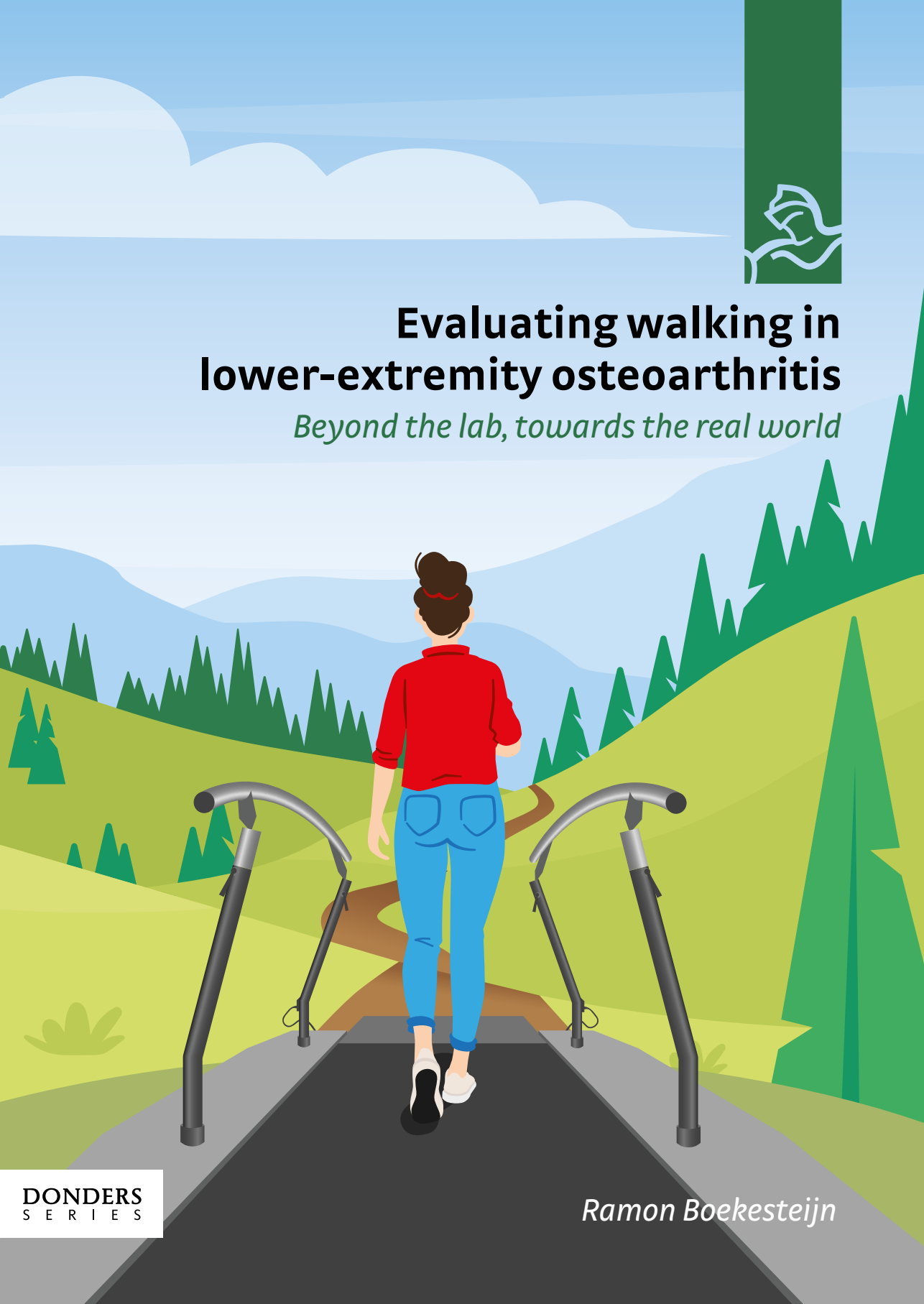
Evaluating walking in lower-extremity osteoarthritis

Beyond the lab, towards the real world



DONDERS SERIES

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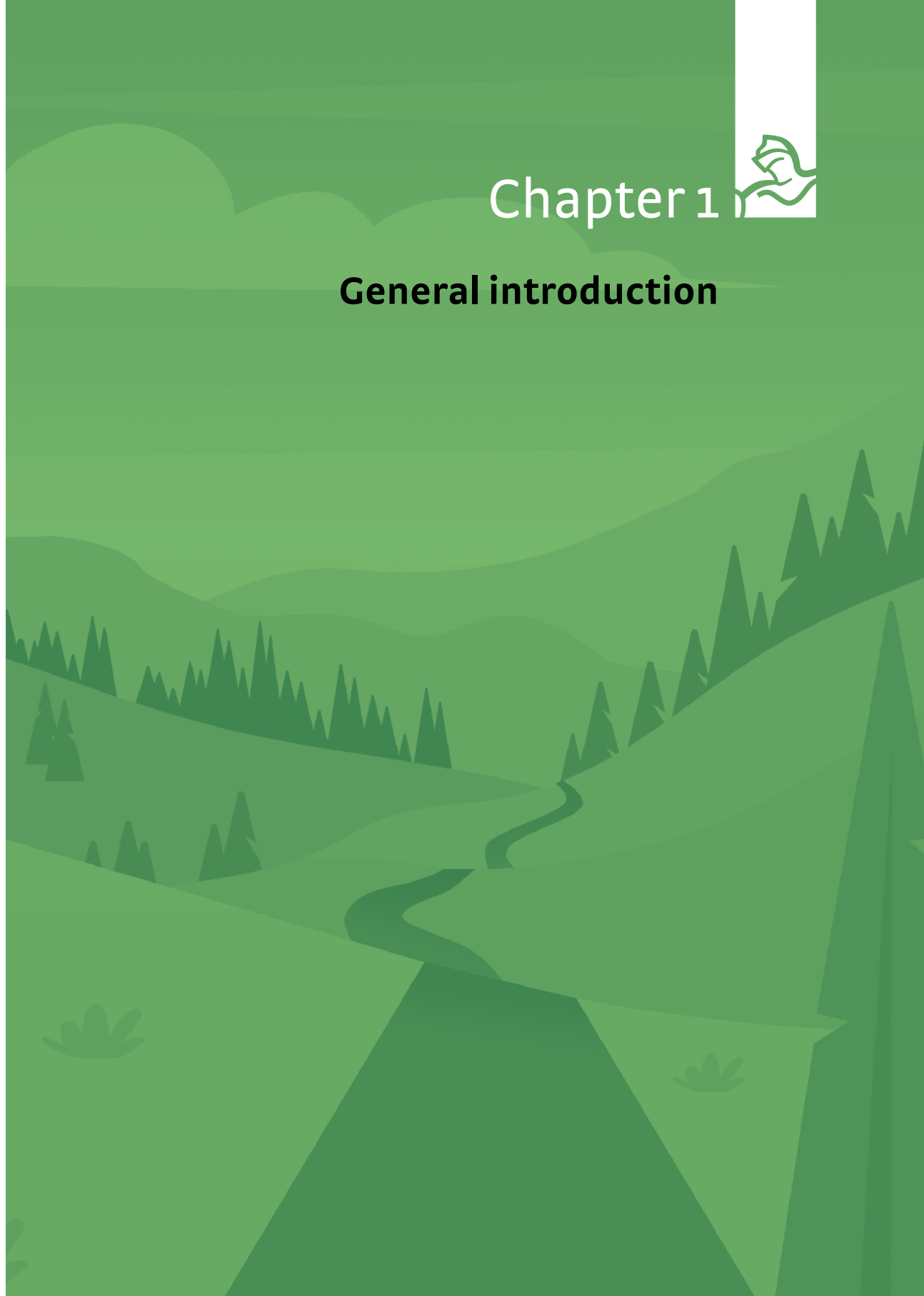
General introduction



General introduction

Osteoarthritis (OA) is one of the most common causes of disability[1]. Worldwide, it is estimated that 10-18% of people older than 60 years have OA[2]. With an aging population and a concomitant increase in risk factors for OA (e.g. obesity[3] and incidence of joint injuries[4]), the prevalence of OA is expected to rise with 36% until 2040[5]. Due to the combination of high prevalence and high disability, the individual and socioeconomic burden of OA is enormous[6]. Besides high (in) direct health-care costs[7], particularly those associated with knee and hip replacement[6], the individual burden related to loss of function, activity limitations, and reduced quality of life is substantial[8]. Roughly four in five people with lower-extremity OA reports to have problems with activities of daily living, and more than 70% reports problems with outdoor mobility[9]. Unsurprisingly, improving mobility – specifically walking – is considered a main treatment goal by individuals with end-stage lower-extremity OA[10,11]. However, an objective indicator for mobility is currently lacking in the clinical evaluation of individuals with lower-extremity OA. This thesis will therefore focus on the evaluation of walking in individuals with lower-extremity OA, both before and after total knee or hip replacement. The results of this thesis may assist in establishing objective measures of mobility that could be implemented in future clinical evaluation of individuals with lower-extremity OA.

Osteoarthritis: what is it?

Osteoarthritis is characterized by degradation of articular cartilage. It predominantly affects weight-bearing joints such as the knee and hip (Figure 1), but is also common in the hand[12]. Instead of manifestation of OA in just one joint, other joints are also frequently involved[13,14]. For example, in a population of individuals with knee pain, 26% had bilateral knee OA[13]. Another study reported that only 18% of individuals scheduled for knee replacement and 13% of individuals scheduled for hip replacement had unilateral OA[14].

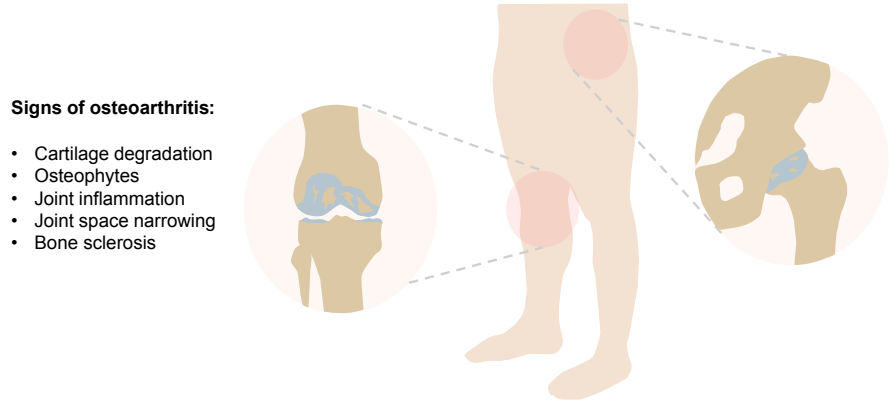


Figure 1: schematic overview of structural manifestation of osteoarthritis in the knee and hip

Traditionally, lower-extremity OA has been considered a 'wear-and-tear' problem of articular cartilage. More recent insights have contributed to an evolution of this definition to one involving degeneration of the whole joint, including structures such as subchondral bone, ligaments, capsule, synovium, and periarticular muscles[15,16]. While the exact pathophysiology remains to be elucidated, lower-extremity OA is considered to be a multifactorial disease[17]. Numerous different pathways, including mechanical[18], inflammatory[19], genetic[20], and metabolic factors[21], may together lead to a disbalance between destruction and repair of structures in and around the joint. In a small number of cases (i.e. approximately 12%[22]) lower-extremity OA is post-traumatic, being attributable to joint injuries such as intra-articular fractures, ligament ruptures, or meniscal tears.

Generally, lower-extremity OA is a progressive disease in which the joint slowly starts to degenerate and pain complaints gradually increase. The pace of progression of radiological features[23] and pain[24], however, varies considerably between individuals, with some people having a stable situation for many years. When people have severe pain complaints, are limited in their daily activities, and have clear narrowing of the joint space, they are considered to have end-stage OA[25].

Researchers have attempted to define distinct phenotypes based on shared disease characteristics within subgroups of people with OA[26]. Such phenotypes could provide guidance in predicting who is likely to show disease progression, and who may benefit from a certain treatment modality. Different determinants, including imaging, biochemical markers, and clinical characteristics have been used to try to delineate these subgroups. In a previous review, six clinical phenotypes were identified: 1) chronic pain, 2) inflammatory, 3) metabolic syndrome, 4) bone and cartilage metabolism, 5) mechanical overload, and 6) minimal joint disease[27]. However, the use of these phenotypes for clinical or research purposes is not yet sufficiently supported[28], as their validation is lacking and individuals can be part of multiple subgroups[29].

Symptoms and consequences of osteoarthritis

Despite the recognized complexity in underlying etiology of OA, its symptoms are frequently shared between individuals. Common symptoms of lower-extremity OA include joint pain, joint stiffness, joint instability, joint swelling, muscle weakness, and fatigue. Of all symptoms, pain is experienced as the most disabling one[12]. Interestingly, pain complaints are poorly correlated with radiographic severity of OA, and not all individuals with OA develop pain complaints[30]. Which factors drive the development of pain in individuals with OA is not yet clear[31], but both central and peripheral sensitization processes are thought to play a role in this[32].

For individuals with lower-extremity OA, pain complaints can lead to substantial limitations in daily functioning. Amongst others, individuals with OA may have difficulty climbing stairs, walking, and rising from a chair[33,34]. Moreover, pain is an important barrier for people with OA to engage in physical activity[35]. A previous meta-analysis found that only 19% of individuals with knee OA and 30% of individuals with hip OA reached the recommended total of 10,000 steps a day[36]. Compared to healthy peers, individuals with OA were 25% less physically active[36]. Limited physical activity leads to further worsening of OA symptoms and is also detrimental for many other health parameters[37]. Hence, maintaining a good level of physical activity is essential for individuals with lower-extremity OA.

Importance of walking and the impact of lower-extremity OA

Walking is one of the most vital human physical activities. Not only is gait speed predictive of many essential health parameters[38], good walking ability is also crucial for participation in our society[39]. Furthermore, taking more steps in daily life has been associated with a lower risk of functional limitation in individuals with knee OA[40]. Individuals with lower-extremity OA often report to have problems with walking[33,41]. For example, they take less steps during daily life[42,43], walk slower[44,45], and are limited in their maximum walking distance[10]. In addition, numerous studies highlight aberrant joint kinematics[45-47] and kinetics[47,48] compared to healthy age-matched controls. These gait deviations can be the result of different factors including pain, stiffness[49], muscle weakness[49,50], and the sense of joint instability[51]. In addition, other symptoms including reduced proprioception[52] and changes in central and neuromuscular control[53] may account for problems with maintaining balance during walking[54]. Together, these symptoms could be linked to the increased fall risk that has been observed in individuals with lower-extremity OA[55-57].

Treatment options for osteoarthritis

Currently, no curative treatment for lower-extremity OA is available. Treatment modalities are focused on controlling or relieving pain, slowing the progression of OA, and improving physical functioning and quality of life. Based on a stepped care approach[58], a combination of self-management, lifestyle modifications (e.g. dietary, exercise), physiotherapy, pain management, and unloading therapies can be considered. When conservative treatment has failed or effects have worn off, surgical management by knee or hip arthroplasty can be considered. Joint arthroplasty is an increasingly common and cost-effective treatment for individuals with end-stage OA[59], with more than 21,000 total knee arthroplasties (TKA) and 31,000 total hip arthroplasties (THA) being performed each year in The Netherlands[60]. The clinical indication for joint arthroplasty is based on 3 main indicators: 1) radiologically confirmed cartilage degeneration (i.e. Kellgren Lawrence score ≥ 2), 2) self-reported pain that impacts quality of life and participation, and 3) limitations in daily life activities due to pain[61,62].

Clinical evaluation of individuals with lower-extremity OA

For individuals with end-stage lower-extremity OA, clinical evaluation concerns the review of medical history, self-report of pain and functional limitations, physical examination, and radiological imaging. After joint replacement, additional attention is being paid to safety (e.g. complications, implant placement) and the recovery of pain and physical function. Furthermore, since 2013, patient-reported outcome measures (PROMs) are routinely collected after total joint arthroplasty in the Dutch registry of orthopedic implants (i.e. LROI).

In general, evaluation of functional limitations in individuals with lower-extremity OA is strongly dominated by self-report, which may be biased by psychosocial factors[63] and daily fluctuations in symptoms[64]. Furthermore, someone's perceived abilities may be discordant from their actual performance of a task[65]. Objective parameters related to physical functioning, however, are currently lacking in clinical evaluation and decision making. Given that 8-20% of individuals after total hip and knee replacement are dissatisfied with their treatment outcome[66,67], there may be room for improvement in clinical decision making. Availability of objective data on physical functioning could contribute to more realistic pre-operative expectations, a better indication, and improved follow-up of individuals scheduled for joint arthroplasty. In particular, the evaluation of walking may be of interest here, due to

the importance of walking improvement to individuals scheduled for joint replacement[10,11] and its overall relevance to daily functioning.

Evaluation of walking

According to International Classification of Functioning, Disability and Health (ICF)[68], the evaluation of walking can be subdivided in two distinct domains, being: 1) gait capacity ('what person can do in a standardized, controlled environment) and 2) gait performance ('what a person actually does in his/her own daily environment'). Perception (i.e. 'what people think they can do and actually do') has later been added as a separate component to this model by Maetzler et al.[69] (Figure 2). As outcomes in these three domains are not necessarily the same, combining them is essential to get a complete overview of someone's walking ability.

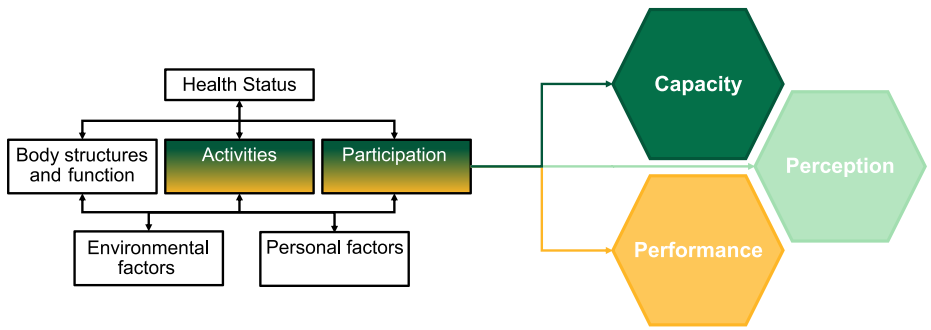


Figure 2: ICF framework. Adapted from: Maetzler et al.[69]

Gait capacity

Sufficient gait capacity is a prerequisite for good gait performance. For an optimal gait capacity, there are three main requirements: 1) stepping, 2) dynamic balance, and 3) gait adaptability[70](Figure 3).

Stepping comprises the ability to generate a cyclical pattern of limb movements to move the body forward, often referred to as "the gait cycle". Stepping can be characterized using outcomes related to 1) spatial and/or temporal features of stepping behavior (i.e. spatiotemporal parameters), 2) joint motion during stepping (i.e. kinematics), and 3) forces that drive stepping behavior (i.e. kinetics).

Dynamic balance is the mechanism that controls the body's center of mass (CoM) within the limits of a constantly moving base of support (BoS) during walking. This mechanism is needed to ensure stable walking, and to prevent falling. This also includes the ability to deal with (un)expected perturbations during walking, and the responses that are needed to regain stability. Dynamic balance can be achieved by modulating foot placement, shifting the center of pressure under the stance foot, and by changing the angular momentum of body segments around the CoM[71].

Gait adaptability refers to the ability to make proactive changes in our walking behavior that are needed to deal with the continuously changing demands of the environment. This may, for example, include adaptations in gait pattern when avoiding an obstacle, when walking over irregular surfaces, or when walking in an area with busy traffic. Although gait adaptability is an important component of gait capacity, it falls beyond the scope of this thesis.

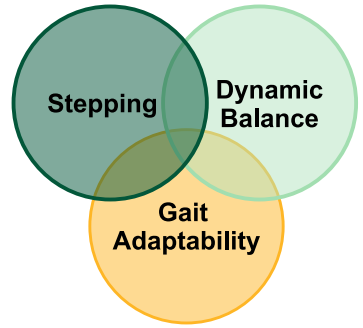


Figure 3: Tripartite model for assessment of gait capacity. Adapted from: Balasubramanian et al.[70].

Gait performance

In contrast to gait capacity, gait performance encompasses what people do in their own, habitual environment. While gait capacity is typically measured in supervised and controlled environments such as gait laboratories, these assessments do not reflect the demands of our actual daily life environment and may, thus, lack ecological validity. In everyday life, there are many external factors and distractions that require modification of the gait pattern, which are typically absent in the laboratory. In addition, daily life walking is composed of many different gait bouts with varying lengths. Long bouts of straight-ahead walking, at best resembled through evaluations on a treadmill, are relatively uncommon in daily life. For instance, only 6.1% of total gait bouts in daily life are longer than 2 minutes[72]. Furthermore, steps during turning can make up 8-50% of total steps, depending on the specific type of environment[73]. Unsurprisingly, previous studies have found that gait speed measured in a clinical setting (i.e. capacity) merely weakly correlated with gait speed in daily life (i.e. performance)[74,75]. This highlights the importance of evaluation of gait performance, in addition to gait capacity.

Use of inertial measurement units to measure gait capacity and performance

Due to advances in the development and miniaturization of wearable sensors, inertial measurement units (IMUs) have become a viable method for human motion analysis. IMUs are sensors that contain 3D accelerometers, gyroscopes, and sometimes magnetometers. For gait assessment, these sensors are typically placed on the lower back or feet. Using the signals derived from IMUs, periods of physical activity and sedentary behavior can be identified[76]. Furthermore, walking periods, so-called 'gait bouts', can be detected and spatiotemporal gait parameters can be computed. Besides spatiotemporal parameters, kinematics can be obtained from IMUs when sensors are placed on the trunk, pelvis, thigh, tibia, and/or feet[77]. Overall, the reliability and validity of IMUs to measure spatiotemporal gait parameters has

been good to excellent[78]. Typically, accuracy of temporal parameters is good[78], but accurately obtaining spatial parameters remains more challenging due to for example sensor drift[79]. The biggest advantage of IMUs compared to optical motion analysis systems is that data collection is not restricted to a fixed laboratory environment. In addition, set-up time is relatively short, handling of the equipment does not require highly specialized knowledge, and data collection can be extended to longer periods. Thus, gait capacity and gait performance measures can be obtained in clinical settings or in someone's home environment by IMUs.

Aim and outline of this thesis

The general aim of this thesis is to comprehensively evaluate walking, including gait capacity and gait performance, in individuals with lower-extremity OA, before and after total joint replacement. In **chapter 2**, I start with the description of a cross-sectional study in which gait capacity is measured with IMUs in individuals with knee or hip OA, and healthy older adults. From a large number of possible outcome measures, non-redundant and sensitive parameters indicative of gait impairment in individuals with lower-extremity OA are identified. In **chapter 3**, a systematic evaluation of the literature studying gait of individuals with knee OA with IMUs is provided. A meta-analysis is conducted to identify parameters that are sensitive to the gait impairment present in knee OA. The results from these first two studies help to select outcome measures to evaluate recovery of gait capacity after TKA and THA in **chapter 4**. In this chapter, I also compare recovery trajectories of self-reported scores of pain and physical functioning with those of gait capacity parameters to better understand the relationship between these two domains. In **chapters 5 and 6** dynamic balance control and gait performance are studied in a new cohort of individuals with knee OA scheduled for cruciate retaining TKA. In **chapter 5**, dynamic balance control of individuals with knee OA is addressed. By comparing balance recovery responses to anteroposterior and mediolateral treadmill perturbations between individuals with knee OA and healthy older adults, insight in the impact of lower-extremity OA on balance control is obtained. In **chapter 6**, I compare gait performance between individuals with knee OA and healthy older adults using IMUs. The results of this study provide relevant parameters of daily life functioning for future follow-up after TKA. In **chapter 7**, I summarize and discuss the work described in this thesis. Furthermore, the implications of this research for clinical practice and new directions for future research are presented.

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Chapter 2

Independent and sensitive gait parameters for objective evaluation in knee and hip osteoarthritis using wearable sensors

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Abstract

Background

Although it is well-established that osteoarthritis (OA) impairs daily life gait, objective gait assessments are not part of routine clinical evaluation. Wearable inertial sensors provide an easily accessible and fast way to routinely evaluate gait quality in clinical settings. However, during these assessments, more complex and meaningful aspects of daily life gait, including turning, dual-task performance, and upper body motion, are often overlooked. The aim of this study was therefore to investigate turning, dual-task performance, and upper body motion in individuals with knee or hip OA in addition to more commonly assessed spatiotemporal gait parameters using wearable sensors.

Methods

Gait was compared between individuals with unilateral knee (n=25) or hip OA (n=26) scheduled for joint replacement, and healthy controls (n=27). For 2 minutes, participants walked back and forth along a 6-meter trajectory making 180° turns, with and without a secondary cognitive task. Gait parameters were collected using 4 inertial measurement units on the feet and trunk. To test if dual-task gait, turning, and upper body motion had added value above spatiotemporal parameters, a factor analysis was conducted. Effect sizes were computed as standardized mean difference between OA groups and healthy controls to identify parameters from these gait domains that were sensitive to knee or hip OA.

Results

Four independent domains of gait were obtained: speed-spatial, speed-temporal, dual-task cost, and upper body motion. Turning parameters constituted a gait domain together with cadence. From the domains that were obtained, stride length (speed-spatial) and cadence (speed-temporal) had the strongest effect sizes for both knee and hip OA. Upper body motion (lumbar sagittal range of motion), showed a strong effect size when comparing hip OA with healthy controls. Parameters reflecting dual-task cost were not sensitive to knee or hip OA.

Conclusion

Besides more commonly reported spatiotemporal parameters, only upper body motion provided non-redundant and sensitive parameters representing gait adaptations in individuals with hip OA. Turning parameters were sensitive to knee and hip OA, but were not independent from speed-related gait parameters. Dual-task parameters had limited additional value for evaluating gait in knee and hip OA, although dual-task cost constituted a separate gait domain. Future steps should include testing responsiveness of these gait domains to interventions aiming to improve mobility.

Introduction

It is well-recognized that osteoarthritis (OA) of the knee or hip impairs gait[1-4]. Indeed, individuals with knee or hip OA walk less during daily life and their quality of gait is compromised[5]. Yet, objective gait assessments are not part of routine clinical evaluation, and gait difficulties in OA are insufficiently captured by patient-reported outcome measures[6-8]. In part, this may be due to limited time available during clinical visits, considering that gait analysis is traditionally conducted in a gait laboratory, making it time consuming and not easily accessible. Recent advances in inertial sensor technology have opened up new avenues to quickly and objectively assess gait quality in a clinical setting.

Small inertial measurement units (IMUs) can be used to quickly and accurately obtain gait parameters without being restricted to a fixed (laboratory) environment[9,10]. Moreover, compared to gait analysis in a lab, substantially more strides can be collected in a shorter period of time. On the downside, an important issue of gait assessment with IMUs is that it typically results in a large number of outcome parameters, with numerous correlated parameters. For example, many gait parameters share covariance with gait speed[11-15]. Hence, for clinical implementation, it is important to identify gait parameters from independent gait domains that best describe the gait adaptations in individuals with knee and hip OA compared to healthy controls.

So far, ambulatory gait assessments in individuals with knee and hip OA have mostly been limited to simple, straight-ahead walking paradigms[16]. Parameters reflecting more complex and relevant aspects of gait, including dual-task gait, turning, and compensatory trunk motion are less frequently reported in studies using IMUs. Turning and dual-task performance have been shown to be important aspects of daily life ambulation in elderly populations and can easily be assessed using wearable sensors[17-20]. Turning is a common cause of falling in community dwelling elderly, and may be more sensitive to sensorimotor impairments than straight-ahead gait[19,21]. Dual-task performance, on the other hand, reflects the amount of attentional resources allocated to gait[22]. In order to compensate for gait difficulties caused by OA, a strategy could be to allocate more attention to gait. The extent to which a secondary cognitive task affects gait performance (i.e. dual-task cost (DTC)) may therefore be larger in individuals with OA. A recent scoping review indicated that DTC was not different between individuals with knee OA and healthy controls during quiet standing and forward induced falls[23]. However, DTC during gait has not yet been compared between those groups. A third gap in literature regarding wearable sensors and OA is the lack of attention for upper body movement. Upper body motion is important for maintaining stability, but may also be indicative of compensatory gait changes that reflect OA-related pain or disability[24-26].

The aim of this study was therefore to investigate turning, dual-task performance, and upper body motion in addition to spatiotemporal gait parameters in individuals with knee or hip OA, taking shared covariance between gait parameters into account. More specifically, we aim to test if 1) turning, dual-task gait, and upper body motion constitute independent domains of gait in our sample, and 2) gait parameters in these gait domains can discriminate individuals with knee or hip OA from healthy controls. Together, these findings may contribute to a better understanding of the multidimensional aspects of gait, and how this is affected in knee and hip OA.

Methods

Participants

In this cross-sectional, comparative study 78 participants were included. The total study population comprised three groups: individuals with unilateral knee OA (n=25), unilateral hip OA (n=26), and healthy controls (n=27). Samples were derived from a longitudinal study investigating gait before and after total knee and hip arthroplasty that was powered for the comparison of spatiotemporal gait characteristics between individuals one year after total knee or hip arthroplasty and healthy controls. Individuals with OA were recruited at the Sint Maartenskliniek and were included if they had both radiological and symptomatic OA and were listed for joint replacement surgery. Participants had to be able to walk for more than 2 minutes without the use of any assistive device. Exclusion criteria were: 1) expectancy of joint replacement within a year, or symptomatic OA, in another weight-bearing joint than the joint scheduled for surgery, 2) BMI > 40 kg/m^2, and 3) any other musculoskeletal or neurological impairment interfering with gait or balance. Healthy controls were recruited from the community and did not have a clinical diagnosis of knee or hip OA, nor did they have any pain in the lower extremities. Healthy controls were recruited in the same age range as individuals with OA. Exclusion criteria for healthy controls were the same as for individuals with knee and hip OA. Informed consent was obtained from all participants prior to testing. Ethical approval was obtained from the CMO Arnhem/Nijmegen (2018-4452). All study methods were carried out in accordance with the Declaration of Helsinki.

Demographic and clinical assessment

Evidence for radiological OA was provided by the Kellgren and Lawrence (KL) score as assessed by experienced orthopedic surgeons[27]. Anthropometric characteristics were obtained during the pre-operative screening visit and were summarized as mass, length, and BMI. For individuals with knee and hip OA, self-reported functioning was assessed using the Knee Injury and Osteoarthritis Outcomes Score (KOOS) or Hip Disability Osteoarthritis Outcome Score (HOOS)[28,29]. All items were scored on a zero to four Likert scale. For the five subscales, total scores were transformed to a 0-100 scale, with 100 representing best function.

Gait assessment

Gait parameters were collected on the same day as the pre-operative screening visit, which took place approximately 1 to 2 months prior to surgery. Four IMUs (Opal V2, APDM Inc., Portland, OR) were used to obtain segment accelerations and angular velocities (sample frequency = 128 Hz). Sensors were attached via elastic straps to the dorsum of both feet, the waist (sacrolumbar level), and the sternum (Figure 1) according to the standardized sensor placement of MobilityLab. Participants walked wearing flat shoes at a self-selected comfortable speed. For a duration of 2 minutes, participants walked back and forth along a 6-meter trajectory making 180° turns (Figure 1). Two 2-minute trials were collected, with and without a secondary cognitive task. The cognitive task consisted of an alternating alphabet task, citing every other letter of the alphabet. Single-task walking was always performed before the dual-task condition. Responses to the cognitive task were recorded by the assessor. Accuracy on the cognitive task was summarized as correct responses (percentage of total responses). DTC was computed as the percentual change of dual-task performance relative to the single-task for the following parameters: gait speed, cadence, stride length, stride time variability, and turn duration.

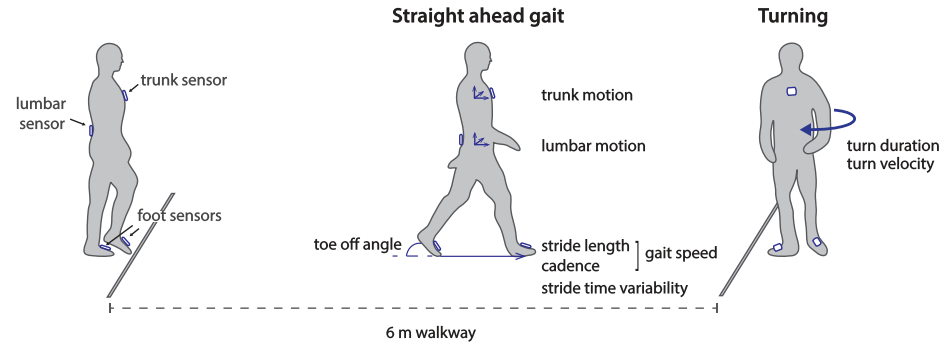

Figure 1: Overview of the experimental set-up. Four IMUs were attached to the dorsum of both feet, lumbar level (L4/L5) of the waist, and the sternum. For 2 min, subjects walked back and forth over the 6 m trajectory, making 180 degree turns.

Data analysis

Gait parameters were extracted from the raw IMU signals using the commercially available and validated Mobility Lab v2.0 software package[30]. Mobility Lab uses a state space model with causal Kalman filter along with zero velocity updates for optimal orientation estimation. Range of motion metrics were described for both the lumbar and trunk sensors using the gyroscope signals. As such, these measures are representative of the rotation of the sensors, which is caused by the movement of the underlying segments. For parameters where side was relevant (i.e. foot elevation at midswing, lateral step variability, circumduction, foot strike angle, toe off angle, and stance duration), we analyzed the affected leg in individuals with knee or hip OA, whereas for healthy controls the average value from the left and right leg was taken. Gait parameters were initially selected based on reliability, theoretical considerations, and completeness (<20% missing values). Based on the reliability criterium, we excluded stance and swing duration as percentage of gait cycle[31]. With regard to theoretical considerations, the following decisions were made: 1) in case gait parameters reflected the same outcome (e.g. gait cycle duration and cadence) only one parameter was kept for further analysis, 2) asymmetry parameters were restricted to meaningful parameters (i.e. stride length cannot be asymmetric when walking over a straight path)[32]. DTC of gait parameters that are ratios (i.e. asymmetry values) were not included in order to prevent inflated values, except for stride time variability, due to the substantial number of other studies evaluating this parameter in the context of fall risk[33]. This resulted in twenty-five gait parameters entered into factor analysis to identify correlated outcomes.

Exploratory factor analysis was used to identify independent gait domains explaining the variance in gait. Adequacy of the dataset for factor analysis was tested using Barlett's test of sphericity and the Kaiser-Meyer-Olkin (KMO) test. In case individual KMO values were lower than 0.5, variables were removed from the analysis[34]. The number of factors to be retained for further analysis was determined using the Kaiser criterium (eigenvalue > 1.0)[35]. Subsequently, factor analysis with varimax rotation was performed to obtain orthogonal factor scores. Within a factor, gait parameters were considered relevant when they met a minimum factor loading of 0.5.

For each relevant gait parameter in the obtained factor, effect sizes were computed as standardized mean differences (SMD) for the comparison between the OA groups and healthy controls (knee OA vs healthy controls and hip OA vs healthy controls). The gait parameter with the highest factor loading in combination with an effect size larger than 0.5 was considered non-redundant and sensitive to either knee or hip OA. For these gait parameters, individual datapoints and means with 95% confidence intervals (CI) were constructed using estimation graphs to assess between-group differences[36].

For demographic and clinical parameters, main group effects (3 levels: knee OA, hip OA, healthy controls) were tested using a one-way ANOVA or non-parametric equivalent when assumptions for parametric testing were not met. In case of a significant main effect, a post-hoc comparison was conducted using independent samples Student's t-test or the non-parametric equivalent. Data was considered statistically significant at an alpha level of 0.05, which was adjusted for multiple comparisons (n=9) for the gait parameters. This resulted in a Bonferroni adjusted alpha level of 0.0056. Data analysis was performed using STATA and custom-written Python scripts incorporating the DABEST library[37].

Results

Participant characteristics

Age, sex, and height did not differ between OA groups and healthy controls (Table 1). Individuals with knee OA had – on average – a 9 kg (95% CI: 2-16; p=0.014) higher mass compared to healthy controls. This difference was 12 kg (95% CI: 3-20; p=0.007) between individuals with hip OA and healthy controls. For individuals with knee OA, this translated into a 2.8 kg/m^2 (95% CI: 0.9-4.7; p=0.005) higher mean BMI compared to the control group, whereas the mean BMI was 2.4 kg/m^2 (95% CI: 0.1- 4.7; p=0.043) higher in individuals with hip OA. Severity of radiographic OA was moderate to severe OA (KL = 3 or 4) in both groups. Furthermore, accuracy on the secondary cognitive task was comparable between individuals with knee (mean: 84%) or hip OA (mean: 87%) and healthy controls (mean: 89%). KOOS and HOOS scores indicated presence of pain, disability, and limited quality of life in individuals with knee and hip OA (Table 1). Gait parameters were based on 32 valid strides (95% CI: 29 – 36) in individuals with knee OA, 34 valid strides (95% CI: 31 – 37) in individuals with hip OA, and 30 valid strides (95% CI: 27 – 34) in healthy participants.

Table 1: Demographic and clinical characteristics of all three subject groups.

Parameter	Controls (n=27)	Knee OA (n=25)	Hip OA (n=26)	ANOVA main group effect	Post-hoc comparisons
Age (y)	66 [63 - 68]	64 [61 - 67]	64 [61 - 66]	F(2,75) = 0.67, p = 0.514	-
Sex (M:F)	13:14	12:13	17:9	x^2 (2, N=78) = 2.09, p = 0.352	-
Height (m)	1.72 [1.68 - 1.75]	1.72 [1.68 - 1.77]	1.76 [1.73 - 1.80]	F(2,75) = 1.72, p = 0.185	-
Mass (kg)	76 [72 - 80]	84 [79 - 90]	88 [80 - 95]	F(2,75) = 4.51, **p = 0.014**	Knee OA vs HC: mean diff = **9 [2 - 16]**, p = 0.014 Hip OA vs HC: mean diff = **12 [3 - 20],** p = 0.007
BMI (kg/m^2)	25.7 [24.6 - 26.8]	28.5 [26.9 - 30.1]	28.1 [26.0 - 30.1]	F(2,75) = 3.52, **p = 0.035**	Knee OA vs HC: mean diff = **2.8 [0.9 - 4.7]**, p = 0.005 Hip OA vs HC: mean diff = **2.4 [0.1- 4.7]**, p = 0.043
KL score (I:II:II:IV)	-	0:0:8:17	0:0:7:19	-	-
DT scores (% correct)	89 [86 - 92]	84 [79 - 89]	87 [84 - 91]	F(2,75) = 1.56, p = 0.217	-
Self-reported outcomes		**KOOS**	**HOOS**		
1) Symptoms	-	50.9 [42.5 - 59.3]	41.4 [33.6 - 49.2]	-	-
2) Pain	-	41.7 [33.8 - 49.5]	39.6 [34.4 - 44.8]	-	-
3) Activities of daily life	-	52.9 [44.9 - 60.9]	39.7 [33.7 - 45.6]	-	-
4) Sport/ Recreation	-	15.6 [7.9 - 23.3]	15.1 [10.5 - 19.8]	-	-
5) Quality of life	-	26.0 [20.4 - 31.6]	23.6 [17.8 - 29.3]	-	-

Data are presented as mean [95% CI]. Significant differences are bold.
Note: OA = osteoarthritis, KL = Kellgren and Lawrence, BMI = body mass index, DT = dual-task, HC = healthy controls, HOOS = hip disability and osteoarthritis outcome score, KOOS = knee injury and osteoarthritis outcome score.

Exploratory factor analysis

Twenty-five gait parameters were entered into the factor analysis (Figure 2). Based on individual KMO values, the following variables were removed from further analysis: DTC of stride length, trunk transverse range of motion (RoM), lateral step variability, toe-out angle, and foot elevation at midswing. Factor analysis of the remaining twenty parameters yielded four orthogonal factors accounting for 87.8% of the total variance in gait (Table 2). The factors were described as speed-spatial, speed-temporal, dual-task cost, and upper body motion. Gait speed had a cross-loading on the factors speed-spatial (0.759) and speed-temporal (0.579). Turning parameters loaded on the factor speed-temporal. In the upper body motion domain, factor loadings of the parameters were relatively low, ranging between 0.53 and 0.61.

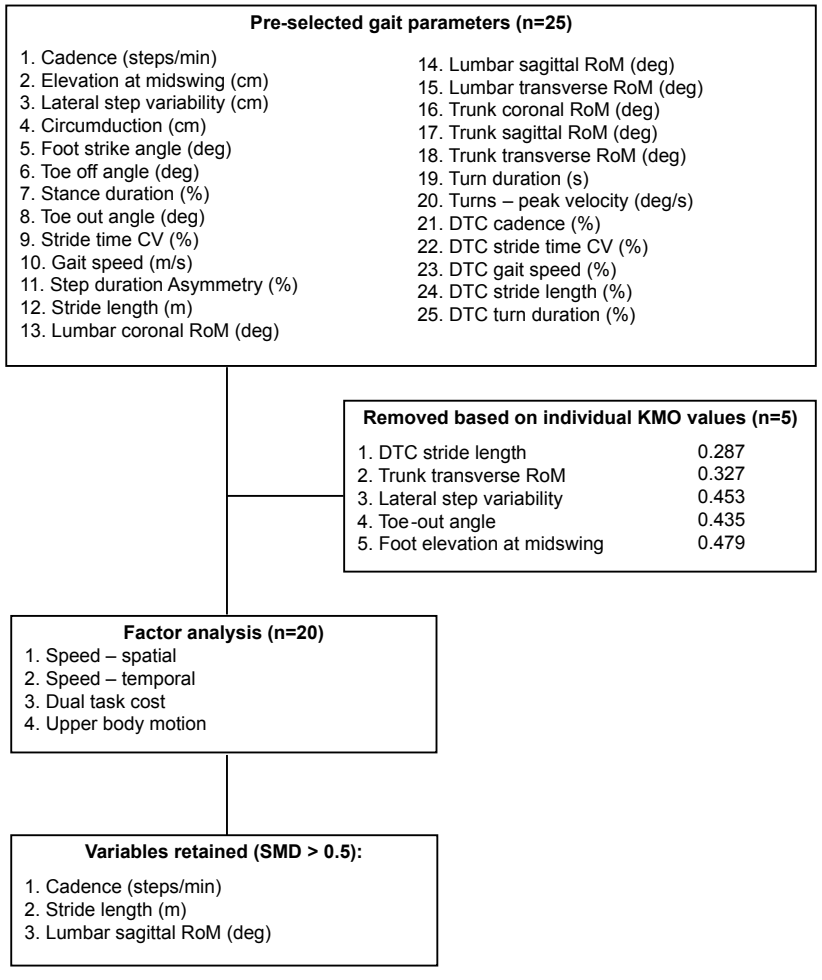

Figure 2: Flowchart describing the selection process of gait parameters. Note: foot elevation at midswing = height of the foot sensor at mid-swing, lateral step variability = spatial deviation in the lateral direction of each foot compared to previous steps, circumduction = amount that the foot travels perpendicular to forward movement during the swing phase

Table 2: Item loadings obtained from the factor analysis (n=4) with varimax rotation.

Gait parameters	Speed-spatial	Speed-temporal	Dual-task cost	Upper body motion
Stride Length (m)	**0.907**	0.270	0.050	-0.000
Gait Speed (m/s)	**0.759**	**0.579**	0.170	-0.062
Foot Strike Angle (deg)	**0.742**	0.120	-0.161	0.257
Toe Off Angle (deg)	**0.628**	0.267	0.129	-0.233
Stride Time CV (%)	**-0.596**	-0.260	-0.077	-0.051
Cadence (steps/min)	0.203	**0.830**	0.284	-0.163
Turns - Peak velocity (deg/s)	0.420	**0.745**	-0.090	0.102
Turn Duration (s)	-0.453	**-0.704**	0.108	0.092
DTC Cadence (%)	0.067	0.010	**0.935**	0.047
DTC Gait Speed (%)	0.060	0.107	**0.921**	0.057
Lumbar Sagittal RoM (deg)	0.113	-0.159	0.028	**0.611**
Lumbar Transverse RoM (deg)	0.029	0.134	0.131	**0.562**
Trunk Sagittal RoM (deg)	0.008	-0.221	0.111	**0.543**
Trunk Coronal RoM (deg)	-0.049	-0.123	-0.008	**0.528**
Explained variance (%)	**30.0**	**22.5**	**20.7**	**14.6**

Note: Barlett's test of sphericity confirmed absence of an identity matrix (χ^2 (190) = 1447.09, $p < 0.001$). Suitability of the dataset was indicated by the Kaiser-Meyer-Olkin measure, which was 0.666. Together the four factors explained 87.8% of the variance in our sample.
CV = coefficient of variation, DTC = dual-task cost, RoM = range of motion.

Selection of gait parameters based on effect size

SMDs for the comparison between OA groups and healthy participants are visualized for all gait parameters in Figure 3. Based on the criterium for effect size, the following gait parameters were selected to represent the corresponding factors: stride length (speed-spatial), cadence (speed-temporal), and lumbar sagittal RoM (upper body motion). Although the factor DTC explained 20.7 % of the total variance in gait, none of the gait parameters within this factor showed an effect size larger than 0.5 (Figure 3). Gait speed showed the largest effect size for both the comparison between knee OA and controls (SMD = 1.59) and hip OA and controls (SMD = 1.70). However, due to cross-loadings on factors speed-spatial and speed-temporal, gait speed was not prioritized over stride length and cadence. In addition, many of the gait parameters from the factor speed-spatial and speed-temporal showed large effect sizes (SMD > 0.8) for both group comparisons.

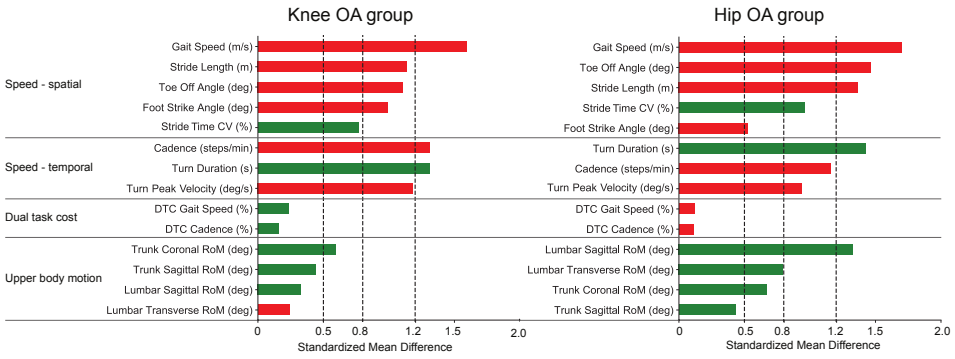

Figure 3: Effect sizes expressed as standardized mean differences of all gait parameters in the different factors for the comparison of healthy controls with individuals with knee OA (left) and individuals with hip OA (right). Red colors indicate OA < healthy controls, green colors represent OA > healthy controls. Please note that gait speed had a cross loading and was also part of the speed-temporal domain. Note: CV = coefficient of variation, DTC = dual-task cost, RoM = range of motion

Between group comparisons of non-redundant gait parameters

Between-group differences of the selected gait parameters were visualized using estimation plots (Figure 4). Both individuals with knee and hip OA walked with a lower cadence and with shorter steps. More specifically, compared to healthy controls stride length was 0.17 m (95% CI: 0.09-0.26, p<0.001) lower in individuals with knee OA and 0.20 m (95% CI: 0.12-0.28, p<0.001) lower in hip OA. In addition, cadence was 10.8 steps/min (95% CI: 6.3-15.4, p<0.001) lower in individuals with knee OA and 9.8 steps/min (95% CI: 5.2-14.4, p<0.001) lower in individuals with hip OA. Lumbar RoM in the sagittal plane was 2.7 degrees (95% CI: 1.7-4.4, p<0.001) higher for individuals with hip OA compared to controls, whereas no differences were found between knee OA individuals and healthy controls (mean difference = 0.5 degrees, 95% CI: -0.33-1.59, p=0.260).

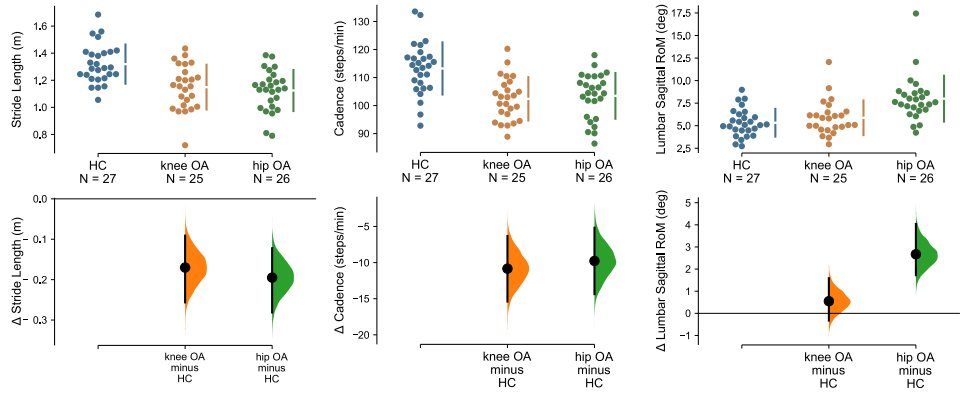

Figure 4: Estimation plots of the mean group differences for stride length, cadence, and lumbar sagittal RoM. In the top panel, dots represent the individual datapoints and bars the mean (± SD). In the bottom panel, the distribution of the mean difference (± 95% CI) for the comparison with healthy controls is visualized. In cases where zero is not in the 95% CI of the mean difference, as indicated by the black bars in the lower panels, data was statistically different at p < 0.05.

Discussion

The aim of the present study was to investigate turning, dual-task performance, and upper body motion in addition to spatiotemporal gait parameters in individuals with knee or hip OA. To avoid redundancy of gait parameters, we conducted a factor analysis. Four independent gait domains were identified: speed-spatial, speed-temporal, dual-task cost, and upper body motion. Turning did not constitute its own domain but was related to speed-temporal. Three domains held parameters sensitive to knee or hip OA: speed-spatial (stride length), speed-temporal (cadence), and upper body motion (lumbar sagittal RoM). Dual-task cost was not sensitive to knee or hip OA.

Factor analysis effectively reduced the dimensionality of our dataset from twenty-five gait parameters to four independent domains of gait, including domains related to dual-task gait and compensatory trunk motion. Turning, however, was part of a factor together with cadence. The factors explaining most of the variance in our sample, i.e. speed-spatial and speed-temporal, were both dependent on gait speed (Table 2). In the literature, these factors reflecting the spatial and temporal aspects of gait speed are consistently reported[38-42]. Other factors related to gait are variability[38,39,41,42], asymmetry[39,41,42], postural control[39], and trunk motion[40]. Dual-task cost has not previously been evaluated in a factor analysis approach, but may contain unique information about gait that is informative of disease-specific compensations related to the re-allocation of attentional resources. Importantly, dual-task cost and upper body motion are interesting domains as they were independent of gait speed, evidenced by the absence of a cross-loading of gait speed on these domains in our study. Dual-task cost and upper body motion may therefore provide promising gait parameters for clinical evaluation of gait, in addition to the more commonly used speed-related measures.

In our analysis steps, turning parameters were excluded in favor of the stronger factor loading that was obtained for cadence. However, effect sizes for turning were large when comparing both knee and hip OA with healthy participants (SMD > 0.9, Figure 3). In addition, factor loadings were not substantially lower compared to cadence. Taken together, we are unsure whether this factor represents a combination of gait and turning, or better reflects turning itself. Future research should therefore indicate as to what extent turning parameters are driven by cadence or gait speed, and how meaningful the unexplained variance is for evaluation of physical functioning in individuals with knee and hip OA.

To facilitate assessment of the between-group differences, we opted to select single gait parameters from the independent factor, to represent the respective factor. From the factors that we obtained, only dual-tasking parameters did not discriminate between knee or hip OA and healthy controls (SMD < 0.5). This indicates that, compared to healthy controls, individuals with OA did not need more attentional resources for the motor task. Thus, although gait was affected in OA, this was not compensated by more attentional resources.

Many of the gait parameters that showed large between-group effect sizes (Figure 3) were grouped either under the speed-spatial or under the speed-temporal domain. This suggests that the two main components determining gait speed, stride length and cadence, are inherently linked with various gait adaptations prominent in individuals with knee and hip OA. As such, gait speed may also be considered as the final common pathway for various gait adaptations, and could be used as a very general, but highly sensitive marker for functional status in individuals with OA. Next to this, our findings further stress the need to take gait speed differences into account when evaluating gait in individuals with OA. More specifically, for parameters that are correlated with gait speed, it may be more appropriate to assess them at a standardized, matched speed, as it may be difficult to separate effects of gait speed from the effects of OA itself[43]. Finally, these findings underline the importance of data reduction techniques when investigating gait using IMUs or motion capture systems, as statistical testing of all gait parameters would increase the probability of finding false positives.

That speed-related gait parameters have good discriminatory capacity in OA has been reported before. Two systematic reviews reported lower gait speed and stride length in individuals with knee and hip OA compared to healthy participants[1,3]. In studies employing IMUs, similar changes in stride length and cadence were found[25,44]. In absolute numbers, slight differences with our values can be discerned. Reasons for this may include the relatively short walking distance (6 meter) in this study that was necessary to reliably assess turning, versus the longer distances (~20 m) that are commonly used. Nevertheless, our findings corroborated previous findings about the discriminatory capacity of stride length and cadence.

In addition to spatiotemporal differences, individuals with hip OA walked with distinct upper body motion, which was most evident in the sagittal plane at the lumbar level. However, upper body motion is difficult to capture by just one parameter, as is illustrated by the relatively low factor loadings lying close together in this domain (Table 1). Altered trunk motion may point toward the use of compensatory strategies to unload the arthritic joint[45]. More specifically, increased pelvic RoM in the sagittal plane may enable more effective anteflexion of the lower limbs and may thereby, to a certain extent, preserve stride length[46]. In addition, anterior pelvic tilt combined with lateral trunk lean can reduce the lever arm between the hip joint center and center of mass[25]. We observed more lumbar sagittal RoM and more RoM of the trunk in the coronal plane in individuals with hip OA compared to healthy controls, in line with previous reports[25,46]. Unfortunately, the exact reason for the use of these compensatory mechanisms remains speculative and may relate to pain, muscle weakness, or joint instability[47]. Future research should therefore investigate the importance of upper body motion in individuals with OA, to inform us about potential mechanisms underlying these gait adaptations.

With regard to the use of wearable sensors in clinical practice, our study showed that quick and easy gait assessments with wearable sensors are useful for evaluating gait impairments in individuals with knee and hip OA. In comparison to optical motion capture systems, wearable sensors are more feasible for large-scale use and could be utilized to routinely assess physical functioning. From all gait parameters, gait speed was found to be a very general but highly sensitive marker for mobility limitations, combining both the effects on stride length and cadence. Besides the basic spatiotemporal measures, trunk motion and turning appeared to be relevant for individuals with knee and hip OA. We therefore recommend to use sensor configurations that allow to look beyond these basic spatiotemporal parameters. In the future, wearable sensors should also be utilized to their fullest potential to enable remote monitoring at home, which would allow to more accurately capture the habitual gait patterns.

This study had several limitations that merit attention. First, we did not obtain factors representing gait asymmetry or variability, which may have been related to the low number of gait parameters related to those domains that were initially entered into factor analysis. We were therefore limited in our conclusions regarding the potential value of those measures for individuals with knee or hip OA. Second, five potentially valuable gait parameters were removed from further analysis due to sampling inadequacy (KMO value < 0.5). Larger sample sizes are therefore required to identify the potential value of these parameters. Related to this, we did not include demographic or clinical variables in the factor analysis, as this could have affected the accuracy of factor analysis due to the relatively small sample size. Finally, including individuals with isolated, unilateral knee or hip OA was important for our study purposes, although the majority of the OA population have complaints in more than one joint[48]. We expect that widening the inclusion criteria would have resulted in larger differences of OA groups compared to healthy controls, but in less specificity for each OA group. In addition, it is important to note that individuals in this study had end-stage OA and were scheduled for joint replacement. Our results may thus not be representative of gait in individuals with less severe OA.

Conclusion

In addition to commonly assessed spatiotemporal parameters, this study provided two other relevant domains of gait: dual-task cost and upper body motion. Although dual-task cost provided unique information about gait, our results did not suggest that individuals with knee or hip OA needed more attention for walking than healthy participants. Adaptations in upper body motion were more subtle than stride length and cadence, but may carry important information about compensatory strategies that are most distinctive for individuals with hip OA. Future steps should include evaluation of the responsiveness of these gait parameters to effects of interventions aiming to improve mobility, such as joint replacement surgery.

Furthermore, longitudinal monitoring of individuals with knee and hip OA starting at earlier stages of the disease may inform us about the development of these gait adaptations and associated compensations over time.

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Chapter 3

Objective gait assessment in individuals with knee osteoarthritis using inertial sensors: A systematic review and meta-analysis

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Abstract

Background
Objective assessment of gait using inertial sensors has shown promising results for functional evaluations in individuals with knee osteoarthritis (OA). However, the large number of possible outcome measures calls for a systematic evaluation of most relevant parameters to be used for scientific and clinical purposes. This systematic review and meta-analysis aimed to identify gait parameters derived from inertial sensors that reflect gait deviations in individuals with knee OA compared to healthy control subjects (HC).

Methods
A systematic search was conducted in five electronic databases (Medline, Embase, Web of Science, CINAHL, IEEE) to identify eligible articles. Risk of bias was assessed using a modified version of the Downs and Black scale. Data regarding study population, experimental procedures, and biomechanical outcomes were extracted. When a gait parameter was reported by a sufficient number of studies, a random-effects meta-analysis was conducted using the inverse variance method.

Results
Twenty-three articles comparing gait between 411 individuals with knee OA and 507 HC were included. Individuals with knee OA had a lower gait speed than HC (standardized mean difference = -1.65), driven by smaller strides with a longer duration. Stride time variability was slightly higher in individuals with knee OA than in HC. Individuals with knee OA walked with a lower range of motion of the knee during the swing phase, less lumbar motion in the coronal plane, and a lower foot strike and toe-off angle compared to HC.

Conclusion
This review shows that inertial sensors can detect gait impairments in individuals with knee OA. Large standardized mean differences found on spatiotemporal parameters support their applicability as sensitive endpoints for mobility in individuals with knee OA. More advanced measures, including kinematics of knee and trunk, may reveal gait adaptations that are more specific to knee OA, but compelling evidence was lacking.

Introduction

Knee osteoarthritis (OA) is a leading cause of disability with a significant impact on daily life mobility and quality of life[1]. Assessment of mobility is therefore crucial for determining the severity and progression of functional impairment and evaluation of interventions in individuals with knee OA. Currently, patient-reported outcome measures (PROMs) prevail in clinical settings to serve these purposes, but their clinical value is limited due to inherent subjectivity, potential ceiling effects, and dependence on pain rather than actual daily life activities[2-5]. As an alternative, simple measures of mobility can be obtained using timed performance-based tests, but these tests only provide an overall impression of performance and do not separate walking from turning or rising from a chair. More advanced measures of mobility, such as gait parameters, can nowadays be easily collected using wearable inertial sensors. However, the wealth of outcomes that can be derived from these assessments warrants thoughtful selection of measures most relevant for clinical practice.

Recent advances in inertial sensor technology have opened avenues for mobile gait assessments. Importantly, the use of inertial sensors enables remote monitoring of gait in a person's own environment, substantially improving the ecological validity of evaluation of physical function. Compared to optoelectronic motion capture systems, objective assessments using inertial sensors feature several advantages, including: low cost, deployment at any location, short preparation time, and ease of use[6]. Signal features of gyroscopes, accelerometers and/or magnetometers are analyzed to accurately detect gait events[7-10]. Subsequently, several spatiotemporal and kinematic gait parameters can be computed for each step or stride, depending on the sensor configuration and processing algorithms[11]. Algorithms processing inertial sensor data have shown good to excellent validity and reliability in healthy adults for spatiotemporal and kinematic parameters, except for some variability and asymmetry metrics[12]. Inertial sensor systems may thus provide the tools for obtaining objective measures of gait quality which are otherwise not available in clinical settings.

Currently, there is a growing interest in the use of inertial sensors in individuals with knee OA, as highlighted by two recent scoping reviews[13,14]. Multiple studies have quantified gait differences between individuals with knee OA and healthy control subjects (HC) across a wide range of parameters[3,15-22], but a comprehensive overview pooling the effects of these studies is lacking. Meta-analysis of these studies may aid the selection of a subset of gait parameters that best reflects gait impairments in individuals with knee OA, to be used to monitor disease progression and as potential endpoints in clinical trials. Therefore, the aims of this systematic review were 1) to provide an overview of the characteristics of studies investigating gait differences between individuals with knee OA and HC using inertial sensors, and 2) to pool effects of knee OA on spatiotemporal and kinematic gait parameters.

Methods

This systematic review was preregistered at PROSPERO (CRD42020182135) and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[23,24].

Search strategy

A systematic search was conducted in the following electronic databases: Medline, EMBASE, Web of Science, IEEE, and CINAHL. Full search codes for all of the databases are provided in Supplementary File 1, accompanied by a detailed search strategy for one of the databases. A post-hoc check of our search was performed by an independent librarian of the Radboud University Medical Centre to ensure that no relevant articles have been missed. Database searches were conducted on May 1st, 2020 and were last updated on June 2nd, 2021. Additional records were identified via reference lists of the relevant articles. All search results were exported to EndNoteX7 and checked for duplicates.

Assessment of eligibility

Eligibility was determined based on a list of in- and exclusion criteria (Table 1). Both comparative studies and longitudinal studies with a pre-intervention comparison with a control group were considered for inclusion. There were no restrictions on study date, disease severity (i.e. Kellgren-Lawrence (KL) grade), OA laterality (i.e. unilateral versus bilateral), or type of OA (i.e. medial versus lateral compartment). Two independent, blinded reviewers (RB and JvG) screened article titles and abstracts. All study records were managed using Covidence (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). Disagreements in screening results were resolved by a third reviewer (KS). Subsequently, full text manuscripts of studies meeting the eligibility criteria were obtained. All full text articles were checked for eligibility by the same reviewers (RB, JvG) and disagreements were resolved by consultation of a third reviewer (KS).

Table 1: In- and exclusion criteria used to determine article eligibility

Inclusion	Exclusion

• Original research article published in a peer-reviewed journal
• Written in English
• Included healthy subjects and individuals with knee OA
• Level walking was measured using wearable inertial sensors
• Minimum group size of 5 subjects in each study group
• Outcome metrics included at least one of the following parameters:
  ○ gait speed
  ○ cadence or an equivalent metric (i.e. step time, stride time, or gait cycle duration)
  ○ step or stride length
  ○ asymmetry of step time or step length
  ○ variability (coefficient of variation or standard deviation) of step/stride length or step/stride time
  ○ range of motion of the knee
	• Studies measuring gait using pressure insoles or pressure sensors, including pressure sensitive mats
	• Previous joint replacement of hip, knee or ankle
	• Presence of neurological or musculoskeletal disorders (other than OA) that affect gait or balance
	• Gait parameters were not derived from sensor data but from other sources (i.e. optoelectronic system, timer, etc.)
	• Subjects with rheumatoid arthritis
	• Systematic reviews
	• Conference proceedings

Risk of bias appraisal

Methodological quality of the included studies was assessed by two reviewers (RB, KS) using a modified version of the Downs and Black scale[25]. Disagreements between the reviewers were resolved during a consensus meeting. The Downs and Black scale assesses risk of bias in both randomized and non-randomized studies, and contains 27 items that cover quality of reporting, internal and external validity, bias, confounding, and power. Also, the validity and reliability of the algorithms used to process the sensor data was specifically evaluated in item 20. To match our study aims, only 11 relevant items of the original scale were retained (Supplementary File 2). In addition, scoring of the studies was based on our study aim, i.e. the comparison between knee OA and healthy subjects, which could be different from the aim of the actual study. All items were scored 0 (no/ unable to determine) or 1 (yes), except for question five (0=no, 1=partially, 2=yes). The maximum possible score to be obtained was 11.

Data extraction

In order to obtain an overview of the employed experimental paradigms, the following study information was extracted: inertial sensor system, number of sensors, sensor location(s), software package/algorithm, walking paradigm (i.e. 2-minute walk test, 20m walk test, etc.), and testing environment. Furthermore, data concerning study groups was obtained: group sizes, population characteristics (i.e. age and sex), OA definition (i.e. medical diagnosis, radiologically confirmed, scheduled for joint replacement, etc.), OA severity (KL grade), and OA laterality (unilateral vs. bilateral). Quantitative data of the following gait parameters were extracted when available: 1) gait speed, 2) step/stride length, 3) cadence or an equivalent metric such as step time, stride time, or gait cycle duration, 4) knee joint range of motion, 5) asymmetry of step length or step time, 6) variability of step/stride length and step/stride time, and 7) upper body motion (i.e. range of motion in the sagittal, frontal or transverse plane). Other outcomes were considered if they were reported by ≥ 3 studies. Gait parameters were only extracted if they were directly derived from the sensor data. More specifically, gait parameters measured with a timer, pressure-based or optoelectronic motion capture system were not extracted. When data could not accurately be extracted from figures, the corresponding author was contacted. In total, authors of seven different studies were contacted, of whom four replied to our request. Two of these authors mentioned that raw data was not available, one author did not reply to our follow-up requests, and in one case the specific outcome (e.g. knee kinematics as absolute joint angles) was not calculated from the raw data by the authors. Data extraction was performed by one reviewer (RB).

Data analysis

A random-effects meta-analysis was performed in RStudio (version 1.2.5001) using the Metafor package (https://github.com/wviechtb/metafor). Given the differences in gait mechanics between overground and treadmill walking[26], studies where participants walked on a treadmill were removed from meta-analysis. For parameters that were uniformly reported in minimally 3 studies, standardized mean differences (SMDs) were calculated for the comparison between individuals with knee OA and healthy subjects. The use of SMDs allowed comparison of effect sizes between the different gait parameters. To facilitate clinical interpretation, mean differences were also calculated, which are provided in Supplementary File 3. Pooled estimates were obtained by the weighted average of the individual study results using the inverse variance method[27]. Results were visualized using forest plots. Comparisons were considered statistically significant at an alpha level of 0.05 (i.e. when zero was outside

of the 95% confidence interval of the SMD). I2 statistics were obtained to assess study heterogeneity. Heterogeneity was considered to be low (I2 < 25%), moderate (I2= 25-49%), or high (I2 >50%)[28]. Data analysis scripts together with the data are available in a separate supplementary file available through the online version of this publication.

Results

Search results

A complete overview of the search and inclusion process is provided in Figure 1. From five databases, a total of 607 articles were identified. After removal of duplicates, 432 articles remained. Title and abstract screening excluded another 393 articles. One additional article was identified via screening of reference lists of relevant articles. The full text of 39 articles were assessed, of which 23 articles met all inclusion criteria (Figure 1).

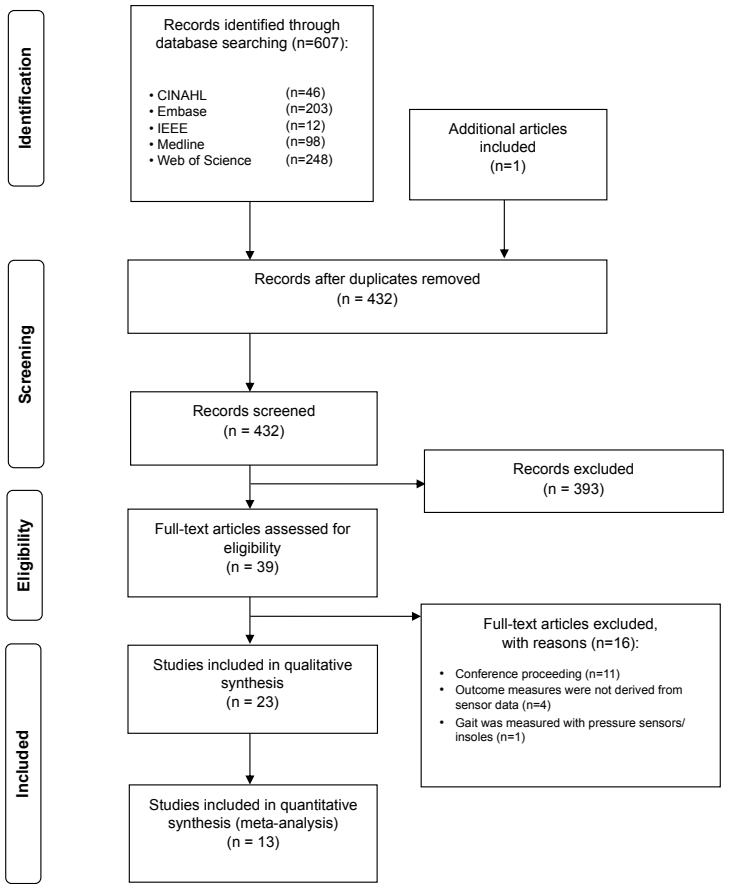

Figure 1: PRISMA flowchart of the article selection process

Study characteristics – Population

Characteristics of the included study are summarized in Table 2. Across the 23 studies that we included, gait was analyzed in 411 individuals with knee OA and 507 HC. Two studies were not included in this total sample[15,20] as they used (part of) the same dataset as other included studies[29,30]. The ratio between men and women was comparable within both groups (i.e. 45% men in HC vs. 44% in knee OA). Mean age was 56.9 (SD 8.3) years for HC and 65.1 (SD 7.7) years for individuals with knee OA. Five studies contained a properly age and sex-matched control group of healthy (older) adults[20,21,29,31,32], whereas four studies had a significantly younger control group[19,33-35]. Studies were heterogeneous in OA laterality and their definition used for knee OA. The majority of studies aimed to include patients with end-stage unilateral knee OA, often scheduled for (total) knee arthroplasty. Two studies specifically recruited individuals with bilateral knee OA[20,29]. Presence of OA was either confirmed radiologically or by clinical diagnosis of an orthopaedic surgeon. Severity of OA differed between studies, ranging from KL grade 1 to 4.

Study characteristics – Experimental set-up

Fourteen different inertial sensor systems were used to quantify gait in individuals with knee OA, with most studies placing inertial sensors at the lower back or pelvis (n=15)[3,15-21,29,30,32,33,35-37] (Table 2). Other commonly used locations were the sternum, thigh, shank, and feet. Nine studies used a single sensor set-up[3,20,21,29,32,35,36,38,39], whereas the other fourteen studies used a multi-sensor system[15-19,22,30,31,33,34,37,40-42], with a maximum number of fifteen sensors in one study[19]. A wide variety of software packages and algorithms were used to process the sensor data (Table 2). Detailed description of the algorithms used in each individual study is provided in Supplementary File 5. Across the included studies, multiple walking paradigms were employed to analyze gait. Most frequently, subjects walked across a 20m walkway at self-selected speed[3,15,21,30,32,36,40,42]. Eight other studies used a similar paradigm, but with alternate walking distances (i.e. unknown, 6m, 7m, 10m, and 40m)[16,18,19,31,33,35,37,41]. In contrast, two studies evaluated gait on a treadmill, with the speed matched to the comfortable walking speed[17,38]. The length/duration of these walking trials was 500m[17] in one study and 11 minutes in the other study[38]. Two studies used a 200m oval track that subjects were asked to walk for a duration of 9 minutes at a self-selected speed[20,29]. In another study subjects walked continuously for 10 minutes[22]. Finally, two studies used inertial sensors to monitor gait in the home environment[34,39]. As for testing location, seven studies used inertial sensors in a lab-based setting[15-17,19,30,33,38] (sometimes to simultaneously compare results with traditional mocap systems[16,17,19]), whereas in fifteen studies gait was assessed outside the lab[3,18,20,21,29,31,32,34-37,39-42]. In one case, testing location was not specified[22]. Of the studies that used inertial sensors outside the lab, three performed their tests in a university setting (e.g. hallway or track)[20,29], ten in clinical/hospital setting[3,18,21,31,32,35-37,40-42], and two studies used inertial sensors to monitor gait during daily life[34,39] (Table 2).

Table 2: Study characteristics

Author	Population	Sensor system	Algorithm	Sensor location / attachment	Walking paradigm	Testing location
Auvinet *et al.* 1999 (35)	HC: n = 139; age = 41.4 (11.2); M/F = 69/70 KOA: n =20; age = 65.9 (9.2), M/F = 10/10; radiological OA	Locométrix *f* = 50 Hz	Custom	Lower back; L3/L4 (n=1)	40m corridor (n=2), self-selected speed	Outside laboratory; clinical
Barden *et al.* 2016 (20)	HC: n=15; age = 66.1 (10.0), M/F = 7/8 KOA: n = 15, age = 64.7 (6.8), M/F = 7/8, medical diagnosis of bilateral OA (KL = 2, 3 or 4)	GENEActiv *f* = 100 Hz	Custom	Lower back; L3 (n=1)	9-min walking on 200 m oval track, self-selected speed	Outside laboratory; university
Boekesteijn *et al.* 2021 (18)	HC: n=27; age = 66 (6); M/F = 13/14 KOA: n=25; age = 64 (7); M/F = 12/13; end-stage OA, scheduled for TKA (KL = 3 or 4)	Opal *f* = 128 Hz	Mobility Lab	Sternum, lower back, feet (n=4)	2 min walking test over 6m, self-selected speed	Outside laboratory; clinical
Bolink *et al.* 2012 (3)	HC: n = 30; age = 61.0 (5.6); M/F = 18/12 KOA: n = 20; age = 67.4 (7.7); M/F = 7/13; end-stage OA, scheduled for TKA (KL = 3 or 4)	Inertia-Link *f* = 100 Hz	Custom	Lower back; between posterior superior iliac spines (n=1)	20m corridor, self-selected speed	Outside laboratory; clinical
Bolink *et al.* 2015 (36)	HC: n = 20; age = 61 (6.1); M/F = 9/11 KOA: n = 20; age = 65.4 (9.3); M/F = 9/11; end-stage OA, scheduled for TKA (KL = 3 or 4)	Inertia-Link *f* = unknown	Custom	Lower back; between posterior superior iliac spines (n=1)	20m corridor, self-selected speed	Outside laboratory; clinical
Chapman *et al.* 2019 (34)	HC: n=10; age = 49.7 (18.5); M/F = 5/5 KOA: n=17; age = 64.9 (6.4); M/F = 10/7; scheduled for TKA	Opal *f* = 20 Hz	Custom	Thigh, shank (n=2)	One week monitoring at home	Outside laboratory; home
Clermont *et al.* 2016 (29)	HC: n=15; age = 66.1 (10.0); M/F = 7/8 KOA: n=15; age = 64.6 (6.8); M/F = 7/8, medical diagnosis of bilateral OA (KL = 2, 3, or 4)	GENEActiv *f* = 100 Hz	Custom	Lower back; L3 (n=1)	9-min walking on 200 m oval track, self-selected speed	Outside laboratory; university
Hafer *et al.* 2020 (16)	HC: n=10; age = 72.3 (3.3); M/F = 5/5 KOA: n=9; age = 69.2 (4.5); M/F = 5/4; radiological OA in at least one knee (KL = 2, 3 or 4)	Opal (*custom*) *f* = 128 Hz	Custom	Pelvis, thigh, shank, foot (n=4)	Overground walking trials (n=10), self-selected speed	Inside laboratory
Ismailidis *et al.* 2020 (15)	HC: n=28; age= 68.8 (6.5); M/F 10/18 KOA: n=23; age = 66.1 (8.9); M/F = 12/11; unilateral knee OA scheduled for TKA (KL = 3 or 4)	RehaGait *f* = 400 Hz	Manufacturers software Hasomed	Lower back (L5) and bilaterally at thigh, lower leg, and foot (n=7)	20m corridor, self-selected speed	Inside laboratory
Ismailidis *et al.* 2021 (30)	HC; n=46; age = 66.8 (7.4); M/F = 16/30 KOA: n=22; age = 65.9 (9.1); M/F = 12/10; unilateral OA scheduled for TKA (KLK = 3 or 4)	RehaGait *f* = 400 Hz	Manufacturers software Hasomed	Lower back (L5) and bilaterally at thigh, lower leg, and foot (n=7)	20m corridor, self-selected speed	Inside laboratory
Kierkegaard *et al.* 2015 (21)	HC: n=29; age = 66.0 (7.9); M/F = 14/15 KOA: n=57 (of which only 54 completed gait tests); age = 65.6 (7.6); M/F = 28/29; isolated medial compartment OA, scheduled for UKA	Inertia-Link *f* = 100 Hz	Custom	Lower back; between posterior superior iliac spines (n=1)	20m corridor, self-selected speed	Outside laboratory; clinical

Note: HC = healthy control, KOA = knee osteoarthritis, KL = Kellgren-Lawrcence, TKA = total knee arthroplasty, UKA = unicompartmental knee arthroplasty, n.s = not specified

Table 2: Study characteristics (continued)

Author	Population	Sensor system	Algorithm	Sensor location / attachment	Walking paradigm	Testing location
Kluge *et al.* 2018 (31)	HC: n=24; age = 62.3 (9.7); M/F = 8/16 KOA: n=24; age = 64.0 (11.0); M/F = 8/16, unilateral end-stage OA scheduled for TKA	Shimmer3 *f* = 102.4 Hz	Custom	Laterally to shoe (n=2)	10m walkway back-and-forth (4 times), self-selected speed	Outside laboratory; university
Lebleu *et al.* 2020 (37)	HC: n=12; age = 50.6 (11.9); M/F = 5/7 KOA: n=14; age = 64.5 (11.3); M/F = 0/14; symptomatic and radiological knee OA, not responding to conservative treatment (KL = 2-4)	x-IMU *f* = 128 Hz	Custom	Lower back (L5), thigh, shank, and feet (n=7)	10m walkway, self-selected speed	Outside laboratory; clinical
McCarthy *et al.* 2013 (40)	HC: n=21; age=71.3 (6.1); M/F = 4/17 KOA: n=23; age = 65.1 (7.7); M/F = 9/14, both patients with symptomatic unilateral and bilateral OA	GaitSmart *f* = 102.4 Hz	Manufacturers software Dynamic Metrics Ltd.	Bilaterally to thigh and shank (n=4)	20m level walking, self-selected speed	Outside laboratory; clinical
Odonkor *et al.* 2020 (22)	HC: n = 10; age = 61.2 (9.9); M/F = 5/5 KOA = n = 10; age = 63.9 (8.1); M/F = 4/6; clinical diagnosis of OA, both unilateral and bilateral (Kl = 3 or 4)	Shimmer3 *f* = 102.4 Hz	Custom	Feet (n=2)	10 minutes free walking, self-selected speed	n.s.
Rahman *et al.* 2015 (41)	HC: n=29; age = 68.1 (7.1); M/F = 12/17 KOA: n=28; age = 66.9 (10.7)*; M/F = 32/42* , radiological and symptomatic OA, scheduled for/ awaiting TKA	GaitSmart *f* = 102.4 Hz	Manufacturers software Dynamic Metrics Ltd.	Bilaterally to thigh and shank (n=4)	10m corridor back-and-forth, self-selected speed	Outside laboratory; clinical
Senden *et al.* 2011 (32)	HC: n=24; age = 70 (8); M/F = 11/13 KOA: n=24; age = 70 (8); M/F = 11/13; symptomatic OA scheduled for unilateral TKA	Dynaport Minimod *f* = 100 Hz	Manufacturers software McRoberts	Lower back, at the level of the sacrum (n=1)	20m corridor (6 times), self-selected speed	Outside laboratory; clinical
Staab *et al.* 2014 (17)	HC: n=7; age = 41.7 (8.8); M/F = 6/1 KOA: n=12; age = 44.4 (7.6); M/F = 10/2, clinical and radiological OA (KL 3-4)	Analog Devices accelerometers and gyroscopes *f* = 1000 Hz	Custom	Lower back and ankle (n=3)	500m treadmill walking, self-selected speed	Inside laboratory
Straaten van der *et al.* 2020 (19)	HC: n=12; age = 59.8 (7.0); M/F = 6/6 KOA: n=19; age = 65.1 (5.2); M/F = 12/7; unilateral end-stage OA, scheduled for TKA	Xsens Awinda *f* = unknown	MVN software	Forehead, sternum, scapulae, upper arm, forearm, lower back, thigh, shank, feet (n=15)	10m walk test; self-selected speed	Inside laboratory
Tadano *et al.* 2016 (33)	HC: n=8; 22.9 (0.8); M/F = unknown KOA: n=10; 68.7 (4.1); M/F = unknown; both unilateral and bilateral OA (KL = 2, 3, or 4)	H-Gait *f* = 500 Hz	Custom	Pelvis and bilaterally to thigh, shank, and feet (n=7)	7m level walking, self-selected speed	Inside laboratory
Tanimoto *et al.* 2017 (38)	HC: n=11; median age = 66.0 (62.5-73.5); M/F = 9/2 KOA: n=12; median age = 73.0 (71.5-73.0); M/F = 10/2; both unilateral and bilateral OA (KL = 1, 3 or 4)	Microstone inertial sensor *f* = 100 Hz	Custom	Shank (n=1)	11-min treadmill walking (incl. 1-min habituation), self-selected speed	Inside laboratory
Vangeneugden *et al.* 2020 (39)	HC: n=11; age = 57.6 (4.5); M/F = 0/11 Lean KOA: n=11, age = 60.2 (4.7); M/F = 0/11 Obese KOA: n = 10, age = 59.9 (4.0); M/F = 0/10; both OA groups had radiological OA (KL = 1, 2 or 3)	KXSD9 tri-axial accelerometer *f* = 25 Hz	Custom	Thigh (n=1)	7-10 days monitoring at home	Outside laboratory; home
Zhang *et al.* 2016 (42)	HC: n=12; 53.2 (6.7); M/F = 6/6 KOA: n=12; 65.3 (8.0); M/F = 5/7; scheduled for TKA	IDEEA3 *f* = 32 Hz	Manufacturers software MiniSun	Sternum and bilaterally to thigh, ankle, and feet (n=7)	20m walkway back-and-forth, self-selected speed	Outside laboratory; clinical

* = based on total group of patients recruited (n=74), demographics of the patients was not reported separately for pre-operative situation.
Note: HC = healthy control, KOA = knee osteoarthritis, KL = Kellgren Lawrence score, TKA = total knee arthroplasty, UKA = unicompartmental knee arthroplasty, n.s. = not specified.

Risk of bias appraisal

Studies had a mean score of 6.6 out of 11 on the modified Downs and Black scale (Table 3). Twenty-three studies scored low on external validity[3,15-22,29-42], with gait being assessed in only selected parts of the total knee OA population. In addition, there was only one study that explicitly reported the time over which cases and controls were recruited[21], and attempted to blind assessors during outcome assessment[21]. In ten studies, accuracy of the main outcomes was difficult to determine, as details and references on algorithm validity and reliability were lacking[3,15,17,19,21,36,37,40-42] (Supplementary File 5).

Table 3: Risk of bias appraisal for the included studies according to a modified version of the Downs and Black scale

Author (year)	3	5	7	11	15	16	18	20	22	25	Total score
Auvinet *et al*. 1999 (35)	0	2	1	U	U	1	0	1	U	0	5
Barden *et al*. 2016 (20)	1	2	1	0	U	0	U	1	U	1	6
Boekesteijn *et al*. 2021 (18)	1	2	1	0	U	1	1	1	U	1	8
Bolink *et al*. 2012 (3)	1	2	1	0	U	1	U	U	U	0	5
Bolink *et al*. 2015 (36)	1	2	1	0	U	1	1	U	U	1	7
Chapman *et al*. 2019 (34)	1	2	1	0	U	1	U	1	U	0	6
Clermont *et al*. 2016 (29)	1	2	1	0	U	1	U	1	U	1	7
Hafer *et al*. 2020 (16)	1	2	1	0	U	1	U	1	U	1	7
Ismailidis *et al*. 2020 (15)	1	2	1	0	U	1	1	U	U	1	7
Ismailidis *et al* 2021 (30)	1	2	1	0	U	U	1	1	U	1	7
Kierkegaard *et al*. 2015 (21)	1	2	1	0	1	1	1	U	1	1	9
Kluge *et al*. 2018 (31)	1	2	1	0	U	1	1	1	U	1	8
Lebleu *et al*. 2021 (37)	0	2	1	0	U	1	1	U	U	0	5
McCarthy *et al*. 2013 (40)	0	2	1	U	U	1	1	U	U	1	6
Odonkor *et al*. 2020 (22)	1	2	1	0	U	1	1	1	U	1	8
Rahman *et al*. 2015 (41)	0	2	1	0	U	1	1	0	U	1	6
Senden *et al*. 2011 (32)	0	2	1	0	U	1	1	1	U	1	7
Staab *et al*. 2014 (17)	0	2	1	0	U	1	1	0	U	1	6
Straaten van der *et al*. 2020 (19)	1	2	1	0	U	1	1	U	U	0	6
Tadano *et al*. 2016 (33)	1	1	1	0	U	1	0	1	U	0	5
Tanimoto *et al*. 2017 (38)	1	2	1	0	U	1	1	1	U	1	8
Vangeneugden *et al*. 2020 (39)	1	2	1	0	U	1	1	1	U	1	8
Zhang *et al*. 2016 (42)	1	2	0	0	U	1	0	0	U	0	4

Included items:
3: Are the characteristics of the patients included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.
5: Are the distributions of principal confounders (i.e. age and sex) in each group of subjects to be compared clearly described?
7: Does the study provide estimates of the random variability in the data for the main outcomes?
11: Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
15: Was an attempt made to blind those measuring the main outcomes of the intervention?
16: If any of the results of the study were based on "data dredging", was this made clear?
18: Were the statistical tests used to assess the main outcomes appropriate?
20: Were the main outcome measures used accurate (valid and reliable)?
22:Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
25: Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
Note: answers should be interpreted as 0 = No, 1 = Yes, U = unable to determine. In case of question 5, answers were 0 = No, 1 = Partially, 2 = Yes.

Synthesis of results

The gait parameters that were investigated in each study are summarized in Table 4. Meta-analysis was conducted for the following thirteen parameters: gait speed, cadence, step/stride time, step/stride length, gait asymmetry, gait variability, sagittal/frontal/transversal plane pelvic motion, maximum knee flexion during swing, stance duration, foot strike angle, and toe-off angle. For these outcomes, the simple summary data of each individual study is presented in Supplementary File 4. Because the metrics that were reported for knee kinematics were substantially different between studies, it was not possible to pool most of these results. Ten studies were not included in the meta-analysis. In two of these studies gait was monitored under free-living conditions[34,39], which may result in substantially different gait patterns than in laboratory or clinical settings. For the same reason, two studies in which subjects walked on a treadmill were excluded[17,38]. Further, two excluded studies did not provide group means or estimates of variability[19,42]. Two other studies[15,20] were not included as they were based on the same dataset as other included studies[29,30]. In this case we included either the study with the largest sample or the earliest study[29,30], as including both of these studies in a meta-analysis would introduce bias towards these study outcomes. In one excluded study, data was skewed and therefore not suitable for meta-analysis[21]. Finally, one study was excluded due to a substantial age difference (e.g. 46 years) between both study groups[33]. In the other study where age was significantly lower (e.g. 25 years) in HC[35] but that we did include in our meta-analysis, a sensitivity analysis was performed to assess the impact of age on our results.

Table 4: Gait parameters investigated per study

Author (year)	Gait speed	Step/ stride length	Cadence	Step/ stride time	Step time asymmetry	Step/stride time variability	Knee Kinematics	Upper body motion	Other
Auvinet et al. 1999 (35)			•						Stride symmetry, stride regularity
Barden et al. 2016 (20)				•					Stride regularity, step regularity, gait symmetry
Boekesteijn et al. 2021 (18)	•	•	•		•	•		•	Foot elevation at mid swing, lateral step variability, circumduction, , foot-strike angle, toe off angle, stance duration (%), toe-out angle, turn duration, turn peak velocity, dual-task cost (cadence, stride time CV, gait speed, stride length, turn duration)
Bolink et al. 2012 (3)	•	•	•	•	•	•		•	
Bolink et al. 2015 (36)	•	•	•	•	•	•		•	Pelvic obliquity asymmetry, pelvic obliquity at heel strike
Chapman et al. 2019 (34)							•		
Clermont et al. 2016 (29)				•		•			Fractal scaling index of stride time
Hafer et al. 2020 (16)	•	•	•				•		Stance time (%)
Ismailidis et al. 2020 (15)	•	•	•	•			•		Hip and ankle kinematics (sagittal plane)
Ismailidis et al 2021 (30)	•	•	•	•			•		Hip and ankle kinematics (sagittal plane)
Kierkegaard et al. 2015 (21)	•							•	
Kluge et al. 2018 (31)	•	•		•		•			Swing/stance time (%), maximum toe clearance, toe-off angle, heel strike angle, variability of gait speed/swing time/stance time/ stride length
Lebleu et al. 2021 (37)			•	•			•	•	Hip and ankle kinematics
McCarthy et al. 2013 (40)				•			•		
Odonkor et al. 2020 (22)	•	•	•						Stance/swing ratio (%), gait event timings (as % gait cycle), double support, peak angular velocity, foot strike angle, toe-off angle, lateral displacement during swing, turn angle between foot-flats
Rahman et al. 2015 (41)				•			•		Excursion of thigh and shank in sagittal and frontal plane
Senden et al. 2011 (32)	•	•	•	•	•	•			Vertical displacement
Staab et al. 2014 (17)	•		•		•				Mediolateral trunk symmetry, limb symmetry (deg)
Straaten van der et al. 2020 (19)							•	•	Hip kinematics
Tadano et al. 2016 (33)		•		•			•		Ankle angles, support ratio, hip, knee and ankle joint centre trajectories (and derived measures)
Tanimoto et al. 2017 (38)				•		•			Peak shank angular velocity, fractal scaling index of stride time
Vangeneugden et al. 2020 (39)				•					Harmonic ratio, fractal scaling index
Zhang et al. 2016 (42)	•	•							Single support time, acceleration at footfall, swing power

Spatiotemporal gait parameters

Individuals with knee OA walked slower compared to HC (SMD = -1.65 [95% CI: -1.90 – -1.40], I2 = 0%)[1,16,18,22,30-32,36] (Figure 1A). This lower gait speed in individuals with knee OA was consistently reported among all studies. The effects on gait speed were the combined result of a lower step/stride length (SMD = -1.28 [95% CI: -1.55 – -1.01], I2 = 20 %)[1,16,18,22,30-32,36], and a lower cadence in individuals with knee OA compared to HC (SMD = -1.19 [95% CI: -1.41, -0.98], I2 = 0%)[1,16,18,22,30,32,35-37]. Removal of Auvinet et al.[35], who included a significantly younger control group, did not modify the effect of knee OA on cadence (i.e. SMD = -1.14, I2 = 0%). In addition, overall step/stride duration was higher in individuals with knee OA (SMD = 1.08 [95% CI: 0.69 – 1.48], I2 = 67%)[1,29-31,36,37,40,41]. Step time asymmetry was slightly higher in individuals with knee OA, although this effect was not statistically significant (SMD = 0.49 [95% CI: -0.02 – 1.01], I2 = 67%) (Figure 1F)[1,18,32,36]. Compared to HC, individuals with knee OA spent a larger percentage of their gait cycle in stance (SMD = 0.80 [95% CI: 0.37 – 1.24], I2 = 37 %)[16,18,22,31]. Finally, gait variability was slightly higher in individuals with knee OA compared to HC (SMD = 0.51 [95% CI: 0.25 – 0.77], I2 = 0.0%) (Figure 1E)[1,18,31,32,36].

Joint kinematics

While multiple studies investigated knee kinematics, there was limited opportunity for meta-analysis due to differences in reporting of outcomes between the included studies. According to our meta-analysis, individuals with knee OA had lower range of motion of knee flexion during the swing phase (SMD = -1.59 [95% CI: -2.37 – -0.81], I2 = 79%) (Figure 1G)[30,40,41]. In two studies, lower knee flexion range of motion was also found during the stance phase[40,41]. Over the whole gait cycle, sagittal plane range of motion of the knee was lower in individuals with knee OA according to two studies[16,37]. This lower range of motion over the whole gait cycle may be explained by lower peak flexion angles in individuals with knee OA that were present during both the stance[19,30,34] and swing phase[19,30,34].

Altered foot kinematics were observed in individuals with knee OA (Figure 1L&M), as illustrated by a lower foot strike angle (SMD = -0.83 [95% CI: -1.20 – -0.45], I2 = 0%)[18,22,31] and a lower toe-off angle (SMD = -1.09 [95% CI:-1.48 – -0.71], I2 = 0%) compared to HC[18,22,31]. At the level of the pelvis, individuals with knee OA showed significantly less coronal range of motion compared to HC (SMD = -0.78 [95% CI: -1.14 – -0.42], I2 = 21%) (Figure 1H)[1,18,36,37]. There were no differences between both groups in range of motion in the sagittal (SMD = 0.36 [95% CI: -0.47 – 1.19], I2 = 80%)[1,18,37] and transversal plane (SMD = -0.12 [95% CI: -0.47 – 0.23], I2 = 0%) (Figure 1I&J)[1,18,37].

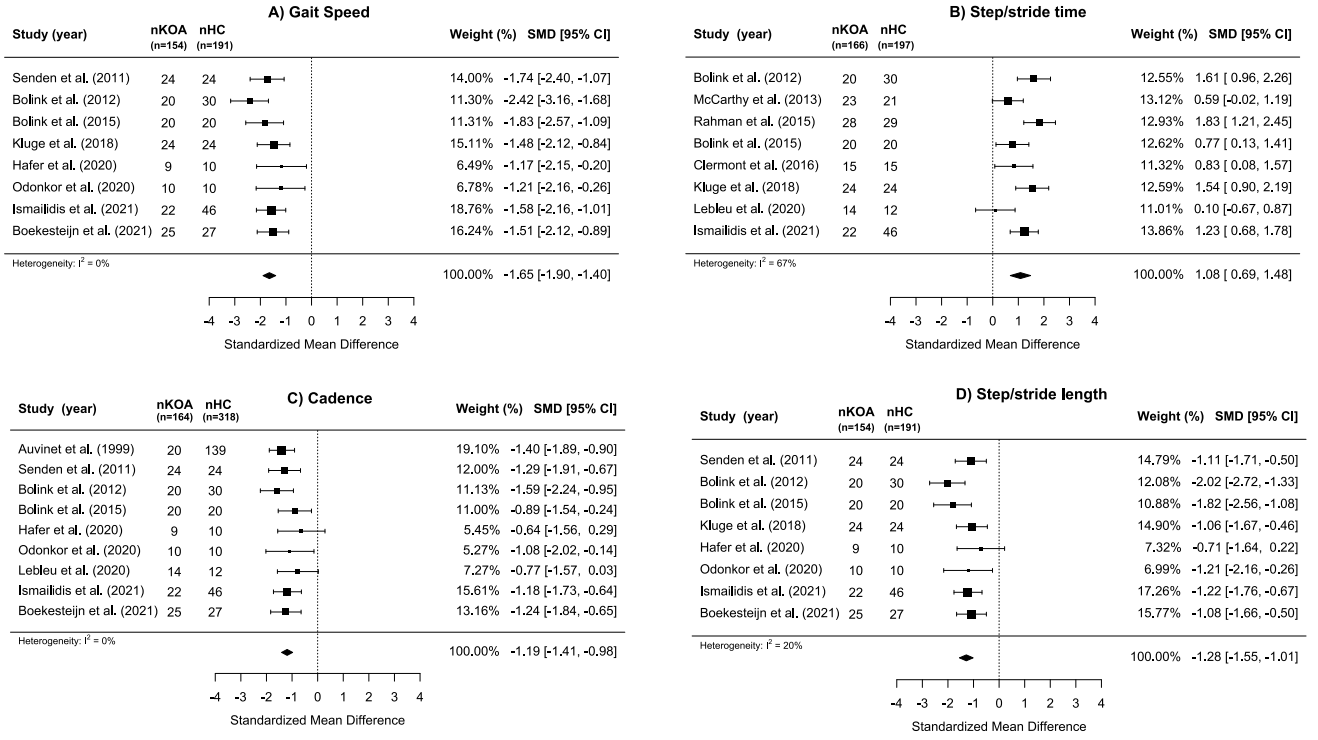

Figure 2: Forest plots for the comparison of gait parameters between individuals with knee osteoarthritis and healthy subjects. Negative standardized mean differences indicate lower values in individuals with knee OA compared to HC. *Note:* ROM = range of motion

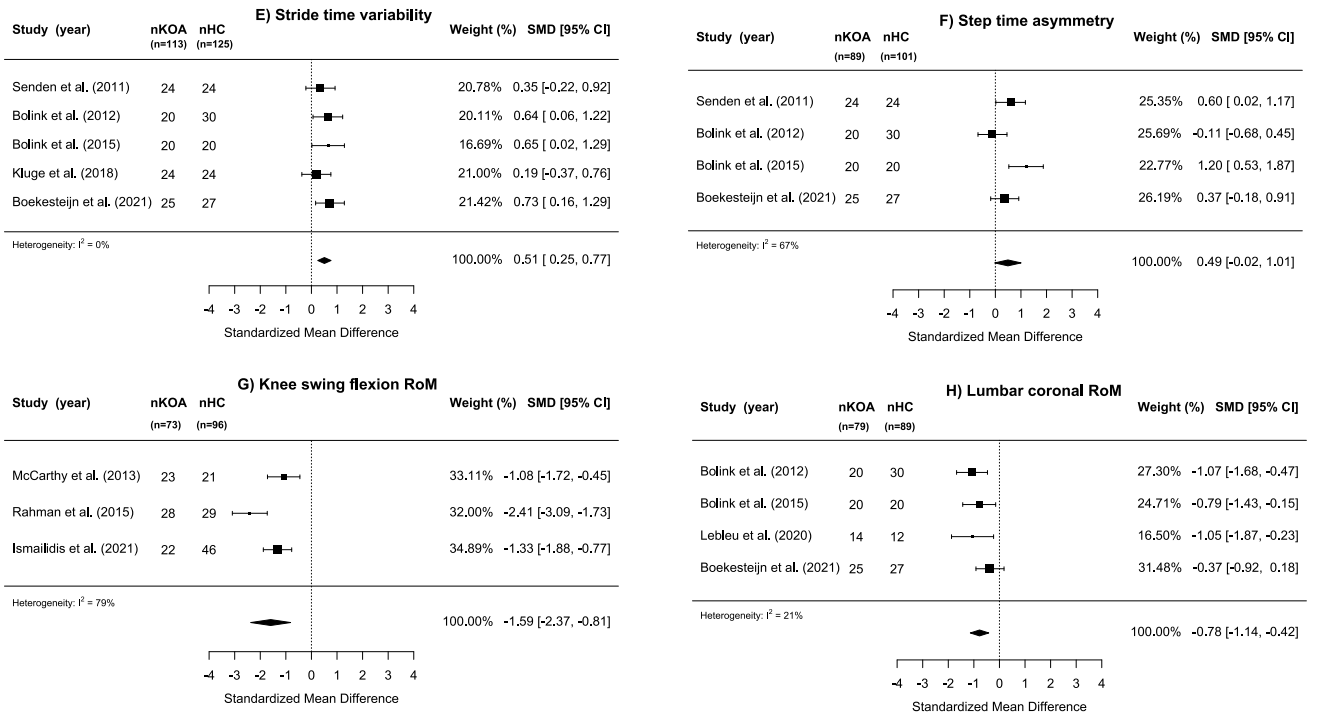

Figure 2 (continued): Forest plots for the comparison of gait parameters between individuals with knee osteoarthritis and healthy subjects. Negative standardized mean differences indicate lower values in individuals with knee OA compared to HC. *Note:* ROM = range of motion

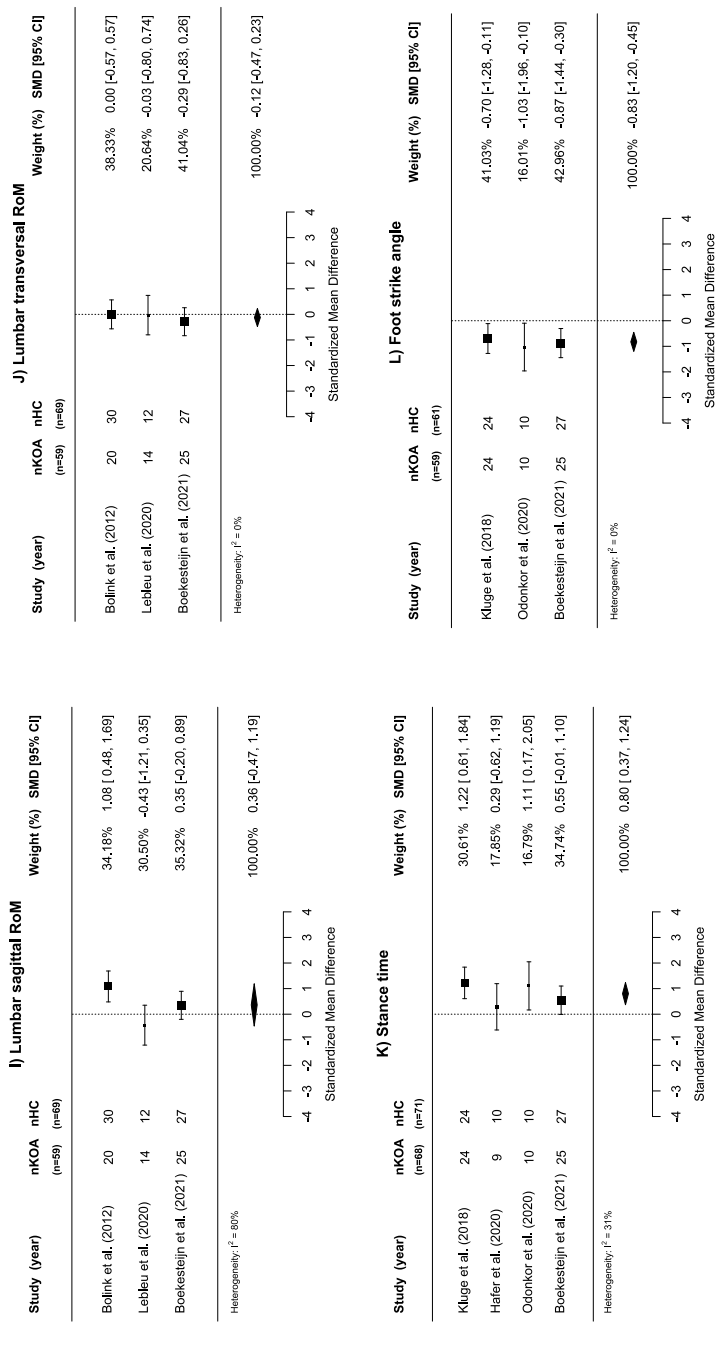

Figure 2 (continued): Forest plots for the comparison of gait parameters between individuals with knee osteoarthritis and healthy subjects. Negative standardized mean differences indicate lower values in individuals with knee OA compared to HC.
Note: ROM = range of motion

Non-linear dynamics

Three studies investigated gait dynamics by assessing stride-to-stride fluctuations using the fractal scaling index[29,38,39]. Two of these studies, where subjects walked for 9 and 11 minutes in a laboratory environment, found no differences in fractal dynamics between individuals with knee OA and healthy individuals[29,38]. However, one study investigating gait during free-living conditions found a significantly lower fractal scaling index in both lean and obese individuals with knee OA compared to HC[39].

Discussion

The most prominent difference between individuals with knee OA and HC in this study was a slower gait speed in individuals with knee OA, which resulted from a combination of smaller steps/strides with a longer duration. In addition, gait variability was slightly higher in individuals with knee OA. Kinematic differences between knee OA and HC were observed as a lower swing range of motion of the knee in the sagittal plane, less pelvic motion in the coronal plane, a lower foot strike angle, and a lower toe-off angle.

Effects of knee OA on spatiotemporal and kinematic outcomes

Our results regarding spatiotemporal gait differences between individuals with knee OA and HC are consistent with a previous meta-analysis of studies using optical motion capture systems[43]. This meta-analysis by Mills et al. reported differences between individuals with knee OA and HC of similar magnitude for gait speed, cadence, stride length, and stride duration in studies using optoelectronic systems. Since most inertial sensor systems have been validated against these systems[12], the consistency with our results is not surprising. However, a key difference is that in the current meta-analysis gait was mainly assessed outside these laboratory settings (Table 2), with assessments most frequently taking place in clinical, out-of-lab settings (e.g. outpatient clinics). The fact that this yields relatively similar results paves the way for future clinical applications of these gait assessments, with the benefit of inertial sensors being well-suited for testing that can be conducted on a larger scale in situations where expensive equipment is not available. Moreover, remote monitoring of gait may capture more natural, habitual walking behavior, independent of so-called "white-coat" effects[44] that may be present during single, snap-shot evaluation in the clinic.

The clinical relevance of spatiotemporal group differences as detected by inertial sensors is further highlighted by their absolute mean differences. The mean difference for gait speed – showing the largest SMD of all parameters – corresponded with -0.29 m/s in this study (Supplementary File 3). Considering that a 0.10 m/s reduction in walking speed is associated with poorer health status and a higher risk of disability[45], this absolute difference between groups is of clinical importance. Although gait speed is not specific to knee OA, when evaluated at multiple timepoints, gait speed could serve as general marker to either track physical functioning over time during disease progression, or to evaluate recovery after interventions.

All studies included in this review assessed gait at self-selected walking speed. While this paradigm results in clinically relevant information about differences in natural walking behavior, differences in gait speed between individuals with knee OA and HC complicates interpretation of differences on other spatiotemporal gait parameters. Statistical correction

for these gait speed differences may be inappropriate, and may have the undesired side-effect of removal of a meaningful part of the main effect (i.e. knee OA)[46]. In general, caution should be taken with interpreting the SMDs of spatiotemporal gait parameters in this study, as these effects are likely the combined result of knee OA and a related slower walking speed.

Besides changes in basic spatiotemporal parameters, a relatively small effect size for step/stride time variability was found in individuals with knee OA compared to HC. Variability of gait has often been assumed to be a marker for gait stability, with larger gait variability being predictive of future falls[47]. Nevertheless, this difference in variability is likely inflated as an effect of the lower gait speed that we found in individuals with knee OA[48,49]. Furthermore, with effect size in individual studies ranging from 0-2%, this effect likely falls within the measurement error of inertial sensors. As such, this between-group difference in variability is considered to be of minor clinical importance.

Step time asymmetry was not significantly different between groups, although it should be noted that large heterogeneity between studies was observed and the confidence interval of the SMD was just below zero. Asymmetries in knee kinematics and joint loading have previously been reported in OA populations[50,51]. Individuals with knee OA may adopt an asymmetrical gait pattern to lower joint loading of the affected leg. However, we did not find unequivocal evidence supporting a more asymmetric gait pattern in individuals with knee OA. Importantly, it should be noted that the literature is inconclusive about the validity and reliability of gait variability and asymmetry metrics derived from inertial sensors[12]. For gait variability specifically, it is important that a sufficient number of steps/strides are included in the analysis[52], preferably during continuous walking – in contrast to short, intermittent walks – or by only including steady-state gait phases. This may minimize the potential perturbing effects of gait initiation and changes in walking direction that may be present during walking paradigms in spatially confined spaces such as short hospital corridors (Table 2).

Analysis of kinematic parameters of the knee and trunk showed that individuals with knee OA walk with lower range of motion of the knee in the sagittal plane, while between-group differences in trunk movement were restricted to the frontal plane. Limited knee flexion during gait is a common characteristic of individuals with knee OA[43,53] and is likely more specific to knee OA than spatiotemporal gait deviations. Stiffness of the knee joint may also be present during stance, and may reflect a deliberate strategy to overcome dynamic knee joint instability[54]. While part of the effect of knee OA on knee kinematics may be explained by differences in gait speed[15], some studies have shown remaining differences between individuals with knee OA and HC at comparable walking speeds[55,56]. As such, sagittal knee joint kinematics could provide important parameters for objective gait evaluations for individuals with (end-stage) knee OA that can be obtained by placing inertial sensors at the thigh and shank. Nevertheless, more research is needed to validate the use of inertial sensors for obtaining knee kinematics in individuals with severe varus/valgus knees[57]. This is especially relevant for absolute joint angles (as opposed to range of motion metrics), since these are often based on assumptions regarding anatomical alignment or alignment of segments relative to gravity that may be less valid[16,58].

Kinematics of the trunk were most frequently measured at the pelvic/lumbar level. The range of motion captured by this lumbar sensor is thought to be an indirect measure reflective of compensatory strategies to reduce pain or overcome muscle weakness[3,21]. Limited frontal plane pelvic motion has indeed been associated with hip abductor weakness, a characteristic that is also found among individuals with knee OA[59]. Trunk motion at the level of the sternum or upper thorax was reported in only two studies, but these parameters could provide further insights into compensatory strategies such as lateral trunk lean[60,61]. Importantly, range of motion captured by lumbar and/or trunk sensors were previously found to be independent of walking speed[18].

Differences in foot kinematics were also observed between individuals with knee OA and HC. However, these parameters were previously found to be strongly related to stride length and gait speed[18]. Whether individuals with knee OA have affected foot kinematics remains thus unclear based on these results, as it seems likely that this effect is either the cause or an epiphenomenon of a lower stride length.

Methodological considerations

First, substantial differences in study designs were apparent between the included studies regarding the investigated study populations and procedures, which may all have contributed to the heterogeneity we observed in our meta-analysis. For example, individuals with both unilateral and bilateral OA were included in our analyses, with most studies aiming at including individuals with (isolated) unilateral knee OA, even though the majority of individuals with knee OA have complaints in more than one joint[62]. Secondly, individuals with mild to moderate OA (KL grade 1 and 2) were underrepresented in the literature (Table 2). This limits the external validity of the included studies (Table 3). Moreover, differences in disease severity make it more difficult to compare studies, as radiological disease severity influences gait parameters[63]. Due to confounding effects of sex[64] and age[65], it is also important that future studies use age- and sex-matched control groups or attempt to correct for these variables, which was not yet the case in all available studies (Table 2).

Regarding the study procedures, it could be recommended that besides assessment of gait at self-selected speed (as was the case in all included studies), gait parameters are compared between groups at a controlled, matched speed. This allows to better separate the true effects of knee OA from the effects of gait speed on gait parameters[66] without the need of (suboptimal) statistical corrections[46]. This can easily be achieved by instructing the control group to walk at a slower speed[15]. An important advantage of inertial sensors for gait assessment is that testing location is not constrained to laboratory-based settings. Nonetheless, most studies measured participants in relatively controlled settings, such as clinical hallways. Since daily life gait is known to be different from gait patterns observed in clinical or laboratory settings[67], it would be interesting to monitor gait remotely during daily life. With only two studies having applied inertial sensors in daily life (Table 2), this may be an important future direction for gait research in individuals with knee OA. Finally, considering the large variety in inertial sensors, possible configurations, and (often non-disclosed or customized) processing algorithms, it is of utmost importance that the validity and reliability of these systems is adequately addressed in each individual study. Open-source software packages to process raw inertial sensor data may significantly push the field forward, for example by increasing transparency and consistency among future studies.

The quality of the evidence provided by the current meta-analysis should be interpreted in light of all possible sources of biases. Limitations in the design and execution of the included studies (e.g. individual risk of bias), as discussed in the paragraphs above, may have influenced the overall SMDs that we obtained. Differences in methodology could also have contributed to the substantial heterogeneity that was observed for step/stride time, step time asymmetry, and knee swing flexion RoM. Other sources of bias, including indirectness and imprecision, were of less relevance for the current review as gait parameters were directly compared between individuals with knee OA and HC, and no a priori thresholds were set on the differences that we aimed to detect. It should however be noted that wide confidence intervals were observed for step time asymmetry, knee swing flexion RoM, and lumbar sagittal RoM. There is thus less certainty in the exact estimates of the SMDs for these parameters compared to those with narrow confidence intervals. Finally, publication bias may have been present. However, the low number of studies that reported each outcome (i.e. lower than 10 for all outcomes), precluded reliable publication bias assessment in the current review. This may have resulted in overrepresentation of studies reporting (significant) differences between individuals with knee OA and HC, inflating the SMDs.

Limitations and future perspectives

This current study had a number of limitations which merit attention. First, we were not able to conduct a subgroup analysis or to correct for OA severity, which is known to influence gait parameters. Hence, this review suffers from heterogeneity in population characteristics between studies, which may have influenced the SMDs that we obtained. Despite this, we think our results are still generalizable to the population of individuals with moderate to severe knee OA as this was the target population of most of the included studies. Secondly, we limited this review to level walking, whereas turning, stair climbing and sit-to-stand transfers are also relevant tasks for individuals with knee OA[57] that are easily measured with inertial sensors, and were investigated in some of the included studies[3,18,19,21,37]. Lastly, outcome metrics were predominantly limited to the spatiotemporal domain in our analysis. Since the evaluation of these simple spatiotemporal parameters does not necessitate the use of inertial sensors, research on more advanced gait measures is required to show the advantages of inertial sensors over timed performance-based tests. Multiple studies have investigated other (non-linear) parameters to assess gait in individuals with knee OA with inertial sensors (Table 3). Examples of this include symmetry/regularity parameters based on autocorrelation procedures[20,29,35], harmonic ratios[2,39,68], sample entropy[69], turning velocity[18], tibial/femoral acceleration[70,71], hip/ankle kinematics[15,30,33,37], and dual-task cost[18]. In addition, development of more advanced algorithms may enable the assessment of joint kinetics[72] and balance related measures, such as the margin of stability[73]. Future studies should continue to explore the potential value of these and other metrics for clinical gait assessments in individuals with knee OA using these inertial sensors.

Conclusions

Inertial sensors have been widely applied to study gait of individuals with knee OA both inside and outside the laboratory. However, gaps in literature were identified with respect to remote monitoring of gait, and the interpretation of effect sizes was limited by confounding effects of gait speed. Gait speed consistently showed large and clinically relevant deviations from healthy controls, and may be considered as a general marker for gait impairment in knee OA. More advanced gait parameters, including knee and trunk kinematics, revealed gait adaptations that may be more specific to individuals with knee OA, but effect sizes were relatively small or had wide confidence intervals. Until now, other potentially meaningful parameters that can easily be obtained with inertial measurement units in the same settings, such as thoracic trunk motion, turning parameters, and (non-linear) stability measures have received less attention.

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Supplementary File 1 – Search strategy

Full search code for all of the databases

Database	Full search
OVID Medline/ Embase	(exp Osteoarthritis, Knee/ OR exp Arthroplasty, Replacement, Knee/) AND (gait OR ambulat* OR walk*) AND (sensor OR wearable OR Inertial OR accelerom* OR acceleration OR gyrosc* OR magnetom* OR unobtrusive) AND (spatiotemporal OR joint angle OR kinematic* OR range of motion OR biomechanic* OR asymmetr* OR variability OR velocity OR gait speed)
Web of Science	(Knee Osteoarthritis OR Knee Replacement OR Knee Arthroplasty) AND (Gait OR Ambulat* OR Walk*) AND (Sensor OR Wearable OR Inertial OR Accelerom* OR Acceleration OR Gyrosc* OR Magnetom* OR Unobtrusive) AND (Spatiotemporal OR Joint angle OR Kinematic* OR Range of motion OR Biomechanic* OR Asymmetr* OR Variability OR Velocity OR Gait speed)
IEEE*	(Knee Osteoarthritis OR Knee Replacement OR Knee Arthroplasty) AND (Gait OR Ambulat* OR Walk*) AND (Sensor OR Wearable OR Inertial OR Accelerom* OR Acceleration OR Gyrosc* OR Magnetometer OR Unobtrusive) AND (Spatiotemporal OR Joint angle OR Kinematic* OR Range of motion OR Biomechanic* OR Asymmetr* OR Variability OR Velocity OR Gait speed)
CINAHL	((MH "Osteoarthritis, Knee") OR (MH "Arthroplasty, Replacement, Knee")) AND (gait OR ambulat* OR walk*) AND (sensor OR wearable OR inertial OR accelerom* OR acceleration OR gyrosc* OR magnetom* OR unobtrusive) AND (Spatiotemporal OR Joint angle OR Kinematic* OR Range of motion OR Biomechanic* OR Asymmetr* OR Variability OR Velocity OR Gait speed)

*= IEEE only allows 7 wildcards. The wildcard for "magnetometer" has therefore been removed

Detailed search strategy for one of the databases

No.	Search terms	Results
	Population	
#1	Osteoarthritis, Knee [MeSH]	22,003
#2	Arthroplasty, Replacement, Knee [MeSH]	26,343
#3	#1 OR #2	41,405
	Activity	
#4	Gait	67,596
#5	Ambulat*	189,275
#6	Walk*	213,237
#7	#4 OR #5 OR #6	290,692
	Sensor system	
#8	Sensor	115,742
#9	Wearable	16,837
#10	Inertial	10,832
#11	Accelerom*	20,238
#12	Acceleration	55,748
#13	Gyrosc*	2,225
#14	Magnetom*	6,054
#15	Unobtrusive	1,738
#16	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	210,194
	Outcome parameter	
#17	Spatiotemporal	33,641
#18	Joint angle	2,340
#19	Kinematic*	39,503
#20	Range of motion	73,978
#21	Biomechanic*	187,322
#22	Asymmetr*	52,197
#23	Variability	290,594
#24	Velocity	213,814
#25	Gait speed	5,616
#26	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	815,241
#27	#3 AND #7 AND #16 AND #26	98

Supplementary File 2 – Modified Downs and Black Checklist

Reporting

3. Are the characteristics of the patients included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.
   - Yes: 1
   - No: 0
5. Are the distributions of principal confounders (i.e. age and sex) in each group of subjects to be compared clearly described? Note: since BMI is inherently linked to the development of OA, it was not considered as a confounder.
   - Yes: 2
   - Partially: 1
   - No: 0
7. Does the study provide estimates of the random variability in the data for the main outcomes?
   - Yes: 1
   - No: 0

External validity

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
    - Yes: 1
    - No: 0
    - Unable to determine: 0

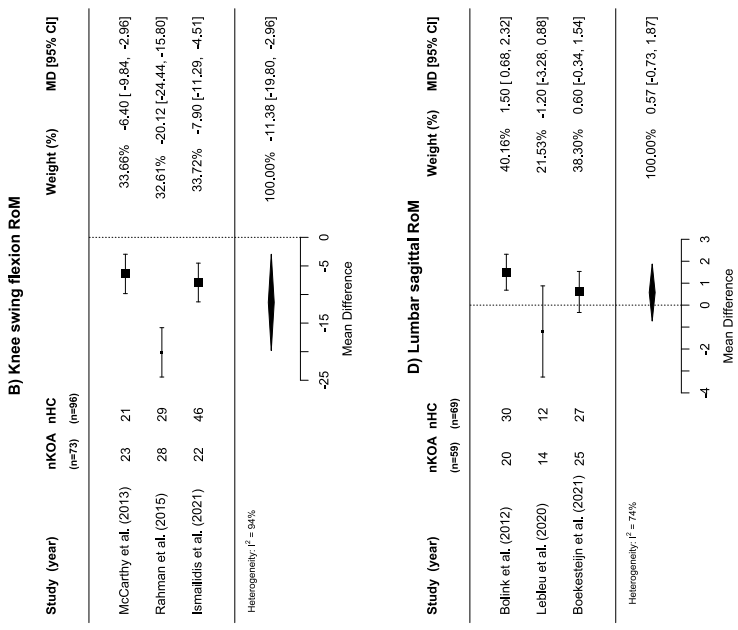
Internal validity – bias

15. Was an attempt made to blind those measuring the main outcome of the intervention (here: to the study groups)?
    - Yes: 1
    - No: 0
    - Unable to determine: 0
16. If any of the results of the study were based on "data dredging", was this made clear?
    - Yes: 1
    - No: 0
    - Unable to determine: 0
18. Were the statistical tests used to assess the main outcomes appropriate?
    - Yes: 1
    - No: 0
    - Unable to determine: 0
20. Were the main outcome measures used accurate (valid and reliable)?
    - Yes: 1
    - No: 0
    - Unable to determine: 0

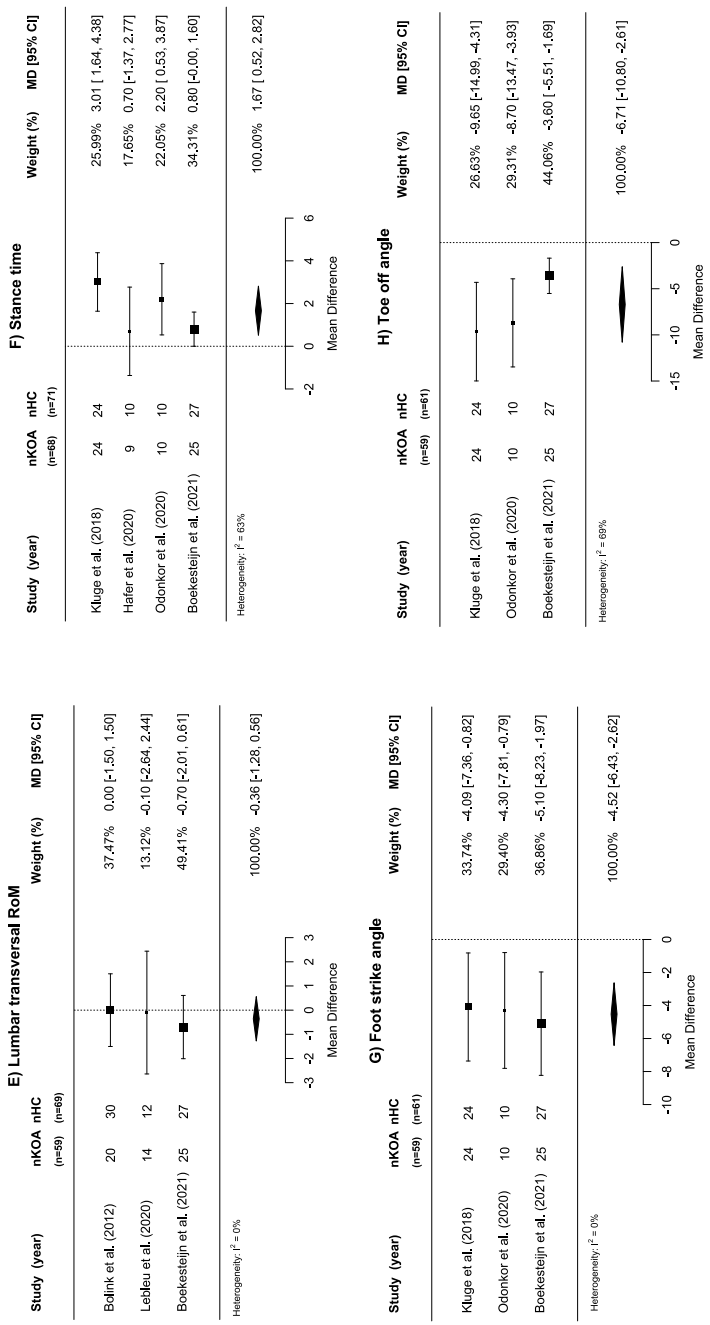
Internal validity – confounding

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
    - Yes: 1
    - No: 0
    - Unable to determine: 0
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
    - Yes: 1
    - No: 0
    - Unable to determine: 0

Supplementary File 3 – Forest plots with mean differences



Supplementary File 3 continued – Forest plots with mean differences



Supplementary File 4 – Summary characteristics of each individual study

Study (author)	Sample size		Mean (SD)	
	Knee OA	Healthy controls	Knee OA	Healthy controls
Gait speed (m/s)				
Boekesteijn *et al.*(2021)	25	27	0.98 (0.18)	1.24 (0.16)
Bolink *et al.* (2012)	20	30	0.85 (0.16)	1.29 (0.19)
Bolink *et al.* (2015)	20	20	0.98 (0.19)	1.30 (0.15)
Hafer *et al.* (2020)	9	10	1.18 (0.08)	1.33 (0.15)
Ismailidis *et al.* (2021)	22	46	0.95 (0.22)	1.24 (0.16)
Kierkegaard *et al.* (2015)	54	29	*1.18 (0.25)**	*1.40 (0.18)**
Kluge *et al.* (2018)	24	24	1.06 (0.24)	1.38 (0.18)
Odonkor *et al.* (2020)	10	10	1.1 (0.1)	1.3 (0.2)
Senden *et al.* (2011)	24	24	1.02 (0.19)	1.33 (0.16)
Staab *et al.* (2014)	12	7	0.74 (0.08)	1.27 (0.14)
Cadence (steps/min; strides/ min; Hz)				
Auvinet *et al.* (1999)	20	139	0.92 (0.08)	1.02 (0.07)
Boekesteijn *et al.*(2021)	25	27	102.4 (7.7)	113.2 (9.3)
Bolink *et al.* (2012)	20	30	98.1 (9.8)	112.0 (7.7)
Bolink *et al.* (2015)	20	20	105.9 (11.3)	114.8 (8.0)
Hafer *et al.* (2020)	9	10	55.3 (3.4)	58.1 (4.8)
Ismailidis *et al.* (2021)	22	46	101.3 (10.9)	112.9 (9.1)
Lebleu *et al.* (2020)	14	12	50.7 (5.8)	60.4 (16.8)
Odonkor *et al.* (2020)	10	10	107.1 (6.7)	116.2 (9.2)
Senden *et al.* (2011)	24	24	1.69 (0.18)	1.92 (0.17)
Staab *et al.* (2014)	12	7	97.8 (11.5)	116.3 (7.4)
Step/stride time (s)				
Bolink *et al.* (2012)	20	30	0.62 (0.06)	0.54 (0.04)
Bolink *et al.* (2015)	20	20	0.57 (0.06)	0.53 (0.04)
Clermont *et al.* (2016)	15	15	0.53 (0.03)	0.50 (0.04)
Ismailidis *et al.* (2021)	22	46	1.20 (0.13)	1.07 (0.09)
Kluge *et al.* (2018)	24	24	1.14 (0.09)	1.02 (0.06)
Lebleu *et al.* (2020)	14	12	1.20 (0.14)	1.15 (0.69)
McCarthy *et al.* (2013)	23	21	1.12 (0.09)	1.06 (0.11)
Rahman *et al.* (2015)	28	29	1.31 (0.16)	1.07 (0.09)
Tanimoto *et al.* (2017)	12	11	1.11 (0.13)	1.12 (0.17)
Step/stride length (m)				
Boekesteijn *et al.* (2021)	25	27	1.15 (0.17)	1.32 (0.14)
Bolink *et al.* (2012)	20	30	0.52 (0.07)	0.69 (0.09)
Bolink *et al.* (2015)	20	20	0.55 (0.07)	0.68 (0.07)
Hafer *et al.* (2020)	9	10	1.29 (0.14)	1.38 (0.10)
Ismailidis *et al.* (2021)	22	46	1.13 (0.21)	1.32 (0.12)
Kluge *et al.* (2018)	24	24	1.19 (0.23)	1.40 (0.15)
Senden *et al.* (2011)	24	24	0.60 (0.08)	0.69 (0.08)
Odonkor *et al.* (2020)	10	10	1.2 (0.1)	1.4 (0.2)

*= Data was not available as mean (SD): in Kierkegaard et al. the data had a non-normal data distribution, and raw data was not available after contacting the author. This data is presented as median (IQR)

Supplementary File 4 – Summary characteristics of each individual study (continued)

Study (author)	Sample size		Mean (SD)	
	Knee OA	Healthy controls	Knee OA	Healthy controls
Step/stride time variability (%)				
Boekesteijn *et al.* (2021)	25	27	2.33 (0.89)	1.79 (0.55)
Bolink *et al.* (2012)	20	30	6.13 (3.34)	4.05 (3.09)
Bolink *et al.* (2015)	20	20	0.06 (0.03)	0.04 (0.03)
Kluge *et al.* (2018)	24	24	3.40 (1.81)	3.11 (1.05)
Senden *et al.* (2011)	24	24	2.9 (1.4)	2.3 (1.9)
Tanimoto *et al.* (2017)	12	11	2.84 (1.18)	2.58 (0.93)
Step time asymmetry (%)				
Boekesteijn *et al.* (2021)	25	27	3.46 (2.40)	2.65 (1.95)
Bolink *et al.* (2012)	20	30	0.42 (0.45)	0.48 (0.57)
Bolink *et al.* (2015)	20	20	5.05 (2.30)	2.50 (1.84)
Senden *et al.* (2011)	24	24	5.8 (4.6)	3.4 (3.2)
Knee swing range of motion (deg)				
Ismailidis *et al.* (2021)	22	46	50.0 (7.3)	57.9 (5.1)
McCarthy *et al.* (2013)	23	21	54.8 (5.5)	61.2 (6.1)
Rahman *et al.* (2015)	28	29	42.51 (10.18)	62.63 (5.77)
Lumbar coronal range of motion (deg)				
Boekesteijn *et al.* (2021)	25	27	7.0 (2.5)	7.9 (2.3)
Bolink *et al.* (2012)	20	30	4.9 (1.8)	8.4 (3.87)
Bolink *et al.* (2015)	20	20	6.7 (1.8)	8.6 (2.8)
Lebleu *et al.* (2020)	14	12	5.3 (2.2)	7.5 (1.8)
Lumbar sagittal range of motion (deg)				
Boekesteijn *et al.* (2021)	25	27	5.9 (1.9)	5.3 (1.5)
Bolink *et al.* (2012)	20	30	5.4 (1.6)	3.9 (1.18)
Lebleu *et al.* (2020)	14	12	5.9 (2.8)	7.1 (2.6)
Lumbar transverse range of motion (deg)				
Boekesteijn *et al.* (2021)	25	27	7.7 (2.5)	8.4 (2.3)
Bolink *et al.* (2012)	20	30	8.1 (2.7)	8.1 (2.59)
Lebleu *et al.* (2020)	14	12	7.5 (3.4)	7.6 (3.2)
Stance time (% gait cycle)				
Boekesteijn *et al.* (2021)	25	27	60.4 (1.8)	59.6 (1.0)
Hafer *et al.* (2020)	9	10	63.6 (2.1)	62.9 (2.5)
Kluge *et al.* (2018)	24	24	66.41 (3.10)	63.40 (1.45)
Odonkor *et al.* (2020)	10	10	64.1 (2.5)	61.9 (1.0)
Foot strike angle (deg)				
Boekesteijn *et al.* (2021)	25	27	19.2 (5.9)	24.3 (5.6)
Kluge *et al.* (2018)	24	24	15.59 (5.91)	19.68 (5.66)
Odonkor *et al.* (2020)	10	10	26.1 (3.9)	30.4 (4.1)
Toe-off angle (deg)				
Boekesteijn *et al.* (2021)	25	27	33.7 (4.3)	37.3 (2.4)
Kluge *et al.* (2018)	24	24	56.55 (12.11)	66.2 (5.62)
Odonkor *et al.* (2020)	10	10	62.4 (6.1)	71.1 (4.7)

Supplementary File 5 – Details on the sensor algorithm of the individual studies

Study (year)	Algorithm description
Auvinet *et al.* 1999	Stable walking periods (~19/20 gait cycles) were analyzed. A Fourier rapid transform was performed on vertical acceleration data to derive the fundamental frequency. Cycle frequency was defined as half the fundamental frequency.
Barden *et al.* 2016	Nine minute walking trials were reduced to 6 min by removing the first and last 90s. Accelerations on all 3 axes were filtered using a zero-leg 4th order Butterworth low-pass filter (cut-off = 10 Hz). A negative peak-detection algorithm was used on the anteroposterior acceleration to determine heel strikes, as described in [1]. From the obtained series of heel strikes, step time and stride time were determined. A median filter was used to remove potential outliers.
Boekesteijn *et al.* 2021	A non-disclosed, validated [2] algorithm (e.g. Mobility Lab v2.0) was used to process the raw inertial data, and extract the gait parameters of interest.
Bolink *et al.* 2012	Start and end of the walking trial were manually selected. Heel strikes were detected based on the anteroposterior acceleration signal, using an algorithm described in [3]. Gait event detection was manually verified. The first and last two steps were deleted due to acceleration/deceleration phases. Based on these gait events, the time to achieve the task, and step count, all spatiotemporal parameters were derived. Lumbar kinematics were calculated from the accelerometer and gyroscope signal, using the algorithm described in [4].
Bolink *et al.* 2015	Similar methods as Bolink *et al.* 2012 (see above).
Chapman *et al.* 2019	Sensor data was low-pass filtered using a 5th order Butterworth filter (cut-off = 5 Hz). Accelerations measured at the thigh and shank were converted to 3D vectors, and an angle was computed between these 3D vectors and gravity. Using equal gravitational reference, comparison of the vector from the thigh sensor and the shank sensor yielded a single knee joint angle. This angle incorporates true knee flexion plus errors related to dynamic accelerations and knee joint motion in other planes (e.g. frontal/transversal). These errors were acknowledged in this study, but considered to be low. Knee flexion angles were computed continuously during the monitoring period. Gait periods were located by frequency analysis of one minute intervals and fast Fourier transforms of each of these intervals. The interval with the largest 0.75-2.25 Hz content magnitude was selected as gait period. Gait events were automatically located [no reference/ further description], and strides were extracted from these gait periods. Strides were normalized as % of gait cycle, and knee flexion curves were averaged over the repeated strides.
Clermont *et al.* 2016	Data was reduced to nine minutes by deleting the first 15s and last 45s, and was low-pass filtered using a 4th order Butterworth filter (cut-off = 10 Hz). Negative peaks of the anteroposterior acceleration signal were used to detect heel strikes [1] and compute step and stride time for each leg.
Hafer *et al.* 2020	Gait events were detected using the vertical acceleration data from the foot sensor in the earth frame (aligned with gravity). This data was first passed through a 1D continuous wavelet transform, and the absolute value of the first wavelet was low-pass filtered using a 2nd order Butterworth filter (cut-off = 4 Hz). Peaks in this signal were identified as gait events, with the assumption that time between an ipsilateral heel strike and toe-off is longer than the time between toe-off and heel strike. Foot accelerometer data were integrated on a stride-to-stride basis to find linear velocity and displacement. The integration was performed using a zero velocity update algorithm similar to [5], and the obtained velocity was corrected for sensor drift. Stride length was defined as the magnitude of horizontal displacement. Spatiotemporal parameters were derived from the gait events, with gait speed defined as stride length divided by stride time. Knee range of motion was calculated from thigh and shank angular velocity in the sensor frame. Angular velocity around the mediolateral axis was integrated between heel strikes and drift corrected. Knee flexion was then calculated by subtracting shank angular displacement from thigh angular displacement. Knee flexion range of motion was defined as the difference between the minimum and maximum knee angular displacement.
Ismailidis *et al.* 2020	Spatiotemporal and kinematic parameters were derived from the manufacturer's software (Hasomed) [no reference/further description].
Ismailidis *et al.* 2021	Spatiotemporal and kinematic parameters were derived from the manufacturer's software (Hasomed), according to [6] and validated in [7,8].
Kierkegaard *et al.* 2015	Blinded data analysis was performed using peak-detection algorithms for the anteroposterior and vertical acceleration peaks [3]. Spatiotemporal measures and lumbar kinematics were derived in a similar manner as in Bolink *et al.* (2012 & 2015) [no further description].
Kluge *et al.* 2018	Strides were detected using the multi-dimensional sub sequence dynamic time warping approach. This method nonlinearly matches time series (with different lengths) to a predefined template, as described in [9]. Heel strikes were detected based on the minima in anteroposterior acceleration of the foot within a region of interest (e.g. the interval between the steepest negative slope and steepest positive slope in the gyroscope signal around the mediolateral axis), and toe-offs using the zero-crossings of the angular velocity around the mediolateral axis [10]. Data from the sensor frame were converted to the earth frame with removal of gravity. Feet trajectories were calculated by double integration, accounting for sensor drift as described in [11]. These obtained trajectories, orientations, and gait events were used to calculate the gait parameters. The system has been validated in healthy and affected (Parkinson's Disease) gait [12].

Supplementary File 5 (continued)

Study (year)	Algorithm description
Lebleu *et al*. 2021	A semi-automatic threshold method was used to segment each task based on the accelerometer signal (flat zone detection, peak detection - see [13]). A combination of vertical shank acceleration and hip and knee angular movement was used to detect gait events. Three gait cycles were normalized on 0-100 points and averaged. Spatiotemporal parameters were derived from the gait events. Joint angles were calculated based on a validated method, using the walking functional sensor-to-segment calibration method described in [14].
McCarthy *et al*. 2013	Data analysis was performed using Poseidon software [reference to dysfunctional link of the Gait Walk system]. Knee joint angles were calculated for the entire test. From this, a section with at least 7 strides of steady-state walking was chosen. The stride with the lowest error to all strides (e.g. 'typical stride') was analyzed.
Odonkor *et al*. 2020	Validated algorithms (e.g. rule-based stance event detection algorithms based on foot kinematics as described in [15, 16]) were used to calculate gait events. Velocity and position of the foot sensor by determined by numerical integration of gravity-corrected acceleration data, and was drift corrected using zero velocity updates as described in [17]. Spatiotemporal parameters were calculated based on gait events and the foot sensor trajectory. Heel strike and toe-off angles were estimated based on integration of de-drifted angular velocity as described in [18].
Rahman *et al*. 2015	Sensor data was analyzed to calculate thigh and shank sagittal and coronal angles, spatiotemporal parameters [no reference/ further description]. Discrete parameters were derived from a 'typical stride'.
Senden *et al*. 2011	Gait parameters were calculated using a commercial, non-disclosed algorithm, based on [19].
Staab *et al*. 2014	Accelerometer data was post-processed using a lowpass filter, fast Fourier transform, and spectral analysis. Gravity was used to calibrate the sensors. Drift correction and calibration of the sensors was performed in accordance with [20,21] . Symmetry parameters were calculated for foot-fall and trunk measurements [no description on gait event detection using sensor data]. Acceleration data was integrated to determine velocity and position.
Straaten van der *et al*. 2020	3D joint angles were directly derived from the MVN BIOMECH software. Participants' body dimensions were measured to scale the model, and a static calibration was performed to align the sensor to the body segments [no further description/ reference to validity of commercial algorithm]. Kinematics were normalized from 0 to 100% using custom algorithms.
Tadano *et al*. 2016	The H-Gait system - first reported in [22] - was used in this study. This system uses a wire frame model to measure lower limb posture during gait, which is based on body measurements, calibration of the coordinate systems, and the sensor data from each segment (detailed description in [23]). An initial static phase was required to estimate each sensors inclination with respect to gravity, based on [24]. This static phase was then used to establish the rotation matrix between the sensor coordinate system and the body segments coordinate systems. During walking, gyroscope data was integrated to determine angular displacement and the updated sensor orientation. From the obtained gait model, joint angles could then be estimated. Details on gait event detection methods of this system were described in [25]. Heel strikes were detected by angular velocity peaks around the mediolateral axis of the shank gyroscope and toe-off by measuring the negative peaks of the relative distance of the toe position to the origin of the pelvis coordinate system. Based on these gait events and the wire frame model, spatiotemporal parameters could be determined.
Tanimoto *et al*. 2017	Angular velocity in the sagittal plane was low-pass filtered using a 4th order Butterworth filter (cut-off = 20 Hz). Angular velocity peaks during swing were extracted. Heel contact points were identified as anteroposterior acceleration peaks. Stride time was defined as the duration between two consecutive heel strikes.
Vangeneugden *et al*. 2020	Data was filtered using a 7th order low-pass Butterworth (cut-off = 0.08 Hz). Static (< 5g) and dynamic phases (≥ 5g) were discriminated based on a 1-second average of the summed magnitude of acceleration vectors. Walking sequences were automatically extracted from the continuous kinematic traces after smoothing of the thresholded traces (pseudo-Gaussian function with four passes of the same sliding average in a 20 seconds window). The kinematic traces were thresholded with a factor 5 to detect walking and a factor 20 to segregate walking from running and or cycling. Walking bouts longer than 1 min were selected and the kinematic traces were concatenated into one continuous trace. The first and last 10s were omitted to account for the width of the smoothing window. From these continuous traces, peaks in the anteroposterior acceleration signal were detected. Left and right steps could reliably be detected, and step and stride time could subsequently be calculated.
Zhang *et al*. 2016	Sensor data was analyzed using Gait-View 3.8 (Minisun) [no reference/ further description]. Data from specific time intervals (10 steps) were selected from steady-state period

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Chapter 4

Objective monitoring of functional recovery after total knee and hip arthroplasty using sensor-derived gait measures

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Abstract

Background
Inertial sensors hold the promise to objectively measure functional recovery after total knee (TKA) and hip arthroplasty (THA), but their value in addition to patient-reported outcome measures (PROMs) has yet to be demonstrated. This study investigated recovery of gait after TKA and THA using inertial sensors, and compared results to recovery of self-reported scores of pain and functioning.

Methods
PROMs and gait parameters were assessed before and at two and fifteen months after TKA (n=24) and THA (n=24). Gait parameters were compared with healthy individuals (n=27) of similar age. Gait data were collected using inertial sensors on the feet, lower back, and trunk. Participants walked for two minutes back and forth over a 6m walkway with 180° turns. PROMs were obtained using the Knee Injury and Osteoarthritis Outcome Scores and Hip Disability and Osteoarthritis Outcome Score.

Results
Gait parameters recovered to the level of healthy controls after both TKA and THA. Early improvements were found in gait-related trunk kinematics, while spatiotemporal gait parameters mainly improved between two and fifteen months after TKA and THA. Compared to the large and early improvements found in of PROMs, these gait parameters showed a different trajectory, with a marked discordance between the outcome of both methods at two months post-operatively.

Conclusion
Sensor-derived gait parameters were responsive to TKA and THA, showing different recovery trajectories for spatiotemporal gait parameters and gait-related trunk kinematics. Fifteen months after TKA and THA, there were no remaining gait differences with respect to healthy controls. Given the discordance in recovery trajectories between gait parameters and PROMs, sensor-derived gait parameters seem to carry relevant information for evaluation of physical functioning that is not captured by self-reported scores.

Introduction

Walking is essential for many activities of daily living, and a good walking capacity is key for participation in society. Previous reports have identified walking speed as 'sixth vital sign', given its correlation with essential health parameters, including quality of life[1], risk of future hospitalization[2], and mortality[3]. In individuals with end-stage osteoarthritis (OA) of the knee and hip, walking capacity is reduced[4], thereby leading to decreased physical functioning and a lower quality of life[5]. As final step in the treatment of severe knee and hip OA, total joint arthroplasty can be performed in order to resolve OA-related symptoms (e.g. pain, stiffness, instability) and improve physical functioning.

Although total knee arthroplasty (TKA) and total hip arthroplasty (THA) are very successful and cost-effective procedures[6], a subset of patients is dissatisfied with treatment outcome[7-9]. In addition to patients with identified complications, this includes patients who had an uneventful procedure, but did not achieve their expected level of functional recovery[7]. Early identification of individuals at-risk of limited functional recovery is crucial in order to enable clinicians to intervene timely, and may help to readjust patient expectations[10]. However, it has been challenging to identify these patients. In part, this is due to a lack of outcomes of physical functioning with good psychometric properties[11]. Current diagnostics (e.g. radiographs, physical exam, self-reported outcomes) are limited to static or non-weightbearing situations, or are not necessarily reflective of someone's actual performance during daily life activities[12,13]. Moreover, patient-reported outcomes (PROMs) are inherently subjective, largely influenced by pain, and suffer from early ceiling effects[14]. Although PROMs often contain subscales related to limitations in activities of daily life, such as KOOS/HOOS-ADL or WOMAC function score, these outcomes seem to be more reliant on a patients' own reflections on their capacity rather than their actual performance[13]. Hence, there is a need for objective data that can bridge this gap in clinical assessment.

As an alternative to these subjective scores, performance-based tests have been proposed to objectively capture physical functioning. For example, evaluation of sit-to-stand transfers, walking short distances, and stair negotiation has been endorsed by the OARSI as core-activities for individuals with knee and hip OA[15]. While these tests are well-suited to quickly obtain a global picture of a patient's physical functioning, they are limited to a single outcome measure, being the time to perform the task or activity, completed distance, or number of repetitions. These tests provide no information about compensations or underlying biomechanics relevant to the performance, and thus may lack important details. Wearable, inertial sensors, are promising tools to instrument performance-based tests in order to obtain more detailed insights into physical functioning. These inertial sensors are easy to use, have been proven to be valid and reliable[16], do not require lengthy procedures or specialized laboratories, and can be used in clinal settings or even remotely in the home environment[17]. Not surprisingly, inertial sensors have gained interest over the past few years to objectively monitor changes in physical functioning after total knee and hip arthroplasty[18,19]. In particular, the focus has been on studying gait recovery[18,19], potentially due to the fact that gait parameters are predictive of limitations in other activities of daily living[20] and gait improvements are an important goal for patients after TKA and THA[21]. In the same settings, turning could also be evaluated[22], which has been suggested to be even more sensitive to sensorimotor impairments than straight ahead gait[23]. However, before such technologies can be clinically adopted, it is important that the

derived outcome measures fulfil the following requirements: they must 1) be sensitive to pre-operative impairment, 2) be responsive to interventions aimed at improving mobility, and 3) provide clinically relevant information about physical functioning.

Multiple gait and turning parameters derived from inertial sensors have shown to be sensitive to mobility impairment in end-stage knee and hip OA[22]. The next step herein is to evaluate responsiveness of these parameters to unilateral TKA and THA, and to assess whether post-operative function recovers to the level of healthy individuals. While recovery of gait has previously been investigated using inertial sensors at different timepoints after TKA[13,17,24-28] and THA[12,29-31], a comprehensive study is lacking that maps the recovery trajectory – including turning capacity – at multiple timepoints matching routine follow-up after TKA and THA. In addition, there is a lack of clarity whether gait can be assumed to be 'normal' one year after joint replacement[32-34]. Finally, little is known about how gait recovery compares to self-reported recovery of physical functioning (e.g. PROMs). Therefore, the aims of this study were threefold: 1) to investigate gait recovery at two and fifteen months after TKA and THA using inertial sensors, 2) to compare gait 15 months after TKA and THA with data from healthy participants, and 3) to compare recovery trajectories between objective gait parameters and self-reported scores physical functioning.

Methods

Participants

Individuals with end-stage OA scheduled for TKA (n=24) or THA (n=24) at the Sint Maartenskliniek participated in this study. A group of healthy controls (HC; n=27) within the same age range of 50 to 75 years old was recruited from the community for reference purposes. Healthy participants had no pain in the lower extremities, nor were they familiar with a clinical diagnosis of knee or hip OA. All participants had to be able to walk for more than two minutes without the use of any assistive device. Exclusion criteria were: 1) joint replacement within a year following surgery (including revisions), or symptomatic OA in another weight-bearing joint than the joint scheduled for surgery, 2) BMI > 40 kg/m^2, and 3) any other musculoskeletal or neurological impairment interfering with gait or balance. Participants who received any other joint replacement to the lower extremities, or had a revision surgery within the period of fifteen months follow-up, were labelled as lost to follow-up. In these cases, data that had been collected until the time of the second surgery was still used for analysis. Written informed consent was obtained from all participants prior to testing. This study was exempt from ethical review by the CMO Arnhem/Nijmegen (2018-4452) as it was not subject to the Medical Research Involving Human Subjects Act (WMO). All study procedures were conducted in accordance with the Declaration of Helsinki.

Power calculation

Sample sizes were based on the smallest difference that we aimed to detect in this study, which was the difference in gait parameters between individuals 15 months after arthroplasty and HC. Effect sizes for this comparison were informed by studies from Senden et al.[25] and Kluge et al.[27]. When using a standardized mean difference for stride length of 1.1, a power of 80%, and a significance level of 0.05, 22 participants were required per group. To account for potential drop-outs, 24 individuals were recruited for each study group.

Surgical procedure

TKA was performed using the medial parapatellar approach. All individuals scheduled for TKA received the Genesis II posterior stabilized knee prosthesis (Smith & Nephew, Memphis, TN). The patella was resurfaced in 58% of the patients. THA was performed using the posterolateral approach. Specific types of hip implants differed among individuals scheduled for THA and are listed in Supplementary File 1. In total, TKA was performed by seven different surgeons in this study, whereas THA was performed by ten different surgeons. All patients followed an enhanced recovery protocol with mobilization on the day of surgery and hospital discharge within two days.

All patients were referred to out-of-hospital physical therapy, which was focused on optimizing functionality, mobility, muscle power, coordination, stability, and walking improvement. Although physical therapy protocols were not standardized, patients usually continued physical therapy for 6-12 months, until their functional goals had been reached.

Demographic and clinical assessment

Severity of radiological OA was determined using Kellgren and Lawrence (KL) grades[35] as scored by JS and VB. Baseline anthropometric characteristics (e.g. body mass, height, and BMI) were obtained during the pre-operative screening visit. In addition, PROMs were assessed using the Knee Injury and Osteoarthritis Outcomes Score (KOOS) for TKA[36] and Hip Disability Osteoarthritis Outcome Score (HOOS)[37] for THA patients. More specifically, HOOS and KOOS subscales "Pain" and "Activities of Daily Living (ADL)" were used to represent pain and physical functioning. PROMs and gait were assessed pre-operatively – on the same day as the pre-operative screening visit – and at two and fifteen months follow-up. Follow-up measurements were initially set to take place at one year, but measurements were delayed with three months due to the COVID-19 pandemic. Timepoints of follow-up were chosen to match routine follow-up after TKA and THA in the Netherlands, and roughly reflect the moments when patients can walk independently without an assistive device (e.g. 2 months) and when full recovery has been achieved (e.g. 1 year). For HC, gait was investigated at only one occasion.

Gait protocol

Experimental procedures of the gait assessments were similar to the methods described in Boekesteijn et al.[22]. Four inertial sensors (Opal V2, APDM Inc., Portland, OR) were attached to the dorsum of both feet, the waist (sacrolumbar level), and the sternum. Participants walked back and forth along a six meter trajectory making 180° turns for a total duration of two minutes (Figure 1). Gait tests were performed at comfortable, self-selected speed.

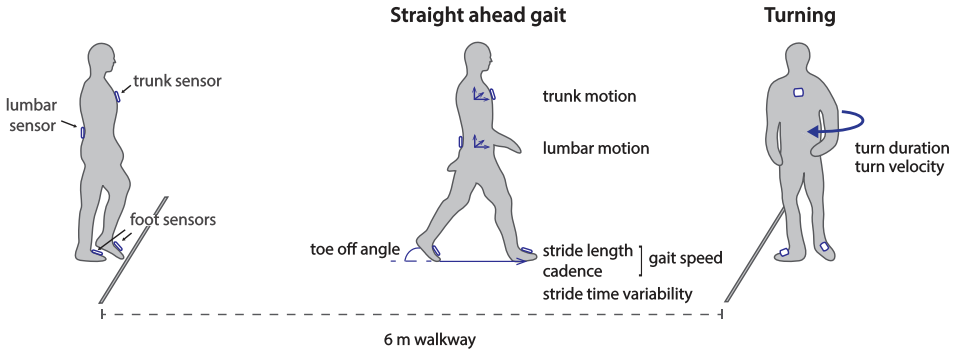

Figure 1: Overview of the experimental set-up and outcome parameters. Wearable inertial sensors were used to capture gait parameters during a 2 min walk test over a six meter walkway with 180 degree turns. The figure is adapted from Boekesteijn et al.[22]

Data analysis

Raw inertial data was processed using validated Mobility Lab v2 software[38]. Turning steps were separated from straight walking based on the gyroscope data of the lumbar sensor[39]. Gait parameters were calculated for each stride during steady-state walking phases, excluding the two steps preceding and following a turn. Parameters were summarized as mean value of all valid strides or turns. Based on non-redundancy and size of the difference between individuals with end-stage knee and hip OA and HC as found previously[22], the following outcomes were extracted (Figure 1): 1) gait speed, 2) stride length, 3) cadence 4), step time asymmetry, 5) stride time variability, 6) peak turning velocity, 7) lumbar sagittal range of motion, 8) lumbar coronal range of motion, and 9) trunk coronal range of motion. Parameters were only evaluated for the TKA or THA group in case they were previously found to be sensitive to mobility impairment in knee or hip OA[22]. For this reason, step time asymmetry, lumbar sagittal range of motion, and lumbar coronal range of motion were not evaluated in the TKA group.

Statistical analysis

Recovery trajectories of gait parameters and KOOS/HOOS scores were visualized on group level by the mean and 95% confidence intervals (CI). Linear mixed models with gait parameters and KOOS or HOOS scores as dependent variable, time as two independent dummy variables (e.g. T2 and T15), and subject ID as random effect factor were constructed to investigate the effect of time on gait and KOOS/HOOS scores for TKA and THA separately. Addition of random slopes was evaluated, but these were not included in the final model for reasons of parsimony, as this did not contribute to a better model fit. Gait parameters of TKA and THA groups were compared with HC at 15 month follow-up using an independent samples t-test or non-parametric Mann-Whitney U test in case data was not normally distributed. Inferences of statistical significance were based on $p<0.05$. Since multiple outcome parameters were used for the same construct (e.g. gait) we controlled the family-wise error rate using the Hommel procedure[40], by adjusting the p-values for the number of gait parameters involved in each comparison. To assess discrepancies between gait and self-reported scores of physical functioning, we compared trajectories between gait speed, which was found to be most sensitive to gait impairment in knee and hip OA[22], and KOOS/HOOS-ADL scores. Meaningful improvements were defined as a change in gait speed >0.10 m/s[41] and a change in KOOS/HOOS ADL score >20 points[42]. Data were processed in Python 3.8.3 and statistical analyses were conducted in RStudio 3.6.1 using the lme4 package (version 1.1-26)[43].

Results

Participant characteristics

The study groups did not differ significantly in age, sex, height, or BMI (Table 1). Compared to HC, body mass was significantly higher in individuals scheduled for TKA and THA. All individuals scheduled for TKA or THA had moderate to severe OA (KL grades 3 or 4). In total we had missing data for eleven participants. Three participants had a complication within the study window. For details regarding missing data and complications, see Supplementary File 1.

Table 1 : Baseline characteristics

	TKA (n=24)	THA (n=24)	HC (n=27)	Main effect	Post-hoc
Age (y)	63 [61, 66]	64 [62, 67]	66 [63, 68]	F(2,72)=0.81, p=0.448	
Sex (M:F)	12:12	16:8	13:14	x^2 (2, N=75)=2.07, p=0.355	
Height (m)	1.73 [1.69, 1.77]	1.75 [1.72, 1.79]	1.72 [1.68, 1.75]	F(2,72)=0.98, p=0.381	
Body mass (kg)	84.6 [78.6, 90.6]	86.0 [78.1, 94.0]	75.7 [71.5, 80.0]	F(2,72)=3.66, p=0.031	TKA vs. HC: t(49)=2.527; p=0.015 THA vs. HC: t(49)=2.428; p=0.019
BMI (kg/m^2)	28.2 [26.6, 29.9]	27.9 [25.6, 30.2]	25.7 [24.5, 26.8]	F(2,72)=2.91, p=0.060	
KL score (I:II:III:IV)	0:0:8:16	0:0:6:18	-		

Note: TKA = total knee arthroplasty, THA = total hip arthroplasty, HC = healthy controls, BMI = body mass index, KL = Kellgren Lawrence. Data are presented as mean [95% CI]

Recovery of gait after arthroplasty

Two months after surgery, gait speed, stride length, and cadence were not significantly different from baseline, both after TKA and THA (Table 2; Figure 2A-C). Peak turning velocity improved with 19.1 deg/s (95% CI: 6.9, 31.5) in the first two months after THA, but not after TKA (Table 2). There were no changes in step time asymmetry within the first two months after THA (Table 2), nor were there changes in stride time variability after TKA and THA at this timepoint (Table 2). As for kinematics of the trunk, trunk coronal RoM was slightly lower two months after TKA (mean diff: -1.0 deg, 95% CI: -1.6, -0.3) compared to pre-operatively, whereas lumbar sagittal RoM was lower two months after THA (mean diff: -1.9 deg, 95% CI: -3.0, -0.8) (Table 2).

Between two and fifteen months, large improvements in gait speed, cadence, and stride length were observed after both TKA and THA (Table 2; Figure 2A-C). For gait speed, the gain between two and fifteen months was 0.22 m/s (95% CI: 0.15, 0.29) after TKA and 0.14 m/s (95% CI: 0.06, 0.20) after THA. Peak turning velocity did not change significantly (mean diff: 17.4 deg/s, 95% CI: 1.7, 33.0, p_{corr} = 0.105) between two and fifteen months after TKA. There were no significant improvements in turning velocity between two and fifteen months after THA (Table 2). Step time asymmetry did not change between two and fifteen months after THA. There were no changes in stride time variability, or trunk coronal RoM between two and fifteen months after TKA and THA (Table 2). Individuals after THA showed an increase of 1.4 degrees (95% CI: 0.6, 2.1) in lumbar coronal RoM between two and fifteen months. Finally, none of the gait parameters were significantly different from HC at fifteen months after TKA and THA (Table 3; Figure 2A-I).

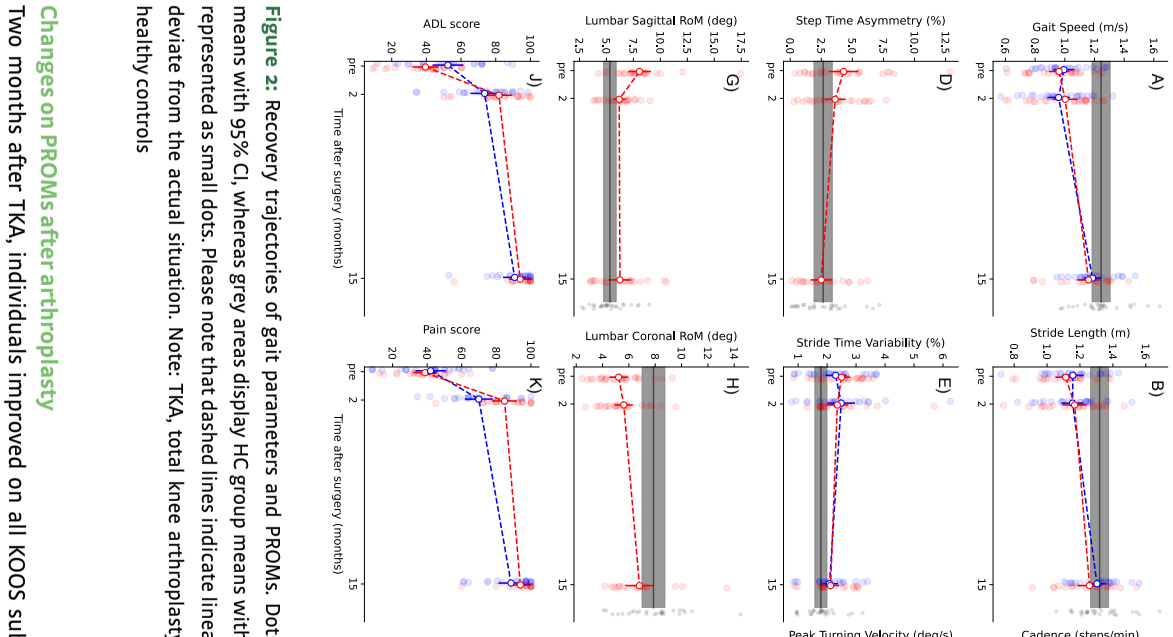

Figure 2: Recovery trajectories of gait parameters and PROMs. Dots with error bars represent group means with 95% CI, whereas grey areas display HC group means with 95% CI. Individual datapoints are represented as small dots. Please note that dashed lines indicate linear recovery trajectories, which may deviate from the actual situation. Note: TKA, total knee arthroplasty; THA, total hip arthroplasty; HC, healthy controls

Changes on PROMs after arthroplasty

Two months after TKA, individuals improved on all KOOS subscales, except for 'Symptoms' (Table 4). For all other subscales, self-reported scores showed large improvements (> 20 points) with some individuals already reaching (sub)maximal scores (≥90 points) within the first two months (Figure 2J & 2K). Further improvements were found for all KOOS subscales from two to fifteen months follow-up (Table 4). As for the HOOS, all subscales improved from baseline to two months after THA, as well as from two to fifteen months follow-up, with the largest magnitude of effects taking place in the first two months (Table 4).

Table 2: Effects of time on gait parameters in the TKA and THA group

	TKA (n=24)							THA (n=24)						
		baseline - 2 months			2 months - 15 months				baseline - 2 months			2 months - 15 months		
Gait parameters	Baseline (intercept)	Mean difference (95% CI)	P_{value}	P_{corr}	Mean difference (95% CI)	P_{value}	P_{corr}	Baseline (intercept)	Mean difference (95% CI)	P_{value}	P_{corr}	Mean difference (95% CI)	P_{value}	P_{corr}
Gait speed (m/s)	0.99	-0.04 (-0.10, 0.03)	0.272	0.569	0.22 (0.15, 0.29)	<0.001	<0.001	0.96	0.04 (-0.02, 0.10)	0.245	0.514	0.14 (0.06, 0.20)	<0.001	0.003
Stride Length (m)	1.16	-0.002 (-0.05, 0.05)	0.924	0.924	0.14 (0.09, 0.19)	<0.001	<0.001	1.11	0.05 (0.002, 0.10)	0.049	0.306	0.07 (0.02, 0.13)	0.013	0.076
Cadence (steps/min)	102.8	-3.8 (-6.8, -0.8)	0.016	0.081	10.1 (7.0, 13.2)	<0.001	<0.001	103.0	-1.1 (-3.9, 1.7)	0.453	0.514	6.9 (3.8, 10.1)	<0.001	<0.001
Peak turning velocity (deg/s)	164.0	8.5 (-6.5, 23.7)	0.275	0.759	17.4 (1.7, 33.0)	0.035	0.105	171.2	19.1 (6.9, 31.5)	0.004	0.033	11.1 (-2.5, 24.9)	0.121	0.484
Step time asymmetry (%)	-	-	-	-	-	-	-	4.3	-0.7 (-2.0, 0.6)	0.292	0.514	-1.0 (-2.4, 0.3)	0.155	0.553
Stride time variability (%)	2.3	0.2 (-0.2, 0.6)	0.380	0.569	-0.3 (-0.8, 0.1)	0.117	0.234	2.5	-0.1 (-0.5, 0.3)	0.514	0.514	-0.2 (-0.7, 0.2)	0.277	0.831
Lumbar sagittal RoM (deg)	-	-	-	-	-	-	-	8.1	-1.9 (-3.0, -0.8)	0.001	0.013	0.1 (-1.1, 1.3)	0.870	0.870
Lumbar coronal RoM (deg)	-	-	-	-	-	-	-	5.2	0.4 (-0.3, 1.3)	0.255	0.514	1.4 (0.6, 2.1)	0.001	0.010
Trunk coronal RoM (deg)	7.8	-1.0 (-1.6, -0.3)	0.009	0.049	0.1 (-0.6, 0.9)	0.710	0.710	8.1	-0.6 (-1.3, 0.1)	0.087	0.439	0.1 (-0.6, 0.8)	0.797	0.870

Note: TKA = total knee arthroplasty, THA = total hip arthroplasty, RoM = range of motion, P_{corr} = Hommel adjusted p-value.
Data are presented as mean (95% CI)

Table 3: Post-operative situation compared to HC

			TKA vs HC				THA vs HC				
Gait parameters	HC (n=27)	TKA - 15 mo (n = 21)	Mean diff (95%CI)	Test statistic (df = 46)	P_{TKA-HC}	P_{corr}	THA - 15 mo (n=18)	Mean diff (95%CI)	Test statistic (df =43)	P_{THA-HC}	P_{corr}
Gait speed (m/s)	1.24 (1.18, 1.31)	1.19 (1.13, 1.24)	-0.06 (-0.15, 0.03)	1.31	0.197	0.569	1.16 (1.10, 1.22)	-0.08 (-0.18, 0.02)	1.70	0.096	0.441
Stride Length (m)	1.32 (1.26, 1.37)	1.30 (1.25, 1.36)	-0.02 (-0.10, 0.07)	0.40	0.691	0.691	1.26 (1.20, 1.31)	-0.06 (-0.15, 0.03)	-1.32	0.194	0.581
Cadence (steps/min)	113 (110, 117)	109 (105, 112)	-4 (-9, 1)	1.66	0.104	0.402	110 (107, 113)	-3 (-8, 2)	-1.13	0.265	0.794
Peak turning velocity (deg/s)	205 (190, 220)	190 (174, 206)	-15 (-38, 8)	1.30	0.201	0.569	207 (190, 223)	1 (-23, 26)	1.40	0.909	0.909
Step time asymmetry (%)	2.7 (1.9, 3.4)	-	-	-	-	-	2.6 (1.9, 3.2)	-0.2 (-1.3, 1.0)	-0.28	0.778	0.909
Stride time variability (%)	1.8 (1.6, 2.0)	2.1 (1.8, 2.4)	0.3 (-0.1, 0.7)	1.68	0.099	0.398	2.1 (1.8, 2.4)	0.3 (-0.03, 0.7)	1.86	0.069	0.397
Lumbar sagittal RoM (deg)	5.3 (4.7, 5.9)	-	-	-	-		6.3 (5.7, 6.8)	0.9 (-0.2, 2.1)	1.63	0.111	0.444
Lumbar coronal RoM (deg)	*8.1 (6.3, 9.0)*	-	-	-	-		*6.5 (5.3, 7.3)*	*-1.6 (-2.7, 0.1)*	U = 165.5	0.074	0.397
Trunk coronal RoM (deg)	6.6 (5.9, 7.3)	7.1 (6.2, 8.1)	0.5 (-0.7, 1.7)	0.89	0.379	0.691	7.5 (6.6, 8.5)	0.8 (-0.6, 2.1)	1.16	0.254	0.761

Note: HC = healthy control, TKA = total knee arthroplasty, THA = total hip arthroplasty, RoM = range of motion, P_{corr} = Hommel adjusted p-value.
Data are presented as mean (95% CI). Non-normal distributed data are presented in *italic* and are summarized as median (IQR) with median difference (95% CI). Test statistics represent either the t-value (normal data) or U (non-normal data)

Table 4: Patient-reported outcome scores for both groups at each timepoint

PROM scores	Baseline (estimate)	TKA (n=24) Pre-operative - 2 months Mean difference (95% CI)	P-value	2 months - 15 months Mean difference (95%CI)	P-value	Baseline (estimate)	THA (n=24) Pre-operative - 2 months Mean difference (95% CI)	P-value	2 months - 15 months Mean difference (95%CI)	P-value
HOOS/KOOS										
1) Symptoms	50	5 (-3, 14)	0.210	27 (18, 36)	<0.001	41	37 (30, 44)	<0.001	12 (4, 20)	0.007
2) Pain	42	28 (20, 36)	<0.001	19 (10, 28)	<0.001	39	45 (39, 52)	<0.001	9 (2, 16)	0.017
3) ADL	52	21 (13, 29)	<0.001	18 (10, 26)	<0.001	39	42 (35, 45)	<0.001	12 (4, 20)	0.004
4) Sports/Recreation	16	22 (9, 34)	0.001	30 (17, 43)	<0.001	15	48 (39, 57)	<0.001	13 (3, 22)	0.014
5) Quality of life	26	25 (17, 33)	<0.001	29 (20, 37)	<0.001	24	42 (32, 51)	<0.001	19 (9, 29)	<0.001

Note: OA = osteoarthritis, TKA = total knee arthroplasty, THA = total hip arthroplasty, HC = healthy controls, ADL = activities of daily living

Relation between recovery trajectories of gait parameters and PROMs

When comparing recovery trajectories of self-reported scores with gait parameters, substantial differences were observed (Figure 2). Where KOOS and HOOS scores showed large improvements over almost all subscales in the first two months after surgery (Table 4), gait parameters generally improved between 2 and 15 months, with the exception of trunk-related gait parameters. More specifically, discrepancies between HOOS/KOOS-ADL scores and spatiotemporal parameters were present at two months after surgery. For gait speed specifically, there were no significant changes between baseline and two months after TKA and THA, while HOOS/KOOS-ADL improved with 42 points and 21 points, respectively. To illustrate, two months after surgery, 10/23 individuals after TKA reported meaningful improvements in ADL scores, while merely 4/23 showed a meaningful improvement in gait speed. Similarly, after THA, 20/23 individuals reported meaningful improvements in ADL scores at 2 months, with 10/23 individuals showing meaningful improvements in gait speed.

Discussion

This study evaluated the use of inertial sensors to monitor functional recovery after TKA and THA. In concordance with our previous work, that sensor-derived gait parameters were sensitive to knee and hip OA[22], this study showed that these parameters were also responsive to TKA and THA at two and fifteen months after surgery, and recovered to the same level as HC fifteen months after surgery. In addition, discrepancies between recovery trajectories of spatiotemporal gait parameters and HOOS/KOOS scores were observed, particularly at two months post-operatively.

Recovery trajectory of gait after TKA and THA

There were limited improvements in spatiotemporal gait parameters two months after TKA and THA, which is in agreement with previous studies[25,33]. However, the observed faster turning in absence of higher gait speed two months after THA is interesting, and may suggest that turning is more sensitive to short-term improvements in physical functioning after THA than gait speed. In contrast to these basic spatiotemporal parameters, normalization of trunk movement was found already two months after TKA and THA. Pre-operatively, individuals with knee OA may increase lateral trunk lean as a strategy to reduce knee joint loading and/or pain[44-46], which is no longer required two months after TKA. Increased lumbar RoM in the sagittal plane, in its turn, may serve as pre-operative compensation for individuals with hip OA to overcome pain and hip joint stiffness[47,48]. Taken together, these results suggest that while two months is too early for meaningful recovery of spatiotemporal gait parameters, pre-operative compensations of the trunk and pelvis already disappear within the first two months after TKA and THA.

Large and clinically relevant improvements were observed on spatiotemporal parameters between two and fifteen months after TKA and THA. This is in agreement with literature investigating gait with inertial sensors one year after TKA[13,24,27] and THA[12,31]. Recovery of muscle strength (e.g. quadriceps and hip abductors) – which coincides with this period[49,50] – may underly these improvements in walking capacity. As for trunk kinematics, both individuals after TKA and THA showed an increase in lumbar coronal RoM from two to fifteen months after surgery, which may relate to the restored ability of the hip abductors to control frontal plane

pelvic movement[12,51]. Compensations like lateral trunk lean, which limit pelvic RoM, are then longer required[52]. When combining these results with those of gait recovery at two months, it can thus be concluded that a wide range of sensor-derived gait metrics is responsive to TKA and THA, with spatiotemporal parameters and trunk kinematics each showing a distinctive recovery trajectory.

None of the gait parameters were different from HC mean values at fifteen months after TKA and THA. This in contrast with some earlier studies reporting remaining gait differences between HC and individuals one year after TKA[27,32,53] or THA[33]. Although one year after arthroplasty is generally considered as endpoint of recovery, these differences between studies might be attributed to the longer follow-up time in our study. This seems like a reasonable explanation given that improvements in gait were larger in our study compared to these earlier studies[27,32,33]. Our findings underscore the success of TKA and THA in improving physical functioning, and indicate that normal spatiotemporal gait parameters and normal trunk kinematics may be achieved 15 months after TKA and THA. Whether other aspects of gait, including lower-extremity kinematics and kinetics, also recover to the level of healthy controls remains to be elucidated. Despite our findings of full recovery after TKA and THA, current literature suggest that more advanced parameters, including lower-extremity kinematics and kinetics, may still reveal deficits in gait one year after surgery[32,33,53].

Relationship between PROMs and objective gait measures

Objective gait parameters showed a different recovery trajectory than subjective reports of physical functioning and pain. Scores on the KOOS and HOOS greatly improved within the first two months, while spatiotemporal gait parameters mainly improved between two and fifteen months after surgery. Similar discrepancies between PROMs, gait, and performance-based tests have previously been recognized in the literature[12,14,32,54-56]. For example, inverse recovery trajectories (i.e. early improvements in PROMs compared to worsening of performance-based outcomes) have been observed between KOOS/HOOS ADL scores and performance-based outcomes, including the 6 minute walk test, stair climbing test, and timed up and go test, during the first month of recovery after TKA and THA[14,54-56]. For sensor-derived gait parameters specifically, poor agreement with PROM scores has been found after TKA and THA[12,24]. On a similar note, Fransen et al. found that, although perceived walking ability and self-reported physical functioning improved, there were no improvements in quality or quantity of daily life gait three months after surgery[17]. The current study adds that the discordance between gait parameters and self-reported physical functioning scores is most prominent at two months after surgery, with the exception of parameters related to trunk motion. The general consensus is that physical functioning subscales of PROMs assess a different domain than performance-based tests and gait analysis[13] This discrepancy may first be related to a strong relation of physical functioning subscales with pain[14], as was also apparent from the similarity between the recovery trajectories of HOOS/KOOS Pain and ADL subscales in our study. One potential explanation for this is that improvements in pain directly translate to a more positive reflection on daily life performance, and that patients considered pain as the main limiting factor in their daily life activities. Second, these self-reported scores ask about experienced difficulty during a wide range of activities, rather than how they execute a specific activity, which is inherently different from what these gait parameters measure. Finally, there is evidence that objective parameters of physical functioning are more sensitive to remaining functional deficits after TKA than PROMs[32], which may be attributed to early ceiling effects of PROMs. Since improving

mobility – specifically walking – is an important goal of joint replacement[57], these sensor-derived parameters may thus add a relevant dimension to evaluation of physical functioning, although their clinical value still has to be demonstrated.

Limitations and future directions

This study has a number of limitations which merit attention. First, we measured gait recovery in a well-defined cohort of patients with unilateral osteoarthritis without pain complaints in any other joint or previous joint replacement. While this was relevant for the aims of the current study, this limits the generalizability of our findings. Second, in the present study, evaluation of physical functioning was limited to gait and turning in the present study while other daily life activities, including sit-to-stand transfers and stair climbing, are also relevant for physical functioning after TKA and THA[15]. Third, gait parameters in this study were limited to spatiotemporal parameters and gait-related trunk kinematics. Other parameters, such as knee and hip kinematics that can be derived from a different set-up of inertial sensors may provide additional information about gait recovery after TKA and THA, especially in light of remaining gait deficits[33]. While the current study touches upon the potential value of objective measurement of physical functioning, the actual value of clinical implementation of gait tests cannot be derived from our study results. Future studies with larger samples and a more diverse population are required to investigate the applicability of objective gait assessment systems to identify poor-responders. Another valuable direction would be to explore whether such data can be used to adjust patient expectations during clinical visits and to further tailor post-operative care. Finally, there is a need for studies employing inertial sensors for remote monitoring during daily life, which may not only enable more efficient (digital) healthcare pathways in the future, but may also contribute to data with greater ecological validity[58,59].

Conclusion

This study showed that objective gait measures derived from inertial sensors are responsive to TKA and THA. Not only speed-related parameters, but also turning and trunk motion provide important information about functional status before and at two and fifteen months after joint replacement. There were no remaining gait differences between individuals after TKA or THA and healthy participants at fifteen months. Recovery trajectories of objective gait data were different from those of KOOS and HOOS ADL subscales, with a marked discordance at two months after surgery. Altogether, these results strengthen the premise that sensor-derived gait metrics may provide meaningful information about recovery of physical functioning after TKA and THA that is not captured by self-reported ADL or pain scores.

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Supplementary File 1

Types of hip implants

Fourteen patients with hip OA received an uncemented acetabular component (Allofit Alloclassic®) with Cementless Spotorno (CLS) stem (Zimmer Biomet, Warsaw, IN). Seven patients received the same acetabular component, but with a cemented Müller stem (Zimmer Biomet, Warsaw, IN) (n=6) or uncemented Wagner Cone Stem (Zimmer Biomet, Warsaw, IN) (n=1). Finally, three patients received a cemented Müller cup (Smith & Nephew, Memphis, TN) with cemented Müller stem (Zimmer Biomet, Warsaw, IN). In all patients a ceramic femoral head (Biolox ®) and polyethylene insert (Durasul ®) was used.

Missing data and complications

Two participants (1 TKA, 1 THA) were unable to complete the gait test without assistive device at two months after surgery. Fifteen months after surgery, three (THA) participants did not participate due to COVID-19 related reasons, two (THA) received a contralateral arthroplasty, one (TKA) moved abroad, one (TKA) was unable to complete the gait test without assistive device, one (THA) did not want to participate for unspecified reasons, and one study visit (TKA) fell outside the study window. Regarding post-operative complications, one patient had stiffness after TKA with good recovery after manipulation under anesthesia (three months post-operatively), one patient had an avulsion fracture of the trochanter major 8 days after THA (without readmission), and one patient had a revision for dislocation after THA (five months post-operatively) with no follow-up measurement at 15 months.

Chapter 5

Individuals with knee osteoarthritis show few limitations in balance recovery responses after moderate gait perturbations

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Abstract

Background
Knee osteoarthritis causes structural joint damage. The resultant symptoms can impair the ability to recover from unexpected gait perturbations. This study compared balance recovery responses to moderate gait perturbations between individuals with knee osteoarthritis and healthy individuals.

Methods
Kinematic data of 35 individuals with end-stage knee osteoarthritis, and 32 healthy individuals in the same age range were obtained during perturbed walking on a treadmill at 1.0 m/s. Participants received anteroposterior (acceleration or deceleration) or mediolateral perturbations during the stance phase. Changes from baseline in margin of stability, step length, step time, and step width during the first two steps after perturbation were compared between groups using a linear regression model. Extrapolated center of mass excursion was descriptively analyzed.

Results
After all perturbation modes, extrapolated center of mass trajectories overlapped between individuals with knee osteoarthritis and healthy individuals. Participants predominantly responded to mediolateral perturbations by adjusting their step width, and to anteroposterior perturbations by adjusting step length and step time. None of the perturbation modes yielded between-group differences in changes in margin of stability and step width during the first two steps after perturbation. Small between-group differences were observed for step length (i.e. 2 cm) of the second step after mediolateral and anteroposterior perturbations, and for step time (i.e. 0.01-0.02 s) of first step after mediolateral perturbations and the second step after outward and belt acceleration perturbations.

Conclusion
Despite considerable pain and damage to the knee joint, individuals with knee osteoarthritis showed comparable balance recovery responses after moderate gait perturbations to healthy participants.

Introduction

Knee osteoarthritis (OA) is a debilitating joint disease characterized by degradation of articular cartilage and structural damage to the knee joint[1]. Common symptoms of knee OA include pain, stiffness, muscle weakness, and fatigue. In addition, knee OA may lead to afferent and efferent neural deficits, expressed by reduced vibratory sense[2], reduced proprioception[3], and poorer control over muscle force generation[4]. These symptoms could lead to impaired stability during walking in individuals with knee OA[5]. Indeed, a large proportion of individuals with knee OA (i.e. 67-76%) experiences local instability at the knee joint[6,7], and observational studies suggest that individuals with knee OA are 25-54% more likely to experience a fall compared to those without knee OA[8-11].

Gait stability comprises the control of the body's extrapolated center of mass (XCoM) – which is the center of mass (CoM) position plus its velocity vector divided by the inverted pendulum's eigenfrequency[12] – with respect to the limits of a continuously changing base of support (BoS). This control mechanism can be challenged by the application of unexpected, external perturbations, which has become a common method to study dynamic balance control in humans[13-18]. The recovery from such perturbations relies on the integration of diverse sensory inputs into an adequate motor response. Dynamic balance control is believed to be actively regulated, particularly in the mediolateral (ML) direction[19], whereas in the anteroposterior (AP) direction, it may be relatively less controlled[20] due to exploitation of passive system dynamics[21]. Three main mechanisms can be used to actively regulate AP and ML gait stability during walking: 1) foot placement, 2) changing the position of the center of pressure under the stance foot, and 3) modulating the body's angular momentum[22]. Among the three mechanisms, foot placement is considered the most dominant[23].

Several earlier studies evaluated stability after ML[24-27] and AP[27-30] perturbations in individuals with knee OA. However, these studies used different operationalizations of the concept stability. That is, most studies focused on local (in)stability at the knee joint[24-27], with outcomes related to muscle activation patterns and/or knee kinematics, rather than focusing on whole body responses. Of the two studies that evaluated stepping responses and/or trunk kinematics following gait perturbations[28,29], Pater et al. found impaired balance recovery responses (i.e. lower step length and higher trunk flexion velocity) in individuals with knee OA after experimentally induced trips[28], whereas Elkarif et al. found differences in pelvic and hip kinematics between healthy individuals and individuals scheduled for total knee replacement following trip-like perturbations[29]. While these results suggest that whole body responses after gait perturbations may be impaired in individuals with knee OA, direct evidence supporting this notion is lacking.

In this study, we examined balance recovery response after moderate ML and AP perturbations in individuals with knee OA, and compared them to responses of healthy peers walking at a predefined, fixed speed. Given that individuals with knee OA show poorer proprioception[3], larger postural sway during standing[31,32], and impaired balance recovery responses after experimentally induced trips[28,29], we hypothesized that, compared to healthy participants, individuals with knee OA would show a larger destabilization following perturbation, leading to a larger XCoM excursion and a lower MoS in the first step after both ML and AP perturbations.

Methods

Participants

This study was part of a longitudinal study investigating real-life and challenging gait skills in individuals scheduled for total knee arthroplasty (TKA) (https://osf.io/64ejm). Real-world gait data of this study has been published as preprint[33]. Thirty-five individuals with end-stage knee OA, scheduled for cruciate retaining TKA, and thirty-two healthy controls (HC) participated in this study. Individuals with knee OA, who were candidates for posterior cruciate retaining TKA at the Sint Maartenskliniek Nijmegen, were screened by a research nurse for eligibility. Eligibility criteria included: 1) symptomatic and radiological knee OA (i.e. Kellgren-Lawrence grade > 2), 2) intact posterior cruciate ligament, 3) correctable or <10° rigid varus or valgus deformity of the knee, and 4) stable health (ASA-score ≤ 3), 5) aged between 40-80 years. Healthy participants were recruited from the community, in the same age range and with similar sex distribution as the group of individuals with knee OA. Healthy participants were matched to the individuals with knee OA that received the Journey II CR implant (Smith & Nephew, Memphis, TN, USA) based on age and sex (which was the case for 32 out of 35 participants), allowing a maximum age difference of 5 years. Healthy participants had no diagnosis of knee OA and had no self-reported pain complaints in the lower-extremities. Exclusion criteria for both groups were: 1) BMI > 35 kg/m^2, 2) moderate to severe knee, hip or ankle pain defined as an average score >4 on items 3-6 of the Short Brief Pain Inventory; excluding the knee indexed for TKA, 3) previous knee, hip, or ankle joint replacement, 4) any other musculoskeletal, neurological, or uncorrected visual disorder impairing gait or balance. Informed consent was obtained from all participants prior to the experiments. Ethical approval was obtained from the CMO Arnhem/Nijmegen (2019-5824). All study methods were carried out in accordance with the Declaration of Helsinki.

Clinical assessments

AP X-rays, available through regular clinical care, were scored by KD using the Kellgren and Lawrence grades[34]. Anthropometric characteristics (height, body mass, and BMI) were obtained on the same day as the gait assessment. For individuals with knee OA, this was on average 1.8 months (IQR = 1.5) before TKA. All participants reported pain scores during activity and rest using a numeric rating scale (NRS). In addition, the Knee injury and Osteoarthritis Outcome Score – Physical Function shortform (KOOS-PS)[35] and the clinical and functional score of the Knee Society Score (KSS)[36] were obtained for individuals with knee OA. Fall history was assessed by asking the participants if they had experienced a fall during the 3 months preceding the study visit[37]. If participants reported they had fallen, the number of falls was recorded.

Equipment

Participants walked on an instrumented split-belt treadmill (GRAIL, Motek Medical BV, The Netherlands) that was surrounded by a 180° semi-cylindrical screen with a virtual environment. For safety reasons, all participants wore a safety harness when walking on the treadmill. Participants were equipped with twenty-three reflective markers, following the Vicon Lower Body model[38], with additional markers placed on C7, and bilaterally on the acromion process, humeral lateral epicondyle, and the ulnar styloid process. These additional markers were used to account for trunk and arm movements in the CoM estimation[39]. Marker data were acquired using a ten-camera motion capture system (Vicon, Oxford, UK).

Procedures

Participants were first familiarized with the experimental set-up, including walking on the treadmill with virtual environment. Subsequently, comfortable walking speed was determined using the protocol described in Hak et al.[40], which started at a speed of 0.5 m/s with increments or decrements of 0.05 m/s. After these procedures, the perturbation protocol was performed. During the perturbation protocol, walking speed was fixed at 1.0 m/s, which was based on the mean overground comfortable walking speed of individuals with knee OA (e.g. 0.97 m/s; SD = 0.17[41]) and confirmed to be feasible during pilot testing.

The perturbation protocol consisted of four different perturbation modalities: 1) ML inward perturbations, 2) ML outward perturbations, 3) AP belt accelerations, and 4) AP belt decelerations (Fig. 1A). ML perturbations were induced by 4.5 cm platform translations in 0.05 s (Fig. 1B), during which the stance leg was either moved towards (i.e. inward) or away from (i.e. outward) the CoM. For ML perturbations the platform always returned to the middle, neutral position 5 seconds after initial perturbation. AP perturbations were induced by changes in unilateral belt speed (i.e. belt accelerations or decelerations) with a speed difference of ± 0.6 m/s in 0.5 s (Fig. 1B). All perturbation modalities were triggered at heel strike and delivered during the stance phase (Fig. 1B), ensuring sufficient time for adjustments in foot placement[42,43]. For both AP and ML perturbations, we aimed to have the largest perturbation magnitude possible within the limits of the system, for which it was still feasible for individuals with knee OA to complete multiple repetitions without falling or touching the handrail. Feasibility of the perturbation magnitudes was qualitatively evaluated during pilot testing in healthy individuals (n=3), individuals with knee osteoarthritis (n=3), and individuals with hip osteoarthritis (n=1). During these pilot tests we evaluated ML platform displacements of 3 and 4.5 cm, and AP belt accelerations and decelerations of ±0.3 m/s, ±0.6 m/s, and ±0.9 m/s. All participants reported 4.5 cm platform translations – which was the maximum possible displacement – and changes in belt speed of ±0.6 m/s to be feasible. In contrast, changes in belt speed of ±0.9 m/s caused too much discomfort or anxiety, and participants commonly grabbed the handrail. Hence, we opted for a magnitude of 4.5 cm for ML perturbations and a change in belt speed of ±0.6 m/s for AP perturbations.

All perturbation modalities were applied to both the affected and the unaffected leg, yielding a total of 8 unique perturbations. The definition of side in healthy participants was matched to the affected side of an individual with TKA with similar sex and age. Each perturbation modality was repeated four times, to account for individual variation in balance recovery responses. In order to keep the uninterrupted walking duration manageable for our participants, perturbations were divided over four blocks of perturbations (Fig. 1C). ML perturbations were administered in the first two blocks, and AP perturbations in the last two blocks. These blocks consisted of 8 trials and lasted approximately 3 minutes. Each block was followed by 2 minutes of rest to prevent unacceptable levels of pain and/or fatigue. The order of perturbations was fixed, but concealed to the participants. The duration between two consecutive perturbations was at least 7 seconds to ensure sufficient recovery from the perturbation[14,44]. The exact interval between perturbations varied in order to prevent anticipation, and was on average 11±2 seconds for ML perturbations and 12±2 seconds for AP perturbations.

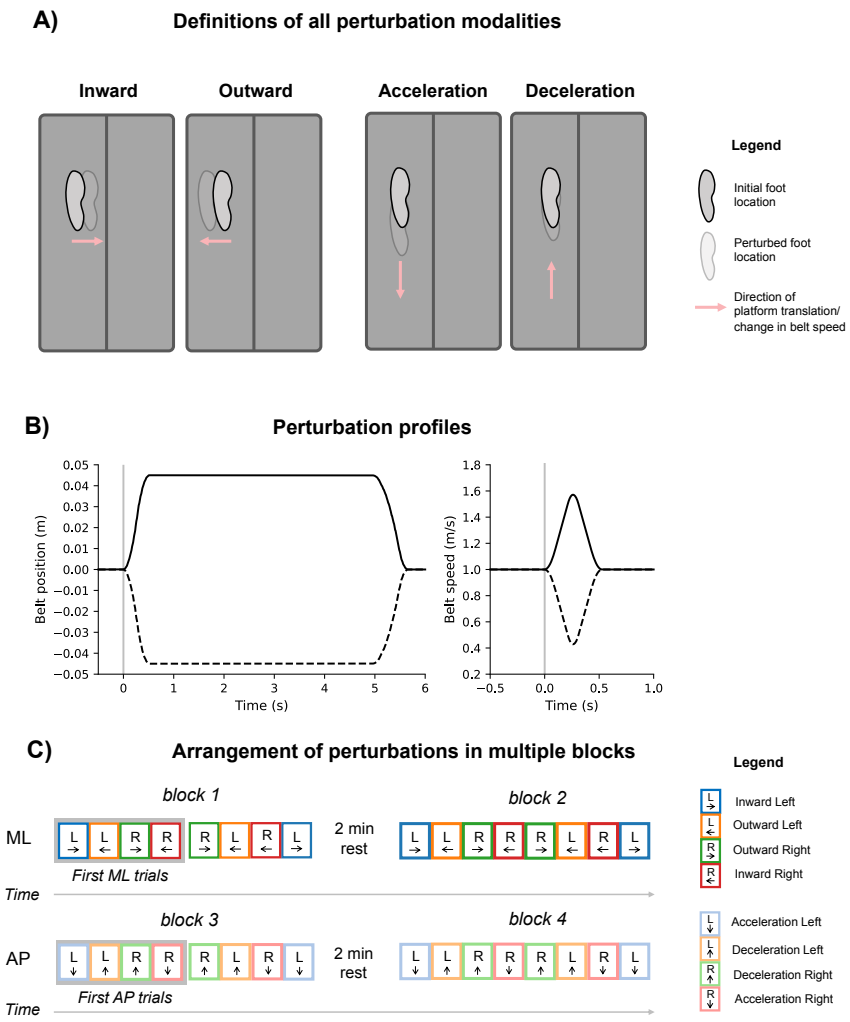

Figure 1: Overview of the experimental design. A) Definitions of the different ML (left) and AP (right) perturbation modalities. The direction of the platform translation or change in belt speed is indicated by the pink arrow. B) The detailed perturbation profiles for ML (left) and AP perturbations (right). T=0, indicated by the grey line, corresponds to the heel strike of the perturbed leg. C) Perturbations were divided into 4 separate blocks of walking. Each color represents a specific perturbation modality. The order of these perturbations was fixed, but concealed to the participant. First trials of each modality, indicated by the grey box, were removed from the analysis.

Outcomes and data analysis

Data were processed in Octave 6.3.0 and figures were prepared in Python 3.8.3. Marker data were filtered using a 2nd order low-pass Butterworth filter with a cut-off frequency of 10 Hz. Gait events were detected using the velocity-based algorithm described by Zeni Jr. et al.[45]. From marker data, the CoM position was determined using the methods described by Tisserand et al.[39]. Subsequently, the XCoM was calculated based on the inverted pendulum model, using the formula presented by Hof et al.[12]:

$$XCoM = CoM + \frac{vCoM + vBelt}{sqrt\left(\frac{g}{l}\right)}$$

where XCoM is the body's extrapolated center of mass, CoM the CoM position, vCoM the CoM velocity, vBelt the belt speed (1.0 m/s for the anteroposterior direction), g the gravitational acceleration (9.81 m/s^2), and l is defined as the pendulum height (height of the CoM).

To descriptively analyze CoM and XCoM, trajectories were time normalized from the second step before perturbation until the fifth step after perturbation. In addition, CoM position at heel strike before perturbation was subtracted from the entire time series, such that group averages could be taken. The MoS was calculated separately in the ML and the AP direction. For the AP direction, MoS was calculated as the difference between the toe marker and XCoM at heel strike. For the ML direction, MoS was calculated as the minimum of the difference between the ankle marker and XCoM position during stance, which was approximately at the instant of opposite toe-off[12]. Positive MoS values indicate instantaneous stability, whereas negative MoS values indicate instantaneous instability. Discrete parameters (MoS, step time, step length, and step width) were calculated for the three steps before each perturbation (i.e. step-2, step-1, and pre) until five steps after perturbation (i.e. post1 – post5). Step length was defined as the difference in AP position of the heel markers between two consecutive heel strikes, plus step time times belt speed. Step width was defined as the difference in ML position of the heel markers between two consecutive heel strikes. For both step length and step width calculations, we accounted for changes in belt speed or platform translation, such that these parameters included the distance from the perturbation. First repetitions of each perturbation mode were removed from analysis, as they may elicit inherently different responses than later repetitions (e.g. due to first trial effect;[46]). In addition, all responses during which the handrail was touched were removed from analysis. Touching of the handrail was visually identified by the investigator. To evaluate whether the omission of first trials impacted our study results, we performed an additional analysis including only the first repetition of each perturbation modality (Supplementary File 1).

Statistical analysis

To reduce the risk of type I errors, between-group effects were only tested in the first two steps after perturbation (i.e. post-1 and post-2). For similar reasons, we only compared data of perturbations to the affected leg between groups, as the largest differences could be expected here. The two steps before each perturbation trial (step-2 and step-1) were combined into a baseline score to reduce noise and average out potential asymmetries. For each outcome measure, two separate linear regression models were created, with difference from baseline as the dependent variable (ΔYpost1/2), group as independent variable, and baseline score (Ybaseline) and trail as covariate:

$$\text{Model 1: } \Delta Y_{post1} = \beta 0 + \beta 1 * group + \beta 2 * Y_{baseline} + \beta 3 * trial$$
$$\text{Model 2: } \Delta Y_{post2} = \beta 0 + \beta 1 * group + \beta 2 * Y_{baseline} + \beta 3 * trial$$

In these models Y was the variable of interest (i.e. MoS, step width, step length, or step time). Between-group differences (i.e. β1 derived from the models) were reported as mean differences with 95% confidence intervals. Furthermore, changes over time (i.e. ΔYpost1 and ΔYpost2) were estimated. If there was no significant group effect ($p > 0.05$), the factor group was removed from the statistical model to estimate ΔYpost1/2 for all participants. XCoM and CoM trajectories were descriptively analyzed. Statistical analysis was performed in RStudio using the stats package (version 4.1.2).

Results

Baseline characteristics are provided in Table 1. Individuals with knee OA had a higher body mass, higher BMI, and experienced more pain during activity and rest compared to healthy controls. Comfortable walking speed was -0.21 m/s lower in individuals with knee OA than in healthy controls. Four participants with knee OA (11%) and two healthy participants (6%) reported they had fallen during the preceding 3 months.

Table 1: Baseline characteristics of both study groups

Parameter	Knee OA (n=35)	Controls (n=32)	Mean difference [95 % CI]
Age (y)	65 (9)	64 (10)	1 [-4 ; 5]
Sex (M:F)	14:21	13:19	-
Body height (m)	1.73 (0.11)	1.75 (0.07)	-0.02 [-0.06; 0.03]
Body mass (kg)	86 (15)	75 (11)	11 [4; 17]
BMI (kg/m^2)	28.5 (3.3)	24.6 (3.1)	3.9 [2.3; 5.4]
KL score (I:II:III:IV)	0:0:10:25	-	-
KOOS-PS (0-100)	54 (13)	-	-
NRS pain at rest (0-10)	4.1 (2.4)	0.5 (1.0)	3.6 [2.7; 4.5]
NRS pain during activity (0-10)	6.2 (2.0)	0.7 (1.0)	5.5 [4.7; 6.3]
Comfortable walking speed (m/s)	0.95 (0.19)	1.16 (0.19)	-0.21 [-0.30; -0.11]
Number of falls per participant during preceding 3 months (0:1:2:3)	31:3:1:0	30:1:0:1	-

Note: BMI = body mass index, KL = Kellgren Lawrence, KOOS-PS = Knee Osteoarthritis Outcome Score – Physical Function Shortform, NRS = numeric rating scale. KOOS-PS scores were transformed to a 0-100 scale with a score of 100 representing no difficulty. For the KSS, only the clinical and functional score were obtained, which were rated on a 0-100 scale with 100 representing best function. For NRS pain ratings, 0 represented no pain and 10 the worst possible pain

We had missing data for one individual with knee OA during the ML perturbations, and for 4 individuals with knee OA during AP perturbation trials. Reasons for missing data were: unable to complete the task due to pain or physical impairment (ML: n=1; AP: n=2), fear (n=1, AP), and lack of time (n=1, AP). Although these participants did not report any falls in the preceding 3 months, their KOOS-PS (range: 38-54) and NRS pain scores during rest (range: 7-9) and activity (range: 7-9) were worse than the group average. Furthermore, six trials of individuals with knee OA (inward affected (n=3), belt acceleration affected (n=1), belt deceleration affected (n=2)) were not analyzed as the handrail was touched during the balance recovery response.

Mediolateral gait perturbations

For inward perturbations, there was no direct effect of the perturbation visible on the XCoM trajectory (Fig. 2). Between the first and second step after perturbation, the XCoM moved approximately 0.05 m less laterally, whereas XCoM excursion was markedly higher between the second and third step after perturbation. XCoM trajectories overlapped between individuals with knee OA and healthy participants. Participants predominantly responded to inward perturbations by lowering their step widths. In both groups, step width decreased with 0.09 m at step 1 and step 2 compared to baseline (Fig. 3 & Table 2). This resulted in a decrease in ML MoS of 0.03 m (95% CI: 0.03, 0.04) in the first step, and an increase of 0.01 m (95%: 0.01, 0.02) in the second step compared to baseline. Small between-group differences were observed for step time in the first step after perturbation (mean diff = -0.01 m, 95% CI: -0.01, -0.00) and for step length in the second step after perturbation (mean diff = -0.02 m, 95% CI: -0.04, -0.00). In the first step after perturbation, step time was 0.01 s longer in healthy individuals, whereas step time did not change in individuals with knee OA. In the second step after perturbation, step length was not different from baseline in healthy individuals, whereas step length was -0.02 m (95% CI: -0.03, -0.01) lower in individuals with knee OA.

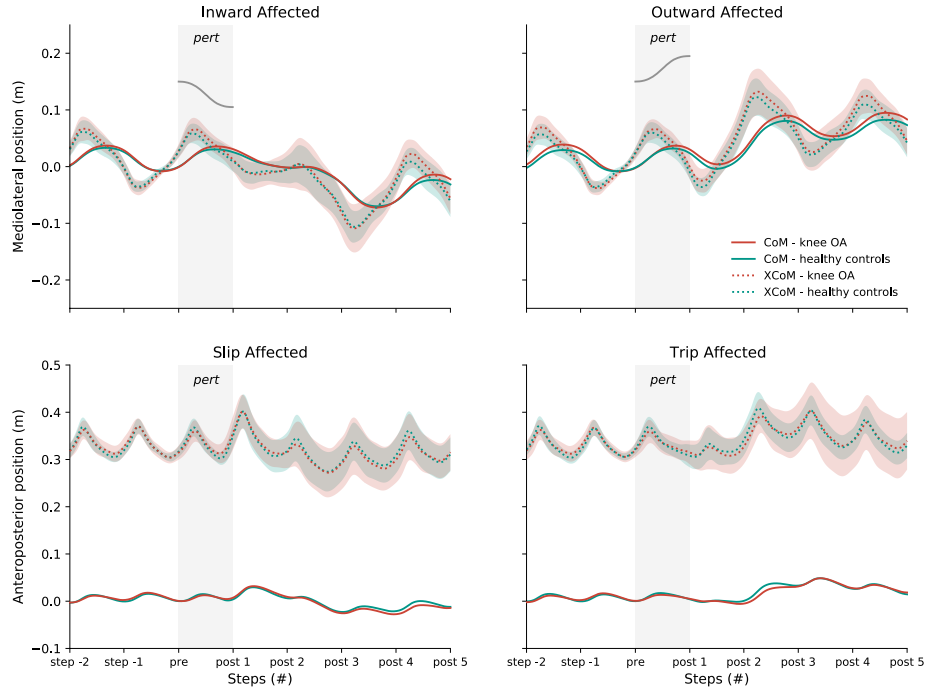

Figure 2: Trajectories of mean center of mass (CoM) and extrapolated center of mass (XCoM) from two steps before until five steps after gait perturbations. Mean values are indicated by the solid and dotted lines. Shaded areas around the extrapolated XCoM represent the standard deviation. Duration of the perturbation ('pert') is highlighted by the grey area. For mediolateral perturbations, belt displacement is also indicated by a black line within the grey area.

Similar to inward perturbations, no instantaneous effect of outward perturbations on the XCoM trajectory was observed. Between the first and second step after perturbation, the XCoM travelled approximately 0.05 m more laterally in both groups (Fig. 2). XCoM trajectories were comparable between the two groups. On average, step width increased in the first (mean diff = 0.07 m, 95% CI: 0.07, 0.07) and second step (mean diff = 0.09 m, 95% CI: 0.08, 0.09) after perturbation. Both for individuals with knee OA and healthy participants, ML MoS was 0.03 m (95% CI: 0.02, 0.03) larger than baseline in the first step after outward perturbation, but was not different from baseline in the second step (mean diff = -0.00 m , 95% CI: -0.01, 0.00). Compared to baseline, step length was 0.06 m (95% CI: 0.06, 0.07) shorter in the first step after outward perturbations. In the second step after perturbation, step length was 0.06 m (95% CI: 0.05, 0.07) shorter in healthy individuals, whereas this was 0.08 (95% CI: 0.07, 0.10) in individuals with knee OA. For step time, small between-group differences were observed in the first (mean diff: -0.01 s, 95% CI: -0.01, -0.00) and second step after outward perturbation (mean diff: -0.01s, 95% CI: -0.02, -0.00).

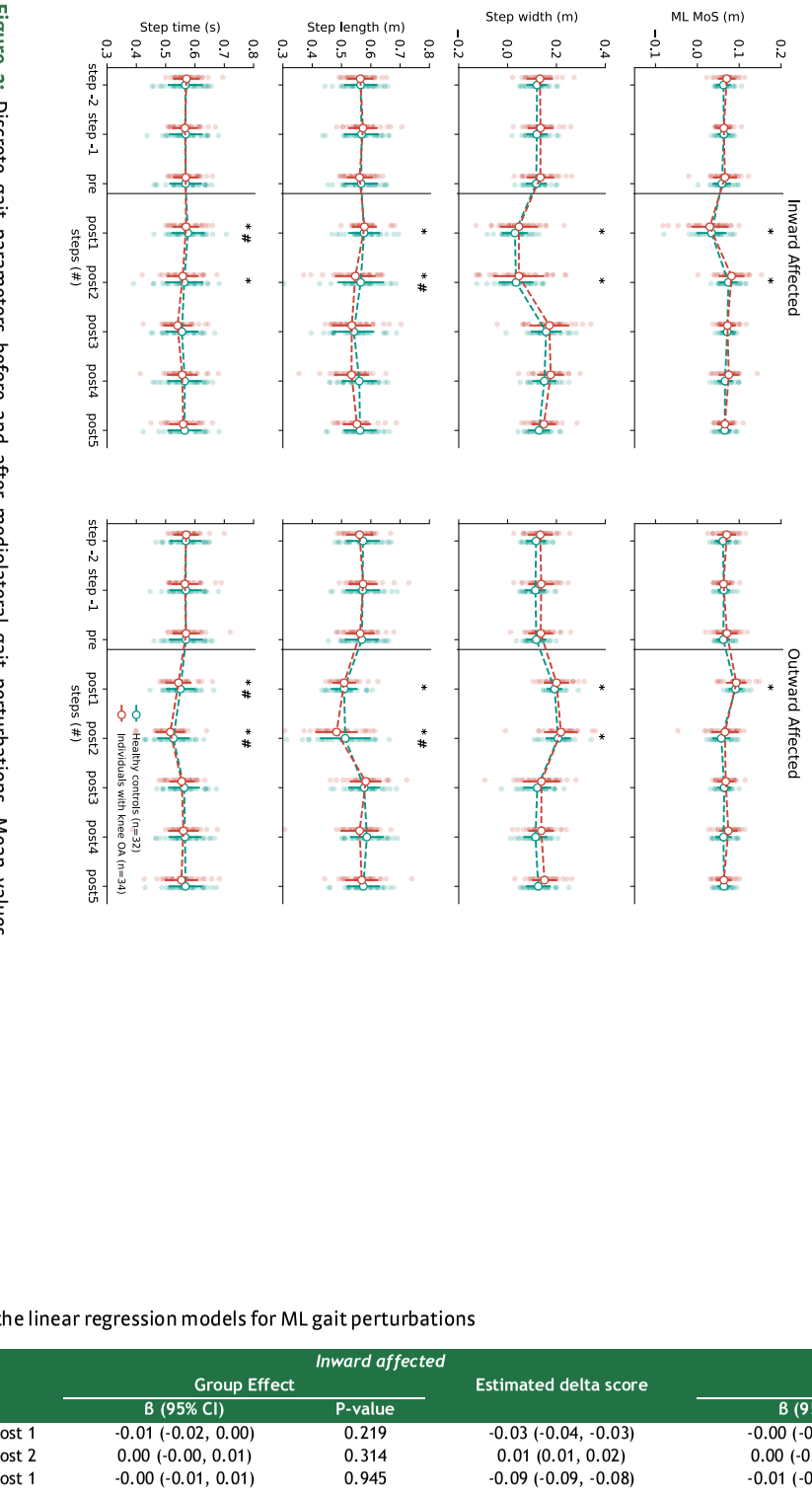

Figure 3: Discrete gait parameters before and after mediolateral gait perturbations. Mean values are indicated by the large white dots, with error bars reflecting the standard deviation. Individual observations are shown with larger transparency. The instance of perturbation is indicated by the black vertical line. Steps before perturbation (i.e. step -2 & step -1) were combined into a baseline score for statistical analysis. Note: * significantly different from baseline, # significantly different between groups.

Table 2: Output of the linear regression models for ML gait perturbations

Parameter		*Inward affected*			*Outward affected*		
		Group Effect		Estimated delta score	Group Effect		Estimated delta score
		β (95% CI)	P-value		β (95% CI)	P-value	
ML MoS (m)	Post 1	-0.01 (-0.02, 0.00)	0.219	-0.03 (-0.04, -0.03)	-0.00 (-0.01, 0.00)	0.701	0.03 (0.02, 0.03)
	Post 2	0.00 (-0.00, 0.01)	0.314	0.01 (0.01, 0.02)	0.00 (-0.00, 0.01)	0.803	-0.00 (-0.01, 0.00)
Step width (m)	Post 1	-0.00 (-0.01, 0.01)	0.945	-0.09 (-0.09, -0.08)	-0.01 (-0.01, 0.00)	0.190	0.07 (0.07, 0.07)
	Post 2	-0.01 (-0.03, 0.01)	0.544	-0.09 (-0.10, -0.08)	-0.01 (-0.02, 0.01)	0.351	0.09 (0.08, 0.09)
Step length (m)	Post 1	-0.00 (-0.01, 0.01)	0.846	0.01 (0.01, 0.01)	0.00 (-0.01, 0.01)	0.699	-0.06 (-0.07, -0.06)
	Post 2	-0.02 (-0.04, -0.00)	0.022	HC: -0.00 (-0.01, 0.01)	-0.02 (-0.04, -0.01)	0.008	HC: -0.06 (-0.07, -0.05)
				Knee OA: -0.02 (-0.03, -0.01)			Knee OA: -0.08 (-0.10, -0.07)
Step time (s)	Post 1	-0.01 (-0.01, -0.00)	0.026	HC: 0.01 (0.00, 0.01)	-0.01 (-0.01, -0.00)	0.025	HC: -0.02 (-0.02, -0.01)
				Knee OA: 0.00 (-0.00, 0.01)			Knee OA: -0.02 (-0.03, -0.02)
	Post 2	-0.01 (-0.01, 0.00)	0.277	-0.01 (-0.01, -0.00)	-0.01 (-0.02, -0.00)	0.048	HC: -0.04 (-0.05, -0.03)
							Knee OA: -0.05 (-0.06, -0.05)

Data are presented as mean difference (95% CI).

Table 3: Output of the linear regression models for AP gait perturbations

Parameter		*Acceleration affected*			*Deceleration affected*		
		Group Effect		Estimated delta score	Group Effect		Estimated delta score
		β (95% CI)	P-value		β (95% CI)	P-value	
AP MoS (m)	Post 1	-0.00 (-0.01, 0.01)	0.733	-0.05 (-0.05, -0.04)	0.01 (-0.00, 0.03)	0.095	-0.03 (-0.03, -0.02)
	Post 2	-0.00 (-0.01, 0.01)	0.691	0.03 (0.02, 0.03)	-0.01 (-0.02, 0.01)	0.261	-0.06 (-0.06, -0.05)
Step width (m)	Post 1	0.00 (-0.01, 0.01)	0.724	-0.01 (-0.02, -0.01)	0.00 (-0.01, 0.01)	0.819	0.02 (0.02, 0.02)
	Post 2	-0.00 (-0.01, 0.01)	0.677	0.02 (0.01, 0.02)	-0.00 (-0.01, 0.01)	0.351	0.02 (0.01, 0.02)
Step length (m)	Post 1	0.00 (-0.01, 0.01)	0.526	0.10 (0.09, 0.10)	0.02 (-0.01, 0.04)	0.237	-0.18 (-0.19, -0.16)
	Post 2	-0.02 (-0.04, -0.00)	0.012	HC: -0.04 (-0.05, -0.03)	-0.02 (-0.04, -0.01)	0.010	HC: 0.06 (0.05, 0.07)
				Knee OA: -0.07 (-0.08, -0.05)			Knee OA: 0.04 (0.02, 0.05)
Step time (s)	Post 1	0.00 (-0.01, 0.00)	0.561	-0.02 (-0.02, -0.02)	-0.00 (-0.02, 0.01)	0.524	-0.01 (-0.01, -0.00)
	Post 2	-0.02 (-0.03, -0.01)	0.002	HC:-0.08 (-0.09, -0.07)	0.01 (-0.00, 0.02)	0.110	0.04 (0.03, 0.04)
				Knee OA: -0.10 (-0.10, -0.09)			

Data are presented as mean difference (95% CI)

Anteroposterior perturbations

Belt acceleration did not have an immediate effect on the XCoM trajectory. Between the first and second step after perturbation, however, the XCoM moved more anteriorly (Fig. 2), with both groups showing overlapping XCoM trajectories. In response to belt acceleration, participants predominantly changed their step length and step time (Fig. 4). In the first step after perturbations, step length was 0.10 m (95% CI: 0.09, 0.10) longer compared to baseline in both groups. Step time was 0.02 s (95% CI: 0.02, 0.02) shorter than baseline in both groups. Compared to baseline, AP MoS was 0.05 m (95%: 0.04, 0.05) lower in the first step, followed by a 0.03 m (95% CI: 0.02, 0.03) higher AP MoS in the second step. Changes in AP MoS after acceleration perturbations were similar between individuals with knee OA and healthy individuals (Table 3). At the second step after perturbation, there was a significant group effect on changes in step length (p=0.012) and step time (p=0.002). Individuals with knee OA showed a 0.02 m (95% CI: 0.00, 0.04) larger decrease in step length compared to baseline, and a 0.02 s (95% CI: 0.01, 0.03) larger reduction in step time. Changes from baseline on step width were small and did not differ between the groups (Table 2).

Belt deceleration perturbations attenuated the forward movement of the XCoM during the first recovery step. Consequently the XCoM was relatively more posterior at the first and second step after perturbation (Fig. 2). There were no differences between groups in XCoM trajectory, although the standard deviation of the XCoM trajectory after belt deceleration seemed to be larger in individuals with knee OA. Belt deceleration resulted in a lower step length (mean diff = -0.18 m, 95% CI: -0.19, -0.16) in the first step after perturbation. In the second step after perturbation, there was a significant group effect on step length (p=0.010). Step length was 0.06 m (95% CI: 0.05, 0.07) higher in healthy individuals compared to baseline, whereas this was 0.04 m (95% CI: 0.02, 0.05) for individuals with knee OA. Compared to baseline, step time was 0.01 s (95% 0.00, 0.01) shorter in the first step after belt deceleration, and 0.04 s (95% CI: 0.03, 0.04) longer in the second step. There were no group effect on AP MoS in the first and second steps after perturbation (Table 3). For both groups, AP MoS was 0.03 m (95% CI: 0.02, 0.03) lower in the first step after belt deceleration, and 0.06 m (95%: 0.05, 0.06) lower in the second step. Similar to belt acceleration, the effects of belt deceleration on step width were small and did not differ between the groups (Table 3).

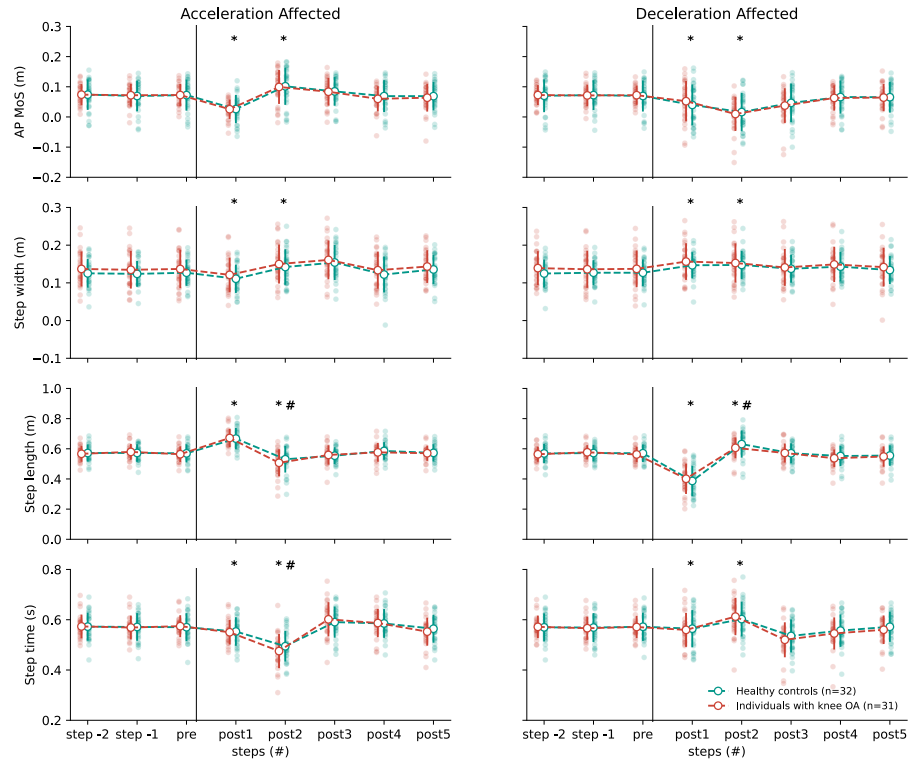

Figure 4: Discrete gait parameters before and after anteroposterior gait perturbations. Mean values are indicated by the large white dots, with error bars reflecting the standard deviation. Individual observations are shown with larger transparency. The instance of perturbation is indicated by the black vertical line. Steps before perturbation (i.e. step -2 & step -1) were combined into a baseline score for statistical analysis. Note: * significantly different from baseline, # significantly different between groups.

Discussion

In this study we compared balance recovery responses to moderate ML and AP gait perturbations between individuals with end-stage knee OA and their healthy peers. After inward as well as outward ML perturbations, individuals with knee OA showed very comparable balance recovery responses to healthy individuals, with only a slightly larger decrease in step length in the second step after perturbation in individuals with knee OA. In both groups, belt acceleration resulted in a lower AP MoS, and longer step lengths with shorter step times during the first step after perturbation. In the second step after belt acceleration, there was a decrease in step length and step time, which was marginally larger in individuals with knee OA than in healthy individuals. Belt deceleration resulted in a lower AP MoS, and shorter steps with shorter step times in the first step after perturbation in both groups. This initial response was followed by longer steps with longer step times in the second step after perturbation, with individuals with knee OA showing a slightly smaller increase in step length.

Thus, in contrast to our hypothesis, we did not find convincing evidence for impaired balance recovery responses to moderate gait perturbations in individuals with end-stage knee OA. None of the perturbation modes resulted in group differences in MoS, which was our main outcome of interest. Although it could be argued that taking relatively faster and shorter steps to regain stability – as we found after ML and AP perturbations – may be indicative of poorer balance control[47], these group differences were relatively small (i.e. 2 cm for step length and 0.02 s for step time). Two main explanations for minor differences between groups can be postulated. To begin with, individuals with knee OA in our study may not have had gait instability, or had only minor localized impairments that they effectively compensated for. Alternatively, our experimental paradigm may not have been challenging enough to trigger large enough balance threats and elucidate instability in the knee OA group. Both options are discussed below.

Given that knee OA leads to a reduced number of mechanoreceptors in the knee capsule and ligaments[48], reduced proprioception[3], lower quadriceps strength[1], and pain, it would be expected that individuals with knee OA have poorer stability than healthy older adults. While postural sway during quiet standing was indeed higher in individuals with knee OA[31,32], and local dynamic stability tended to be lower during unperturbed walking when compared to healthy adults[5], these reported differences were relatively small. Moreover, it is yet unclear if deviations in these type of balance metrics translate to problems with recovery from external perturbations. So far, studies investigating responses to perturbations in individuals with knee OA have shown mixed results[25-30]. For example, Schrijvers et al. found larger knee flexion angles and increased co-contraction after AP perturbations in individuals with knee OA with self-reported instability[27]. Pater et al. found a less optimal recovery strategy from trips over an obstacle during overground walking in individuals with mild to moderate knee OA compared to their healthy peers[28], although the number of fallers after perturbation was similar between groups. In contrast, Kumar et al.[25] and Baker et al.[26] found no effect of moderate to severe knee OA on change in knee muscle activation and knee kinematics after ML gait perturbations (i.e. 5.8 cm and 3 cm, respectively). Interestingly, none of these studies focused on whole body movement. It may thus well be that individuals with knee OA use adaptations in knee joint kinematics and muscle activation to achieve similar balance recovery responses as healthy individuals. Moreover, to overcome poorer proprioception due to knee OA, the redundancy of afferent input to and processing within the sensorimotor control system can be exploited[25,49]. By using sensory reweighting, individuals with knee OA may rely more on somatosensory information from other, unaffected structures[50]. In light of our results, dynamic balance control may thus still be maintained in individuals with knee OA. Our observation that – in this study – fall rates of individuals with knee OA were relatively low and comparable to healthy individuals further supports that individuals with knee OA in this study may not have had large gait stability problems.

A second explanation for the absence of evident instability in the knee OA group could be that the perturbation was insufficiently destabilizing. That is, the ML and AP MoS values before onset of the perturbations in both study groups were higher than (or close to) the perturbed distance (i.e. 4.5 cm for ML perturbations and 12.5 cm for AP perturbations), indicating that there was already some room to cope with these perturbations at baseline. Since the current perturbations were relatively well tolerated by individuals with knee OA, a larger intensity perturbation with potentially better discriminatory capacity may have been feasible. Despite this point, our perturbation paradigm led to clear adaptations in the gait pattern, suggesting that it did challenge the sensorimotor control system. In general, responses to these type of treadmill perturbations seem to be robust, as balance recovery responses in our study were comparable to perturbation responses of healthy young[13,16,51,52] and older adults[16,51] in previous studies with very similar paradigms. Although it might be expected that these paradigms would result in different responses in groups with evident balance problems, this is not yet confirmed in the literature.

This study had a number of limitations that warrant mentioning. First, standardization of walking speed may have led to unnatural walking behavior in some participants as well as differences in experienced difficulty between study groups. Nonetheless, standardization was necessary to separate a potentially confounding influence of walking speed from the effects of knee OA on balance recovery responses. Moreover, the fixed walking speed was very close to the comfortable walking speed of individuals with knee OA. Secondly, our sample of individuals with unilateral, end-stage knee OA who were scheduled for cruciate retaining total knee arthroplasty may not be representative of all individuals with knee OA. Given that our study group was relatively active, did not have complaints in other joints, and fall rates were low, generalization of our results to the whole knee OA population should be done cautiously. Another important methodological consideration is that we opted for relatively short intervals between perturbations to keep the total walking duration manageable. Although our data indicates that stepping characteristics sufficiently returned to baseline within this timeframe, these intervals may have been too short for other factors to recuperate, such as muscle activation and anxiety. In addition, we used a simplified definition of the BoS in our calculation of the MoS – which was based on marker data rather than center of pressure data – due to the disruptive effects of the perturbation on the center of pressure estimation. Modulation of the center of pressure in response to the perturbations may have been different between groups, but could not be captured in our study. Finally, we omitted first trials from analysis as they elicited startle-like responses and were difficult to quantify in a uniform way. In light of fall risk, however, it is important to note that first trials are most ecologically valid to assess. Nevertheless, additional analysis of only the first trials (Supplementary File 1) indicated that the impact of this choice in data analysis on our results was minimal, given that between-group differences were relatively similar for first trials compared to those of later trials.

Conclusions

Despite considerable knee pain and structural damage to the knee joint, balance recovery responses to moderate gait perturbations in individuals with knee OA were not substantially different from healthy individuals.

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Supplementary File 1 – Results of supplementary analysis including only first trial responses

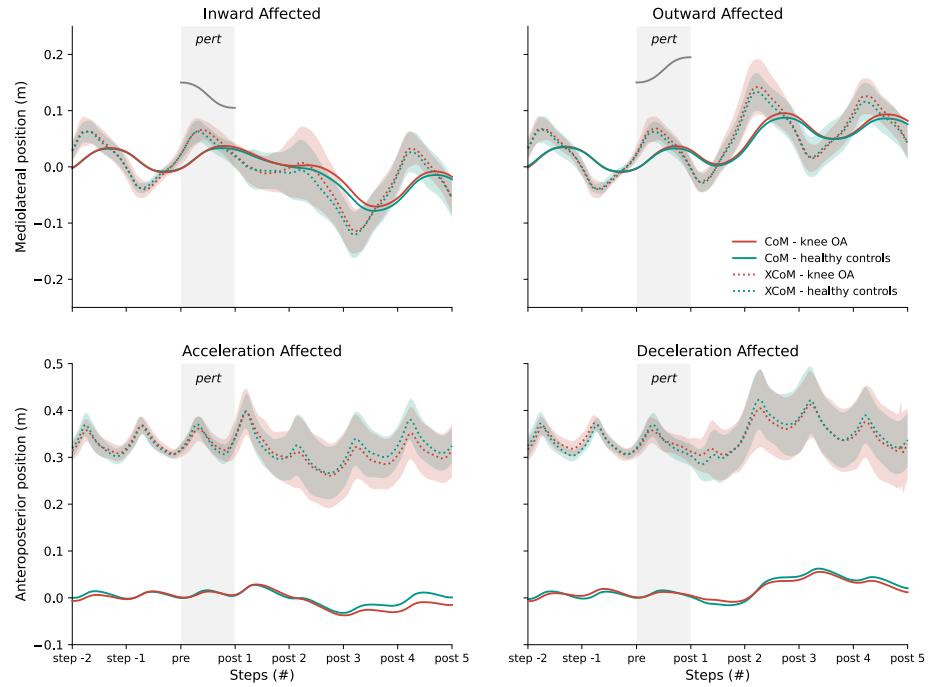

Figure 1: Trajectories of mean center of mass (CoM) and extrapolated center of mass (XCoM) from two steps before until five steps after gait perturbations for only the first trials. Mean values are indicated by the solid and dotted lines. Shaded areas around the extrapolated XCoM represent the standard deviation. Duration of the perturbation ('pert') is highlighted by the grey area. For mediolateral perturbations, belt displacement is also indicated by a black line within the grey area.

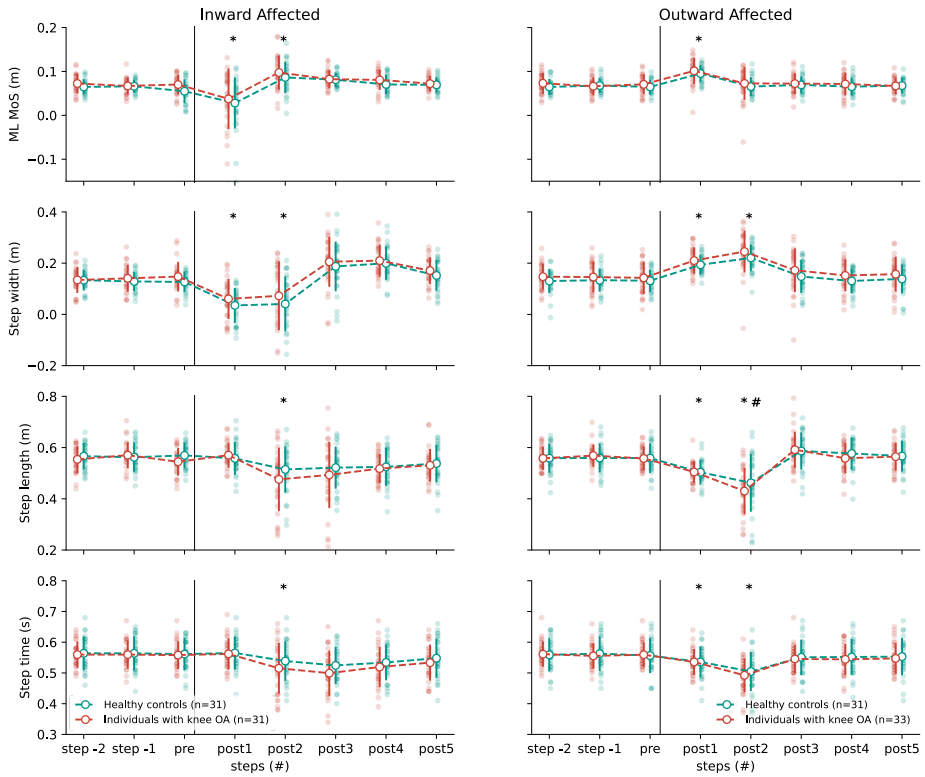

Figure 2: Discrete gait parameters before and after mediolateral gait perturbations for only the first trials. Mean values are indicated by the large white dots, with error bars reflecting the standard deviation. Individual observations are shown with larger transparency. The instance of perturbation is indicated by the black vertical line. Steps before perturbation (i.e. step -2 & step -1) were combined into a baseline score for statistical analysis. *Note:* * significantly different from baseline, # significantly different between groups.

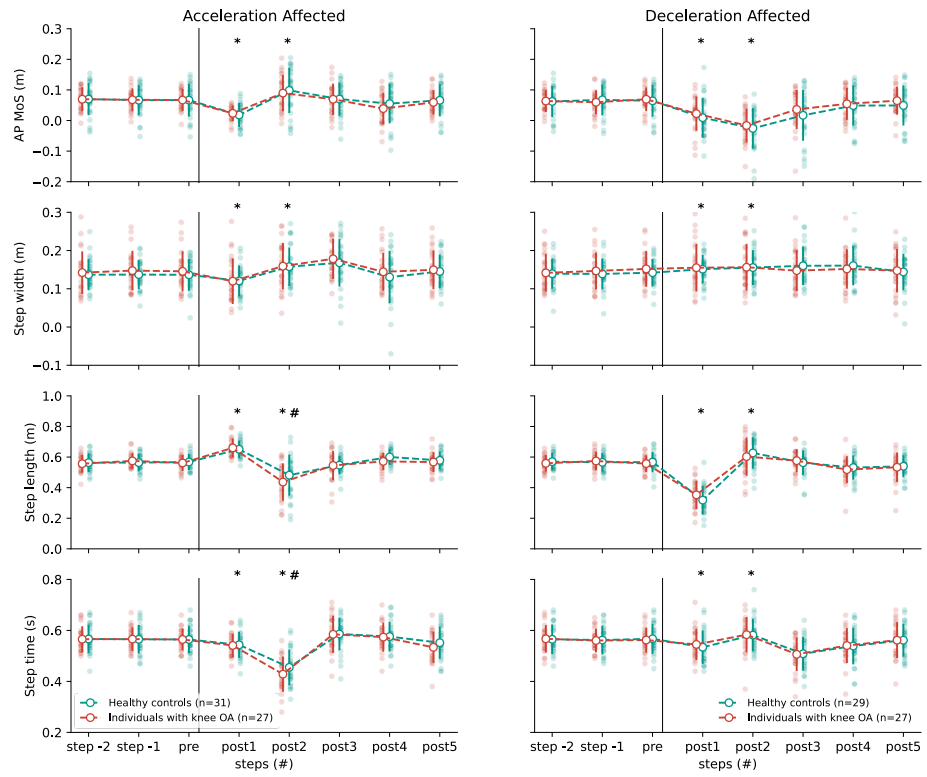

Figure 3: Discrete gait parameters before and after anteroposterior gait perturbations for only the first trials. Mean values are indicated by the large white dots, with error bars reflecting the standard deviation. Individual observations are shown with larger transparency. The instance of perturbation is indicated by the black vertical line. Steps before perturbation (i.e. step -2 & step -1) were combined into a baseline score for statistical analysis. *Note:* * significantly different from baseline, # significantly different between groups.

Table 1: Output of the linear regression models for ML gait perturbations, only including the first trials.

Parameter		*Inward affected*			*Outward affected*		
		Group Effect		Estimated delta score	Group Effect		Estimated delta score
		β (95% CI)	P-value		β (95% CI)	P-value	
ML MoS (m)	Post 1	0.00 (-0.03, 0.03)	0.846	-0.03 (-0.05, -0.02)	0.00 (-0.01, 0.01)	0.526	0.03 (0.03, 0.04)
	Post 2	0.01 (-0.01, 0.03)	0.381	0.02 (0.02, 0.03)	0.00 (-0.01, 0.01)	0.598	0.00 (-0.00, 0.01)
Step width (m)	Post 1	0.02 (-0.01, 0.04)	0.153	-0.09 (-0.10, -0.07)	0.01 (-0.01, 0.02)	0.338	0.06 (0.06, 0.07)
	Post 2	0.03 (-0.03, 0.08)	0.398	-0.08 (-0.10, -0.05)	0.01 (-0.01, 0.03)	0.391	0.09 (0.08, 0.11)
Step length (m)	Post 1	0.01 (-0.00, 0.03)	0.128	0.00 (-0.01, 0.01)	-0.00 (-0.02, 0.02)	0.860	-0.06 (-0.07, -0.05)
	Post 2	-0.04 (-0.08, 0.01)	0.113	-0.07 (-0.09, -0.05)	-0.04 (-0.07, -0.00)	0.047	HC: -0.10 (-0.12, -0.07) KneeOA: -0.13 (-0.16, -0.11)
Step time (s)	Post 1	0.00 (-0.01, 0.01)	0.844	0.00 (-0.00, 0.01)	0.00 (-0.01, 0.01)	0.612	-0.02 (-0.03, -0.02)
	Post 2	-0.02 (-0.04, 0.01)	0.145	-0.03 (-0.05, -0.02)	-0.01 (-0.03, 0.01)	0.291	-0.06 (-0.07, -0.05)

Data are presented as mean difference (95% CI)

Table 2: Output of the linear regression models for AP gait perturbations, only including the first trials.

Parameter		*Acceleration affected*			*Deceleration affected*		
		Group Effect		Estimated delta score	Group Effect		Estimated delta score
		β (95% CI)	P-value		β (95% CI)	P-value	
AP MoS (m)	Post 1	0.01 (-0.01, 0.02)	0.376	-0.05 (-0.05, -0.04)	0.02 (-0.01, 0.04)	0.244	-0.05 (-0.06, -0.03)
	Post 2	-0.01 (-0.03, 0.01)	0.416	0.03 (0.01, 0.04)	0.01 (-0.01, 0.03)	0.192	-0.08 (-0.09, -0.07)
Step width (m)	Post 1	-0.01 (-0.02, 0.00)	0.172	-0.02(-0.03, -0.01)	-0.00 (-0.02, 0.02)	0.934	0.01 (0.00, 0.02)
	Post 2	-0.00 (-0.03, 0.02)	0.659	0.02 (0.01, 0.03)	-0.00 (-0.02, 0.02)	0.786	0.01 (0.00, 0.03)
Step length (m)	Post 1	0.01 (-0.01, 0.03)	0.478	0.09 (0.08, 0.10)	0.04 (-0.01, 0.08)	0.108	-0.23 (-0.25, -0.21)
	Post 2	-0.05 (-0.09, -0.01)	0.026	HC: -0.08 (-0.11, -0.05) KneeOA: -0.13 (-0.16, -0.10)	-0.02 (-0.06, 0.01)	0.224	0.05 (0.03, 0.07)
Step time (s)	Post 1	-0.00 (-0.01, 0.01)	0.646	-0.02 (-0.03, -0.02)	0.01 (-0.01, 0.03)	0.192	-0.02 (-0.03, -0.02)
	Post 2	-0.03 (-0.05, -0.00)	0.023	HC: -0.11 (-0.13, -0.10) KneeOA: -0.14 (-0.15, -0.12)	0.00 (-0.02, 0.03)	0.893	0.02 (-0.01, 0.03)

Data are presented as mean difference (95% CI)

Chapter 6

Real-world gait and turning in individuals scheduled for total knee arthroplasty

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Abstract

Background
Improving mobility is a key treatment goal of total knee arthroplasty (TKA), however, objective indicators to evaluate mobility are lacking in clinical settings. The aim of this study was to compare real-world gait and turning between individuals scheduled for total knee arthroplasty (TKA) and healthy controls, using continuous monitoring with inertial measurement units (IMUs).

Methods
Real-world gait and turning data were collected for 5-7 days in individuals scheduled for TKA (n=34) and healthy controls (n=32) using IMUs on the feet and lower back. Gait and turning parameters were compared between groups using a linear regression model. Data was further analyzed by stratification of gait bouts based on bout length, and turns based on turning angle and turning direction.

Results
Dominant real-world gait speed was 0.21 m/s lower in individuals scheduled for TKA compared to healthy controls. The between-group difference in gait speed was -0.10 m/s for bouts containing 0-10 strides and -0.15 m/s for bouts with 160+ strides. Stride time was 0.05 s higher in individuals scheduled for TKA. Step time asymmetry was not different between the groups. Regarding walking activity, individuals scheduled for TKA walked 72 strides/hour less than healthy controls, and maximum bout length was 316 strides shorter. Irrespective of the size of the turn, turning velocity was lower in individuals scheduled for TKA. Turning velocity did not differ between turns over the affected leg compared to the unaffected leg.

Conclusion
Individuals scheduled for TKA showed specific walking and turning limitations in the real-world. Parameters derived from IMUs reflected a rich profile of real-world mobility measures indicative of walking limitation of individuals scheduled for TKA, which may provide a relevant outcome dimension for future studies.

Introduction

Individuals with knee osteoarthritis (OA) have difficulty walking, illustrated by reduced gait capacity compared to their healthy peers[1,2]. Gait capacity, defined as what people 'can do', is essential for activities of daily living and to participate in society[3]. These limitations in gait capacity can translate to a lower gait performance, i.e. to what people 'actually do' in the real-world, including a lower walking activity[4,5]. As walking itself may counteract functional decline[6-9], low walking activity could lead to further worsening of gait capacity in individuals with knee OA. Given this apparent vicious circle between limitations in gait capacity and walking activity, mitigating walking limitations is of great importance to individuals with knee OA[10] and constitutes a reason to consider total knee arthroplasty (TKA)[11,12]. Insights about the extent of walking limitation is therefore relevant for individuals with knee OA opting for TKA.

A drawback of measuring of gait capacity is that it not necessarily corresponds with measures of gait performance[13,14]. With assessment of gait capacity usually being conducted in gait laboratories or other relatively controlled settings, its ecological validity may be limited[15,16]. Furthermore, data collection is typically restricted to a few short bouts of straight-ahead walking. This does not align with the fact that individuals with knee OA often report problems with longer bout durations, when pain becomes the dominating factor. Also, the focus on only straight-ahead gait does not match with real-world walking, when changes in direction are very common[17]. Moreover, turning during walking has been associated with fall risk, which is increased in individuals with OA[18].

Inertial measurement units (IMUs) have facilitated research into real-world mobility, enabling unobtrusive and continuous recording of gait and turning performance. In contrast to elderly and neurological populations[13,19-26], studies evaluating real-world gait and turning in individuals with knee OA are scarce[27-29]. Of these studies, only Chapman et al.[27] compared individuals scheduled for TKA with a healthy control group. However, only knee kinematics were evaluated in this study[27]. Moreover, in this study, the data from different gait bouts were collapsed into one mean value, while the capture of gait during multiple days also enables to differentiate between short and longer walking periods[20,22-24,30].

The aim of this study was to compare real-world gait and turning between individuals with knee OA, who are scheduled for TKA, and healthy individuals. We hypothesized that individuals scheduled for TKA would show poorer real-world gait and turning metrics compared to healthy individuals in the same age range. Capitalizing on the rich data set capturing multiple days of activity for each individual, we also explored the role of gait bout length on between-group differences in gait performance.

Method

Participants

Thirty-four individuals scheduled for TKA and thirty-two healthy individuals participated in this study. This study was part of a longitudinal study investigating real-life and challenging gait skills in individuals receiving posterior cruciate retaining TKA (https://osf.io/ec6nf/). This

study was powered to detect differences in real-world gait speed between individuals 1 year after TKA compared to healthy participants. As the difference in real-world gait speed between these groups is likely higher before than 1 year after TKA, we expected to have sufficient power for the current study. Individuals, aged 40-80 years, who were candidates for posterior cruciate-retaining TKA at the Sint Maartenskliniek were screened for eligibility by a research nurse. Eligibility criteria included: 1) symptomatic and radiographic knee OA (i.e. Kellgren-Lawrence grade ≥ 2), 2) intact posterior cruciate ligament, 3) correctable or <10° rigid varus or valgus deformity of the knee, and 4) stable health (ASA-score ≤ 3). Healthy participants did not have a diagnosis of knee OA, and were recruited from the community, striving for a similar distribution of age and sex as our study group with individuals scheduled for TKA. Participants were excluded based on the following criteria: 1) BMI > 35 kg/m^2, 2) moderate to severe knee, hip or ankle pain defined as an average score >4 on items 3-6 of the Short Brief Pain Inventory; excluding the knee indexed for TKA, 3) previous knee, hip, or ankle joint replacement, 4) any other musculoskeletal, neurological, or uncorrected visual disorder impairing gait or balance. This study was approved by the CMO Arnhem Nijmegen (2019-5824). All participants provided written informed consent and all procedures were in accordance with the Declaration of Helsinki. This sub-analysis was pre-registered on OSF (https://osf.io/dawv6).

Data collection

Clinical assessment

Anterior-posterior X-rays of the knee were obtained through regular care and were graded by an experienced orthopedic surgeon (KD) using the Kellgren and Lawrence classification system[31]. Anthropometric measurements, including height, body mass, and BMI were obtained pre-operatively, which was 1.8 months (IQR = 1.5) before TKA. Both for individuals scheduled for TKA and healthy controls, pain scores during activity and rest over the last week were obtained using a numeric rating scale (NRS), with a range 0-10 with higher scores indicating higher pain ratings. For individuals scheduled for TKA, the Knee injury and Osteoarthritis Outcome Score – Physical Function shortform (KOOS-PS)[32] and Knee Society Score (KSS)[33] were also obtained. KOOS-PS scores were transformed to a 0-100 scale with a score of 100 representing no difficulty. For the KSS, only the clinical and functional score were obtained (both on a 0-100 scale) with 100 representing best function.

Real-world gait and turning assessment

Participants wore three IMUs, two of which were embedded in instrumented socks (prototype developed by APDM Wearable Technologies, Portland, OR, USA; similar as in[26]) (Figure 1) and one was placed on the lower back at the sacrolumbar level (Opal v2, APDM Wearable Technologies, Portland, OR, USA). The IMUs in the socks were placed on the dorsum of both feet. Participants started wearing the sensors the day after the clinical assessments were performed. Participants wore the sensors during daytime for a total period of 5-7 days, always including at least one weekend day. Participants were instructed to start wearing the sensors in the morning, when they started performing their daily activities. Battery life of the sensors was approximately 10-12 hours. Sensor batteries were charged overnight. All data was stored on a local memory drive (8 GB) embedded in the sensors. When data collection was completed, sensors were returned via a postal office after which data was transferred to a desktop computer for offline processing.

Figure 1: Overview of the IMUs embedded in socks. The sensor system consisted of a large casing (positioned above the lateral malleolus) containing the battery and memory drive, which was connected to the IMU on the dorsum of the foot via a small cable (left panel).

Data processing and analysis

Sensor data were processed using algorithms described in Shah et al.[25]. Using a time domain approach, alternating periods of movement and stillness – corresponding to stance and swing – were identified from accelerometer and gyroscope signals from the feet to detect potential gait bouts. Individual strides were combined into the same gait bouts as long as the duration between strides was less than 2.5 seconds. Subsequently, all gait bouts containing more than 3 strides were processed via the Mobility Lab algorithm (APDM Wearable Technologies, Portland, OR) to compute spatiotemporal gait parameters for each stride per gait bout[34]. This algorithm has shown good concurrent validity and acceptable absolute errors compared to a gold standard pressure mat system[34]. In older adults, absolute errors were -0.11 m/s for gait speed (ICC = 0.934) and 0.01 s for stride time (ICC = 0.998). Turns during walking were identified from the gait bouts based on the gyroscope data of the sensor on the lower back, using algorithms described in[35]. This algorithm looks for periods where the angular velocity around the vertical axis exceeds 15°/ s. The start and end of the turn are defined by the point where the angular velocity around the vertical axis drops below 5°/ s. Turns with an angle larger than 45° and a duration between 0.5 and 10 seconds were labeled as valid turns. Compared to an optical motion capture system, this algorithm had a sensitivity of 0.90 and specificity of 0.75[35].

For each individual, a normalized frequency distribution of gait speed of all included strides was constructed. From this distribution, the following parameters were determined: real-world gait speed defined as the dominant peak of the distribution, maximum real-world gait speed defined as the 95th percentile of frequency distribution, and the interquartile range (IQR) of the distribution. Based on previous studies reporting a bimodal distribution for real-world gait speed[13,36], we opted for the value at the dominant peak to approximate real-world gait speed. Stride time was calculated as the median of the stride times of all collected strides per participant, as this parameter did not follow a bimodal distribution. Step time asymmetry was defined as the difference in step time between the affected leg and the unaffected leg, divided by the mean value, multiplied by 100%. Parameters reflecting walking activity included the maximum gait bout length of all included gait bouts over all days, the average number of gait bouts per monitored hour, and number of strides per monitored hour. In order to study the effect of gait bout length on gait speed, we first evaluated availability of gait data for bouts of a specific length. This analysis was used to define 6 bins (i.e. 0-10, 11-20, 21-40, 41-80, 81-160, and 160+ strides). For each bin, the average gait speed of all gait bouts was taken.

For all identified turns per participant, the maximum turning velocity was derived from the transversal angular velocity signal of the IMU on the lower back. For each participant, a frequency distribution of this parameter was constructed. The median of this distribution was chosen to characterize turning velocity. In addition, the number of turns per monitored hour was compared between groups. Turning velocity was analyzed separately for turns over affected and unaffected leg for individuals scheduled for TKA, whereas for healthy controls the median over all turns was used. To better evaluate if group differences in turning velocity might have been due to differences in the size of the turning angle[21], an exploratory analysis was performed by categorizing turns based on turning angles < 90 degrees, 90-180 degrees, or >180 degrees. Post-processing of gait and turning parameters was performed in Python 3.8.3.

Statistical analysis

Gait and turning parameters were compared between groups using a linear regression model with the specific gait or turning parameter as dependent variable, group as the between-group factor, and age, sex, and height as covariates. In case model assumptions (i.e. normal distribution of the residuals) were violated, data was log-transformed. Estimates were back transformed by taking the exponent of the estimate. If model assumptions were still not met, groups were compared using the Mann-Whitney U test. Furthermore, to study the effect of gait bout length on gait speed, an independent samples t-test was conducted for each bin that contained at least data from 70% of all participants. When parametric testing was possible, between-group differences were reported as mean differences (i.e. individuals scheduled for TKA - healthy participants) with 95% confidence intervals. Statistical analyses were conducted in RStudio using the stats package (version 4.1.2).

Results

Participant characteristics

Participant characteristics are provided in Table 1. Individuals scheduled for TKA had on average higher body mass and BMI, and experienced more pain during rest and activity compared to healthy controls. Monitored time was similar between the two groups and corresponded to approximately 10-12 hours/day of monitoring per participant. Data of one healthy control could not be analyzed due to an error in one of the sock sensors. Furthermore, for one participant scheduled for TKA turning data was lacking due to a lumbar sensor error.

Table 1: Baseline characteristics of both study groups.

Parameter	Individuals scheduled for TKA (n=34)	Healthy controls (n=31)	Mean difference [95 % CI]
Age (y)	65 (9)	65 (10)	0 [-4 ; 5]
Sex (M:F)	13:21	12:19	-
Height (m)	1.73 (0.11)	1.75 (0.07)	-0.02 [-0.06; 0.03]
Mass (kg)	86 (15)	75 (11)	11 [4; 17]
BMI (kg/m^2)	28.5 (3.4)	24.5 (3.1)	4.0 [2.4; 5.6]
KL grade (I:II:III:IV)	0:0:10:24	-	-
KOOS-PS (0-100)	55 (12)	-	-
KSS - clinical score (0-100)	65 (8)	-	-
KSS - functional score (0-100)	65 (14)	-	-
NRS pain rest (0-10)	4.1 (2.5)	0.5 (1.0)	3.6 [2.7; 4.6]
NRS pain activity (0-10)	6.2 (2.0)	0.7 (1.0)	5.5 [4.7; 6.3]
Monitored time (h)	60 (17)	58 (17)	2 [-7; 10]

Note: Data are provided as mean (SD). BMI = body mass index, KL = Kellgren Lawrence, KOOS-PS = Knee Osteoarthritis Outcome Score – Physical Function Shortform, KSS = knee society score, NRS = numeric rating scale. For KOOS-PS and KSS scores, higher scores indicate better function. For the NRS, higher ratings indicate more pain.

Differences in real-world gait parameters

Distributions of real-world gait speed are provided on an individual level in Figure 2. In most individuals, the data distribution was left-skewed, with a wide range of gait speeds for each participant. The value at the dominant peak was 0.21 m/s ($p<0.001$) lower in individuals scheduled for TKA compared to healthy controls. Similarly, values at the 95th percentile were 0.17 m/s (95% CI: 0.09; 0.25, $p<0.001$) lower in individuals scheduled for TKA. No difference between the two groups was observed in the IQR of the distribution (Table 2). Furthermore, individuals scheduled for TKA walked with a higher stride time (median diff = 0.05 s, p = 0.003) than healthy controls (Figure 3D). Step duration asymmetry was not different between the two groups (mean diff = 0.6 %, 95% CI: -0.9; 2.0, p = 0.426; Figure 3E).

With respect to parameters related to walking activity, maximum gait bout length was lower in individuals scheduled for TKA (median diff = -316 strides, p = 0.005; Figure 3F). Although there was no difference in the number of gait bouts per hour (mean diff = -0 bouts/hour, 95% CI = -1; 1, p = 0.904; Figure 3G), the number of strides per hour was lower in individuals scheduled for TKA compared to healthy controls (median diff = -72 strides, p < 0.001; Figure 3H).

Differences in real-world turning parameters

For turning velocity, individual data distributions are shown in Figure 2. Velocity was not different between turning over the affected vs. the unaffected leg in individuals scheduled for TKA (mean diff = 1.4 deg/s; 95% CI = -0.0; 2.7, p=0.053; Figure 4A). Compared to healthy controls, turning velocity for turns over the affected (mean diff = -6.2 deg/s, 95% CI = -11.7; -0.8, p=0.026) as well as for turns over the unaffected leg (mean diff = -7.6 deg/s; 95 CI: -13.0; -2.2, p=0.007) was lower than in healthy participants. Further exploration of this data revealed that turning velocity increased with larger turning angles. The direction of the group differences was similar for different angle sizes (Figure 4C-E). The number of turns per hour was not different between individuals scheduled for TKA and healthy controls (mean diff = -1.8 turns; 95% CI: -7.2; 3.7, p = 0.520; Figure 4B).

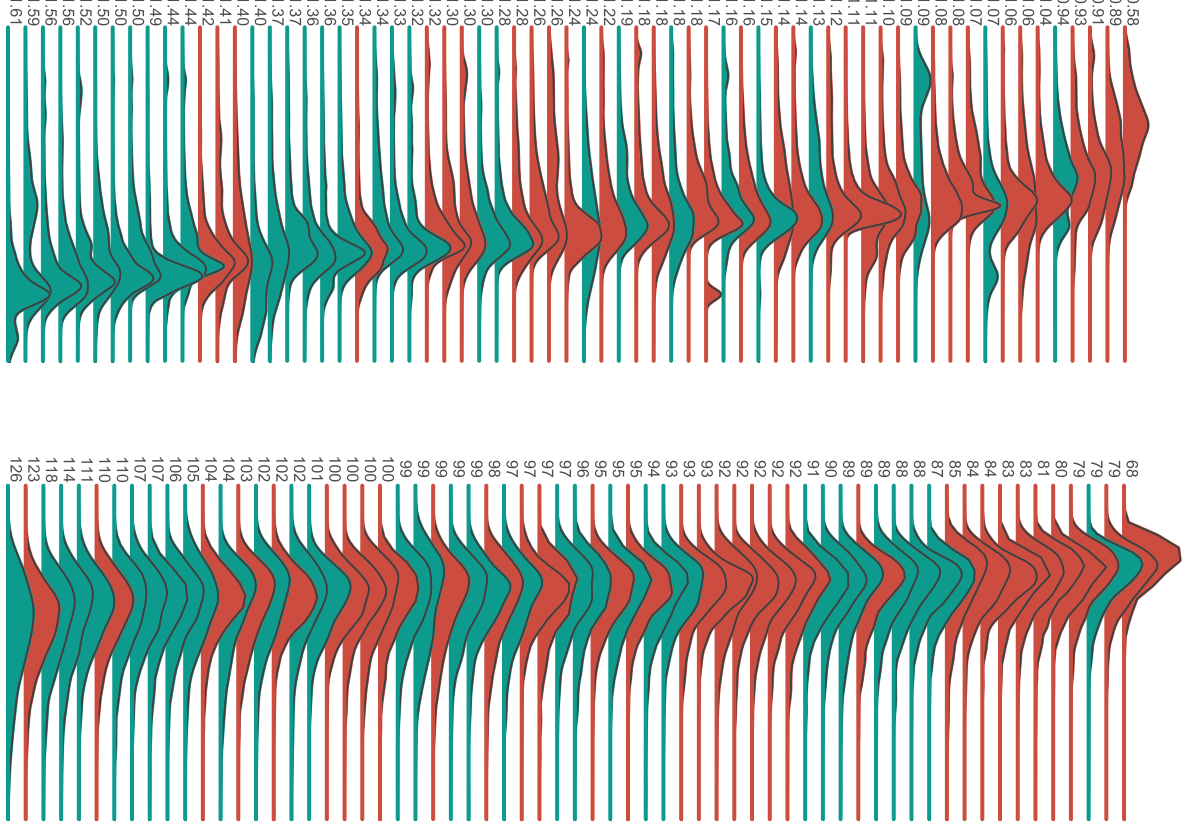

Figure 2: Ridgeplots showing all individual distributions of real-world gait speed (left panel) and maximum turning velocity (right panel) for individuals scheduled for TKA (red) and for healthy controls (green). For individuals scheduled for TKA both turns over the affected and unaffected leg were included. Data are ordered from low to high based on the value at the dominant peak of real-world gait speed or the median of maximum turning velocity (exact values are indicated on the y-axis).

Table 2: Detailed output of the statistical models comparing individuals scheduled for TKA and healthy controls. Data are presented as mean (SD) for both groups if not otherwise indicated. In the case data were log-transformed or non-parametric tests were conducted, data were presented as median (IQR) (*in italic*).

Parameter	Individuals scheduled for TKA (n=34)	Healthy controls (n=31)	Median difference	Estimate (95% CI) of the group difference	Test statistic	P-value
Gait speed - value at dominant peak (m/s)	*1.15 (0.17)*	*1.36 (0.28)*	-0.21	-	U = 840	<0.001
Gait speed - 95th percentile (m/s)	1.35 (0.17)	1.53 (0.16)	-	-0.17 (-0.25; 0.09)	t(63) = -4.32	<0.001
Gait speed - IQR (m/s)	*0.27 (0.08)*	*0.26 (0.10)*	0.01	1.01 (0.86; 1.20)*	t(63) = 0.17	0.863
Stride time - median (s)	*1.14 (0.12)*	*1.09 (0.07)*	0.05	-	U = 321	0.007
Step time asymmetry (%)	1.4 (3.2)	0.6 (2.7)	-	0.6 (-0.9; 2.0)	t(63) = 0.80	0.426
Maximum bout length (strides)	*248 (306)*	*564 (714)*	-316	0.52 (0.34; 0.82)*	t(63) = -2.93	0.005
#Bouts/hour	6.1 (2.9)	6.1 (2.5)	-	-0.0 (-1.4; 1.3)	t(63) = -0.07	0.941
#Strides/hour	*123 (114)*	*195 (237)*	-72	0.55 (0.37; 0.81)*	t(63) = -3.08	0.003
Maximum turning velocity - median (deg/s)						
Affected	93.1 (10.9)	-	-	Aff vs. HC: -6.2 (-11.7; -0.8)	t(62) = -2.29	0.026
Unaffected	91.7 (10.7)	-	-	Unaff vs. HC: -7.6 (-13.0; -2.2)	t(62) = -2.81	0.007
Combined	-	99.4 (10.1)	-	Aff vs Unaff: 1.4 (-0.0; 2.7)	t(32) = 2.01	0.053
#Turns/hour	24.1 (10.0)	25.8 (11.3)	-	-1.8 (-7.2 ; 3.7)	t(62) = -0.65	0.520

Aff = affected leg, Unaff = unaffected leg, HC = healthy controls
* = parameter was log-transformed. Estimates should be interpreted as relative change of the parameter compared to the value of healthy control

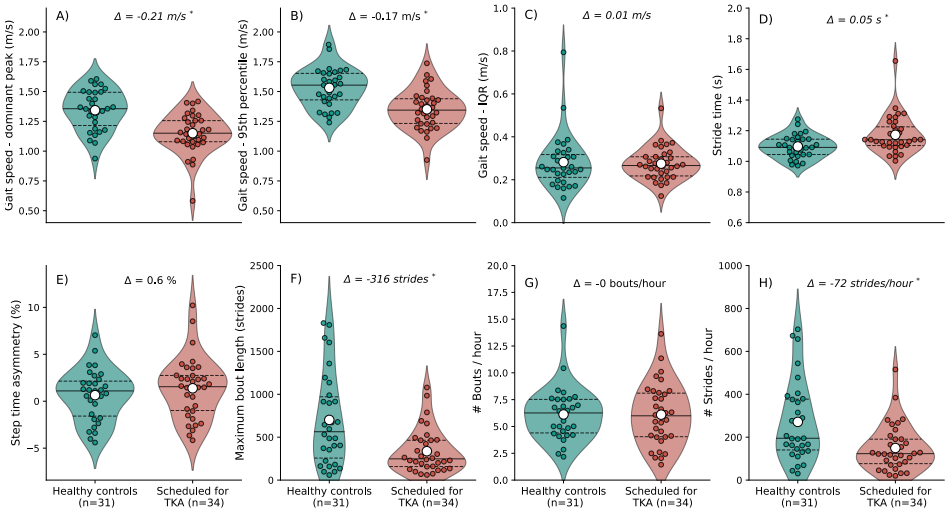

Figure 3: Violin plots with for all gait parameters with an overlay of individual datapoints. Mean values are indicated by the large white dots in the distributions, median values by the solid lines, and 1st and 3rd quartiles are indicated by the dashed lines. Mean or median differences (in italic) are reported in each panel. A complete overview of the output of the statistical models is provided in Table 2. * = statistically significant at $p<0.05$

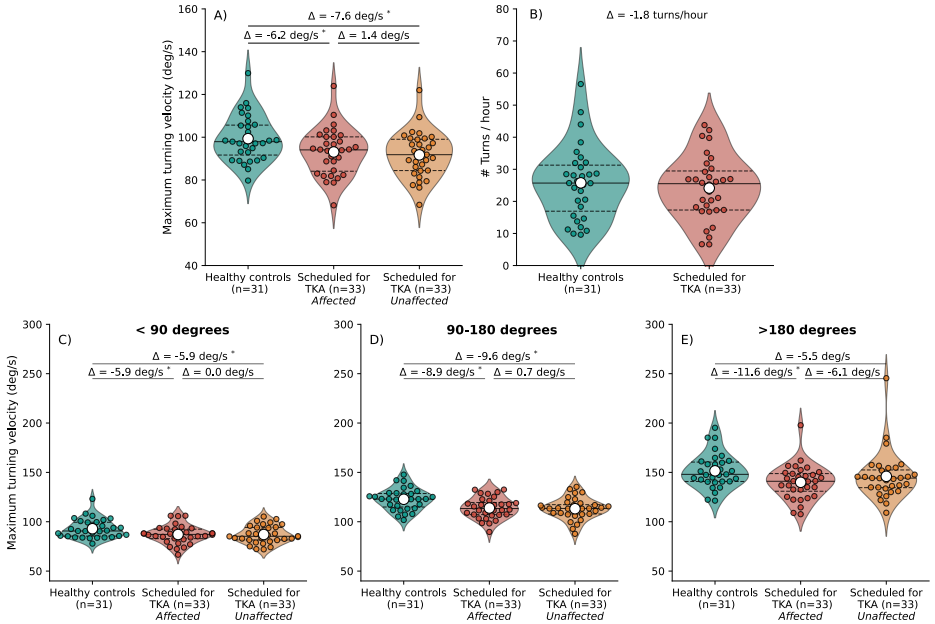

Figure 4: Violin plots with for all turning parameters with an overlay of individual datapoints. Mean values are indicated by the large white dots in the distributions, median values by the solid lines, and 1st and 3rd quartiles are indicated by the dashed lines. Mean differences are reported in each panel. A complete overview of the output of the statistical models is provided in Table 2. * = statistically significant at $p<0.05$

Effect of gait bout length on gait parameters

To determine the effect of gait bout length on gait speed, we first evaluated the presence of gait bouts of different lengths in both groups. Definition of the final bin was based on a cut-off value of 70% data availability for each of the groups. At a final bin size of 160+ strides, 71% of individuals scheduled for TKA and 83% of healthy individuals had data available (Figure 5). From Figure 5, it can also be observed that the group scheduled for TKA had smaller maximum bout lengths than the healthy control group.

Analysis of gait speed depending on bout length revealed that for both individuals scheduled for TKA and healthy participants, gait speed was higher for longer bout lengths (Figure 5). More specifically, in individuals scheduled for TKA gait speed increased from 0.86 ± 0.12 m/s for bouts between 0-10 strides, to 1.18 ± 0.13 m/s for bouts longer than 160 strides. In healthy controls, gait speed changed from 0.96 ± 0.16 m/s for bouts between 0-10 strides to 1.33 ± 0.15 m/s for bouts longer than 160 strides. Mean differences between groups were -0.10 m/s for the shortest gait bouts and -0.15 m/s for the longest gait bouts (Figure 5).

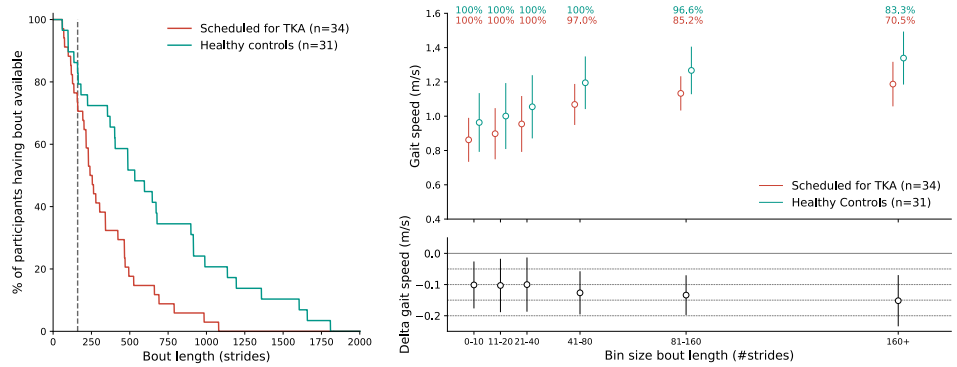

Figure 5: Left panel: availability of gait bouts of a specific bout length in both groups. The dashed line at a bout length of 160 strides indicates our maximum bin size, with 83% availability in healthy participants and 71% in individuals scheduled for TKA. Right panel: effect of bout length on gait speed. In the top panel mean and standard deviations are displayed for each bin size for both groups. In addition, data availability for each group is indicated as the percentage of individuals for whom data are available in each bin. Mean differences with 95% confidence intervals are provided in the bottom panel.

Discussion

In this study, we provide a detailed account of real-world gait and turning performance in individuals scheduled for TKA. Consistent with our hypothesis, real-world gait and turning performance of individuals scheduled for TKA was markedly poorer than healthy controls, evidenced by a lower gait speed, a lower turning velocity, a lower maximum gait bout length, and less strides per hour. In addition, the group difference in real-world gait speed was -0.10 m/s for shortest gait bouts and -0.15 m/s for the longest gait bouts. Notably, individuals scheduled for TKA did not walk with higher step time asymmetry compared to healthy participants.

Individuals scheduled for TKA had on average a 0.21 m/s lower dominant walking speed than their healthy peers. Similar differences have been reported for gait speed in supervised settings (i.e. gait capacity)[1,2]. Not only the value at the peak of the distribution (i.e. the most frequently observed gait speed per individual), was lower in individuals scheduled for TKA, but also the 95th percentile of the distribution (resembling gait capacity[13,37]) was lower. In combination with our finding that the IQR was not different between groups, these results indicate that in the group of individuals scheduled for TKA the whole distribution of individual gait speeds was shifted towards lower values. With the median group difference in stride time being 0.05s, this difference in gait speed can be explained as a combined effect of longer stride times and shorter stride lengths.

Continuous monitoring of walking enabled a profound analysis of the potential factors underlying differences in gait speed between individuals scheduled for TKA and their healthy peers. A major advantage of this data capture mode is the possibility to evaluate the effect of gait bout length on the derived gait speed. In line with previous studies[23,24,30], we found that in both groups gait speed scaled with bout length. The between-group difference became somewhat larger with increasing bout length, although the magnitude of this effect was relatively small (i.e. from -0.10 m/s in the shortest gait bouts to -0.15 m/s in the longest gait bouts) and was lower than the overall group difference in gait speed. However, it is important to note that longer, uninterrupted gait bouts were scarce in individuals scheduled for TKA. Together, these results may indicate that the overall mean group difference in gait speed can partly be explained by the finding that individuals with advanced knee OA walk shorter distances per gait bout. This latter finding is consistent with low activity levels observed in knee OA groups[38], and with the lower number of steps taken as observed in the current as well as in other studies[4,5].

In line with a previous meta-analysis of studies measuring gait capacity[2], there was no group difference in step time asymmetry. Although asymmetries in knee joint loading[39] and kinematics[40] have been reported in individuals with unilateral knee OA, this does not seem to be reflected in temporal asymmetries, particularly given that mean asymmetry was close to zero (i.e. perfect symmetry) in the current study. This finding is also consistent with our data collected during a 2-minute walk test[41].

In addition to real-world gait parameters, turning velocity was lower in individuals scheduled for TKA than in healthy controls, irrespective of the size and direction of the turn. Individuals scheduled for TKA may thus exploit a generally more cautious turning strategy. In a previous study, we also found slower turning in individuals scheduled for TKA for 180 degree turns during a 2-minute walking trial[42]. Importantly, lower real-world turning velocity has been associated with a higher fall risk[21,43], adding relevance to these findings. The absence of a difference between turning in the direction of the affected vs. the unaffected leg in individuals scheduled for TKA may not be surprising, given that compensation is possible as both legs are involved in making the turn, which typically consist of 2-4 steps according to real-world data[21,43].

Our findings hold important clinical relevance. For individuals with knee OA, walking activity is important to protect against further disease progression[6-9]. Moreover, individuals scheduled for TKA list improving walking ability as a main treatment goal[11,44]. Our data clearly indicate walking limitations for the average individual scheduled for TKA. In fact, most individuals scheduled for TKA did not show uninterrupted gait bouts lasting longer than 10 minutes, which may be a limiting factor for recreational walking or purposeful trips to, for example, a shopping center. On the other hand, a large proportion of individuals scheduled for TKA walked at relatively high speed (i.e. > 1.25 m/s[3]), and were well able to scale up gait speed with increasing bout length. In this group, the room for improvement is limited, which is important information when discussing expectations regarding knee arthroplasty.

This study has a number of limitations that merit attention. First, as of yet, no consensus or standard exists on how to process real-world gait data collected with IMUs. Choices made in the sensor configuration and processing algorithms – including sensor location (i.e. lower back vs. feet), definitions of gait bout start and stops, and degrees of freedom in heading direction – may have had a substantial impact on the derived gait and turning performance parameters. Although such influences on the between-group comparisons in our study are likely small, they limit comparison of results with other studies that used different sensor configurations and/or algorithms[13,20,28-30]. Secondly, battery life of the sensors was limited to 10-12 hours. Thus, we did not capture gait and turning data for the full day. However, total monitored time was similar between groups, and quantitative parameters were normalized to the number of hours. Nevertheless, this limits interpretation of our results in terms of physical activity, for example when comparing our data to guidelines for the recommended number of steps per day[38]. Finally, our sample included individuals with unilateral knee OA without previous joint replacement surgery in any other joint. This resulted in a selected group, not representative for all individuals scheduled for TKA, who may have a relatively high walking performance. Nonetheless, compared to the Dutch population undergoing TKA, our group only had a slightly lower age (i.e. 4 years), while BMI and male/female ratio were relatively similar[45].

Conclusion

Real-world monitoring of gait and turning using IMUs revealed that individuals scheduled for TKA had lower walking activity and lower real-world gait and turning speed compared to healthy peers of similar age. Parameters derived from IMUs provided a rich profile of real-world mobility measures that were indicative of walking and turning limitations, which may provide a relevant dimension for future studies.

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Chapter 7

Summary and general discussion

Summary

The overarching aim of this thesis was to comprehensively evaluate walking, including gait capacity and gait performance, in individuals with lower-extremity OA, from the perspective that this knowledge can contribute to the establishment of objective indicators of physical functioning relevant for clinical evaluation of individuals with lower-extremity OA.

Chapter 2 detailed a cross-sectional study, in which four independent domains of gait capacity measures were identified from a large set of correlated parameters: speed-spatial, speed-temporal, dual-task cost, and upper body motion. The first two domains were dependent on gait speed and provided multiple parameters that were sensitive to the presence of knee or hip OA, including cadence and stride length. Dual-task cost, however, was not sensitive to knee or hip OA, which indicated that gait of people with lower-extremity OA did not require disproportionate amounts of attention. Individuals with hip OA, but not those with knee OA, walked with larger lumbar range of motion in the sagittal plane than healthy controls.

In **chapter 3** the scope of studies that used IMUs to quantify limitations in gait capacity and gait performance in individuals with knee OA was further examined. In a systematic review, I showed that most studies focused on spatiotemporal parameters, while parameters related to knee and trunk kinematics were also commonly reported. Despite the advantage of IMUs to enable measurement of gait outside controlled laboratory settings, there was a clear gap towards remote monitoring of gait performance. A meta-analysis confirmed that spatiotemporal parameters had good discriminatory capacity, similar to the results of chapter 2. In addition, kinematics of the knee and trunk also showed relatively large effect sizes, and may thus hold value for the evaluation of gait capacity in individuals with knee OA.

The recovery of gait capacity and self-reported pain and physical functioning after TKA or THA was investigated in **chapter 4**. In both patient groups, gait parameters gradually improved towards the level of healthy individuals 15 months after TKA and THA. These recovery trajectories were markedly different from self-reported scores, which showed large improvements within the first two months. This suggests that gait parameters carry important information about gait recovery that is not captured by patient-reported outcome measures (PROMs).

In **chapter 5**, I focused on a different part of gait capacity: dynamic balance. In this chapter, I compared balance recovery responses after mediolateral and anteroposterior gait perturbations between individuals with knee OA and healthy participants. Despite having pain and structural impairments in and around the knee, individuals with knee OA showed no clear differences in balance recovery compared to their healthy peers. Two potential explanations for this finding can be postulated: 1) individuals with knee OA may exploit the redundancy in the sensorimotor control system to achieve similar stepping characteristics, or 2) the perturbation paradigm used in this study was insufficiently challenging to reveal possible differences in dynamic balance control.

In **chapter 6**, I switched focus from gait capacity to gait performance in the real-world. Using continuous monitoring, gait and turning performance were compared between individuals scheduled for TKA and healthy individuals. Real-world mobility parameters derived from IMUs

were indicative of walking limitations. That is, individuals scheduled for TKA had a slower gait and turning speed, exhibited shorter gait bouts, and a lower number of strides per hour than healthy individuals. Given that real-world gait more closely relates to participation, and may be different from gait capacity, parameters of real-world gait performance may contain valuable information about physical functioning of individuals scheduled for TKA.

General Discussion

According to the framework proposed by Maetzler et al.[1] (see Figure 2 in Introduction), comprehensive assessment of walking requires evaluation of gait capacity, gait performance, and someone's own perception of walking. In this thesis, I attempted to gain insights into which of these domains (and which associated outcomes) carry valuable information about walking of individuals with lower-extremity OA, relevant to patients, medical specialists, and/or researchers. This General Discussion will be centered around this theme. I will start the discussion by reviewing the gait capacity and gait performance measures used throughout this thesis in light of some key measurement properties (i.e. discriminatory ability, specificity, and responsiveness). I will follow-up with a discussion on the relationship between the domains gait capacity, gait performance, and perception, and how this impacts the evaluation of walking in individuals with lower-extremity OA. Moreover, I will reflect on the results of this thesis with respect to the methodological issues associated with evaluation of walking, particularly when using IMUs. Finally, I will discuss the clinical implications of the work presented in this thesis and provide some directions for future research.

Discriminatory ability of gait capacity and gait performance measures

For an outcome measure to be of value for the evaluation of walking, a minimal requirement is that the measure can discriminate pathological gait (here of individuals with lower-extremity OA) from unimpaired gait. **Chapters 2 and 3** focused on evaluating the discriminatory ability of gait capacity measures derived from IMUs. Generally, spatiotemporal parameters were found to have very good discriminatory ability. The most commonly used spatiotemporal parameter, gait speed, has previously been designated as the 'sixth vital sign', given that it is a general marker of physical health[2]. For example, gait speed has been reported as predictor of mortality[3], risk of future hospitalization[4], and fall-risk[4]. Due to its measurement properties, gait speed can be applied as a general biomarker for mobility in many different populations[5], including individuals with lower-extremity OA.

In addition to spatiotemporal measures obtained during straight-ahead walking, dynamic balance and gait adaptability may be relevant components of gait capacity[6]. Both components are crucial for maintaining gait stability in daily life, particularly when walking in challenging environments. With epidemiological studies showing that individuals with lower-extremity OA are 25-54% more likely to experience a fall compared to those without OA[7-11], evaluation of these two domains seems of particular interest. For individuals with lower-extremity OA, it can be hypothesized that local impairments in the knee or hip, including joint pain, reduced muscle strength, poor proprioception, and joint instability[12], translate into a poorer ability to withstand balance perturbations. However, the results of **chapter 5** showed that measures of dynamic balance did not discriminate balance recovery responses of individuals with knee OA from those of healthy individuals. We are, thus, left with the question if knee OA leads to an impaired gait stability. That is, we are unable to fully disentangle whether the absence of evident balance problems in **chapter 5** was due to 1) unaffected gait stability, or 2) the ability to compensate for local problems within the sensorimotor control system, or 3) an insufficiently challenging experimental paradigm that did not reveal possible differences in gait stability. Considering the comparable fall rates between groups in **chapter 5**, it seems likely that OA does not necessarily lead to poor gait stability. Rather, presence of knee OA may interact with other risk factors for falls, such as physical inactivity, slow gait speed (i.e. <0.7 m/s[4]), and muscle weakness[13]. This seems to be a plausible explanation, given that the individuals with knee OA in this study still showed a relatively good physical function, indicated by a relatively high gait speed (on average 1.15 m/s in **chapter 6**).

The evaluation of gait adaptability was considered to be beyond the scope of this thesis. Nonetheless, this does not rule it that gait adaptability could be a relevant component of gait capacity with good discriminatory ability. In light of the scarcity of studies examining gait adaptability in individuals with lower-extremity OA (i.e. only one pilot study investigated gait adaptability in individuals with knee OA[14]), this question is still open for future research.

For a more extensive assessment of gait capacity, we also investigated gait during a dual-task paradigm and during turning in **chapter 2**. Dual-task paradigms provide a way to make inferences about the attentional resources allocated to walking, via the calculation of dual-task costs. Furthermore, dual-tasking is a relevant aspect of our daily life behavior (i.e. people commonly walk while talking, carrying bags, or while scanning the environment or traffic). While it can be expected that pain results in increased attention being paid to someone's gait (i.e. people may walk more carefully to avoid pain), dual-task costs were not different from healthy controls in individuals with lower-extremity OA. This result may imply that the extra attentional resources needed for walking with pain do not exceed the maximum attentional capacity of individuals with lower-extremity OA, who are otherwise unaffected in their movement control. Hence, based on our study results, evaluation of dual-task gait does not seem relevant for individuals with lower-extremity OA.

Turning steps are highly prevalent in daily life walking[15]. This was confirmed by the results of **chapter 6** showing that healthy participants, on average, made 27 turns per hour. In addition, turning involves rotational forces at the knee and hip joint that may lead to more discomfort than during straight-ahead gait. Results of **chapter 2** indicated that turning capacity showed large effect sizes for the comparison between individuals with knee or hip OA and healthy participants. Together with the fact that individuals scheduled for TKA list turning as a relevant functional activity[16], evaluation of turning capacity may thus be of interest, although its additional value over gait speed was not immediately clear from results of the factor analysis. Furthermore, more detailed assessment of knee or hip kinematics and kinetics during turning could provide additional insights into why individuals with knee or hip OA turn slower.

With respect to gait performance (**chapter 6**), various parameters showed good discriminatory ability with potential value for the evaluation of individuals with knee OA – and potentially also hip OA. In line with results on gait capacity (**chapters 2 and 3**), spatiotemporal measures showed large effects when comparing individuals with knee OA with their healthy peers. In the evaluation of gait performance, advantage can be taken of the wealth of strides collected during multiple day, continuous monitoring. A more detailed assessment can be done using

the frequency distribution of gait speed rather than collapsing all the data into a mean value. This approach could also enable individual pre-post comparisons to statistically test changes in gait performance after an intervention.

Aside from parameters related to the 'quality' of gait, walking activity is an important aspect of gait performance. Engaging in physical activity, including walking, is important for individuals with lower-extremity OA. Furthermore, higher levels of physical activity can counteract functional decline[17-20] and are beneficial to overall health status. Although the experimental set-up in **chapter 6** was not focused on capturing physical (in)activity (i.e. we did not monitor our participants the entire day), our data on walking activity aligned with previous studies showing that individuals with lower-extremity OA were less active than those without OA[21-23]. That is, individuals with knee OA took less strides per hour than their healthy peers, and their maximum gait bout length was lower. Maximum gait bout length approaches someone's maximum walking distance, which is commonly asked for by orthopedic surgeons to indicate limitations in daily life activities. However, it is important to note that maximum bout length is heavily dependent on cut-off values used to separate gait bouts in the processing algorithm. Given the fact that improving mobility, including walking distance, is an important treatment goal of individuals scheduled for TKA and THA[24,25], these parameters might be used as indicators for joint replacement surgery and to evaluate treatment success. Availability of data on walking activity may further help to counsel patients with respect to their physical activity level.

Specificity of gait parameters to individuals with lower-extremity OA

A drawback of spatiotemporal gait capacity and gait performance parameters is that they are general, non-specific markers of functional limitation. Similar differences in gait capacity compared to healthy individuals were observed in other (e.g. neurological) populations with mobility limitations[26-29]. The same holds for previously described gait performance parameters, including maximum gait bout length and walking activity. Lower-extremity and trunk kinematics, on the other hand, revealed gait deviations and compensations (i.e. lateral trunk lean[30], circumduction[30], stiff knee gait[31]) that may be more specific to individuals with knee or hip OA[32,33]. In line with these results, in **chapter 2**, we found that parameters from the upper-body domain in individuals with hip OA were different from healthy controls, but this was not the case for individuals with knee OA. Overall, compared to spatiotemporal parameters, kinematic parameters may be better suited to pinpoint disease-specific gait deviations and compensations that individuals with knee or hip OA may employ during walking. Availability of these data could therefore lead to a more specific gait characterization.

Responsiveness of gait capacity and gait performance measures

Another indicator of good measurement properties is responsiveness, i.e. the ability to detect change after an intervention. **Chapter 4** indicated that measures of gait capacity were well able to detect changes after TKA and THA. In fact, we found that gait capacity recovered to the level of healthy peers 15 months after TKA and THA. Importantly, the literature shows that a significant proportion (i.e. 7-20%[34-36]) of individuals after THA and TKA is dissatisfied with treatment outcome due to insufficient pain relief and/or poor functional recovery. While, on average, we found good recovery on gait capacity and PROMs in **chapter 4**, some individuals showed poor recovery on gait capacity after TKA and THA. That is, 15 months after surgery, 5 out of 18 individuals after THA and 3 out of 21 individuals after TKA did not reach an

improvement in gait speed larger than 0.10 m/s, which is considered the minimal clinically important difference[37]. Whether gait performance and dynamic balance measures provide similar results remains to be elucidated from the 1-year follow-up data of the participants scheduled for TKA in **chapters 5 and 6**.

Relationship between gait capacity and gait performance

Assessment of gait performance seems to be important for individuals with lower-extremity OA, as it includes the daily life settings that are relevant to an individual's walking behavior. For example, in **chapter 6** we observed relatively wide ranges of real-world gait speed within an individual, which may be reflective of the variety of environments that a person encounters during daily life. This large variety of environments when measuring gait performance is in strong contrast with the controlled and consistent settings used to measure gait capacity such as in **chapters 2, 4, and 5**. Consequently, these differences in contextual and environmental factors between gait capacity and gait performance assessment may contribute to different results between these two domains.

A drawback of measuring gait performance is that we are unaware of the actual context of walking due to the unsupervised nature of this data capture mode. That is, from IMU data it is unknown in which environment someone has been walking, what the terrain was, and what the purpose of the walk was (e.g. to catch up with a friend, to walk your dog, to stroll in the shopping district, etc.). All these factors impact the observed walking behavior, but cannot be distilled from the data. The only information of context in this type of data collection is the length of the walking period (i.e. 'gait bout length'). The importance of gait bout length in the evaluation of gait performance is confirmed by our results in **chapter 6**. Irrespective of whether people had OA, we found a faster gait speed in longer gait bouts compared to short gait bouts, in line with previous literature[38-41]. Furthermore, the observed between-group differences in gait speed for bouts of equal length (i.e. -0.10 to -0.15 m/s) were consistently smaller than the overall between-group difference (i.e. -0.21 m/s) in gait speed. The fact that individuals with knee OA walked shorter gait bouts – when gait speed is lower – therefore also contributed to the overall mean group difference in real-world walking speed in **chapter 6**.

When comparing the results on gait capacity in **chapters 2 and 3** with the results on gait performance in **chapter 6**, we show that the average comfortable walking speed during evaluation of gait capacity was lower than the dominant real-world walking speed (i.e. performance). More specifically, average walking speed was 0.99 m/s (knee OA) and 1.25 m/s (healthy controls) for gait capacity, compared to 1.15 m/s (knee OA) and 1.36 m/s (healthy controls) for gait performance, respectively. Although the difference in gait speed between these chapters may be explained by differences in sensor hardware and participant characteristics, it could also imply that results on gait capacity do not necessarily have to align with those of gait performance. The observation of a weak correlation between gait speed derived from these two domains (r=0.33) also points in this direction[42]. Considering that gait speed obtained from the 2-minute walking test over 6 meter (i.e. capacity in **chapters 2 and 3**) was most comparable to gait speed during gait bouts of approximately 41-80 strides (i.e. performance in **chapter 6**), the observed differences between gait capacity and gait performance assessments might be attributed to gait bout length. In daily life, people may walk longer uninterrupted gait bouts (i.e. over longer distances) – when gait speed is higher – compared to assessment in the clinic, leading to a relatively higher walking speed.

The variety in contextual factors between evaluation of gait capacity and gait performance can also contribute to differences in effect sizes for the comparison between individuals with knee OA and healthy controls. That is, mean differences for the comparison between individuals scheduled for TKA and healthy controls tended to be smaller for evaluation of gait performance (**chapter 6**) compared to the evaluation of gait capacity (**chapters 2 and 3**). This was even more evident for turning, where we found a much larger effect size for turning capacity (SMD = 1.2) compared to performance (SMD = 0.7) for turns of the same turning angle. Presence of different contextual factors (i.e. different types of terrains, distractions, other people, obstacles, etc.) inherent in gait performance assessment may lead to a larger variety in the observed walking behavior, both within and among individuals. This may subsequently lead to a relatively lower effect size compared to assessment of gait capacity, where these factors are absent or standardized.

Altogether, this discussion raises the question as to which domain provides the best characterization of walking in individuals with lower-extremity OA. The answer to this question is likely dependent on the purpose of the assessment. Where evaluation of gait capacity results in a highly controlled evaluation with presumably larger effect sizes, evaluation of gait performance may be more relevant to an individual, with the additional benefit that it provides insight into walking activity. From a patient and clinical perspective, evaluation of gait performance may be more relevant, as functional limitations occur in the specific context of a patient's daily life. For scientific research purposes, however, it may be desirable to have good discriminatory ability and optimal statistical power, requiring a controlled environment with specific instructions, i.e. the evaluation of gait capacity. The decision to evaluate either gait capacity or gait performance may be further shaped by considerations with respect to feasibility. For example, assessment of gait capacity requires people to visit the laboratory or clinic, which cannot always be achieved. On the other hand, with gait performance assessment, data is typically remotely captured for multiple days, requiring logistics for sending and receiving the sensor systems. Many more factors, including the available financial resources, may eventually need to be factored into the equation.

Perception versus objective measures of gait capacity and gait performance

In current clinical practice, assessment of walking and physical functioning of individuals with lower-extremity OA primarily occurs through the patient's own perception. In addition, PROMs are routinely obtained in Dutch hospitals for large registry datasets (i.e. Dutch Arthroplasty Registry (LROI)) to evaluate physical functioning after TKA and THA. A major concern with self-reports, however, is that they capture a different domain of physical functioning than objective capacity or performance measures[43,44], and may be more strongly related to pain than to someone's capacity or performance[44]. In line with these observations, we found in **chapter 4** that recovery on self-reported scores of pain and physical functioning were similar to each other, but markedly different from those of gait capacity measures. Given that TKA and THA result in a faster relief of pain compared to recovery of physical functioning, the disparity between these two domains is particularly evident in the early post-operative period (i.e. until 3 months)[44]. Sailing on a patient's perception of physical functioning alone would thus be insufficient to capture the influence of lower-extremity OA on someone's health status. This not only holds for clinical decision making, but is also relevant for the orthopedic research community using PROMs as a proxy for physical functioning. Additional evaluation of someone's physical capacity or performance, such as recommended by the OARSI guidelines[45], is thus supported by the results of this thesis. Given that the execution of functional tests or the evaluation walking requires an additional time investment, studies evaluating the additional value of having objective indicators of physical capacity or performance available are required.

Methodological considerations for the use of IMUs in research and clinical settings

The main tools to capture gait capacity and gait performance in this thesis were IMUs. While IMUs enable quick and unobtrusive use within clinical settings as well as in the real-world, there are some methodological considerations that warrant attention. Two main points will be discussed below, being 1) the accuracy of IMUs and related algorithms to measure gait capacity and gait performance, and 2) the additional value of IMUs over other (more simple) tools to evaluate gait.

First, the value of gait capacity and gait performance parameters derived from IMUs is inherently linked to the accuracy of the measurement, including the assumptions coded in the algorithms. Plenty of studies have been conducted to evaluate the validity and reliability of algorithms for gait capacity measures based on IMU data, with numerous algorithms that have been validated against optical motion capture systems or pressure mats[46–51]. According to a recent systematic review and meta-analysis[52], performance of these algorithms is good to excellent for temporal aspects of gait, while errors for spatial parameters are generally larger. Importantly, the accuracy of gait parameters depends on sensor location, with sensors on the feet and related algorithms yielding the most accurate results[47]. For reference, the mean errors of the algorithm used in **chapters 2, 4, and 6** in this thesis were 0.01 s for stride time, -0.10 m for stride length, and -0.10 m/s for gait speed[48]. These errors tended to be larger at higher walking speeds[48]. Pre-operative differences in spatiotemporal parameters between individuals scheduled for TKA and healthy controls (**chapters 2, 3, and 6**) in this thesis, as well as changes after TKA and THA (**chapter 4**), exceeded these measurement errors. Nonetheless, it is important to keep these errors in mind as they determine the landscape with respect to the usefulness of these parameters. For data processing with IMUs, it is important to realize that: 1) sensors are affected by noise and bias, 2) gait events need to be accurately identified, 3) (double) integration of angular velocity or acceleration signals is often required, which may result spatial errors, and 4) the orientation of each sensor needs to be obtained by sensor fusion[53]. How all these issues are handled is directly related to the accuracy of each individual algorithm. Unfortunately, in the literature, open source algorithms are the exception rather than the rule, as we observed in our systematic review in **chapter 3**. This hampers technical progression of the field, causing each research group to reinvent the wheel. In addition, it leads to opacity and makes judgement of the underlying assumptions of an algorithm hard. This also holds for the commercial algorithm that we used in **chapters 2, 4, and 6**. Recently, a number of studies have set a good example by making their algorithms publicly available[54–56], and hopefully more will follow in the future.

In contrast to the literature on reliability and validity of gait capacity measures, there is a paucity of literature on how gait performance data is analyzed, what the validity of these algorithms is, and how reliable these assessments are. Analysis of gait performance from multiple day recordings comprises the additional challenge of correctly identifying and defining walking bouts. A recent study on this topic found that three promising algorithms in the literature had a sensitivity between 0.60 – 0.92 and a specificity of 0.95 – 0.99 for the

detection of walking bouts[55]. Importantly, these algorithms were only evaluated during walking activities. As such, these results cannot directly be translated to real-world data collection, where activities other than walking are ubiquitous. More work is needed to ensure good reliability and validity of real-world gait measurements. Importantly, best practices for the detection and definition of gait bouts need to be established to increase consistency among studies (i.e. how to handle pauses between gait bouts[57], what the minimum number of strides is for a gait bout, how to handle turns during walking, etc.).

The second main methodological consideration is that other tools may be superior than IMUs to evaluate walking, depending on the purpose of the assessment. Traditionally, motion capture systems have been used to provide a detailed account of gait capacity. Such assessments can provide insights about the mechanical factors involved in the disease processes of lower-extremity OA, which cannot yet be accurately obtained with IMUs. For a detailed evaluation of gait biomechanics, including kinematics and kinetics, use of three-dimensional motion capture is still the best option. However, gait assessment with motion capture systems is restricted to a laboratory environment, and recurrent (clinical) evaluation is often not feasible due to its labor intensive nature and relatively long set-up times. In these cases, IMUs can be prioritized. Given their ease of use, IMUs are better suited for large-scale assessments of gait capacity, with the downside that they not do provide the same level of detail as three-dimensional motion capture systems. Alternatively, pressure mats can offer the same ease of use as IMUs, but their outcomes are limited to spatiotemporal gait parameters and measurement volume is restricted to the size of the mat. Other more simple tools to evaluate walking would be to use a stopwatch during standardized mobility test, such as the 2-Minute Walk Test, Timed-Up-and-Go test, and the stair climbing test. While simple temporal measures could easily be obtained at every location with stopwatches, more detailed parameters (i.e. lower and upper-extremity kinematics) cannot be derived. Given that gait speed consistently showed the largest effect size in our studies, the use of a stopwatch could be an effective way to obtain insights into walking and physical functioning when time and resources are limited.

An advantage of wearables is that they enable capture of gait performance over longer periods of time, like in **chapter 6**. Use of wearables (i.e. IMUs) can thus offer the possibility of longer monitoring periods, without being restricted to a laboratory environment. Extending the measurement period to longer durations, such as the 5-7 days in **chapter 6**, may specifically be relevant for individuals with lower-extremity OA given the within-day[58] as well as day-to-day fluctuations in symptoms[59]. Other wearables such as smartphones or smartwatches may also be used to capture gait performance. In the newest smartphones, inertial sensor specifications are satisfactory to enable gait assessment. Since accessibility to smartphones is very large (i.e. nowadays 96% of the Dutch population between 16-64 years old has a smartphone[60]), smartphones could potentially be a new tool that may be exploited for large-scale assessments with a high measurement frequency. An important drawback is that sensor location is not standardized, and signals may be noisier when the phone is worn in a back or in a front pocket. Hence, the validity and reliability of parameters derived from this data capture mode will likely be more questionable[61]. Finally, smartwatches can provide reasonable estimates of walking activity, but the wrist is a less optimal location to derive other gait parameters.

Clinical implications and future perspectives

Based on the fact that self-report (including PROMs) insufficiently captures physical functioning, and (real-world) gait speed is an important indicator of mobility limitation in individuals with lower-extremity OA, objective gait data may have additional value for (clinical) evaluation of individuals with lower-extremity OA. However, strong evidence supporting its use in clinical decision making is currently lacking. There are, however, a couple of steps to take in the future, which may help to evaluate the value of objective gait parameters for clinical decision making.

First, individuals at risk of poor functional recovery could be identified based on IMU-derived gait data. Previous studies assessing recovery after TKA and THA using PROMs have identified distinct subgroups (i.e. high risers, gradual progressors, and non-responders) sharing similar recovery profiles after joint replacement surgery[62,63]. Given the large heterogeneity in recovery trajectories observed in **chapter 4**, it seems reasonable that such subgroups also exist for gait capacity measures. Establishing the existence of those subgroups in recovery of gait capacity using, for example, latent class modeling, could then lead to identification of these 'poor responders'. Subsequently, prediction models can be developed to identify who is at-risk of having a poor response. Given that we found high pre-operative walking speeds (i.e. >1.25 m/s) in 10 out of 34 individuals before TKA in **chapters 6**, and thus little room for improvement, patients could also be adequately counseled with regard to the suitability and expectations of joint arthroplasty when data on gait capacity or gait performance is available.

Another interesting possibility is to return data on (recovery of) gait capacity and gait performance to the patient and caregiver as feedback, to improve patient engagement and to monitor recovery. For example, simply providing feedback on walking activity (i.e. step counts) has been shown to be effective in promoting physical activity[64,65]. However, such application strongly hinges on the fact that data is readily available by use of an integrated health-care application or other digital health platform/application.

Overall conclusion

Without a doubt, evaluation of gait capacity and gait performance provides relevant information on physical functioning that is not captured by self-report of someone's physical functioning or walking ability. Spatiotemporal measures – both in the real world and in the laboratory – as well as data on walking activity were excellent indicators of mobility limitations in individuals with lower-extremity OA, illustrated by their good discriminatory ability and responsiveness. Kinematic parameters may provide better specificity and reflect gait compensations. Despite the strong potential of gait capacity and gait performance measures to evaluate mobility in individuals with lower-extremity OA, it is yet unclear how availability of this data may be used to improve clinical evaluation and decision making. Given that time with the patient is limited in clinical settings, there should be a strong case showing the additional value to support the use of objective gait parameters in clinical decision making. Remotely capturing gait performance using IMUs seems to be an interesting avenue, but future studies should further evaluate how this data can be used to transform clinical processes, such that it will benefit the patient in the future.

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Chapter 8

Nederlandse samenvatting

Artrose van de onderste ledematen is wereldwijd een van de belangrijkste oorzaken van fysieke beperking. Artrose wordt gezien als een aandoening van het hele gewricht, waarbij de hoeveelheid kraakbeen in het gewricht steeds verder afneemt. Dit proces gaat vaak gepaard met een geleidelijke toename van pijn en lichamelijke klachten. Wanneer er sprake is van eindstadium artrose en conservatieve behandeling geen goed resultaat meer geeft, dan kan er voor een gewrichtsvervangende operatie worden gekozen. Naast het verbeteren van pijn, zien patiënten het verbeteren van lopen als een belangrijk doel van deze operatie. Bij de beslissing voor deze operatie wordt mobiliteit echter alleen door zelf-rapportage in kaart gebracht. Een objectieve maat voor mobiliteit wordt niet in de beoordeling gebruikt. Het overkoepelende doel van dit proefschrift is om het lopen bij mensen met knie- en heupartrose uitgebreid te evalueren, voor en na een gewrichtsvervangende operatie. De resultaten van dit proefschrift kunnen vervolgens bijdragen aan het opstellen van objectieve maten voor mobiliteit, die relevant kunnen zijn voor klinische beoordeling van mensen met knie- of heupartrose.

De relevante achtergrond voor dit proefschrift wordt besproken in **hoofdstuk 1**. Hierin bespreek ik onder andere wat artrose inhoudt, wat de gevolgen zijn van artrose in de onderste ledematen, en hoe dit momenteel behandeld en beoordeeld wordt. Daarnaast laat ik aan de hand van een theoretisch kader zien hoe het lopen kan worden geëvalueerd. Zo kan er onderscheid worden gemaakt tussen de loopcapaciteit ('wat mensen kunnen doen'), de looprestatie ('wat mensen daadwerkelijk doen'), en de perceptie van het lopen ('wat mensen denken dat ze (kunnen) doen'). Tot slot wordt het gebruik van draagbare sensoren om het lopen te meten in dit hoofdstuk besproken.

In **hoofdstuk 2** bekeek ik hoe goed loopparameters verkregen uit sensoren onderscheid maken tussen mensen met knie- of heupartrose en gezonde controles. In dit onderzoek droegen deelnemers draagbare sensoren op de voeten, lage rug, en romp. De sensoren verzamelden gegevens over het lopen tijdens een 2 minuten looptest. Uit een grote hoeveelheid loopparameters identificeerde ik vier domeinen: spatiële loopparameters, temporele loopparameters, dubbeltaakkosten, en rompbewegingen. De eerste twee domeinen toonden een sterke relatie met loopsnelheid, en hadden een goed onderscheidend vermogen voor het lopen van mensen met knie- of heupartrose. Dubbeltaakkosten verschilden niet tussen mensen met knie- of heupartrose en gezonde controles. Dit resultaat suggereert dat het lopen bij mensen met knie- of heupartrose niet om meer aandacht vraagt. Bij mensen met heupartrose, maar niet bij mensen met knieartrose, vonden we grotere rompbewegingen in vergelijking met gezonde controles, wat kan duiden op compensaties die worden toegepast tijdens het lopen.

In **hoofdstuk 3** beschreef ik een literatuuronderzoek en meta-analyse gericht op studies die met behulp van draagbare sensoren het lopen vergeleken tussen mensen met knieartrose en gezonde leeftijdsgenoten. Uit dit literatuuronderzoek bleek dat spatiotemporele loopparameters, maar ook de bewegingen van de knie en romp vaak gerapporteerd werden. Een meta-analyse van de studies uit dit literatuuronderzoek bevestigde dat spatiotemporele loopparameters goed onderscheid kunnen maken tussen het lopen van mensen met knieartrose en gezonde controles. Daarnaast toonden kinematica van de knie en romp ook goed onderscheidend vermogen. Deze maten hebben dus een potentiële waarde voor het evalueren van lopen bij mensen met knieartrose.

Het herstel van lopen na plaatsing van een knie- of heupprothese werd onderzocht in **hoofdstuk 4**. Net zoals in hoofdstuk 2 werd het lopen gemeten met behulp van draagbare sensoren tijdens een 2 minuten looptest. De gemiddelde loopparameters verbeterden gestaag tussen 2 en 15 maanden na plaatsing van een knie- of heupporthese, zelfs tot het niveau van gezonde controles. De hersteltrajecten van de loopparameters verschilden sterk van de trajecten van zelf-gerapporteerde scores op pijn en functioneren, waar een sterke verbetering zichtbaar was in de eerste 2 maanden. Deze resultaten suggereren dat loopparameters belangrijke informatie bevatten over het herstel na een knie- of heupprothese, wat niet gereflecteerd wordt door zelf-gerapporteerde scores.

In **hoofdstuk 5** richtte ik me op een ander onderdeel van de loopcapaciteit, namelijk de dynamische balanscontrole. Ik vergeleek de staprespons na zijwaartse en voorwaartse balansverstoringen tijdens het lopen tussen mensen met knieartrose voorafgaand aan een gewrichtsvervangende operatie en gezonde controles. Ondanks dat artrose zorgt voor pijn en structurele veranderingen in de knie, vond ik geen verschil in het herstel van de balans tussen deze groepen. Dit kan op twee mogelijke manieren worden verklaard: 1) mensen met artrose maken effectief gebruik van de flexibiliteit in ons sensorisch-motorisch systeem om tot dezelfde stapreactie te komen als gezonde controles, of 2) de balansverstoringen waren niet uitdagend genoeg om mogelijke verschillen in dynamische balanscontrole aan het licht te brengen.

In **hoofdstuk 6** werd het lopen in het dagelijks leven gemeten door mensen continu te monitoren met draagbare sensoren. Mensen droegen een soort sok met sensoren erin, gedurende 5 tot 7 dagen. In dit onderzoek vergeleek ik mensen voorafgaand aan een gewrichtsvervangende operatie met gezonde leeftijdsgenoten. De meetmethode in deze studie maakte het mogelijk verschillende relevante inzichten op te doen over de loopbeperking in het dagelijks leven. Zo vond ik een lagere loop- en draaisnelheid, een korte maximale loopafstand, en een lager aantal stappen bij mensen met knieartrose in vergelijking met gezonde leeftijdsgenoten. Deze resultaten bevatten zeer waardevolle informatie over de daadwerkelijke loopbeperkingen die mensen met knie- of heupartrose ervaren in het dagelijks leven.

De resultaten van dit proefschrift worden overkoepelend besproken in **hoofdstuk 7**. Specifiek gaat deze discussie in op welke domeinen en parameters relevant zijn voor het evalueren van lopen bij mensen met knie- of heupartrose. Daarnaast worden de methodologische overwegingen ten aanzien van het meten van lopen met behulp van sensoren onder de loep genomen. Tot slot presenteer ik de klinische implicaties van dit proefschrift en beschrijf ik mogelijke richtingen voor vervolgonderzoek.

Concluderend, de resultaten van dit proefschrift laten zien dat het meten van lopen – zowel in het laboratorium als in het dagelijks leven – relevante informatie kan geven over het fysiek functioneren van mensen met knie- of heupartrose, die momenteel niet verkregen wordt uit zelf-rapportage. Zowel spatiotemporele loopparameters als data over de hoeveelheid en maximale lengte van het lopen bleken zeer goede indicatoren voor de loopbeperkingen van mensen met knie- of heupartrose. Kinematische loopparameters, daarentegen, kunnen mogelijk informatie geven over compensatiemechanismen die worden toegepast tijdens het lopen. Met behulp van deze loopparameters kan bovendien het herstel na een

gewrichtsvervangende operatie worden geobjectiveerd. Ondanks het potentieel wat er schuilt in het meten van lopen, blijft het nog onduidelijk hoe deze resultaten kunnen worden toegepast in de klinische praktijk, om bijvoorbeeld de beoordeling en besluitvorming te verbeteren. Sterker bewijs over de aanvullende waarde van deze data zal in de toekomst moeten worden geleverd, zeker in het licht van de beperkte tijd die er in de kliniek per patiënt beschikbaar is. Het op afstand meten van lopen met behulp van draagbare sensoren kan hier mogelijk uitkomst voor bieden, maar de methodologische en logistieke uitdagingen die hieraan zitten gekoppeld zullen dan eerst moeten worden overwonnen.

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Dankwoord

Dankwoord

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Dan **de mannen uit Horst (en omstreken)**. Het maakt niet uit of het gaat om een weekje Rock Werchter, een legendarische trip naar Starnberg, carnaval in het mooie zuiden, of het fietsen van de Stoneman in Oostenrijk, gezelligheid is met jullie altijd gegarandeerd. Onder het genot van een biertje was het voor mij de perfecte gelegenheid om het drukke (?) bestaan als promovendus even te ontvluchten. Ik hoop dat er nog vele avonturen mogen volgen!

Over naar de **vrienden uit Maastricht** (hebben we echt geen groepsnaam?). Als een van de weinige niet-artsen uit de groep ben ik maar wat blij dat ik me ook doctor mag gaan noemen. Zo voelt het toch een beetje alsof ik er bij hoor. Bedankt voor al jullie interesse en steun tijdens mijn promotietraject. Ik ben benieuwd wie er nog allemaal gaan volgen. Super fijn dat we elkaar in Maastricht (of Lanaken zelfs), Nijmegen, of Den Bosch nog steeds zo goed weten te vinden. Met een jaarlijks terugkerend vriendenweekend én wintersport zit dat voor de toekomst ook wel goed denk ik.

Dear **'Sport Pants' friends**, what started as a group project during our Master's became a group of friends over the year. With everyone living in different places around the globe, we don't see each other as often as I would like to, but I still very much enjoy the time we spend together. Let's find some time to celebrate (or spot alpacas at the beach) very soon!

Lieve **Jordi**, **Annick**, en **Jenna**, wat een mazzel heb ik met jullie als broer en zussen. Met jullie is er altijd bedrijvigheid in huize Boekesteijn. Zoals jullie weten kom ik altijd graag op bezoek voor een kop koffie, een middagje spellen, een 'rundje um of met het hundje', of welk ander gezellig uitje er dan ook verzonnen wordt. Lieve **pap**, de toewijding voor mijn werk en de affiniteit met het schrijven van teksten heb ik van geen vreemde. De wetenschap dat jij dan ook zo trots zou zijn geweest op mijn promotie geeft me veel steun, maar maakt het gemis niet minder groot. Lieve **mam**, het boekje over 'iets met lopen en knieën' is dan eindelijk af. Bedankt voor alle kansen die je me hebt geboden en jouw onvoorwaardelijk steun, ongeacht welk pad ik ook kies. Ik ben super trots op waar we nu met zijn allen staan.

About the author

About the author

Ramon Boekesteijn was born on the 22nd of October 1997 in Horst, the Netherlands. After graduating from secondary school (Dendron College in Horst) with the distinction *cum laude*, he moved to Maastricht to study Biomedical Sciences. He did his Bachelor's internship with Dr. Loek Verlaan and Dr. Kenneth Meijer to study the effect of obesity and knee osteoarthritis on the biomechanics of sit-to-stand movement and stair negotiation. This research was awarded with the best thesis prize in the program Biomedical Sciences. After obtaining his Bachelor's degree he continued his education in the field of Human Movement Sciences in Maastricht. For his Master's internship he studied the intermuscular coherence between lower-extremity muscles during sit-to-stand movement with Dr. Tjeerd Boonstra and Dr. Kenneth Meijer. He obtained both his Bachelor's and Master's degree with the distinction *cum laude*. After his graduation in 2019, Ramon started working as a junior researcher at the Research department of the Sint Maartenskliniek. At the same time he was PhD candidate at the Donders Institute for Brain, Cognition and Behaviour, supervised by Prof. Dr. Sander Geurts, Prof. Dr. Noël Keijsers, and Dr. Katrijn Smulders. Currently, Ramon is working as postdoctoral researcher at the Sint Maartenskliniek.

List of publications

List of publications

This thesis

Boekesteijn RJ, Keijsers NLW, Defoort K, Mancini M, Bruning F, El-Gohary M, Geurts ACH, Smulders K. Real-world gait and turning in individuals scheduled for total knee arthroplasty. *Submitted*

Boekesteijn RJ, Keijsers NLW, Defoort K, Geurts ACH, Smulders K. Individuals with knee osteoarthritis show few limitations in balance recovery responses after moderate gait perturbations. Clin Biomech (Bristol, Avon). 2024 Mar 5;114:106218.

Boekesteijn RJ, Smolders JMH, Busch VJJF, Keijsers NLW, Geurts ACH, Smulders K. Objective monitoring of functional recovery after total knee and hip arthroplasty using sensor-derived gait measures. PeerJ. 2022;10:e14054.

Boekesteijn RJ, van Gerven J, Geurts ACH, Smulders K. Objective gait assessment in individuals with knee osteoarthritis using inertial sensors: A systematic review and meta-analysis. Gait Posture. 2022;98:109-20.

Boekesteijn RJ, Smolders JMH, Busch VJJF, Geurts ACH, Smulders K. Independent and sensitive gait parameters for objective evaluation in knee and hip osteoarthritis using wearable sensors. BMC Musculoskelet Disord. 2021;22(1):242.

Other publications

Boekesteijn RJ, van de Ven MPF, Wilders LM, Bisseling P, Groen BE, Smulders K. The effect of functional calibration methods on gait kinematics in adolescents with idiopathic rotational deformity of the femur. Clin Biomech (Bristol, Avon). 2023;107:106028.

Verlaan L, **Boekesteijn RJ**, Oomen PW, Liu WY, Peters MJM, Emans PJ, van Rhijn LW, Meijer K. Knee adduction moments are not increased in obese knee osteoarthritis patients during stair negotiation. Gait Posture. 2019;73:154-60.

Verlaan L, **Boekesteijn RJ**, Oomen PW, Liu WY, Peters MJM, Witlox MA, Emans PJ, van Rhijn LW, Meijer K. Biomechanical Alterations during Sit-to-Stand Transfer Are Caused by a Synergy between Knee Osteoarthritis and Obesity. Biomed Res Int. 2018;2018:3519498.

PhD portfolio

PhD Portfolio

Name PhD student: Ramon J. Boekesteijn
Department: Research, Sint Maartenskliniek
Graduate School: Donders Graduate School

Training Activities	Year	ECTS
Courses		
• eBROK	2019, 2023	1.5
• GRAIL operator	2019	0.33
• Python 2 (online)	2019	1
• R Basics (online)	2019	0.66
• Scientific Integrity	2020	0.66
• Graduate School Day	2020, 2022	0.66
• Project Management voor Promovendi	2020	2
• Longitudinal data analysis and multilevel modeling	2022	3
• Science Communication and Journalism	2022	3
• Next step in your career	2022	1
• Sensorimotor control and learning	2022-2023	6
Lectures, webinars, workshops, other		
• Research lunch & lab lunch Sint Maartenskliniek	2019-2023	2.0
• Journalclub Orthopedics department	2019-2023	1.0
• OREO – content meeting orthopedic research SMK	2019-2022	1.0
• Workshop “Schrijven voor patiënten”	2020	0.1
• RIHS webinar ‘Online recruitment of study participants’	2020	0.1
• RIHS PhD council workshop: “Supervising your students”	2020	0.1
• Webinar Balance –NeuroControl	2021	0.1
• Closing event “Mobile monitoring of movement and joint loading in persons with degenerative hip- and knee problems” – UHasselt	2021	0.1
• Webinar Perturbation Training – Motek	2021	0.1
• ICMS Lecture	2021-2023	0.3
• Communicatie workshops “writing for scientists” and “talking to the media”	2022	0.2
• Data visualisatie workshop Sint Maartenskliniek	2022*	0.1
• Regionale Refereeravond Reumatalogen	2022*	0.1
• Radboud Research Rounds +	2022	0.1
• Meet the PhD	2022	0.1
• Webinar Knee osteoarthritis: new insights and emerging technology-based interventions - OA Tech	2022	0.1
• ISEK JEK Tutorials: An introduction into the analysis of stabilizing feedback control of walking	2022	0.1
• ICMS annual event	2022	0.25
• GRAIL demonstrations	2022, 2023	0.2
• LEC scholingsavond	2023*	0.1

Training Activities	Year	ECTS
Conferences and symposia		
• ISTA News	2020*	0.5
• Dynamic walking	2020*	0.5
• ISPGR online symposium – current evidence for cortical control of balance and gait	2020	0.1
• ISPGR online symposium – advances in markerless tracking used for human movement analysis	2020	0.1
• ICAMPAM	2021*	0.25
• EHS congress	2021*	0.5
• ISPGR world congress	2022*	1.5
• VVBN PhD day	2022*	0.25
• SMALLL	2022, 2023*	0.5
Teaching Activities	**Year**	**ECTS**
Supervision		
• BSc Students (2 students)		
- Biomedical Sciences (Radboud)	2020, 2022	3
• MSc Students (5 students)		
- Biomedical Sciences (Radboud)	2020, 2022	3
- Human Movement Sciences (VU)	2021	1.5
- Biomedical Engineering (UTwente)	2022, 2023	3

*= presenter

Research data management

Research data management

General information about the data collection

The conduct of the studies included this thesis was in accordance with applicable laws and ethical guidelines. Furthermore, research data management was conducted according to FAIR principles. The paragraphs below specify in detail how this was achieved.

Ethics

Chapters 2, 4, 5, and 6 were based on the results of human studies that were conducted in accordance with the statements of the Declaration of Helsinki. These study protocols were reviewed and approved by the CMO Arnhem-Nijmegen; with dossier numbers 2018-4452 and 2019-5824, respectively. In all these studies, written informed consent was obtained from all participants prior to testing.

FAIR principles

Findable

Data were stored on the server of the research department at the Sint Maartenskliniek: V:\research_ortho_studies\o833_iGait and V:\research_ortho_studies\o867_ChallengeCR. Digital case report forms for the studies in chapters 5 and 6 are findable in the Challenge CR Castor EDC database. Analog versions of the informed consent forms and case report forms were stored at the research department (room B1.13) and will be transferred to the department's archive after publication of the study results.

Accessible

All data will be available on reasonable request by contacting the staff secretary of the research department at the Sint Maartenskliniek (secretariaat.research@maartenskliniek.nl) or the corresponding author. Furthermore, datasets leading to the results of chapters 2, 3, and 4 are published along with the research articles.

Interoperable

Documentation was added to the datasets to make the data interpretable. The documentation contains links to publications, references to the location and description of the datasets. The data were stored in the following file formats: .h5 (raw Opal sensor data), .c3d (raw Vicon motion capture data), .mat (processed data in Matlab) and .csv (exported datasets during various processing steps). No existing data standards were used such as vocabularies, ontologies or thesauri.

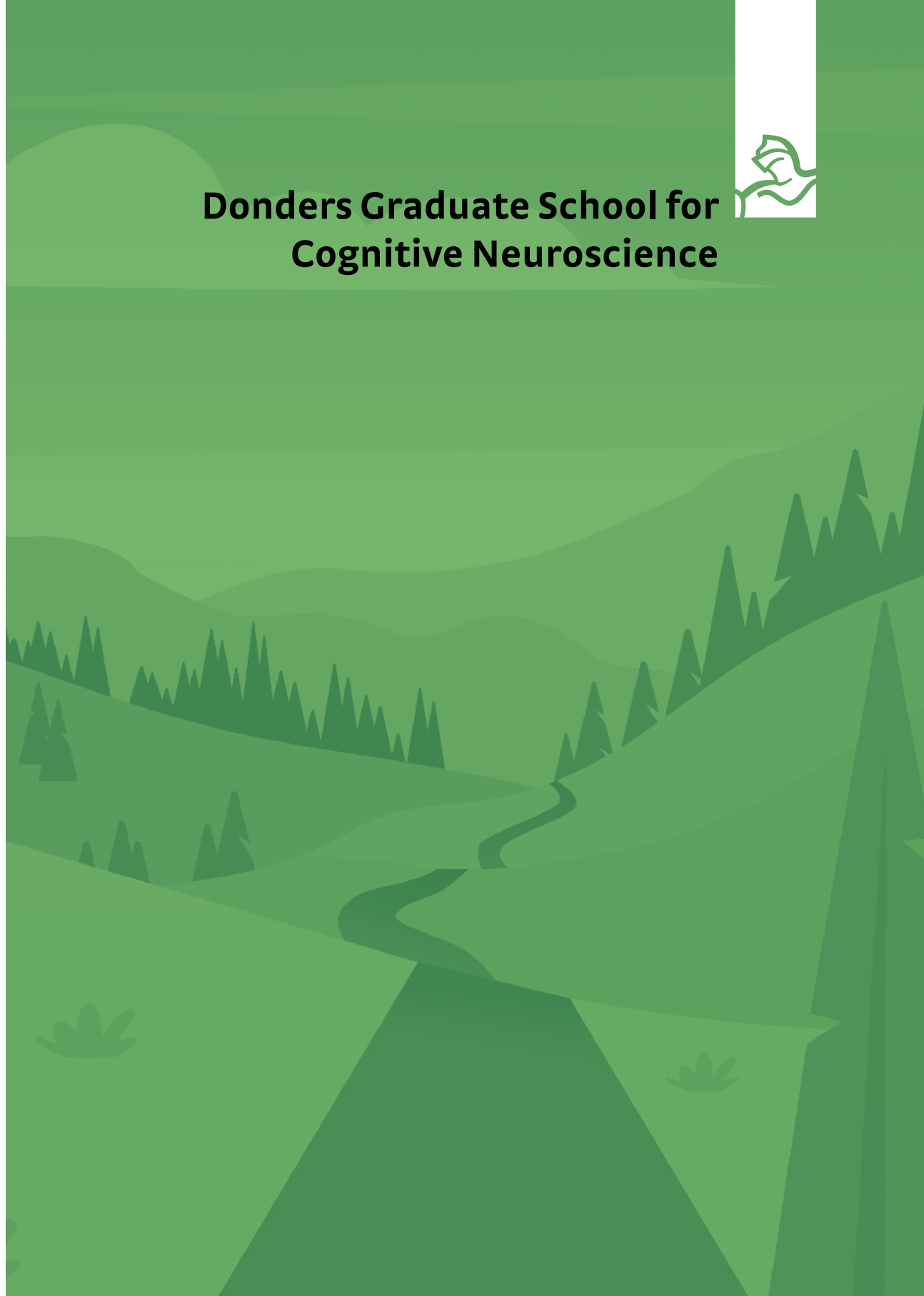
Reusable

Study data will be saved for at least 15 years after termination of the study. Reuse of these data in future research is only possible after a renewed permission by the participants as recorded in their informed consents.

Privacy

The privacy of the study participants has been warranted using encrypted and unique individual subject codes. The encryption key was stored separately from the research data and is only accessible to members of the project who need access for study conduct.

Donders Graduate School for Cognitive Neuroscience



Donders Graduate School for Cognitive Neuroscience

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioral science, medicine and related disciplines. Selective admission and assessment centers guarantee the enrolment of the best and most motivated students.

The DGCN tracks the career of PhD graduates carefully. More than 50% of PhD alumni show a continuation in academia with postdoc positions at top institutes worldwide, e.g. Stanford University, University of Oxford, University of Cambridge, UCL London, MPI Leipzig, Hanyang University in South Korea, NTNU Norway, University of Illinois, North Western University, Northeastern University in Boston, ETH Zürich, University of Vienna etc.. Positions outside academia spread among the following sectors: specialists in a medical environment, mainly in genetics, geriatrics, psychiatry and neurology. Specialists in a psychological environment, e.g. as specialist in neuropsychology, psychological diagnostics or therapy. Positions in higher education as coordinators or lecturers. A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high-quality positions that play an important role in our knowledge economy.

For more information on the DGCN as well as past and upcoming defenses please visit:
http://www.ru.nl/donders/graduate-school/phd/

Theses Sint Maartenskliniek

Theses Sint Maartenskliniek

Te Molder, M. (2024). *The unhappy patient after TKA. A paradigm shift in assessing outcome.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Kuijpers, R. (2024). *Adapt your step: Clinical assessment and training of walking adaptability in children with mild motor disorders.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Den Broeder, A. (2024). *More than tapering, less than full dose - Efficient use of biologics in the treatment of rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

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Stöcker, J. (2023). *Accessible and effective non-pharmacological care for persons with systemic sclerosis*. Radboud University Nijmegen, Nijmegen. The Netherlands.

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Marsman, D. (2022). *Polymyalgia rheumatica. Clinical characteristics and new treatment opportunities.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Alingh, J. (2021). *Effect of robotic gait training on the post-stroke gait pattern. Evaluation of LOPES II.* Radboud University Nijmegen, Nijmegen. The Netherlands.

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Bikker, I.(2018). *Organizing timely treatment in multi-disciplinary care.* University of Twente, The Netherlands.

Bouman, C. (2018). *Dose optimisation of biologic DMARDs in rheumatoid arthritis: long-term effects and possible predictors.* Radboud University Nijmegen, The Netherlands.

Mahler, E. (2018). *Contributors to the management of osteoarthritis.* Utrecht University, The Netherlands.

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Zedlitz, A. (2013). *Brittle brain power. Post-stroke fatigue, explorations into assessment and treatment.* Radboud University, Nijmegen, The Netherlands.

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Van Lankveld, W. (1993). *Coping with chronic stressors of rheumatoid arthritis.* University of Nijmegen, Nijmegen, The Netherlands.

Geurts, A. (1992). *Central adaptation of postural organization to peripheral sensorimotor impairments.* University of Nijmegen, Nijmegen, The Netherlands.

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