring the KAM (the parameter of interest) in real-time. In the past years, significant progress has been made towards measurement of the KAM using wearable technology, but nonetheless, the measurements remain complex. For example, Karatsidis, et al. (2016) recently developed a method for calculating the ground reaction force based on data from IMUs only, with potential to expand to calculation of KAM. This work builds on that of van den Noort, et al. (2013) who used IMUs together with an instrumented shoe to measure the forces. Whilst this force-shoe offers a method of estimating the KAM, it is not a practical solution for the real world and does not offer the sufficient accuracy, hence the need for algorithms that can estimate the moments based only on the movement of the body. Kim, et al. (2014) developed a more advanced force shoe that uses a light-intensity modulation technique to estimate the ground reaction force. This novel technique resulted in an average error of <10% in the resulting hip, knee and ankle torques. However, the researchers estimated the torque in only one plane, thus at present it is difficult to speculate on the performance for KAM measurement.

A modified elliptical trainer, developed by Kang, et al. (2014), allows KAM to be estimated through 3D inverse dynamics, using 6-axis force-torque sensors and a 6DoF (Degrees-of-Freedom) goniometer to measure the movement of the ankle joint. This device provides an alternative to the high-cost and low-availability equipment used in research labs and could be used in clinical practice or perhaps even gyms/ sport schools. Comparison of the resulting real-time KAM with that calculated using kinematic data from an opto-electric system revealed excellent correlation (r=0.96, p<0.001) and good agreement (Bland Altman lower limit of agreement -0.384 and upper limit 0.68 %BW/Ht) between the two methods. Nevertheless, this device is limited to measuring KAM during elliptical training. From the results presented in Kang, et al. (2014), the KAM during elliptical training appears to be significantly lower than during normal walking, or stair climbing etc.

Small pressure sensors attached to the socks under the sole have also been used independently of any IMUs or other motion capture sensors to estimate the KAM. However, whilst the results showed that estimated moments were largely comparable to the KAM measured using force plates in a lab, the proposed system was based on a neural network which required motion-capture data as an input. Therefore, in its current form it does not offer an alternative to the current reliance on laboratory measurements.

As the technology continues to advance, it is important to also consider patient and clinician’s acceptability of wearable sensors. Papi, et al. (2015) proposed that the current low clinical adoption of wearable technology is partly due to the fact that research in this area has largely focussed on the technical development without considering the user preferences. In two qualitative studies with a) KOA patients and b) musculoskeletal health professionals, Papi et al investigated the patients and health professionals requirements for wearable technology. Comfort and appearance were considered important to the patient while the clinicians considered that wearable technology could be used to support and enhance patient care and to monitor the patients status, related to specific gait related parameters such as knee joint loading, range of motion and knee flexion angle.

These are important issues which must be considered in future research in this area to accelerate the transition from research to clinical practice. The increasing importance of home-based care and technological advances in e-health and m-health (health care via mobile phones), coupled with an ageing population and increasing prevalence of osteoarthritis, means that there is huge potential for impact and a real need to invest in further research in this area.

6.2 Randomised Control Trials
At present, there have been no randomised control trials (RCTs) comparing the effects on the KAM of gait modifications with the effects of usual care or to other forms of therapy (i.e. lateral wedged insoles or knee unloader braces). There has, however, been one study which compared the effects of gait retraining over a period of three months with the effects of usual care on patient reported outcome measures and functional measures, such as the timed 400m walk test. Therefore, there is a clear and urgent need for a RCT assessing the effects on the KAM and KFM. At the time of
writing there are three RCT’s currently in progress. The first RCT (clinical trials identifier: NCT02019108) is led by Professor MA. Hunt at University of British Columbia, Canada and spans a period of four months. In this RCT the investigators plan to compare the effects of increasing daily walking duration with a toe-out gait modification vs. increasing daily walking duration only. Primary outcome measures are change in knee pain and change in knee joint loading (KAM). Secondary outcome measures are change in self-reported physical function and change in objective physical function. The second RCT (clinical trials identifier: NCT02765750), led by Professor G. Beaupré at the VA Palo Alto Health Care System, United States, aims to compare the effect on the KAM of walking with a toe-in gait vs. walking with a more consistent foot progression angle. In this study patients will receive training for six weeks and will be followed up for one year. The primary outcome measure is the change in the KAM and change in knee pain on a Visual Analog or Numeric Rating scale. Secondary outcome measures include change in cartilage thinning and change in cartilage MRI properties. The third RCT is a five arm RCT led by Maria A. Fiatarone Singh M.D. at the University of Sydney, Australia (trial number: ACTRN12612000501842). The five arms of this RCT are 1) gait retraining, 2) progressive resistance training 3) high-protein/low-glycaemic index energy-restricted diet, 4) a combination of these three interventions 5) a lifestyle-advice control group. The primary outcome measure is the first peak KAM and secondary outcomes include radiological changes in the joint, pain and muscle strength91. After baseline, measurements outcomes will be re-measured at 6 and 12 months. The results of these three studies have the potential to change the way gait retraining is viewed in the research field and indeed in the clinics by providing higher quality evidence for the efficacy of gait training for reducing the KAM and reducing radiological changes in the joint.

6.3 Other considerations

At present, we can only speculate on the long-term effects of changes in the gait pattern on the cartilage structure and morphology and on the end-point of the disease (knee replacement). In a chronic condition such as KOA long-term effects are hugely important, but despite this, long-term studies, especially those with sufficient power, are rather uncommon in research of biomechanical interventions. Ideally, gait analysis and the outcomes thereof would be routinely included in databases such as the Osteoarthritis Initiative (https://oai.epi-ucsf.org) to facilitate such longitudinal biomechanical studies using gait data alongside the existing imaging data. However, given the lack of standardisation in collection of gait data, there are several intermediate steps that should be taken before this can be made possible. There are currently efforts underway to standardise the collection of gait data in KOA patients in Canada and if successful these initiatives may be implanted in other countries, which would allow higher powered and longer-term studies to be conducted across multiple sites.

7. Implications of this thesis for clinic

In total we recruited 40 persons for our first single-session and of these, 21 participated in study B. While these numbers are relatively high compared to the numbers in previous studies in this area in people with medial KOA, it represents only a minuscule proportion of the total number of people with KOA. We advertised for the project in local newspapers and using the Reumafonds electronic newsletter and through these methods we received a large response of interested people. However, we found that a large proportion of the responders did not meet our inclusion criteria due to co-morbidities or osteoarthritis in the hip or ankle or in the lateral or patellofemoral compartments of the knee joint. In fact, despite medial KOA being more common than lateral or patellofemoral, in our experiences isolated medial KOA was rather rare. The effect of gait modifications, such as those used in our study, on the lateral or patellofemoral compartments of the joint has to date not been thoroughly investigated, but it is of utmost importance. We consider that by reducing the KAM, we are reducing the forces on the medial compartment and therefore reducing the stresses in the cartilage in the medial compartment. If the total load is not reduced but only redistributed, then the cartilage stress in the lateral compartment of the knee may increase leading to potentially adverse effects.

At present, the lack of structure for this type of therapy within health care insurance would present a barrier to its clinical adoption. This is likely to remain a problem for the foreseeable future and therefore continuing efforts to develop simpler and more cost-effective methods of providing gait retraining are required. Use of a system such as the GRAIL system used in our studies is unfortunately not a clinically viable or practical option. With a simpler system for measurement and training, the gait training program used in our study could be transferable to the clinic. An intermediate step may be required, such as use of a more complex motion capture system to perform an initial baseline assessment to determine the required gait modifications, before the training part of the program which could be conducted in a gym or other facility with access to a regular treadmill. In this way, feedback on the FPA only would be needed and the patient would be reassessed after the training to evaluate change in the KAM.

Finally, while we showed that toe-in gait was in general beneficial for reducing the KAM and hence the knee loading, there is insufficient evidence to adopt this type of training into therapy clinics at the present moment. More information is required to allow responders and non-responders to be identified based on their baseline gait pattern and other characteristics and to do follow-up studies to assess disease progression.
8. Overall Conclusions

During the course of this thesis we present:

1. the first study to investigate the use of real-time feedback on the knee adduction moment (KAM) itself in patients with medial knee osteoarthritis.
2. the first study to investigate the longer-term effects of gait training in KOA subjects, with follow-up measurements at three and six months post-training.
3. the first study to investigate the cognitive loading of learning a gait modification.
4. the first study to investigate the effects of gait modifications on the internal knee contact forces in a large group of KOA patients (n=35).

Based on these studies, we conclude that gait retraining using toe-in gait modification with real-time biofeedback does result in reduced first peak KAM with the potential to reduce the knee joint forces. Given the association between KAM and progression of the disease in terms of damage to the cartilage within the joint, we suggest gait retraining using toe-in gait modification with real-time biofeedback has the potential to slow disease progression. Longer-term studies assessing radiographic changes or changes in MRI images are required to confirm or dispute this suggestion.

Further, we conclude that six weeks of gait retraining may not be sufficient for the modified gait pattern to become truly second nature, truly autonomous, meaning that some conscious effort is required to walk in the desired attire. This may lead to poor compliance with the technique and calls for the use of wearable technology solutions to provide extra training opportunities and therefore extra opportunities for slow learning.

Finally, we conclude that a statistically significant relationship between KAM, KFM and KCF exists; thus while musculoskeletal modeling may be preferable, use of external joint moments to assess the effects of an intervention such as that described in this thesis may be sufficient.

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General discussion


