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The relation of MRI-detected structural damage in the medial and lateral patellofemoral joint to knee pain: The Multicenter and Framingham Osteoarthritis Studies

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Abstract

Objective—To examine the relation of cartilage loss and bone marrow lesions (BMLs) in the medial and lateral patellofemoral joint (PFJ) to knee pain.

Methods—We categorized the location of full-thickness cartilage loss and BMLs in the PFJ on knee MRIs from the Multicenter Osteoarthritis (MOST) and Framingham Osteoarthritis (FOA)

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Author Contributions

All authors contributed to the conception and design of the study, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and approved the final version submitted. Dr. Stefanik takes responsibility for the integrity of the work as a whole, from inception to finished article.

Competing Interest Statement

Dr. Guermazi has received consultancies, speaking fees, and/or honoraria from Sanofi-Aventis, Merck Serono, and TissueGene and is President and shareholder of Boston Imaging Core Lab (BICL), LLC a company providing image assessment services. Dr. Roemer is Chief Medical Officer and shareholder of BICL, LLC.

Studies as no damage, isolated medial, isolated lateral, or both medial and lateral (mixed). We determined the relation of MRI lesions in each PFJ region to prevalent knee pain. Differences in knee pain severity were compared among categories of PFJ full-thickness cartilage loss and BMLs using quantile regression.

Results—In MOST (n=1137 knees), compared with knees without full-thickness cartilage loss, knees with isolated lateral or mixed PFJ full-thickness cartilage loss had 1.9 (1.3, 2.8) and 1.9 (1.2, 2.9) times the odds of knee pain, respectively, while isolated medial cartilage loss had no association with knee pain.. BMLs in both the medial and lateral PFJ had 1.5 (1.1, 2.0) times the odds of knee pain compared with knees without BMLs. Knee pain severity was lowest in knees with isolated medial PFJ cartilage loss or BMLs. In FOA (n=934 knees), neither isolated medial nor lateral cartilage loss was associated with knee pain, whereas isolated BMLs in either region were associated with pain.

Conclusions—Results were not completely concordant but suggest that knee pain risk and severity is greatest with cartilage loss isolated to (MOST) or inclusive of (MOST and FOA) the lateral PFJ. While BMLs in either the medial or lateral PFJ are related to pain.

Keywords

osteoarthritis; patellofemoral; pain; magnetic resonance imaging

Introduction

Patellofemoral joint (PFJ) osteoarthritis (OA) is common[1-3] and has strong associations with pain and functional limitation[4-8]. Under the presumption that painful PFJ OA results from excessive loading of the lateral PFJ, many taping, bracing, and other rehabilitative interventions attempt to redistribute load to the medial PFJ. Yet, contrary to the expectations of biomechanical models suggesting that PFJ stress is greatest in the lateral compartment[9, 10], we previously demonstrated a remarkably high prevalence of MRI-detected cartilage loss in the medial PFJ[11], both in a community cohort of older adults unselected for knee pain or pathology, and in a population at high risk of knee OA.

While the exact mechanism of medial PFJ cartilage loss is unknown, it has been suggested that insufficient loading of the medial PFJ may lead to cartilage degeneration[12, 13]. If this is correct, then bone marrow lesions (BMLs), which are closely related to increased joint loading[14], would not be expected to occur in the medial PFJ. Additionally, while BMLs are strongly associated with knee pain[15, 16], cartilage, being aneural, is not expected to be a frequent cause of pain. It is unknown if the prevalence of BMLs in the medial and lateral PFJ differs, and whether any such differences are associated with differences in prevalence of knee pain.

Knowledge about the relation of medial and lateral PFJ structural damage to pain is important to inform prescription of appropriate compartment-specific non-pharmacological treatments (e.g. rehabilitation, bracing, etc.) for PFJ OA. The few clinical trials published for PFJ OA have included knees with lateral PFJ disease severity greater than medial[17-19]. The taping or bracing interventions prescribed in these studies aimed to realign the patella

medially. While this type of treatment may be appropriate for isolated lateral PFJ OA, it may be inappropriate for painful medial PFJ OA. If medial and lateral PFJ OA are similarly associated with pain, careful assessment of the PFJ is warranted in order to consider appropriate compartment-specific treatment.

The purpose of the current study was to: 1) Describe the prevalence of MRI-detected full-thickness cartilage loss and BMLs in the medial and lateral PFJ and 2) Examine the relationship of cartilage loss and BMLs in these regions to the presence and severity of knee pain in two large cohorts of older adults.

Methods

Study Samples

Subjects for the current study were participants in the Multicenter OA (MOST) Study and Framingham OA (FOA) cohort. The MOST cohort consists of older adults who have or are at risk of knee OA. 3,026 participants were recruited from Iowa City, Iowa and Birmingham, Alabama. For the current study we used data from the 84-month visit when all eligible participants had knee MRI acquired and cartilage morphology and BMLs assessed (see below). Data was used from the 84-month visit in order to maximize numbers of knees with PFJ cartilage loss and BMLs.

The FOA cohort is a sample of the general population of older adults, unselected for knee pain or OA, living in Framingham, MA. The FOA study included ambulatory persons age 50 and over. Participants were recruited by random digit dialing. Of the 2582 individuals contacted, 1039 expressed interest and were examined between 2002-2005. Those with inflammatory arthritis, bilateral total knee replacement, dementia, terminal cancer, or contraindications to MRI were excluded[20-23].

MRI Acquisition

In MOST, a 1.0 Tesla extremity MRI system (OrthOne^{TM}, ONI Medical Systems Wilmington, MA) was used with a phased array knee coil to obtain the following sequences: Fat-suppressed fast spin echo proton density (PD) weighted sequences in two planes, sagittal (TR 4800 ms, TE 35 ms, 3 mm slice thickness, 0 mm interslice gap, 32 slices, 288 × 192 matrix, 140 mm2 FOV, echo train length 8) and axial (TR 4680 ms, TE 13 ms, 3 mm slice thickness, 0 mm interslice gap, 20 slices, 288 × 192 matrix, 140 mm2 FOV, echo train length 8) and a STIR sequence in the coronal plane (TR 6650 ms, TE 15 ms, TI 100 ms, 3 mm slice thickness, 0 mm interslice gap, 28 slices, 256 × 192 matrix, 140 mm2 FOV, echo train length 8).

In FOA, MRI scans of both knees were acquired using a 1.5-Tesla scanner (Siemens Medical Systems, Erlangen, Germany) with an eight-channel phased-array knee coil. Images from four pulse sequences were used in the assessment of OA features: axial, sagittal and coronal fat-suppression, proton density-weighted, turbo spin echo sequences (repetition time, 3610 msec; echo time, 40 msec; slice thickness, 3.5 mm; interslice gap, 0 mm; echo spacing, 13.2 msec; turbo factor, 7; field of view, 140 mm × 140mm; matrix 256 × 256) and sagittal T1-weighted spin echo sequence without fat-suppression (repetition time, 475 msec;

echo time 24 msec; slice thickness, 3.5 mm; interslice gap, 0 mm; field of view, 140 mm × 140 mm; matrix, 256 × 256). Due to costs, only one knee MRI per subject was read in both studies. In FOA, it was generally the right knee that was read, while in MOST, a random selection of one knee was made for each eligible subject.

Structural Damage Assessment

In both the FOA and MOST studies, two musculoskeletal radiologists (FWR, AG) used the Whole-Organ Magnetic Resonance Imaging Score (WORMS)[24] to assess cartilage morphology and BMLs in four PFJ regions (medial/lateral patella and medial/lateral trochlea). Full-thickness cartilage loss was identified by WORMS scores of 2.5, 5, or 6, which denote single, multiple, or diffuse full-thickness loss, respectively. Any size BMLs and large BMLs were defined as WORMS scores of ≥1 and ≥2, respectively. For each type of structural damage, we identified the PFJ region(s) in which damage was present as: no PFJ damage, isolated medial, isolated lateral, and both medial and lateral (mixed). In MOST, the inter-reader reliability (weighted kappa) for PFJ cartilage and BMLs was 0.72 and 0.63, respectively; in FOA, it was 0.74 and 0.64, respectively. Additionally, a comparison of the WORMS method using a 1.0 Tesla extremity MRI and large-bore 1.5 Tesla MRI yielded similar inter- and intra-reader reliability[25].

Knee Pain Assessment

Participants in both studies were assessed for the presence of any knee pain by asking: “In the past month, have you had any pain, aching, or stiffness in your knees?” In MOST, frequent knee pain (FKP) was assessed in each knee by asking participants: “Do you have pain, aching or stiffness on most days of the month?” In the FOA cohort, participants were asked: “On most days do you have pain, aching or stiffness in either of your knees?” If they answered “yes” to this question, participants were asked for the right and left knee: “Is the pain, aching or stiffness in your knee mild, moderate or severe?” We considered pain greater than none to be FKP in the FOA cohort. Severity of knee pain was assessed only in MOST by asking: “How bad has the pain been in your knee, on average, in the past 30 days?” Participants used a knee-specific visual analog scale (VAS) from 0-100 to rate their pain severity. Severity of pain was not assessed in FOA.

Statistical Analysis

We first described the prevalence of full- thickness cartilage loss, any BML and large BMLs within each PFJ region. Next, we examined the relation of full-thickness cartilage loss and BMLs to prevalent knee pain and FKP in each PFJ region using logistic regression models. We compared the differences in knee pain severity among PFJ regions in each percentile of VAS pain using quantile regression. Because VAS pain scores were not normally distributed, quantile regression allowed us to assess the relation of the exposure (structural damage in PFJ regions) to the outcome (pain severity) across all pain percentiles. Thus, it provided a more comprehensive assessment of the association between the location of PFJ structural damage and knee pain severity instead of simply comparing the mean or median values. Since 40% of participants had a pain score of 0, we evaluated the 40^{th} to the 90^{th} percentiles with increments of 10 percentile points, and compared the pain scores of the different PFJ structural damage categories within each percentile category using no damage

as the reference. Logistic and quantile regression models were adjusted for age, sex, BMI and the presence of depressive symptoms (as determined by a score ≥ 16 on the Center for Epidemiologic Studies Depression Scale[26]). We recognize that tibiofemoral joint (TFJ) disease can contribute to knee pain, but without knowing the temporal sequence of events (whether TFJ disease is antecedent or consequent to PJF structural damage), adjusting for it could bias the results. Because of this, our main analyses are not adjusted for TFJ disease, but we performed sensitivity analyses adjusting for concurrent structural damage in the TFJ. Additionally, TFJ frontal plane alignment is associated with the location of PFJ OA[27, 28] and in further sensitivity analyses we included the alignment category (varus, valgus, neutral) assessed from long limb films at the 60-month visit in MOST (alignment was not assessed in FOA or at the 84-month visit in MOST).

Results

1137 and 934 knees from MOST and FOA, respectively, had complete MRI data, knee pain assessments, and covariates. In MOST, the mean (sd) age and BMI was 68.9 (7.5) and 29.3 (4.7), respectively; 63.8% were female. In FOA, the mean (sd) age and BMI was 63.4 (8.8) and 28.5 (5.6); 57.4% were female. The prevalence of any knee pain in the last month was 55.3% in MOST and 36.0% in FOA. The prevalence of FKP was 28.8% in MOST and 22.9% in FOA.

The distribution of full-thickness cartilage loss and BMLs in the PFJ varied depending on the definition used (Table 2); the majority of knees did not have any cartilage loss or BMLs in either compartment of the PFJ. When present, full-thickness cartilage loss that was isolated to the medial PFJ was the most common pattern observed, having a greater prevalence in both cohorts than either cartilage loss isolated to the lateral PFJ, or mixed medial and lateral PFJ cartilage loss. In contrast, large BMLs (WORMS ≥2) were most commonly isolated to the lateral PFJ. With regard to the occurrence of any size BMLs (WORMS ≥1), results from the two cohorts were inconsistent. In MOST, any size BMLs most commonly occurred in the mixed pattern of medial and lateral PFJ involvement, while, in FOA, any size BMLs (WORMS ≥1) were most commonly isolated to the medial PFJ.

In MOST, full-thickness cartilage loss in the lateral PFJ, whether occurring in isolation [OR= 1.9 (95% CI: 1.3, 2.8)] or in combination with full-thickness medial cartilage loss [OR= 1.9 (1.2, 2.9)] was associated with nearly twice the odds of experiencing any knee pain during the last month. In contrast, isolated full-thickness cartilage loss in the medial PFJ, despite being the most prevalent site of cartilage loss, had no association [OR= 0.8 (0.6, 1.1)] with reports of any knee pain (Table 3). Similar patterns of association were observed with any size BMLs and the odds of experiencing any knee pain during the past month. When BMLs of any size were either isolated to [OR= 1.5 (0.98, 2.1)], or inclusive of [OR= 1.5 (1.1, 2.0)] the lateral PFJ, participants had 1.5 times the odds of experiencing any knee pain during the past month as compared to knees without any PFJ BMLs. In contrast, there was no association between isolated medial PFJ BMLs and any knee pain. Finally, when only large BMLs were considered, their isolated presence in the lateral PFJ was associated with 1.8 (1.2, 2.6) times the odds of any knee pain, while no association with knee pain was found between large BMLs isolated to the medial PFJ or large BMLs in both the medial and

lateral PFJ. The results of the quantile regression demonstrated that knee pain severity scores were similar between knees with isolated lateral and mixed PFJ full-thickness cartilage loss across a range of VAS pain percentiles. In contrast, pain severity in knees with isolated medial full-thickness cartilage loss was the lowest of all groups (Table 4). A similar pattern was observed in the relation of BMLs to knee pain severity. Knee pain severity was greatest across all VAS pain percentiles among knees with BMLs (WORMS ≥1) isolated to the lateral PFJ, while knees with isolated medial PFJ BMLs had the lowest knee pain severity scores.

In FOA, a clear pattern of findings was slightly less evident. Neither isolated medial nor isolated lateral PFJ full-thickness cartilage loss was associated with any knee pain, while knees having both medial and lateral PFJ (mixed) damage had twice (OR=2.0;1.2, 3.4) the odds of knee pain compared to knees without cartilage loss (Table 3). While the association of any size BMLs with knee pain was of similar magnitude for isolated medial (OR=1.7; 1.2, 2.5) and isolated lateral (OR=1.5; 0.9, 2.7) PFJ lesions, results were only statistically significant for isolated medial lesions. Large BMLs were similarly associated with any knee pain when isolated to the lateral or medial PFJ, but while any size BMLs in both the medial and lateral PFJ had the strongest association with any knee pain (OR=2.4; 1.7, 3.5), large BMLs in both the medial and lateral PFJ had no association with knee pain.

Similar results were observed when using FKP as the pain outcome (Supplemental Table 1) and in sensitivity analysis when adjusting for concurrent TFJ damage (Supplemental Tables 2 and 3). Further adjustment for TFJ alignment did not alter these results.

Discussion

While many studies have demonstrated a relationship between PFJ OA and knee pain[4-8], no study to date has investigated whether knee pain is related to the location of PFJ OA (i.e., medial vs. lateral), which would have bearing on biomechanically directed treatments for PFJ OA-related pain. Contrary to long-held assumptions about PFJ OA being exclusively or primarily a disease of the lateral joint, the present study demonstrates that cartilage loss and BMLs are both highly prevalent in the medial PFJ. The prevalence of isolated full-thickness cartilage loss and any size BMLs in the medial PFJ consistently exceeded the prevalence of these same lesions isolated within the lateral PFJ. Only when attention was focused exclusively on large BMLs was the prevalence of isolated lateral and isolated medial PFJ lesions found to be similar in the two study cohorts. Additionally, knee pain was commonly reported in knees with either medial or lateral PFJ structural damage.

However, the relation of the location of MRI lesions to knee pain was not entirely consistent. In general, knee pain was most prevalent and most severe among knees with full-thickness cartilage loss that was either isolated to or inclusive of the lateral PFJ, particularly in the MOST sample. Additionally, in MOST, there was no association with isolated medial BMLs, while isolated lateral BMLs were consistently associated with prevalent knee pain of any frequency. In contrast, in FOA, isolated medial large BMLs (WORMS ≥2) had the strongest association with prevalent knee pain, albeit quite similar to that of isolated lateral large BMLs. The differences noted could be attributed to the study samples themselves.

While FOA is a community-based cohort recruited without regard to knee pain, MOST is a selected population of individuals that either had or were at risk of developing OA at the time of recruitment based on the presence of one or more known risk factors. Such differences between the two cohorts may affect the prevalence of MRI lesions, and thereby affect the effect estimates obtained. Additionally, although the two cohorts had some differences in MRI acquisition, the inter-reader reliability for cartilage loss and BMLs was virtually identical and both studies used the same experienced readers (AG, FWR). The assessment of pain in MOST and FOA was slightly different (see methods), which may also explain the differences in the results between studies.

A potential explanation for why there may be differences in knee pain prevalence and severity between the medial vs. lateral PFJ may be related to differences in stress across these compartments. When the knee is flexed and the quadriceps contracts to prevent the knee from buckling, PFJ stress is greatest in the lateral PFJ[9]. This increased stress during functional activities that require knee flexion may increase the pain perceived from damage to the lateral PFJ. However, Gross et al. reported that cartilage damage commonly occurs in the medial PFJ, contrary to existing biomechanical theories. One potential mechanism for medial PFJ cartilage damage is insufficient loading of the medial PFJ[12, 13], which prevents chondrocytes in that area from receiving nourishment from synovial fluid being pushed under intermittent loads into and out of the interstitial space. However, our finding that BMLs commonly occur isolated to the medial PFJ or in conjunction with lateral BMLs does not support this posited mechanism of medial PFJ cartilage damage. BMLs are related to excessive joint loading[14] and would not be present in the medial PFJ if this compartment was insufficiently loaded. Clearly, further investigations are warranted to determine the mechanisms by which medial vs. lateral PFJ OA occur to prescription of compartment-specific interventions.

In the current study, we found BMLs of any size are at least as common in the medial PFJ as in the lateral PFJ and large BMLs are consistently more common in the lateral PFJ. This finding is consistent with our previous findings demonstrating that cartilage damage of minimal severity (low WORMS score) is most common in the medial PFJ, but that damage in the lateral PFJ becomes increasingly common when our attention is limited to only more severe damage (high WORMS scores)[11]. Together these findings may imply that damage (both cartilage damage and BMLs) in the medial PFJ is highly prevalent, but that it is less frequently driven to worsen than is damage that occurs in the lateral PFJ. If this interpretation is correct, damage in the lateral PFJ, being generally of greater severity, is also more strongly associated with knee pain than is damage in the medial PFJ. The few randomized controlled trials investigating interventions for PFJ OA have focused on bracing or taping interventions that attempt to realign the patella medially[17-19]. This intervention may not be appropriate for knees with painful medial PFJ structural damage. Realigning treatments may be appropriate for many painful knees that present with PFJ damage that is of greater severity laterally than medially, but the effects of this medial realignment on the medial PFJ should be monitored. Clinicians managing the care of individuals with PFJ must carefully assess the PFJ in an attempt to determine the affected compartments. Further study is needed regarding compartment-specific interventions for medial and lateral PFJ OA.

A limitation of the current study is that we do not have a detailed assessment of pain location or pain with palpation around the knee, although patient-reported localization of pain may not be highly specific to lesion location[29]. Additionally, the pain experience in OA is multifactorial, involving factors beyond structural lesions alone. Pain can also be caused by inflammation of synovium and joint effusion, which are not compartment-specific findings. Thus, while these features may be related to pain, they would not have specific implications for compartment specific interventions. We also adjusted for TFJ damage in sensitivity analyses and found similar results. However, a limitation of this approach is that it could lead to bias because temporal sequence of PFJ and TFJ damage was not known. For a similar reason, we did not attempt to adjust for cartilage lesions or BMLs in the respective analyses to avoid introduction of bias. It would be of interest in future studies to explore potential mediating effects of various MRI lesions on pain, which is difficult to do presently given the lack of sufficient understanding of the temporal sequence of MRI lesions.

In summary, similar to previous findings that cartilage loss is common in the medial PFJ[11], BMLs are also common in the medial PFJ. Knee pain prevalence and severity is greatest, for the most part, in knees with cartilage loss that is isolated to or inclusive of the lateral PFJ. The relationship between location of BMLs and pain was conflicting, but suggest that large BMLs isolated to the medial or lateral PFJ are related to pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Descriptive statistics

	MOST (n=1137 knees)	FOA (n=934 knees)
Age, mean (+/− sd), years	68.9 (7.5)	63.4 (8.8)
Sex (% female)	63.8	57.4
BMI, mean (+/− sd), kg/m^2	29.3 (4.7)	28.5 (5.6)
Presence of any knee pain (%)*	55.3	36.0
Presence of frequent knee pain (%)	28.8	22.9
Severity of knee pain**, median (Interquartile range)	5 (0-18)	N/A

*Any knee pain= any pain, aching, or stiffness in the past month

**0-100 visual analog scale

Table 2

Prevalence of full-thickness cartilage loss and BMLs in the patellofemoral joint

	Full-thickness Cartilage Loss (WORMS 2.5; 5-6)	Bone Marrow Lesion (WORMS ≥1)	Bone Marrow Lesion (WORMS ≥2)
MOST (n=1137)	**Number of knees (%)**	**Number of knees (%)**	**Number of knees (%)**
None	690 (60.7)	421 (37.0)	848 (74.6)
Isolated Medial	196 (17.2)	254 (22.3)	88 (7.7)
Isolated Lateral	133 (11.7)	150 (13.2)	148 (13.0)
Mixed	118 (10.4)	312 (27.4)	53 (4.7)
FOA (n=934)			
None	689 (73.8)	564 (60.4)	800 (85.7)
Isolated Medial	127 (13.6)	156 (16.7)	48 (5.1)
Isolated Lateral	49 (5.3)	61 (6.5)	59 (6.3)
Mixed	69 (7.4)	153 (16.4)	27 (2.9)

Table 3

Odds of 'any knee pain' in knees with MRI-detected structural damage in the patellofemoral joint

	Full-thickness cartilage loss (WORMS= 2.5, 5 or 6)		Bone Marrow Lesion (WORMS ≥1)		Bone Marrow Lesion (WORMS ≥2)	
MOST (n=1137)	**n of painful knees/ N of knees (%)**	**Adjusted OR* (95%CI)**	**n of painful knees/ N of knees (%)**	**Adjusted OR* (95%CI)**	**n of painful knees/ N of knees (%)**	**Adjusted OR* (95%CI)**
None	361/690 (52.3)	Reference 1.0	210/421 (49.9)	Reference 1.0	446/848 (52.6)	Reference 1.0
Isolated Medial	97/196 (49.5)	0.8 (0.6, 1.1)	138/254 (54.3)	1.1 (0.8, 1.5)	53/88 (60.2)	1.2 (0.8, 1.9)
Isolated Lateral	89/133 (66.9)	1.9 (1.3, 2.8)	91/150 (60.7)	1.5 (0.98, 2.1)	99/148 (66.9)	1.8 (1.2, 2.6)
Mixed	82/118 (69.5)	1.9 (1.2, 2.9)	190/312 (60.9)	1.5 (1.1, 2.0)	31/53 (58.5)	1.2 (0.7, 2.1)
FOA (n=934)						
None	224/689 (32.5)	Reference 1.0	166/564 (29.4)	Reference 1.0	267/800 (33.4)	Reference 1.0
Isolated Medial	53/127 (41.7)	1.4 (0.96, 2.1)	67/156 (43.0)	1.7 (1.2, 2.5)	26/48 (54.2)	2.4 (1.3, 4.4)
Isolated Lateral	24/49 (49.0)	1.8 (0.98, 3.2)	24/61 (39.3)	1.5 (0.9, 2.7)	31/59 (52.5)	2.1 (1.2, 3.6)
Mixed	35/69 (50.7)	2.0 (1.2, 3.4)	79/153 (51.6)	2.4 (1.7, 3.5)	12/27 (44.4)	1.4 (0.6, 3.1)

*Adjusted for age, sex, BMI and depressive symptoms

Table 4

Difference (95% CI) in knee pain severity scores between categories of MRI-detected structural damage in the patellofemoral joint in MOST

	Full-thickness cartilage loss* (WORMS 2.5, 5 or 6)			Bone Marrow Lesions* (WORMS ≥1)		
Percentiles of VAS Pain	**Isolated Medial vs. None**	**Isolated Lateral vs. None**	**Mixed vs. None**	**Isolated Medial vs. None**	**Isolated Lateral vs. None**	**Mixed vs. None**
40th	0.3 (−0.4, 1.0)	4.7 (2.5, 6.8)	4.5 (2.0, 7.0	−0.6 (−1.2, −0.03)	3.3 (1.4, 5.1)	1.9 (0.8, 3.0)
50th	−0.2 (−1.4, 0.9)	5.4 (2.8, 8.0)	5.3 (2.4, 8.1)	−0.9 (−2.4, 0.7)	4.2 (2.2, 6.1)	2.3 (0.2, 4.6)
60th	−1.2 (−3.2, 0.8)	5.5 (1.4, 9.6)	5.5 (1.4, 9.6)	−1.8 (−4.1, 0.6)	4.8 (0.1, 9.5)	3.3 (0.9, 5.7)
70th	−3.3 (−6.9, 0.3)	5.9 (−0.4, 12.2)	8.3 (2.0, 14.7)	−4.3 (−8.8, 0.7)	11.3 (4.0, 18.7)	5.2 (1.1, 9.3)
80th	−3.8 (−9.1, 1.5)	6.2 (1.5, 10.8)	6.2 (−0.4, 12.7)	−7.4 (−12.5, −2.3)	10.2 (4.3, 16.0)	3.3 (−2.2, 8.8)
90th	−6.4 (−20.5, 7.7)	−0.5 (−9.4, 8.5)	0.8 (−9.5, 11.2)	−16.9 (−32.0, −1.8)	13.0 (4.2, 21.9)	7.4 (−2.3, 17.2)

*Adjusted for age, sex, BMI and depressive symptoms