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Brief Report

Excessive alcohol consumption and the risk of knee osteoarthritis: a prospective study from the Osteoarthritis Initiative

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SUMMARY

Objective: To examine the association of alcohol consumption with risk of incident knee osteoarthritis (OA) in a large prospective cohort study.
Design: In the Osteoarthritis Initiative, 2,846 participants aged 45–79 years and free from radiographic knee OA in at least one knee at baseline were followed up to 96 months. Information on baseline alcohol consumption was obtained from the Block Brief Food Frequency Questionnaire. Incident cases of radiographic knee OA (ROA) were defined as Kellgren–Lawrence grade changing from zero or one to $\geq$ two during the follow-up time. Incident symptomatic OA (SxOA) was defined as ROA with knee pain worsening. The Cox proportional hazards models were used to assess the independent association between alcohol consumption and risk of knee.
Results: During 96 months' follow-up, we identified 691 knees with incident ROA, and 496 knees with incident SxOA among 2,846 subjects. Compared to non-drinkers, excessive alcohol consumption was significantly associated with increased risk of ROA ($HR_{\geq 30\ g/d\ vs\ none} = 1.93$, 95% CI: 1.28–2.89) and SxOA ($HR_{\geq 30\ g/d\ vs\ none} = 1.61$, 95% CI: 1.04–2.48). Similar association was observed for liquor consumption ($HR_{liquor \geq 15\ g/d\ vs\ none} = 1.71$, 95% CI: 1.16–2.52 for ROA; $HR_{liquor \geq 15\ g/d\ vs\ none} = 1.59$, 95% CI: 1.04–2.39 for SxOA). Light to moderate alcohol consumption was not associated with knee OA risk.
Conclusion: Our results suggest that excessive alcohol drinking was associated with an increased risk of knee OA. Further studies are needed in other populations.

Introduction

Osteoarthritis (OA) is a degenerative disease characterized by slow and progressive deterioration of articular cartilage, intra-articular inflammation, subchondral bony sclerosis, and joint pain[1]. As a leading cause of disability, knee OA has become a major life and economic burden for the elderly population[2]. Knee OA is currently treated at severe stages with joint arthroplasties. Although knee OA is traditionally regarded as the elderly's disease, its onset starts much earlier than was previously thought.

Alcohol consumption has been associated with the risk of different chronic diseases, such as cancers[3] and cardiovascular disease[4]. Meanwhile, chronic alcohol exposure may increase susceptibility to the development and progression of OA in an animal model[5]. Several studies have examined the cross-sectional association of alcohol consumption with knee OA prevalence but had mixed findings[6,7]. Moreover, most previous studies incorporated alcohol consumption as a covariate other than the primary exposure[7]. In the present study, we firstly investigated the prospective association of alcohol consumption with risk of incident knee OA in a large cohort study.

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Method

Study population

The Osteoarthritis Initiative (OAI), a large multicenter, prospective cohort study, sampled 4,796 participants aged 45–79 years with established symptomatic knee OA or at risk for developing knee OA. The follow-up rate during the first 48 months was >90%. Each of the four clinical sites (Memorial Hospital of Rhode Island, The Ohio State University, University of Maryland/Johns Hopkins University, and the University of Pittsburgh) had IRB approval. All participants provided informed consent. Details of the OAI study protocol have been published elsewhere[8].

At baseline, we included participants with at least one knee free of radiographic OA (Kellgren and Lawrence [KL] grade of 0 or 1), as well as having plausible dietary data (daily total energy intake 800–4,200 kcal for men, 500–3,500 kcal for women). The excluded participants had similar baseline characteristics with the original sample. Ultimately, 2,846 participants (4,590 knees) were followed up to 12, 24, 36, 48, 72, and 96 months after the baseline visit, and more than 83% of them had at least 4 follow-up visits.

Assessment of alcohol consumption

We assessed dietary intake including alcohol consumption with the Block Brief Food Frequency Questionnaire (FFQ) at baseline. Participants provided their average consumption frequency for each alcoholic beverage (beer, wine, liquor) consumption in the past 12 months (coded as: never, a few times/year, once/month, 2–3 times/month, once/week, twice/week, 3–4 times/week, 5–6 times/week and every day) and their portion size over the past year. We specified standard portions as a glass, bottle, or can of beer; a glass of wine; and a shot of liquor. The estimated alcohol content of each beverage was 13.2 g per bottle or can of beer, 10.8 g per glass of wine, and 15.1 g per standard drink of liquor. Total alcohol intake (grams per day) was calculated as the sum of alcohol grams from these three beverages[9]. The validity of a Block FFQ was estimated using as the reference data the mean of three 4-day diet records collected over the year prior to the administration of the questionnaire. Correlations of nutrients intake between Block FFQ and diet records were reasonably high[10]. The reproducibility and validity of the assessment of alcohol intake using FFQ has been evaluated in previous studies, for example, among 173 participants who completed written one-week dietary records every three months for a year during which time they weighed or measured all their food and drinks. The correlation of alcohol intake on the questionnaire with alcohol intake on the dietary records was 0.9.

Assessment of knee OA onset

Participants received bilateral weight-bearing, fixed-flexion posterior-anterior radiographs of their knee joints at baseline, 12, 24, 36, 48, 72, and 96 months[8]. The central reader, blind to the sequence of subsequent X-rays, scored the images for KL grade. These readings have good read-reread consistency (weighted Kapa = 0.70–0.80). The KL grade records were publicly available (files: kXR_SQ_BU##_SAS [versions 0.6, 1.6, 3.5, 5.5, 6.3, 8.2, and 10.2])[8]. We defined the onset of radiographic knee OA as KL grade changing from 0 or one at baseline to ≥two during the follow-up period for a specific knee. The follow-up time was from baseline to knee OA onset, total knee replacement (TKR), death, loss to follow up or follow up ends (96 months), whichever came first. In addition, we also examined the association between alcohol consumption and risk of symptomatic knee OA (SxOA). The definition of incident SxOA was the combination of ROA onset and knee pain worsening (WOMAC knee pain score increase >14% between baseline and follow-up years) according to the previous study[11].

Information on covariates

At baseline, demographic and other socioeconomic characteristics, such as age, gender, race/ethnicity (characterized as African American, non-hispanic white, or “other”), education level (as high school or less, college, and above college), and the annual family income were acquired. Besides, we identified lifestyle and clinical factors at baseline including smoking, KL grades (0 or 1), depression, traumatic knee injury/surgery, PASE (Physical Activity Scale for the Elderly)[12], total energy intake, and body mass index (BMI).

Statistical analyses

Daily alcohol consumption was grouped into five groups (none, >0 to <5, 5 to <15, 15 to <30, and ≥30 g) based on previous studies[13]. Baseline characteristics were expressed as mean (SD) for continuous variables, and percentage was used for categorical variables according to levels of alcohol consumption (grams/day). In our sample, <1% of participants had missing values for BMI or PASE score. We replaced missing values with the sex-specific sample median. Data analyses were conducted with SAS 9.4 (SAS Institute, NC), and statistical significance was defined as $p < 0.05$.

The multivariable analysis was based on knee level. The event of interest was only observed in a time interval. We used interval-censored Cox proportional hazards models to examine the association between alcohol consumption and risk of knee OA. We used robust sandwich covariance estimates to account for the intraclass dependence between two knees within the same participant. Models were adjusted for baseline covariates, including age, sex, race, KL grades, injury/surgery, income, education, depression, smoking, PASE score, total energy intake, and BMI. Linearity assumption of the model was assessed for all continuous predictors using restricted cubic splines. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to measure the strength of associations. The proportional hazard assumption was evaluated by including an interaction term between alcohol consumption and logarithm of follow-up time and was met in all analyses. Interaction terms of age, sex, injury/surgery, and BMI with alcohol consumption were included in the model to assess potential effect-modifications. To address the potential confounding from knee OA in the contralateral knee, we included a sensitivity analysis where only persons with no radiographic OA in both knees were included. To adjust for other nutrients intake, we have also performed a sensitivity analyses that additionally adjust for some major nutrients, such as Vitamins A, D, E, K, B1, B2, B6, calcium, zinc, fiber, and total fat intake.

We performed an exploratory analysis to examine the associations of separate alcoholic beverages with knee OA risk, we developed a Cox proportional hazards model in which daily grams of alcohol intake from beer, wine, and liquor were mutually adjusted and included simultaneously in the model.

Results

In 2,846 individuals (4,590 knees) without knee OA at baseline, the mean age was 60.5 ± 9.2 years, 42.7% were male, 84.5% were white, and mean BMI was 27.9 ± 4.5 kg/m^2. Over 96-month follow-up period (mean follow-up time of 78.48 ± 27.25 months), 518 participants (691 knees) developed knee OA. Table I details the baseline characteristics by the increasing alcohol intake (none; >0 to <5 g/d, 5 to <15 g/d, 15 to <30 g/d, and ≥30 g/d). The range of daily alcohol intake was from 30.0 g/d to 97.4 g/d among 168 heavy

	Total alcohol intake (g/d)					
	Total $N = 2846$	None $N = 508$	<5 $N = 1,266$	5-<15 $N = 599$	15-<30 $N = 305$	≥30 $N = 168$
Age, mean ± SD years	60.48 (9.20)	61.12 (9.34)	60.39 (9.05)	60.61 (9.40)	58.98 (9.50)	58.70 (8.57)
Male, %	42.66	34.25	34.91	49.08	60.66	70.83
Race, %						
Non-Hispanic white	84.50	70.47	84.28	92.32	92.13	86.90
Non-Hispanic black	12.75	24.80	13.03	6.34	5.57	10.12
Other	2.74	4.72	2.69	1.34	2.30	2.98
Education, %						
≤ High School	13.42	22.05	13.82	9.02	7.87	10.12
College	45.08	47.24	45.58	43.41	43.41	47.62
> College	41.46	30.71	40.60	47.58	50.82	41.67
Missing	0.04	0.00	0.00	0.00	0.00	0.60
Family income, %						
≤ 25 k	11.14	20.28	11.06	6.51	6.89	8.33
25–50 k	22.63	27.76	25.28	18.70	15.08	14.88
50–100 k	35.73	30.71	36.26	37.06	37.05	39.88
> 100 k	24.91	13.19	22.83	30.72	38.03	31.55
Missing	5.59	8.07	4.58	7.01	2.95	5.36
Depressed, %	7.84	10.04	8.45	5.51	5.90	8.33
Smoking status, %						
Never	52.88	59.25	59.87	45.74	41.97	26.19
Current	6.39	5.51	4.42	6.01	9.84	19.05
Past	40.72	35.24	15.70	48.25	48.20	54.76
PASE, mean ± SD	164.25 (81.43)	155.71 (83.77)	164.07 (80.53)	166.93 (79.34)	172.76 (84.15)	167.96 (84.31)
BMI (kg/m^2), %						
< 25	28.13	26.77	27.25	30.72	29.84	26.19
25-30	41.06	36.24	40.60	45.08	41.31	42.86
≥ 30	30.77	36.81	32.07	24.21	28.85	39.05
Missing	0.04	0.00	0.08	0.00	0.00	0.00
KL grade = 1, %	36.05	37.80	36.89	34.56	34.43	32.74
Total calories, mean ± SD, 1,000 kcal	1.42 (0.53)	1.40 (0.55)	1.33 (0.50)	1.44 (0.50)	1.56 (0.55)	1.91 (0.64)

PASE: Physical Activity Scale for the Elderly; KL: Kellgren–Lawrence grades.

Table I

Osteoarthritis and Cartilage

Baseline characteristics of study participants according to alcohol consumption

drinkers. Compared to alcohol abstainers, individuals with higher alcohol consumption were more likely to be male, non-hispanic white, current smokers, more physical active, have higher education levels and household income, and have higher total energy intake.

The associations between alcohol consumption and the risk of knee OA were revealed in Table II. Excessive drinking (total alcohol intake ≥30 g/day) was significantly associated with an increased risk of ROA compared to no use (HR $\geq_{30\ g/d\ vs\ none}$ = 1.93, 95% CI: 1.28–2.89). No clear dose-response relationship was observed with increasing alcohol intake. Consistent results for SxOA incidence were observed. There was a significant association between excessive alcohol consumption and risk of SxOA (HR $\geq_{30\ g/d\ vs.\ none}$ = 1.61, 95% CI: 1.04–2.48). No effect modifications by age, sex, and BMI were observed. In the sensitivity analysis only including participants free of OA for both knees at baseline, the findings were consistent (results not shown). In addition, in sensitivity analyses that additionally adjust for some major nutrients, the results were consistent with the primary analysis (Supplementary Table 2).

In specific alcoholic beverage analysis, a relationship was observed for liquor intake (Supplementary Table 1). Participants who consumed ≥15 g/day alcohol from liquor had a higher risk of developing ROA (HR $\geq_{15\ g/d\ vs.\ none}$ = 1.71, 95% CI: 1.16–2.52) and for SxOA incidence (HR $_{liquor\geq 15\ g/d\ vs\ none}$ = 1.59, 95% CI: 1.04–2.39) when compared to non-liquor drinkers after adjusting for the consumption of other alcoholic beverages. No significant associations were observed for beer and wine.

Discussion

In this large longitudinal study with 96 months of follow-up, excessive alcohol consumption was associated with a significantly increased risk of knee OA. There was about 2-fold increase in risk of knee OA among participants who drank over 30 g/day alcohol (equivalent to 2 standard drinks per day) compared to non-drinkers. A similar result was observed for liquor.

Evidence from experiments *in vivo* showed that chronic alcohol exposure led to increased OA development or progression susceptibility[5]. Several human studies have examined cross-sectional association of alcohol consumption with prevalence of knee OA[6,7]. A cross-sectional study revealed that alcohol consumption was not associated with serum C-reactive protein (hsCRP) in patients with early ROA[7]. Another cross-sectional study from Korea among the 25,534 participants surveyed implying that radiological knee OA, rather than symptomatic knee OA, is associated with alcohol consumption[6]. Evidences form OAI data revealed that moderate alcohol consumption (1–7 drinks/week) was significantly associated with 2-fold higher odds of erosive hand OA[14]. However, to date, no studies have examined the prospective association of alcohol consumption with risk of developing knee OA in a large cohort study. Compared with the previous studies, here we observed a significant association for total alcohol intake and liquor spirit consumption to knee OA risk, where excessive drinkers had over double the risk of developing knee OA compared to non-drinkers, but not the light to moderate alcohol drinkers. Our study

	Cases, n	Person-years	HR (95% CI)
Radiographic knee OA			
Total alcohol (g/d)			
None	125	4503	1.00
0 < 5	318	12,704	1.02 (0.80, 1.31)
5-<15	140	6032	1.10 (0.83, 1.47)
15-<30	60	3077	1.00 (0.69, 1.46)
≥30	48	1,396	1.93 (1.28, 2.89)
Symptomatic knee OA			
Total alcohol (g/d)			
None	91	4526	1.00
0 < 5	229	12,749	0.95 (0.72,1.25)
5-<15	105	6067	1.04 (0.75,1.45)
15-<30	36	3097	0.74 (0.47,1.15)
≥30	35	1,416	1.61 (1.04,2.48)

* Adjusted for age, sex, race (African American, white, other), baseline Kellgren–Lawrence grades (0 or 1), injury/surgery (yes, no), income, education, depression, smoking status, Physical Activity Scale for the Elderly (PASE), BMI, and total energy intake (kcal/d).

Table II Osteoarthritis and Cartilage

Hazard ratios (HR) and 95% CI for incident knee osteoarthritis according to alcohol consumption ($n = 2,846$)*

provided preliminary evidence that excessive alcohol consumption may be a modifiable risk factor of knee OA, and may enable evaluation of prevailing recommendations of alcohol use, and thus have potential public health implications.

The underlying mechanism between alcohol drinking and the OA onset remains controversial, while plausible explanations have been proposed. An animal study demonstrated a pathologic effect of alcohol that chronic alcohol exposure increased the matrix proteoglycans loss in both the knee and the shoulder joints of mice and stimulated multiple inflammatory mediators involved in cartilage[5]. Also, the laboratory evidence showed that excessive alcohol consumption had an apparent U-shaped association with inflammatory mediator IL-6 levels and modulated various components of the immune system[15]. The observed association on knee OA risk might also be attributed to inflammatory mediator variations affected by chronic excessive alcohol consumption.

Our study's strengths include the prospective cohort design with the large number of incident knee OA cases, and repeated knee radiographs over 8-year. There are several limitations. First, with only baseline FFQ data, misclassification of alcohol consumption may result from imprecise self-reported data and time-varying drinking behavior. However, FFQ collected general consumption of alcohol in the past year, and using categorical alcohol consumption may reduce the influence of outliers in the analysis. Because few participants consumed beer, wine, or liquor of ≥30 g alcohol per day, we could not present the same quantitative categories of drinking for each type of alcohol as for total alcohol consumption. Our analyses for specific alcohol beverages were exploratory. Inevitably, due to the study's observational nature, patients were not randomly assigned to the drinking group. Although we controlled confounding factors plausibly associated with alcohol and OA, there is still the possibility of residual confounding. Finally, given the limited sample size our study participants from the OAI cohort may not be representative of general population in the USA and other countries. However, it is unlikely that the underlying biological mechanisms differ substantially in other populations.

In conclusion, we found that daily excessive alcohol consumption (alcohol consumption ≥30 g/day) was significantly associated with an increased risk of knee OA in a large prospective study. Further studies are warranted to replicate our findings.

Disclosures

The study sponsor was not involved in the study design, data analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributions

TL and CX were co-lead authors and were responsible for assembling OAI data and writing the first draft. CX and BL developed the conception and design of the study and analysis plan. CE, TMA, JD, and BL contributed to statistical expertise. BL obtained funding for this research project. CX, TL, CE, TMA, JD, and BL contributed to revising the article critically for intellectual content, data analysis, and interpretation. All authors contributed to the final approval of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Role of the funding source

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Supplementary data

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