Relationship between motion, using the GaitSmartTM system, and radiographic knee osteoarthritis: an explorative analysis in the IMI-APPROACH cohort

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Original article

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Abstract

Objectives. To assess underlying domains measured by GaitSmart™parameters and whether these are additional to established OA markers including patient reported outcome measures (PROMs) and radiographic parameters, and to evaluate if GaitSmart analysis is related to the presence and severity of radiographic knee OA.

Methods. GaitSmart analysis was performed during baseline visits of participants of the APPROACH cohort ($n = 297$). Principal component analyses (PCA) were performed to explore structure in relationships between GaitSmart parameters alone and in addition to radiographic parameters and PROMs. Logistic and linear regression analyses were performed to analyse the relationship of GaitSmart with the presence (Kellgren and Lawrence grade $\geq$2 in at least one knee) and severity of radiographic OA (ROA).

Results. Two hundred and eighty-four successful GaitSmart analyses were performed. The PCA identified five underlying GaitSmart domains. Radiographic parameters and PROMs formed additional domains indicating that GaitSmart largely measures separate concepts. Several GaitSmart domains were related to the presence of ROA as well as the severity of joint damage in addition to demographics and PROMs with an area under the receiver operating characteristic curve of 0.724 and explained variances (adjusted R^2) of 0.107, 0.132 and 0.147 for minimum joint space width, osteophyte area and mean subchondral bone density, respectively.

Conclusions. GaitSmart analysis provides additional information over established OA outcomes. GaitSmart parameters are also associated with the presence of ROA and extent of radiographic severity over demographics and PROMS. These results indicate that Gaitsmart™ may be an additional outcome measure for the evaluation of OA.

Key words: IMI-APPROACH, Osteoarthritis, Gait

CLINICAL SCIENCE

Rheumatology key messages

- GaitSmart™ provides additional information above parameters currently used to assess OA.
- GaitSmart is associated with the presence and to a limited extent severity of radiographic OA.
- GaitSmart might serve as additional non-invasive and easily applicable parameter to assess OA.

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Introduction

Conventional radiography, despite its limitations, is the gold standard imaging technique to assess progression of tissue damage in OA. It enables detection of OA-associated bony features but lacks the ability to directly detect changes in other articular tissues (e.g. synovial tissue, meniscus and cartilage) [1]. Besides, clinical signs and symptoms of OA might be present even 2–3 years before radiographic changes appear on conventional images [2]. Magnetic resonance imaging (MRI) techniques do have the ability to visualize pathologies that are not detectable on radiographs. However, the high costs make it less suitable for standard use in clinical practice [1]. OA patients learn to avoid pain, but this avoidance leads to functional limitations and may change movement patterns. Structural changes may lead to functional limitations with a corresponding change in gait. Questionnaires assessing pain and functional limitations have the drawback of reflecting the subjective opinion of a patient rather than an objective measurement of the functional severity of OA. As such, there is still an unmet need for non- or minimal invasive techniques that add to the evaluation of OA.

Gait analysis might be such an additional measurement. Significant correlations were found between gait and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [3] and the Short Form (36) health survey (SF-36) [4] subscales in patients fulfilling the American College of Rheumatology (ACR) clinical criteria for knee OA [5], radiographically confirmed according to Kellgren and Lawrence (KL) [6, 7].

A commonly used gait parameter from tests performed in an optical gait lab, the peak knee adduction moment (KAM), was found to have a negative correlation with cartilage thickness in OA knees, defined by KL grade $\geq$2 [8]. KAM is increased in patients with OA, compared with controls, and this increase is higher for patients with severe OA than for patients with mild OA [9, 10]. General gait parameters also differed between patients with knee OA and matched (for sex, age, height and weight) control subjects, walking at a similar speed. Knee flexion at heel strike (beginning of stance phase) was less in OA patients compared with controls [10]. Disadvantages of the optical gait lab are the time and costs required to complete one analysis.

The GaitSmart^{TM} hardware solution is a user-friendly and objective method to assess gait. It takes about 10–15 min and can be carried out virtually anywhere. Knee flexion range of motion (ROM) in stance and swing phase, measured using an earlier version of the GaitSmart system than used in this study, is significantly lower in OA patients, fulfilling the ACR clinical criteria for OA, compared with healthy volunteers. A cut-off value of 13.6° of knee ROM in stance phase could discriminate between knee OA patients and healthy controls with a specificity of 0.952 and sensitivity of 0.783. Knee ROM in swing phase was less discriminative [11].

As such, gait analysis, as an additional measurement, may improve the assessment of presence and severity of OA, in addition to standard outcome measures based on radiographic measurements and patient reported outcome measures (PROMs). The objectives of this study are (i) to assess underlying domains measured by GaitSmart parameters and whether these are additional to established OA markers including PROMs and radiographic parameters, (ii) to evaluate if gait analysis using GaitSmart is related to the presence of radiographic knee OA (ROA), and (iii) to evaluate if gait analysis using the GaitSmart system is related to the severity of ROA, on top of demographics and PROMs. If GaitSmart provides a potential useful additional measurement to assess OA, we hypothesize that GaitSmart parameters measure domains different from PROMS and radiographic outcomes, and that these GaitSmart domains add to the relationship of demographics and PROMS with the presence and severity of ROA.

Methods

Participants

Two hundred and ninety-seven people with knee OA were included in the Applied Public-Private Research enabling OsteoArthritis Clinical Headway (APPROACH) study from January 2018 until April 2019 [age 66.5 (7.1) years, female 230 (77%), BMI 28.1 (5.3) kg/m^2] [12]. APPROACH is an exploratory, European, five-centre, 2-year prospective follow-up cohort study. It obtains extensive clinical, imaging, biomechanical and biochemical parameters of participants recruited using machine learning models based on retrospective and, to a limited extent, prospectively collected patient data, to display a high likelihood of radiographic joint space width loss and/or knee pain over the 2-year course of the study. For each participant the index knee was selected based on ACR clinical criteria for knee OA, using history and physical examination. If both knees fulfilled these criteria, the index knee was the most painful knee according to the participant. If both knees were equally painful, the right knee was chosen. A radiograph of the index knee was taken afterwards. Hence, the index knee was not necessarily the knee with the highest KL grade, since KL grade was determined after selecting an index knee and index knees can have KL grade 0 or 1.

The study is being conducted in compliance with the protocol Good Clinical Practice (GCP), the Declaration of Helsinki, and the applicable ethical and legal regulatory requirements (for all countries involved), and is registered under ClinicalTrials.gov no.: NCT03883568. All participants have received oral and written information and provided written informed consent. The present analysis focused on the baseline data.

GaitSmart measurement

The GaitSmart system uses six inertial measurement units (IMU) to evaluate gait mechanics. These IMUs comprise three tri-axial accelerometers and three tri-axial

gyroscopes, making it possible to measure movements in the sagittal and frontal plane [13]. After synchronizing the IMUs using Poseidon software (Dynamic Metrics Limited, Codicote, UK) they were attached to the body. Two IMUs were placed on the pelvis, under the iliac crest, following the alignment of the pelvis. Then two other IMUs were placed on the widest part of the thighs, aligned in a straight vertical line. The last two IMUs were placed on the calves, on the belly of the gastrocnemius muscles [11, 13] (see Supplementary Fig. S1, available at *Rheumatology* online). Subsequently, participants were asked to stand still for 5 s to calibrate the IMUs. The participants were then asked to walk 15–20 m at their own self-selected speed and return. After performing the test, the IMUs were removed and attached to the laptop for analysis. The IMUs are accurate to 0.11°, although the measurement error depends on positioning on the body. A previous study showed a reproducibility of ±2.8° and ±3.4° for knee ROM in swing and stance phase, respectively [11, 14].

Poseidon software was used to extract and analyse data from the IMU sensors. The result is a report containing ROM of pelvis, hips, thighs, knees in swing and stance phase, and calves in the sagittal plane, stride duration, medial–lateral movement of thighs and calves, and symmetry scores between left and right. All parameters are presented in graphs and tables.

Fifteen GaitSmart parameters were selected for statistical analysis based on previous research [11, 14] and clinical expertise; ROM for both knees in swing and stance, both hips and both calves were determined. Gait is considered as a measurement at patient level as opposed to a measurement at joint level. Therefore, the differences between both legs were also determined and included in the analysis as separate parameters. In addition, average stride duration, calculated speed and stride length were used.

Radiographic assessments

Standardized semi-flexed posterior–anterior weight bearing knee radiographs of both knees were taken according to Buckland-Wright *et al*. [15]. KL grading was performed by one blinded observer. The intra- and interobserver correlation were both previously found to be good (>0.83) [6], and in the current study an intraclass correlation coefficient (ICC) of 0.88 was found (using 10% of the radiographs). Additionally, knee images digital analysis (KIDA) [16] was performed by one single experienced observer. Minimum joint space width of the tibiofemoral joint (minJSW in mm), osteophyte area (mm^2) and subchondral bone density (mm aluminium equivalent) were used as radiographic parameters. Previous studies demonstrated an ICC of 0.73–0.99 for the different features [17].

Assessment of pain and function

Pain and function were evaluated at patient level using the corresponding subscales of the Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire [18], assessing pain in the most affected knee (MAK), the Numeric Rating Scale (NRS) pain for both knees and the Intermittent and Constant OsteoArthritis Pain (ICOAP) questionnaire [19], again assessing pain in the MAK. The KOOS questionnaire comprises nine items for pain and 17 items for daily function, each question scored on a 5-point scale. A normalized score is calculated where 0 means maximal limitations and 100 means no limitations. The NRS pain consists of an 11-point scale on which participants score pain from 0 (no pain) to 10 (worst imaginable pain). The ICOAP questionnaire contains 11 questions, five for constant pain and six for intermittent pain, each question scored on a 5-point scale. A higher total score reflects more pain.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 25.0.0.2 (IBM Corp., Armonk, NY, USA). *P*-values <0.05 were considered statistically significant.

Relationship between individual GaitSmart parameters and conventional parameters

A principal component analysis (PCA) was performed to explore structure in relationships between individual GaitSmart parameters and to reduce the total set of parameters to a limited set of underlying domains. This analysis was performed with GaitSmart parameters alone as well as with radiographic parameters or PROMs as additional parameters to see how or if these parameters would underlie the same domains or measure something different.

PCA was also performed in different severity subgroups to investigate the stability of the identified underlying domains as associations in different OA severity subgroups could differ. Subgroups were based on radiographic parameters (KL grade and minJSW) and PROMs (KOOS pain and daily function) using mean values as cut-offs to dichotomize.

Relationship with presence of radiographic knee OA

Logistic regression was used to evaluate the relationship of identified GaitSmart domains with the presence of ROA in a patient, defined as KL ≥ 2 in *at least* one knee, in addition to currently used parameters. Independent variables were entered stepwise starting with demographic variables (age, sex and BMI), then KOOS pain and KOOS daily function, and finally the GaitSmart domains.

It was also evaluated whether the association of the relevant GaitSmart domains with the presence of ROA depended on pain severity, by testing interaction terms in the model. Statistically significant interactions were retained in the model. The area under the receiver operating characteristics curve (AUC-ROC) was calculated for all models as a measure of (increase in) model fit.

Relation with severity of radiographic knee OA

To explore the relationship between identified GaitSmart domains and the severity of ROA, in addition to currently used parameters, linear regression was performed. The

value of the MAK regarding minJSW (mm), osteophyte area (mm^2) and mean subchondral bone density (mm aluminium equivalent) was used as outcome within these analyses. The independent variables were again entered stepwise in the same blocks as in the analysis used for the presence of ROA and interactions between KOOS pain and relevant GaitSmart domains were tested, and, if statistically significant, retained in the model.

Results

Participant characteristics

A successful GaitSmart analysis was performed for 284 participants. The 13 missing analyses were due to user errors ($n = 9$) or technical issues ($n = 4$). Patient characteristics of the total population and separately for those with/without ROA are described in Table 1. The 13 excluded patients did not (statistically) significantly differ from the patients included in the study (data not shown).

Principal component analysis

The PCA of GaitSmart parameters (GS) identified five underlying domains (Supplementary Table S1, available at *Rheumatology* online): one mainly related to ROM in hips (GS Hip, component no. 1), one mainly related to ROM of knees and calves (GS Knee, component no. 2), and three mainly related to differences in either ROM of knees and calves in swing phase (GS Difference Knee,

Table 1 Baseline characteristics of the included patients

	Total ($n = 281$[a])	ROA present ($n = 159$)	ROA absent ($n = 122$)
Demographics			
Age, mean (S.D.), years	66.4 (7.0)	66.9 (7.2)	65.8 (6.9)
Female, *n* (%)	217 (77)	126 (79)	91 (74)
BMI, mean (S.D.), kg/m^2	28.0 (5.4)	28.5 (5.3)	27.4 (5.4)
Patient reported outcome measurements			
KOOS, mean (S.D.)			
Pain	66.4 (18.8)	63.7 (17.8)	69.9 (19.4)
Daily function	69.3 (19.0)	67.4 (18.1)	71.6 (19.8)
Symptoms	69.7 (17.0)	66.5 (16.8)	73.7 (16.6)
Sports and recreational activities	43.0 (26.9)	36.6 (23.7)	51.0 (28.6)
Quality of life	53.4 (20.3)	49.5 (18.4)	58.5 (21.6)
NRS, mean (S.D.)			
Index knee	4.5 (2.7)	4.7 (2.6)	4.3 (2.8)
Contralateral knee	2.9 (2.6)	3.0 (2.5)	2.9 (2.6)
Radiographic damage index knee[b]			
KL grade, *n* (%)			
0	47 (17)	3 (2)	44 (36)
1	88 (31)	10 (6)	78 (64)
2	85 (30)	85 (54)	—
3	51 (18)	51 (32)	—
4	10 (4)	10 (6)	—
KIDA			
minJSW, mean (S.D.), mm	2.5 (1.2)	2.1 (1.4)	3.1 (0.8)
Osteophyte area, mean (S.D.), mm^2	21.1 (19.8)	30.6 (21.5)	8.8 (5.5)
Subchondral bone density, mean (S.D.), mm Al eq	31.0 (5.1)	31.5 (5.1)	30.5 (5.0)
GaitSmart			
Range of motion, mean (S.D.), °			
Index knee in stance phase	15.8 (4.9)	15.0 (5.0)	17.0 (4.5)
Index knee in swing phase	58.0 (7.3)	56.4 (6.7)	60.0 (7.5)
Contralateral knee in stance phase	16.8 (5.1)	16.5 (5.0)	17.1 (5.3)
Contralateral knee in swing phase	59.0 (7.1)	58.0 (7.1)	60.3 (6.9)
Index calf	71.9 (6.6)	70.6 (6.9)	73.6 (5.9)
Contralateral calf	72.3 (6.3)	71.7 (6.6)	73.1 (5.9)
Index hip	33.4 (7.5)	33.1 (7.6)	33.7 (7.3)
Contralateral hip	34.0 (7.1)	34.1 (6.9)	33.9 (7.4)
Stride length, mean (S.D.), m	1.1 (0.2)	1.0 (0.2)	1.1 (0.2)
Duration per stride, mean (S.D.), s	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)
Speed, mean (S.D.), m/s	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)

[a]In three participants the radiograph of the index knee was made incorrectly. [b]The index knee in the APPROACH cohort was not by definition the most radiographically damaged knee. Al eq: aluminium equivalent; BMI: body mass index, KOOS: Knee injury and Osteoarthritis Outcome Score, NRS: Numeric Rating Scale, KL: Kellgren and Lawrence, KIDA: knee image digital analysis, minJSW: minimum joint space width, ROA: radiographic osteoarthritis.

component no. 3), ROM in hips (GS Difference Hip, component no. 4) and ROM in knees during stance phase (GS Difference Stance, component no. 5). PROMs and radiographic parameters each formed an additional component when added to the PCA, suggesting that the parameters measure different domains of a patient's disease status (see Supplementary Table S1, available at *Rheumatology* online). The PCA in different subgroups showed that the domains identified were relatively stable (data not shown). Therefore the GaitSmart domains were used in further analyses.

Relation with the presence of radiographic knee OA

One hundred and fifty-nine participants (56%) had ROA in at least one knee (KL grade $\geq$2). Logistic regression showed that addition of GaitSmart data to the model with demographics and PROMs improved the association with the presence of ROA (Table 2 and Fig. 1); Nagelkerke's R^2 increased from 0.075 to 0.150 when adding GaitSmart parameters after demographics and PROMs, but the discriminatory value of this model was still only moderate (AUC = 0.698, 95% CI: 0.637, 0.760). Sensitivity and specificity were 71.0% and 52.0%, respectively, using a probability of 0.50 as cut-off. KOOS pain [odds ratio (OR) = 0.964, 95% CI: 0.935, 0.994], GS Knee (OR = 0.624, 95% CI: 0.457, 0.850), and GS Difference Knee (OR = 1.319, 95% CI: 1.004, 1.733) were statistically significant contributing factors.

The association of GS Knee and GS Difference Knee with ROA statistically significantly depended on the level of pain. With less pain the effect of GaitSmart domains on the likeliness of having ROA decreased. Including both interaction terms, the models' Nagelkerke R^2 increased to 0.212 (Table 2). The AUC-ROC increased to 0.724 (95% CI: 0.665, 0.783; Table 2 and Fig. 1).

Relation with severity of radiographic knee OA: minimum JSW

In the model with minJSW as outcome parameter age (B (beta) = −0.024, 95% CI: −0.043, −0.005), GS Hip (B = −0.647, 95% CI: −1.148, −0.146), GS Knee (B = −0.696, 95% CI: −1.174, −0.218), GS Difference Knee (B = −0.153, 95% CI: −0.281, −0.025), and GS Difference Stance (B = −0.134, 95% CI: −0.262, −0.005) were statistically significant contributing factors (Table 3). In this model statistically significant interactions between KOOS pain and GS Hip (B = 0.009, 95% CI: 0.002, 0.017) and between KOOS pain and GS Knee (B = 0.012, 95% CI: 0.005, 0.019) were found. The adjusted R^2 of the final model, including both statistically significant interaction terms, was 0.107.

Relation with severity of radiographic knee OA: osteophyte area

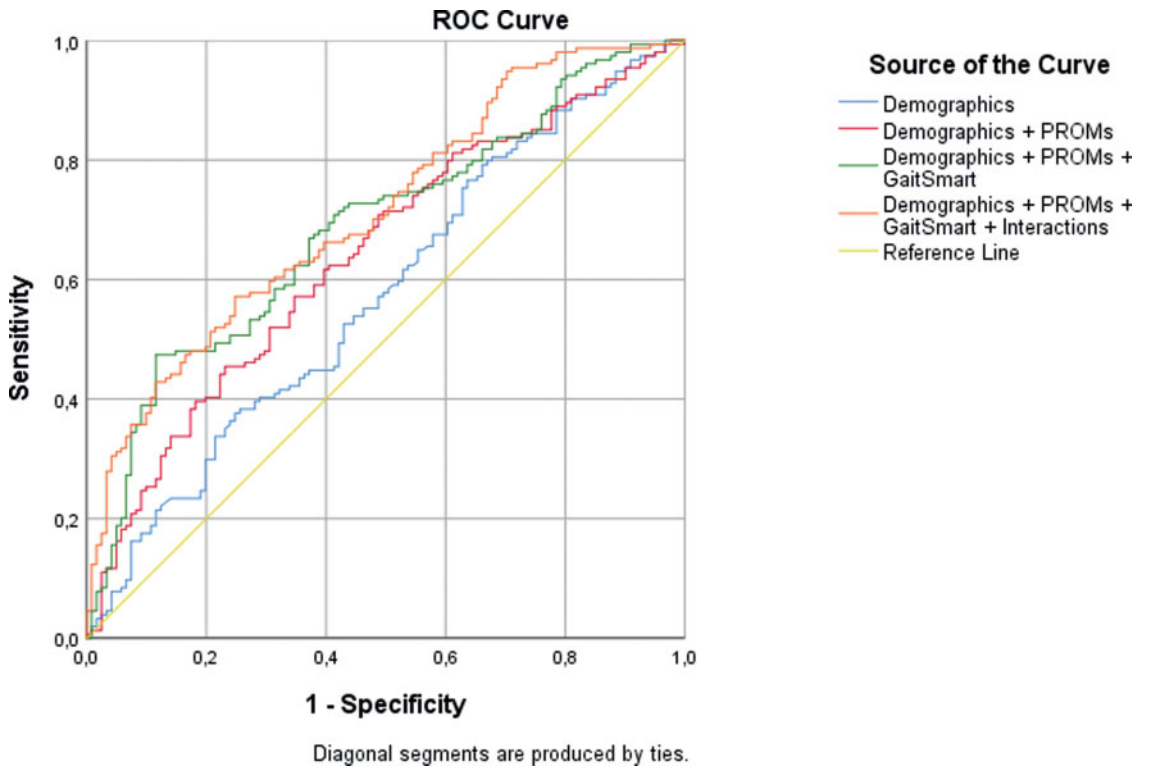
In the model for osteophyte area sex (B = −10.117, 95% CI: −16.409, −3.825) and GS Difference Knee (B = 2.568, 95% CI: 0.120, 5.017) were statistically significant contributors. Only one statistically significant interaction term was found, between KOOS pain and GS Knee (B = −0.228, 95% CI: −0.361, −0.095). The final adjusted R^2 was 0.132 (Table 4).

Table 2 Results of logistic regression analysis on presence of radiographic osteoarthritis

Independent variable	OR (95% CI)			
	Model 1	Model 2	Model 3	Model 4
Constant	**0.058**	0.068	0.104	0.069
Age	1.025 (0.990, 1.061)	**1.037 (1.000, 1.075)**	1.032 (0.993, 1.073)	1.035 (0.994, 1.077)
Sex	1.418 (0.802, 2.509)	1.165 (0.643, 2.112)	0.923 (0.480, 1.773)	0.959 (0.486, 1.894)
BMI	1.043 (0.996, 1.092)	1.045 (0.994, 1.099)	1.034 (0.978, 1.093)	1.048 (0.989; 1.109)
KOOS pain		**0.959 (0.931, 0.988)**	**0.964 (0.935, 0.994)**	**0.960 (0.930, 0.991)**
KOOS daily function		1.029 (0.999, 1.059)	1.029 (0.998, 1.062)	1.032 (0.999, 1.066)
GS Hip			1.079 (0.819, 1.421)	1.071 (0.808, 1.421)
GS Knee			**0.624 (0.457, 0.850)**	2.794 (0.976, 8.000)
GS Difference Knee			**1.319 (1.004, 1.733)**	**4.548 (1.453, 14.230)**
GS Difference Hip			1.104 (0.848, 1.438)	1.162 (0.882, 1.531)
GS Difference Stance			1.202 (0.913, 1.582)	1.213 (0.916, 1.604)
KOOS pain × GS Knee				**0.978 (0.962, 0.993)**
KOOS pain × GS Difference Knee				**0.981 (0.964, 0.998)**
Nagelkerke R^2	0.029	0.075	0.150	0.212
ΔR^2 *vs* previous model		0.46	0.075	0.062
AUC (95% CI)	0.578 (0.510, 0.645)	0.641 (0.576, 0.706)	0.698 (0.637, 0.760)	0.724 (0.665, 0.783)
Sensitivity, %	81.9	74.8	71.0	74.2
Specificity, %	25.2	43.9	52.0	51.2

P-values <0.05 are indicated in bold. AUC: area under the curve; BMI: body mass index; GS: GaitSmart™; KOOS: Knee injury and Osteoarthritis Outcome Score; OR: odds ratio.

FIG. 1 ROC curve



Diagonal segments are produced by ties. PROM: patient reported outcome measure; ROC: receiver operating characteristic.

TABLE 3 Linear regression models for minJSW

Independent variable	Unstandardized *B* (95% CI)			
	Model 1	Model 2	Model 3	Model 4
Constant	**4.074 (2.555, 5.593)***	**3.358 (1.671, 5.045)***	**3.435 (1.717, 5.5153)***	**3.398 (1.727, 5.069)***
Age	**−0.021 (−0.040, −0.002)**	**−0.24 (−0.043, −0.005)**	**−0.024 (−0.044, −0.005)**	**−0.024 (−0.043, −0.005)**
Sex	0.021 (−0.296, 0.338)	0.094 (−0.227, 0.416)	0.108 (−0.230, 0.446)	0.072 (−0.257, 0.401)
BMI	−0.018 (−0.043, 0.007)	−0.010 (−0.037, 0.016)	−0.007 (−0.034, 0.021)	−0.010 (−0.037, 0.017)
KOOS pain		0.011 (−0.004, 0.026)	0.007 (−0.008, 0.023)	0.005 (−0.010, 0.020)
KOOS daily function		−0.001 (−0.016, 0.015)	0.000 (−0.016, 0.016)	0.003 (−0.013, 0.019)
GS Hip			−0.006 (−0.149, 0.136)	**−0.647 (−1.148, −0.146)**
GS Knee			0.105 (−0.045, 0.254)	**−0.696 (−1.174, −0.218)**
GS Difference Knee			**−0.139 (−0.270, −0.008)**	**−0.153 (−0.281, −0.025)**
GS Difference Hip			−0.049 (−0.179, 0.081)	−0.070 (−0.197, 0.057)
GS Difference Stance			**−0.147 (−0.279, −0.015)**	**−0.134 (−0.262, −0.005)**
KOOS pain × GS Hip				**0.009 (0.002, 0.017)**
KOOS pain × GS Knee				**0.012 (0.005, 0.019)**
Adjusted R^2	0.011	0.031	0.054	0.107
ΔR^2 *vs* previous model		0.020	0.023	0.053

P-values <0.05 are indicated in bold; *$P < 0.0001$. B: Beta (represents slope); BMI: body mass index; GS: GaitSmart™; KOOS: Knee injury and Osteoarthritis Outcome Score.

Table 4 Linear regression models for osteophyte area

Independent variable	Unstandardized *B* (95% CI)			
	Model 1	Model 2	Model 3	Model 4
Constant	5.257 (−24.271, 34.785)	10.876 (−22.215, 43.968)	23.592 (−9.017, 56.202)	22.932 (−9.066, 54.930)
Age	0.174 (−0.194, 0.542)	0.224 (−0.150, 0.598)	0.085 (−0.282, 0.451)	0.074 (−0.285, 0.433)
Sex	−5.262 (−11.424, 0.900)	−6.258 (−12.563, 0.046)	**−10.401 (−16.811, −3.991)**	**−10.117 (−16.409, −3.825)**
BMI	0.385 (−0.096, 0.865)	0.332 (−0.188, 0.852)	−0.012 (−0.534, 0.509)	0.073 (−0.442, 0.587)
KOOS pain		−0.176 (−0.478, 0.127)	−0.130 (−0.426, 0.166)	−0.119 (−0.410, 0.171)
KOOS daily function		0.072 (−0.235, 0.378)	0.164 (−0.142, 0.469)	0.153 (−0.147, 0.453)
GS Hip			−2.061 (−4.762, 0.641)	−2.060 (−4.710, 0.591)
GS Knee			**−7.118 (−9.956, −4.280)***	7.839 (−1.305, 16.983)
GS Difference Knee			2.230 (−0.257, 4.718)	**2.568 (0.120, 5.017)**
GS Difference Hip			1.014 (−1.456, 3.484)	1.336 (−1.095, 3.767)
GS Difference Stance			1.745 (−0.760, 4.249)	1.620 (−0.838, 4.079)
KOOS pain × GS Knee				**−0.228 (−0.361, −0.095)**
Adjusted R^2	0.011	0.013	0.098	0.132
ΔR^2 *vs* previous model		0.002	0.085	0.034

P-values <0.05 are indicated in bold; *$P < 0.0001$. B: Beta (represents slope); BMI: body mass index; GS: GaitSmart™; KOOS: Knee injury and Osteoarthritis Outcome Score.

Table 5 Linear regression models for mean subchondral bone density

Independent variable	Unstandardized *B* (95% CI)		
	Model 1	Model 2	Model 3
Constant	**30.628 (23.665, 37.590)***	**33.067 (25.260, 40.874)***	**34.272 (26.309, 42.234)***
Age	−0.083 (−0.170, 0.004)	−0.078 (−0.166, 0.010)	**−0.094 (−0.183, −0.004)**
Sex	**−1.507 (−2.960, −0.054)**	**−1.618 (−3.106, −0.131)**	**−2.007 (−3.573, −0.442)**
BMI	**0.323 (0.210, 0.436)***	**0.293 (0.171, 0.416)***	**0.250 (0.122, 0.377)***
KOOS pain		−0.008 (−0.080, 0.063)	0.002 (−0.070, 0.074)
KOOS daily function		−0.019 (−0.091, 0.054)	−0.009 (−0.083, 0.066)
GS Hip			−0.351 (−1.011, 0.309)
GS Knee			**−0.880 (−1.573, −0.187)**
GS Difference Knee			0.223 (−0.385, 0.830)
GS Difference Hip			0.094 (−0.509, 0.697)
GS Difference Stance			0.569 (−0.043, 1.180)
Adjusted R^2	0.128	0.129	0.147
ΔR^2 *vs* previous model		0.001	0.018

P-values <0.05 are indicated in bold; *$P < 0.0001$. B: Beta (represents slope); BMI: body mass index; GS: GaitSmart™; KOOS: Knee injury and Osteoarthritis Outcome Score.

Relation with severity of radiographic knee OA: subchondral bone density

In the model for mean subchondral bone density age ($B = -0.094$, 95% CI: −0.183, −0.004), sex ($B = -2.007$, 95% CI: −3.573, −0.442), BMI ($B = 0.250$, 95% CI: 0.122, 0.377) and GS Knee ($B = -0.880$, 95% CI: −1.573, −0.187) were statistically significant contributing factors (Table 5). No statistically significant interaction terms were found. The adjusted R^2 of the final model was 0.147.

Discussion

This study showed that GaitSmart parameters as measured at baseline in the APPROACH cohort can be grouped in five main underlying domains: one mainly related to ROM in hips (GS Hip, component no. 1), one mainly related to ROM of knees and calves (GS Knee, component no. 2), and three mainly related to differences in either ROM of knees and calves in swing phase (GS Difference Knee, component no. 3), ROM in hips (GS Difference Hip, component no. 4) and ROM in knees during stance phase (GS Difference Stance, component no. 5). The GaitSmart analysis relates to the whole individual, including (possible) OA in multiple joints. To account for this, differences in gait parameters (component 3–5, see above) are also used as input variables. These five domains contain additional information above radiographic parameters and PROMs and appear

stable in different subgroups. The adjusted R^2 of the linear regression models shows moderate correlations with the severity of ROA. However, the increase in adjusted R^2 compared with the models using only demographics and PROMs is considerably.

Therefore, combining GaitSmart parameters in five 'domains' as proposed provides a concise set of relevant parameters that may have value as additional outcome measurements to assess OA and can be further validated in future analyses.

The main limitation of this study is the translation to the general OA population. APPROACH participants were selected based on a high probability of structural and/or pain progression. This may restrict the generalizability of the results. However, the domains identified were stable over subgroups of severity, and selection bias regarding the associations found, taking into account other demographic and PROM outcomes, is likely limited. However, the specific size of the association may be different in e.g. very early disease. Another limitation is the lack of follow-up data. Any prognostic value of the GaitSmart parameters or any time relationship (e.g. does progression lead to a difference in GaitSmart or the other way around?), which is highly relevant, could not be evaluated. Furthermore, the development of gait characteristics over time might be of additional value above a single gait analysis.

The association of GaitSmart (specifically the GS Difference Knee domain) additional to other parameters, was highest for osteophyte area. One can imagine that a certain relationship exists between the size of osteophytes and limitation in knee movement. The concept of mechanical hindering has also been linked to the presence of a relationship between osteophytes and synovial inflammation [20, 21].

In this study, the severity of ROA was evaluated by parameters related to cartilage (minJSW) and bone (mean subchondral bone density). The fact that the association is limited indicates that other joint structures (e.g. ligaments and/or muscles) also play a substantial role in someone's gait. Although the exclusion criteria of APPROACH rule out secondary osteoarthritis and generalized pain syndromes, other comorbidities influencing gait (e.g. neuromuscular disorders) might also be present. Therefore, contribution of other joint structures and/or comorbidities related to gait might have influenced the relations found between gait and ROA. Some people are also able to manage pain better when walking than others, and neuropathic OA pain might be involved. These may influence the possibility of obtaining strong relations, but given the finding that GaitSmart measures another underlying domain of OA, these associations probably should not be too strong.

The association with the presence of ROA (KL grade $\geq$2) was quite strong for GaitSmart. This is in line with Naili *et al.* who found that peak KAM and a positive KAM impulse were able to discriminate between mild OA (KL grade 1–2) and severe OA (KL grade 3–4) [9]. Using the GaitSmart system has the benefit of assessing the full motion of walking, in contrast to peak value measurements, which only represent a single moment during walking [22].

The gait analysis used by Naili *et al.* was conducted at motion analysis laboratories. At present, 3D optical gait analysis is considered to be the gold standard for testing a person's movement [23]. The strong advantage of the GaitSmart system is the possibility of using it in a natural environment, since no cameras and force plates are required. Moreover, significantly less time is needed to perform a GaitSmart measurement, ~15 min, where measurements in gait laboratories require up to half a day [23]. When comparing the use of IMUs to 3D analysis using an optical tracking system, no differences were found in determining pelvic tilt and knee ROM. The intraclass correlation coefficients were 0.83 (0.72–0.90) for right knee ROM, 0.86 (0.77–0.92) for left knee ROM, 0.75 (0.34–0.89) for right hip ROM and 0.73 (0.22–0.89) for left hip ROM [13]. This indicates that GaitSmart produces valid data for pelvic tilt and, more importantly in our case, knee ROM.

Factors that alter proper joint biomechanics trigger the onset or acceleration of the degenerative process of OA, facilitating the beginning of structural changes and clinical symptoms [24]. The reverse sequence of events will likely occur as well: degenerative and inflammatory changes in the joint will alter biomechanics. Gait characteristics related to medial compartment knee OA depend on the OA severity [10]. Patients with less severe knee OA may adopt a strategy of gait compensation, lowering the load at the medial compartment, reducing their progression risk, whereas patients with more severe knee OA are unable to lower the load on the medial compartment, increasing the risk for disease progression [10]. By adapting the gait pattern in an early OA stage, assisting the natural compensation strategy, it might be possible to slow down disease progression and postpone surgery. Therefore, first a prognostic value of GaitSmart parameters for disease progression should be established. These data become available within the APPROACH project when follow-up data are collected. When gait characteristics prove to be possibly modifiable prognostic factors, early detection of an unfavourable gait in combination with adequate adaptation strategies to this might become a feasible preventive strategy.

Patients scheduled for total knee arthroplasty had a typical OA gait pattern (reduced knee ROM in stance and swing phase) before surgery. Fifty-two weeks post-operation, two-thirds of the patients still had OA gait characteristics, even though pain was reduced [25]. This study also suggested a potential value of gait analysis, in this case in the rehabilitation after joint replacement. GaitSmart could monitor ROM progression of patients after total knee arthroplasty and identify patients that do not improve and might benefit from additional rehabilitation.

In conclusion, our study shows that GaitSmart provides additional information above parameters currently used to asses OA, and is associated with the presence of ROA and, to a limited extent, the severity of OA

above demographics and PROMs. This may indicate that GaitSmart could be an additional parameter to asses OA, but longitudinal studies are required to evaluate how GaitSmart could optimally serve as an additional non-invasive and easily applicable parameter to assess knee OA.

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Data availability statement

Data are available on reasonable request, but in order to gain and govern access to the central APPROACH databases, tranSMART and XNAT, access has to be approved by the APPROACH Steering Committee.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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