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Using Cumulative Load to Explain How Body Mass Index and Daily Walking Relate to Worsening Knee Cartilage Damage Over Two Years: The MOST Study

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Abstract

Objective.—Knee cartilage damage is often linked to mechanical overloading. However, cartilage requires mechanical load to remain healthy, suggesting that underloading may be detrimental. We examined knee overloading and underloading by defining cumulative load as the joint effects of body mass index (BMI) and daily walking, and examined the relation of cumulative load to worsening cartilage damage over two years.

Methods.—We used data from the Multicenter Osteoarthritis Study. BMI and steps/day via accelerometry were measured at the 60-month visit. Cartilage damage on magnetic resonance imaging (MRI) was semi-quantitatively scored using WORMS at the 60-month and 84-month visits; worsening damage was defined as increased WORMS between visits. Risk ratios and 95% confidence intervals (RR[95%CI]) were calculated using binomial regression, adjusting for potential confounders.

Results.—We included 964 participants (66.9 ± 7.5 years, 62% female, BMI: 29.7 ± 4.8 kg/m^2, 7153 ± 2591 steps/day). Participants with moderate (6000–7900) or high (>7900) steps/day and high BMI (>31 kg/m^2) had 2.83[1.46–5.48] and 2.61[1.50–4.54] times the risk for worsening medial tibiofemoral damage, respectively, compared with those with similar steps/day and low

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BMI (18–27 kg/m^2). Participants with low (<6000) steps/day and low BMI had 2.03[1.06–3.92] and 2.28[1.06–4.85] times the risk for worsening medial tibiofemoral and lateral patellofemoral damage, respectively, compared with those with high steps/day and low BMI. Effect estimates for other compartments did not reach statistical significance.

Conclusions.—This study provides preliminary evidence that both overloading and underloading may be detrimental to medial tibiofemoral cartilage, and underloading may be detrimental for lateral patellofemoral cartilage.

Introduction

Knee osteoarthritis (OA) is a chronic, debilitating disease that affects between 15 and 45 million Americans(1, 2). A key risk factor for knee OA is obesity(3). Mechanistically, obesity places excessive loads on knee cartilage that lead to cartilage damage(4–6), the hallmark feature of knee OA. Obesity-related cartilage damage is common in both the medial tibiofemoral (TF) joint(7, 8) and patellofemoral (PF) joint(9, 10). Given the strong link between obesity and cartilage damage(11), knee OA has historically been considered a disease of mechanical overloading(12).

Conversely, knee cartilage requires a minimum amount of mechanical load to remain healthy. Mechanical load stimulates chondrocyte activity, promoting the synthesis of structural macromolecules and nutrient exchange with synovial fluid(13). These normal cellular processes are detrimentally affected when the knee, a weight-bearing joint, is underloaded. Underloading at its most extreme, i.e., the complete absence of weight-bearing load, causes cartilage atrophy(14, 15) and thinning(16). It is unknown whether such changes are transient, but it is plausible that they may lead to irreversible cartilage damage.

Underloading may occur due to low levels of physical activity, which is highly common in people with or at risk for knee OA(17–19). There is mixed evidence regarding the relationship between physical activity and knee cartilage damage(20, 21), with most studies focused on consequences of high-volume or moderate-to-high-intensity physical activity(22–24). Little is known about the consequences of low levels of physical activity and knee cartilage health, but we hypothesize that low levels of activity increase the risk for knee cartilage damage through underloading.

Because obesity is linked to cartilage overloading and low physical activity is linked to cartilage underloading, the magnitude of knee joint load as well as the number of loading cycles can provide a valid(25) and reliable(26) estimate of knee joint load accumulated over time. A previous study found that an estimate of cumulative load, incorporating both knee adduction moment (KAM) and steps/day, better predicted worsening medial TF cartilage damage than KAM alone(7). As gait lab-based measures (such as KAM) are not feasible for large-scale studies and do not account for daily physical activity, we developed another estimate of cumulative load that incorporated BMI and steps/day. We then examined how our estimate of cumulative load related to worsening cartilage damage.

Therefore, the purpose of this study was to examine the relation of BMI combined with steps/day to worsening cartilage damage over two years. We hypothesize that higher BMI increases the risk for worsening cartilage damage through overloading, and lower steps/day increases the risk for worsening cartilage damage through underloading. The novelty of this study lies in the use of a cumulative load approach to include two feasibly-assessed measures (i.e., BMI and steps/day) that uniquely contribute to joint loading, which may improve our understanding of how knee joint load relates to cartilage damage.

Patients and Methods

The MOST Study

Data for these analyses are from the Multicenter Osteoarthritis (MOST) Study. MOST is an ongoing prospective, longitudinal NIH/NIA-funded cohort study that included 3,026 community-dwelling, ambulatory men and women, aged 50–79 years, who had knee OA or were at high risk for developing knee OA at their baseline study visit(27). Inclusion and exclusion criteria for MOST have been described elsewhere(28). Enrollment and clinical measurements were collected at study sites in Birmingham, Alabama and Iowa City, Iowa(28). Institutional review boards at both sites provided approval for data collection. Because the 60-month visit is the earliest visit using accelerometry to measure physical activity, we refer to the 60-month visit as our study baseline.

Additional Study Inclusion/Exclusion Criteria

MOST participants were included if they had knee magnetic resonance (MR) images assessed at 60- and 84-month visits. MOST participants were excluded if they had 1) invalid or missing physical activity data at baseline, 2) missing BMI at baseline, 3) missing co-variate data (i.e., previous knee injury or surgery) at baseline (Figure 1).

Exposure: Physical Activity at Baseline

Physical activity was objectively measured at baseline using the StepWatch 3 Activity Monitor (Orthocare Innovations LLC, Oklahoma City, OK). The StepWatch 3 is an ankle-worn step monitor that demonstrates high validity and reliability for estimating physical activity in older adults(29). Participants were asked to wear the monitor for 7 days during waking hours. Participants were considered to have valid physical activity data if they met the following criteria(19): ≥4 valid wear days, with a valid wear day defined as ≥10 hours of wear during that day. We calculated average steps/day using valid wear days for each participant.

Exposure: BMI at Baseline

BMI was calculated using weight and height measured at baseline. Weight was measured in kilograms ([kg], to the nearest 0.1 kg) using a standard balance beam scale. Standing height was measured twice in millimeters (mm) using a wall-mounted Harpenden stadiometer, and then average height (mm) was calculated. BMI (kg/m^2) was then calculated using the following formula: Weight (kg) / [(Average Height (mm) * 1000)^2].

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Outcome: Worsening Knee Cartilage Damage from Baseline to Two Years

Knee MRIs were obtained in all participants at the 60- and 84-month visits (the baseline and two-year follow-up time point for the current study, respectively) using a 1.0-Tesla extremity magnetic resonance imaging (MRI) system (OrthOneTM; ONI Medical Systems Wilmington, MA, USA). A subset of participants had one knee MRI read longitudinally, reflecting a random sample. MR images were scored by two musculoskeletal radiologists (AG, FWR) using the Whole Organ MRI Score (WORMS)(30).

Cartilage morphology was assessed in 14 knee subregions, wherein each subregion was assigned a cartilage morphology WORMS on an eight-point scale(30). The tibiofemoral joint (TFJ) consisted of 10 subregions, which were grouped into: the medial TFJ compartment (5 subregions: medial central femur, medial posterior femur, medial anterior tibia, medial central tibia, medial posterior tibia), and the lateral TFJ compartment (5 subregions: lateral central femur, lateral posterior femur, lateral anterior tibia, lateral central tibia, lateral posterior tibia). The patellofemoral joint (PFJ) consisted of 4 subregions, which were grouped into: the medial PFJ compartment (2 subregions: medial anterior femur, medial patella), and the lateral PFJ compartment (2 subregions: lateral anterior femur, lateral patella). If one or more subregions within a compartment had a maximum cartilage morphology WORMS at baseline (i.e., grade 6) or had missing cartilage morphology WORMS at either time point, the compartment was excluded from the analysis.

The primary outcome, worsening cartilage damage, was defined as the increase in cartilage morphology WORMS in any subregion within a compartment from baseline to two years. This included within-grade changes for definite visually detectable progression that does not fulfill the criteria of a full grade change(31). Inter-rater agreement for change/no change in cartilage morphology WORMS over a similar time frame (30 months) range from 0.81 to 1.00(31).

Potential Confounders (Age, Sex, Previous Knee Injury, Previous Knee Surgery)

We adjusted our analyses for the following potential confounders: baseline age (years), given its association with physical activity(18, 32) and worsening cartilage defects(33); sex (male/female), given its association with physical activity(32) and worsening knee cartilage defects(33); history of injury to the MRI knee that limited walking for at least 2 days (yes/no), given its association with incident knee OA(34); and history of surgery to the MRI knee (yes/no), given its association with incident knee OA(35).

Statistical Analysis

We identified tertiles of BMI for the study sample using baseline BMI. The tertiles were: Low BMI (18.2–27.2 kg/m^2), Mid BMI (27.2–31.6 kg/m^2), and High BMI (31.6–50.6 kg/m^2). We also identified tertiles using baseline steps/day: Low Steps (1277–6004 steps/day), Mid Steps (6004–7894 steps/day), or High Steps (7894–19450 steps/day). Combining the two sets of tertiles resulted in nine groups (Table 1); the characteristics of these groups can be found in Supplemental Table 1.

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To examine the effect of BMI as a mechanism of mechanical overloading, we compared groups of BMI (Low, Mid, High) within each stratum of steps/day. We used binomial regression and robust standard error estimation to obtain risk ratios (RR) and 95% confidence intervals (95% CI) for worsening cartilage damage in the Mid BMI and High BMI groups compared with the Low BMI (referent) group.

To examine the effect of steps/day as a mechanism of mechanical underloading, we compared groups of steps/day (Low, Mid, High) within each stratum of BMI. We again used binomial regression and robust standard errors to obtain RR and 95% CI for worsening cartilage damage in the Low Steps/day and Mid Steps/day groups compared with the High Steps/day (referent) group.

Sensitivity Analysis

Using the same approach as above (and adjusting for the same potential confounders), we examined overloading in participants in the highest loading group (High BMI and High Steps/day, n=70) compared with participants in the moderate loading group (Mid BMI and Mid Steps/day, n=116). We also examined underloading in participants in the lowest loading group (Low BMI and Low Steps/day, n=66) compared with participants in the moderate loading group.

Results

Study Sample

We included 964 MOST participants in our analysis (Figure 1). This sample consisted of older adults (mean age: 66.9 ± 7.5 years) who were mostly female (62%) and had a mean BMI of 29.7 ± 4.8 kg/m^2. These older adults engaged in moderate daily walking (7,153 ± 2591 steps/day), which is consistent with previous analyses in the MOST cohort(23) and is slightly higher than adults aged 60–69 years in the general population (3302–6127 steps/day)(36). Some participants had a history of knee injury (26%) or surgery (9%) and reported at least mild knee pain in the past 30 days (43%). Characteristics of the study sample can be found in Table 2.

Worsening Cartilage Damage

Worsening cartilage damage over two years was most common in the medial TFJ (192/905 [21%]); of the medial TFJ compartments with worsening damage, 30% (58/192) were based on within-grade changes. Worsening cartilage damage was least common in the medial PFJ (116/881 [13%]), with 45% (52/116) based on within-grade changes. The lateral TFJ and lateral PFJ compartments with worsening damage had 19% (30/157) and 39% (46/117) based on within-grade changes, respectively. In all compartments, the majority of within-grade changes occurred within a WORMS of 3 (59–75%), although some occurred within a WORMS of 2 (4–26%) or a WORMS of 5 (3–35%) depending on the compartment. In all compartments, participants with worsening cartilage damage tended to have a higher BMI and lower steps/day than those without worsening cartilage damage (Table 3).

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Effect of BMI: Hypothesized Overloading with High BMI

In the medial TFJ, among participants who had High Steps/day (7900–19500 steps/day), those with a High BMI had 2.61 [1.50–4.54] times higher risk compared with those with a Low BMI (referent group). Similarly, among participants who had Mid Steps/day (6000–7900 steps/day), those with a High BMI had 2.83 [1.46–5.48] (RR[95%CI]) times higher risk of worsening medial TFJ cartilage damage compared with those with a Low BMI (referent group). Among those who had Low Steps/day, there was no increased risk for worsening cartilage damage in participants with a Mid BMI or a High BMI compared with a Low BMI (referent group).

In the other joint compartments (lateral TFJ, medial PFJ), BMI was not associated with higher risk of worsening cartilage damage in any of the steps/day strata (Figure 2).

Effect of Steps/day: Hypothesized Underloading with Low Steps/day

In the medial TFJ, among participants with Low BMI (18.2–27.2 kg/m^2), those who had Low Steps/day had 2.03 [1.06–3.92] times higher risk of worsening medial TF cartilage damage compared with those who had High Steps/day (referent group). Similarly, in the lateral PFJ, among participants with Low BMI, those who had Low Steps/day had 2.28 [1.06–4.85] times higher risk of worsening cartilage damage compared with those who had High Steps/day (referent group). No associations were noted for steps/day among the Mid BMI and High BMI strata for the medial TFJ or lateral PFJ. Further, steps/day were not associated with higher risk of worsening cartilage damage in any of the BMI strata in the lateral TFJ and medial PFJ (Figure 3).

Sensitivity Analysis

In the medial TFJ, participants in the highest loading group (i.e., High BMI and High Steps/day) had 1.84 [1.09–3.11] times higher risk of worsening cartilage damage compared with the moderate loading group (referent group, i.e., Mid BMI and Mid Steps/day). Participants in the lowest loading group (i.e., Low BMI and Low Steps/day) also had a higher risk of worsening cartilage damage (1.31 [0.73–2.38]) compared with the moderate loading group (referent group), although this did not reach statistical significance.

In the lateral PFJ, participants in the highest loading group did not have higher risk of worsening cartilage damage (1.41 [0.60–3.33]) compared with the moderate loading group (referent group). Participants in the lowest loading group had 2.17 [0.97–4.61] times higher risk of worsening cartilage damage compared with the moderate loading group (referent group), although this also did not reach statistical significance.

In the lateral TFJ and medial PFJ, the highest and lowest loading groups did not have any higher risk of worsening cartilage damage compared with the moderate loading group (referent group).

Discussion

We found that knee overloading is related to worsening cartilage damage over two years. Among participants who walked 6000–19000 steps/day, those with a high BMI (>31 kg/m^2)

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had higher risk for worsening cartilage damage in the medial TFJ compared with participants who had a low BMI (18–27 kg/m^2). We also found preliminary evidence that knee underloading is related to worsening cartilage damage over two years. Specifically, we found that among participants with low BMI (18–27 kg/m^2), those with low daily walking (<6000 steps/day) had higher risk of worsening cartilage damage in the medial TFJ and lateral PFJ compared with participants with higher daily walking (8000–19000 steps/day). Thus, it seems that the combination of BMI and steps/day had the most detrimental effect with regards to both overloading (i.e., High BMI and High steps/day) and underloading (i.e., Low BMI and Low steps/day). It should be noted that 50% of the participants with Low BMI (18–27 kg/m^2) had a BMI of at least 25 kg/m^2, which is classified as overweight by the World Health Organization. Our sensitivity analysis yielded similar findings, although many effect estimates did not reach statistical significance. This can be attributed to the substantially reduced sample size for our sensitivity analysis (n=252) compared to that of our primary analyses (n=964).

Our findings underscore the usefulness of cumulative load in that it incorporates objectively measured physical activity (i.e., steps/day) and other mechanical factors to provide insight into the relationship between mechanical load and knee cartilage health. Our findings are consistent with those of previous studies that estimated cumulative load (i.e., steps/day and KAM(7), steps/day and body weight(37)) and related it to cartilage damage over time. Studies relating only steps/day to cartilage damage have had mixed results(20, 21, 24), while those relating cumulative load to cartilage damage have yielded more consistent results.

Our findings support a theoretical ‘U-shaped’ relationship between loading and cartilage damage in the medial TFJ compartment, where both overloading and underloading increased risk of worsening knee cartilage damage (Supplemental Table 2). The medial TFJ is designed to withstand higher loads than lateral TFJ during walking(38), but these loads are further increased in people who are obese (45% of our sample)(39), have varus frontal knee alignment (44% of our sample)(40), or have radiographic knee OA(38% of our sample)(41). Excessive medial TFJ loads can be compounded by walking several thousand steps/day; thus, it was unsurprising to find that persons with high BMI and in the highest tertile of steps/day had evidence of worsening cartilage damage in the medial TFJ.

Our finding of potential medial TFJ underloading is intriguing. Persons with a history of knee injury and prevalent knee OA (12% of our sample) demonstrate lower medial TFJ contact forces during gait(42); similarly, reduced medial TFJ loads may occur in persons with valgus frontal knee alignment (13% of our sample). These characteristics were fairly uncommon in our sample, so it is more likely that worsening cartilage damage related to underloading of the medial TFJ is due to inadequate steps/day and low BMI rather than altered joint kinetics or knee malalignment.

We did not find evidence of worsening cartilage damage in the lateral TFJ related to overloading. This was expected, given that the lateral TFJ experiences higher loads and subsequent cartilage damage in persons with valgus frontal knee alignment (13% of our sample)(38), which was relatively uncommon. However, we had expected to find evidence

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of lateral TFJ *underloading* for the same reasons as medial TFJ underloading (i.e., low steps/day and low BMI); the absence of this finding remains unclear.

We also did not find evidence of worsening cartilage damage in the medial PFJ or lateral PFJ related to overloading, for which our explanation is two-fold. First, a study by Gross et al. using data from three large cohort studies (including MOST) found that PFJ cartilage damage was less likely to be associated with certain load-related biomechanical factors than was previously thought. More specifically, they found that medial PFJ cartilage damage was not associated with knee alignment, and lateral PFJ cartilage damage was not explained by increased lateral PFJ loading(43). Second, our exposure variable, steps/day, captures an activity that primarily loads the TFJ; thus, we have likely underestimated the frequency of PFJ loading. Because neither biomechanical factors nor steps/day can adequately explain PFJ overloading, it is unsurprising that we did not find evidence of worsening cartilage damage in the medial or lateral PFJ related to overloading.

Finally, we did find evidence of worsening cartilage damage in the lateral PFJ, but not medial PFJ, that may be related to underloading. This may be explained by the high prevalence of varus frontal knee alignment (44% of our sample). Varus alignment is associated with external femoral rotation, relative internal tibial rotation, and reduced contact pressures in the lateral PFJ(44). Decreased lateral PFJ loading, compounded by low steps/day and low BMI, can explain our findings of underloading in the lateral PFJ and not in the medial PFJ. Further, increased dynamic knee stiffness in persons with radiographic OA (38% of our sample) may indicate guarding and offloading of that knee, and has been linked to higher risk of worsening cartilage damage in the lateral PFJ, but not the medial PFJ(45).

The current study has several strengths. First, we used longitudinal data from a large cohort study (MOST) with a rigorous, standardized collection of clinical data and MR images. MOST provides a rich dataset for epidemiological studies in knee OA research. Second, we included the medial and lateral PFJ compartments in our study, whereas previous studies of cumulative load have included the TFJ only. In a population-based cohort (Framingham Osteoarthritis Study), the PFJ had a greater prevalence of isolated cartilage damage on MRI than the TFJ(46). The PFJ was historically overlooked as a site for OA-related cartilage damage, but our study found the lateral PFJ to be a site of potential underloading. Third, we used an objective measure of physical activity (steps/day measured via accelerometry), which is less sensitive to sex and age differences compared with self-reported measures of physical activity(47).

Our findings should be interpreted in light of several limitations. The first limitation, as mentioned above, is that we are unable to capture specific activities that load the PFJ such as stair climbing or repeated squatting/bending(48). The StepWatch 3 Activity Monitor accurately measures walking (steps/day), but no other specific physical activities. Hence, we are unable to investigate the relationship between these other activities and PF and TF cartilage worsening. However, a previous study showed that MOST participants do not frequently engage in activities other than walking(49). Further, given the link between

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altered gait mechanics and PF cartilage damage(45), objective measures of steps/day only (without other activities) may still be of interest for future studies.

A second limitation is that our length of follow-up (two years) may be inadequate to capture worsening cartilage damage. However, worsening cartilage damage was present in 12–23% of participants (depending on joint compartment), which is consistent with other studies having a two-year follow up (7, 45, 50). A third limitation is that we did not have measures of systemic inflammation, which may confound the relationship between obesity and cartilage worsening. While obesity clearly increases joint loading to the detriment of cartilage health(5, 9), obesity also creates systemic inflammation that may contribute to cartilage damage; thus, the mechanism of the BMI association cannot be further specified. A final limitation is that we did not adjust our analyses for frontal knee alignment, which may have influenced our findings in the medial vs. lateral joint compartments. Because knee alignment can change due to worsening cartilage damage, we could only adjust for knee alignment as a time-varying co-variate. Unfortunately, we did not have data on changes in knee alignment over the course of the study, and therefore could not include it as a time-varying co-variate. Future work will examine the effects of frontal knee alignment on cartilage damage in the context of knee overloading and/or underloading.

To conclude, we have found preliminary evidence that knee joint underloading, in addition to overloading, may relate to worsening cartilage damage in certain compartments of the knee, particularly the medial TFJ and lateral PFJ. Identifying the consequences of knee underloading (i.e., through low levels of physical activity) may provide additional justification for the use of physical activity interventions and guide what types of interventions should be prioritized in those with or at risk for knee OA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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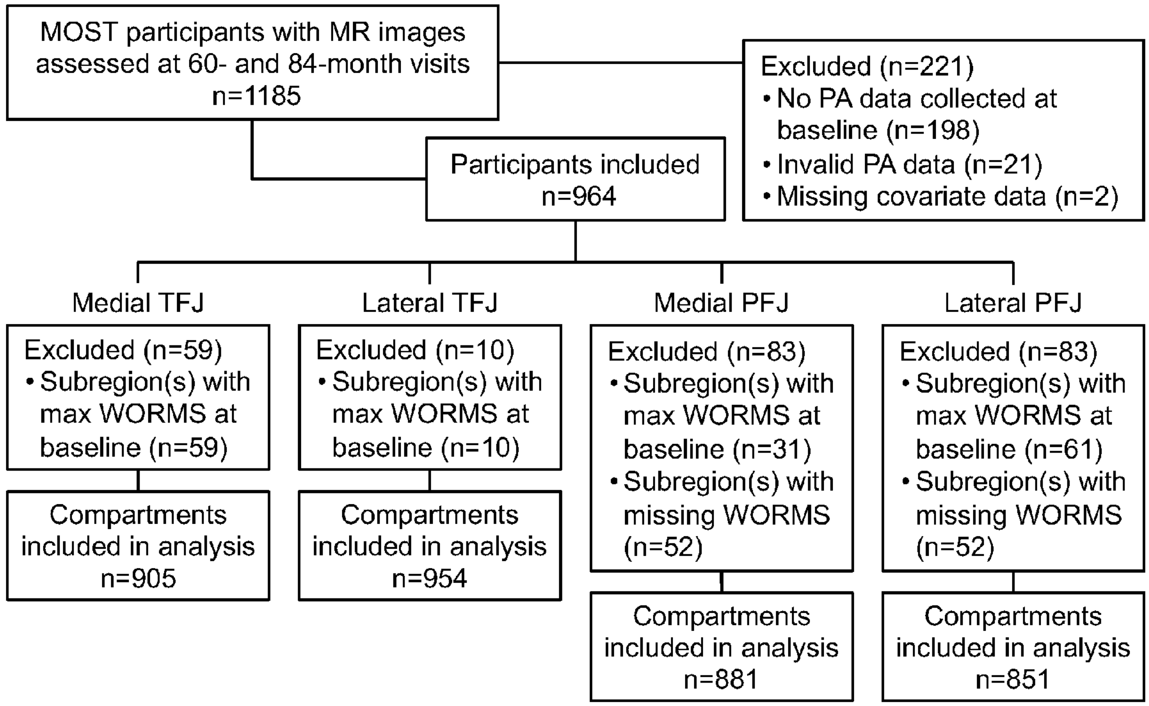

Figure 1.
Flow diagram depicting sample size reduction.

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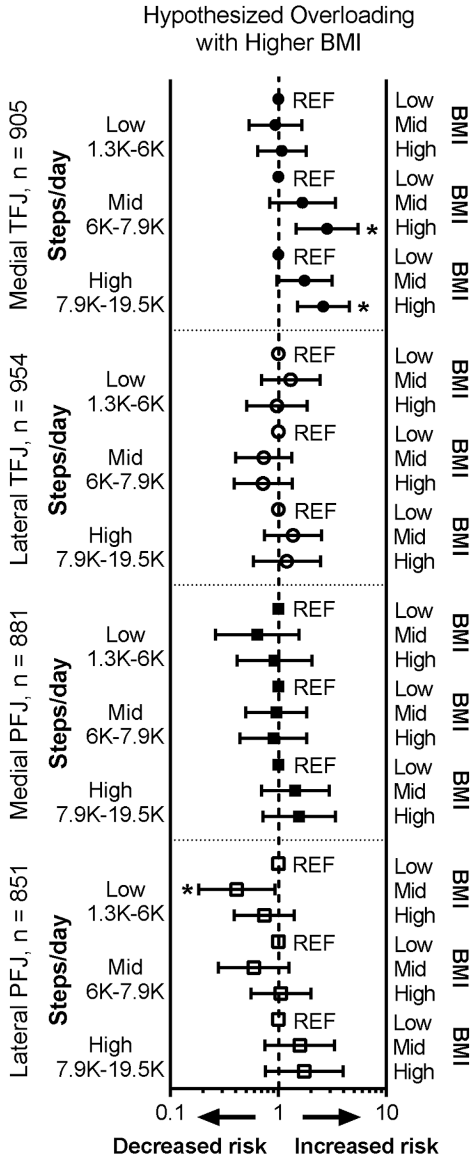

Figure 2.
Adjusted RR and 95% CI (represented by error bars) for worsening cartilage damage related to overloading. Analyses were adjusted for age, sex, and previous knee injury/surgery.

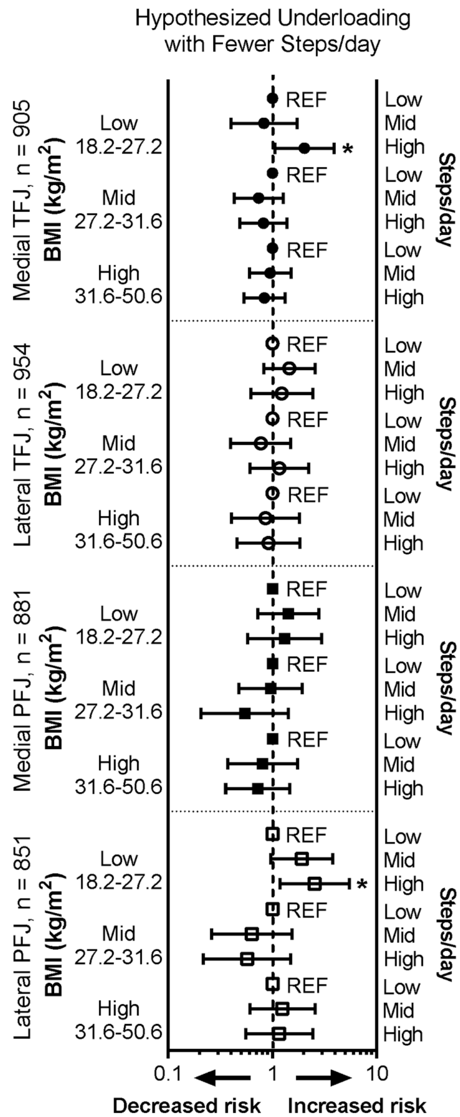

Figure 3.

Adjusted RR and 95% CI (represented by error bars) for worsening cartilage damage related to underloading. Analyses were adjusted for age, sex, and previous knee injury/surgery.

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Table 1.

3×3 table depicting stratification by BMI and steps/day and creation of nine groups

	Low Steps/day 1277–6004 steps/day	Mid Steps/day 6004–7894 steps/day	High Steps/day 7894–19450 steps/day	
Low BMI 18.2–27.2 kg/m^2	**66**	**104**	**151**	321
Mid BMI 27.2–31.6 kg/m^2	**106**	**116**	**100**	322
High BMI 31.6–50.6 kg/m^2	**149**	**102**	**70**	321
	321	322	321	**964**

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Table 2.

Characteristics of study participants (n=964)

Characteristic	Mean ± SD or n (%)
Age	66.9 ± 7.5
Sex (female)	594 (62%)
History of previous knee injury (yes)	253 (26%)
History of previous knee surgery (yes)	90 (9%)
BMI (kg/m^2)	29.7 ± 4.8
Steps/day	7153 ± 2591
Presence of radiographic OA (yes)	364 (38%)
Presence of knee pain in past 30 days	
None (Visual Analogue Scale 0–9/100)	554 (57%)
Mild (Visual Analogue Scale 10–39/100)	328 (34%)
Moderate/Severe (Visual Analogue Scale >40/100)	82 (9%)
Frontal Knee Alignment (defined by HKA angle)	
Normal (178° < HKA < 182°)	415 (43%)
Varus (HKA < 178°)	424 (44%)
Valgus (HKA > 182°)	125 (13%)

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Table 3.

Characteristics of participants without vs. with worsening cartilage damage

	BMI (Mean ± SD)	Steps/day (Mean ± SD)	BMI Tertile	Steps/day Tertile
Medial TFJ (n=905)			36% Low	32% Low
No Worsening (79%)	29.4 ± 4.7	7254 ± 2562	34% Mid	34% Mid
			30% High	34% High
			26% Low	39% Low
Worsening (21%)	30.7 ± 4.9	6820 ± 2665	31% Mid	30% Mid
			43% High	31% High
Lateral TFJ (n=954)			33% Low	33% Low
No Worsening (84%)	29.7 ± 4.8	7188 ± 2641	33% Mid	33% Mid
			34% High	34% High
			34% Low	37% Low
Worsening (16%)	29.5 ± 4.8	6987 ± 2333	35% Mid	33% Mid
			31% High	30% High
Medial PFJ (n=881)			33% Low	34% Low
No Worsening (87%)	29.7 ± 4.8	7150 ± 2609	34% Mid	33% Mid
			33% High	33% High
			34% Low	29% Low
Worsening (13%)	29.3 ± 4.4	7180 ± 2472	32% Mid	37% Mid
			34% High	34% High
Lateral PFJ (n=851)			34% Low	33% Low
No Worsening (86%)	29.6 ± 4.8	7207 ± 2593	34% Mid	33% Mid
			32% High	34% High
			32% Low	34% Low
Worsening (14%)	30.0 ± 4.7	6804 ± 2563	28% Mid	39% Mid
			40% High	28% High