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Knee joint loading in children with valgus malalignment predicted by conventional gait analysis parameters and musculoskeletal simulations

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Contents

Abstract

Gait analysis as a clinical examination method has been increasingly used in recent years. In particular, the external knee adduction moment was often used as a surrogate measure for internal medial knee joint loading, e.g., in elderly individuals with medial knee osteoarthritis. Therefore, the knee adduction moment is also associated with the progression of knee osteoarthritis. Children and adolescents with valgus malalignment have been found to experience a reduced external knee adduction moment, but internal knee joint contact forces, particularly in the lateral compartment, were not previously studied.

First, medial and lateral knee joint contact forces were studied using muskuloscele-tal modeling in young individuals with and without valgus malalignment treated by guided growth. In addition, a systematic literature review was conducted to explore the relationship between external joint moments and internal joint contact forces. Finally, this relationship was investigated in children and adolescents with and without valgus malalignment. Furthermore, we examined whether statistical models could be determined to accurately predict internal knee joint contact forces by commonly used parameters from three-dimensional gait analysis, such as external knee joint moments.

It was found that guided growth normalized knee joint contact forces after treatment. In addition, the static radiographic mechanical axis angle correlated better after the treatment when the patients showed a typical limb alignment compared to the correlation before guided growth with the valgus malalignment due to compensating strategies during gait. Furthermore, the systematic review showed that the peak medial knee joint contact force was best predicted by the knee adduction moment and even better together with the knee flexion moment in the first half of stance.

However, for the second half of stance of the medial knee joint contact force and the entire stance of the lateral knee joint contact force, only low correlations with knee adduction and/or flexion moment were found. Finally, statistical models could be determined with high accuracy for both medial and lateral knee joint contact force, for both peaks in the first and second half of stance, and for both study groups of children and adolescents with and without valgus malalignment by including knee adduction and flexion moment as predictors.

These results demonstrate the importance of examining not only the external knee adduction moment but also the knee flexion moment and, even better, the medial and lateral knee joint contact forces when evaluating knee joint loading. With these statistical models, clinicians can predict the medial and lateral knee joint contact forces without the need to perform musculoskeletal simulations and can therefore use standard three-dimensional gait analysis parameters such as knee adduction and flexion moment. This can improve guided growth treatment in children and adolescents with valgus malalignment with regard to implantation or explantation of the growth restricting plates or to rebound. Instrumented gait analysis could be particularly helpful in borderline cases, as kinematic compensation mechanisms during gait may play a role and the static radiograph alone does not provide information about dynamic joint loads.

Zusammenfassung

Die Ganganalyse als klinische Untersuchungsmethode hat in den letzten Jahren zunehmend an Bedeutung gewonnen. Insbesondere das externe Knieadduktionsmoment wird häufig als Maß für die interne mediale Kniegelenkbelastung verwendet, z. B. bei älteren Personen mit medialer Gonarthrose. Daher wird das Knieadduktionsmoment auch mit dem Fortschreiten der Gonarthrose in Verbindung gebracht. Bei Kindern und Jugendlichen mit Valgusfehlstellung wurde ein geringeres externes Knieadduktionsmoment festgestellt, aber die internen Kniekontaktkräfte, insbesondere im lateralen Kompartiment, wurden bisher nicht untersucht.

In dieser Arbeit wurden zunächst die medialen und lateralen Kniegelenkkontaktkräfte mittels muskuloskelettaler Modellierung bei jungen Kindern und Jugendlichen mit und ohne Valgusfehlstellung untersucht, die durch eine Wachstumslenkung behandelt wurden. Außerdem korrelierte die röntgenologische mechanische Beinachse nach der Behandlung mit korrigierter Beinachse besser, als vor der Wachstumslenkung mit einer Valgusfehlstellung, da hier Kompensationsstrategien beim Gehen eine größere Rolle spielen. Schließlich wurde dieser Zusammenhang bei Kindern und Jugendlichen mit und ohne Valgusfehlstellung untersucht. Darüber hinaus wurde untersuchten, ob statistische Modelle erstellt werden können, um die internen Kniegelenkkontaktkräfte anhand von häufig verwendeten Parametern aus der dreidimensionalen Ganganalyse, wie z. B. den externen Kniegelenkmomenten, genau vorherzusagen.

Es zeigte sich, dass durch die Wachstumslenkung die Kniegelenkkontaktkräfte normalisiert wurden. Darüber hinaus verbesserte sich das Verhältnis zwischen dynamisch gemessenen Kniegelenkkontaktkräfte und statisch gemessener mechanischer Beinachse. Des Weiteren zeigte die systematische Literaturrecherche, dass die maxi-

male mediale Kniegelenkkontaktkraft in der ersten Hälfte der Standphase am besten durch das Knieadduktionsmoment und noch besser zusammen mit dem Knieflexionsmoment vorhergesagt wurde. Für die zweite Hälfte der Standphase der medialen Kniegelenkkontaktkraft und die gesamte Standphase der lateralen Kniegelenkkontaktkraft wurden jedoch nur geringe Korrelationen mit dem Knieadduktionsmoment und/oder dem Knieflexionsmoment gefunden. Schließlich konnten statistische Modelle mit hoher Genauigkeit sowohl für die mediale als auch für die laterale Kniegelenkkontaktkraft, für beide Maxima in der ersten und zweiten Hälfte der Standphase und für beide Studiengruppen von Kindern und Jugendlichen mit und ohne Valgusfehlstellung bestimmt werden, indem Knieadduktionsmoment und Knieflexionsmoment als Prädiktoren einbezogen wurden.

Diese Ergebnisse zeigen, wie wichtig es ist, bei der Bewertung der Kniegelenkbelastung nicht nur das externe Knieadduktionsmoment, sondern auch das Knieflexionsmoment und noch besser die medialen und lateralen Kniegelenkkontaktkräfte zu untersuchen. Mit diesen statistischen Modellen können Untersucher:innen die medialen und lateralen Kniegelenkkontaktkräfte vorhersagen, ohne muskuloskelettale Simulationen durchführen zu müssen und können daher Standardparameter der dreidimensionalen Ganganalyse wie das Knieadduktionsmoment und Knieflexionsmoment verwenden. Dadurch kann die Wachstumslenkung bei Kindern und Jugendlichen mit Valgusfehlstellung im Hinblick auf die Implantation oder Explantation der wachstumshemmenden Platten oder auf den Rebound verbessert werden. Insbesondere bei Grenzfällen kann die instrumentelle Ganganalyse hilfreich sein, da kinematische Kompensationsmechanismen beim Gehen eine Rolle spielen können und das statische Röntgenbild alleine keine Aussage über die dynamischen Gelenkbelastungen zulässt.

Abbreviations

3D	three-dimensional
KAM	knee adduction moment
KCF	knee joint contact force
KFM	knee flexion moment
OA	osteoarthritis

Chapter 1

Overall summary

Introduction

The clinical problem

Osteoarthritis (OA) is one of the most occurring diseases in adults. Knee OA affects approximately one-fifth to one-fourth of all adults older than 45 years and even two-fifth of all adults older than 60 years in the American society.[1] Knee OA is not only a burden for the people themselves but also for the health insurances and medical care with an increase of 50 % of performed total knee replacements in Germany since 2005.[2] There are several factors that increase the risk for knee OA, e.g., high body mass[3], or severe knee injuries[4,5]. Moreover, varus or valgus malalignment is associated with increased risk for and the progression of medial or lateral knee OA, respectively.[6–10] These aspects provoke modified knee motion and achieve a threshold that causes a regional displacement of the load bearing contact positions of the joint. This load shift to an area that is not made for a more frequent loading can cause articular surface damage what can ultimately lead to OA.[6]

In adults, a frontal plane lower limb malalignment can be corrected by surgery, mostly with an osteotomy near the knee joint which improves joint function, reduce pain and the risk for early knee OA.[11] In this surgery, basically the bone that causes the malalignment is cut and realigned by means of removing or inserting a bony wedge.[12] However, in children and adolescents with remaining growth, a temporary hemiepiphyseodesis can be performed instead of a high tibial osteotomy. This treatment, also called guided growth, is thought to be less invasive compared to the high tibial osteotomy.[13] The medical decision for a temporary hemiepiphyseodesis is made with a static weight bearing full length X-ray image which is used for measuring several parameters as the static mechanical axis angle or the mechanical axis deviation.[14] With these parameters the severity and location of the malalignment is quantified.[15] During a temporary hemiepiphyseodesis, small plates on either the medial or lateral part of the growth plate at the femur and/or tibia are implanted depending on which bone causes the leg alignment. The plates restrict the growing on one side of the growth plate and therefore guide the growing of the bone. After a few months, the lower limb alignment is changed if enough growth potential existed. When the lower limb alignment is within a normal range compared to an age-matched typically developed healthy control group, the plates are removed in another surgery.[13] Side-effects of guided growth can be over-correction, i.e., a valgus malalignment is corrected to a varus alignment; an incomplete correction of the leg alignment, because the growth potential of the bones was not enough; or the rebound phenomenon. A rebound describes the reappearing of the initially corrected leg alignment after implant removal. Over-correction and not enough growth potential is relatively rare[16] but a recent evaluation revealed a rebound rate of about 50 % of all performed guided growth interventions[17].

Three-dimensional instrumented gait analysis

Three-dimensional (3D) instrumented gait analysis can be used as additional tool for evaluating the movement of joints, impairments or the joint loading regarding clinical decision-making or treatment and rehabilitation planning[18]. A 3D instrumented gait analysis has the potential to improve the treatment of patients[19,20], and was used for surgery[21] or rehabilitation planning as return-to-sport testings[22]. Common parameters from gait analysis are spatio-temporal parameters as step width, step length or walking speed. Further on, instrumented 3D gait analysis determines the joint movement for the three anatomical planes and allows a quantified assessment. The main method to estimate joint loading is the inverse dynamics approach that describes the applied forces in the joints by calculating external joint moments from ground reaction forces, the rotational joint movement, and the inertia of body segments.[23]

The external knee adduction moment (KAM) is an important parameter from 3D gait analysis for evaluating the knee joint loading in the frontal plane. A pathological KAM, i.e., an increased KAM compared to a normative curve from a control group, is associated with an increased loading in the medial compartment of the knee. This might be a reason why KAM is a commonly-used surrogate measure for the medial compartment loading and is associated with knee OA status[24], the progression of knee OA[25] or an increased anterior cruciate ligament injury risk[22]. In typically aligned lower limbs the loading in the medial compartment consists of about 60-80 % of the total knee joint loading[26]. A frontal plane deformity can change KAM, e.g., a varus alignment increases KAM[27] and a valgus alignment reduces KAM[8,9,28], and therefore shifts the loading from one compartment to the other. These changed loading patterns could not only be seen in adults with knee OA but also in children and adolescents with varus or valgus malalignment.[29,30] Though, for the relation between the static mechanical axis angle and dynamic KAM only weak to moderate correlations were found indicating the need for further research about the effect of lower limb alignment on knee joint loading during walking.[30,31]

Not only a frontal plane deformity, but also spatio-temporal parameters can affect the knee joint loading, i.e., an increased step width can reduce KAM or a faster walking speed increases KAM.[32,33] Additionally, kinematic parameters as foot progression angle, trunk lean or knee medial thrust can change KAM.[34–36] These parameters were often used as conservative treatments to reduce the knee joint loading and therefore reduce pain or the progression of knee OA.[34,37] Problematically, often those changes are small or show up in combinations which makes it difficult to evaluate without a 3D motion capture system and an instrumented gait analysis. Moreover, all these aspects happen in a dynamic movement as walking and cannot be measured with a static two-dimensional image. With a 3D gait analysis, more insights can be gained which therefore can be used for treatment, e.g., in children and adolescents with valgus malalignment and therefore, have the potential to reduce side-effects after guided growth as the rebound phenomenon.[18]

Musculoskeletal simulations

In a clinical environment external joint moments play a major role in evaluating joint loading because these parameters are usually calculated during standard processing pipelines in the motion capture software. Therefore, these parameters are easy accessible in a short amount of time. In recent years, a more advanced method to estimate cartilage loading was developed and used in analyzing motion analysis data. Musculoskeletal modeling allows the calculation of joint loading not only with external forces but also with internal muscle or tendon forces.[38] These calculations of the internal joint contact forces are thought to be more accurate compared to external joint moments because more individual input variables can be integrated in the estimations of joint loading.[39] Musculoskeletal modeling additionally allows the implementation of participant-specific parameters as leg alignment, tibial torsion but also muscle activities from electromyography measurements.[40–44] Moreover, for the knee joint, other calculation definitions exist so that not only a total applied internal force can be determined but also separately for the medial and lateral compartment.[40,41] These knee joint models increase the possibility for a more advanced evaluation of the knee joint in regards of, e.g., frontal plane deformities and knee joint loading during walking.

Only few research groups used musculoskeletal modeling for evaluating the knee joint contact force (KCF) and mainly in elderly with knee OA.[45] Young individuals and additionally valgus malalignment and its effect on the KCF was not yet studied. Nevertheless, both external joint moments and internal joint contact forces are only estimations of the real internal joint loading. The real internal joint force was rarely studied in some elderly with instrumented total knee joints.[31] In this study, the relationship between KAM and medial KCFs was also evaluated and they only found moderate to poor correlation indicating that KAM not necessarily was a sufficient surrogate measure for the medial compartment loading in the knee joint. However, calculating external joint moments as surrogate measure for internal joint loading measures is still the main approach because musculoskeletal modeling takes more time and needs special expertise instead of using external joint moments as output from the motion capture system. Nevertheless, musculoskeletal modeling reveals great potential to enhance joint loading evaluation.

Overall research question and aims

With this thesis, musculoskeletal modeling was performed on gait data from young individuals with and without valgus malalignment. The thesis aims to conclude which outputs from standard gait analysis software or musculoskeletal modeling should be preferred for an accurate determination of knee joint loading in this young study cohort. Hence, in a clinical environment, a fast but accurate prediction of joint loading is needed. Therefore, a better understanding of the relationship between external and internal joint loading parameters shall be gained. To reach that goal three studies were performed:

1. The effect of guided growth on internal medial and lateral KCFs calculated by musculoskeletal modeling was investigated. Moreover, the correlation between dynamic loading parameters during walking and the statically measured mechanical axis angle from X-ray was evaluated.

2. A systematic review was performed to investigate the relationship between external hip and knee joint moments and internal hip and knee joint contact forces. The literature review shall reveal if different aspects affect the relationship and how well the relationship was already investigated.

3. The relationship between external knee joint moments and internal KCFs in children and adolescents with and without valgus malalignment was studied. In addition, accurate prediction of internal KCFs was aimed to investigate loading of the medial and lateral compartments with knee joint moments from gait analysis without the need to perform musculoskeletal modeling.

Included publications

Study 1: Effect of guided growth intervention on static leg alignment and dynamic knee contact forces during gait

With this study the effect of the guided growth intervention on internal KCFs in children and adolescents with valgus malalignment and in comparison with typically developed healthy controls was investigated. Additionally, the relationship between the static radiographically measured mechanical axis angle and the dynamic KCFs during gait was evaluated. In general this study showed that guided growth improves medial and lateral KCFs. Before the intervention, when the patients had a static valgus malalignment, the lateral KCF was significantly increased and the medial KCF was significantly reduced compared to KCFs from the control group. Afterwards, the KCFs in both compartments improved and were not significantly different compared to typically developed healthy controls. Moreover, the static radiographic mechanical axis angle correlated better after the treatment when the patients showed a typical limb alignment compared to the correlation before guided growth with the valgus malalignment due to compensating strategies during gait. As a result it was shown that guided growth not only improves static leg alignment but also dynamic KCFs.

Study 2: A Systematic Review of the Associations Between Inverse Dynamics and Musculoskeletal Modeling to Investigate Joint Loading in a Clinical Environment

This systematic review investigated the relationship between external and internal hip and knee joint loading measures from gait analysis in different study cohorts. In total, 17 studies have been included. Most of the studies found a moderate to good relationship between KAM and medial or total KCFs for the first half of stance. Only low correlations were found for the second half of stance for the medial and the total KCFs. For the relationship between the lateral KCF and external measures as KAM or knee flexion moment (KFM), in general only low correlations were found. Therefore, it was recommended to calculate medial and lateral KCFs especially when the lateral compartment of the knee joint is for interest, e.g., in patients with valgus malalignment.

Study 3: Knee joint moments can accurately predict medial and lateral knee contact forces in patients with valgus malalignment

This study investigated the relationship between external knee joint moments from the sagittal and frontal plane and medial and lateral KCFs in children and adolescents with and without valgus leg malalignment. For the analysis, linear mixed-effects models were used. The statistical models revealed high to very high relationships for the peaks in the first and second half of stance, the medial and lateral compartment and both study cohorts ($R^2 > 0.85$, $p < 0.001$). KFM and KAM were significant covariates in most of the models, strengthening the understanding of the contribution of both moments to medial and lateral KCFs. Those equations could be used to predict internal joint loading in young individuals with and without valgus malalignment when musculoskeletal modeling cannot be performed and therefore improve the evaluation of the effect of frontal plane deformity on the knee joint loading.

Discussion

Three studies were conducted as part of this thesis and the overall results are now discussed. The effect of guided growth on internal KCFs during gait in young individuals with and without valgus malalignment were investigated. In addition, the relationship between internal KCFs and external knee joint moments was considered, both by means of a systematic literature review in various study cohorts and additionally by means of a prospective study in young individuals with and without valgus malalignment.

Guided growth normalized medial and lateral KCFs and also corrected static leg alignment. The static leg alignment correlated little with the dynamic KCFs, particularly little with the lateral compared with the medial KCF, and less before guided growth than after (Chapter 3)[46]. These results indicate that calculation of the lateral KCF is necessary because the static leg alignment does not allow accurate assessment of dynamic joint loading. In addition, gait analysis could improve the clinical decision making when implants should be removed to avoid over-correction but also to ensure that joint loading is fully normalized. Gait analysis and the calculation of internal KCFs could be an additional tool for medical indication in individuals where the static X-ray does not allow a clear medical indication, or in general to exclude compensatory mechanisms, which is why static and dynamic measurements do not fit together as well.

The knee adduction moment, which is commonly used as a parameter to evaluate knee joint loading[24,25], does not necessarily reflect internal medial and especially lateral KCF. The predictability using KAM alone is relatively low; therefore, the predictability for internal lateral KCF, as previous studies had found in predominantly elderly individuals, is low.[43,44,47] The relationship between external knee joint moments and internal KCFs has rarely been studied, especially in young individuals. The systematic review (Chapter 4)[48] found a moderate correlation between KAM and medial KCF for the first half of stance, mainly in subjects with knee OA. Only low correlations were found between KAM and medial KCF for the second half of stance and between KAM and lateral KCF for the entire stance. It was found that the correlation was sometimes better when KFM was included. Some studies even found a better correlation between lateral KCF and KFM, which shows that not only KAM but also KFM and its influence on internal KCFs must be evaluated. Moreover, the effect of valgus malalignment on this relationship is still unknown. Therefore, musculoskeletal modeling should be preferred to calculating external knee joint moments when evaluating knee joint loading in young people with valgus malalignment, especially when evaluating the lateral compartment of the knee joint.

As the systematic review showed, medial and lateral knee joint loading in elderly individuals can be mostly poorly predicted by external joint moments. In children and adolescents, with and without valgus malalignment, the relationship between external knee joint moments and internal KCFs has not been studied. The statistical models and equations developed allow rapid determination of internal medial and lateral KCFs by using commonly used parameters, i.e., KAM and KFM from gait analysis (chapter 5)[47]. Both parameters contribute to internal KCFs and therefore increase the importance of determining internal KCFs compared with calculating a single parameter such as external KAM. These findings are particularly important and interesting when the question arises whether guided growth must be performed or how severe the deformity is in terms of medial and lateral compartment loading in the knee joint during walking. In addition, estimating internal medial or lateral KCFs in a clinical setting requires a fast and accurate prediction method, so estimating external joint moments through commonly used motion capture software would be the preferred method. These equations also eliminate the need to perform time-consuming musculoskeletal simulations to evaluate internal joint loading. In addition, the influence of possible gait modifications to reduce internal KCFs can also be more easily investigated.

Clinical significance and outlook

The determination of internal KCFs could improve the assessment of knee joint loading and thus guided growth in young people with lower extremity deformities. A 3D gait analysis makes it possible to consider the individual gait pattern. This is important, because the statically measured mechanical axis angle from the radiograph does not always adequately reflect the dynamic knee joint loading. Therefore, when assessing a possible frontal plane malalignment, not only the possible deviation of the static mechanical axis angle from an averaged normal value should be used as an indication parameter for a temporary hemiepiphysiodesis, but also the possible deviation of the dynamic knee joint parameter from an age-matched, typically developed healthy control group. This could be particularly important in borderline cases where the use of only one parameter does not allow a clear decision. In addition, a high rate of rebound occurs in these patients.[17] It was noted that preoperative KAM could be a predictor of rebound[49], which could allow adjustment of the treatment algorithm, e.g., by aiming for a slight overcorrection to prevent possible rebound.

In addition, the effect of flatfeet in combination with varus or valgus deformities on dynamic loading of the knee joint is still unclear. Although KAM was reduced in young individuals with flatfeet compared with typically developed healthy controls, the effect of flatfeet in combination with varus or valgus deformities on both KAM and internal KCFs has not yet been investigated.[50] This could be done in the future by randomized control studies. Randomized control studies could not only evaluate the effect of flatfeet on internal KCFs, but also improve the acceptance and importance of using instrumental 3D gait analysis as a standard method in the clinical environment.[20] The additional use of 3D-gait analysis and participant-specific treatment plans may improve guided growth and reduce rebound rates in this cohort in the future.

Conclusion

All three studies improve the understanding of internal knee joint loading in children and adolescents with and without valgus malalignment and thus the treatment of these patients. An image in a static position alone does not provide accurate information about dynamic internal knee joint loading during walking. Therefore, instrumented gait analysis and preferably musculoskeletal modeling should be performed to obtain an accurate prediction of internal knee joint loading. The information from gait analysis and musculoskeletal modeling is particularly useful in individuals in whom kinematic compensatory mechanisms might influence knee joint loading. If musculoskeletal modeling is not possible, internal knee joint contact forces could be estimated using external knee joint moments from standard motion capture software as input to the linear models.

Chapter 2

Overview of included publications

- Chapter 3: Effect of guided growth intervention on static leg alignment and dynamic knee contact forces during gait
  Published in *Gait & Posture*, 78:80-88, 2020. doi: 10.1016/j.gaitpost.2020.03.012.

- Chapter 4: A Systematic Review of the Associations Between Inverse Dynamics and Musculoskeletal Modeling to Investigate Joint Loading in a Clinical Environment
  Published in *Frontiers in Bioengineering & Biotechnology*, 8(1382):603907, 2020. doi: 10.3389/fbioe.2020.603907.

- Chapter 5: Knee joint moments can accurately predict medial and lateral knee contact forces in patients with valgus malalignment
  Submitted to *Scientific Report* on February 16, 2022 (Preprint published on *Research Square*). doi: 10.21203/rs.3.rs-1366268/v1.

Chapter 3

Effect of guided growth intervention on static leg alignment and dynamic knee contact forces during gait

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Full length article

Effect of guided growth intervention on static leg alignment and dynamic knee contact forces during gait

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ABSTRACT

Background: Lower limb malalignment in the frontal plane is one of the major causes of developing knee osteoarthritis. Growing children can be treated by temporary hemiepiphysiodesis when diagnosed with lower limb malalignment.

Research question: Is there a difference between medial or lateral knee contact force (KCF) before (PRE) and after (POST) hemiepiphysiodesis in patients with valgus malalignment and compared to a typically developed control group (TD)? Does a linear relationship exist between the static radiographic mechanical axis angle and dynamic medial/lateral KCF?

Methods: In this prospective study, an OpenSim full body model with an adapted knee joint was used to calculate KCFs in the stance phase of 16 children with diagnosed genu valgum and 16 age- and sex-matched TDs. SPM was applied to compare KCFs before and after guided growth and to test a linear relationship between the mechanical axis angle and KCFs.

Results: After the intervention, POST revealed a significantly increased medial KCF ($p < 0.001$, 4–97 % of stance) and decreased lateral KCF ($p < 0.001$, 6–98 %) compared to PRE. Comparing POST with TD, short phases with a significant difference were found (medial: $p = 0.039$, 84–88 %; lateral: $p = 0.019$, 3–11 %). The static mechanical axis angle showed a longer phase of a significant relation to KCFs for POST compared to PRE.

Significance: This study showed that temporary hemiepiphysiodesis in patients with valgus malalignment reduces the loading in the lateral compartment of the knee and thus the risk of developing osteoarthritis in this compartment. The determination of dynamic KCFs can be clinically relevant for the treatment of lower limb malalignment, especially for decision making before surgery, when compensatory mechanisms may play an important role. Additionally, the static radiographic mechanical axis angle does not necessarily represent the dynamic loading of the lateral knee compartment.

1. Introduction

Lower extremity malalignment in the frontal plane is one of the major reasons for developing knee osteoarthritis (OA) [1,2]. Limbs with a naturally neutral alignment show a higher loading at the medial than the lateral compartment [3]. This may explain the higher occurrence rate of OA in the medial compartment [3,4]. A varus malalignment increases the loading in the medial compartment, whereas valgus deformity shifts the loading to the lateral compartment of the knee and the patients tend to develop OA in this compartment [3]. The aforementioned studies investigated elderly patients with knee OA. Children and adolescents with frontal plane malalignment in the knee also show an increased loading in the medial or lateral compartment depending on the varus or valgus malalignment, respectively [5,6]. Guided growth by temporary hemiepiphysiodesis is a minimally invasive treatment to correct lower limb malalignment during growth [7] instead of a more severe high tibial osteotomy. Guided growth is commonly performed with a plate fixed by non-locking screws acting as a tension band across the medial or lateral epiphysis of the femur or tibia. This implant leads to asymmetric growth into valgus or varus, respectively. The decision for performing a guided growth intervention is commonly indicated by a static weight bearing full length radiograph [8], which does not

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represent the loading during a dynamic task such as walking.

A common variable describing the loading of the knee is the external knee adduction moment (KAM). Stevens and colleagues [9] analyzed the kinetic outcome after guided growth with gait analysis in patients with valgus malalignment. Prior to the guided growth intervention, the children had a reduced varus moment. After the treatment when the frontal plane alignment was corrected, the varus moment improved and approximated the data of the control group with a slight tendency to varus overcorrection [5,6]. However, the external KAM represents the entire knee moment in the frontal plane and cannot be divided over the compartments. Furthermore, the KAM is only a surrogate measure for the total knee contact force (KCF), as the knee flexion moment also contributes significantly to the KCF [10]. Generally, contact forces are the result of both externally applied forces and muscle forces [11]. Only few studies investigated the KCFs in elderly people with and without OA [10,12,13] and no known study exists evaluating the KCFs in children and adolescents with valgus or varus malalignment. Significant correlations between KAM and medial knee contact force (mKCF) has been shown in elderly patients with an instrumented knee prosthesis [12]. A simulation study found significant correlations between the first and second peak mKCF and KAM [14]. Contrary to these findings, other studies found minor or no relationship between mKCF and KAM [10,13]. Especially at the second peak during stance phase and in activities with excessive, direct co-activation of the muscles the correlations are less strong [13].

In the past, studies showed varying results for the correlation between KAM and the static mechanical axis angle (MAA) [5,6,15]. Farr and colleagues [5] showed a weak correlation between several radiographic parameters, especially the MAA, and mean KAM ($r = 0.32$, $p = 0.009$). Böhm and colleagues [6] investigated patients with frontal plane malalignment before and after guided growth and found a weak correlation between MAA and mean KAM ($r = 0.33$, $p = 0.23$; $r = 0.36$, $p = 0.18$). On the contrary, they found a high correlation between the change of MAA and the change of mean KAM ($r = 0.97$, $p = 0.00$). Kutzner and colleagues [12] found that static frontal plane limb alignment was significantly correlated to the peak mKCF ($R^2 = 0.60$, $p = 0.01$) during early stance but not in late stance.

Besides divergent results regarding the association between static MAA and the knee joint moments [5,6,15], no study exists showing the effect of guided growth intervention in children and adolescents with valgus malalignment on dynamic KCFs. Consequently, the mKCF and lateral knee contact force (lKCF) were analyzed before (PRE) and after (POST) guided growth and compared to a typically developed control group (TD). Additionally, kinematic variables affecting the KAM (trunk lean angle, knee angles in the sagittal and frontal plane, foot progression angle) were analyzed regarding potential compensatory mechanisms [5,16–18]. We hypothesized that (1), there is a significant difference in the mKCF and the lKCF between PRE and POST, (2), the mKCF and lKCF return to normal range after guided growth and (3), the static radiographic MAA is not linear related to the dynamic mKCF or lKCF.

2. Materials and methods

2.1. Participants

Sixteen children and adolescents with valgus malalignment of the knee were consecutively included during clinical visits. They had a median age of 13.0 (11.3–13.0) years at baseline (Table 1). Solely patients with a clinical indication for a temporary hemiepiphysiodesis and a pathological valgus alignment of at least one knee (11 patients were bilaterally affected) according to the mechanical bearing line of the lower limb based on a full-length standing anteroposterior radiograph were included [5,8,19]. In our hospital, the indication for a temporary hemiepiphysiodesis is given when the deviation from the physiological mechanical bearing line was more than 10 mm [20], which is approximately 3° deviation of the physiological MAA. Static MAA was measured as the angle formed by the line from the hip center to the knee center and the line from the knee center to the ankle center [8]. Patients were excluded if they showed signs of rheumatoid arthritis, anterior cruciate ligament deficiency, neuromuscular dysfunction, achondroplasia, sagittal or transverse plane deformities of the leg tested by clinical examination, flexion contractures in the knee or hip joint, leg length discrepancy of more than 1 cm, avascular necrosis, history of major trauma or a sports injury of the lower extremity, knee surgery within the last 12 months, chronic joint infection or received intraarticular corticosteroid injection. After the surgical treatment with a tension band implant, the patients were seen every 3 months by a medical doctor to check the leg alignment by static weight bearing full length radiograph until the leg was straight and the implant could be removed.

The second gait analysis (POST) was performed before implant removal. No special physiotherapy was needed during the treatment period. After surgery the patients were advised to avoid sports activities for a few days. The average time between PRE and POST was 13.4 ± 5.4 months. Sixteen healthy children and adolescents of 12.0 (12.0–12.8) years of age were included in the age- and sex-matched control group (Table 1). For TD, only one leg was randomly chosen to be included in the analyses. All participants and their parents were thoroughly familiarized with the gait analysis protocol. Participants and their parents gave written informed consent to participate in this study, as approved by the local ethics committee (182/16) and in accordance with the Helsinki Declaration.

2.2. Gait analysis methods

Kinematic data were collected barefoot at 200 Hz using an 8-camera motion capture system (MX 10, VICON Motion Systems, Oxford, UK). Ground reaction forces were recorded synchronously at 1000 Hz using two force plates (Advanced Mechanical Technology, Inc., Watertown, MA, USA) situated at the mid-point of the 15 m long level walkway. To improve the reliability and accuracy when analyzing frontal and transverse plane gait data, a lower body protocol (called MA), described in a previous investigation [21], was used. In addition to the standardized Plug-in-Gait marker set [22], reflective markers on the medial malleolus, medial femoral condyle and greater trochanter were applied to determine the joint centers of rotation for the ankle, knee and hip. The centers of rotation for the ankle and knee joints were defined statically as the midpoint between the medial and lateral malleolus and femoral condyle markers. The center of the hip joint was calculated with a standardized geometrical prediction method using regression equations [23] which is common in the clinical gait community [24]. During the static upright standing trial, participants stood barefoot, feet shoulder width apart, knees fully extended, in a forward knee position with the patella centered over the femoral condyles to control for any foot rotation effects [25]. Five dynamic trials with a clear foot-force plate contact were selected for further processing. Kinematic parameters were calculated using the above described MA marker set. The knee angles in the sagittal and frontal plane are of clinical relevance. In the sagittal plane a positive value describes the knee flexion angle. In the frontal plane, a negative value refers to a knee abduction angle (valgus). In addition, we investigated the lateral trunk displacement in the frontal plane and the foot progression angle in the transverse plane throughout the stance phase. The lateral trunk displacement was measured as the marker-based thorax angle, which is the movement of the trunk in relation to the global coordinate system, while walking. Here, a negative value refers to a lateral displacement of the trunk with respect to the limb that has ground contact (toward stance side) [26]. The foot progression angle was defined as the angle of the long axis of the foot segment in the global coordinate system relative to the walking direction axis. Here a negative foot progression angle equals outward foot rotations. As a complement, the other kinematic parameters are presented in the supplementary material (Appendix Figure A1 − 4). The

Table 1
Study population characteristics.

	PRE (N = 16)	POST (N = 16)	TD (N = 16)
Number of legs	27 (13 left, 14 right)	27 (13 left, 14 right)	16 (7 left, 9 right)
Number of bilateral affected patients	11	11	
Sex [male / female]	12 / 4	12 / 4	12 / 4
Age * [years]	13.0[a] (11.3 – 13.0)	14.0[a,c] (13.0 – 14.8)	12.0[c] (12.0 – 12.8)
Body weight [kg]	68.6 ± 12.0[a,b]	78.5 ± 13.6[a,c]	44.3 ± 9.0[b,c]
Height [m]	1.69 ± 0.09[a,b]	1.75 ± 0.09[a,c]	1.57 ± 0.10[b,c]
BMI [kg/m^2]	23.9 ± 3.1[a,b]	25.6 ± 3.4[a,c]	17.7 ± 2.0[b,c]
MAA * [°]	−5.0[a] (−6.0 – −3.0)	−2.0[a] (−1.0 – 0)	not available
Gait velocity * [m/s]	1.25 (1.19 – 1.40)	1.23 (1.17 – 1.34)	1.30 (1.19 – 1.40)
Normalized gait velocity * [$v/\sqrt{g \times leglength}$]	0.43 (0.40 – 0.47)	0.42 (0.39 – 0.43)[c]	0.44 (0.41 – 0.48)[c]
Step width [cm]	10.8 ± 2.6	10.1 ± 2.8	8.9 ± 1.6
Normalized step length [step length/leg length]	0.73 ± 0.05	0.73 ± 0.04[b,c]	0.77 ± 0.08[b,c]

Normal distributed data are summarized as mean with standard deviation. Not normal distributed data are shown as median with interquartile range and indicated with *.
PRE: Gait analysis 1 of the patients before guided growth intervention; POST: Gait analysis 2 of the patients after guided growth intervention; TD: Gait analysis of the typically developed control group; BMI: Body mass index; MAA: Static radiographic mechanical axis angle for PRE and POST, negative angles = valgus alignment.
[a] Significant difference between PRE and POST.
[b] Significant difference between PRE and TD.
[c] Significant difference between POST and TD.

kinematic parameters were time normalized to 100 % of stance phase. In order to account for differences in height and leg length during the treatment period, step length and gait velocity were normalized according to Hof [27].

2.3. Musculoskeletal modeling

The MOtoNMS toolbox (version 3) in MATLAB (version 2018b, The MathWorks, Inc., Natick, MA, USA) was used to process marker and force plate data for subsequent use in OpenSim (version 3.3) [28]. The force data were filtered with a fourth order zero-lag low-pass Butterworth filter with a cut-off frequency of 10 Hz. The knee model by Lerner and colleagues [29] (https://simtk.org/projects/med-lat-knee) allows for the prediction of mKCF and lKCF separately. The model is based on the previously described full body musculoskeletal model [30,31] and includes 18 body segments and 92 muscle-tendon actuators. To adapt the frontal plane alignment of the femur and tibia and to calculate the medial and lateral tibiofemoral forces, a distal femoral condyle body and a tibial plateau body are integrated in the model. The complete description of the model is published in Lerner and colleagues [29].

The model was adapted and scaled to fit the participants' body weight. In accordance to Lerner and colleagues [29] who showed that implementing a participant-specific alignment improves the simulation results, the alignment-informed model was used and the patient-specific MAA observed by a full-length standing anteroposterior radiograph was implemented. For TD, a standing radiograph was not available. Here, the frontal plane alignment was calculated during the static trial with the VICON system, since a previously performed study showed that this method is highly correlated with the MAA calculated from the standing radiographs [17]. To determine the MAA non-invasively, the ankle, knee, and hip joint centers anteroposterior component in global coordinates was set to zero to align all joints in the same plane. The MAA was calculated as the arc cosine of the vectors from the hip to the knee and the knee to the ankle joint center in the frontal plane. A descriptive workflow on how the participant-specific models were created and the outputs were generated is included in the supplementary material (Appendix Figure B). Inverse kinematics, inverse dynamics, static optimization and a joint reaction analysis were performed within OpenSim for all patients for PRE and POST and once for TD. The KCFs as output of the joint reaction analysis were time-normalized to 100 % stance phase, beginning with the foot strike and ending with foot off. KCFs were normalized to body weight.

2.4. Statistical analysis

Statistical data analysis for the anthropometric and spatio-temporal variables were performed with SPSS (version 25, IBM Corporation, New York, NY, USA). The Shapiro-Wilk test was used to test normal distribution of the abovementioned parameters. All variables were normally distributed except age, MAA, gait velocity and the normalized gait velocity. Differences between PRE and POST were tested for significance using paired two-tailed Student *t*-tests for normal and Wilcoxon-Test for non-normal distributed data. Differences between PRE vs. TD and POST vs. TD were tested for significance using an unpaired, two-tailed Student's *t*-tests for normal and a Mann-Whitney-U-tests for non-normal distributed data.

Statistical parametric mapping (SPM) [32] was used to compare kinematic variables, mKCF and lKCF over time between conditions/groups. Normal distribution was tested by SPM and confirmed. To test hypothesis 1, paired *t*-tests were used to compare PRE and POST. For proving hypothesis 2, two-sample *t*-tests were used to compare groups. To evaluate hypothesis 3, a non-parametric linear regression SPM analysis was performed. The critical threshold was calculated at which only $\alpha = 5$ % of smooth random curves would be expected to traverse. Significant differences or a significant relation was considered when the critical threshold was passed for more than 4 successive time points, i.e. at least 4 % of the stance phase of the gait cycle [33]. This approach is based on Random Field Theory [34] and has been validated for 1D data [35]. All SPM analyses were implemented using the open-source spm1d code (version M.0.4.5, www.spm1d.org) in MATLAB.

To investigate a potential effect of the body mass index (BMI) and the normalized gait velocity on mKCF and lKCF, a MANCOVA analysis in SPSS was performed (fixed effect: groups, covariates: BMI and normalized gait velocity). Therefore, the peaks in the first and second half of the stance phase of mKCF were detected. The values of lKCF were determined at the instant times of the mKCF peaks.

3. Results

The results for the anthropometric and spatio-temporal variables are summed up in Table 1. The analyses revealed significant differences in age between POST and TD ($p = 0.001$) (younger TDs), but not between PRE and TD. Significant differences ($p < 0.001$) were found for the anthropometrics (height, body weight and BMI) between all three conditions at which both patient groups showed a higher body weight,

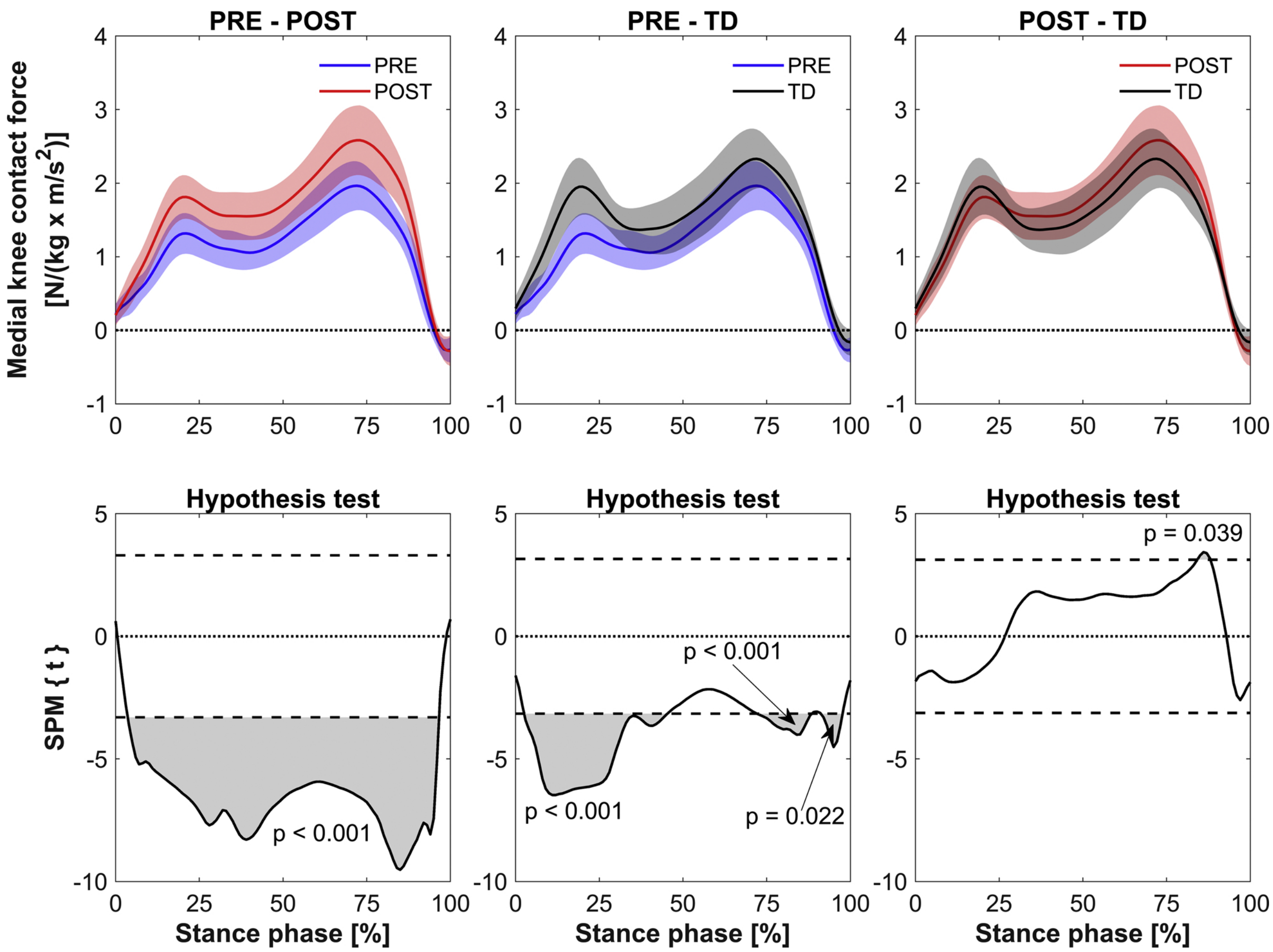

Fig. 1. Statistical analyses of the medial knee contact force.
The Figure shows the result comparing the medial knee contact force of the different conditions/groups by using the statistical parametric mapping (SPM) approach. The top row displays the comparison of the conditions/groups (PRE in blue, POST in red and TD in gray) and the bottom row presents the results of the SPM.

a higher BMI and a larger height compared to TD. The comparison of the static radiographic MAA between PRE and POST showed a significant larger MAA (more valgus) for PRE compared to POST ($p < 0.001$). No significant differences were observed for gait velocity for any of the tested conditions. For TD a significant faster normalized gait velocity was detected between POST and TD ($p = 0.037$). TD showed a significant larger normalized step length compared to PRE ($p = 0.039$) and POST ($p = 0.021$). PRE showed a trend for a wider step width compared to TD ($p = 0.079$). No significant difference in step width were found for PRE compared to POST ($p = 0.201$) and POST compared to TD ($p = 0.417$).

The comparison between PRE and POST revealed a significant lower mKCF ($p < 0.001$, 4–97 % of stance phase) and a significant larger lKCF ($p < 0.001$, 6–98 %) for PRE (Figs. 1 and 2). The mKCF increased and the lKCF decreased after guided growth intervention. Comparing PRE and TD, the statistical analysis also revealed significant lower mKCF ($p < 0.001$, 3–45 %; $p < 0.001$, 72–89 %; $p = 0.022$, 91–98 %) and larger lKCF ($p < 0.001$, 36–96 %) for PRE. When comparing mKCF between POST and TD, only a short phase was found to be significantly different ($p = 0.039$, 84–88 %) with POST demonstrating a slightly larger mKCF. The comparison of lKCF between POST and TD revealed a short phase with a significant difference ($p = 0.019$, 3–11 %) where POST presented a lower lKCF.

When observing the kinematic variables trunk lean angle, knee flexion angle, knee adduction angle and foot progression angle, significant differences were observed for the knee adduction angle (Fig. 3). PRE showed a significant larger valgus angle compared to POST during almost the whole stance phase ($p < 0.001$, 0–96 %) and also compared to TD ($p < 0.001$, 0–99 %). Between POST and TD significant differences were found ($p < 0.001$, 0–89 %) were POST showed a valgus and TD a varus angle. Additionally, a significant difference was found for foot progression angle ($p = 0.048$, 90–98 %) with PRE showing a slightly more outward rotated foot progression angle compared to POST. The complete representation of the kinematics is presented in the supplementary material (Appendix Figure A1 – 4). For the hip angles in the frontal plane significant differences were found. PRE showed a significant larger adduction angle compared to POST ($p < 0.001$, 0–100 %) and TD ($p < 0.001$, 0–100 %). POST also revealed a significant larger adduction angle compared to TD ($p < 0.001$, 0–93 %). All other kinematic parameters showed no significant differences.

The linear regression analyses between the static MAA and mKCF or lKCF revealed significant relationships. For PRE phases with a significant relationship were found for MAA and mKCF ($p = 0.003$, 23–33 % of stance) and for MAA and lKCF ($p = 0.003$, 6–15 %; $p = 0.002$, 18–35 %; $p < 0.001$, 43–89 %). For POST phases with a significant relationship were found for both mKCF ($p < 0.001$, 5–86 %) and lKCF ($p < 0.001$, 2–84 %) and the MAA. The SPM demonstrated that for POST a greater proportion of the stance phase was significantly correlated with MAA compared to PRE for both mKCF (81 % vs. 10 %) and lKCF (82 % vs. 72 %) (Fig. 4).

The MANCOVA analysis (Appendix Table A) revealed significant differences between PRE and TD after controlling for the effect of BMI and normalized gait velocity in the peaks of the first and second half of stance in mKCF (each $p < 0.001$) and lKCF ($p = 0.001$ and $p < 0.001$,

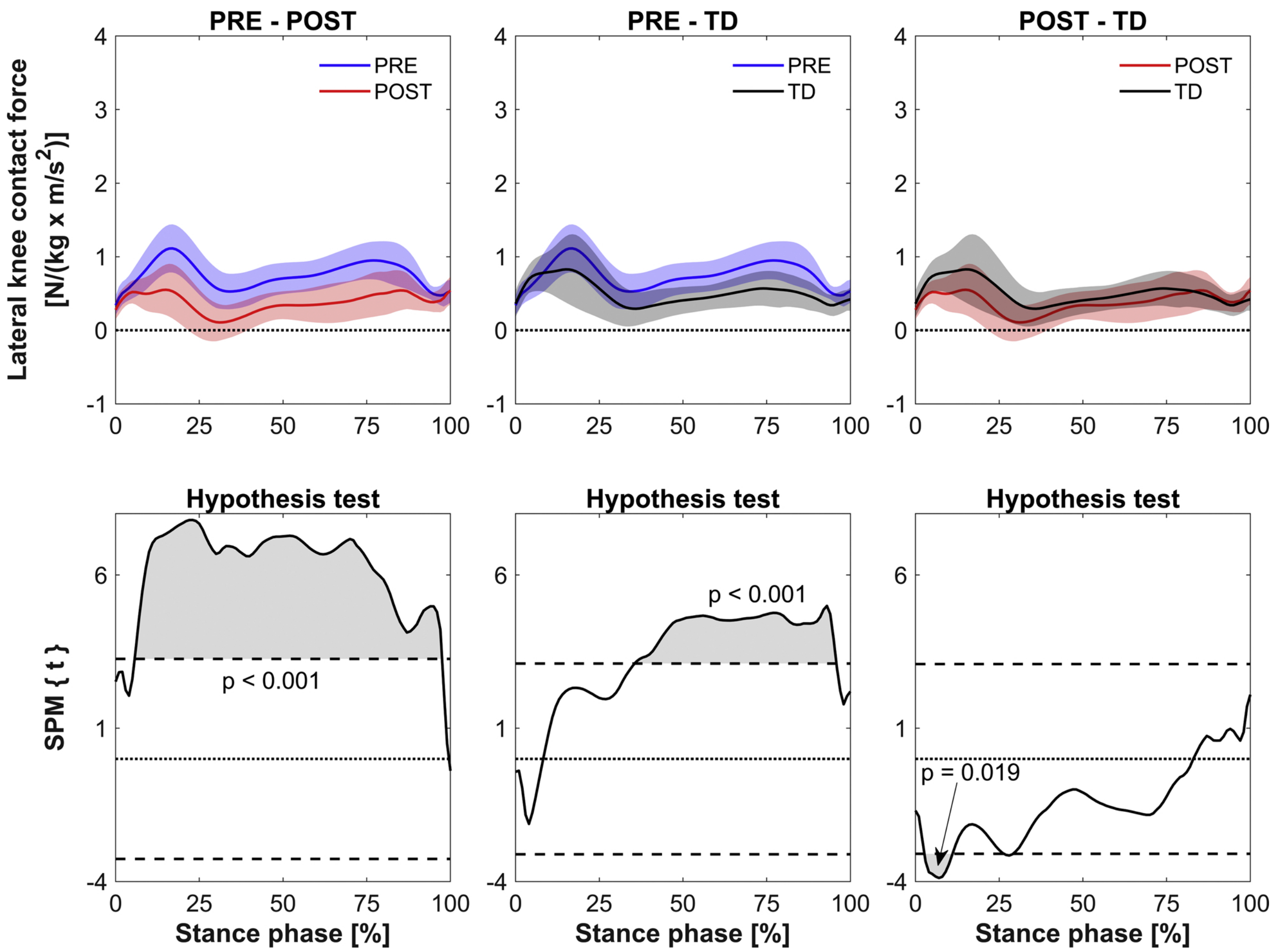

Fig. 2. Statistical analyses of the lateral knee contact force.
The Figure presents the result comparing the lateral knee contact force of the different conditions/groups by using the statistical parametric mapping (SPM) approach. The top row shows the comparison of the conditions/groups (PRE in blue, POST in red and TD in gray) and the bottom row displays the results of the SPM.

respectively). These results were the same as without controlling for the effect of the covariates (mKCF: $p < 0.001$ and $p = 0.002$, respectively; lKCF in the second half of stance: $p < 0.001$), except for lKCF in the first half of stance where lKCF was not significant different ($p = 0.108$). Between POST and TD no significant differences for mKCF and lKCF were found after controlling for the effect of the covariates in the first and second half of stance (mKCF: $p = 0.290$ and $p = 0.624$, respectively; lKCF: $p = 0.897$ and $p = 0.466$, respectively). These results were equal when the effect of the covariates were not controlled (mKCF: $p = 0.148$ and $p = 0.070$, respectively; lKCF in the second half of stance: $p = 0.203$), except for lKCF in the first half of stance. Here, lKCF showed a significant difference without controlling for the effect of the covariates ($p = 0.012$) but no significant difference when controlling for the effect of BMI and the normalized gait velocity ($p = 0.897$).

4. Discussion

To the best of our knowledge, prior studies did not provide any insight into the changes in the loading of the medial and lateral compartment of the knee after correction of valgus malalignment by guided growth intervention. To investigate this issue, gait analyses in young patients diagnosed with unilateral or bilateral genu valgum and who received a temporary hemiepiphysiodesis were performed. The first and second hypotheses were confirmed by the results. Significant differences between PRE and POST were shown and the mKCFs as well as the lKCFs returned within normal range of TD. Not only the static malalignment was corrected as already shown in earlier studies [6,9] but also the mKCFs and lKCFs improved. Our results suggest that guided growth is an important treatment to prevent long-term damage by reducing the loading in the lateral compartment of the knee. This is important information due to a highly increased risk for lateral compartment OA in patients with valgus malalignment [3,36]. The third hypothesis could not completely be confirmed for PRE and was rejected for POST due to a high significant correlation for more than 80 % of stance between static MAA and dynamic mKCF and lKCF.

Other studies investigated the knee joint moments of gait [6,9,18] and showed an increased and therefore improved KAM after guided growth in patients with valgus malalignment. These findings confirm our results with which we also showed increased POST-mKCF. Regarding the linear relationship between MAA and the dynamic loading, hypothesis 3 had to be refuted for POST for both mKCF and lKCF. A weaker correlation was found for PRE (mKCF: 23–33 % of stance; lKCF: 6–15 %, 18–35 %, 43–89 %) compared to POST (5–86 % and 2–84 %, respectively). The results lead to the assumption that it is more important to evaluate the PRE-KCFs compared to POST-KCFs because before guided growth other aspects obviously influence the KCF more than static alignment. One aspect might be compensatory gait patterns in patients with an increased valgus malalignment. Nevertheless, similar to previous studies [5,9], we only found significant differences with a clinical relevance in the frontal plane knee and hip angle. While the slight valgus angle of POST compared to TD during gait support the static MAA, the frontal plane angle during gait did not completely support the outcome of the POST-KCFs which were similar compared to TD. We did not find any significant differences in the transverse plane

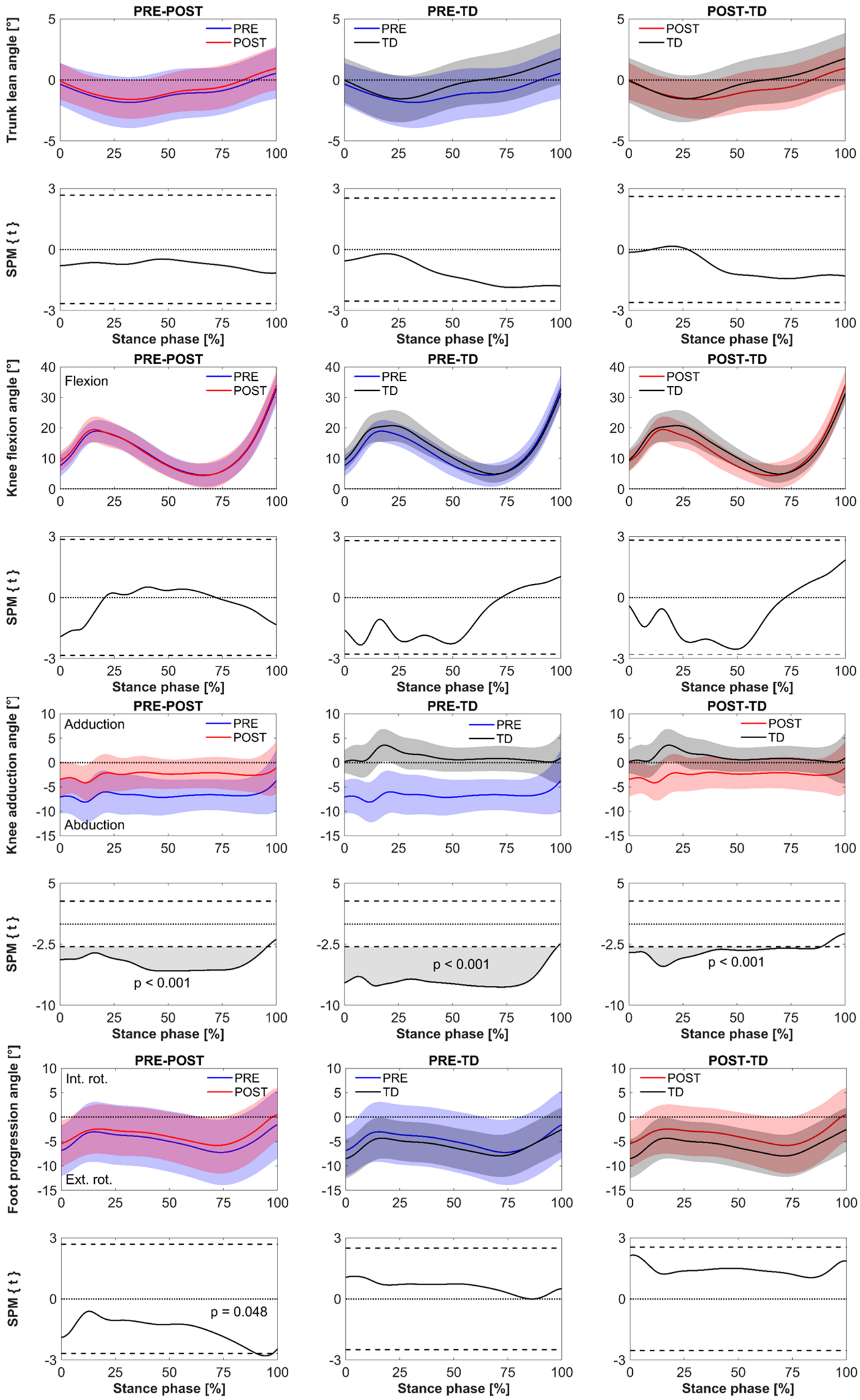

Fig. 3. Statistical analyses of the kinematics.
The Figure shows the comparison of the trunk lean angles in the frontal, knee flexion angles in the sagittal, the knee adduction angles in the frontal plane and the foot progression angles in the transverse plane between the different conditions/groups by statistical parametric mapping (SPM). In the first column, the comparisons between PRE (in blue) and POST (in red) are presented, in the middle column the PRE vs. TD (in gray) comparison and in the last column the POST vs. TD comparison. The related statistical analysis is displayed beneath the graphs of the kinematic curves.

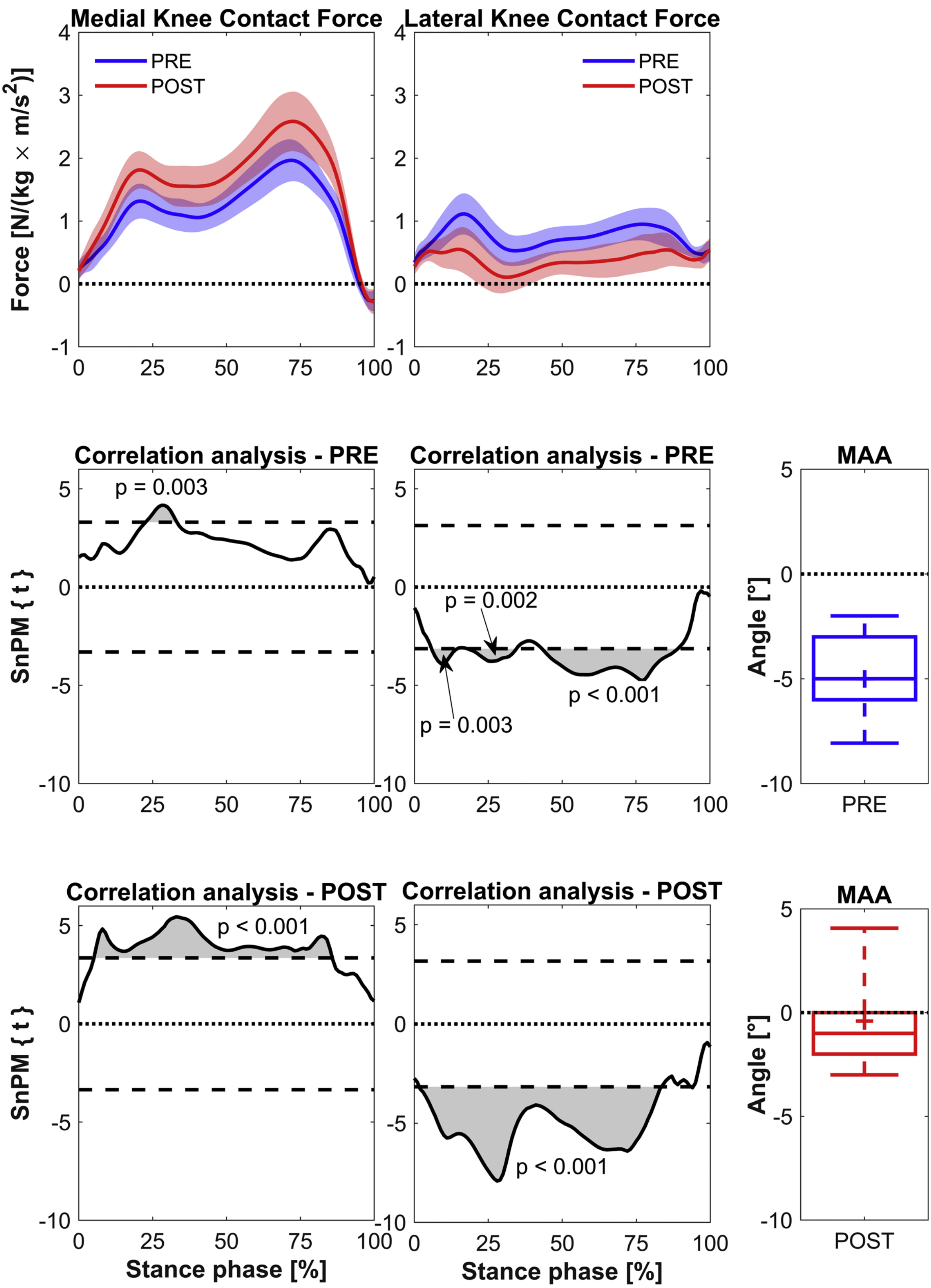

Fig. 4. Correlation of the static radiographic mechanical axis angle (MAA) and the medial (mKCF) or lateral knee contact force (lKCF).
The Figure presents the results of the non-parametric linear regression by using a statistical non-parametric mapping (SnPM) approach. The left column shows the results of the mKCF, the middle column the lKCF and the right column describes the MAA in a boxplot. In the top row the mean and standard deviation of the mKCF and lKCF of PRE (in blue) and POST (in red) are shown. In the middle row the linear regression of the PRE-MAA and the PRE-mKCF or the -lKCF are displayed. In the bottom row the linear regression of the POST-conditions are shown.

of the hip and knee joint (Appendix Figure A1 − 4) which is in contrast to Farr and colleagues [18]. The large standard deviation of the foot progression angle might be explained by the mixture of patients with inward and outward rotated feet during walking, such that the means of the groups/conditions were not significantly different [9,18]. A wider step width in children with valgus malalignment compared to neutral aligned controls was shown by Farr and colleagues [5]. The same tendency was also found in our study population for PRE compared to TD and may explain the lower correlation for PRE between mKCF and MAA since a larger step width is associated with reduced KAM [37]. Therefore, it can be assumed that mKCF is also reduced by greater step width. Nevertheless, this conclusion should be treated with some caution because only a slightly wider step width could be detected in our patients with valgus malalignment before surgery. After the correction of the valgus malalignment, compensatory gait patterns may no longer be necessary and therefore the correlation between dynamic KCFs and the static MAA might be better.

Besides kinematic and kinetic reasons, other factors may explain the increased loading on the knee joint in children with leg malalignment. For instance, obese children with a higher BMI showed a higher loading on the medial compartment compared to children of healthy weight although contact forces were normalized to body weight [38]. Our patient group (PRE and POST) showed significantly higher BMI compared to TD. In addition, for TD a faster normalized gait velocity was detected between POST and TD. However, when controlling for the effect of BMI and normalized gait velocity, the results of the MANCOVA (Appendix Table A) confirmed our results of the original SPM analysis in the sense that for the entire stance phase patients had significantly different KCFs before guided growth compared to TD and that KCFs normalized after correction. Therefore, we assume that the differences in KCFs between PRE vs. POST and PRE vs. TD can be explained by the valgus malalignment. Additionally, we suppose that also the improvements of the KCFs after guided growth can be explained by the correction of the frontal plane alignment.

The results of the present study should be interpreted in light of its limitations. The knee model of Lerner and colleagues [29] is based on a male patient aged 83 and up to date no special child model for this knee model is available. Furthermore, OpenSim offers a lot of options for participant-specific settings and weighting of different markers. Currently, the state-of-the-art approach the subjective adaptation of a general model to best fit the participants' body constitution. However, the flexibility of the models allows the implementation of a participant-specific MAA which is an important benefit for this study population. An effect on the main hypotheses and the corresponding results is not to be expected, since all adaptations of the model for patients and controls were made by the same experienced investigator (JH).

In conclusion, our results indicate that guided growth is an important intervention to normalize the mKCF and lKCF. From a mechanical perspective, we therefore suggest that the guided growth intervention reduces the risk to develop OA in the knee joint. Nevertheless, other factors also affect the risk to develop OA. Other approaches to estimate the knee joint load during gait (e.g. the KAM calculated by inverse dynamics) derive only one moment for the entire knee, without a separate distribution over the medial and lateral compartment. The additional time required to create a participant-specific, scaled model is important to understand how the knee loading behaves during valgus or varus deformation in both the medial and lateral knee compartment. The static radiographic MAA does not necessarily represent the expected additional loading of the lateral compartment of the knee during a dynamic task as walking. The determination of dynamic KCFs can be therefore clinically relevant for the treatment of lower limb malalignment, especially for decision making before surgery, when compensatory mechanisms may play an important role in the distribution of the joint loading. In addition to a corrected radiographic MAA of the lower extremity, the lKCF could also be used to optimize the timing for the removal of the tension bands, as there is the possibility of obtaining information on physiological dynamic knee joint loading.

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CRediT authorship contribution statement

Jana Holder: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. **Zoe Feja:** Software, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing, Visualization. **Stefan van Drongelen:** Software, Formal analysis, Investigation, Data curation, Writing - review & editing. **Stefanie Adolf:** Methodology, Software, Formal analysis, Investigation, Data curation, Writing - review & editing. **Harald Böhm:** Conceptualization, Methodology, Software, Formal analysis, Writing - review & editing, Visualization, Supervision, Funding acquisition. **Andrea Meurer:** Investigation, Resources, Writing - review & editing, Project administration, Funding acquisition. **Felix Stief:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

All authors do not have any financial and personal relationships with other people or organizations that inappropriately influence the work performed.

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Appendix D. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.gaitpost.2020.03.012.

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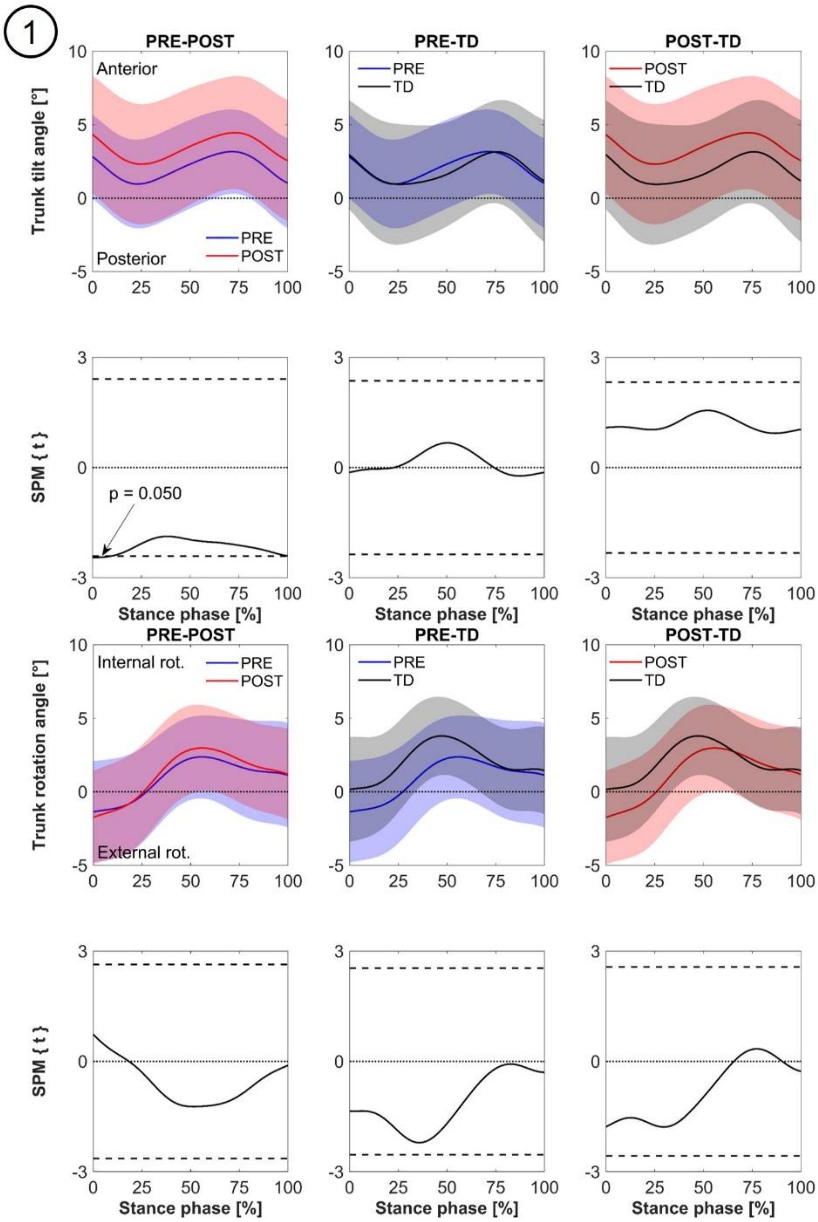
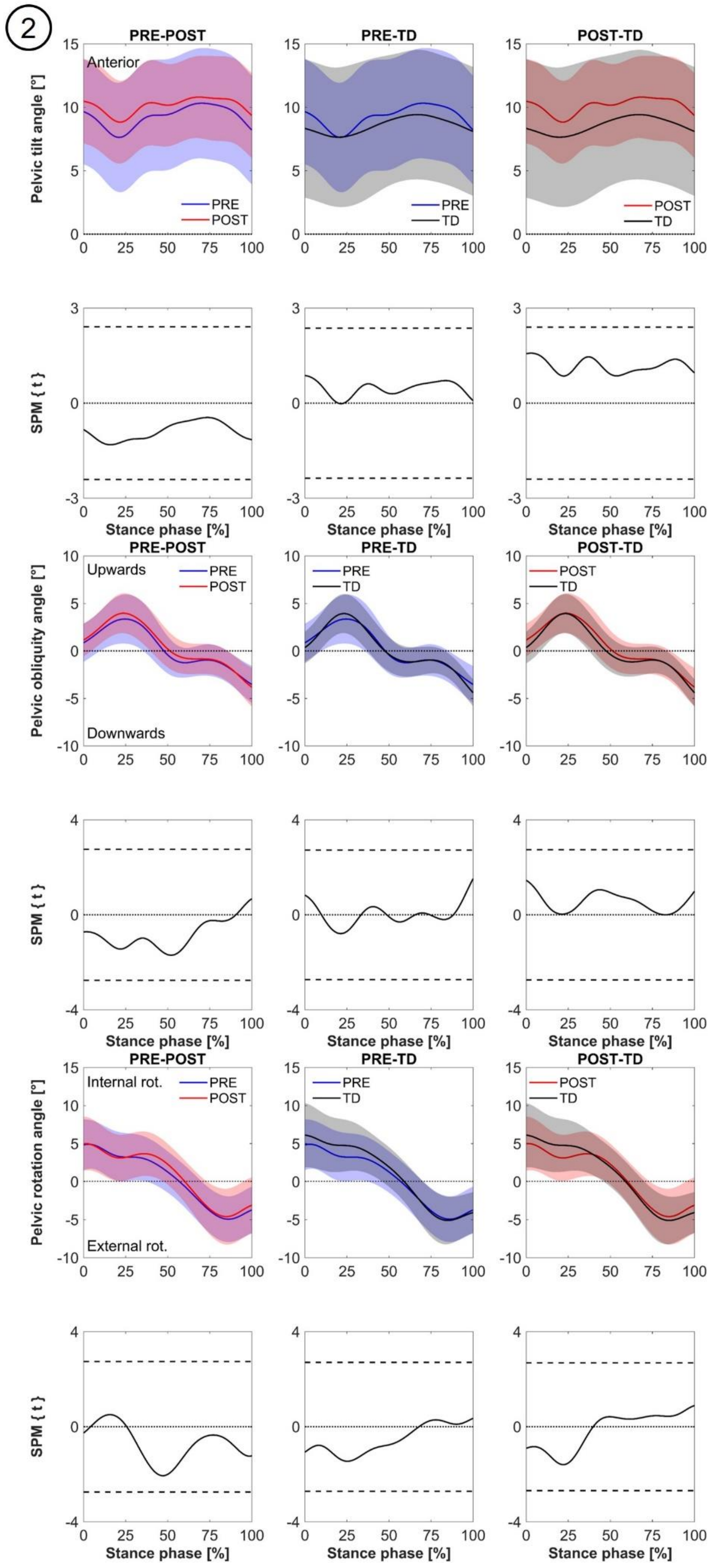
Supplementary material

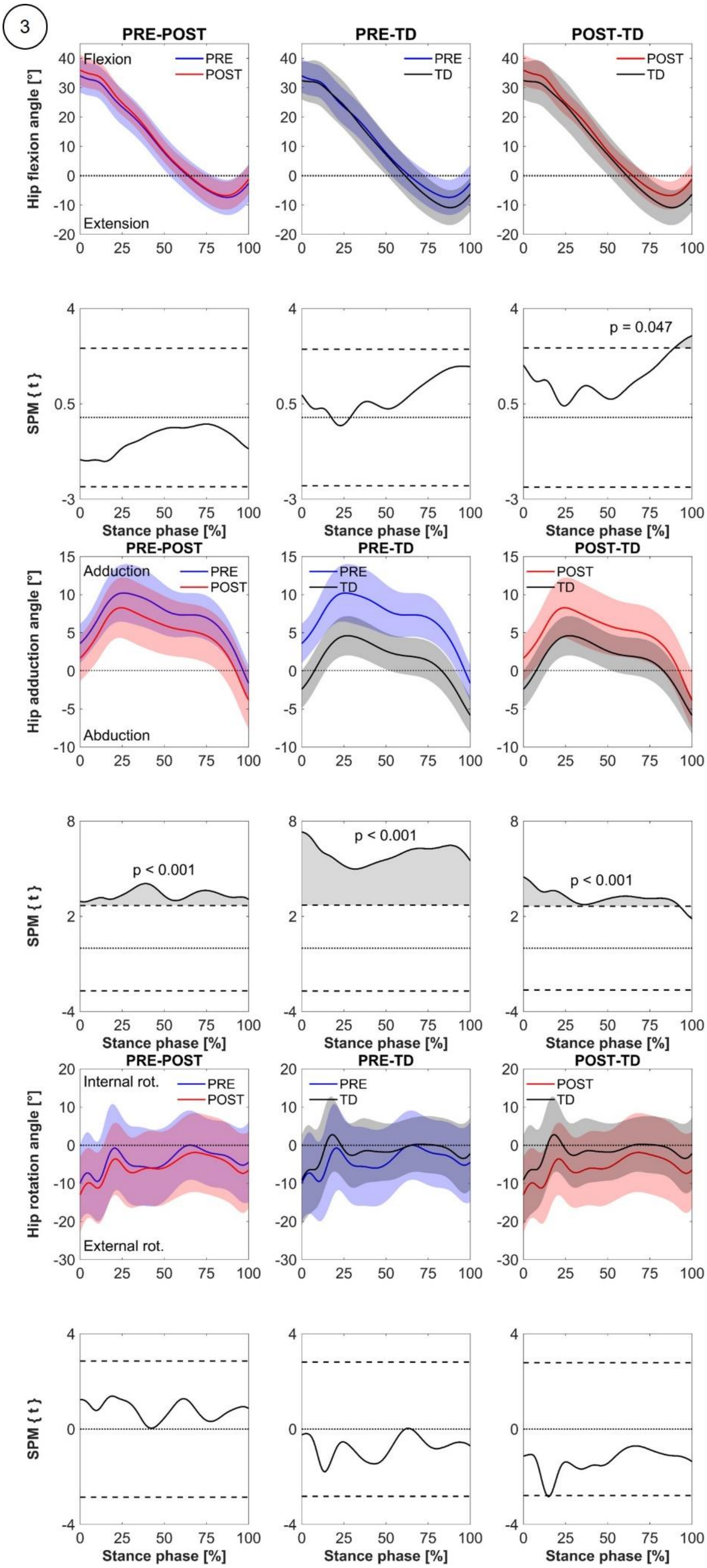
Appendix Figure A1: Trunk kinematics



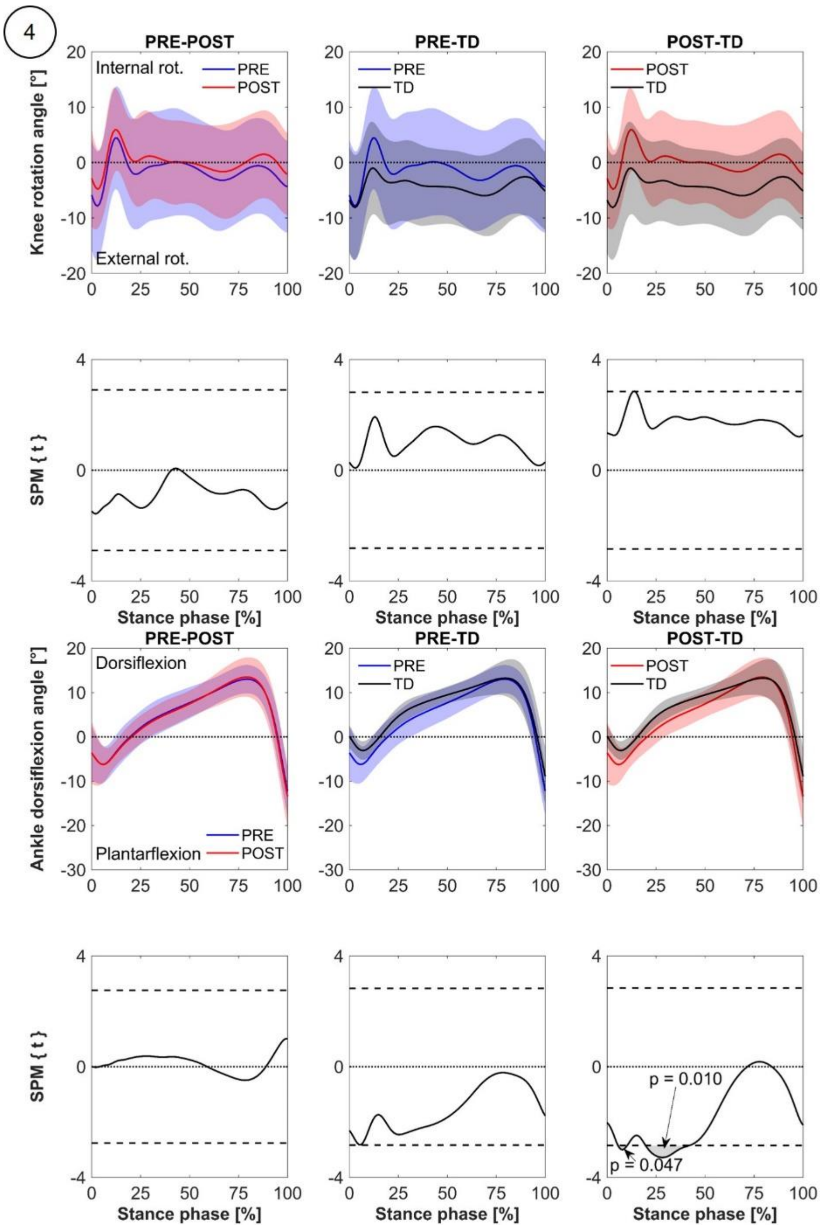
Appendix Figure A2: Pelvic kinematics



Appendix Figure A3: Hip kinematics



Appendix Figure A4: Knee and ankle kinematics

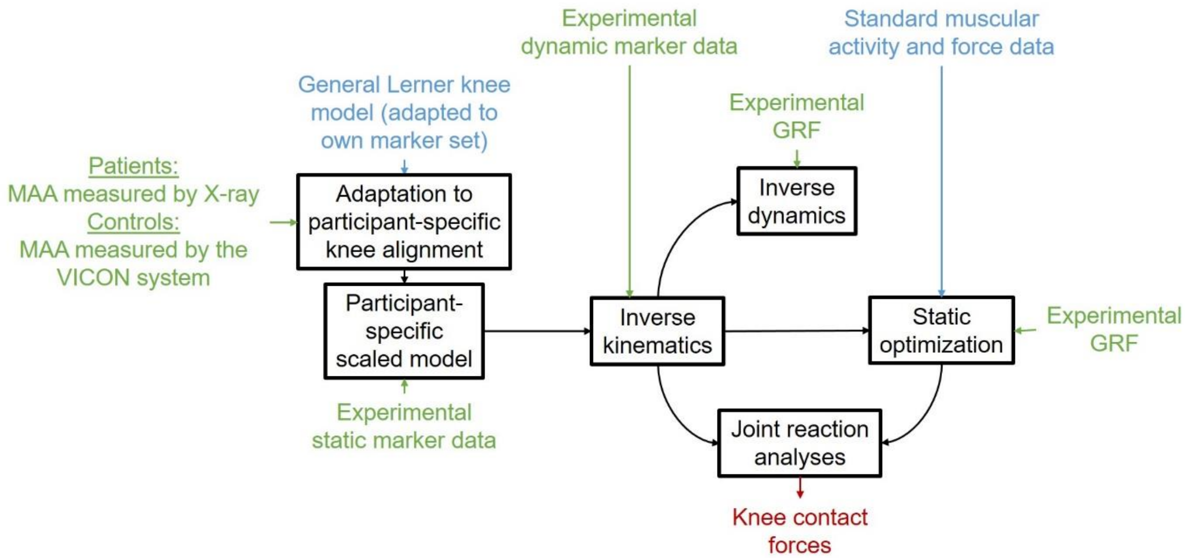


Appendix Figure A1-4: Kinematic analyses performed by statistical parametric mapping.

In the first column, the comparisons between PRE (in blue) and POST (in red) are presented, in the middle column the PRE and TD (in gray) comparison and in the last column the POST and TD comparison. The related statistical analysis is displayed beneath the graphs of the kinematic curves. A1 describes the kinematics of the trunk, A2 the kinematics of the pelvis, A3 the kinematics of the hip and A4 the kinematics of the knee and ankle.

Supplementary material

Appendix Figure B: Workflow



Appendix Figure B: Workflow to implement the motion capture data into OpenSim and to calculate the knee contact forces.

This Figure describes the workflow how the captured marker data are implemented in OpenSim. The green colored inputs are participant-specific data. The blue colored inputs are generalized data implemented into the OpenSim model. The black colored boxes describing the performed steps and the knee contact forces (red) displays the output in the end of the workflow.

Supplementary material

Appendix Table A: MANCOVA analysis

Appendix Table A: Results of the MANCOVA analysis to investigate the effect of the body mass index (BMI) and the normalized gait velocity on mKCF and lKCF between the patients and the typically developed controls (fixed effect: groups, covariates: BMI and normalized gait velocity).

	PRE-TD							
	t-test		MANCOVA					
	group		BMI		normalized gait velocity		group	
	p-value	effect size	*p*-value	effect size	*p*-value	effect size	*p*-value	effect size
mKCF_1	**< 0.001**	0.70	0.135	0.24	**0.022**	0.36	**< 0.001**	0.61
lKCF_1	0.108	0.26	**0.012**	0.39	**< 0.001**	0.55	**0.001**	0.52
mKCF_2	**0.002**	0.48	**0.023**	0.36	0.152	0.23	**< 0.001**	0.56
lKCF_2	**< 0.001**	0.59	**0.003**	0.45	**0.023**	0.36	**< 0.001**	0.69
	POST-TD							
	t-test		MANCOVA					
	group		BMI		normalized gait velocity		group	
	p-value	effect size	*p*-value	effect size	*p*-value	effect size	*p*-value	effect size
mKCF_1	0.148	0.23	0.325	0.24	**< 0.001**	0.36	0.290	0.61
lKCF_1	**0.012**	0.39	0.130	0.39	0.128	0.55	0.897	0.52
mKCF_2	0.070	0.29	0.069	0.36	0.487	0.23	0.624	0.56
lKCF_2	0.203	0.21	0.113	0.45	0.867	0.36	0.466	0.69

PRE: Gait analysis 1 of the patients before guided growth intervention; POST: Gait analysis 2 of the patients after guided growth intervention; TD: Gait analysis of the typically developed control group; BMI: Body mass index; mKCF: medial knee contact force; lKCF: lateral knee contact force; _1: peak in the first half of stance phase; _2: peak in the second half of stance phase.
Significant p-values are displayed in ***bold****.*

Chapter 4

A Systematic Review of the Associations Between Inverse Dynamics and Musculoskeletal Modeling to Investigate Joint Loading in a Clinical Environment

J. Holder, U. Trinler, A. Meurer, F. Stief. A Systematic Review of the Associations Between Inverse Dynamics and Musculoskeletal Modeling to Investigate Joint Loading in a Clinical Environment. *Frontiers in Bioengineering & Biotechnology*, 8(1382):603907, 2020. doi: 10.3389/fbioe.2020.603907.

SYSTEMATIC REVIEW
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A Systematic Review of the Associations Between Inverse Dynamics and Musculoskeletal Modeling to Investigate Joint Loading in a Clinical Environment

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The assessment of knee or hip joint loading by external joint moments is mainly used to draw conclusions on clinical decision making. However, the correlation between internal and external loads has not been systematically analyzed. This systematic review aims, therefore, to clarify the relationship between external and internal joint loading measures during gait. A systematic database search was performed to identify appropriate studies for inclusion. In total, 4,554 articles were identified, while 17 articles were finally included in data extraction. External joint loading parameters were calculated using the inverse dynamics approach and internal joint loading parameters by musculoskeletal modeling or instrumented prosthesis. It was found that the medial and total knee joint contact forces as well as hip joint contact forces in the first half of stance can be well predicted using external joint moments in the frontal plane, which is further improved by including the sagittal joint moment. Worse correlations were found for the peak in the second half of stance as well as for internal lateral knee joint contact forces. The estimation of external joint moments is useful for a general statement about the peak in the first half of stance or for the maximal loading. Nevertheless, when investigating diseases as valgus malalignment, the estimation of lateral knee joint contact forces is necessary for clinical decision making because external joint moments could not predict the lateral knee joint loading sufficient enough. Dependent on the clinical question, either estimating the external joint moments by inverse dynamics or internal joint contact forces by musculoskeletal modeling should be used.

Keywords: musculoskeletal modeling, inverse dynamics, gait analysis, joint contact forces, joint moments, knee joint, hip joint

1. INTRODUCTION

1.1. State-of-the-Art

Hip and knee joint osteoarthritis (OA) is a common disease investigated by motion analysis laboratories. Patients with hip or knee OA usually show a different gait pattern (Mündermann et al., 2005; Eitzen et al., 2012), different muscle activities and forces (Loureiro et al., 2013; Rutherford et al., 2013) and also different joint loading (Kaufman et al., 2001; Andriacchi et al., 2004; Foucher, 2017) compared to healthy controls in a similar age. Regarding knee joint OA, an increased external knee adduction moment (KAM) is mainly associated with the progression of medial knee osteoarthritis (mKOA) (Miyazaki et al., 2002; Andriacchi et al., 2004). Patients with hip OA often experience decreased external hip joint moments and especially a decreased hip extension moment (HEM) is significantly correlated with increased pain (Hurwitz et al., 1997). In clinical environments, joint loadings, particularly KAM, are used to conclude about various therapies, e.g., physiotherapy or gait retraining (Shull et al., 2013; van Rossom et al., 2018), treatment with insoles or orthoses (Lindenfeld et al., 1997; Tokunaga et al., 2016), but also for surgeries (Prodromos et al., 1985).

Inverse dynamics (ID) is the mainly used approach to calculate external joint moments allowing the differentiation of moments around the three anatomical axes (frontal, sagittal and transverse axis) of a specific joint center. External joint moments are calculated using external forces (ground reaction forces) which are applied to the body, the kinematics of the joints, the distance from the force vector to the mass center and moments of inertia about the mass center. These parameters are the input variables for the equations of motion which define the underlying model (Pandy and Berme, 1988) (**Figure 1**). Nevertheless, in patients with valgus malalignment of the lower limb, the loading not only around the knee joint center is important to know, but separately for the medial and lateral compartments. A valgus malalignment increases the internal knee joint contact force (KCF) in the lateral compartment of the knee joint and decreases the KCF in the medial compartment (Holder et al., 2020). While only taking external knee joint moments around a joint center into consideration, these differentiation cannot be made. However, ID is still the most frequently used approach for evaluating the joint loading in clinical gait analysis.

For investigating the above mentioned example of valgus malalignment, other approaches for estimating the joint loading can be considered. Musculoskeletal (MSK) modeling, performed with specific software (e.g., OpenSim or Anybody), is able to do so by estimating the internal joint contact forces. The internal joint contact forces not only take into account the externally applied forces which are also considered by ID, but also the internally applied forces from muscles which act on the joint (Steele et al., 2012) (**Figure 1**). Even more detailed models also include ligament forces working on the specific joint (Steele et al., 2012). Besides a more detailed calculation, special knee models are available allowing the estimation of medial and lateral compartment loading individually (Winby et al., 2009; Lerner et al., 2015). Moreover, with appropriate medical CT or MRI images, MSK models can be individualized according to the participant (Davico et al., 2020), while experimental electromyography (EMG) data give information about the actual participant-specific muscle activity and muscle force (Pizzolato et al., 2015). This is a clear advantage over ID, because ID does not consider muscle forces or muscle activities (i.e., internal forces) in the calculation.

One problem using MSK modeling for estimating internal joint loads is mainly the higher computational cost in data processing and modeling. In contrast, the calculation of the external joint moments using ID is included in the main processing routine after a classical gait analysis, thus, joint moments are available directly after data collection. MSK modeling software offer generic models based on a single person and anthropocentric information from the literature (Delp et al., 2007). The generic models are scaled to fit the participants body weight (BW) and height using information of a static or dynamic trial. In most of the modeling software, scaling is performed manually which is time consuming and might induce subjectivity. It was shown, that models based on medical images reduce the error of joint moment or joint contact force calculations compared to data from instrumented prosthesis (Wesseling et al., 2016). While medical images are included for scaling, the time for creating a participant-specific model increases (Davico et al., 2020). In marker based scaled models, errors in joint loading or muscle forces (Martelli et al., 2015b) can occur based on soft tissue artifacts (Wesseling et al., 2016) or incorrect defined joint centers (Martelli et al., 2015c; Kainz et al., 2017; Bahl et al., 2019). Moreover, the different definitions of the joints in case of degree of freedom (DoF) or muscle positioning have been shown to influence the outcome (Valente et al., 2014, 2015). A study comparing the outcome of an Anybody and OpenSim model relied the discrepancies mainly on the different muscle definitions and segmental coordinate systems (Trinler et al., 2019). Especially in a clinical environment, time consuming MSK modeling can hardly be performed, because the results need to be available soon after the gait analysis for, e.g., surgery or rehabilitation planning.

Apart from MSK modeling, internal joint contact forces and moments can be directly measured using instrumented prosthesis. Only a few studies exist investigating internal joint contact forces from instrumented prostheses in patients with total hip replacement or total knee replacement (TKR) (Mündermann et al., 2008; Arami et al., 2013; Bergmann et al., 2016). This approach is thought to be the most accurate approach compared to MSK modeling and ID (Schellenberg et al., 2018). Additionally, internal joint contact force distribution can be measured individually with different measuring elements

Abbreviations: ACLR, anterior cruciate ligament reconstruction; APM, arthroscopic partial meniscectomy; BMI, body mass index; BW, body weight; DoF, degree of freedom; EMG, electromyography; F_sup, superior force; HAM, hip adduction moment; HCF, hip joint contact force; HEM, hip extension moment; HFM, hip flexion moment; HRM, hip rotation moment; ID, inverse dynamics; KAM, knee adduction moment; KCF, knee joint contact force; KEM, knee extension moment; KFM, knee flexion moment; lKCF, lateral knee joint contact force; mKCF, medial knee joint contact force; mKOA, medial knee osteoarthritis; MSK, musculoskeletal; OA, osteoarthritis; RMSE, root mean squared error; tKCF, total knee joint contact force; TKR, total knee replacement.

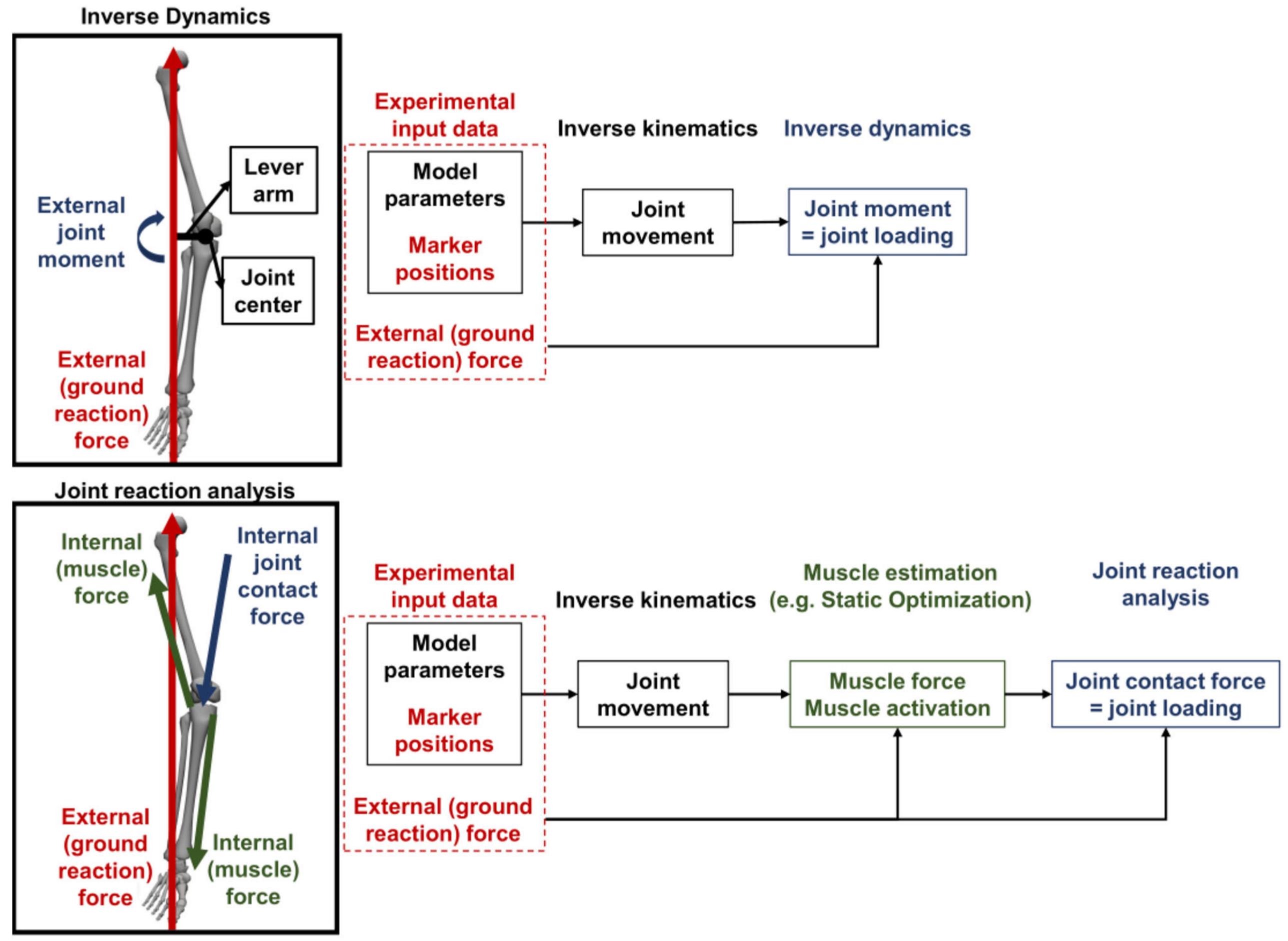

FIGURE 1 | Simplified schematic comparison of inverse dynamics (ID) and musculoskeletal (MSK) modeling for calculating the internal joint contact forces. ID only takes external forces as the ground reaction force (GRF) and a lever arm from the joint center to the GRF vector into consideration when calculating the joint moment as surrogate measure for joint loading. In contrast, with MSK modeling not only the external forces but also internal (muscle) forces are considered for calculating the internal joint contact forces as the representation of the joint loading.

installed in the instrumented prosthesis. Though, patients equipped with an instrumented prosthesis (patients after joint replacement) are rare. Additionally, it is known, that patients after total hip replacement or TKR walk with different gait pattern compared to healthy controls (Meyer et al., 2018; Ro et al., 2020). Therefore, the internal joint contact forces measured in patients after total joint replacement cannot be directly compared to other populations because for these groups data from internal instruments are not available. Nevertheless, forces and moments measured with instrumented prostheses allow the validation of MSK modeling approaches with internally measured data (Schellenberg et al., 2018).

While above calculations all claim to estimate joint loading, it is not clear, however, if a direct general relationship between internal joint contact forces and external joint moments exist. It has not yet been discussed to what extent the calculation of the external joint moments is sufficient to determine the internal joint contact forces.

1.2. Research Question and Goals

The goal of this systematic review is, therefore, to examine the quantitative relationship between external joint moments and internal joint contact forces at the hip and knee during walking. Both parameters are used to predict joint loading. However, it is not clear whether the different methodological approaches lead to the same results and clinical conclusions. Furthermore, it is unclear whether it is sufficient to determine external joint moments to draw conclusions regarding internal joint loading. To be able to give a precise overview a clear definition of what we define as external and internal joint loading is necessary, similar to Vigotsky et al. (2019). "External joint moments" or "external joint forces" are defined as parameters which are calculated using the ID approach. "Internal joint moments" and "internal joint contact forces", on the other hand, define parameters which describe internal loads calculated with MSK modeling or measured with an instrumented prosthesis.

The systematic review shall give a general overview related to the relationship between external joint moments and internal joint contact forces during walking. We additionally aim to identify factors affecting the relationship, e.g., study population or used methods, for which clinical decisions made based on external joint moments would lead to other conclusions compared to the usage of internal joint contact forces. Finally, we targeted to draw conclusions on the preferable method, i.e., ID or MSK modeling, and on corresponding parameters, i.e., external joint moments or internal joint contact forces, for clinical reasoning in gait analysis.

The systematic review is registered at PROSPERO (CRD42020160805) (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=160805).

2. METHODS AND MATERIALS

2.1. Search Strategy and Study Selection

The electronic databases "Pubmed" and "Web of Science" were searched for articles fitting into the inclusion criteria. The search included the key words "(gait OR walk) AND (hip OR knee) AND (force OR moment OR torque) AND (model OR musculoskeletal OR musculosceletal) (inverse dynamics OR simulation)". The complete search terms can be found in the **Supplementary Material** ("*A Full search terms*").

Studies published in English or German as full text versions with abstracts in a peer-reviewed journal have been included in this systematic review. The studies were published between January 1, 1990 (first attempt to model walking with MSK models Pandy and Berme, 1988; Delp et al., 1990) and October 31, 2019. Systematic reviews or meta-analysis, randomized controlled trials, research studies or articles and case reports or series were included. Participants had to be healthy or with orthopedic diseases, e.g., OA in the hip or knee joint. Additionally, participants with an instrumented prosthesis at the hip or knee joint were included, while, in general, participants of all ages were accounted for if they were able to walk independently, without walking aids, e.g., insoles, crutches, braces or an exoskeleton, or any other assistance. Furthermore, data of barefoot walking or walking with defined shoes were analyzed. For data collection, a three-dimensional multi-camera system with integrated force plates able to accurately capture reflective marker data and ground reaction forces had to be used. Joint moments and joint contact forces had to be presented and calculated with an ID approach, with MSK modeling or using an instrumented prosthesis. A quantitative relationship between joint moments and joint contact forces had to be calculated and statistically analyzed.

2.2. Quality Assessment

Titles of all qualified articles from the database search were screened by one reviewer (JH). Duplicates and papers without an abstract or full text version available were eliminated. Titles and abstracts were assessed and excluded by two independent reviewers (JH, UT) if not fitting the above mentioned inclusion criteria. All full text versions were checked by two independent reviewers (JH, UT) for inclusion eligibility. Data extraction was performed by one researcher (JH). The data of the articles were only extracted when fulfilling the inclusion criteria. If full text articles were not accessible, authors were contacted. The reviewers were not blinded on title or author names of the studies. One reviewer (JH) screened each study for bias. The quality assessment checklist, adopted from Downs and Black (1998), reviews each included study according to parameters like reporting methods, external and internal validity and was performed by both reviewers (JH, UT).

Data extraction of included studies was documented in one central excel spreadsheet. It contained the following information: author, title, and year of publication, the cohort of the study (healthy or orthopedic patients, children or adults), anthropometric parameters (age, height, weight, body mass index (BMI), knee joint alignment), the measuring equipment (cameras, force plates, when necessary instrumented prosthesis or EMG), data processing, the applied models and software for calculating joint angles, moments and joint contact forces, data of extracted joint moment and joint contact force values (peak(s), total maximum or mean, whole stance or parts of stance, standard deviation), the statistical method and the outcome measures (walking speed, statistical relationship (r/R^2 and/or p-value, root mean squared error (RMSE)), and existence and content of discussion and conclusion.

The quality assessment checklist covered points related to predefined parameters and categories (see **Supplementary Table 1**). In total 68 parameters were rated in 9 categories and a total points of 75 was reachable. The categories were: Aims & study population; patients; controls; cameras, markers & force plates; EMG; external loads (angles and moments); internal loads (joint contact forces); general & statistics; discussion & conclusion. A total score (in %) for every category and an overall total score (in %) were calculated for every study dividing the reached points per category with the maximal possible points in this category. The overall score of each paper was calculated by dividing the total reached points with the maximal possible points. A maximal score of 100% could be reached. Both reviewers (JH, UT) rated the included studies independently, while the final score of each paper was the average score of both raters. Large discrepancies in scores between the two reviewers were discussed and in case of disagreement a third reviewer was planned to be consulted, which, however, was not necessary. It must be mentioned that this quality assessment scoring concentrated on the performed and reported methods to estimate the external and internal joint loading parameters and to estimate the statistical relationship between these measures. The scoring does not rank how well the studies were performed. Therefore, as recommended by the guidelines of Cochrane, we do not categorize the studies according to the total scores (https://handbook-5-1.cochrane.org/chapter_8/8_3_2_reporting_versus_conduct.htm).

2.3. Calculation of Joint Loading Parameters

As already stated in the previous subsection, joint moments and joint contact forces had to be calculated either by an ID approach, by MSK modeling or with an instrumented prosthesis. Extracted joint loading parameters from ID were classified as external joint loading measures. Parameters from MSK modeling which also take internal forces, e.g., muscle forces, into consideration when calculating the internal joint contact forces, or joint loading parameters directly measured with the instrumented prosthesis, were categorized as internal joint loading parameters (see **Figure 1**). To be able to compare the different studies, the detailed description of the used models were extracted. We focused on the model description, segments and joint DoF, the applied software and the used methods to calculate the external and internal joint loading parameters. Additionally, the values which were used for the statistical analysis were extracted (e.g., peak values or the mean of a parameter).

2.4. Statistical Analyses of the Relationship Between External and Internal Joint Loading Measures

Studies were only included if a statistical relationship between joint moments and joint contact forces was calculated and statistically analyzed. Therefore, either r-, R^2-values and/or the p-value, the RMSE or other statistical output parameters had to be available. To compare the output between studies, a separate spreadsheet was used in which only the statistical output of included studies were summarized. The findings were divided into several parts: Results for peak values (e.g., medial knee joint contact force (mKCF)) in the first half of stance or in the second half of stance as well as results for overall peak values. R^2-values below 0.25 were interpreted as low, between 0.25 and 0.49 as moderate and above 0.49 as high similar to Hinkle et al. (1988) and Kotrlik and Williams (2003).

3. RESULTS

3.1. Search Strategy Yield and Quality Assessment

Figure 2 presents the study selection process and the final outcome. Searching the databases yielded a total of 4,554 studies. After scanning for duplicates and publication types other than journal articles, a total of 3,253 studies were included in the title, abstract and full text scanning. In the end, 17 studies were included in the systematic review for quality assessment. A total of 14 studies evaluated the relationship between external and internal joint loading parameters at the knee joint and three studies at the hip joint. Of the 14 studies that investigated the relationship at the knee joint, three studies assessed patients according to TKR with instrumented knee prosthesis (Kutzner et al., 2013; Meyer et al., 2013; Trepczynski et al., 2014). Seven additional studies investigated either patients with mKOA (Kumar et al., 2013; Meireles et al., 2016; Richards et al., 2018) or after anterior cruciate ligament reconstruction (ACLR) (Noyes et al., 1992; Manal et al., 2015; Wellsandt et al., 2017; Khandha et al., 2019). In one study, patients were evaluated approximately 16 weeks after arthroscopic partial meniscectomy (APM) (Winby et al., 2013). Three studies analyzed the relationship at the knee joint in healthy participants (Ogaya et al., 2014; Saxby et al., 2016; Esculier et al., 2017). The remaining three studies studied the hip joint relationship (Giarmatzis et al., 2015, 2017; Wesseling et al., 2015). The detailed description of the anthropometric data of the study populations and the methodology used to determine the internal joint contact forces are summarized in **Table 1**.

Table 2 reveals the scores of the quality assessment. The total score was 80 ± 10% and varied between 61 and 93%. The largest variance between scores was found for the categories "Equipment" (75 ± 24%), "External joint moments/forces" (77 ± 20%) and "Internal joint contact forces" (74 ± 25%).

3.2. Statistical Methods

The applied statistical analyses were well-reported in most of the studies with an average score of 84%. All studies conducted a correlation or linear regression analysis with various input (external and internal joint loading parameters) and output variables (r-/R^2 and p-values or other parameters). Only Trepczynski et al. (2014) did not set r-/R^2 or p-values individually for walking. They also performed movements other than walking, such as ascending or descending stairs, and calculated a R^2 and p-value for all activities together. Therefore, we included this study in the systematic review, but not in the summary tables for the reported relationships. Kumar et al. (2013) performed a multiple regression analysis and reported the p-value and the β value, a standardized regression coefficient that can be compared to r-values when only one independent variable is used in the multiple regression analysis. For better understanding, the R^2 values were calculated from the original r-values if the R^2 values were not specified by the authors. The calculated R^2 values are highlighted in **blue**. Most authors did not report the relative time of the gait cycle at which they extracted the total maximal values. Therefore, the results for the first or second peak and the total maximal value were reported separately in different figures and tables (**Figures 3–5**, and **Table 3**). A summary table of the performed statistical analyses and the extracted statistical parameters is included in the **Supplementary Table 2**).

3.3. Estimation of External Joint Moments and Internal Joint Contact Forces

All included studies used ID to determine the external joint moments and forces. Different approaches, however, were used to calculate the internal joint contact forces. In three studies, patients with an instrumented prosthesis were examined to directly measure the internal joint contact forces. In two studies, the same type of instrumented prosthesis consisting of 6 strain gauges was used (Kutzner et al., 2013; Trepczynski et al., 2014). As a result, 3 force and 3 moment components were analyzed, of which the axial force was transmitted through the medial and lateral compartments. Meyer et al. (2013) used an implant also consisting of 6 DoFs (3 for the force and 3 for the moment components) but the geometry varied slightly compared to the instrumented prosthesis used in the other 2 studies.

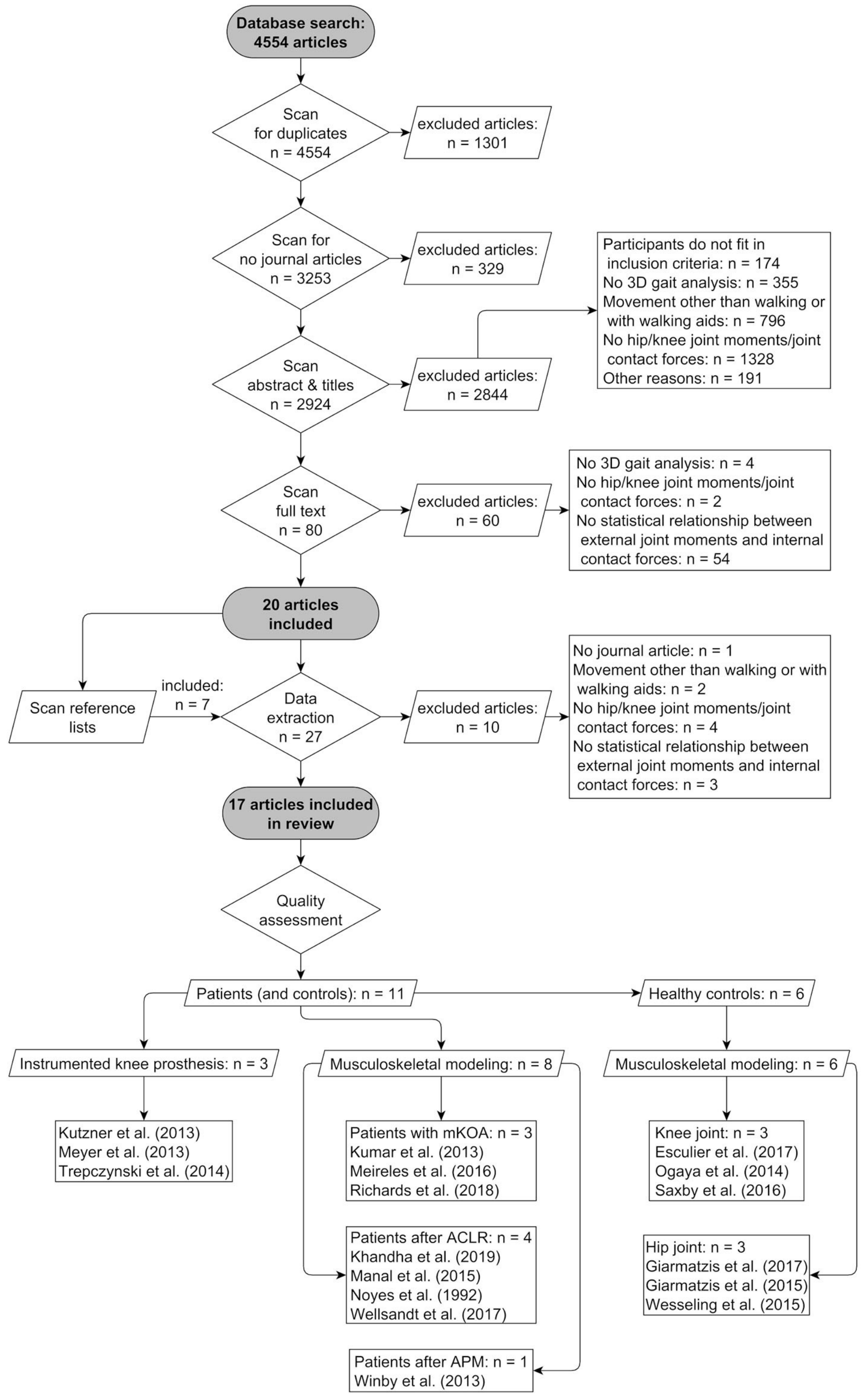

FIGURE 2 | Flow diagram of study selection and results. *mKOA*, medial knee osteoarthritis; *ACLR*, anterior cruciate ligament reconstruction; *APM*, arthroscopic partial meniscectomy.

The studies, which used an EMG-informed MSK model (Kumar et al., 2013; Winby et al., 2013; Manal et al., 2015; Saxby et al., 2016; Wellsandt et al., 2017; Khandha et al., 2019), based their calculations of the internal KCF on the same equations (Lloyd and Besier, 2003; Winby et al., 2009), which allow separate calculation of the medial and lateral

TABLE 1 | Summary of the study population characteristics and methods of calculating the internal joint contact forces.

Study	Population	No. (m/f)	Age [years]	BMI [kg/m^2]	Internal joint contact forces
Knee joint					
Kutzner et al., 2013	Patients after TKR	9 (6/3)	69.9 ± 4.8	30.6 ± 4.3	Instrumented prosthesis
Meyer et al., 2013	Patients after TKR	1 (1/0)	83.0	24.2	Instrumented prosthesis
Trepczynski et al., 2014	Patients after TKR	9 (6/3)	70.0 ± 5.0	30.6	Instrumented prosthesis
Kumar et al., 2013	Patients with mKOA	16 (8/8)	65.2 ± 9.5	28.6 ± 4.3	EMG-informed MSK model
	Controls	12 (6/6)	59.5 ± 10.4	28.4 ± 5.2	EMG-informed MSK model
Meireles et al., 2016	Patients with early mKOA	16 (0/16)	64.9 ± 6.0	-	MSK modeling
	Patients with established mKOA	23 (0/23)	65.6 ± 7.2	-	
	Controls	20 (0/20)	64.6 ± 8.7	-	
Richards et al., 2018	Patients with mKOA	35 (13/22)	62.3 ± 5.9	25.5 ± 2.6	MSK modeling
Khandha et al., 2019	Patients after ACLR	36 (23/13)	29.0 ± 10.0	21.1	EMG-informed MSK model
	Controls	12 (7/5)	23.0 ± 5.0	26.0	
Manal et al., 2015	Patients after ACLR	10 (5/5)	30.1 ± 7.9	28.8	EMG-informed MSK model
Noyes et al., 1992	Patients after ACLR	32 (20/12)	27.0 (15-41)	-	Mathematical model
	Controls	16 (9/7)	26.0 (19-45)	-	
Wellsandt et al., 2017	Patients after ACLR	30 (19/11)	30.5 ± 11.1	26.7 ± 4.0	EMG-informed MSK model
Winby et al., 2013	Patients after APM and controls	27	46 ± 6	25.3	EMG-informed MSK model
Esculier et al., 2017	Controls	87 (51/36)	23.0 ± 3.8	23.0 ± 3.1	Mathematical model
Ogaya et al., 2014	Controls	122 (31/91)	73.8 ± 6.3	21.6	MSK modeling
Saxby et al., 2016	Controls	60 (35/25)	27.3 ± 5.4	22.8	EMG-informed MSK model
Hip joint					
Giarmatzis et al., 2017	Controls (young)	14 (0/14)	21.4	22.6	MSK modeling
	Controls (elderly)	14 (0/14)	69.6	24.4	
Giarmatzis et al., 2015	Controls	20 (10/10)	22.2 ± 1.6	21.5 ± 1.7	MSK modeling
Wesseling et al., 2015	Controls	5 (2/3)	56.0 (52-61)	22.3 ± 1.6	MSK modeling

BMI, body mass index; MSK, musculoskeletal; EMG, electromyography; ACLR, anterior cruciate ligament reconstruction; mKOA, medial knee osteoarthritis; TKR, total knee replacement; APM, arthroscopic partial meniscectomy.

compartmental loading. An extension (Lloyd and Buchanan, 1996) of the generic 1 DoF knee model (Delp et al., 1990) was used as the anatomical model. This EMG-informed model contains in the included studies participant-specific EMG data of the medial and lateral hamstrings, medial and lateral vastii, medial and lateral gastrocnemii and the rectus femoris (Kumar et al., 2013; Manal et al., 2015; Wellsandt et al., 2017; Khandha et al., 2019), additionally of the tensor fascia latae (Saxby et al., 2016), the sartorius and the gracilis (Winby et al., 2013). Two other studies (Ogaya et al., 2014; Meireles et al., 2016) based their calculations on the same generic OpenSim model "gait2392" with the 1 DoF generic knee model (Delp et al., 1990, 2007). Richards et al. (2018) were the only investigators using the Anybody software and the corresponding Twente Lower Extremity Model (TLEM) with a 1 DoF knee model (Klein Horsman et al., 2007; Carbone et al., 2015). In this model, ligament and muscle forces were included in the calculation of the knee joint loading. Noyes et al. (1992) was the oldest study presented in this systematic review and was based on the calculations according to Schipplein and Andriacchi (1991) which allowed rotation about an axis (flexion-extension) and the calculation of mKCF as a proportion of total knee joint contact force (tKCF). As in the previous model, ligament forces from the medial and lateral collateral ligament were also included in the calculation of the internal KCF. Esculier et al. (2017) used a different knee model considering quadriceps, hamstrings and gastrocnemius muscle forces (DeVita and Hortobagyi, 2001; Messier et al., 2011). The proportion of mKCF was estimated using the equations from Schipplein and Andriacchi (1991). All studies that analyzed the relationship between external and internal joint loading measures at the hip joint (Giarmatzis et al., 2015, 2017; Wesseling et al., 2015) applied either the generic "gait2392" OpenSim model (Delp et al., 1990, 2007) or another OpenSim model for the lower extremities (Hamner et al., 2010) that was also based on the generic "gait2392" model. The hip joints in these models were modeled as 3 DoF ball joints.

3.4. Relationship Between External and Internal Joint Loading

The studies mainly examine the internal mKCF (**Figures 3**, **4**). Four studies additionally studied lateral knee joint contact force (*l*KCF) (**Table 3**), while four other studies explored the relationship between external knee joint loading parameters and tKCF (**Figure 5**). The studies investigated the relationship between internal KCF and external KAM and/or the external knee flexion moment (KFM)/knee extension moment (KEM). The transverse plane was not considered. Meyer et al. (2013) looked into the relationship between a superior force (F_sup) acting on the knee joint in combination with

TABLE 2 | Results of the quality assessment screening for each study and additionally a total score is showed in %.

Study	Aims	Pat.	Cont.	Equip-ment	EMG	Ext.	Int.	Stat.	Disc. & conc.	Tot.
Knee joint										
Kutzner et al., 2013	50	90	-	54	-	83	54	89	100	74
Meyer et al., 2013	50	65	-	19	75	70	39	67	100	61
Trepczynski et al., 2014	50	90	-	54	-	50	43	61	100	64
Kumar et al., 2013	100	100	91	46	88	55	55	67	100	78
Meireles et al., 2016	100	83	82	62	-	100	100	100	100	91
Richards et al., 2018	75	88	-	92	-	100	100	67	100	89
Khandha et al., 2019	75	92	-	92	100	55	55	94	100	83
Manal et al., 2015	75	92	-	87	100	85	90	100	100	91
Noyes et al., 1992	100	67	55	46	-	50	30	83	100	66
Wellsandt et al., 2017	50	75	-	81	100	70	80	89	100	81
Winby et al., 2013	88	56	55	92	100	68	85	56	100	78
Esculier et al., 2017	75	-	82	92	-	40	43	94	100	75
Ogaya et al., 2014	50	-	91	92	-	90	90	89	100	86
Saxby et al., 2016	75	-	91	100	100	100	90	89	100	93
Hip joint										
Giarmatzis et al., 2017	88	-	55	100	-	98	100	78	100	88
Giarmatzis et al., 2015	50	-	91	100	-	100	100	94	100	91
Wesseling et al., 2015	50	-	59	65	-	90	100	78	100	77
Mean ± SD	71 ± 19	81 ± 13	75 ± 16	75 ± 24	95 ± 9	77 ± 20	74 ± 25	82 ± 14	100 ± 0	80 ± 10

Pat., patients; Cont., controls; Ext., external joint moments/forces; Int., internal joint contact forces; Stat., General information and statistics; Disc. & conc., discussion and conclusion; Tot., total score; SD, standard deviation.

external knee joint moments (KEM/KFM) and the internal tKCF. Here, F_sup described the external force applied by the ground reaction force along the vertical axis of the shank.

Mainly, the relationship at the peak in the first and/or second half of stance (**Figures 3**, **5** and **Table 4**) were considered, while a few studies examined the relationship between the total maximal values (**Figure 4** and **Table 3**). Not all of the latter studies provided information about the time at which the total maximal value occurred, which is why we analyzed the total maximal value independently of the values of the first and second peaks—although they may occur at similar times in the gait cycle than the first or second peak.

3.4.1. Medial Knee Joint Contact Force

Moderate to strong correlations between mKCF and KAM were observed for the peak in the first half of stance across all populations included. For the peak in the second half of stance, however, a less strong relationship was mainly detected. Also, only low associations were noted between KFM and mKCF for both peaks. The relationship was enhanced when KAM and KFM were combined to predict mKCF.

Significant moderate to strong associations between total maximal values of KAM and mKCF were reported for patients after ACLR as well as for healthy controls. Moderate correlations were detected between the total maximal values of KEM and mKCF, but not between the total maximal values of KFM and mKCF. Again, the relationship was stronger when KAM and KFM were combined to predict mKCF (**Figures 3**, **4**).

3.4.2. Lateral Knee Joint Contact Force

The correlation between *l*KCF and external joint loading measures was only less researched (total: 4 studies). These studies only revealed a low association between KAM or KFM and *l*KCF for the peak in the first half of stance and the total maximal values. Almost no connection was observed for the peak in the second half of stance. A strong relationship was found only between the total maximal KEM and *l*KCF and when combining several external joint loading measures to predict *l*KCF for the peak in the first half of stance (**Table 3**).

3.4.3. Total Knee Joint Contact Force

Studies examining patients with mKOA and healthy controls mostly reported moderate to strong associations between tKCF and KAM or KFM for the peak in the first half of stance and a stronger correlation for the combination of KAM and KFM. For the peak in the second half of stance, low correlations between KAM and tKCF and stronger interactions between KFM and tKCF were observed (**Figure 5**).

3.4.4. Hip Joint Contact Force

The external hip adduction moment (HAM) correlated strongly with the internal hip joint contact force (HCF) for all investigated study groups (Giarmatzis et al., 2015, 2017; Wesseling et al., 2015)

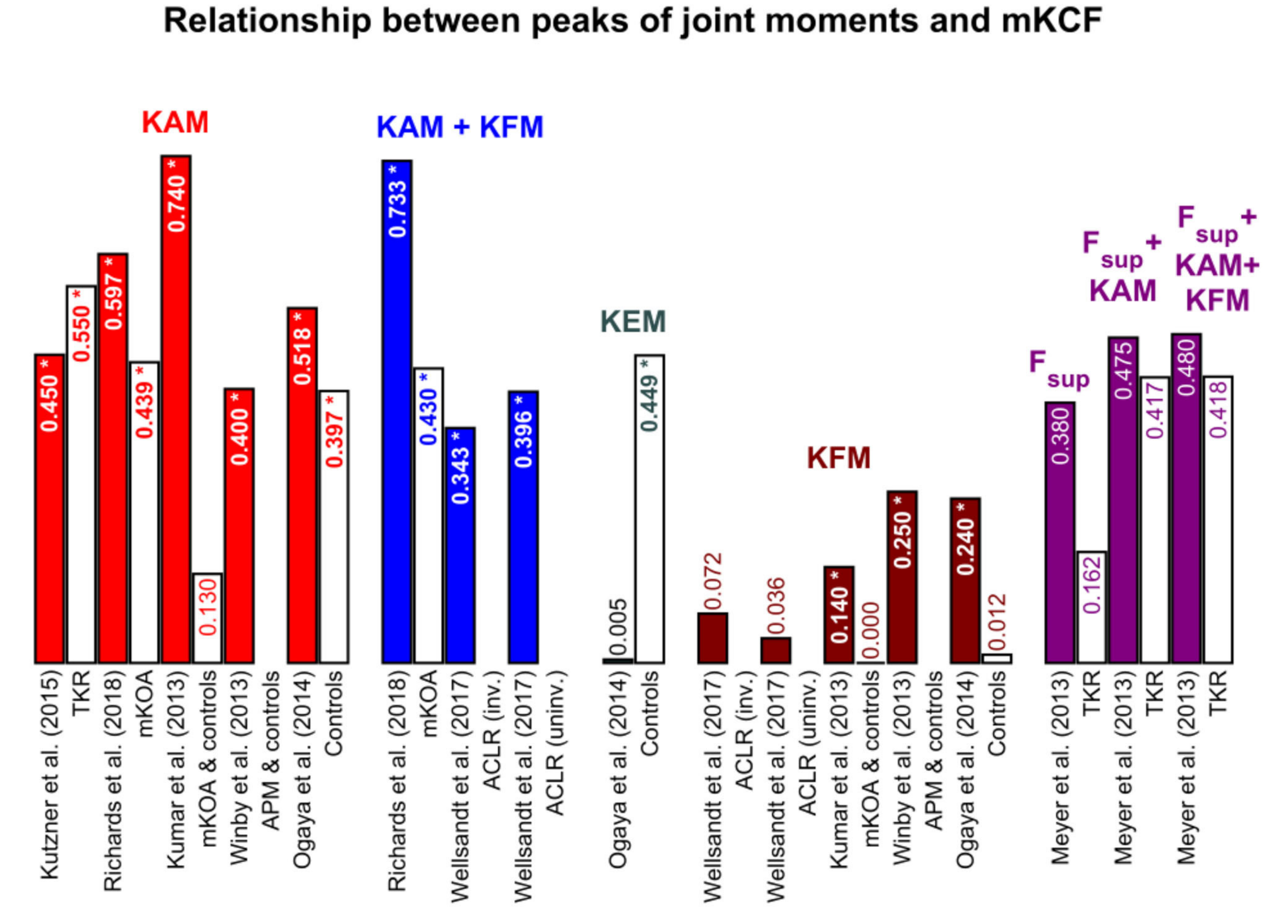

FIGURE 3 | Coefficient of determinations between the first and second peaks of the joint moments and medial knee joint contact force (mKCF). The * indicates significant correlations. The exact *p*-values can be found in the **Supplementary Table 4**. Colored bars represent the findings for the first peak and the white bars with colored text for the second peak of the same study. *KAM*, knee adduction moment; *KFM*, knee flexion moment; *KEM*, knee extension moment; *F_sup*, superior force; *TKR*, Patients after total knee replacement; *mKOA*, Patients with medial knee osteoarthritis; *APM*, Patients after arthroscopic partial meniscectomy; *ACLR*, Patients after anterior cruciate ligament reconstruction; *inv.*, involved leg; *uninv.*, uninvolved leg.

and for all walking speeds in the first half of stance. Whereas between HCF and HEM and hip rotation moment (HRM), respectively, were predominantly low correlations observed. In contrast, the peak in the second half of stance of HAM showed only a low correlation with HCF, while strong relations were observed for hip flexion moment (HFM) or HEM and partly for HRM. Similar to the results for the knee joint, the relationship can be improved by combining more than one external joint moment to predict HCF (**Supplementary Table 3**).

4. DISCUSSION

The aim of this systematic review was to analyze the relationship between external joint moments and internal joint contact forces at the hip and knee for healthy participants as well as patients (patients after TKR, patients with mKOA, after ACLR or after APM). In total, 14 and 3 studies were found that investigated the relationship between external and internal measures at the knee and hip joint, respectively. External joint moments were calculated using ID while internal joint contact forces were estimated by MSK modeling, other mathematical approaches or measured with an instrumented prosthesis. A meta-analysis was not performed due to the variability of the studied populations and the different clinical questions. Only a few studies were included, so that only a limited number of data sets were available that could be used for a meta-analysis. Furthermore, the aim of this systematic review was to provide a general overview, so we decided to prepare a statistical summary of the results from the included studies.

4.1. Relationship Between External and Internal Joint Loading

A schematic summary of the observed correlations between mKCFs or tKCFs and the external knee joint moments are shown in **Table 4**. In general, for the maximal values and the peak in the first half of stance, mKCFs was best predictable by KAM and in

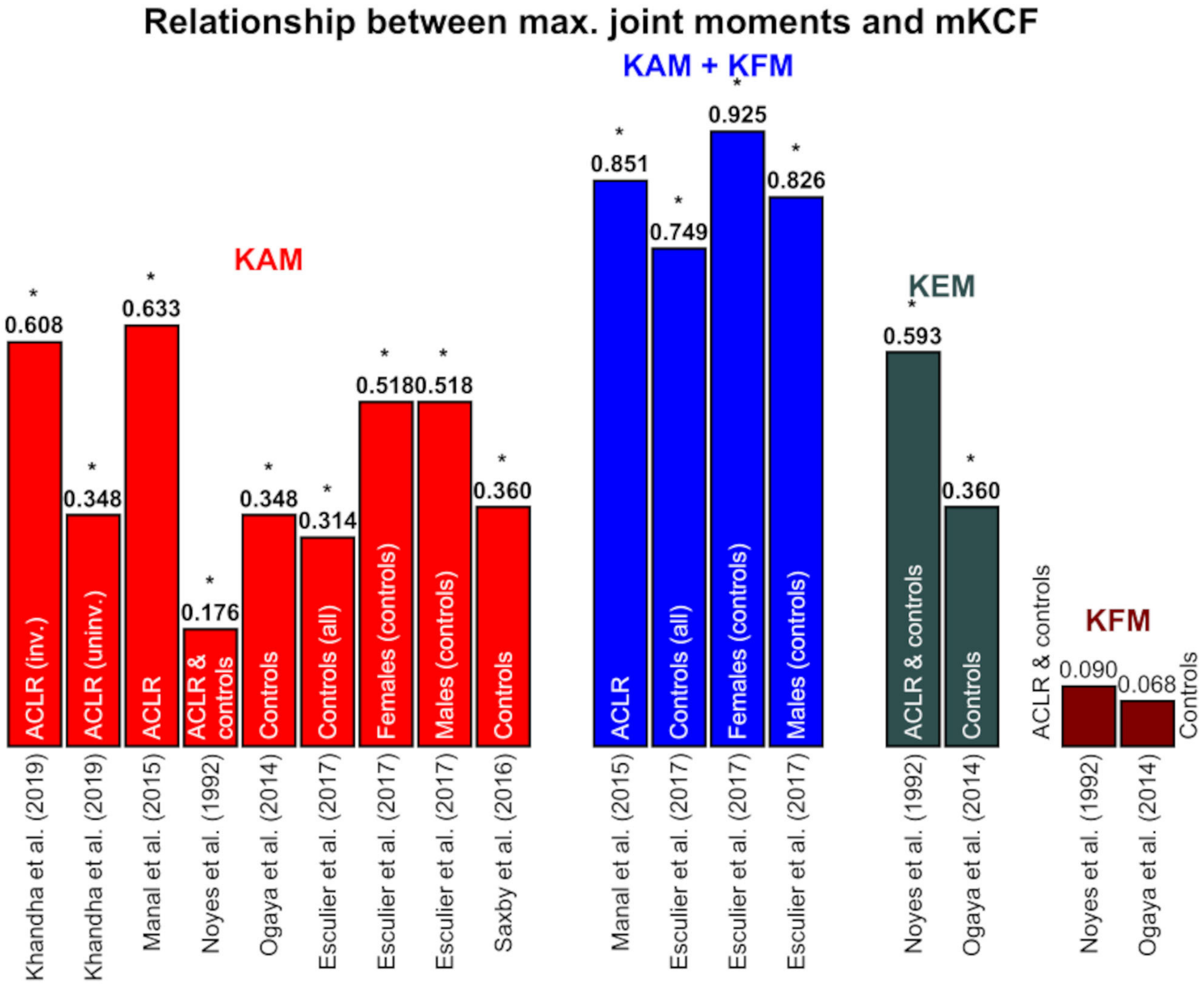

FIGURE 4 | Coefficient of determinations between the maximal values of the joint moments and medial knee joint contact force (mKCF). The * indicates significant correlations. The exact *p*-values can be found in the **Supplementary Table 5**. *KAM*, knee adduction moment; *KFM*, knee flexion moment; *KEM*, knee extension moment; *ACLR*, Patients after anterior cruciate ligament reconstruction; *inv.*, involved leg; *uninv.*, uninvolved leg.

combination with KFM. The *l*KCF was only less strong predicted by knee joint moments throughout the whole stance phase. KAM strongly predicted the tKCFs in the first half of stance and even more accurate together with KFM. Included studies examining the hip joint found similar results compared to the knee joint. The HAM correlated better with the HCF peak in the first half of stance compared to the peak in the second half of stance. When combining several external measures (e.g., HAM and HEM) the relationship was stronger than only with one external measure.

Joint moments and joint contact forces can be divided in its three plane components, meaning that one plane component might not be sufficient enough to explain the full load of a joint. Only one external component might be accurate enough if the joint loading is mostly distributed in one direction. Therefore, describing the internal joint contact forces with more than one external joint moment component (i.e., KAM and KFM) result in a better correlation. Still, the reason that the relationship between KAM and the internal KCFs is frequently investigated, might be because KAM is mainly associated as a surrogate measure for internal KCFs (Andriacchi et al., 2004). An increased KAM during stance was reported as an indicator for increased medial compartment loading and for the progression of mKOA (Miyazaki et al., 2002; Andriacchi et al., 2004). A separate medial and lateral calculation of internal KCF is only possible with MSK modeling or instrumented prosthesis. This might explain why the relationship between external joint moments and internal *l*KCFs were only investigated in 4 previous studies. As a conclusion, we do not recommend to use external joint moments to predict the internal loading in the lateral compartment of the knee joint.

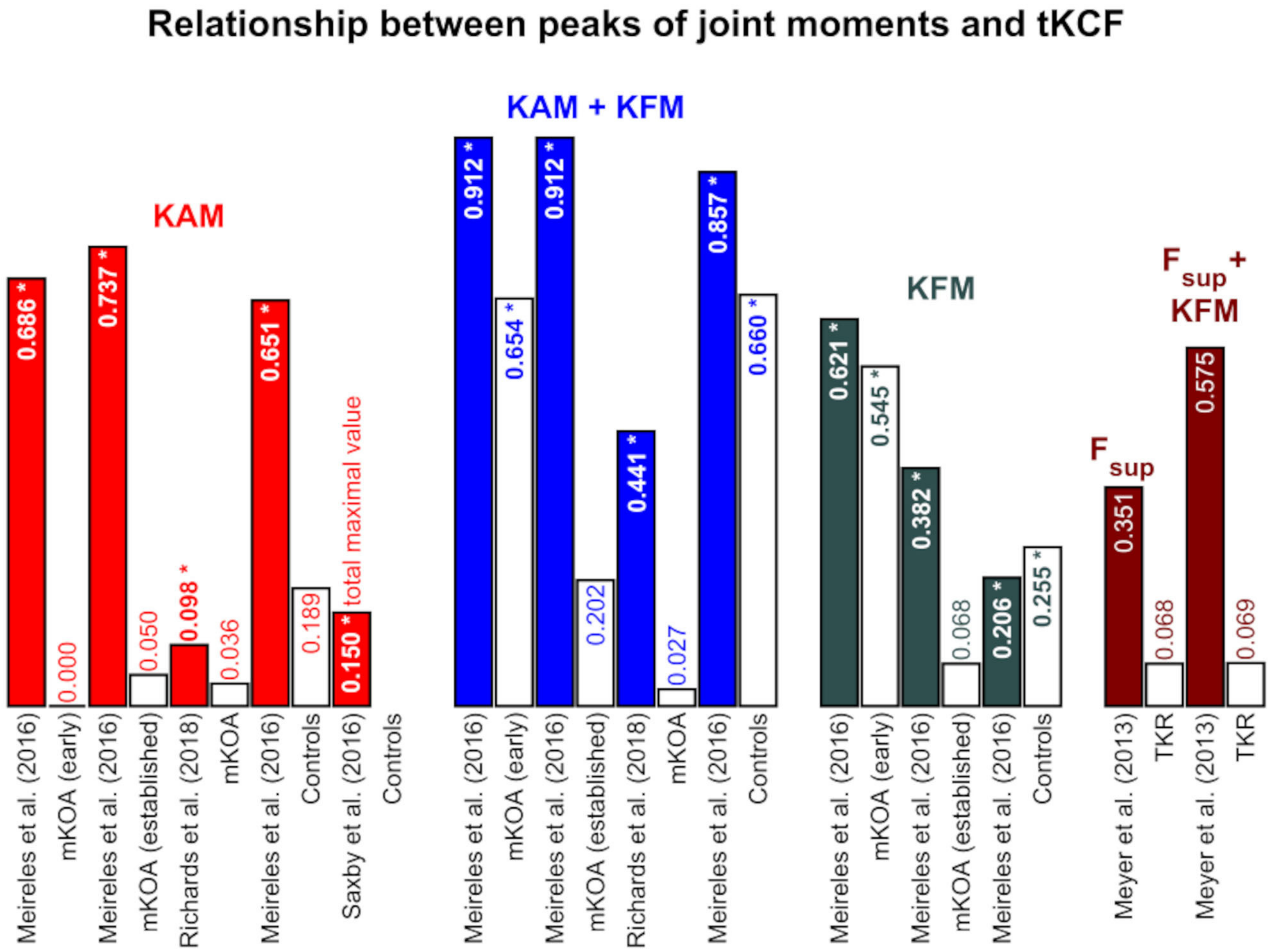

FIGURE 5 | Coefficient of determinations between the first and second peaks of the joint moments and total knee joint contact force (tKCF). The * indicates significant correlations. The exact *p*-values can be found in the **Supplementary Table 6**. Colored bars represent the findings for the first peak and the white bars with colored text for the second peak of the same study. *KAM*, knee adduction moment; *KFM*, knee flexion moment; *F_sup*, superior force; *TKR*, Patients after total knee replacement; *mKOA*, Patients with medial knee osteoarthritis.

4.2. Factors that May Influence the Relationship

4.2.1. Time of Stance

The main difficulty in summarizing the statistical results of included papers was the variety of the point in time of stance which was used to analyze the relationship between external and internal forces. In other words, some studies extracted peak values for the first and/or second peak of stance, others extracted the overall maximal value. Especially, using the total maximal value of the joint moment or joint contact force without reporting the point of time of this value, makes it more difficult to set the findings and conclusions in perspective to the outcome at the first and second peak. Furthermore, only a few studies additionally reported the point in time (% of stance) at which the maximum occurred. Therefore, it was decided to separately report the external-internal force relationship of the first and second peak in stance as well as the overall maximum during stance. For the future we suggest to report the point of time of the extracted values or when possible to use other statistical methods to analyze the whole stance or gait phase and not only one discrete value.

In various findings, an increased first peak knee or hip joint moment was associated with pathological changes (e.g., knee or hip joint OA, Baliunas et al., 2002; Liao et al., 2019) and disease severity (Sharma et al., 1998) or pain (Thorp et al., 2007). This might be the reason, why the first peak was also more often considered in terms of clinical decision making. For these populations, the first peak KAM or HAM can be used as surrogate measure for mKCF respectively HCF. In contrast, the second half of stance phase should be investigated by estimating the internal KCFs while the studies showed less contribution of the hip and knee joint moments in the joint contact forces and therefore a less accurate interpretation of internal joint loading. Additionally, loading in the lateral compartment of the knee joint should be analyzed by using the *l*KCFs throughout the whole stance phase.

TABLE 3 | Results for lateral knee contact force: Relationship for the total maximum, first, and second peaks.

Study	Population	Independent variable	Total maximal value		First peak		Second peak
			R^2	p	R^2	p	R^2
Noyes et al., 1992	Patients (ACLR) & controls	KAM	0.002	> 0.05			
Winby et al., 2013	Patients (APM) & controls	KAM			0.12	< 0.05	
Noyes et al., 1992	Patients (ACLR) & controls	KFM	0.096	> 0.05			
Winby et al., 2013	Patients (APM) & controls	KFM			0.29	< 0.05	
Noyes et al., 1992	Patients (ACLR) & controls	KEM	0.810	< 0.01			
Saxby et al., 2016	Controls	KAM	0.01	> 0.05			
Meyer et al., 2013	Patients (TKR)	F_sup			0.175		0.002
		F_sup + KAM			0.797		0.006
		F_sup + KAM + KFM			0.822		0.007

ACLR, anterior cruciate ligament reconstruction; APM, arthroscopic partial meniscectomy; KFM, knee flexion moment; KEM, knee extension moment; KAM, knee adduction moment; F_sup, superior force.
Values in blue: R^2 is calculated from original r-value.

For the hip and knee joint, a stronger correlation between internal and external forces was observed for the first peak compared to the second peak. An explanation for this could be the different muscle activities during the gait cycle. The first peak mostly occurs approximately at around 12% of the gait cycle. At this point mainly the vastii muscles (for the knee joint) and gluteus medius and maximus (for the hip joint) are active and contribute mainly to the internal joint contact forces (Pandy and Andriacchi, 2010; Sasaki and Neptune, 2010). Additionally, at this point, the double leg support is still ongoing or the contralateral leg just left the ground, therefore, the stability of the leg should be almost at optimum (Perry and Burnfield, 2010). The second peak usually occurs at the end of terminal stance (at approximately 45% of the gait cycle), where the leading leg is still in single support. At this point, the gastrocnemii muscles move the body forward and, therefore, contribute the most to the joint contact forces (Pandy and Andriacchi, 2010; Sasaki and Neptune, 2010). Moreover, it is assumed that co-activation has a greater influence in the calculation of the internal joint contact forces in the second peak compared to the first peak (Pedersen et al., 1987). This might explain the lower correlation between external joint moments and internal joint contact forces at the second peak. In other words, we can conclude that during first peak the hip and knee spanning muscles are active, giving stability to the joints, which might lead to a better internal-external force relationship.

4.2.2. Differences in Study Population

Five different populations have been, in total, analyzed in included studies (three studies: patients after TKR, three studies: patients with mKOA, four studies: patients after ACLR, one study: patients after APM, 10 studies: healthy controls). In general, more extracted values were compared and analyzed for healthy populations than for patient groups.

Depending on the patient groups, variations in kinematics, kinetics and muscle activation can occur. Patients 24 and 33 months after TKR still exhibit a changed gait pattern and muscle activity compared to age-matched healthy controls (Lundberg et al., 2016; Ro et al., 2020). To add on, patients with mKOA adapted compensatory mechanisms as an increased trunk lean in the direction of the affected limb or a more outward rotated foot compared to healthy controls to reduce the load in the affected joint (Arnold et al., 2014; Kuwahara et al., 2020). Furthermore, patients 2 years after ACLR still performed a different gait pattern and knee joint loading compared to healthy controls (Noehren et al., 2013; Erhart-Hledik et al., 2018). Also, patients 2 years after total hip replacement still show decreased KAMs and increased HAMs for the peak in the second half of stance compared to controls for both the affected and unaffected limb (Stief et al., 2018). Also, gait adaptations altering the external KAM do not necessarily affect internal KCF (Walter et al., 2010; Kinney et al., 2013; Richards et al., 2018). The effect of gait adaptations on internal HCFs have also been investigated. Decreased HCFs were associated with a reduced hip adduction angle which also reduced HAM (Wesseling et al., 2015). Pelvis rotation also highly contributes in HAM (Ardestani et al., 2015). Nevertheless, the direct influence of kinematic changes on the relationship between joint moments and joint contact forces was not yet evaluated. As a result, we recommend examining the effect of gait adaptations separately on joint moments and joint contact forces and, additionally, its direct impact on the relationship between external and internal joint loading measures. Thus, more studies should be performed on different patients investigating the relationship between external and internal joint loading parameters while also considering larger sample sizes.

Previous studies showed an increased KAM (Hurwitz et al., 2002) and mKCF (Smith et al., 2016) in patients with varus malalignment, while a valgus malalignment decreased KAM and increased *l*KCF (Holder et al., 2020). Additionally, the static limb alignment contribute largely on the joint loading

TABLE 4 | Summary table of the findings about the relationship between external knee joint moments and internal mKCFs and tKCFs.

			KAM	KFM	KEM	KAM + KFM
Patients after TKR	mKCF	First peak	Moderate	-	-	-
		Second peak	Strong	-	-	-
		Maximal	-	-	-	-
	tKCF	First peak	-	-	-	-
		Second peak	-	-	-	-
		Maximal	-	-	-	-
Patients with mKOA	mKCF	First peak	Strong	-	-	Strong
		Second peak	Moderate	-	-	Moderate
		Maximal	-	-	-	-
	tKCF	First peak	Strong	Strong	-	Strong
		Second peak	Low	Moderate	-	Moderate
		maximal	-	-	-	-
Patients after ACLR	mKCF	first peak	-	x	-	Moderate
		Second peak	-	-	-	-
		Maximal	Strong	-	-	Strong
	tKCF	First peak	-	-	-	-
		Second peak	-	-	-	-
		Maximal	-	-	-	-
Patients after APM	mKCF	First peak	Moderate	Low	-	-
Healthy controls	mKCF	First peak	Strong	low	x	-
		Second peak	Strong	x	Moderate	-
		Maximal	Moderate	low	Moderate	Strong
	tKCF	First peak	Strong	Low	-	Strong
		Second peak	x	Moderate	-	Strong
		Maximal	Low	-	-	-

The predictability of the internal joint contact forces is classified in four different stages: -: relationship was not investigated; x: no predictability (in red); low: low predictability (in orange); moderate: moderate predictability (in yellow); strong: strong predictability (in green). The stages are related to the investigated R^2-values which were interpreted as low below 0.25, between 0.25 and 0.49 as moderate and above 0.49 as high Hinkle et al. (1988); Kotrlik and Williams (2003).

KAM, knee adduction moment; KFM, knee flexion moment; KEM, knee extension moment; mKCF, medial knee joint contact force; tKCF, total knee joint contact force; TKR, total knee replacement; mKOA, medial knee osteoarthritis; ACLR, anterior cruciate ligament reconstruction; APM, arthroscopic partial meniscectomy.

distribution on the medial and lateral compartment (Smith et al., 2016). The lower limb alignment was, however, not reported for all participants in the included studies. Kutzner et al. (2013) performed correlation analyses between external knee joint moments and internal KCFs for varus and valgus aligned knee joints separately and did not find significant differences between them. Consequently, we suggest to evaluate the impact of lower limb alignment on the relationship between joint moments and joint contact forces although its effect separately on these parameters was already investigated.

4.2.3. Limitations of Musculoskeletal Modeling

In a few studies, basic information about the used model were missing, e.g., about the number of segments in the model, degrees of freedom or the used software. A previous study showed that diverse coordinate systems were a key factor in contrasting kinematics, kinetics and also muscle activation and forces (Roelker et al., 2017). In this systematic review the studies investigating the internal KCFs with OpenSim or SIMM software used either the generic "gait2392" OpenSim model (Meireles et al., 2016) or equations by Winby et al. (2009), which are also based on Delp et al. (1990) Kumar et al. (2013), Winby et al. (2013), Manal et al. (2015), Saxby et al. (2016), Wellsandt et al. (2017), Khandha et al. (2019). We assume that similar coordinate system definitions were used. Additionally, a higher number of DoF at the knee joint was shown to overestimate the KCF because of an increased force in the quadriceps muscle. In contrast, more physiological constraints at the knee joint lead to an underestimation of KCF (Valente et al., 2015). Furthermore, models vary in muscle parameters as muscles' peak isometric force and affecting the calculation of muscle activation and forces during gait (Roelker et al., 2017). A previous study, which compared muscle force estimation between OpenSim and Anybody, reported that variations in muscle forces were mainly caused by dissimilar anatomical definitions, contrasts in calculated joint centers and segmental interactions of the models (Trinler et al., 2019). Further on, the calculation of joint contact forces and muscle forces appear to be more sensitive for changes in musculoskeletal definitions compared to joint angles and moments when varying body landmark positions, musculotendon geometry, or maximum muscle tension (Valente et al., 2014). Nevertheless, these changes only moderately affect model outcomes like joint contact forces and muscle forces. These aspects imply that a detailed description of the used MSK model is necessary and helpful for comparisons between studies.

Another parameter influencing the estimated outcome of the internal KCFs could be the implementation of participant-specific EMG data. Six studies (Kumar et al., 2013; Winby et al., 2013; Manal et al., 2015; Saxby et al., 2016; Wellsandt et al., 2017; Khandha et al., 2019) used a similar MSK model (Winby et al., 2009) and 4 of these studies (Kumar et al., 2013; Manal et al., 2015; Wellsandt et al., 2017; Khandha et al., 2019) implemented the EMG data from the same muscles. Two other studies (Winby et al., 2013; Saxby et al., 2016) used 1 respectively 3 additional EMG data from other muscles. Nevertheless, these 6 studies demonstrated similar results regarding the correlation between mKCF with KAM and KFM. Additionally, no substantially differences between studies using EMG-informed models compared to models without implementing participant-specific EMG data (Ogaya et al., 2014; Meireles et al., 2016; Richards et al., 2018) could be observed. However, other studies found a better correlation of estimated muscle forces, calculated with a best-fit solution taking muscle co-contraction into account with muscle forces measured with EMG compared to a static optimization approach (Martelli et al., 2015a). Therefore, we suggest that in case of movements with large muscle co-contraction, either EMG-driven musculoskeletal models or other approaches calculating the muscle forces are used.

Previous studies found that the different scaling approaches, e.g., body mass based scaling, scaling based on shape modeling or linear scaling affect the outcome of MSK modeling (Kainz et al., 2017; Bahl et al., 2019). In general, scaling based on medical images or with the inclusion of calculated joint centers into the scaling process improves the accuracy of the calculation of the hip joint center location compared to scaling with surface markers alone (Kainz et al., 2017; Bahl et al., 2019). However, the included studies in this systematic review performing MSK modeling only reported the usage of linear scaling based on marker positions and/or anatomical/anthropometrical data and no scaling based on medical images (Kumar et al., 2013; Winby et al., 2013; Ogaya et al., 2014; Giarmatzis et al., 2015, 2017; Manal et al., 2015; Wesseling et al., 2015; Meireles et al., 2016; Saxby et al., 2016; Wellsandt et al., 2017; Richards et al., 2018; Khandha et al., 2019). Moreover, the effect of soft tissue artifacts on MSK modeling should be considered as well. A previous study found a 5–25% variation of the joint moments and muscle forces and a relative variation of 5–15% of the joint contact forces when simulating soft tissue artifacts (Lamberto et al., 2017). Researchers should be aware of this aspect when interpreting gait analysis results with MSK modeling especially in cases with large soft tissue artifacts.

The studies using instrumented prosthesis to define the internal KCFs reported a good relationship between external knee joint moments and internal KCFs (**Figure 3**). The calculated external knee flexion-extension moments with the OpenSim model used from Kumar et al. (2013) and Winby et al. (2013) were previously validated with good reliability against data from an isokinetic dynanometer (Lloyd and Besier, 2003). In addition, the results obtained with another MSK model (Manal et al., 2015; Saxby et al., 2016; Wellsandt et al., 2017; Richards et al., 2018; Khandha et al., 2019) were already validated against directly measured internal KCFs of an instrumented prosthesis (Gerus et al., 2013; Manal and Buchanan, 2013; Lund et al., 2015), also with good agreement. Since the generic models were previously validated against different methods and have been used by a large number of researchers, we assume that the calculation of external joint moments and internal joint contact forces measured by MSK models is valid to assess the internal joint loading.

4.2.4. Effect of Walking Speed

In former investigations it was reported that walking speed affects KAM and KCF but also HAM and HCF. A fast walking speed increases the first peak and decreases the second peak of KAM and HAM (Schwartz et al., 2008) whereas both peaks of tKCF (Lerner et al., 2014) and HCF (Giarmatzis et al., 2015) increase. Included studies reported walking speed between 1.1 m/s and 1.6 m/s while Trepczynski et al. (2014) and Richards et al. (2018) did not state any walking speed information. The effect of walking speed on the relationship between external knee joint moments and internal KCFs was investigated by Kutzner et al. (2013). They found an increased R^2 but no significant R^2-change when combining walking speed with first peak of the external KAM to predict mKCF. While an effect of walking speed on the external and internal joint loading parameter exists, we suggest to further study its influence on the relationship between external knee joint moments and internal KCFs.

5. CONCLUSION AND GENERAL RECOMMENDATIONS

Seventeen studies have been found that analyzed a relationship between internal and external joint loading parameters. For the investigated populations, it can be summarized that the first peak or total maximal value of mKCF were best predicted by KAM alone and in combination with KFM. Additionally, the first peak of tKCF was well predictable by KAM. In contrast, the internal mKCF and tKCF in the second half of stance were only low correlated with the external knee joint moments. The internal *l*KCF also correlated only weakly with the external knee joint moments during the entire stance phase. The peak HCF in the first half of stance is strongly predictable by HAM, however, less strong at the second peak during the second half of stance. For the first half of stance, the determination of HAM is sufficient enough whereas statements about the second half of stance should be made by calculating the internal HCF.

The estimation of external joint moments is useful for a general statement about the mKCF or tKCF peak in the first half of stance or for a maximal loading. In addition, the calculation of external joint moments is implemented in most gait labs in the general processing procedures and therefore easily accessible. In contrast, MSK modeling is usually not part of the clinical assessment and therefore requires higher computational cost. Moreover, when evaluating joint contact forces from MSK modeling, output errors due to misaligned muscle point positions or marker based scaling should be taken into account. Nevertheless, investigating diseases like valgus malalignment of the lower limb, calculating the *l*KCF by MSK modeling should be preferred, or at least additionally consulted, because the external joint moments from ID do not correlate strongly with *l*KCF.

Altogether ID and MSK modeling are two different methods of analyzing joint loading. The method that should be used in the clinical environment depends on the clinical question, since for some applications computing external joint moments is sufficient, whereas a greater amount of time may be justified, e.g., for patients with valgus malalignment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR'S NOTE

All of the authors listed in the byline were fully involved in the study and preparation of the manuscript. They have made substantial contributions to the conception, design, execution, or interpretation of the reported study and fulfill the requirements for authorship established by the International Committee of Medical Journal Editors. Each of the authors has read and concurs with the content in the final manuscript.

AUTHOR CONTRIBUTIONS

JH and FS conceived the presented idea. JH and UT drafted the overview of the review and performed the analysis and interpretation. JH drafted the manuscript and visualized the results. UT, AM, and FS reviewed the manuscript, suggested improvements in the content and approved the final version. All authors agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

A Systematic Review of the Associations Between Inverse Dynamics and Musculoskeletal Modeling to Investigate Joint Loading in a Clinical Environment

Supplementary Material

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A FULL SEARCH TERMS

The search was performed on November 14, 2019.

- Pubmed:
  ((((gait OR walk*) AND (hip OR knee) AND (force* OR moment* OR torque*) AND ((model* OR muskuloskeletal OR musculoskeletal) OR (“inverse dynamics” OR simulation*)) AND ((full text[sb] AND hasabstract[text]) AND (“1990/01/01”[PDat] : “2019/10/31”[PDat]) AND Humans[Mesh] AND (English[lang] OR German[lang])))))
- Web of Science:
  (((TS=(gait OR walk*) AND TS=(hip OR knee)) AND TS=(force* OR moment* OR torque*)) AND TS=((model* OR muskuloskeletal OR musculoskeletal) OR (“inverse dynamics” OR simulation*)))
  AND TS = human*
  Databases= WOS, BIOABS, BCI, CCC, DRCI, DIIDW, KJD, MEDLINE, RSCI, SCIELO, ZOOREC
  Timespan=1990-2019
  Search language=English

B QUALITY ASSESSMENT CATEGORIES AND PARAMETERS

Table S1. Quality assessment categories and parameters adopted from Downs and Black (1998).
A total score (in %) for every category and an overall total score (in %) are calculated for every study dividing the reached points per category with the maximal possible points in this category. The overall score of each paper was calculated by dividing the total reached points with the maximal possible points.

	Category	Parameter	Maximal points
1	Aims	Aim	2
		Patients & controls	2
2 & 3	Patients & Controls	Pathology	1
		Inclusion/exclusion criteria	2
		Quantity	4
		Gender	2
		Age & spread	4
		Body height, BW or BMI + spread	8
		Knee alignment	2
4	Equipment	Capture system	2
		Nr. of cameras	1
		Frequency cameras	1
		Nr. of markers	1
		Marker locations	1
		Filter (cameras)	2
		Force plates	1
		Nr. of force plates	1
		Frequency force plates	1
		Filter (force plates)	2
5	EMG	EMG system	1
		Frequency EMG	1
		Muscles	1
		Data processing	1

BW: body weight; BMI: body mass index; EMG: electromyography; DoF: degree of freedom.

Continued on next page

Table S1. *Continued from previous page*

	Category	Parameter	Maximal points
6	External joint moments/forces	Segments Nr.	1
		Segments name	1
		DoF	2
		Software (angles)	1
		Description of model (angles)	1
		Software (moments)	1
		Description of model (moments)	1
		Peak, mean, etc. (moments)	1
		Unit (moments)	1
7	Internal joint contact forces	Segments Nr.	1
		Segments name	1
		DoF (knee or hip)	1
		Software	1
		Description of model	1
		Scaling approach	1
		Optimization type	1
		Nr. of muscle-tendon units	1
		Peak, mean, etc.	1
		Unit	1
8	Statistics	Walkway or treadmill	1
		Walking speed + spread	2
		Shod/barefoot	1
		Software	1
		Clear description	2
		Statistical output	2
9	Discussion & conclusion	Discussion & conclusion	2
		Total points	75

BW: body weight; BMI: body mass index; EMG: electromyography; DoF: degree of freedom.

C STATISTICAL METHODS AND EXTRACTED PARAMETERS

Table S2. Statistical methods and full list of extracted parameters. *RMSE*: root mean squared error.

Study	Statistical method	Extracted parameters
Knee joint		
Esculier et al. (2017)	Linear regression	Unstandardized regression coefficients (*B*, standard error), *t*, *p*, cumulative *R*, cumulative adjusted R^2, significant *F* changes
Khandha et al. (2019)	Pearson correlation	*r*, *p*
Kumar et al. (2013)	(Multiple) linear regression	Unstandardized regression coefficients (*B*, standard error), β, *p*
Kutzner et al. (2013)	Linear regression	R^2, *p*
Manal et al. (2015)	Linear regression	Unstandardized regression coefficients (*B*, standard error), *t*, *p*, *r*, adjusted R^2, significant *F* changes
Meireles et al. (2016)	(Multiple) linear regression	R^2, *p*
Meyer et al. (2013)	Linear regression	R^2 and RMSE
Noyes et al. (1992)	Pearson correlation	*r*, *p*
Ogaya et al. (2014)	Pearson correlation	*r*, *p*
Richards et al. (2018)	Linear regression	Regression coefficients (*B*, standard error) and 95 % confidence intervals, *p*, adjusted R^2, RMSE, % error
Saxby et al. (2016)	General linear models	*p*, R^2, normalized RMSE
Trepczynski et al. (2014)	Linear mixed-effects models	Regression coefficients, RMSE (Across all activities: R^2, RMSE, *p*)
Wellsandt et al. (2017)	Hierarchical linear regression	R^2, *p*
Winby et al. (2013)	Pearson correlation	R^2, *p*
Hip joint		
Giarmatzis et al. (2017)	Stepwise regression	R^2, *p*
Giarmatzis et al. (2015)	Regression (linear mixed models)	R^2, *p*
Wesseling et al. (2015)	(Multiple) linear regression	R^2, *p*

D RELATIONSHIP BETWEEN THE HIP JOINT CONTACT FORCE AND EXTERNAL HIP JOINT MOMENTS

Table S3. Results for hip joint contact force: Relationship for the first and second peaks.

Study	Age [years]	Independent variable	Walking speed [m/s]	First peak R^2	First peak p	Second peak R^2	Second peak p
Giarmatzis et al. (2017)	69.6	HAM	0.83	0.82	< 0.05		
			1.11	0.81	< 0.05		
			1.38	0.81	< 0.05		
			1.67	0.67	< 0.05	0.60	< 0.05
	21.4	HAM	0.83	0.65	< 0.05		
			1.11	0.55	< 0.05		
			1.38	0.55	< 0.05		
			1.67	0.67	< 0.05		
	69.6	HEM	0.83			0.57	< 0.05
			1.11			0.70	< 0.05
			1.38			0.46	< 0.05
		HEM + HAM + HRM	0.83			0.87	< 0.05
	21.4	HRM	0.83			0.40	< 0.05
			1.11			0.63	< 0.05
			1.38			0.66	< 0.05
			1.67			0.76	< 0.05

HAM: hip adduction moment; *HEM*: hip extension moment; *HRM*: hip rotation moment.

Continued on next page

Table S3. *Continued from previous page*

Study	Age	Independent variable	Walking speed [m/s]	First peak R^2	First peak p	Second peak R^2	Second peak p
Giarmatzis et al. (2015)	22.2	HAM	0.83	0.53	< 0.05	0.16	> 0.05
			1.11	0.53	< 0.05	0.17	> 0.05
			1.38	0.54	< 0.05	0.09	> 0.05
			1.67	0.78	< 0.05	0.12	> 0.05
		HEM	0.83	0.001	> 0.05	0.52	< 0.05
			1.11	0.04	> 0.05	0.51	< 0.05
			1.38	0.14	> 0.05	0.61	< 0.05
			1.67	0.17	> 0.05	0.7	< 0.05
		HRM	0.83	0.04	> 0.05	0.44	< 0.05
			1.11	0.02	> 0.05	0.03	> 0.05
			1.38	0.07	> 0.05	0.01	> 0.05
			1.67	0.02	> 0.05	0.12	> 0.05
		HAM + HEM	1.67	0.93	< 0.05		
		HFM + HRM	0.83			0.66	< 0.05
Wesseling et al. (2015)	52-61	HAM	1.28	0.87	< 0.001	0.54	< 0.001
		HFM		0.02	0.007	0.20	< 0.001
		HRM		0.85	< 0.001	0.32	< 0.001
		HAM + HRM		0.88	< 0.001	0.55	< 0.001
		HFM + HAM		0.89	< 0.001	0.76	< 0.001
		HRM + HFM		0.90	< 0.001	0.57	< 0.001
		HRM + HFM + HAM				0.76	< 0.001

HAM: hip adduction moment; *HEM*: hip extension moment; *HRM*: hip rotation moment.

E RELATIONSHIP BETWEEN JOINT MOMENTS AND THE MEDIAL KNEE JOINT CONTACT FORCE FOR THE FIRST AND SECOND PEAK

Table S4. Results for medial knee contact force: Relationship for the first and second peak.

Study	Population group	Independent variable	First peak R^2	First peak p	Second peak R^2	Second peak p
Kutzner et al. (2013)	Patients (TKR)	KAM	0.45	0.046	0.55	0.022
Richards et al. (2018)	Patients (mKOA)	KAM	0.597	< 0.05	0.439	< 0.05
Wellsandt et al. (2017)	Patients (ACLR) (involved leg)	KFM	0.072	0.150		
	Patients (ACLR) (uninvolved leg)		0.036	0.319		
Richards et al. (2018)	Patients (mKOA)	KAM + KFM	0.733	< 0.05	0.430	< 0.05
Wellsandt et al. (2017)	Patients (ACLR) (involved leg)	KFM + KAM	0.343	0.003		
	Patients (ACLR) (uninvolved leg)		0.396	0.001		
Kumar et al. (2013)*	Patients (mKOA) & controls	KAM	**0.74**	0.002	**0.13**	0.297
Winby et al. (2013)	Patients (APM) & controls	KAM	0.40	< 0.05		
Kumar et al. (2013)*	Patients (mKOA) & controls	KFM	**0.14**	0.047	**0.00**	0.896
Winby et al. (2013)	Patients (APM) & controls	KFM	0.25	< 0.05		
Ogaya et al. (2014)	Controls	KAM	**0.518**	< 0.001	**0.397**	< 0.001
		KFM	**0.240**	< 0.001	**0.012**	0.252
		KEM	**0.005**	0.483	**0.449**	< 0.001
Meyer et al. (2013)	Patients (TKR)	F_sup	0.380		0.162	
		F_sup + KAM	0.475		0.417	
		F_sup + KAM + KFM	0.480		0.418	

TKR: total knee replacement; *mKOA*: medial knee osteoarthritis; *ACLR*: anterior cruciate ligament reconstruction; *APM*: arthroscopic partial meniscectomy; *KAM*: knee adduction moment; *KFM*: knee flexion moment; *KEM*: knee extension moment; *F_sup*: superior force.
Values in **blue**: R^2 is calculated from original *r*-value.
* The authors performed a multiple linear regression analysis and reported β, a standardized regression coefficient which can be compared to *r* if only one independent variable is used in the multiple linear regression analysis.

F RELATIONSHIP BETWEEN JOINT MOMENTS AND THE MEDIAL KNEE JOINT CONTACT FORCE FOR THE TOTAL MAXIMAL VALUES

Table S5. Results for medial knee contact force: Relationship for the total maximal values.

Study	Population group	Independent variable	Total maximal value R^2	Total maximal value p
Khandha et al. (2019)	Patients (ACLR) (involved leg)	KAM	**0.608**	< 0.001
	Patients (ACLR) (uninvolved leg)		**0.348**	< 0.001
Manal et al. (2015)	Patients (ACLR)	KAM	0.633	0.004
		KAM + KFM	0.851	0.009
Noyes et al. (1992)	Patients (ACLR) & controls	KAM	**0.176**	< 0.05
		KFM	**0.090**	> 0.05
		KEM	**0.593**	< 0.01
Ogaya et al. (2014)	Controls	KAM	**0.348**	< 0.001
Esculier et al. (2017)	Controls (all)	KAM	0.314	< 0.001
	Females (only)		0.518	< 0.001
	Males (only)		0.518	< 0.001
Saxby et al. (2016)	Controls	KAM	0.36	< 0.05
Ogaya et al. (2014)	Controls	KFM	**0.068**	0.122
		KEM	**0.360**	< 0.001
Esculier et al. (2017)	Controls (all)	KAM + KFM	0.749	< 0.001
	Females (only)		0.925	< 0.001
	Males (only)		0.826	< 0.001

ACLR: anterior cruciate ligament reconstruction; *KAM*: knee adduction moment; *KFM*: knee flexion moment; *KEM*: knee extension moment.
Values in **blue**: R^2 is calculated from original r-value.

G RELATIONSHIP BETWEEN JOINT MOMENTS AND THE TOTAL KNEE JOINT CONTACT FORCE FOR THE FIRST AND SECOND PEAK

Table S6. Results for total knee contact force: Relationship for the first and second peaks.

Study	Population group	Independent variable	First peak R^2	First peak p	Second peak R^2	Second peak p
Meireles et al. (2016)	Patients (early mKOA)	KAM	0.686	< 0.01	0.000	> 0.05
	Patients (established mKOA)		0.737	< 0.01	0.050	> 0.05
Richards et al. (2018)	Patients (mKOA)	KAM	0.098	< 0.05	0.036	> 0.05
Meireles et al. (2016)	Patients (early mKOA)	KFM	0.621	< 0.01	0.545	< 0.01
	Patients (established mKOA)		0.382	< 0.01	0.068	> 0.05
	Patients (early mKOA)	KAM + KFM	0.912	< 0.01	0.654	< 0.01
	Patients (established mKOA)		0.912	< 0.01	0.202	> 0.05
Richards et al. (2018)	Patients (mKOA)	KAM + KFM	0.441	< 0.05	0.027	> 0.05
Meireles et al. (2016)	Controls	KAM	0.651	< 0.01	0.189	> 0.05
		KFM	0.206	< 0.05	0.255	< 0.05
		KAM + KFM	0.857	< 0.01	0.660	< 0.01
Saxby et al. (2016) (total maximal value)	Controls	KAM	0.15	< 0.05		
Meyer et al. (2013)	Patients (TKR)	F_sup	0.351		0.068	
		F_sup + KFM	0.575		0.069	

mKOA: medial knee osteoarthritis; *KAM*: knee adduction moment; *KFM*: knee flexion moment; *F_sup*: superior force.

Chapter 5

Knee joint moments can accurately predict medial and lateral knee contact forces in patients with valgus malalignment

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Knee Joint Moments Can Accurately Predict Medial and Lateral Knee Contact Forces in Patients With Valgus Malalignment

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Abstract

Compressive knee joint contact force during walking is thought to be related to initiation and progression of knee osteoarthritis. However, joint loading is often evaluated with surrogate measures, like the external knee adduction moment, due to the complexity of computing joint contact forces. Statistical models have shown promise for predicting joint contact force from easily measured joint moments in individuals with osteoarthritis or joint replacements. This approach may also be effective in young patients with valgus deformities. The purpose of this study was to evaluate how accurately medial and lateral knee joint contact forces could be estimated by linear mixed-effects models during walking for children with and without valgus malalignment. Knee joint moments were strongly correlated ($R^2 > 0.85$, $p < 0.001$) with both medial and lateral knee joint contact forces. The knee flexion and adduction moments were significant covariates in most of the models, strengthening the understanding of the contribution of both moments to medial and lateral knee joint contact force. In the future, these models could be used to predict knee joint contact forces using joint moments from motion capture software, obviating the need for time-consuming musculoskeletal simulations.

Introduction

In the last five years the number of studies has tripled (see supplementary material for the full search terms used in Pubmed) that performed sports or clinical gait analysis and investigated internal joint contact or muscle forces rather than joint moments[1]. Both joint moments and joint contact forces aim to characterize cartilage loading during dynamic movements[2]. The knee adduction moment (KAM) is a commonly used surrogate measure for medial compartment knee loading because it is related to osteoarthritis (OA) initiation and progression[3,4] and is relatively simple to compute. Reducing the external KAM is often the target for non-surgical interventions, like changing the foot progression angle or by increasing the step width[5], that aim to reduce medial compartment loading. However, the external KAM only characterizes the effects of external forces (e.g., ground reaction force), frontal-plane kinematics, and segment inertia on the distribution of loading between the medial and lateral compartments[6]. In contrast, internal joint forces, like the medial and lateral knee joint contact force (medKCF, latKCF), additionally represent the forces that oppose muscle forces[7,8].

Both methods for estimating joint loading demonstrate advantages: joint moments are easily calculated, but knee contact forces are more representative of cartilage loading. Joint moments are usually available almost directly after the movement analysis because this method is often implemented in standard movement analysis pipelines, which may explain its acceptance as a surrogate measure for the dynamic internal knee joint loading. The external knee flexion/extension moment (KFM/KEM) also contributes to the internal knee joint contact force (KCF) as it relates to knee flexor and extensor muscle force. Linear models that use both the KAM and KFM as covariates have higher correlations with KCF than models that use KAM alone.[9–11] Calculating the internal joint contact, muscle and/or tendon forces requires additional time and expertise[1,12,13]. Therefore, the calculation of joint moments has the advantage of quick availability and lower cost in terms of time or human capacity. Estimating internal joint contact forces with musculoskeletal models includes the contribution of internal forces, like muscles and ligaments, making internal joint contact forces a potentially more accurate surrogate measure for dynamic joint loading. Nevertheless, both methods are estimations of the loading in a joint[2]. *In vivo* measurement of joint contact force can only be done by invasive methods as an instrumented prosthesis. Patients with instrumented prostheses are rare[14,15], and their loading patterns may not be representative of other populations of interest, like children. Additionally, highly dynamic movements like side-cutting have not been investigated in patients with instrumented prosthesis. The other two named methods, calculating external joint moments and internal joint contact forces, are therefore used in a more dynamic environment when younger study cohorts and other dynamic movements except for walking are investigated.

In a clinical setting, methods for estimating joint loading that are both accurate and inexpensive are needed. Previous studies showed that with a valgus malalignment, the external KAM amd medKCF during walking are reduced[16,17] whereas latKCF is increased[18]. Similarly, results were found in patients with medial knee OA who walk with an increased KAM[19] and a larger medKCF compared to age-matched healthy controls[20]. The KAM and medKCF are highly correlated during first half of stance, but weaker correlations exist between KAM and latKCF[20–22]. In general, the relationship between knee joint moments (KJMs) and latKCF has been less studied, and most cohorts are older adults or individuals with knee OA.[23–25] The ability of joint moments to predict medKCF and latKCF in these cohorts is promising, but further work is needed to understand these relationships in young individuals with valgus malalignment who are at increased risk of developing OA.

The aim of this study was to develop statistical models that relate external knee joint moments, (i.e., the knee adduction and flexion moments) to internal knee joint contact forces (i.e., medial and lateral knee joint contact forces) during walking in young patients with and without valgus malalignment. We hypothesized that 1) the prediction accuracy of the knee contact forces for children with and without valgus malalignment from external joint moments is high[21,26] ($R^2 > 0.49$; RMSE < 10%); 2) the prediction accuracy for the medial knee joint contact force by the external knee joint moments is larger compared to the lateral knee joint contact force; and 3) the prediction accuracy of the statistical models that use both sagittal and frontal plane moments to predict the knee joint contact forces will be greater than those that use joint moments from a single plane.

Results

Anthropometrics and walking speed

For comparing the anthropometrics and walking speed between groups, we performed independent *t*-tests or Mann-Whitney-*U*-test for not normally distributed data. These results are summarized in Table 1. All parameters except for age were normally distributed. The study groups were significant different in body height ($p = 0.014$), body mass ($p < 0.001$), body mass index ($p < 0.001$) and the mechanical axis angle ($p < 0.001$) but not for age and walking speed ($p > 0.05$). The effect sizes were large for all parameters except for age, body height and walking speed.

Table 1
Anthropometrics and walking speed.

	Patient group		TD group		Comparison between groups	
		Shapiro-Wilk (*p*-value)		Shapiro-Wilk (*p*-value)	*t*-test / Mann-Whitney-*U*-test (*p*-value)	Effect size *r*
Number of participants	50		21			
Sex [female / male]	19 / 31		7 / 14			
Bilateral / left / right affected limbs	38 / 5 / 7		- / 10 / 11			
Age [years]	13.0 (11.0–13.0)	< 0.001	12.0 (12.0–14.0)	0.004	0.294 *	0.124
Body height [m]	1.66 ± 0.10	0.379	1.59 ± 0.10	0.612	0.014	0.291
Body mass [kg]	63.5 ± 13.7	0.680	46.1 ± 10.7	0.364	< 0.001	0.530
Body mass index [kg/m²]	23.0 ± 3.4	0.204	18.1 ± 2.5	0.132	< 0.001	0.585
Mechanical axis angle [°]	-6.0 ± 1.8	0.248	-0.0 ± 2.3	0.379	< 0.001	0.811
Walking speed [m/s]	1.25 ± 0.16	0.569	1.29 ± 0.17	0.810	0.368	0.109

TD: Typically developed healthy control group; Mechanical axis angle of the patients was measured by an X-ray image; mechanical axis angle of the TD group was measured from the static trial from the three-dimensional gait analysis; Normal distributed data displayed as mean ± standard deviation; not normally distributed data are displayed as median (25. quartile - 75. quartile) and marked with a *; Mann-Whitney-*U*-tests have been performed instead of independent *t*-tests for not normally distributed data; significant *p*-values are highlighted in bold; Effect size $r > 0.1$: small; $r > 0.3$: medium; $r > 0.5$: strong.

Gait kinematics and kinetics

The mean curves of the dynamic KJMs and KCFs were compared between the two groups using statistical parametric mapping (Fig. 1). The KFM did not significantly differ between the patient and typically developed healthy control (TD) group. KAM was significantly smaller in the patient group between 3–52% ($p < 0.001$) and 61–66% ($p = 0.010$) of the gait cycle. The medKCF was significantly smaller in the patient group between 0–25% ($p < 0.001$), between 46–52% ($p = 0.005$), between 58–88% ($p < 0.001$), and between 91–100% ($p < 0.001$). The latKCF was significantly increased for the patient group between 37–50% ($p < 0.001$) and between 75–80% ($p = 0.018$) of the gait cycle. Other kinematic and kinetic curves and comparisons are included in the supplementary material.

Linear models

To establish the relationships between single-plane KJMs and KCFs, we first investigated correlations of KAM or KFM and medKCF or latKCF for the peaks in the first and second half of stance individually. Low to moderate correlations of $R^2 < 0.49$ were detected except between KAM2 and latKCF2 ($R^2 = 0.68$) for the patient group and KAM2 and medKCF2 ($R^2 = 0.59$) for the TD group. The root mean squared error (RMSE) ranged between 14–29%. See full results in the supplementary material, Table 1 and Table 2.

Linear mixed-effects models

For testing the possibility of accurately predicting peaks of medKCF and latKCF by combining KAM and KFM/KEM, we used linear mixed-effects models (LMM). For improvement of the model, random effects for both included limbs from bilaterally affected patients and different numbers of included trials per participant were added.

Patients

Equations 1 to 4 describe the LMMs that relate knee moments to the first and second peaks of medKCF and latKCF in the patient group. The first and second peaks of the variables are denoted by appending the peak number to the end of the variable (e.g., the first peak KAM is KAM1). The results of the LMMs are summarized in Table 2. For all four LMMs, KAM, and the squared knee flexion/extension moment (qKFM1, qKEM2) were included as significant fixed and random effects. The first model describing the relationship between medKCF1 and KAM1 and qKFM1 reported an adjusted $R^2 = 0.90$ (Eq. 1). The relationship between KAM1 and qKFM1 and the first peak of latKCF was also strong with an adjusted $R^2 = 0.89$ (Eq. 3). For the second peak of medKCF and latKCF, both LMMs were highly correlated with an adjusted $R^2 = 0.96$ (Eq. 2) and $R^2 = 0.95$ (Eq. 4), respectively.

$$medKCF1 = 1.411 + 2.187 \times KAM1 + 0.551 \times qKFM1 + (1 + KAM1 + qKFM1|subjVar) + (1|subjVar{:}\ footVar) \tag{1}$$

$$medKCF2 = 1.202 + 3.012 \times KAM2 + 4.158 \times qKEM2 + (1 + KAM2 + qKEM2|subjVar) + (1|subjVar{:}\ footVar) \tag{2}$$

$$latKCF1 = 1.544 + (-1.559) \times KAM1 + 1.498 \times qKFM1 + (1 + KAM1 + qKFM1|subjVar) + (1|subjVar{:}\ footVar) \tag{3}$$

$$latKCF2 = 1.754 + (-2.176) \times KAM2 + 0.454 \times qKEM2 + (1 + KAM2 + qKEM2|subjVar) + (1|subjVar{:}\ footVar) \tag{4}$$

Table 2
Statistical summary of the linear mixed-effects models between the internal knee joint contact forces and external knee joint moments for the patient group.

Response Variable	Predictor Variable	Estimate	Standard Error	*t*-value	Degrees of freedom	*p*-value	Lower 95 % CI	Upper 95 % CI	Adj. R^2	RMSE	RMSE [%]
medKCF1	Intercept	1.411	0.049	29.009	417	< 0.001	1.315	1.506	0.90	0.14	7.01
	KAM1	2.187	0.166	13.206	417	< 0.001	1.861	2.513			
	qKFM1	0.551	0.073	7.513	417	< 0.001	0.407	0.695			
medKCF2	Intercept	1.202	0.054	22.272	417	< 0.001	1.096	1.308	0.96	0.13	6.0
	KAM2	3.012	0.228	13.184	417	< 0.001	2.563	3.462			
	qKEM2	4.158	0.209	19.863	417	< 0.001	3.747	4.570			
latKCF1	Intercept	1.544	0.044	35.012	417	< 0.001	1.457	1.630	0.89	0.15	10.3
	KAM1	-1.559	0.162	-9.649	417	< 0.001	-1.876	-1.241			
	qKFM1	1.498	0.117	12.819	417	< 0.001	1.269	1.728			
latKCF2	Intercept	1.754	0.042	41.818	417	< 0.001	1.671	1.836	0.95	0.10	6.8
	KAM2	-2.176	0.135	-16.146	417	< 0.001	-2.441	-1.911			
	qKEM2	0.454	0.141	3.218	417	0.001	0.177	0.731			

CI: Confidence interval; Adj. R^2: adjusted R^2; *RMSE*: root mean squared error [$N/(kg\times ms^{-2})$]; medKCF1/medKCF2: max. value in the first/second half of stance of the medial knee joint contact force [$N/(kg\times ms^{-2})$]; latKCF1/latKCF2: max. value in the first/second half of stance of the lateral knee joint contact force [$N/(kg\times ms^{-2})$]; KAM1/KAM2: max. value in the first/second half of stance of the external knee adduction moment [Nm/kg]; qKFM1/qKEM2: squared maximal/minimal value in the first/second half of stance of the external knee flexion/extension moment (KFM1, KEM2; [Nm/kg]).

Typically developed healthy controls

For the TD group LMMs were also performed for the four parameters medKCF1, medKCF2, latKCF1 and latKCF2 and shown in Eq. 5 to 8. Similar R^2 values were found with the chosen model (medKCF1: $R^2 = 0.95$ (Eq. 5); medKCF2: $R^2 = 0.97$ (Eq. 6); latKCF1: $R^2 = 0.93$ (Eq. 7); latKCF2: $R^2 = 0.92$ (Eq. 8)) compared to the results from the patient group (Table 3).

$$medKCF1 = 1.322 + 2.466 \times KAM1 + 0.744 \times KFM1 + (1 + KAM1 + KFM1|subjVar) \quad (5)$$

$$medKCF2 = 1.289 + 2.902 \times KAM2 + 4.133 \times qKEM2 + (1 + KAM2 + qKEM2|subjVar) \quad (6)$$

$$latKCF1 = 1.414 + (-1.288) \times KAM1 + 3.589 \times KAM1{:}\,qKFM1 + 1.563 \times KFM1{:}\,qKFM1 + (-4.750) \times KAM1{:}\,KFM1{:}\,qKFM1 + (1 + KAM1 + KFM1 + qKFM1|subjVar) \quad (7)$$

$$latKCF2 = 1.726 + (-2.160) \times KAM2 + (1 + KAM2|subjVar) \quad (8)$$

Table 3
Statistical summary of the linear mixed-effects models between the internal knee joint contact forces and external knee joint moments for the typically developed healthy control group.

Response Variable	**Predictor Variables**	**Estimate**	**Standard Error**	***t*-value**	**Degrees of Freedom**	***p*-value**	**Lower 95 % CI**	**Upper 95 % CI**	**Adj. *R²***	**RMSE**	***RMSE* [%]**
medKCF1	Intercept	1.322	0.142	9.307	93	< 0.001	1.040	1.604	0.95	0.13	5.1
	KAM1	2.466	0.413	5.965	93	< 0.001	1.645	3.287			
	KFM1	0.744	0.128	5.822	93	< 0.001	0.490	0.997			
medKCF2	Intercept	1.289	0.123	10.495	93	< 0.001	1.045	1.533	0.97	0.13	4.7
	KAM2	2.902	0.485	5.984	93	< 0.001	1.939	3.865			
	qKEM2	4.133	0.483	8.550	93	< 0.001	3.173	5.093			
latKCF1	Intercept	1.414	0.166	8.515	91	< 0.001	1.084	1.743	0.93	0.11	9.3
	KAM1	-1.288	0.500	-2.576	91	0.012	-2.281	-0.295			
	KAM1: qKFM1	3.589	1.431	2.508	91	0.014	0.746	6.431			
	KFM1: qKFM1	1.563	0.510	3.067	91	0.003	0.551	2.575			
	KAM1: KFM1: qKFM1	-4.750	1.242	-3.823	91	< 0.001	-7.218	-2.282			
latKCF2	Intercept	1.726	0.094	18.372	94	< 0.001	1.539	1.912	0.92	0.11	9.5
	KAM2	-2.160	0.279	-7.745	94	< 0.001	-2.714	-1.607			

CI: Confidence interval; Adj. *R²*: adjusted *R²; RMSE*: root mean squared error [N/(kg×ms^{-2})]; medKCF1/medKCF2: max. value in the first/second half of stance of the medial knee joint contact force [N/(kg×ms^{-2})]; latKCF1/latKCF2: max. value in the first/second half of stance of the lateral knee joint contact force [N/(kg×ms^{-2})]; KAM1/KAM2: max. value in the first/second half of stance of the external knee adduction moment [Nm/kg]; qKFM1/qKEM2: squared maximal/minimal value in the first/second half of stance of the external knee flexion/extension moment (KFM1, KEM2; [Nm/kg]).

Similar trends of LMM structures between the patient and TD group were observed. The knee adduction moment plays a major role for predicting medKCF1 and latKCF2. Predicting medKCF2, KEM2 was found to have a larger impact compared to KAM2. Only for latKCF1 different structures between the patient and TD group were seen. The lateral KCF was negatively correlated with KAM for both peaks in patients and TDs.

Discussion

We investigated the accuracy of statistical models that predict internal knee joint contact forces from knee joint moments in children and adolescents with and without valgus malalignment. We found that the models could predict medial and lateral knee contact force peaks with a high accuracy of $R^2 > 0.85$ and *RMSE* < 11% when including knee joint moments from both the sagittal and frontal plane. The first hypothesis was confirmed that for both study groups, the knee contact forces can be predicted with high accuracy with their individual statistical models. The second hypothesis was rejected, because both medial and lateral knee contact force, could be predicted with high accuracy ($R^2 > 0.85$) from joint moments. Our third hypothesis was confirmed, as models that included knee moments in the sagittal and frontal plane predicted joint contact forces with higher accuracy (R^2 = 0.89–0.97) than those that used a moment in a single plane (R^2 = 0.01–0.68). These results suggest that internal knee joint loading can be accurately predicted with statistical models that use inputs from commonly-used gait analysis tools, mitigating the need for complex musculoskeletal modeling procedures, potentially enabling these estimates to be made in a clinical setting.

Previous studies found that KAM correlated well with medKCF in the first half of stance with a prediction accuracy of about $R^2 \approx$ 0.4 and were performed in patients with knee OA or after knee replacement[22,24,27]. Previous studies also investigated the relationship between KFM and medKCF with, in general, low correlations ($R^2 < 0.25$) for both peaks[20,24,28,29]. Moreover, in few studies, multivariate models were used to study the effect of KAM and KFM on medKCF. These studies improved the prediction of medKCF for the first peak (R^2 improved by approximately 0.2) but not for the second peak. In general, the reported R^2 for the first peak of medKCF using KAM and KFM varied between 0.54 and 0.85 in older adults with and without musculoskeletal pathologies[10,11,21]. The lateral knee joint contact force has been less investigated and the few studies performed only found low relations with KAM ($R^2 < 0.15$) and slightly stronger correlations with KFM ($R^2 < 0.3$)[23–25]. In the present study, for both study groups the LMMs revealed large predictive power of $R^2 > 0.88$ and a RMSE ≤ 10.3%. These results strengthen the possibility of an accurate determination of internal KCFs by external KAM and KFM/KEM for young individuals with and without valgus malalignment.

Studies found that reducing KAM with gait modifications does not necessarily also change medKCF because other joint loading parameters as KFM or muscle co-contraction might be affected[11,30,31]. A possible successful gait modification for reducing medKCF could be in-toeing that potentially reduces KAM but not substantially affecting KFM[32–34]. The effect of gait modifications on latKCF has not been investigated in the past. Previous studies found KFM or KEM as the main contributor to latKCF[35], suggesting that offloading gait should target these parameters.[31,33] All four statistical models from the present study revealed a negatively directed correlation between KAM and latKCF. This suggests that an increase of KAM and no change of KFM could reduce latKCF. Nonetheless, gait modifications often alter both KAM and KFM and affect both medKCF and latKCF; though, the relative contribution of the moments differ between compartments and peak times. Future studies should use models, like the ones presented here, that consider the effects of both KAM and KFM on KCF.

Most other studies relating KJMs to KCFs investigate older populations with knee OA who likely have varus or neutral frontal plane alignment[27]. Our results provide estimates of loading in young patients with valgus malalignment that may inform the need for guided growth intervention in these children. Currently, the decision for a guided growth intervention is based on the static mechanical axis angle from an X-ray image, which is not highly correlated with medKCF and latKCF[18]. Consequently, this study may be helpful in the decision-making for guided growth. Moreover, the coefficients of our models are mostly different from those in models that used patients with varus alignment. In our models, the extracted values of KFM/KEM were included as squared parameters because a high variance was found. This highlights the importance of using population-specific models to determine internal KCFs.[20,36,37]

Limitations

It is important to identify the limitations of the study. With the linear regression model, we aimed to predict the KCFs by only using the KJMs. This study demonstrates that KCFs can be accurately predicted using KJMs from OpenSim; however, a more clinically applicable solution would be to use the KJMs directly from the three-dimensional motion capture system. We used KJMs from OpenSim to avoid confounding effects of differing coordinate systems, which can influence kinematic and kinetic results[38,39]. Future studies should investigate the influence of different coordinate systems or models on the relationship between joint moments and joint contact forces. Alternatively, a transformation between the motion capture and OpenSim coordinate systems could be determined and applied to the joint moment data prior to using our model. Moreover, to be able to include further parameters in this linear regression analysis, the dataset needs to be increased, especially for the TD group. Lastly, for fulfilling a complete view of leg alignment in children and adolescents and the influence of leg alignment on internal joint contact force, patients with varus alignment should be included. Although, in our hospital children and adolescents with varus alignment are also part of a large study, the number of participants is still small and therefore were not included.

Conclusion

We investigated the relationship between knee joint moments and knee joint contact forces in children with and without valgus malalignment during walking. The predictions from linear models were strongly related to knee joint contact forces from musculoskeletal simulations. This suggests that knee joint contact forces could be estimated in the future using knee joint moments from standard motion capture software as input to the linear models. Furthermore, including both the knee flexion/extension and adduction moments in the linear models increased the prediction accuracy. This supports the importance of evaluating the role of both muscle forces and dynamic mechanics in medial and lateral knee joint contact forces. By simplifying the evaluation of internal joint loading, the statistical models may enable clinicians and researchers to study and prescribe gait modifications that reduce knee joint contact force without needing to perform time-consuming musculoskeletal simulations.

Methods And Materials

Participants

In total, 71 children and adolescents were included in this study, 50 of them with a valgus malalignment of the knee joint and 21 TDs (Table 1). Solely patients with a clinical indication for a temporary hemiepiphysiodesis were included. More specifically, a pathological valgus alignment of at least one knee (38 patients were bilaterally affected) of the lower limb based on a full-length standing anteroposterior radiograph was necessary[17,40,41]. In our hospital, the indication for a temporary hemiepiphysiodesis is given when the deviation from the physiological mechanical bearing line was more than 10 mm[42], which is approximately 3° deviation of the physiological mechanical axis angle. The static mechanical axis angle was measured as the angle formed by the line from the hip center to the knee center and the line from the knee center to the ankle center[40]. Patients did not show any other pathological disorders at the lower limb as described previously[18]. The participants for the TD study cohort were recruited from local schools. All participants and their parents were thoroughly familiarized with the gait analysis protocol. Participants and their parents gave written informed consent to participate in this study, as approved by the local ethics committee of the Goethe University Frankfurt, Germany (182/16) and in accordance with the Helsinki Declaration. The study is registered in the German Clinical Trials Register (DRKS) (number: DRKS00010296).

Gait analysis

Kinematic data were collected barefoot at 200 Hz using an 8-camera three-dimensional motion capture system (MX 10, VICON Motion Systems, Oxford, UK). Ground reaction forces were recorded synchronously at 1000 Hz using two force plates (Advanced Mechanical Technology, Inc., Watertown, MA, USA) situated at the mid-point of the 15 m long level walkway. When analyzing frontal and transverse plane gait data, a custom made lower body protocol was used for improvement of the reliability and accuracy described in a previous study[43]. In addition to the standardized Plug-in-Gait marker set[44], reflective markers were attached on the medial malleolus, medial femoral condyle and greater trochanter. The statically measured midpoints between the medial and lateral malleolus and condyle markers defined the centers of rotation of the ankle and knee joints[43]. The center of the hip joint was calculated with a standardized geometrical prediction method using regression equations[6] which is common in the clinical gait community[45]. During the static upright standing trial, participants stood barefoot, feet shoulder width apart, knees fully extended, in a forward knee position with the patella centered over the femoral condyles to control for any foot rotation effects[46]. Three to five dynamic trials with a clear foot-force plate contact were selected for further processing.

Musculoskeletal modeling

OpenSim (4.1) was used for musculoskeletal modeling of joint angles, joint moments, muscle activations, and forces and joint contact forces[47]. Input from marker positions and ground reaction forces were prepared with the MOtoNMS toolbox (version 3) in MATLAB (2020b, The MathWorks, Inc., Natick, MA, USA) for usage in OpenSim[48]. Ankle and knee joint centers were calculated in MOtoNMS. The joint centers were the midpoints between the medial and lateral malleolus and femoral condyle markers. Force data were filtered with a zero-lag low-pass Butterworth filter and a cut-off frequency of 10 Hz. An OpenSim model[7,49] with 23 degrees of freedom was used: six degrees of freedom for the pelvis relative to the ground frame, three for the lumbosacral joint, three for the hip joint, two for the knee joint, one for the ankle joint and one for the subtalar joint. The knee joint had sagittal and frontal-plane rotational degrees of freedom, and medial and lateral contact forces were resolved using a multi-compartment knee model[8,50]. The model was actuated by 80 muscle-tendon actuators[7,51] and passive muscle force-length curves were calibrated using experimental data[49,52].

The generic musculoskeletal model was linearly scaled based on marker positions and participant anthropometrics. Models were further personalized by adjusting the neutral frontal-plane alignment with the mechanical axis angle measured from X-Ray images[8]. X-rays were not available for the TD group, and the mechanical axis angle was calculated using a static gait analysis trial.[18,53]. It has been shown that this non-invasive marker-based approach correlated well with the determination of lower limb alignment in the frontal plane using radiographs in young patients with varus or valgus malalignment[53]. Inverse kinematics and inverse dynamics were calculated with the standard OpenSim processing pipelines. A static optimization implementation that incorporates tendon compliance and passive muscle forces was used to solve for muscle activations, with a cost function that minimized the sum of squared muscle activation[49]. Knee contact forces were computed and are reported as the reaction force in the medial and lateral compartments of the knee in the direction of the long axis of the tibia. All calculations were performed in MATLAB. Kinematic and kinetic parameters were segmented by gait cycle. External KJMs were normalized by body mass and KCFs were normalized by bodyweight.

Statistical analysis

The anthropometrics (age, body height, body mass, body mass index and the mechanical axis angle) and the walking speed of the patient group and the TD group were tested for normality using a Shapiro-Wilk test. Differences between patients and TDs of normal distributed data were compared with an independent *t*-test and non-normal distributed data with a Mann-Whitney-*U*-test (SPSS, 26, IBM Corporation, New York, NY, USA). The effect size *r* of the anthropometrics and the walking speed was calculated[54]. $r > 0.1$ described a small effect size, $r > 0.3$ a medium effect size and $r > 0.5$ a large effect size[55]. KJM and KCF mean curves between groups were statistically tested for normality and compared using a two-sample parametric *t*-test within statistical parametric mapping[56] in MATLAB. Significant differences were considered when the critical threshold of $\alpha = 0.05$ was passed for more than four successive time points, i.e. at least 4% of the gait cycle[57]. In the patient group, 38 participants were bilaterally affected by valgus malalignment. For the mechanical axis angle, walking speed, kinematic and kinetic comparisons between the study groups, only the more affected limb in regards of the mechanical axis angle was included. For the LMMs, both affected limbs were included. For TD, only one leg was randomly chosen to be included in all performed analyses.

For investigating the linear relationship between external KJMs and KCFs, maximal values in the first and second half of stance of the medKCFs and latKCFs and KAMs were detected (medKCF1, medKCF2, etc.). For KJM in the sagittal plane the maximal value in the first half and the minimal value of the second half of stance were extracted (KFM1 and KEM2). First, linear regression analyses between **one** predictor (e.g. KAM) and the response (e.g. medKCF) variable for the peaks in the first and second half of stance were performed. The detailed description of this analysis is reported in the supplementary material (paragraph “Linear regression analysis”). Next, LMMs were used to include multiple predictor variables and to account for both included limbs in bilateral affected patients as well as different numbers of trials included per participant and limb. In general, a minimum of three and a maximum of five trials per leg were included in the analysis. The joint moments were included as fixed and random effects. Categorical variables for the participants (subjVar) and for the analyzed leg (footVar) were implemented as random effects associating each trial with an ascending participant number and the analyzed foot (left: 1, right: 2). The KFM peaks were additionally included as squared parameters qKFM1 or qKEM2 because extracted small KFM/KEM values showed deviations from a linear trend what was checked visually. medKCF1/medKCF2 and latKCF1/latKCF2 were selected as response variables. In total, four LMMs were built for both study cohorts. For finding the best fitted LMM for the four response variables, backward selection of all included parameters (KAM, KFM, qKFM) was performed. This means that the parameters KAM, KFM, qKFM and all their possible interactions were included in the first fitted LMM. Step by step, non-significant fixed effects have been removed from the model until only significant related effects have been left. Additionally, only fixed effects that significantly improved R^2 were included in the model to keep the models as small as possible. Random effects were excluded from the model when the variance was very small, as identified by visual inspection (approximately 10 times smaller than the variance of the residuals). In this study, the estimates, standard errors, *p*-values, the lower and upper bounds of the 95% confidence intervals, the adjusted R^2, the root mean squared error (RMSE) in $N/(kg \times ms^{-2})$ and as a percentage of the associated average KCF, and the coefficients for the linear regression equation are reported for each LMM. Adjusted $R^2 \leq 0.09$ were interpreted as little, $0.09 < R^2 \leq 0.25$ as low, $0.25 < R^2 \leq 0.49$ as moderate, $0.49 < R^2 \leq 0.81$ as high, and $R^2 > 0.81$ as very high correlations[26]. Statistical significance for all tests was set to $\alpha = 0.05$.

List Of Abbreviations

KAM knee adduction moment

KCF knee joint contact force

KFM/KEM knee flexion/extension moment

KJM knee joint moment

latKCF lateral knee joint contact force

LMM linear mixed-effects model

medKCF medial knee joint contact force

qKFM/qKEM squared knee flexion/extension moment

TD typically developed healthy controls

Declarations

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

J. H., F. S and A. M. conceived the presented idea. J. H. and F. S. and S. v. D. performed the data collection, analysis and interpretation. J. H, S. v. D and S. D. U. performed the modeling procedures. J. H. performed the statistical analysis and F. S., S. v. D. and E. H. checked and approved it. J. H. drafted the manuscript and visualized the results. All authors reviewed the manuscript, suggested improvements in the content and approved the final version. All authors agreed to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figures

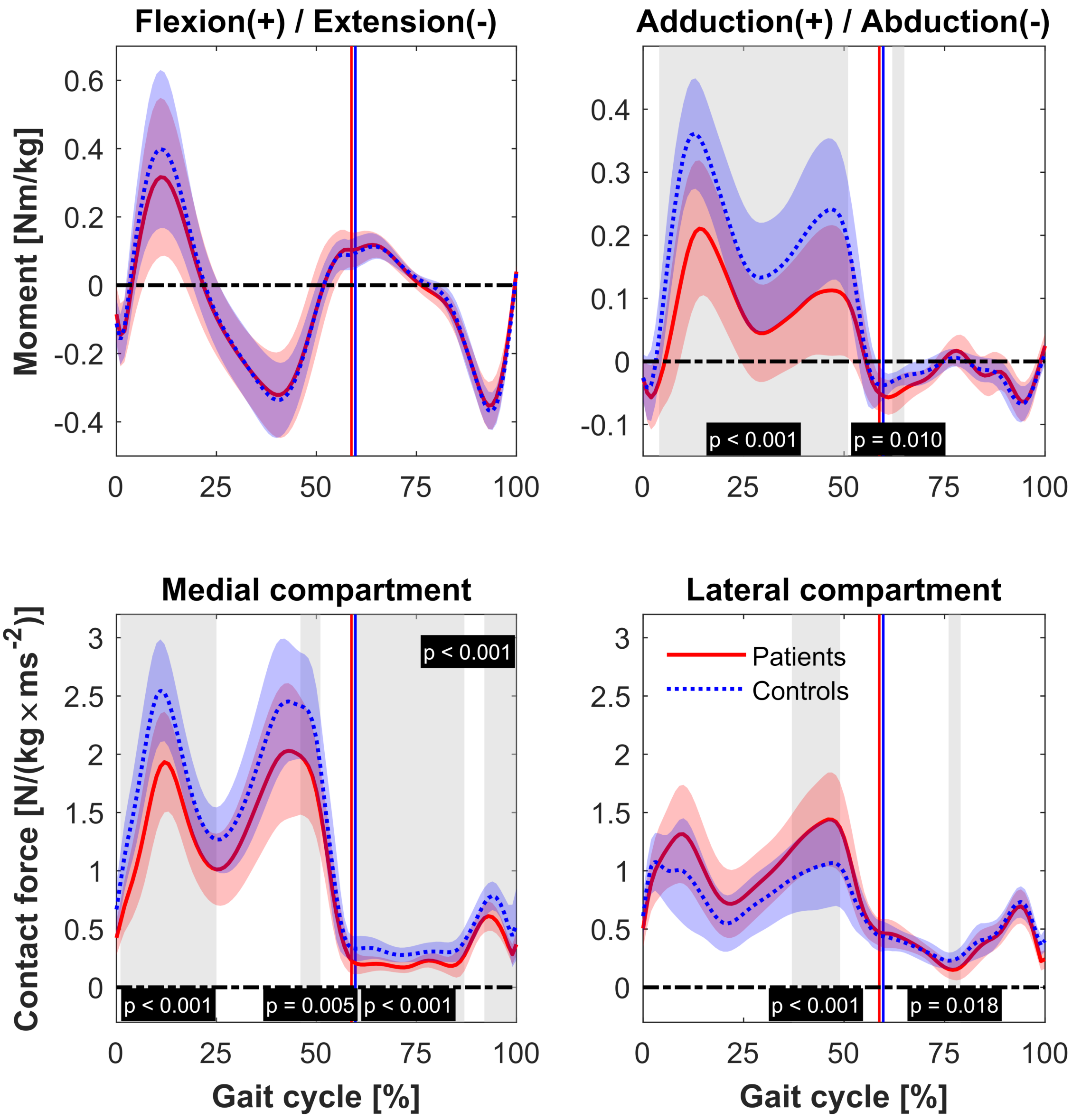

Figure 1

The mean (line) and standard deviation (shaded) of the external knee flexion and adduction moment and the medial and lateral knee contact force of the patients with valgus malalignment (red, solid) and the typically developed healthy controls (blue, dashed) are displayed. Vertical lines mark the end of the stance phase. Joint moments were normalized by body mass (unit: Nm/kg) and the joint contact forces by bodyweight (unit: N/(kg×ms-2)). Significant different phases ($p < 0.05$) during the gait cycle (normalized to 100 %) calculated with a statistical parametric mapping two-sample t-test are highlighted with gray areas and are described with the associated p-value (black boxes).

Supplementary Files

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Supplementary Material

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- Search term 2: ((((opensim) OR (Anybody Technology)) AND ((gait analysis) OR (motion capture))) AND ("2017/01/01"[Date - Publication] : "2021/11/03"[Date - Publication])); performed on 2021/11/03

Joint angles

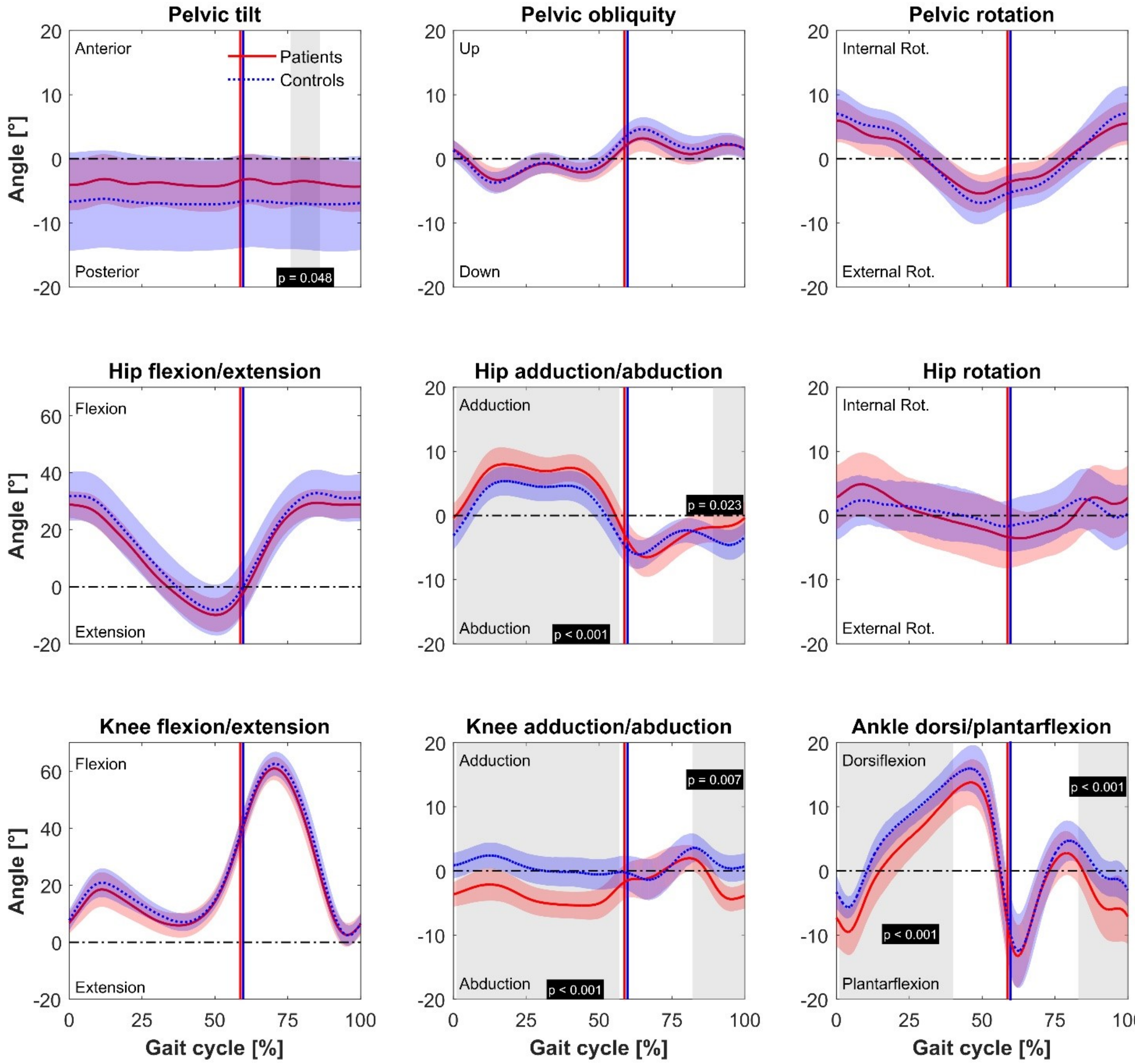

Figure 1: The mean and standard deviation of the joint angles of the pelvis, hip, knee and ankle joint between the patient (red, solid) and typically developed healthy control group (TD) (blue, dashed) are displayed. Vertical lines mark the end of the stance phase. Significant different phases (*p* < 0.05) during the gait cycle (normalized to 100 %) calculated with a statistical parametric mapping two-sample t-*test* are highlighted with gray areas and are described with the associated *p*-value (black boxes).

2

Joint moments

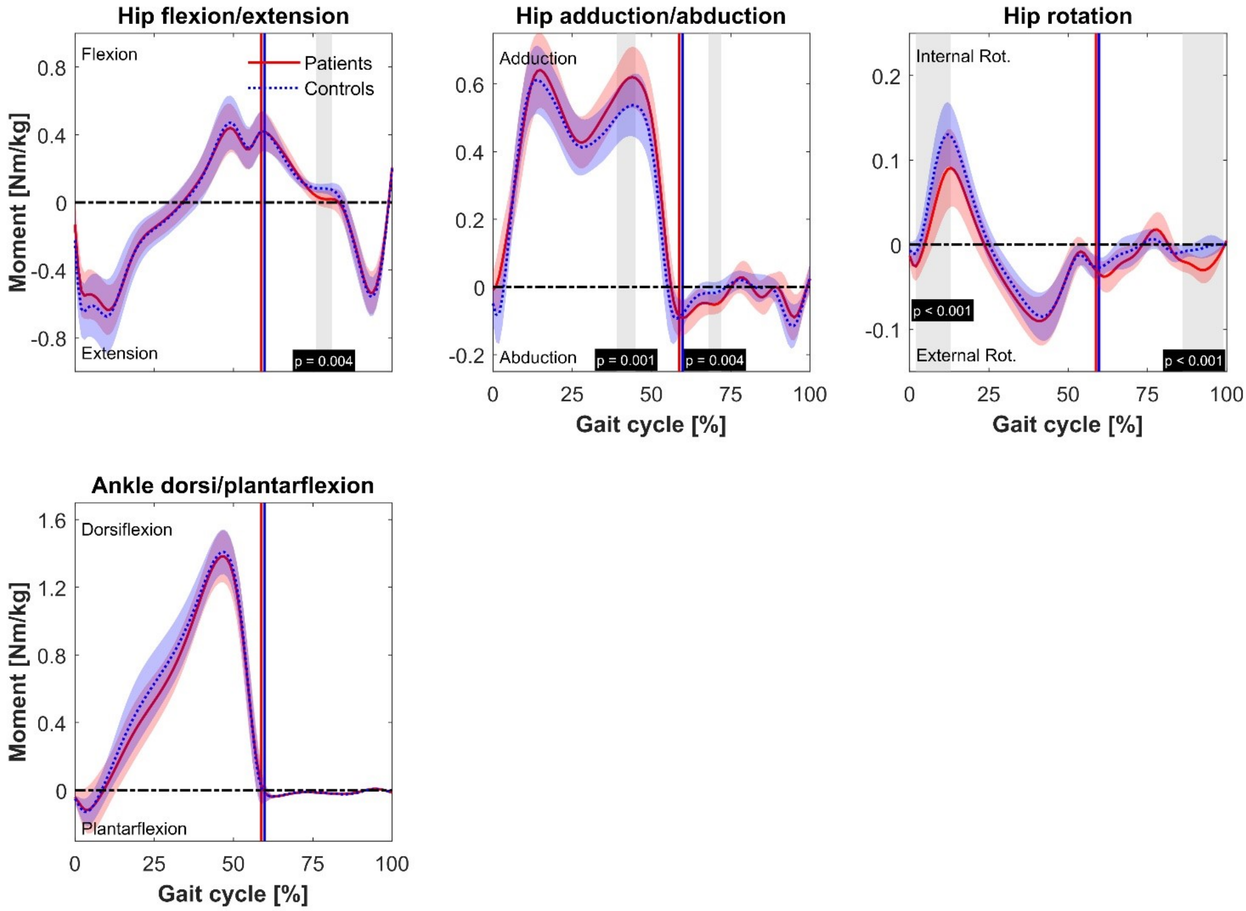

Figure 2: The mean and standard deviation of external joint moments of the hip and ankle joint between the patient (red, solid) and typically developed healthy control group (blue, dashed) are displayed. Vertical lines mark the end of the stance phase. Joint moments were normalized for body mass (unit: Nm/kg). Significant different phases ($p < 0.05$) during the gait cycle (normalized to 100 %) calculated with a statistical parametric mapping two-sample t-*t*est are highlighted with gray areas and are described with the associated *p*-value (black boxes).

Linear regression analysis

For investigating the linear relationship between **one** predictor variable (i.e., the knee flexion/extension or adduction moment) and the response variable (i.e. the medial or lateral knee joint contact force) only the more affected limb of bilateral affected patients was included in the dataset. Moreover, the mean of extracted peaks in the first and second half of stance of three trials per participant was used. In total, 50 data points per parameter for the patient group and 21 for the typically developed healthy controls group were included in the analysis. Adjusted $R^2 <= 0.09$ were interpreted as little, $0.09 < R^2 <= 0.25$ as low, $0.25 < R^2 <= 0.49$ as moderate, $0.49 < R^2 <= 0.81$ as high, and $R^2 > 0.81$ as very high correlations adapted from Hinkle, et al. [1]. MATLAB (2020b, The MathWorks, Inc., Natick, MA, USA) was used to determine the linear relation between the predictor and response variable.

Table 1: Linear regression analysis between individual predictor variables (external knee flexion/extension or adduction moment) and the response variable (internal medial or lateral knee joint contact force) for the patient group.

Response Variable	Predictor Variables	Estimate	Standard Error	*t*-value	*p*-value	Lower 95 % *CI*	Upper 95 % *CI*	Adj. R^2	RMSE	RMSE [%]
medKCF1	Intercept	1.405	0.101	13.928	< 0.001	1.202	1.607	0.47	0.29	14.40
	KAM1	2.582	0.389	6.635	< 0.001	1.800	3.365			
	Intercept	1.826	0.066	27.824	< 0.001	1.694	1.958	0.26	0.34	16.98
	qKFM1	1.134	0.266	4.268	< 0.001	0.600	1.668			
medKCF2	Intercept	1.710	0.135	12.645	< 0.001	1.438	1.981	0.26	0.48	21.48
	KAM2	3.454	0.803	4.300	< 0.001	1.839	5.070			
	Intercept	1.640	0.105	15.553	< 0.001	1.428	1.852	0.46	0.41	18.43
	qKFM2	4.157	0.639	6.507	< 0.001	2.873	5.442			
latKCF1	Intercept	1.716	0.119	14.462	< 0.001	1.477	1.954	0.11	0.34	24.02
	KAM1	-1.243	0.458	-2.714	0.009	-2.163	-0.322			
	Intercept	1.241	0.059	21.084	< 0.001	1.123	1.360	0.29	0.31	21.59
	qKFM1	1.080	0.238	4.531	< 0.001	0.601	1.559			
latKCF2	Intercept	2.075	0.062	33.523	< 0.001	1.951	2.200	0.68	0.22	14.34
	KAM2	-3.814	0.368	-10.369	< 0.001	-4.554	-3.075			
	Intercept	1.420	0.100	14.223	< 0.001	1.220	1.621	0.01	0.39	25.45
	qKFM2	0.710	0.605	1.173	0.247	-0.507	1.927			

CI: Confidence interval; Adj. R^2: adjusted R^2; RMSE: root mean squared error [N/(kg×ms-2)]; medKCF1/medKCF2: max. value in the first/second half of stance of the medial knee joint contact force [N/(kg×ms-2)]; latKCF1/latKCF2: max. value in the first/second half of stance of the lateral knee joint contact force [N/(kg×ms-2)]; KAM1/KAM2: max. value in the first/second half of stance of the external knee adduction moment [Nm/kg]; qKFM1/qKEM2: squared maximal/minimal value in the first/second half of stance of the external knee flexion/extension moment (KFM1, KEM2; [Nm/kg]).

Table 2: Linear regression analysis between individual predictor variables (external knee flexion/extension or adduction moment) and the response variable (internal medial or lateral knee joint contact force) for the typically developed healthy control group.

Response Variable	Predictor Variables	Estimate	Standard Error	*t*-value	*p*-value	Lower 95 % *CI*	Upper 95 % *CI*	Adj. R^2	RMSE	RMSE [%]
medKCF1	Intercept	1.498	0.361	4.147	0.001	0.742	2.255	0.27	0.38	15.30
	KAM1	2.772	0.960	2.887	0.009	0.762	4.782			
	Intercept	2.071	0.158	13.080	< 0.001	1.739	2.402	0.32	0.37	14.71
	KFM1	1.059	0.326	3.248	0.004	0.376	1.741			
medKCF2	Intercept	1.555	0.212	7.346	< 0.001	1.112	1.998	0.59	0.37	14.15
	KAM2	4.231	0.782	5.409	< 0.001	2.594	5.869			
	Intercept	1.828	0.223	8.193	< 0.001	1.361	2.295	0.41	0.44	16.82
	qKEM2	5.470	1.404	3.895	0.001	2.531	8.410			
latKCF1	Intercept	1.214	0.333	3.651	0.002	0.518	1.910	-0.05	0.35	28.13
	KAM1	0.119	0.884	0.135	0.894	-1.731	1.969			
	Intercept	0.952	0.128	7.451	< 0.001	0.684	1.219	0.25	0.30	23.72
	KFM1	0.732	0.263	2.783	0.012	0.181	1.282			
	Intercept	1.063	0.089	11.952	< 0.001	0.877	1.249	0.30	0.29	22.95
	qKFM1	0.792	0.256	3.096	0.006	0.256	1.327			
latKCF2	Intercept	1.761	0.138	12.730	< 0.001	1.471	2.050	0.48	0.24	20.21
	KAM2	-2.260	0.511	-4.420	< 0.001	-3.330	-1.190			

CI: Confidence interval; Adj. R^2: adjusted R^2; RMSE: root mean squared error [N/(kg×ms-2)]; medKCF1/medKCF2: max. value in the first/second half of stance of the medial knee joint contact force [N/(kg×ms-2)]; latKCF1/latKCF2: max. value in the first/second half of stance of the lateral knee joint contact force [N/(kg×ms-2)]; KAM1/KAM2: max. value in the first/second half of stance of the external knee adduction moment [Nm/kg]; qKFM1/qKEM2: squared maximal/minimal value in the first/second half of stance of the external knee flexion/extension moment (KFM1, KEM2; [Nm/kg]).

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Chapter 6

Illustration of the author's contribution to the individual publications

- **Chapter 3: Effect of guided growth intervention on static leg alignment and dynamic knee contact forces during gait**
  Jana Holder performed the data analysis, interpretation and the modelling procedures. She performed the statistical analysis, drafted the original manuscript and visualized the results.

- **Chapter 4: A Systematic Review of the Associations Between Inverse Dynamics and Musculoskeletal Modeling to Investigate Joint Loading in a Clinical Environment**
  Jana Holder conceived the presented idea; drafted the overview of the review, performed the analysis and interpretation. She drafted the manuscript and visualized the results.

- **Chapter 5: Knee joint moments can accurately predict medial and lateral knee contact forces in patients with valgus malalignment**
  Jana Holder conceived the presented idea; performed the data collection, analysis, interpretation and the modelling procedures. She performed the statistical analysis, drafted the manuscript and visualized the results.

Chapter 7

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Schriftliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Johann Wolfgang Goethe-Universität Frankfurt am Main zur Prüfung eingereichte Thesis mit dem Titel

"Knee joint loading in children with valgus malalignment predicted by conventional gait analysis parameters and musculoskeletal simulations"

in der Klinik für Orthopädie im Bewegungsanalyselabor des Universitätsklinikums Frankfurt unter Betreuung und Anleitung von PD Dr. phil. Dr. med. habil. Felix Stief mit Unterstützung durch Univ.-Prof. Dr. Andrea Meurer ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Thesis angeführten Hilfsmittel benutzt habe.

Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion oder zu einem PhD-Verfahren eingereicht. Die vorliegende Arbeit wurde bisher nicht als Thesis oder Dissertation eingereicht.

Die Grundsätze der Johann Wolfgang Goethe-Universität Frankfurt am Main zur Sicherung guter wissenschaftlicher Praxis in ihrer gültigen Form liegen mir vor und wurden bei der wissenschaftlichen Arbeit eingehalten.

Vorliegende Ergebnisse der Arbeit wurden (oder werden) in folgendem Publikationsorgan veröffentlicht:

- J. Holder, Z. Feja, S. van Drongelen, S. Adolf, H. Böhm, A. Meurer, F. Stief. Effect of guided growth intervention on static leg alignment and dynamic knee contact forces during gait. *Gait Posture*, 78:80-8, 2020. doi: 10.1016/j.gaitpost.2020.03.012.

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- J. Holder, S. van Drongelen, S. D. Uhlich, E. Herrmann, A. Meurer, F. Stief. Knee joint moments can accurately predict medial and lateral knee contact forces in patients with valgus malalignment. Submitted to *Scientific Report* on February 16, 2022 (Preprint published on *Research Square*). doi: 10.21203/rs.3.rs-1366268/v1.

(Ort, Datum)	(Jana Holder)