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Relationship of unilateral total hip arthroplasty (THA) to contralateral and ipsilateral knee joint degeneration — a longitudinal 3T MRI study from the Osteoarthritis Initiative (OAI)

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SUMMARY

Objective: To evaluate the association of prevalent unilateral total hip arthroplasty (THA) with worsening of degenerative knee abnormalities and clinical outcomes in the ipsilateral and contralateral knee.

Methods: Both knees of 30 individuals in the Osteoarthritis Initiative (OAI) with unilateral THA ($n = 14$ left, $n = 16$ right) at baseline were assessed at baseline and at 4-year follow-up for Whole-organ MR Imaging Scores (WORMS), cartilage T_2 relaxation times (only available for right knees), Western Ontario and McMasters Universities Arthritis Index (WOMAC) scores and upper leg isometric strength. Right knees of 30 individuals without THA were analyzed as controls. Contralateral knees were compared to ipsilateral knees with paired *t*-tests and to control knees with multivariate regression analysis adjusting for covariates.

Results: In paired analyses, compared to ipsilateral knees, contralateral knees had higher WORMS total ($P = 0.008$) and cartilage scores ($P = 0.007$) at baseline. Over 4 years contralateral knees worsened more on WORMS total score ($P = 0.008$). Cartilage T_2 values were higher in knees contralateral to the THA (baseline, $P = 0.02$; follow-up, $P < 0.001$). Contralateral knees had greater declines in knee extension strength ($P = 0.04$) and had a trend for greater worsening in WOMAC pain, stiffness, function and total scores ($P = 0.04-0.09$). Similar results were found comparing contralateral knees with control knees in multivariate regression models.

Conclusions: Prevalent unilateral THA is associated with an greater progression of degenerative findings for the knee contralateral to THA.

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Introduction

Osteoarthritis (OA) of the knee or hip joint is a major cause for disability in our aging society[1]. Joint degeneration of one large joint is associated with degenerative changes in other large joints[2]. Interestingly, patients with unilateral total hip arthroplasty (THA) have a higher rate of total knee replacements on the contralateral side rather than the ipsilateral side[3,4]. However, the association of THA with degenerative changes in the ispi-versus contralateral knee is not well understood. No longitudinal follow-up studies have evaluated the influence of unilateral THA on knee pain and function or on degenerative changes at the knee joint assessed with MRI[5]. MRI provides detailed information on morphological abnormalities in OA[6,7]. Recently, T_2 mapping techniques have been developed to visualize and quantitatively evaluate early cartilage matrix damage, mainly collagen disruption and elevation of cartilage water content[8,9].

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The Osteoarthritis Initiative (OAI) is an ongoing longitudinal, NIH initiated multi-center, prospective observational study of knee OA (https://oai.epi-ucsf.org/datarelease/StudyOverview.asp). The overall aim is to develop a public domain research resource to facilitate the scientific evaluation of biomarkers for OA as potential surrogate endpoints for disease onset and progression. Four clinical centers and a data coordinating center conduct the OAI, a public-private partnership, that bring together new resources and commitment to help find biochemical, genetic and imaging biomarkers for development and progression of OA. The OAI establishes and maintains a natural history database for OA that includes clinical evaluation data, radiological images, and a biospecimen repository from 4796 men and women[10].

The purpose of this study was to determine the association of prevalent unilateral THA with degenerative changes at the ipsilateral and contralateral knee at baseline and in a 4 year longitudinal follow-up. We hypothesized that unilateral THA is associated with more advanced degenerative changes (3T MRI assessment), knee symptoms and muscle weakness in the contralateral compared to the ipsilateral knee, and in particular, that these findings show greater progression in contralateral knees over 4 years.

Methods

Subjects

Individuals from the OAI with a unilateral THA at baseline were included in the study if they had no metallic implants in either knee at either time-point, no additional THA at the contralateral hip at the 4 year follow-up and had complete MRIs in both knees at baseline and 4 year follow-up. There were 30 subjects with a unilateral THA (14 left, 16 right) who met these criteria (23/30 from the OAI incidence cohort, 7/30 from the OAI progression cohort). As a reference group, 30 subjects without THA were age, gender, Body mass index (BMI) and OAI cohort matched (24/30 from the OAI incidence cohort, 6/30 from the OAI progression cohort). The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The study protocol, amendments, and informed consent documentation were approved by the local institutional review boards. Specific OAI datasets used in this study were baseline datasets 0.2.2 and 0.E.1 and the 4 year follow-up datasets 6.2.1 and 6.E.1 (http://www.oai.ucsf.edu/).

Imaging: pelvic and knee radiography

Bilateral standing anterior-posterior pelvic radiographs and posterior-anterior knee radiographs were acquired (http://oai.epi-ucsf.org/datarelease/OperationsManuals.asp). Pelvic radiographs were screened for presence of unilateral THA at baseline and year 4. Baseline Kellgren–Lawrence (K–L) scores for both knees of each individual were obtained from the OAI database (central K–L readings).

Imaging: knee MRI

MRI sequences for semiquantitative Whole-organ MR Imaging Scores (WORMS) readings and for quantitative T_2 mapping were acquired in right knees at four clinical sites using 3T MRI scanners (Siemens Magnetom Trio; Siemens, Erlangen, Germany) and quadrature transmit-receive knee coils (USA Instruments, Aurora, OH). Details of the acquisition protocol are given in Table I[11].

Semi-quantitative morphological knee MRI analyses

Morphological MR images (Table I) of both knees of the unilateral THA subjects and of right knees of those without a THA were assessed for OA-related abnormalities using a modified WORMS[12,13]. MR images were reviewed on picture archiving communication system (PACS) workstations (Agfa, Ridgefield Park, NJ). MRIs were evaluated by two musculoskeletal radiologists separately (P.M.J., L.N.; 6 and 8 years of experience, respectively), blinded for the THA side and for the time-point; if scores were not identical consensus readings by both radiologists and a third independent radiologist (T.M.L., 23 years of experience) were performed. A total WORMS summation score, with a potential maximum of 110 was calculated as the sum of grades for all of the knee features: (1) meniscus abnormalities (score 0–4 in six regions), (2) cartilage lesions (score 0–6 in six regions), (3) bone marrow lesions (score 0–3 in six regions) (4) ligament abnormalities (score 0–4 in six locations), and (5) other abnormalities (effusion (0–3), intraarticular body (0–2), baker cyst (0–3)). Additionally, meniscus scores were calculated for the medial and for the lateral meniscus (score 0, all meniscus subregions "0"; score 1, no > 1; score 2, "2" in one subregion; score 3, "2" in >1 subregion; score 4, "3" in ≥1 subregion; score 5, "4" in one subregion; score 6, "4" in ≥1 subregion). For the parameters cartilage, bone marrow lesions, ligament abnormalities and other abnormalities maximum scores were determined, indicating the maximum score of all subregions for each parameter. The total maxWORMS score with a potential maximum of 28 was defined as the sum of the meniscus scores and the maximum scores.

T_2 relaxation time measurements

T_2 mapping MSME spin echo sequences, available for all right knees were analyzed on a remote workstation (SPARC; Sun Microsystems, Mountain View, CA) using an in-house software implemented in MATLAB (The Mathworks Inc., Natick, MA)[14–16]. Semi-automated spline-based segmentation was performed by two radiologists (P.M.J. and H.L.; 6 and 2 years of experience) under supervision of an experienced radiologist (T.M.L.; 23 years of experience) in five compartments: (1) patella, (2) medial and (3) lateral femoral condyle and (4) medial and (5) lateral tibia. The trochlea was excluded because of interfering flow artifacts from the popliteal artery. Segmentation was performed on all slices of the first echo images. T_2 maps were created using a monoexponential decay model as fitting function to calculate the signal intensity at the different echo times. T_2 calculations were measured from the second (20 ms) to the last (70 ms) echo images, dropping the first echo time[17–19]. T_2 values of baseline and 4-year follow-up time points were calculated. "Global" T_2 value was defined as mean of all compartments combined. Four-year progression was calculated as the difference ($T_{2\ follow-up} - T_{2\ baseline}$). Since T_2 mapping sequences were only available for right knees, comparisons of T_2 values between the groups were non-paired. The "contralateral THA" group was represented by the 14 individuals with a left THA and the "ipsilateral THA" group was represented by the 16 individuals with a right THA.

Reproducibility of MRI measurements

Reproducibility was calculated in a randomly selected sample of 10 OAI subjects. For WORMS measurements, images were graded twice by two radiologists (P.M.J., L.N.) on two separate occasions (2 weeks in-between) and linear weighted Cohen's Kappa values were calculated. For cartilage defects, inter-observer kappa was 0.89, intra-observer kappa was 0.91 and 0.95, respectively. For meniscus

Table I
MR pulse sequences

Parameter	2D IM-w FSE	3D DESS WE	3D T1-w FLASH WE	2D IM-w FS FSE	2D T2-w MSME SE
Plane	Coronal	Sagittal	Coronal	Sagittal	Sagittal
Field of view (FOV; mm)	140	140	160	160	120
Matrix	128×256	307×384	512×512	313×448	269×384
Number of slices	35	160	80	37	21
Slice thickness (mm)	3	0.7	1.5	3	3
Repetition time (RT; ms)	3700	16.3	20	2700	3200
Echo time (ET; ms)	29	4.7	7.6	10,20,30,40,50,60,70	30
Refocusing flip angle (°)	180	25	12	180	n/a
Bandwidth (Hz/Pixel)	352	185	130	248	250
Echo train length	7	1	1	5	1
Acquisition time (min)	3.4	10.6	8.6	4.7	10.6

IM-w, intermediate-weighted; FSE, fast spin echo; DESS, dual-echo steady-state; WE, water-excitation; FLASH, fast low-angle shot; 3D, three-dimensional; 2D, two-dimensional; FS, fat saturated; MSME, multislice-multiecho; SE, spin echo.

defects, inter-observer kappa was 0.80, intra-observer kappa was 0.89 and 0.95. For ligament abnormalities, inter-observer kappa was 0.65, intra-observer kappa was 0.76 and 0.77. For bone marrow abnormalities, inter-observer kappa was 0.80, intra-observer kappa was 0.81 and 0.87. For other scorings, inter-observer kappa was 0.70, intra-observer kappa was 0.79 and 0.79. Inter-observer agreement for T_2 measurements (coefficient of variation) was described previously with an inter-reader reproducibility error for mean T_2 of 1.57%, respectively 0.53 ms[13]. Mean intra-reader reproducibility for T_2 measurements was 1.66%, respectively 0.55 ms.

Western Ontario and McMasters Universities Arthritis Index (WOMAC)

Knee symptoms assessed by WOMAC (University of Western Ontario and the McMaster University in Canada) scores in both knees[20,21]. The WOMAC score is an established multidimensional health status instrument. It quantifies the degree of three different domains of disease status (pain, stiffness and functional impairment) through a 5-point scale (none, slight, moderate, severe and extreme), with higher scores indicating increasing disease severity.

Physical activity scale for the elderly (PASE)

Physical activity levels were measured using the PASE score[22,23]. The PASE score aims to assess general activity and health status in older adults. This established score includes questions on household chores and occupational activities, as well as individual activities such as knee bending, squatting and stair climbing. It has a scale range from 0 to 400 and was described as valid and reliable for epidemiologic studies.

Isometric strength

Isometric strength measurements were performed using a Good Strength apparatus (Metitur, Jyväskylä, Finland; www.oai.ucsf.edu/datarelease/OperationsManuals.asp) for knee flexion and extension. Two submaximal practice trials were completed before force was measured three times for 3 s, each separated by 30 s; the highest value for a limb is used for maximal strength reported (N).

Other baseline measurements

Heberden's nodes were considered present if bony enlargements were found in ≥3 DIP joints in either hand during an examination of the hand at baseline (http://oai.epi-ucsf.org/datarelease/forms.asp). History of knee injury or surgery, familial

predisposition of OA, defined as a total knee replacement for OA in a biological parent or sibling, were assessed by self-report (https://oai.epi-ucsf.org/datarelease/operationsManuals.asp). BMI was calculated as weight in kg/height m².

Statistical analysis

Statistical analysis was performed with JMP software Version 9 (SAS Institute, Cary, NC, USA). The analyses compared knees contralateral to THA with knees ipsilateral to THA and with knees of controls without THA for change in measures of knee OA over 4 years, for baseline scores and for scores at year 4 of follow-up. Paired *t*-tests were used to compare outcomes between paired ipsilateral and contralateral knees in the same subject. Multivariable linear regression was used for comparisons between contralateral and control knees in different subjects and for comparisons of T_2. From the regression models adjusted means and standard errors (SEM), adjusted mean differences and 95% confidence intervals were obtained. Covariates were OA risk factors including: self-reported history of knee injury or surgery, familial predisposition of OA, defined as a total knee replacement for OA in a biological parent or sibling, Heberden's nodes, age, gender BMI and PASE score. Sensitivity analyses were also performed by including preexisting knee OA (K–L grade) at baseline as a covariate in mixed model fits (Stata Ver 13, College Station, TX, USA) and in the linear regression models. The level of significance was set at $P < 0.05$.

Results

Baseline characteristics

There were no statistically significant differences in gender, age, BMI or physical activity between subjects with unilateral THA and controls with no THA ($P > 0.05$; Table IIA). Subjects with a THA in the left hip (i.e., the right knee is 'contralateral' and also used in comparisons to right control knees) had lower PASE physical activity scores than controls (113 ± 47 vs 158 ± 73, $P = 0.04$). K–L grades were significantly different between the groups (Table IIB).

WOMAC

WOMAC scores of knees contralateral to prevalent THA worsened on average over 4 years (Total score, 2.0 ± 2.6) while improving in ipsilateral knees (Total score, -3.4 ± 2.6, $P = 0.06$; Table III). WOMAC scores in control knees also improved during follow-up (Total score, -2.3 ± 2.6; contralateral vs control, $P = 0.13$). Baseline WOMAC scores in contralateral knees were not significantly different compared to ipsilateral knees (Total scores,

Table IIa
Baseline characteristics. 2A. Subject characteristics by baseline THA status. BL = Baseline; SD = Standard deviation; PASE = Physical Activity Scale for the Elderly; THA = Total hip arthroplasty; R = right; L = left

BL characteristic	Subjects with			
	1. Unilateral THA	2. Unilateral THA in L hip	3. Unilateral THA in R hip	4. Controls, No THA
Subjects (n)	30	14	16	30
Gender (n; Male/Female)	43% (13/17)	43% (6/8)	44% (7/9)	47% (14/16)
Age ± SD (years)	67 ± 10	67 ± 10	67 ± 11	66 ± 10
Body mass index ± SD (kg/m^2)	28.5 ± 4.3	28.8 ± 3.4	28.2 ± 4.9	27.9 ± 4.7
PASE ± SD	127 ± 53	113 ± 47[*]	140 ± 56	158 ± 73

[*] 2 vs 4, $P = 0.038$. All other comparisons are NS, $P > 0.05$.

8.4 ± 2.3 vs 5.9 ± 2.2, $P = 0.29$) or compared to control knees (Total score, 8.8 ± 2.3, $P = 0.38$; Table III). Adjusting for baseline K−L grade had little impact on these comparisons, except that worsening in WOMAC total ($P = 0.03$) and function ($P = 0.03$) scores were now significantly greater in contralateral vs ipsilateral knees.

Morphological analysis of knee abnormalities (WORMS)

While WORMS scores tended to worsen during follow-up in all knees, the increase in contralateral knees was greater than ipsilateral knees for total score (7.9 ± 1.1 vs 4.6 ± 1.1, $P = 0.008$; replacing the sum score with the maximum score of bone marrow lesions in the total WORMS score, $P = 0.03$; total maxWORMS score, $P = 0.05$) and ligaments (2.4 ± 0.5 vs 0.8 ± 0.5, $P = 0.01$; ligament maximum score, $P = 0.10$) and compared to control knees for total score ($P = 0.03$; total maxWORMS score, $P = 0.04$), medial meniscus ($P = 0.009$; medial meniscus score, $P = 0.008$) and ligaments ($P = 0.009$; ligament maximum score, $P = 0.13$) (Table III). Baseline WORMS scores in contralateral knees were significantly worse compared to ipsilateral knees for cartilage of the whole knee (13.4 ± 1.2 vs 10.1 ± 1.2, $P = 0.007$; cartilage maximum score, $P = 0.06$), medial meniscus (2.9 ± 0.4 vs 2.0 ± 0.4, $P = 0.01$; medial meniscus score, $P = 0.01$) and total WORMS scores (28.1 ± 2.4 vs 21.3 ± 2.4, $P = 0.008$; replacing the sum score with the maximum score of bone marrow lesions in the total WORMS score, $P = 0.006$; total maxWORMS score, $P = 0.008$) and compared to control knees for cartilage and lateral meniscus ($P < 0.05$; Table III). In analyses adjusting for baseline K−L grade, results for worsening of WORMS scores were largely unchanged (total WORMS score, $P = 0.02$), although no longer significant for contralateral vs ipsilateral ligaments ($P = 0.07$) nor for contralateral vs control knee total score worsening ($P = 0.07$). After K−L adjustment no significant differences in baseline WORMS scores between groups were found (total WORMS score, $P = 0.71$).

Examining WORMS cartilage scores in individual cartilage plates (Table IV), there were no significant differences for change in cartilage score. Trochlea ($P = 0.02$) and medial femoral condyle ($P = 0.008$) cartilage worsened more in contralateral knees than control knees. At baseline contralateral knees had significantly

worse scores than ipsilateral knees at the trochlea (2.6 ± 0.3 vs 1.7 ± 0.3, $P < 0.001$), lateral femoral condyle (1.7 ± 0.3 vs 1.0 ± 0.3, $P = 0.02$), and lateral tibia (2.1 ± 0.3 vs 1.4 ± 0.3, $P = 0.02$) and worse scores compared control knees at the lateral femoral condyle ($P = 0.03$). Plate-specific cartilage results were essentially unchanged by additional adjustment for baseline K−L grade (change contralateral vs control: trochlea, $P = 0.02$, medial femoral condyle, $P = 0.01$; baseline contralateral vs ipsilateral: trochlea, $P = 0.05$, lateral femoral condyle, $P = 0.04$, lateral tibia, $P = 0.10$; baseline contralateral vs control: lateral femoral condyle, $P = 0.04$).

Cartilage T$_2$ relaxation time measurements

T$_2$ relaxation time measurements were only available in right knees so all comparisons are non-paired between different subjects, adjusting for covariates in a multivariate regression model (contralateral, $n = 14$; ipsilateral, $n = 16$; controls, $n = 30$; Fig. 1; Table V). The increase in T$_2$ of the whole knee over 4 years was significantly greater in contralateral compared to ipsilateral knees (2.9 ± 0.9 ms vs 0.4 ± 0.8 ms, $P = 0.02$) and compared to control knees (2.9 ± 0.9 ms vs −0.3 ± 0.7 ms, $P < 0.001$). T$_2$ in contralateral medial femoral condyles increased more compared to ipsilateral (3.7 ± 1.0 ms vs 0.5 ± 0.8 ms, $P = 0.004$) and compared to control knees (3.7 ± 1.0 ms vs 0.2 ± 0.7 ms, $P = 0.001$). At baseline, cartilage T$_2$ relaxation times were non-significantly higher in contralateral knees (all $P > 0.05$; Table V). Results for T$_2$ were essentially unchanged by additional adjustment for baseline K−L grade (Contralateral vs ipsilateral whole knee T$_2$; change, $P = 0.006$; baseline, $P = 0.64$).

Isometric upper leg strength

Isometric extension strength decreased significantly more in contralateral compared to ipsilateral knees (−51.6 ± 21.9 vs −15.5 ± 22.4, $P = 0.04$) and compared to control knees ($P = 0.009$), but there were no differences in change in flexion strength ($P = 0.52$ and $P = 0.12$; Table VI). There were no differences in baseline strength between groups. These results were essentially unchanged when K−L grade was included as a covariate (Change

Table IIb
Baseline characteristics. 2B. Knee K−L grade by baseline THA status. 1 vs 2, $P = 0.04$ 1 vs 5, $P = 0.04$; 3 vs 4, $P = 0.02$; 3 vs 5, $P = 0.04$; 4 vs 5, $P = 0.56$. THA = Total hip arthroplasty; K−L = Kellgren−Lawrence

BL KL grade	Subjects with unilateral THA				No THA (controls)
	1. All contralateral knees	2. All ipsilateral knees	3. Right contralateral knees[*]	4. Right ipsilateral knees[*]	5.Rt knees
0−1	50/100% (15/30)	70/100% (21/30)	43/100% (6/14)	75/100% (12/16)	73/100% (22/30)
2	23/100% (7/30)	20/100% (6/30)	21/100% (3/14)	19/100% (3/16)	10/100% (3/30)
3	17/100% (5/30)	7/100% (2/30)	29/100% (4/14)	6/100% (1/16)	17/100% (5/30)
4	10/100% (3/30)	3/100% (1/30)	7/100% (1/14)	0/100% (0/16)	0/100% (0/30)
Knees (n)	30	30	14	16	30

[*] Only right knees are included in analyses of differences in T$_2$ relaxation times.

Table III
Baseline Knee pain and MRI findings, and change, in knees contralateral and ipsilateral to THA. Adjusted mean baseline values and adjusted mean changes over 4years ± standard error of the mean (s.e.m.) for WOMAC and WORMS scores by THA status. Contralateral vs ipsilateral knee comparisons are paired within subject differences. Contralateral compared to right knees of subjects with No THA are adjusted means from multivariate linear regression models, adjusted for age, gender, PASE, BMI and risk factors

Baseline		Unilateral THA		No THA) (controls) right knee	Contralateral vs ipsilateral		Contralateral vs control	
		Contralateral knee	Ipsilateral knee		P-value (paired t-test)*	Paired difference (95% CI)*	P-value† (95% CI)	Adj. mean difference (95% CI)†
WOMAC	Total score	8.4 ± 2.3	5.9 ± 2.2	8.8 ± 2.3	0.29	2.4 (−2.1; 6.9)	0.38	−2.3 (−7.6; 2.9)
	Pain	1.9 ± 0.5	1.3 ± 0.5	2.0 ± 0.6	0.20	0.6 (−0.3; 1.5)	0.42	−0.5 (−1.8; 0.8)
	Stiffness	1.1 ± 0.4	1.0 ± 0.4	1.5 ± 0.4	0.61	0.2 (−0.5; 0.8)	0.16	−0.6 (−1.4; 0.2)
	Function	5.7 ± 1.7	4.1 ± 1.7	5.3 ± 1.7	0.39	1.5 (−2.0; 5.0)	0.56	−1.2 (−5.1; 2.8)
WORMS	Total score	28.1 ± 2.4	21.3 ± 2.4	19.7 ± 2.4	0.008	6.8 (1.9; 11.7)	0.07	5.4 (−0.4; 11.1)
	Med. meniscus	2.9 ± 0.4	2.0 ± 0.4	1.7 ± 0.4	0.01	0.8 (0.0; 1.6)	0.06	0.8 (−0.0; 1.6)
	Lat. meniscus	2.0 ± 0.4	1.6 ± 0.4	0.9 ± 0.4	0.28	0.4 (−0.3; 1.1)	0.05	0.9 (0.0; 1.9)
	Ligaments	3.8 ± 0.7	3.0 ± 0.7	3.8 ± 0.7	0.25	3.0 (−0.6; 2.1)	0.59	−0.4 (−2.0; 1.1)
	Cartilage	13.4 ± 1.2	10.1 ± 1.2	8.9 ± 1.3	0.007	3.4 (1.0; 5.8)	0.04	3.1 (0.2; 6.1)
	BME‡	3.4 ± 0.6	2.6 ± 0.7	2.9 ± 0.7	0.21	0.7 (−0.4; 1.9)	0.71	−0.3 (−1.9; 1.3)
Change baseline to 4 years								
WOMAC	Total score	2.0 ± 2.6	−3.4 ± 2.6	−2.3 ± 2.6	0.06	5.1 (−0.2; 10.4)	0.13	4.8 (−1.4; 11.1)
	Pain	0.5 ± 0.7	−0.5 ± 0.6	−0.7 ± 0.7	0.09	1.0 (−0.2; 2.2)	0.31	0.8 (0.8; 2.4)
	Stiffness	0.0 ± 0.3	−0.7 ± 0.3	−0.2 ± 0.3	0.04	0.7 (0.1; 1.3)	0.34	0.4 (−0.4; 1.2)
	Function	1.8 ± 1.9	−2.3 ± 1.9	−1.5 ± 1.9	0.06	3.9 (−0.1; 7.8)	0.10	2.9 (−0.7; 8.5)
WORMS	Total score	7.9 ± 1.1	4.6 ± 1.1	5.7 ± 1.2	0.008	3.3 (0.9; 5.7)	0.03	2.8 (0.2; 5.4)
	Med. meniscus	0.8 ± 0.2	0.4 ± 0.2	0.2 ± 0.2	0.06	0.4 (−0.0; 0.8)	0.009	0.6 (0.2; 1.1)
	Lat. meniscus	0.6 ± 0.2	0.4 ± 0.2	0.6 ± 0.2	0.26	0.4 (−0.2; 0.6)	0.70	−0.1 (−0.6; 0.4)
	Ligaments	2.4 ± 0.5	0.8 ± 0.5	0.6 ± 0.5	0.01	0.8 (0.3; 2.8)	0.009	1.7 (−0.4; 2.9)
	Cartilage	3.8 ± 0.6	3.0 ± 0.6	3.2 ± 0.6	0.25	3.0 (−0.6; 2.3)	0.19	1.0 (−0.5; 2.5)
	BME‡	−0.1 ± 0.5	−0.9 ± 0.5	0.6 ± 0.6	0.26	0.9 (−0.6; 2.3)	0.69	−0.3 (−1.6; 1.0)

 * Paired difference = contralateral−ipsilateral; P-value and 95% from paired t-test.
 † P-value and adjusted mean difference and 95% CI from the multivariate regression model, contralateral vs control knees. Covariates were OA risk factors including: self-reported history of knee injury or surgery, familial predisposition of OA, defined as a total knee replacement for OA in a biological parent or sibling, Heberden's nodes, age, gender BMI and PASE score.
 ‡ BME: bone marrow edema-like lesions; P-values are given for the sum of the compartment specific BME scores. P-values for maximum BME scores: $P_{baseline} = 0.19$; $P_{increase} = 0.45$ (ipsi-versus contralateral).

extension strength; contralateral vs ipsilateral, $P = 0.03$, contralateral vs control, $P = 0.005$).

Main knee outcome measures at the year 4 follow-up

At the 4 year follow-up (Fig. 2), compared to ipsilateral knees the contralateral knees had significantly higher WOMAC total scores (11.5 ± 2.6 vs 3.5 ± 2.5, $P = 0.01$); higher WORMS total scores

(35.9 ± 3.0 vs 25.8 ± 3.0, $P = 0.001$; total maximum WORMS scores, $P = 0.001$) and higher whole knee T_2 values (39.8 ± 0.9 vs 36.1 ± 0.7, $P < 0.001$), while extension and flexion strength did not differ between groups (286 ± 23.4 vs 332 ± 23.9, $P = 0.12$ and 144 ± 12 vs 131 ± 12, $P = 0.43$). At the 4 year follow-up, contralateral knees also had significantly (all $P < 0.05$) worse scores for WOMAC pain, stiffness and function subscale scores, worse scores for WORMS cartilage, medial meniscus and bone marrow lesion subscale scores,

Table IV
Baseline MRI findings, and change, by compartment, in knees contralateral and ipsilateral to THA. Adjusted mean baseline values and change over 4years ± standard error of the mean (s.e.m.) for WORMS compartment-specific cartilage scores by THA status. Contralateral vs ipsilateral knee comparisons are paired, within subject differences. Contralateral and ipsilateral comparisons to right knees of subjects with No THA and adjusted mean values are from multivariate linear regression models.* = P < 0.05 for contralateral or ipsilateral knee vs No THA control knees

WORMS baseline	Unilateral THA		No THA	Contralateral vs ipsilateral		Contralateral vs control	
	Contralateral knee	Ipsilateral knee	(Controls) right knee	P-value (paired t-test)*	Paired difference (95% CI)*	P-value†	Adj mean difference (95% CI)†
Patella	3.1 ± 0.4	3.0 ± 0.4	2.5 ± 0.4	0.80	0.1 (−0.6; 0.7)	0.16	0.6 (−3; 1.5)
Trochlea	2.6 ± 0.3	1.7 ± 0.3	1.6 ± 0.4	<0.001	1.0 (0.5; 1.4)	0.13	0.6 (−0.2; 1.5)
MFC	2.1 ± 0.4	1.7 ± 0.4	1.5 ± 0.4	0.26	0.4 (−0.3; 1.1)	0.65	0.2 (−0.7; 1.1)
LFC	1.7 ± 0.3	1.0 ± 0.3	0.9 ± 0.3	0.02	0.8 (0.2; 1.3)	0.03	0.7 (0.1; 1.4)
MT	1.8 ± 0.3	1.3 ± 0.3	1.1 ± 0.3	0.21	0.5 (−0.3; 1.3)	0.43	0.3 (−0.5; 1.0)
LT	2.1 ± 0.3	1.4 ± 0.3	1.2 ± 0.3	0.02	0.7 (0.1; 1.3)	0.05	0.6 (0.0; 1.3)
Change baseline to 4 years							
Patella	0.7 ± 0.3	0.7 ± 0.3	0.4 ± 0.3	0.94	0.0 (−0.5; 0.5)	0.20	0.4 (−0.2; 1.0)
Trochlea	0.8 ± 0.2	0.5 ± 0.2	0.3 ± 0.2	0.25	0.3 (−0.2; 0.7)	0.02	0.5 (0.1; −1.0)
MFC	0.9 ± 0.2	0.6 ± 0.2	0.3 ± 0.2	0.31	0.2 (−0.2; 0.7)	0.008	0.7 (0.2; 1.2)
LFC	0.5 ± 0.2	0.5 ± 0.2	0.7 ± 0.3	0.94	0.0 (−0.4; 0.5)	0.32	−0.3 (−0.9; 0.3)
MT	0.7 ± 0.2	0.4 ± 0.2	0.3 ± 0.2	0.32	0.3 (−0.3; 0.9)	0.05	0.5 (0.0; 1.0)
LT	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.87	0.0 (−0.4; 0.4)	0.82	−0.0 (−0.4; 0.4)

 * Paired difference = contralateral−ipsilateral; P-value and 95% from paired t-test.
 † P-value and adjusted mean difference and 95% CI from the multivariate regression model, contralateral vs control knees. Covariates were OA risk factors including: self-reported history of knee injury or surgery, familial predisposition of OA, defined as a total knee replacement for OA in a biological parent or sibling, Heberden's nodes, age, gender BMI and PASE score.
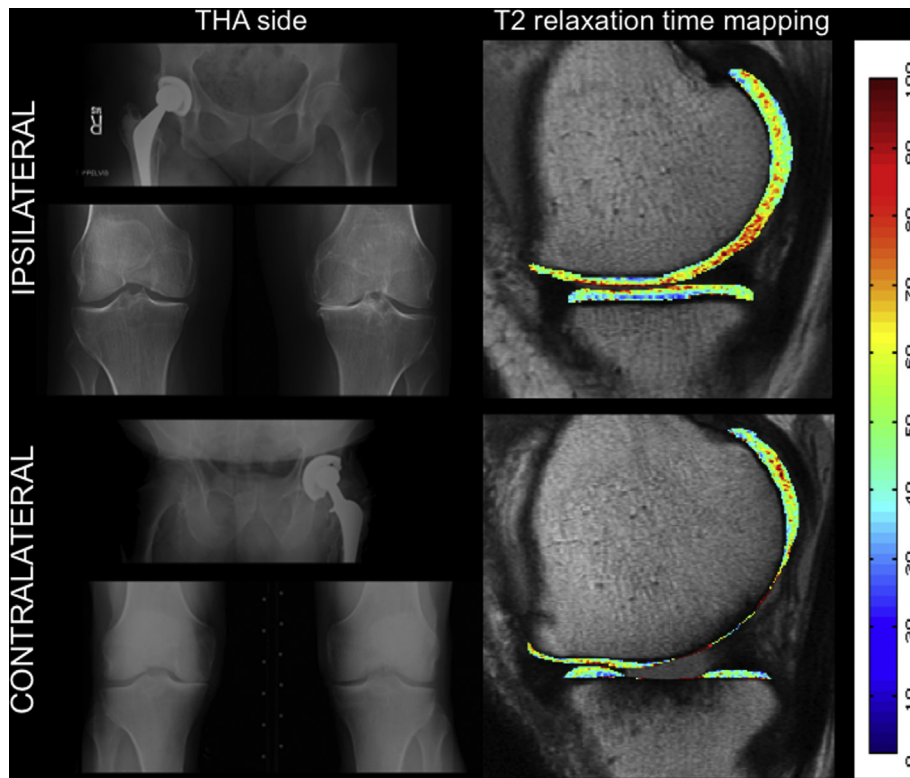
Fig. 1. T_2 relaxation time color maps of right knees of individuals with ipsilateral and contralateral THA, overlaid with the first-echo images of the MSME sequence. Blue color indicates low, red color high cartilage T_2 values. The most severe cartilage, medial meniscus and bone marrow pathologies were found in individuals with contralateral THA.

and higher T_2 values in both medial and lateral femoral condyles and lateral tibia (data not shown). Results were essentially unchanged in models that included baseline K−L grade.

Discussion

In individuals with a prevalent THA and two native knees, we found that some, but not all, measures of degenerative morphological and T_2 cartilage abnormalities assessed by knee MRI and knee strength showed greater worsening over 4 years in the knee contralateral to the THA compared to these individuals' knees ipsilateral to the THA and compared to control knees of individuals without a THA. These findings are generally consistent with the hypothesis that prevalent unilateral THA, increases the risk of developing OA in the knee contralateral to the THA.

OA of one large joint is known to be associated with degenerative changes in other large joints within an individual[2], with the contralateral side of the same joint being at risk for OA and with the contralateral side of the other big joint also having an increased risk for OA[2,3]. Individuals with a joint replacement are likely to have a

Table V
Adjusted mean baseline values ± S.E.M. and 4 year change for the T_2 relaxation time (ms). *P*-values are from multivariate regression models comparing right contralateral knees with right ipsilateral knees of different subjects with unilateral THA and comparing right contralateral knees of unilateral THA subjects with right knees of control subjects with no THA. MFC = Medial femoral condyle; LFC = Lateral femoral condyle; MT = Medial tibia; LT = Lateral tibia.* = $P < 0.05$ for contralateral or ipsilateral knee vs No THA control knees

T_2 relaxation time baseline	Unilateral THA		No THA	Contralateral vs ipsilateral		Contralateral vs control	
	Contralateral right knee	Ipsilateral right knee	(Controls) right knee	*P*-value*	Adj mean difference (95% CI)*	*P*-value*	Adj mean difference (95% CI)*
Global	37.0 ± 0.8	35.9 ± 0.6	36.0 ± 0.6	0.42	0.7 (−1.0; 2.4)	0.60	0.4 (−1.1; 2.0)
Patella	37.5 ± 1.4	36.5 ± 1.1	36.3 ± 1.0	0.84	0.3 (−2.7; 3.2)	0.51	0.9 (−1.8; 3.6)
MFC	39.8 ± 1.2	38.5 ± 0.9	38.7 ± 0.9	0.51	0.8 (−1.7; 3.4)	0.43	0.9 (−1.4; 3.3)
LFC	36.3 ± 0.9	35.0 ± 0.7	34.9 ± 0.7	0.08	1.7 (−0.2; 3.7)	0.06	1.8 (−0.0; 3.6)
MT	37.7 ± 1.2	36.5 ± 0.9	36.6 ± 0.8	0.74	0.4 (−2.1; 2.9)	0.76	0.3 (−1.9; 2.6)
LT	33.5 ± 1.3	32.8 ± 1.0	32.0 ± 0.9	0.43	1.1 (−1.7; 3.9)	0.28	1.4 (−1.2; 3.9)
Change baseline to 4 years							
Global	2.9 ± 0.9	0.4 ± 0.8	−0.3 ± 0.7	0.02	2.5 (0.5; 4.5)	0.001	2.4 (1.6; 5.2)
Patella	5.3 ± 2.1	1.3 ± 1.7	0.6 ± 1.5	0.20	2.9 (−1.6; 7.4)	0.10	3.5 (−0.6; 7.6)
MFC	3.7 ± 1.0	0.5 ± 0.8	0.2 ± 0.7	0.004	3.2 (1.6; 5.3)	0.001	3.4 (1.4; 5.3)
LFC	2.7 ± 1.1	0.7 ± 0.8	0.8 ± 0.7	0.14	1.7 (−0.6; 3-9)	0.07	1.9 (−0.2; 3.9)
MT	0.3 ± 1.4	−0.7 ± 1.1	−0.7 ± 1.0	0.73	0.5 (−2.4; 3.4)	0.94	0.1 (−2.6; 2.8)
LT	2.3 ± 2.0	−1.4 ± 1.6	0.7 ± 1.4	0.09	3.7 (−0.6; 7.9)	0.36	1.8 (−2.1; 5.7)

* *P*-value and adjusted mean difference and 95% CI from the multivariate regression model. Covariates were OA risk factors including: self-reported history of knee injury or surgery, familial predisposition of OA, defined as a total knee replacement for OA in a biological parent or sibling, Heberden's nodes, age, gender BMI and PASE score.

Table VI
Baseline and change in isometric extension and flexion strength in knees contralateral and ipsilateral to THA. Adjusted mean baseline isometric values and change over 4 years ± standard error of the mean (S.E.M.) (Newtons) for isometric strength by THA status. Contralateral vs ipsilateral knee comparisons are paired, within subject differences. Contralateral and ipsilateral comparisons to right knees of subjects with No THA and adjusted mean values are from multivariate linear regression models

Maximum isometric strength (Newtons) baseline:	Unilateral THA		No THA (controls) right knee	Contralateral vs ipsilateral		Contralateral vs control	
	Contralateral knee	Ipsilateral knee		*P*-value (paired *t*-test) [*]	Paired difference (95% CI)*	*P*-value†	Adj mean difference (95% CI)†
Extension	334.1 ± 26.1	327.0 ± 25.9	340.9 ± 26.1	0.64	−7.1 (−37.3; 23.2)	0.90	−3.6 (−65.7; 33.7)
Flexion	137.7 ± 15.6	138.1 ± 15.5	131.6 ± 15.6	0.94	0.4 (−9.7; 10.5)	0.72	−0.6 (−39.3; 27.2)
Change: baseline to 4 years							
Extension	−51.6 ± 21.9	−15.5 ± 22.4	−4.1 ± 21.8	0.04	−42.0 (−2.8; −81.1)	0.009	−73-3 (−127.4; −19.3)
Flexion	−33.9 ± 16.1	−44.7 ± 16.3	−58.7 ± 16.0	0.52	−11.3 (−46.8; 24.2)	0.12	30.1 (−67.8; 7.6)

 [*] Paired difference = contralateral−ipsilateral; *P*-value and 95% from paired *t*-test.
 † *P*-value and adjusted mean difference and 95% CI from the multivariate regression model, contralateral vs control knees. Covariates were OA risk factors including: self-reported history of knee injury or surgery, familial predisposition of OA, defined as a total knee replacement for OA in a biological parent or sibling, Heberden's nodes, age, gender BMI and PASE score.

subsequent replacement of the same joint on the contralateral side[3,29]. Umeda *et al.* reported increasing radiographic degenerative changes at the contralateral medial knee compartment after unilateral THA, although there was no difference between the ipsilateral and contralateral knee at baseline[5]. Causes for an increased progression of degenerative changes at the knee contralateral to the THA were not investigated in the present study. Despite, potential factors include biomechanical and neuromuscular factors[24], such as muscle weakness[25–27]. Increased peak dynamic knee loads and increased medial compartment tibial bone mineral density in the knee contralateral to end stage hip OA was described previously[28]. Gillam *et al.* stated, that the consequence of gait alterations due to a diseased hip or leg length discrepancy may be responsible for the subsequent development of OA in the contralateral knee[29]. A reduced offset of conventional femoral prostheses may be responsible for shifts in mechanical axes. Increased dynamic loads and elevated knee adduction moments in the knee contralateral to a THA have been found[30]. Foucher *et al.* found that the peak adduction moment was higher on the contralateral vs the ipsilateral knee in patients with unilateral THA[31]. The authors concluded, that implant positioning could influence the biomechanical risk of

knee OA progression after THA. On the other hand, Metcalfe *et al.* reported, that also patients with knee OA had significant increases in adduction moment impulse at both knees and the contralateral hip[32]. Alternatively to altered lower limb biomechanics, knee injury, disease and pathomechanics could precede and may lead to altered hip mechanics and hip OA.

Previous studies of this topic however have several limitations. Some focused only on whether replacement of one hip or knee affects the risk of contralateral joint replacement[3,33]. Other studies have been cross-sectional[2,33]. Two studies have examined longitudinal changes of hip or knee OA contralateral to the same joint with OA. Spector *et al.*[34] found that over a third of women with unilateral radiographic knee OA will have incident or worsening OA in other knee within 2 years. Vossinakis *et al.*[35] found that patients with idiopathic OA of one hip are at increased risk of developing OA in the other hip. These studies evaluated plain radiographs and did not address hip–knee or knee–hip associations, although MRI can provide substantially more detailed information about joint tissue damage[36,37]. Additionally, it is important to evaluate both structural changes and clinical symptoms because they often deviate[38].
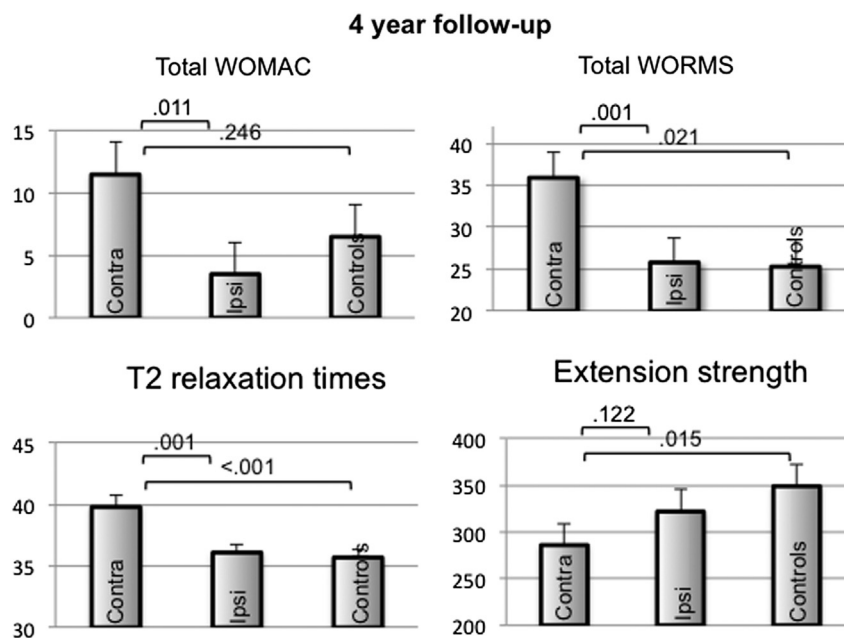

Fig. 2. Mean values at 4-year follow-up ± S.E.M. for the parameters total WOMAC score, total WORMS score, global T_2 relaxation time (ms), and isometric strength in knee extension (Force; N) in knees contralateral and ipsilateral to THA. *$P < 0.05$ in a multivariate regression model, adjusted for age, gender, PASE, BMI and OA risk factors.

A strength of our study is that the main analyses examined longitudinal progression over 4 years of knee joint findings that occurred subsequent to unilateral THA. Adjustment for baseline K−L grades had little or no impact on any these associations. Greater increases in T_2 values were found for contralateral knees. WOMAC scores also showed consistent but nonsignificantly greater progression in contralateral knees. Of note, WOMAC scores improved in ipsilateral knees over time. Possibly, this may be due to specific physiotherapy for this extremity or transferred symptoms (hip complaints transferred to knee complaints) may have resolved over time. Also, replacing one major lower extremity joint may improve the overall lower extremity biomechanics, neuromuscular control and may therefore impact function and loading of the entire extremity. Contralateral knees showed greater worsening over 4 years than ipsilateral knees and than control knees in overall degenerative morphological changes. Surprisingly, 4-year change in cartilage WORMS score and in bone marrow lesion WORMS score was not significant. This may be either due to the small sample size or due to ceiling effects, since cartilage and bone marrow lesion WORMS scores were higher in contralateral knees at baseline (Table III).

Our findings for contralateral compared to ipsilateral knees differed somewhat for cartilage morphological damage and T_2 relaxation times. T_2 relaxation time detects early degenerative changes of the biochemical composition of cartilage, mainly collagen disruption and increase of the water content[14,39,40]. Therefore is able to detect cartilage changes independently of morphological substance loss[8,9]. But T_2 may be less sensitive than WORMS in assessing progression in more advanced stages when large areas of cartilage are lost[40,41]. The medial compartments of contralateral knees had consistently greater worsening than the lateral compartment in WORMS cartilage and meniscus scores and T_2 values. This pattern is consistent with increases in loading in the medial compartment of contralateral knees associated with endstage hip OA[30].

We observed a significantly greater decline in knee extension strength in limbs contralateral to THA, which may have several explanations. First, it is consistent with the trends seen for increases in WOMAC scores and significantly greater symptoms at year 4 in contralateral limbs, since knee pain can result in loss of strength[42–44]. Altered gait patterns in persons with endstage hip OA may also contribute to contralateral quadriceps weakness[43,45]. Weakness in the contralateral limb may contribute to an increased risk of OA progression and thus a vicious cycle of worsening[46–48].

Our study has several limitations. Since the time-point of THA implantation was not known for all subjects, results were not adjusted for this parameter. However, the strength of the present study is the longitudinal study design. All observations clearly occured after THA implantation. It is possible that pre-existing knee OA preceded and may be associated with clinical and MRI findings at baseline and with worsening of these outcomes during follow-up. Due to concern about introducing collider selection bias when adjusting for a variable (preexisting knee OA) that may be a result of unilateral hip OA and THA, adjustment for baseline K−L grade was limited to sensitivity analyses. Not surprisingly, in the cross-sectional analyses this adjustment had the effect of attenuating associations of unilateral THA with knee OA outcomes. Importantly, associations of THA with changes in knee OA outcomes in longitudinal analyses were unchanged by adjusting for K−L grade, indicating that the effect of unilateral THA on these outcomes is independent of preexisting knee OA.

Although we included all subjects with a unilateral THA at baseline, the precision of our study is limited by small numbers and this is reflected in wide confidence intervals. While this should not affect statistically significant results, it may have contributed to a lack of statistical significance in some instances, for example, comparison of paired difference changes in WOMAC scores. On the other hand our subjects are from a large community-based cohort and represent a diverse sample of those with unilateral hip OA treated in many different health care settings, which enhances the generalizability of our results.

In conclusion, in individuals with a prevalent unilateral THA and two native knees, we found moderate evidence for worse clinical and structural outcomes assessed by MRI in the knees contralateral to the THA compared to ipsilateral knees in the same individuals and compared to control knees in persons with a THA. These findings are consistent with the hypothesis that endstage unilateral hip OA and consequent altered lower limb biomechanics increase the risk of developing and worsening of OA in the knee contralateral to the THA. They indicate a need for strategies and interventions, that likely need to start early preoperatively and to continue post surgery, to prevent the development and worsening of OA in the contralateral limb. However, additional studies with larger patient populations are needed to confirm the observation, that THA leads to worsening of knee degeneration in contralateral knees.

Author contributions

Drs Pia M Jungmann (pia.jungmann@tum.de), Michael Nevitt (mnevitt@psg.ucsf.edu) Thomas M Link (Thomas.Link@ucsf.edu) take responsibility for the integrity of the work as a whole, from inception to finished article. Conception and design: Link TM, Jungmann PM, Nevitt MC, Lane NE. Acquisition of data: Lynch J, Liu F, Jungmann PM, Nevitt MC, McCulloch CE, Nardo L, Liebl H, Baum T. Analysis and interpretation of the data: Jungmann PM, Baum T, Nevitt MC, McCulloch CE, Link TM. Drafting of the article: Jungmann PM, Nevitt MC, McCulloch CE. Critical revision of the article for important intellectual content: all authors. Final approval of the article: all authors. Final approval of the version to be submitted: all authors.

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Competing interest statement
Nothing to declare for any of the authors.

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