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Ambulatory activity interacts with common risk factors for osteoarthritis to modify increases in MRI-detected osteophytes

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SUMMARY

Objective: To investigate the longitudinal association between objectively measured ambulatory activity (AA) and knee MRI-detected osteophytes (OPs), and to test whether this relationship was modified by common risk factors for OA including sex, obesity, disease severity and knee injury history.
Methods: 408 community-dwelling adults aged 51–81 years were assessed at baseline and 2.7 years. T1-weighted fat-suppressed MRI was used to evaluate knee OPs at both time points. AA was assessed at baseline by pedometers and categorized as: less active (≤7499 steps per day), moderately active (7500–9999 steps per day) and highly active (≥10,000 steps per day).
Results: Statistically significant interactions were detected between knee OA risk factors and AA on increases in MRI-detected OPs (all $P < 0.05$). In stratified analyses, being moderately active, compared to being less active, was protective against an increase in MRI-detected OPs (score change of ≥1) in females (relative risk (RR) = 0.42, 95%CI, 0.25–0.70, $P < 0.01$), those who were obese (RR = 0.50, 95%CI, 0.30–0.83, $P < 0.01$), those with radiographic OA (ROA) (RR = 0.68, 95%CI, 0.47–0.97, $P = 0.02$) and those with a history of knee injury (RR = 0.27, 95%CI, 0.08–0.88, $P = 0.02$) in almost every knee compartment, after adjustment for confounders. No statistically significant associations were found in males, non-obese, non-ROA or non-injury groups.
Conclusions: Being moderately active is protective against an increase in MRI-detected OPs in females, those with ROA, those who are obese and those with a history of knee injury. These findings suggest that being moderately active is beneficial for individuals who are at higher risk of knee OA.

Introduction

Physical activity (PA) is widely promoted by health care professionals in the prevention and management of chronic health conditions including cardiovascular diseases, mental illness and obesity[1,2]; however, the effect of ambulatory activity (AA) on the development or progression of osteoarthritis (OA) is conflicting. Although some studies have demonstrated PA has no effect on OA occurrence[3] or joint health[4,5], AA was shown to have protective effects on joint space loss[6]. In contrast, elderly adults who performed high levels of heavy PA had an increased risk of radiographic knee OA[7], and participants with a body mass index (BMI) greater than the median value further increased their risk of knee OA among those who exercised[8]. The factors that contribute to these inconsistencies may include: self-reported PA assessments which demonstrate only moderate reproducibility[9]; the use of radiographs to assess OA, which provides only a limited view of the disease process[10]; and failure to account for effect modification by co-existing risk factors such as obesity, female sex, joint injury.

Osteophytes (OP) are one of the hallmarks of OA and are a fundamental sign of disease incidence and progression[11]. The relationship between PA and OP has previously been investigated[3,6,12–14], however, in these studies PA was assessed subjectively using questionnaires and OP were assessed using radiographs. We have shown that OP detected on MRI are clinically relevant and can predict knee structural changes[15]. Using MRI-

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detected OP and objectively measured AA may provide a better understanding of the effect of AA on OA structural progression. So far, there is no guideline on the amount of PA required to prevent OA progression, and it is still uncertain what level of AA should be promoted to individuals with certain knee OA risk factors. Therefore, the aims of this study were to investigate the longitudinal association between objectively measured AA (steps/day by pedometer) and knee MRI-detected OPs, and to test whether this relationship was modified by common risk factors for OA including sex, obesity, radiographic OA (ROA) and knee injury history.

Material and method

Participants

This study was conducted as part of the Tasmania Older Adult Cohort (TASOAC) Study, a population-based, prospective longitudinal cohort study. The original aim of TASOAC study was designed to identify the genetic, environmental, and biochemical factors associated with the development and progression of OA[16]. Participants (mean age 62) were randomly selected from the electoral roll in Southern Tasmania (population 229, 000) using sex-stratified sampling (Supplementary Figure 1). Participants who were institutionalised or had contraindications to MRI were excluded. Follow-up data such as pedometer and questionnaire data was available for 875 participants at approximately 2.7 years later[17]. There were 174 participants who lost at 2.7-year follow-up (875/1049) and supplementary analyses were performed to examine the characteristics of these participants. The MRI machine was decommissioned halfway through the follow-up period, thus, follow-up MRI scans were only available for about half of the participants ($n = 408/875$). This research was conducted in compliance with the Declaration of Helsinki and was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee. Informed written consents were obtained from all subjects.

Ambulatory activity

AA was assessed at baseline as steps per day determined by pedometer (Omron HJ-003 & HJ-102, Omron Healthcare, Kyoto, Japan). All participants were instructed to wear a pedometer for seven consecutive days and were re-assessed 6 months later to account for seasonal variation[18]. Verbal and written instructions were given regarding pedometer wear and how to keep a pedometer diary. In general we had good compliance of pedometer wear. Of the 408 participants in the current study, the average days worn was 13.6 (standard deviation (SD) 1.6). There were strong correlation between pedometer assessment at baseline and 6 month repeated (Supplementary Figure 2). Mean steps per day was calculated as the average of the days worn at both time points. 14 participants only wore the pedometer for one time thus steps/day value at this time point were used. We categorised AA into three groups based on the Tudor-Locke *et al.*[19] reommondations which we modified slightly based on the average steps per day taken amongst older adults with self-reported functional limitation, reported to be 7681 steps per day[20]. Participants in our study were considered to be less active (≤7499 steps per day); moderately active (7500/9999 steps per day), or highly active (≥10,000 steps per day).

Anthropometrics

Weight was measured to the nearest 0.1 kg (Seca Delta Model 707). Height was measured to the nearest 0.1 cm using a stadiometer[21]. BMI was calculated (kg/m^2).

History of knee injury

Knee injury was assessed at follow-up by asking ‘Have you ever had a previous knee injury requiring non-weight-bearing treatment for more than 24 h or surgery?'.

X-Ray assessment

A standing anteroposterior semi-flexed view of the right knee with 15° of fixed knee flexion was performed in all participants at baseline. Baseline joint space narrowing (JSN) and radiographic osteophytes (OPs) were assessed at the medial tibia, medial femur, lateral tibia and lateral femur sites on a scale of 0–3 (0 = normal, 3 = severe) according to the Osteoarthritis Research Society International (OARSI) atlas developed by Altman et al.[22]. As this study did not have skyline radiographs, patellar radiographic OPs were not able to be measured. The presence of ROA was defined as any JSN or OP score of ≥ 1[21]. Two readers assessed the radiographs simultaneously with immediate reference to the atlas. Intra-observer repeatability was tested in 40 subjects 1 month apart with ICCs of 0.65–0.85[23].

Magnetic Resonance Imaging

MRI scans on the right knees were imaged on baseline and follow-up in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Picker, Cleveland, OH) using a commercial transmit-receive extremity coil were conducted[21]. Following are the image sequences: a T1-weighted fat saturation 3D gradient recall acquisition in the steady state; flip angle 30°; repetition time 31 ms; field of view 16 cm; echo time 6.71 ms; 512 × 512 matrix; 60 partitions; acquisition time 11 min 56 s; one acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.31 (512 × 512 pixels). An independent computer workstation using the software program Osirix (University of Geneva, Geneva, Switzerland) were used to transfer the image database as previously described[9,24].

MRI-detected osteophytes

ZZ measured MRI-detected OPs both baseline and follow-up using a combination of Whole-Organ Magnetic Resonance Imaging (MRI) Score (WORMS) and the Knee Osteoarthritis Scoring System (KOSS)[25,26]. OPs were defined as focal bony excrescences, seen on sagittal, axial or coronal images, extending from a cortical surface[16]. Size was measured from the base to the tip of the OP. The base of OP was defined as distinguished from that of adjacent articular cartilage with a normal MRI appearance[27]. Each of the following 14 sites were assessed separately: the anterior (a), central weight bearing (c) and posterior (p) margins of the tibial plateaus and femoral condyles, and the medial (M) and lateral (L) margins of the tibia, femora and patella[26]. OPs were graded as follows: grade 0, absent; grade 1, minimal (<3 mm high); grade 2, moderate (3–5 mm); grade 3, severe (>5 mm)[25]. The score of each individual site in the relevant compartment (or whole/total knee) was summed up to calculate the total OP score in that compartment (or whole/total knee). OP present was defined as MRI-detected OP score of ≥1. An increase in the MRI-detected OP score at any site was defined as change of ≥1 from baseline to follow-up at that site. Intra-observer reliability (expressed as intraclass correlation coefficients, ICCs) was 0.94–0.97 and inter-observer reliability was 0.90–0.96[28]. Our previous study reported that MRI is far more sensitive and reliable than X-ray to detect OPs[16].

Statistical analysis

One-way analysis of variance or χ^2 tests were used to compare means or proportions between participants with different AA levels. Crude and adjusted log binomial regression was used to examine the longitudinal association between objectively measured AA categories and increases in MRI-detected OPs in the total study sample, with age, sex, BMI, presence of ROA and knee injury history as covariates. A least significant change criteria (LSC) was used to set the threshold of an increased MRI-detected OP from baseline to follow-up. This take into consideration of measurement error and correlation between the baseline and follow-up measurements. The formula was as follows:

$LSC = 1.96 \times \sigma\sqrt{2(1-\rho)}$ (σ = the stand error of the mean; ρ = the serial correlation). The LSC of MRI-detected OP was calculated to be 0.33 (where $\sigma = 0.42$, $\rho = 0.918$). Thus, an increase in the MRI-detected OP score at any site was defined as change of ≥ 1 from baseline to follow-up.

Interactions between knee OA risk factors (sex, BMI, knee injury history, radiographic OA) and AA levels on MRI-detected OPs were tested in all multivariable models. When statistically significant interactions were identified, estimates were presented separately for each risk factor. The analyses were adjusted for, age, sex and BMI because these factors were considered to be the most obvious confounders. Directed acyclic graphs (DAGs) analyses were routinely performed to select potential confounders. Presence of ROA and history of knee injury was also adjusted to rule out potential confounding effects. A *p* value less than 0.05 (two tailed) was regarded as statistically significant. All statistical analyses were performed on Stata version 14.0 for Windows (StataCorp, College Station, TX, USA)[29].

Results

Characteristic of study population at baseline

Four hundred and eight participants with pedometer measures at baseline and MRI measures at baseline and follow-up were included. Steps/day at baseline were highly correlated to steps/day at the 2.7-year follow-up ($r = 0.8$). There were 174 participants who lost at 2.7-year follow-up, however, supplementary analyses showed that there were no significant differences between participants who lost to follow-up and the rest in terms of age, sex, BMI, presence of obesity, ROA and baseline MRI-detected OPs except for knee injury history (data not shown). Characteristics of the participants at baseline are presented in Table I. At baseline, participants with different levels of AA were statistically significantly different in terms of age ($P < 0.01$), weight ($P < 0.01$), BMI ($P < 0.01$), obesity ($P < 0.01$), baseline total MRI-detected OP score ($P = 0.01$), baseline patellar MRI-detected OP score ($P = 0.03$) and proportion of increased MRI-detected OP score in any compartment ($P = 0.03$).

Association between AA and increases in MRI-detected OP, stratified by OA risk factors

Interactions between knee OA risk factors (sex, BMI, ROA, knee injury history) and AA levels on increased MRI-detected OPs were statistically significant (Fig. 1). Therefore, all analyses were stratified based on sex (Table II), obesity (Table III), baseline ROA (Table IV) and history of knee injury (Table V).

In analyses stratified by sex, moderately active female participants had a statistically significantly reduced risk of having an increase in MRI-detected OPs in the medial tibiofemoral (TF) compartment (RR = 0.24, 95%CI = 0.07–0.78), lateral TF compartment (RR = 0.39, 95%CI = 0.20–0.79), patellar compartment (RR = 0.28, 95%CI = 0.11–0.69) and total compartment (RR = 0.42, 95%CI = 0.25–0.70), after adjustment for age, BMI, knee injury history and baseline ROA. No statistically significant association was found for males (Table II).

In analyses stratified by obesity, moderately active and highly active obese participants had a statistically significantly reduced risk of having an increase in MRI-detected OPs in the lateral TF compartment (RR = 0.36, 95%CI = 0.17–0.78; RR = 0.25, 0.07–0.87, respectively), after adjustment for age, sex, knee injury history and baseline ROA. Being moderately active was also protective against MRI-detected OPs increases in the patellar compartment (RR = 0.33, 95%CI = 0.15–0.74) and total compartment (RR = 0.50, 0.30–0.83) in obese participants. Moderately active non-obese participants had a statistically significantly reduced risk of having an increase in MRI-detected OPs in the patellar compartment only (RR = 0.48, 95%CI = 0.24–0.95), after adjustment for covariates. No statistically significant association was found in the non-obese group in any other compartment (Table III).

In analyses stratified by baseline ROA status, moderately active participants with baseline ROA had a statistically significantly reduced risk of having an increase in MRI-detected OPs at the lateral TF compartment (RR = 0.52, 95%CI = 0.31–0.86) and total compartment (RR = 0.68, 95%CI = 0.04–0.97), after adjustment for age, sex, BMI and knee injury history. The associations were of

Table I
Characteristics of participants at baseline

	Less active (≤7499)	Moderately active (7500/9999)	Highly active (≥10,000)	*p*
	N = 147	*N* = 123	*N* = 138	
Age	**65.3 ± 7.7**	**61.7±6.4**	**60.1 ± 6.0**	**<0.01**
Females (%)	56	50	44	0.15
Weight	**80.4 ± 15.6**	**77.6 ± 14.1**	**74.9 ± 11.8**	**<0.01**
BMI	**29.1 ± 5.3**	**27.6 ± 4.2**	**26.2 ± 3.2**	**<0.01**
Obesity (%)	**37**	**26**	**11**	**<0.01**
ROA (%)	61	58	57	0.81
Knee injury (%)	10	11	10	0.94
Presence of baseline OPs (%)	89	87	82	0.20
Baseline total OP Score (range 0–36, median and IQR)	**3(8)**	**2(5)**	**3(4)**	**0.01**
Baseline Medial TF OP Score (median and IQR)	0(1)	0(1)	0(1)	0.06
Baseline Lateral TF OP Score (median and IQR)	1(3)	1(2)	1(2)	0.21
Baseline Patellar TF OP Score (median and IQR)	**2(2)**	**2(1)**	**1(1.5)**	**0.03**
Increased OP score in any compartment (%)	**54**	**37**	**46**	**0.03**

One-way analyses of variance (ANOVA) were used for differences between groups, and χ2 tests were used for proportions (percentages). Statistically significant differences are shown in bold. Mean ± SD except for percentages.
*IQR: Interquartile range; BMI: body mass index; ROA: radiographic osteoarthritis; OP: osteophyte; TF: Tibiofemoral.

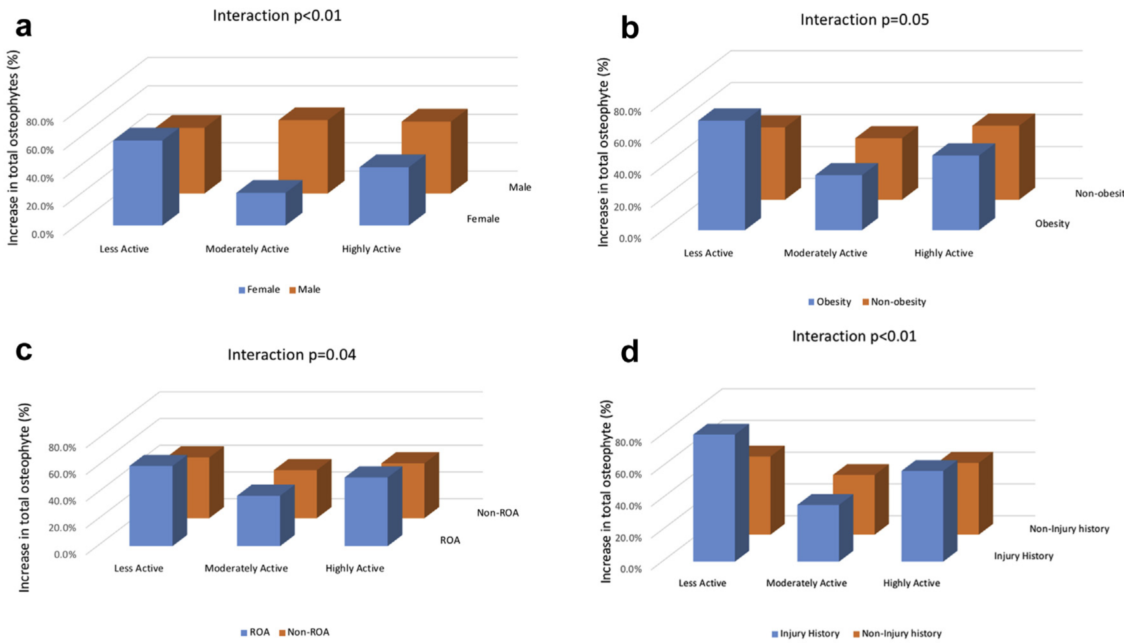

Fig. 1. Interactions between ambulatory activity (AA) and risk factors for knee OA on increases in total MRI-detected osteophytes. There was a statistically significant interaction between (**a**) sex and physical activity; (**b**) obesity and physical activity; (**c**) radiographic OA (ROA) and physical activity; (**d**) knee injury history and AA, on increases in total OP.

Table II
Association between ambulatory activity (AA) and an increase in MRI-detected OPs, stratified by sex

	Males, $n = 204$					Females, $n = 204$				
		Multivariable*		Multivariable†			Multivariable*		Multivariable†	
		RR	(95%CI)	RR	(95%CI)		RR	(95%CI)	RR	(95%CI)
Medial TF compartment										
Less active (≤7499)	$n = 65$		Ref		Ref	$n = 82$		Ref		Ref
Moderately Active (7500/9999)	$n = 62$	1.74	(0.83, 3.64)	1.44	(0.70, 2.95)	$n = 61$	**0.20**	**(0.05, 0.71)**	**0.24**	**(0.07, 0.78)**
Highly Active (≥10,000)	$n = 77$	1.90	(0.93, 3.88)	1.66	(0.84, 3.30)	$n = 61$	0.54	(0.18, 1.61)	0.60	(0.22, 1.66)
Lateral TF compartment										
Less active (≤7499)	$n = 65$		Ref		Ref	$n = 82$		Ref		Ref
Moderately Active (7500/9999)	$n = 62$	1.18	(0.70, 1.98)	0.98	(0.57, 1.68)	$n = 61$	**0.27**	**(0.11, 0.63)**	**0.39**	**(0.20, 0.79)**
Highly Active (≥10,000)	$n = 77$	0.97	(0.57, 1.68)	0.92	(0.55, 1.54)	$n = 61$	0.72	(0.32, 1.63)	0.76	(0.42, 1.37)
Patellar compartment										
Less active (≤7499)	$n = 65$		Ref		Ref	$n = 82$		Ref		Ref
Moderately Active (7500/9999)	$n = 62$	0.82	(0.39, 1.72)	0.83	(0.38, 1.81)	$n = 61$	**0.20**	**(0.07, 0.56)**	**0.28**	**(0.11, 0.69)**
Highly Active (≥10,000)	$n = 77$	1.25	(0.66, 2.36)	1.38	(0.72, 2.63)	$n = 61$	0.53	(0.21, 1.33)	0.63	(0.28, 1.38)
Any compartment										
Less active (≤7499)	$n = 65$		Ref		Ref	$n = 82$		Ref		Ref
Moderately Active (7500/9999)	$n = 62$	1.25	(0.87, 1.79)	1.17	(0.81, 1.70)	$n = 61$	**0.23**	**(0.11, 0.48)**	**0.42**	**(0.25, 0.70)**
Highly Active (≥10,000)	$n = 77$	1.29	(0.90, 1.84)	1.27	(0.89, 1.81)	$n = 61$	0.61	(0.28, 1.31)	0.75	(0.49, 1.16)

Significant differences are shown in bold.
* Adjusted for age and BMI.
† Further adjusted for radiographic OA and knee injury history; BMI, body mass index; TF, tibiofemoral; *n*, number of participants in the subgroup.

borderline significance at the medial TF compartment (RR = 0.57, 95%CI = 0.31–1.04, $P = 0.07$) and patellar compartment (RR = 0.43, $P = 0.06$) after adjustment for covariates. No statistically significant association was found in the non-ROA group (Table IV).

In analyses stratified by knee injury history, moderately active participants with a prior history of knee injury had a statistically significantly reduced risk of having an increase in MRI-detected OPs at the lateral TF compartment (RR = 0.17, 95%CI = 0.04–0.68) and the total compartment (RR = 0.27, 95%CI = 0.08–0.88), after adjustment for age, sex, BMI and baseline ROA. No statistically significant association was found in the non-injury group (Table V).

Apart from a protective effect in obese participants on lateral TF OP increases, being highly active was not associated with increases in MRI-detected OPs in all the specified analyses. The relationships between AA and the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) knee pain change were also conducted, but no statistically significant association was found (data not shown).

Discussion

This longitudinal study has used objectively-assessed AA and sensitive MRI techniques to examine the optimal range of AA for knee OP development and progression, among those participants with OA risks factors. The findings suggest that being moderately active (7500/9999 steps per day) is protective against an increase in MRI-detected OPs in females and participants who are obese, have baseline ROA and have a prior history of knee injury. In contrast,

Table III
Association between AA and an increase in MRI-detected OPs, stratified by body mass index (BMI) = 30

	BMI < 30, n = 307					BMI ≥ 30, n = 101				
		Multivariable*		Multivariable†			Multivariable*		Multivariable†	
		RR	(95%CI)	RR	(95%CI)		RR	(95%CI)	RR	(95%CI)
Medial TF compartment										
Less active (≤7499)	n = 93		Ref		Ref	n = 54		Ref		Ref
Moderately Active (7500/9999)	n = 91	1.02	(0.42, 2.49)	0.87	(0.41, 1.86)	n = 32	0.51	(0.21, 1.24)	0.50	(0.22, 1.15)
Highly Active (≥10,000)	n = 123	1.49	(0.66, 3.39)	1.27	(0.62, 2.62)	n = 15	0.62	(0.18, 2.06)	0.69	(0.24, 1.94)
Lateral TF compartment										
Less active (≤7499)	n = 93		Ref		Ref	n = 54		Ref		Ref
Moderately Active (7500/9999)	n = 91	0.85	(0.44, 1.67)	0.81	(0.49, 1.33)	n = 32	**0.36**	**(0.17, 0.77)**	**0.36**	**(0.17, 0.78)**
Highly Active (≥10,000)	n = 123	0.98	(0.51, 1.85)	0.92	(0.58, 1.45)	n = 15	**0.26**	**(0.07, 1.00)**	**0.25**	**(0.07, 0.87)**
Patellar compartment										
Less active (≤7499)	n = 93		Ref		Ref	n = 54		Ref		Ref
Moderately Active (7500/9999)	n = 91	**0.40**	**(0.18, 0.88)**	**0.48**	**(0.24, 0.95)**	n = 32	**0.34**	**(0.15, 0.76)**	**0.33**	**(0.15, 0.74)**
Highly Active (≥10,000)	n = 123	0.79	(0.40, 1.54)	0.92	(0.54, 1.55)	n = 15	0.51	(0.23, 1.13)	0.57	(0.26, 1.24)
Any compartment										
Less active (≤7499)	n = 93		Ref		Ref	n = 54		Ref		Ref
Moderately Active (7500/9999)	n = 91	0.91	(0.62, 1.34)	0.84	(0.59, 1.22)	n = 32	**0.50**	**(0.30, 0.84)**	**0.50**	**(0.30, 0.83)**
Highly Active (≥10,000)	n = 123	1.10	(0.77, 1.59)	1.04	(0.75, 1.45)	n = 15	0.66	(0.36, 1.22)	0.67	(0.37, 1.21)

Significant differences are shown in bold.
* Adjusted for age and sex.
† Further adjusted for radiographic OA and knee injury history; BMI, body mass index; TF, tibiofemoral; n, number of participants in the subgroup.

Table IV
Association between AA and an increase in MRI-detected OPs, stratified by radiographic OA (ROA)

	No-ROA, n = 161					ROA, n = 228				
		Multivariable*		Multivariable†			Multivariable*		Multivariable†	
		RR	(95%CI)	RR	(95%CI)		RR	(95%CI)	RR	(95%CI)
Medial TF compartment										
Less active (≤7499)	n = 55		Ref		Ref	n = 85		Ref		Ref
Moderately Active (7500/9999)	n = 50	1.68	(0.43, 6.60)	1.75	(0.43, 7.07)	n = 69	**0.56**	**(0.30, 1.04)**	**0.57**	**(0.31, 1.04)**
Highly Active (≥10,000)	n = 56	2.65	(0.78, 9.07)	2.51	(0.72, 8.76)	n = 74	0.78	(0.40, 1.53)	0.82	(0.42, 1.62)
Lateral TF compartment										
Less active (≤7499)	n = 55		Ref		Ref	n = 85	R	Ref		Ref
Moderately Active (7500/9999)	n = 50	0.86	(0.42, 1.77)	0.86	(0.42, 1.79)	n = 69	**0.54**	**(0.33, 0.87)**	**0.52**	**(0.31, 0.86)**
Highly Active (≥10,000)	n = 56	0.66	(0.32, 1.36)	0.63	(0.31, 1.30)	n = 74	0.85	(0.54, 1.34)	0.92	(0.59, 1.43)
Patellar compartment										
Less active (≤7499)	n = 55		Ref		Ref	n = 85		Ref		Ref
Moderately Active (7500/9999)	n = 50	0.52	(0.22, 1.23)	0.52	(0.22, 1.23)	n = 69	**0.51**	**(0.25, 1.05)**	**0.43**	**(0.18, 1.03)**
Highly Active (≥10,000)	n = 56	0.89	(0.44, 1.76)	0.88	(0.44, 1.77)	n = 74	1.09	(0.58, 2.05)	1.16	(0.51, 2.67)
Any compartment										
Less active (≤7499)	n = 55		Ref		Ref	n = 85		Ref		Ref
Moderately Active (7500/9999)	n = 50	0.83	(0.51, 1.35)	0.83	(0.51, 1.36)	n = 69	**0.67**	**(0.41, 0.96)**	**0.68**	**(0.47, 0.97)**
Highly Active (≥10,000)	n = 56	0.96	(0.60, 1.53)	0.95	(0.59,1.51)	n = 74	0.98	(0.71, 1.36)	1.01	(0.73, 1.40)

Significant differences are shown in bold.
* Adjusted for age, sex and BMI.
† Further adjusted for knee injury history; ROA, radiographic osteoarthritis; TF, tibiofemoral; n, number of participants in the subgroup.

being highly active (≥10,000 steps per day) was neither protective nor deleterious towards an increase in MRI-detected OPs in any subgroups. No statistically significant association was found between AA and knee pain change overtime (data not shown).

Walking is a fundamental activity performed on a daily basis and provides the most common means of AA for older adults[30]. Pedometers have been successfully used as an appropriate objective tool for monitoring AA[31–33]. The decline of walking ability among OA patients has been linked to adverse health outcomes including cardiovascular events, diabetes and deaths[34–36]; however, high levels of walking may lead to detrimental mechanical stress on joint tissues[37]. We previously showed that doing ≥10,000 steps/day was detrimental for MRI-assessed structural changes, mostly in those with pre-existing structural abnormalities[18]. Considering potential threshold effects such as this, we set out to examine what the optimal AA level was in relation to MRI-detected OP development and progression. Our cut-points were defined based on the Tudor-Locke *et al.*[19] recommendations which we modified slightly based on the average steps per day taken amongst older adults with self-reported functional limitations[20].

Our study uniquely found that AA's effect on OP development and progression was modified by common risk factors of OA. This is in line with the suggestion that there may be subgroups of individuals who differ in their response to AA. The adjustments we did in current study would not completely eliminate residual confounding or adjustment bias, and there are a number of other factors, such as personal habit, socio-economic status and even weather condition, that may also affect levels of AA and osteoarthritic changes[38,39]. In the current study we used an increase in MRI-detected OP as a surrogate measure for OA development. Our previous work has shown that OPs detected on MRI are clinically relevant and predict increases in cartilage defects, BMLs, loss of cartilage volume and total knee pain change[16]. Additionally, the

Table V
Association between AA and an increase in MRI-detected OPs, stratified by knee injury history

		Non-knee injury, $n = 365$					Knee injury, $n = 43$			
		Multivariable*		Multivariable†			Multivariable*		Multivariable†	
		RR	(95%CI)	RR	(95%CI)		RR	(95%CI)	RR	(95%CI)
Medial TF compartment										
Less active (≤7499)	$n = 132$		Ref		Ref	$n = 15$		Ref		Ref
Moderately Active (7500/9999)	$n = 109$	0.87	(0.47, 1.60)	0.73	(0.40, 1.33)	$n = 14$	0.35	(0.08, 1.55)	0.39	(0.12, 1.31)
Highly Active (≥10,000)	$n = 124$	1.23	(0.67, 2.26)	1.07	(0.59, 1.93)	$n = 14$	0.43	(0.10, 1.94)	0.45	(0.12, 1.67)
Lateral TF compartment										
Less active (≤7499)	$n = 132$		Ref		Ref	$n = 15$		Ref		Ref
Moderately Active (7500/9999)	$n = 109$	0.82	(0.55, 1.23)	0.75	(0.50, 1.14)	$n = 14$	0.10	(0.00, 6.78)	**0.17**	**(0.04, 0.68)**
Highly Active (≥10,000)	$n = 124$	0.92	(0.61, 1.40)	0.85	(0.56, 1.30)	$n = 14$	0.16	(0.00, 14.6)	0.51	(0.24, 1.10)
Patellar compartment										
Less active (≤7499)	$n = 132$		Ref		Ref	$n = 15$		Ref		Ref
Moderately Active (7500/9999)	$n = 109$	0.66	(0.38, 1.16)	0.64	(0.36, 1.15)	$n = 14$		Empty		Empty
Highly Active (≥10,000)	$n = 124$	1.02	(0.61, 1.69)	1.06	(0.63, 1.76)	$n = 14$	0.64	(0.20, 2.02)	0.68	(0.23, 2.06)
Any compartment										
Less active (≤7499)	$n = 132$		Ref		Ref	$n = 15$		Ref		Ref
Moderately Active (7500/9999)	$n = 109$	0.84	(0.62, 1.13)	0.80	(0.59, 1.08)	$n = 14$	**0.32**	**(0.11, 0.91)**	**0.27**	**(0.08, 0.88)**
Highly Active (≥10,000)	$n = 124$	1.04	(0.78, 1.39)	1.00	(0.74, 1.34)	$n = 14$	0.62	(0.37, 1.03)	0.62	(0.32, 1.21)

Significant differences are shown in bold.
* Adjusted for age, sex and BMI.
† Further adjusted for radiographic OA; TF, tibiofemoral; n, number of participants in the subgroup.

development of MRI-detected OPs was not due to pre-existing disease processes as the results remainded unchanged after further adjustment for other disease (such as rheumatoid arthritis, cardiovascular diseases, and diabetes) status (data not shown).

We found moderately active AA prevented MRI-detected OP worsening in females but not in males. Females are known to be at a greater risks of developing OA compared to males[40]. A nested case–control study reported that males exhibited a reduced risk for hip or knee OA if they performed moderate/high AA, while females had reduced risk for OA regardless of the level of AA that they performed[41]. The reason that moderately active AA among men was not found to be preventive on OP development is not clear. But our results are consistent with Keegan et al.[42] who found moderate-strenuous exercise associated with higher medial femoral condyle T2 values in females, whereas this relationship was not found in males. A possible explanation for the discrepancy between sexes may be the differences in loading behaviours inherent to males and females[43].

White *et al.*[44] found that people with underlying structural worsening trended towards less walking and were more likely to fall below the 6000 step/day threshold, suggesting functional limitation. People who are predisposed to OA or have confirmed OA should not be discouraged from walking and can benefit from AA[45]. Our current study demonstrated that participants with ROA taking 7,500 to 9999 steps per day reduced their future risks of OP development. This is somewhat consistent with a previous study which reported that patients with all grades of OA severity on MRI could benefit from professional supervised exercise therapy, although the effects might be reduced in patients with advanced patellofemoral osteoarthritis (PF OA)[46]. The Multicentre Osteoarthritis (MOST) study reported no association between daily walking and structural changes over 2 years in people at risk of mild knee OA[47], however, this study was limited by the assessment of a narrow range of step frequency.

Obesity is a major risk factor for the development of knee OA[48], and the increased risk of OA occurs on a dose–response gradient of increasing BMI[49]. Moreover, obesity is related to worse PA scores, lower quality of life, and higher risk of 6-year disability[50]. It is still uncertain what level of PA is appropriate for obese individuals[51]. On one hand, AA such as walking may exacerbate wearing out of articular cartilage in the presence of excess axial loads[52]; on the other hand, it may also reduce BMI and decrease risk of OA progression consequently. Our present study found that moderately active obese participants had a statistically significantly reduced risk of increased MRI-detected OPs. This result provides support for the use of moderate levels of AA in obese individuals.

It is well established that previous knee injury increases the risk of developing OA[53,54]. Knee injury and subsequent knee pain are anecdotally thought to further contribute to a decline in walking in people with knee OA that is related to aging. It is possible that psychological affirmation restricts PA after knee injury which leads to the increased risk of OA progression. Additionally, better understanding the types and intensities of AA appropriate for individuals who have suffered knee injury previously is clinically instructive. Our current study suggested that 7,500 to 9999 steps per day is appropriate and beneficial for participants with knee injury history in regards to OPs prevention.

The findings of current study would have implications in clinical practice and public health. We observed that comparing to those doing less than 7500 steps per day, females doing 7500 to 9999 steps per day would have about 60% reduced risk of OP progression at any knee compartment, obese people doing 7500 to 9999 steps per day would have about 50% reduced risk of OP progression at any compartment, people with ROA doing 7500 to 9999 steps per day would have 30% reduced risk of OP progression at any compartment, and people with previous knee injury history doing 7500 to 9999 steps per day would have 70% reduced risk of OP progression at any compartment. These findings would be clinically relevant, and clinical practitioners could encourage moderate AA particularly among OA susceptible groups such as women, obese people and those who had knee injury history and ROA. On the other hand, although non-statistically significant associations were found between AA and MRI-detected OPs in males, people who were not obese, without baseline ROA or knee injury history, being moderately active may still be recommended among these people[55]. A number of factors may have increased the estimation uncertainly in these models, such as limited sample size in stratified analyses. We have previously reported that doing ≥10,000 steps per day was deleteriously associated with increasing knee cartilage defect score, meniscal pathology score and BML score, mostly in those with pre-existing knee structural abnormalities (BMLs, cartilage loss and meniscal damage)[18]. However, in the current study having OP at baseline did not affect the relationship between AA and OP increases in the total sample or subgroups (data not shown). The reasons underlying the differences are unknown but may reflect the fact that OP formation was more prevalent, would predate and have a different pathophysiology compared to other structural abnormalities[56].

Several limitations of the current study should be acknowledged. First, follow-up MRI scans were only available in 408 out of 1049 participants (worn pedometer) due to decommissioning of MRI scanner. However, there were no statistically significant differences between the participants in the current study and the rest of cohort in terms of demographic factors and other study factors (apart from a slightly higher baseline steps per day in studied individuals). Second, we had a relatively limited follow-up duration of 2.7 years. The effects of AA on OA structural changes may occur over a longer period of time. Nevertheless, MRI-detected OP has been proven to be a sensitive measurement in depicting changes of OP within this time frame. Third, as AA was measured by pedometer, temporal changes in AA were not considered. We also did not have information on the intensity or nature of the activity (e.g., kneeling, climbing, squatting, running, twisting, manual labour and workload). The biomechanical aspects of different types of PA including the effects of joint loading is likely to have different effects on OP development and progression. Therefore, our study results may not be generalizable to broader types of PA. Last, potential residual confounding or adjustment bias may exist[57]. We hereby performed DAGs routinely to select potential confounders and to illustrate correlations between them in the model fitting procedures. Sensitive analyses were then conducted based on DAGs results using different models and covariates subsets. We found that effect sizes and 95%CIs only changed slightly between models, indicating the potential residual confounding or adjustment bias was unlikely to affect our findings.

In conclusion, being moderately active is protective against an increase in MRI-detected OPs in females, those with ROA, those who are obese and those with a prior history of knee injury. These findings indicate that a moderately active level of AA is beneficial for individuals who are at risk of knee OA.

Contributors

ZZ had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study design: CD, FC and GJ. Acquisition of data: ZZ, CD and DA. Analysis and interpretation of data: ZZ, DA, GJ and CD. Manuscript preparation and approval of submission: ZZ, DA, FC, GJ and CD.

Conflict of interests

The authors declare that they have no competing interests.

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Patient consent

Obtained.

Ethics approval

This study was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee, and written informed consent was obtained from all participants.

Supplementary data

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