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Associations between alcohol, smoking, and cartilage composition and knee joint morphology: Data from the Osteoarthritis Initiative

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SUMMARY

Objective: To determine the cross-sectional associations of alcohol consumption and smoking history with magnetic resonance imaging (MRI) measures of cartilage composition (T2) and joint structure using data from the Osteoarthritis Initiative (OAI).

Design: Subjects with radiographic Kellgren Lawrence right knee grades 0–2 were selected from the OAI database, and those with previously analyzed MRI cartilage T2 and semi-quantitative joint morphology gradings (WORMS) were included (n = 2061). Alcohol consumption was categorized as: no drinks to <1 drink/week, 1–7 drinks/week, >7 drinks/week. Smoking history was categorized as none, current, or former. Linear regression was used to assess the relationships of alcohol consumption and smoking history with both WORMS scores and cartilage T2.

Results: Subjects who consumed >7 drinks/week had significantly higher cartilage T2 than subjects who consumed <1 drink/week in the average of all cartilage regions and in three of five individual regions (coefficient range: 0.45–0.90, $p < 0.05$). Subjects with moderate alcohol consumption (1–7 drinks per week) had higher cartilage and meniscus WORMS scores than subjects who consumed <1 drink/week ($p < 0.05$). Current smokers had significantly higher cartilage T2 compared to non-smokers in the average of all cartilage regions and in three of five individual regions (coefficient range: 0.47–0.74, $p < 0.05$).

Conclusions: Alcohol consumption (1–7 drinks/week) was associated with worse cartilage and meniscus joint morphology, and >7 drinks/week was associated with elevated cartilage T2. Compared to non-smokers, current smokers had a more degenerated cartilage matrix as evidenced by greater cartilage T2.

1. Introduction

Osteoarthritis (OA) is a heterogeneous joint disease that affects approximately 250 million people [1] and causes severe disability [2]. There are many established risk factors for OA including obesity, genetic predisposition, and joint injury; and recently alcohol and smoking patterns have been implicated as potential risk factors possibly due to increased inflammation. While an estimated 967 million people are daily smokers (data from 2012) [3], and smoking is considered a risk factor for rheumatoid arthritis, the relationship between smoking and OA development is unclear [4]. Similarly, the effects of alcohol consumption on knee joint degeneration are not well understood.

Previous studies have reported conflicting evidence on the relationships between smoking, alcohol and OA. A meta-analysis reported an overall negative association between smoking and OA (OR = 0.87; 95% CI: 0.80 to 0.94) possibly confounded by lower BMI in smokers [4]; however, other studies have reported no association [5,6]. While one pre-clinical study in mice reported that chronic alcohol consumption induced pathological OA-like changes [7], few studies have investigated the associations between alcohol consumption and OA in humans. Haugen et al. [8] reported a positive association between moderate alcohol consumption and radiographic OA in the finger joints. Thus, the current study aims to enhance knowledge on the associations of smoking and alcohol consumption on the knee joint in a large sample (n = 2061)

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using advanced MR imaging techniques.

While previous studies on the impact of smoking and alcohol on OA have primarily used radiographic outcomes, MRI provides information on cartilage compositional changes in OA using T2 mapping, which provides more sensitive information on the cartilage extracellular matrix including its collagen fiber orientation [9]. MRI T2 probes early stages of cartilage degeneration that are not visualized on a standard MRI. Thus, quantifying both cartilage T2 and joint structure features using MR imaging may be beneficial and more sensitive when studying the effects of alcohol and smoking patterns on knee joint pathology in OA compared to standard radiographs.

The purpose of this study was therefore to determine the cross-sectional associations of alcohol consumption and smoking history with magnetic resonance (MR) imaging measures of cartilage composition (T2) and joint structure using data from the Osteoarthritis Initiative (OAI).

2. Method

2.1. Subject selection

This study utilizes data from the Osteoarthritis Initiative (OAI; http://www.oai.ucsf.edu/) [10], a multi-center, longitudinal study of persons aged 45–79 years at enrollment, aimed at assessing biomarkers in knee OA including those derived from MR imaging. The study protocol, amendments, and informed consent documentation were reviewed and approved by the local institutional review boards of all participating centers.

For the present study, we analyzed a sample of OAI subjects by selecting all subjects that had a Kellgren Lawrence score (KL) ≤ 2 in the right knee from which we had previously obtained both T2 relaxation time and semi-quantitative joint morphology measures from 3T MR images for other analyses [11–15]. KL ≤ 2 was included to study subjects with none to mild OA. Subjects were only included in the analysis if they had alcohol consumption or smoking history questionnaire data available. The OAI exclusion criteria were: (i) inflammatory arthropathies (including rheumatoid arthritis and seronegative spondyloarthropathies), (ii) MRI contraindications, (iii) use of ambulatory aids and co-morbid conditions that may affect the ability to participate in the study. For this analysis we excluded knees with (i) history of knee injury with post-traumatic deformity of the knee joint, (ii) total joint replacements at the lower extremities, (iii) MRI evidence of fractures or abnormalities, that did not fit into the spectrum of OA such as tumor or inflammation at baseline. Finally, a total of 2061 participants were included in the analysis on alcohol consumption, and 2050 were included in the analysis on smoking patterns.

2.2. Alcohol measurements

Participants were asked about their alcoholic beverage consumption during the 12 months prior to the clinic. The question was stated as "During the past 12 months, how many drinks did you have in a typical week? If you are unsure, please make your best guess", and the response options included 8 different ranges for drinks per week. Alcoholic beverages included beer, ale, wine, wine coolers, liquor (such as whiskey, gin, rum or vodka), cocktails or mixed drinks containing liquor, and any other drink that contains alcohol. One drink was described as equal to one 12 ounce can of beer, one five ounce glass of wine (a full glass), or a drink contain a shot, jigger, or finger of liquor (approximately one and one quarter ounces). Alcohol consumption was categorized as: no drinks to <1 per week, 1–7 drinks/week, >7 drinks/week.

2.3. Smoking measurements

Participants were also asked about their tobacco cigarette smoking history. They were considered for smoking history if they responded with Yes to the question "Have you smoked at least 100 cigarettes (5 packs) in your entire life?". Those who answered No were considered as "never smoked". Participants with smoking history were then asked if they currently smoked cigarettes, smoked cigarettes fairly regularly but only in the past, or if they never smoked regularly. Respondents were categorized as "never smoked", "former smoker", "current smoker", or "current smoker but never regular". Pack years (PY) were calculated by dividing the number of cigarettes smoked per day by 20 (the number of cigarettes in a pack) and multiplying by the number of years smoked. Based on previous studies, smoking was categorized as low (<15 PY) or high (≥ 15 PY) [16,17].

2.4. Imaging of the knee

2.4.1. Radiographs

Fixed flexion knee radiographs were obtained at baseline, and radiographic KL grades [18] were provided in the OAI dataset. Subjects with baseline KL grades of 0–2 were selected.

2.4.2. MR Imaging

MR images were obtained using four identical 3.0 T (Siemens Magnetom Trio, Erlangen, Germany) scanners in Columbus, Ohio; Baltimore, Maryland; Pittsburgh, Pennsylvania; Pawtucket, Rhode Island. The following four sequences were obtained for the morphological analysis: (i) 2D intermediate-weighted fast spin echo (FSE) sequences with fat suppression in the sagittal plane (3200/30 ms (ms), repetition time (TR)/echo time (TE)); (ii) 2D proton density-weighted FSE sequences in the sagittal plane (2700/20 ms, TR/TE); (iii) 3D T1-weighted fast low-angle shot (FLASH) gradient-echo sequences (20/7.6 ms/12°, TR/TE/flip angle), 512 × 512 matrix and (iv) 3D dual echo steady-state gradient-echo (DESS) obtained in the sagittal plane (16.3/4.7 ms/25°, TR/TE/flip angle), 307 × 384 matrix. Further details about the image acquisition are available in the OAI MR protocol [10]. A sagittal 2D multi-slice multi--echo sequence (MSME, TR = 2700 ms, TE_1-TE_7 = 10–70 ms, spatial resolution = 0.313 mm × 0.446 mm, slice thickness = 3.0 mm, and 0.5 mm gap) was used for cartilage T2 measurements [19].

2.5. MR image analysis

2.5.1. WORMS scoring

WORMS scoring was performed at baseline. MR images of the right knee obtained at the baseline visit were reviewed on picture archiving communication system (PACS) workstations (Agfa, Ridgefield Park, NJ, USA). Three radiologists with 8, 6- and 6-years of experience graded cartilage lesions. In equivocal cases, a consensus reading was performed with a musculoskeletal radiologist with 25-years of experience. Baseline cartilage lesions were assessed in six regions (patella, trochlea, medial femur, medial tibia, lateral femur and lateral tibia) using a modified semi-quantitative whole-organ magnetic resonance imaging score (WORMS) [20].

Cartilage lesions were evaluated with an 8-point scale: 0 = normal, 1 = normal thickness but increased or otherwise abnormal signal on fluid sensitive sequences, 2 = partial-thickness focal defect <1 cm in greatest width, 2.5 = full-thickness focal defect <1 cm in greatest width, 3 = multiple areas of partial-thickness defects (grade 2) intermixed with areas of normal thickness, or grade 2 defect wider than 1 cm but $<75\%$ of the entire region, 4 = diffuse ($\geq 75\%$ of the region) partial-thickness loss, 5 = multiple areas of full-thickness defect (grade 2.5) but $<75\%$ of the region, and 6 = diffuse ($\geq 75\%$ of the region) full-thickness loss. Meniscal lesions were graded separately in 6 regions (medial/lateral and anterior/body/posterior) using the following 4-point scale: 0-normal; 1-intrasubstance signal; 2-non-displaced tear; 3-displaced or complex tear; 4-complete destruction/maceration.

The maximum (*MAX*) cartilage or meniscus score was defined as the maximum score in any region. The reproducibility results for WORMS readings have been previously published [21,22]: the intra-observer

reproducibility in all tissues (meniscus, cartilage) was ≥96%, while the inter-observer reproducibility was ≥97%.

2.6. T2 measurements

Cartilage T2 measurements were performed at baseline. Semi-automatic cartilage segmentation of lateral/medial femur, lateral/medial tibia, and patella regions was performed as previously described, using an in-house, spline-based software based on MATLAB (MathWorks, Natick, Massachusetts) [22]. The average cartilage T2 value in the knee was defined as the average T2 in all the regions described above. Trained investigators segmented the entire cartilage but used rigorous criteria to exclude sections with compromised image quality.

Validated methods for obtaining a T2 map of the cartilage have been previously published by our group [21,22]. T2 maps were computed from the MSME images on a pixel-by-pixel basis using 6 echoes (TE = 20–70 ms) and 3 parameter fittings accounting for noise [23,24], and averaged over all of the slices in each cartilage region (lateral/medial femur, lateral/medial tibia, and patella). The first echo (TE = 10 ms) was not included in the T2 fitting procedure in order to reduce potential errors resulting from stimulated echoes, and a noise-corrected algorithm was implemented [23,24]. The cartilage T2 reproducibility results have been described previously [21,22]. The mean T2 values had root mean square (RMS) coefficients of variation (CV) ranging from 0.83% in the medial femur to 3.21% in the patella for intra-reader reproducibility, and from 1.22% in the patella to 1.86% in the lateral tibia for inter-reader reproducibility.

2.7. Statistical analysis

Statistical analysis was performed using STATA version 14 software (StataCorp LP, College Station, TX). Linear regression models were used to assess the relationships between baseline alcohol consumption and smoking history (exposures) and baseline WORMS scores and cartilage T2 (outcomes). As described in the methods section, alcohol consumption and smoking history were categorized as follows: alcohol: no drinks to <1 drink/week, 1–7 drinks/week, > 7 drinks/week); smoking history: none, current, former; pack years (PY): none, <15 PY, ≥15 PY. All models were adjusted for baseline age, gender, BMI, race, and education. We performed a sensitivity analysis by adjusting for baseline physical activity levels using The Physical Activity Scale for the Elderly (PASE), as well as alcohol consumption (for smoking), and smoking (for alcohol consumption) and occupation. We also performed a sensitivity analysis to assess whether there was a gender-dependency or BMI dependency (grouped as <30 kg/m^2, ≥30 kg/m^2) in the relationship between alcohol (or smoking) and T2/WORMS parameters by including an interaction between gender (or BMI) and alcohol consumption (or smoking status).

3. Results

3.1. Subject characteristics

2061 participants were included in the cross-sectional analysis of alcohol consumption. The three alcohol consumption groups were similar in age; however, subjects consumed <1 drink/week had significantly higher body mass index (BMI) (28.98 ± 4.87 kg/m^2) than the other two groups (1–7 drinks/week: 27.98 ± 4.19 kg/m^2; >7 drinks/week 27.75 ± 4.15 kg/m^2). There was a significant difference in the distribution of right knee KL scores between subjects that did not consume alcohol and those that consumed 1–7 drinks/week (p = 0.04). In addition, there were significant differences in the distribution of race among the three alcohol consumption groups (p < 0.001 for <1 drink/week vs. 1–7 drinks/week and p < 0.001 for <1 drink/week vs. >7 drinks/week), Table 1. Subject characteristics for the smoking subgroups are also reported in Table 1.

Corresponding author. Alcohol Consumption and Knee Cartilage T2.

Of the 2061 subjects with alcohol consumption and T2 data available, 1165 did not consume alcohol or consumed <1 drink/week, 642 consumed 1–7 drinks/week, and 254 consumed >7 drinks week. Subjects that consumed >7 drinks per week had significantly higher cartilage T2 than subjects that did not consume alcohol in the average of all regions (coeff. = 0.49; p = 0.002; 95% CI = 0.19–0.79), the medial tibia (coeff. = 0.90; p < 0.001; 95% CI = 0.51–1.30), the lateral femur (coeff. = 0.46; p = 0.02; 95% CI = 0.07–0.84), the lateral tibia (coeff. = 0.45; p = 0.04; 95% CI = 0.02–0.87). There were non-significant trends for association in the medial femur (p = 0.08), Table 2. The results were unchanged after adjusting for baseline PASE scores, smoking status, or occupation (sensitivity analysis). There were no significant (p > 0.05) gender-specific or BMI-specific differences in the relationship between alcohol consumption and cartilage T2 (sensitivity analysis).

3.2. Alcohol consumption and knee joint morphology

Of the 1767 participants with alcohol consumption and WORMS scoring data available, 1001 did not consume alcohol or consumed <1 drink/week, 559 consumed 1–7 drinks/week, and 207 consumed >7 drinks week. Overall, subjects that consumed alcohol had higher cartilage and meniscus WORMS scores than subjects that consumed <1 drink/week. The results were significant when comparing cartilage MAX scores in subjects that consumed 1–7 drinks per week to those consumed <1 drink/week (coeff. = 0.22 (i.e. subjects that consumed 1–7 drinks per week had 0.22 greater cartilage MAX scores than those consumed <1 drink/week); p = 0.02; 95% CI = 0.04–0.40). When examining specific cartilage regions, subjects that consumed alcohol (both 1–7 drinks/per week and >7 drinks/week) had higher cartilage WORMS scores in the lateral femur and lateral tibia compared to those consumed <1 drink/week (p < 0.05, Table 2, Fig. 1). For the meniscus tissues, elevated WORMS scores were evident in the medial anterior region (p = 0.02) and all lateral regions (anterior, body, and posterior) when comparing subjects that consume alcohol and subjects that do not (p ≤ 0.03, Table 2). The results were unchanged after adjusting for baseline PASE scores, smoking status, or occupation (sensitivity analysis). There were no significant (p > 0.05) gender-specific or BMI-specific differences in the relationship between alcohol consumption and WORMS scores (sensitivity analysis).

3.3. Smoking and knee cartilage T2

Of the 2050 subjects with smoking history and cartilage T2 data available, 1125 did not smoke, 136 were current smokers, and 789 were former smokers. Current smokers had significantly higher cartilage T2 compared to non-smokers in the average of all cartilage regions (coeff. = 0.47; p = 0.02; 95% CI = 0.07–0.87) and in three of five individual cartilage regions: medial tibia (coeff. = 0.70; p = 0.007; 95% CI = 0.19–1.21), lateral femur (coeff. = 0.74; p = 0.004; 95% CI = 0.24–1.23), and the lateral tibia (coeff. = 0.58; p = 0.04; 95% CI = 0.03–1.12). In addition, former smokers had significantly elevated cartilage T2 in the medial tibia compared to non-smokers (coeff. = 0.33; p = 0.01; 95% CI = 0.07–0.59) (Table 3).

In addition, in current and former smokers, high pack years of smoking (≥15) were associated with more cartilage degeneration: subjects with ≥15 pack years of smoking had greater cartilage T2 in the medial tibia (coeff. = 0.40; p = 0.008; 95% CI = 0.11–0.71), lateral femur (coeff. = 0.46; p = 0.009; 95% CI = 0.09–0.67), and lateral tibia (coeff. = 0.37; p = 0.02; 95% CI = 0.05–0.69) than subjects that did not smoke. There was a non-significant trend for association in the average of all cartilage regions (coeff. = 0.20; p = 0.07; 95% CI = −0.02–0.44). When subdividing the analysis into current and former smokers, the results remained significant in current smokers; however, the results became not significant (p > 0.10) in former smokers. The results were unchanged after adjusting for baseline PASE scores, alcohol consumption, or occupation (sensitivity analysis). There were no statistically significant interactions between gender and smoking status in any joint

Table 1
Participant characteristics.

# of alcoholic drinks/week	None to <1 drink/week		1-7 drinks/week		>7 drinks/week		p (none vs. 1–7)	p (none vs. >7)
n = 2061	n = 1165		n = 642		n = 254			
Age (mean ± SD)	59.08	8.77	58.41	9.01	59.43	9.23	0.12	0.59
BMI (kg/m^2) (mean ± SD)	28.98	4.78	27.98	4.19	27.75	4.15	<**0.001**	<**0.001**
Gender (females %)	754	64.72%	330	51.40%	88	34.65%	<**0.001**	<**0.001**
Right Knee KL[a]								
0	528	45.32%	310	48.29%	126	49.61%	**0.04**	0.45
1	273	23.43%	167	26.01%	56	22.05%		
2	364	31.24%	165	25.70%	72	28.35%		
Race								
Other Non-white	20	1.72%	5	0.78%	4	1.57%	<**0.001**	<**0.001**
White or Caucasian	847	72.77%	582	90.65%	236	92.91%		
African American	283	24.31%	53	8.26%	14	5.51%		
Asian	14	1.20%	2	0.31%	0	0.00%		
Smoking status	Never		Current		Former		p (never vs. current)	p (never vs. former)
n = 2050	n = 1125		n = 136		n = 789			
Age (mean ± SD)	58.07	8.81	54.82	7.57	60.83	8.89	<**0.001**	<**0.001**
BMI (kg/m^2) (mean ± SD)	28.29	4.62	28.46	4.73	28.84	4.42	0.68	**0.01**
Gender (females %)	657	58.40%	74	54.41%	440	55.77%	0.97	**0.01**
Right Knee KL[a]								
0	545	48.44%	59	43.38%	355	44.99%	**0.046**	**0.048**
1	266	23.64%	24	17.65%	199	25.22%		
2	314	27.91%	53	38.97%	235	29.78%		
Race								
Other Non-white	15	1.33%	3	2.21%	10	1.27%	<**0.001**	**0.008**
White or Caucasian	915	81.41%	85	62.50%	653	82.76%		
African American	181	16.10%	47	23.56%	124	15.72%		
Asian	13	1.16%	1	0.74%	2	0.25%		

Bold signifies $p < 0.05$.
[a] KL = Kellgren Lawrence Score.

regions except the medial femur: For former smokers and non-smokers, we found a significant gender difference at the medial femur; medial femur T2 was 0.67 ms less in females than in males ($p = 0.01$) (sensitivity analysis), which suggests that former female smokers have less cartilage degeneration (T2) in the medial femur than males. There were no significant ($p > 0.05$) BMI-specific differences in the relationship between smoking and cartilage T2 (sensitivity analysis).

3.4. Smoking and knee joint morphology

There were no significant associations ($p > 0.05$) between smoking history (or pack years) and cartilage or meniscus WORMS scores in any region, except in the lateral anterior meniscus where former smokers had lower WORMS scores than non-smokers (coeff. = −0.09; $p = 0.03$; 95% CI = −0.17 to −0.007). The results were unchanged after adjusting for baseline PASE scores alcohol consumption, or occupation (sensitivity

Table 2
Cartilage MRI T2 values and cartilage WORMS scores in subjects with varied weekly alcohol consumption.

Outcome		Number of Alcoholic Drinks in a Typical Week				
		Group 1	Group 2	Group 3	p (1 vs. 2)	p (1 vs. 3)
		None to <1 drink/week (mean ± SE)	1–7 drinks/week (mean ± SE)	>7 drinks/week (mean ± SE)		
Cartilage T2 [ms]	n = 2061	n = 1165	n = 642	n = 254		
	Average T2	33.04 ± 0.06	33.17 ± 0.09	33.53 ± 0.14	0.29	**0.002**
	MFC T2	38.46 ± 0.08	38.62 ± 0.11	38.81 ± 0.18	0.28	0.08
	MT T2	30.28 ± 0.08	30.46 ± 0.11	31.19 ± 0.18	0.20	<**0.001**
	LFC T2	35.25 ± 0.08	35.36 ± 0.11	35.71 ± 0.18	0.42	**0.02**
	LT T2	28.71 ± 0.09	28.77 ± 0.12	29.16 ± 0.19	0.70	**0.04**
	PAT T2	32.50 ± 0.10	32.44 ± 0.14	32.80 ± 0.22	0.72	0.23
WORMS MAX Scores	n = 1767	n = 1001	n = 559	n = 207		
	Meniscus Max	1.26 ± 0.04	1.30 ± 0.06	1.30 ± 0.10	0.53	0.69
	Cartilage Max	2.35 ± 0.05	2.58 ± 0.07	2.42 ± 0.12	**0.02**	0.58
Regional Cartilage WORMS	MFC Cartilage	0.68 ± 0.04	0.62 ± 0.05	0.69 ± 0.08	0.32	0.87
	MT Cartilage	0.20 ± 0.02	0.22 ± 0.03	0.25 ± 0.05	0.72	0.46
	LFC Cartilage	0.36 ± 0.03	0.47 ± 0.04	0.55 ± 0.07	**0.03**	**0.01**
	LT Cartilage	0.60 ± 0.03	0.71 ± 0.05	0.76 ± 0.08	**0.05**	0.05
	PAT Cartilage	1.97 ± 0.06	2.16 ± 0.08	1.97 ± 0.12	0.05	0.96
Regional Meniscus WORMS	Medial Anterior	0.12 ± 0.02	0.10 ± 0.03	0.01 ± 0.04	0.41	**0.02**
	Medial Body	0.61 ± 0.04	0.53 ± 0.05	0.49 ± 0.09	0.24	0.25
	Medial Posterior	0.85 ± 0.04	0.84 ± 0.05	0.80 ± 0.09	0.83	0.54
	Lateral Anterior	0.26 ± 0.03	0.29 ± 0.04	0.41 ± 0.06	0.57	**0.03**
	Lateral Body	0.28 ± 0.03	0.40 ± 0.04	0.48 ± 0.06	**0.02**	**0.01**
	Lateral Posterior	0.32 ± 0.03	0.42 ± 0.04	0.41 ± 0.06	**0.03**	0.17

Abbreviations: MFC, medial femur; MT, medial tibia; LFC, lateral femur; LT, lateral tibia; PAT, patella.
Bold signifies $p < 0.05$.

Table 3
Cartilage T2 values in subjects that have never smoked, current smokers, and former smokers. Current smokers have higher T2 than non-smokers in the average of all regions and in three of five individual regions.

Outcome		Smoking Status for Cigarettes				
		Never (mean ± SE)	Current (mean ± SE)	Former (mean ± SE)	p (Never vs. Current)	p (Never vs. Former)
Cartilage T2 [ms]	n = 2050	n = 1125	n = 136	n = 789		
	Average T2	33.05 ± 0.06	33.53 ± 0.19	33.20 ± 0.08	**0.02**	0.17
	MFC T2	38.48 ± 0.08	38.80 ± 0.24	38.59 ± 0.10	0.21	0.39
	MT T2	30.26 ± 0.08	30.96 ± 0.25	30.59 ± 0.10	**0.007**	**0.01**
	LFC T2	35.21 ± 0.08	35.94 ± 0.24	35.43 ± 0.10	**0.004**	0.09
	LT T2	28.66 ± 0.09	29.24 ± 0.26	28.86 ± 0.11	**0.04**	0.15
	PAT T2	32.51 ± 0.11	32.43 ± 0.31	32.58 ± 0.13	0.80	0.67

Abbreviations: MFC, medial femur; MT, medial tibia; LFC, lateral femur; LT, lateral tibia; PAT, patella.
Bold signifies $p < 0.05$.

analysis). There were no significant ($p > 0.05$) gender-specific or BMI-specific differences in the relationship between smoking status and WORMS scores (sensitivity analysis).

4. Discussion

In this study, alcohol consumption was associated with worse cartilage and meniscus joint morphology (at least 1–7 drinks per week) and elevated cartilage T2 (>7 drinks/week). In addition, compared to non-smokers, current and former smokers had more degenerated cartilage biochemical composition, as evidenced by increased cartilage T2. Interestingly, higher pack years (≥15) of smoking was also associated with worse cartilage T2 outcomes.

The results of this study suggest that alcohol consumption is associated with knee joint degeneration. While various studies have shown no associations between alcohol and OA [25,26], others have reported that alcohol is damaging for the joint [8], potentially due to increased inflammation. Haugen et al. [8] reported a significant association between moderate alcohol consumption (1–3 alcoholic drinks per weak) and hand OA as measured by KL SUM score (OR = 1.55, 95% CI = 0.43–2.67); however, the association was not significant for higher alcohol intake. Similarly, in the present study, drinking alcohol 1–7 times per week was associated with greater cartilage and meniscus morphologic joint damage; however, the results for these morphologic features were not significant with alcohol intake at >7 drinks per week but were significant when studying cartilage T2. These results are not consistent with results from another study showing that moderate alcohol use is anti-inflammatory and chronic heavy consumption is proinflammatory [27]. However, since the present study had a greater number of subjects with moderate alcohol consumption compared to severe (n = 642 vs n = 254; ~60% fewer in the severe group), it is challenging to make conclusions about the relative differences in T2 and WORMS findings between the two groups. Nonetheless, in the present study, both moderate and higher alcohol consumption were associated with damaging effects to the joint tissue.

Various mechanisms through which alcohol consumption may impact joint tissue have been postulated, the primary being an increased inflammatory response. One study with an *in vivo* mouse model reported that chronic alcohol consumption has cellular toxic effects and not only increases proteoglycan loss, but also simulates cartilage inflammatory mediators in knee and shoulder joints [7]. The authors hypothesize that chronic alcohol consumption may be a risk factor for OA development as a result of an inflammatory response. Such inflammatory changes have been shown to predict radiographic OA progression in the finger joint [28], and cartilage loss in the knee [29], highlighting a role of inflammation in the pathogenesis of OA. Thus, alcohol consumption may adversely impact the pathogenesis of joint degeneration in OA, both directly by proteoglycan loss and indirectly through an inflammatory response.

Studies have reported varying results on the associations between smoking and OA, some reporting a protective effect [4,30] and others suggesting a damaging effects to the knee joint [31] and associations with incident knee pain [32]. Felson et al. published that smokers had a lower risk for OA than did nonsmokers (OR = 0.4, 95% CI 0.2–0.8) [30], while Ding et al. reported that smoking leads to knee cartilage loss (annual change in tibial cartilage volume (β = −2.20% for current smokers) in subjects with a family history of knee OA [31]. The present study suggests that current and former smokers have altered cartilage

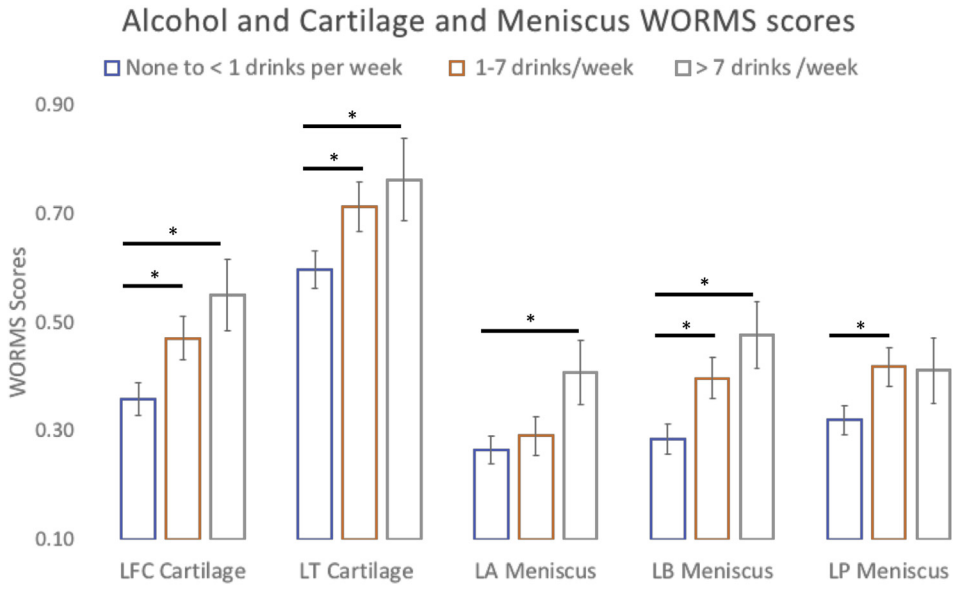

Fig. 1. Association between alcohol consumption and cartilage and meniscus WORMS scores in the lateral joint regions. Abbreviations: LFC: lateral femur, LT: lateral tibia, LA: lateral anterior; LB: lateral Body; LP Lateral Posterior Horn. The * in the graph represents $p < 0.05$.

biochemical composition, as evidenced by elevated cartilage T2 compared to non-smokers, thus supporting the hypothesis that smoking is damaging to cartilage tissue. The effects of smoking on OA are multifaceted, and the mechanisms through which smoking impacts joint degeneration are unclear. One proposed hypothesis is that smoking causes generalized inflammation [8] which is associated with joint degeneration. Overall, this study suggests that smoking is harmful for the knee cartilage; however further investigation is needed to establish the mechanisms underlying these damaging effects.

The primary limitation of this study is its observational, cross-sectional design and use of self-reported alcohol and smoking history. A randomized controlled design would be better-suited to account for confounding and other factors; thus, the presented results should be interpreted with caution. However, as the OAI dataset can only be analyzed retrospectively, we have performed statistical adjustment in order the address any potential biases due to confounding by indication. In addition to age, gender, BMI and race, we adjusted for education to account for potential differences in knowledge about the effects of alcohol and smoking on overall health. Data on alcohol consumption history (similar to that of smoking) was not available in the OAI database at baseline, thus we were limited in assessing only 12 month alcohol consumption data (prior to the visit). We analyzed the alcohol consumption data as categorical variables, as alcohol consumption categories were the data format provided in the OAI database. We grouped the last category of >7 drinks per week by combining 8–14 drinks/week, 15–21 drinks/week 22–27 drinks/week and 28 + drinks per week as there were few subjects in these categories with high alcohol consumption. For pack years, we subdivided the data into categories because the data was heavily skewed and using a log model would complicate the interpretation of the results. We did not perform additional analyses on types of alcohol because consumption of alcoholic drinks in general had a different output scale compared to that of individual types of beverages, and doing so may have led to multiple comparisons issues. Given the different output scales, we therefore could not systematically compare overall alcohol consumption with consumption of beer, wine and liquor separately, but we did an exploratory analysis and found similar trends. In addition, the categorization for pack years used in this study has been previously reported [16,17]. Since this is a cross-sectional study, it cannot be excluded that OA damage may have led to increased alcohol consumption or smoking. While it would be valuable to analyze the relationships between markers of inflammation such as CRP and the present findings, CRP was not included in the OAI database, and we were therefore unable to analyze these relationships. In addition, we only analyzed T2 measurements of cartilage composition as provided by the OAI, and it would be beneficial to study other quantitative cartilage assessments such as T1rho mapping. Despite these limitations, we believe that this study is valuable given its large sample size and use of advanced MR imaging outcome measures that include cartilage T2.

Overall, the results of this study showed that alcohol consumption and smoking were associated with worse cartilage biochemical composition. In addition, alcohol consumption was also negatively associated with cartilage and meniscus joint morphology.

5. Author contributions

Conception and design: GBJ, CEM, MCN, SF, FL, NEL, TML

Analysis and interpretation of the data: GBJ, CEM, MCN, SF, FL, NEL, TML

Drafting of the article: GBJ, CEM, MCN, NEL, TML

Critical revision of the article for important intellectual content: GBJ, CEM, MCN, SF, FL, NEL, TML

Statistical expertise: GBJ, CEM

Collection and assembly of data: GBJ, SF.

Final approval of the article: GBJ, CEM, MCN, SF, FL, NEL, TML.

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Declaration of Competing Interest

None.

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