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ORIGINAL ARTICLE

Milk Consumption and Progression of Medial Tibiofemoral Knee Osteoarthritis: Data From the Osteoarthritis Initiative

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Objective. **Milk consumption has long been recognized for its important role in bone health, but its role in the progression of knee osteoarthritis (OA) is unclear. We examined the prospective association of milk consumption with radiographic progression of knee OA.**

Methods. **In the Osteoarthritis Initiative, 2,148 participants (3,064 knees) with radiographic knee OA and dietary data at baseline were followed up to 12, 24, 36, and 48 months. Milk consumption was assessed with a Block Brief Food Frequency Questionnaire completed at baseline. To evaluate progression of OA, we used quantitative joint space width (JSW) between the medial femur and tibia of the knee based on plain radiographs. The multivariate linear models for repeated measures were used to test the independent association between milk intake and the decrease in JSW over time, while adjusting for baseline disease severity, body mass index, dietary factors, and other potential confounders.**

Results. **We observed a significant dose-response relationship between baseline milk intake and adjusted mean decrease of JSW in women ($P = 0.014$ for trend). With increasing levels of milk intake (none, ≤3, 4–6, and ≥7 glasses/week), the mean decreases of JSW were 0.38 mm, 0.29 mm, 0.29 mm, and 0.26 mm, respectively. In men, we observed no significant association between milk consumption and the decreases of JSW.**

Conclusion. **Our results suggest that frequent milk consumption may be associated with reduced OA progression in women. Replication of these novel findings in other prospective studies demonstrating the increase in milk consumption leads to delay in knee OA progression are needed.**

INTRODUCTION

Osteoarthritis (OA), a slowly progressing disease characterized by pain, deformity, and loss of function, is a major cause of physical disability in older people (1,2). Nearly 27 million people in the US have clinical OA (2). With the aging of the population, the health care burden from OA is expected to increase dramatically during the next few decades (3). However, little is known about the course of disability over time in patients with OA. Therefore, it is of great importance to identify modifiable risk factors for OA progression. Over the past few decades, many observational studies have examined risk factors for the incidence and progression of knee OA. Several risk factors (i.e., obesity, joint injury, and certain sports) have been found to be strongly associated with an increased risk for

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Significance & Innovations

- There are scarce data on the possible role of diet in osteoarthritis (OA) progression. We found frequent milk consumption may be a significant protective factor for OA progression in women.
- We used state-of-the-art quantitative measures of structural change from computerized technology.
- Consistent findings were found using both quantitative and semiquantitative measures of joint space narrowing.
- Our study had a prospective design and a large number of subjects with knee OA.

incident knee OA (4,5). However, findings on risk factors for OA progression have been inconclusive. There are scarce data on the possible role of dietary factors, although low intake of antioxidant vitamins (A, C, and E) and vitamin D may be associated with increased risk of progression of knee OA (6–8).

Milk is an excellent source of vitamins and minerals, dairy calcium, and protein. It has long been recognized for its important role in bone health (9–11). The 2010 Dietary Guidelines for Americans recommend that milk and other dairy products should be consumed daily as part of a balanced diet (12). Our interest in the role of milk consumption related to OA was triggered by 2 small studies: an earlier report by Colker et al (13) and a cross-sectional study in Turkey (14). Based on the protective role of bone health in OA progression and these previous preliminary findings, we hypothesized that milk consumption may prevent OA progression. We therefore examined the prospective association between milk consumption and progression of knee OA using publicly available data from the Osteoarthritis Initiative (OAI).

PATIENTS AND METHODS

Subjects. The OAI was launched in 2002 by the National Institutes of Health to develop resources for the identification of new biomarkers and treatment targets for knee OA. The objective of the OAI was to pool public and private scientific expertise and funding to collect, analyze, and make widely available the largest research resource to date of clinical data, radiologic information, and biospecimens from those at risk for or with knee OA. The OAI began enrolling people ages 45–79 years in 2004 and followed them annually for the development or progression of OA. The clinical sites involved were located in Baltimore, Maryland; Columbus, Ohio; Pittsburgh, Pennsylvania; and Pawtucket, Rhode Island. The OAI has been a longitudinal study of 4,796 subjects with either established knee OA or significant risk factors for the development of knee OA followed over an 8-year period. The followup rate was >90% over the first 48 months. The detailed OAI protocol can be found elsewhere (15).

For the current study, we included individuals with medial radiographic knee OA in at least 1 knee based on OAI central radiograph reading at baseline. We excluded knees with severe radiographic OA, defined as a baseline Kellgren/Lawrence (K/L) grade of 4 or those with primarily lateral joint space narrowing (JSN), and knees in which the difference of rim distance (from the tibial plateau to the tibial rim closest to the femoral condyle) between any followup visit and the baseline visit was ≥2 mm to minimize possible effects of knee positioning changes on measurement error of joint space width (JSW). The 2,148 participants (3,064 knees) with a K/L grade of 2 or 3 and having dietary data at baseline constituted the study sample (Figure 1). Followup at 12, 24, 36, and 48 months was included in this analysis.

Radiographic progression of OA. In the OAI, current radiographic assessment techniques on plain radiographs involved both quantitative and semiquantitative assessment of JSN. A quantitative approach was used to provide a precise measure of JSW in millimeters between the adjacent bones of the knee (16,17). Multiple JSWs were measured at fixed locations along the joint in the medial compartment, denoted as JSW(x), at intervals of 0.025 for x = 0.15–0.30. The reproducibility of this technique and the responsiveness to change have been documented elsewhere (16,18), including one study using OAI data that demonstrated a responsiveness that compared favorably to magnetic resonance imaging (18). We used medial JSW at x = 0.25 with the best responsiveness of change to quantify the progression of OA (18). We defined the repeated measures of the changes of JSW from baseline to 12, 24, 36, and 48 months as the outcome variable. To account for changes in beam angle and alignment at each visit, which introduces measurement error in serial JSW measurements, we also adjusted for changes of the beam angles and rim distances (from the tibial plateau to the tibial rim closest to the femoral condyle between followup visits and baseline). For the semiquantitative approach, the Osteoarthritis Research Society International (OARSI) grade

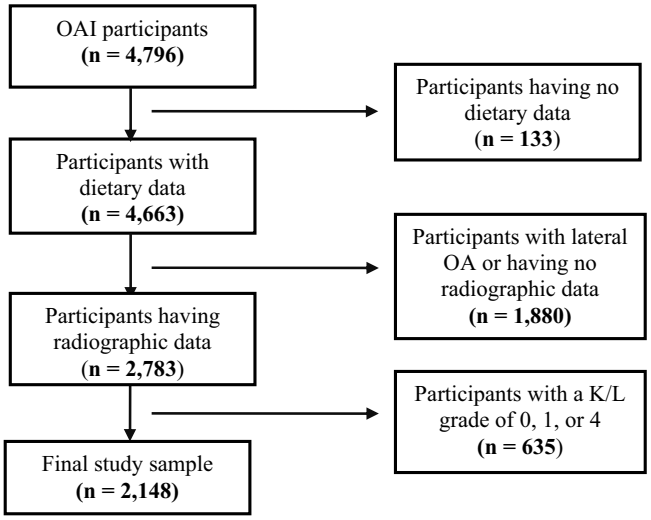

Figure 1. Osteoarthritis Initiative (OAI) participants included in the current study at baseline. OA = osteoarthritis; K/L = Kellgren/Lawrence.

Table 1. Baseline characteristics of participants with osteoarthritis according to milk intake*

	Total (n = 2,148)	Men (n = 888), glasses/week					Women (n = 1,260), glasses/week				
		None (n = 133)	≤3 (n = 342)	4–6 (n = 173)	≥7 (n = 240)	*P*	None (n = 238)	≤3 (n = 473)	4–6 (n = 246)	≥7 (n = 303)	*P*
Age, years	62.4 ± 9.0	62.5 ± 9.7	61.7 ± 8.9	63.3 ± 9.4	62.6 ± 9.5	0.372	61.3 ± 8.8	61.9 ± 8.4	62.8 ± 9.1	64.0 ± 8.5	0.001
Race, %						< 0.001					< 0.001
Non-Hispanic white	76.1	66.2	82.2	85.6	87.5		59.2	69.1	74.4	84.5	
Non-Hispanic black	20.7	27.8	14.9	11.6	10.0		37.8	29.6	19.9	11.2	
Other	3.2	6.0	2.9	2.9	2.5		2.9	1.3	5.7	4.3	
Education, %						0.700					0.128
High school or less	18.4	12.9	15.5	13.3	14.6		22.3	21.8	21.1	19.5	
College	45.9	44.7	42.4	44.5	40.4		44.5	47.4	47.2	53.5	
Above college	35.7	42.4	42.1	42.2	45.0		33.2	30.9	31.7	27.1	
Household income ($), %						0.562					0.252
<25,000	15.2	8.5	8.2	10.7	9.8		21.1	17.0	21.8	20.6	
25,000–49,999	27.9	25.6	23.1	19.1	20.9		27.2	35.3	27.1	34.8	
50,000–99,999	36.0	34.9	40.1	38.7	45.8		34.3	33.3	30.6	32.3	
≥100,000	21.0	31.0	28.6	31.6	23.6		17.4	14.5	20.5	12.4	
Married, %	65.1	79.7	79.2	80.9	78.3	0.821	49.8	55.2	56.3	57.4	0.098
Employed, %	58.2	66.9	64.0	60.1	62.5	0.346	58.0	55.4	52.4	52.5	0.158
Depressed, %	8.8	7.5	7.0	6.9	6.3	0.635	8.4	12.9	9.8	7.6	0.273
Smoker, %						0.010					< 0.001
Never	54.1	48.1	44.5	48.6	58.3		56.3	54.6	59.4	60.4	
Current	6.4	8.3	6.4	8.1	5.0		10.5	7.8	2.4	3.3	
Past	39.6	43.6	49.1	43.4	36.7		33.2	37.6	38.2	36.3	
Alcohol (gm/day), %						0.600					0.154
0–<5	53.9	54.1	54.1	51.5	55.4		70.2	77.4	71.5	76.2	
5–10	11.2	7.5	11.1	13.9	11.3		10.5	8.9	11.8	12.2	
>10	34.9	38.4	34.8	34.7	33.3		19.3	13.7	16.7	11.6	
PASE	157.5 ± 82.9	168.1 ± 81.3	173.7 ± 92.3	160.9 ± 75.9	186.6 ± 90.6	0.024	151.3 ± 82.6	141.7 ± 72.9	146.5 ± 75.0	146.7 ± 73.9	0.444
BMI (kg/m^2), %						0.048					0.657
<25	15.7	12.8	9.4	14.5	12.5		23.1	15.6	16.7	20.8	
25–29	38.4	41.4	43.9	52.6	48.3		31.5	33.0	27.3	36.3	
≥30	45.9	45.9	46.8	33.0	39.2		45.4	51.4	54.1	42.9	
Gout, %	6.1	5.4	7.2	7.7	3.9	0.335	1.3	2.8	0.8	2.4	0.870
K/L grade (index knee), %						0.527					0.101
2	56.9	57.9	58.2	54.9	55.8		73.5	68.3	63.8	67.3	
3	43.1	42.1	41.8	45.1	44.1		26.5	31.7	36.2	32.7	
NSAID use, %†	22.0	15.4	24.4	19.2	19.2	0.828	18.0	23.6	27.4	22.1	0.262
Dietary/supplement											
Vitamin A, 1,000 IU/day	14.0 ± 10.0	12.2 ± 9.0	12.7 ± 11.0	13.0 ± 7.8	14.7 ± 10.7	0.012	13.1 ± 11.6	13.5 ± 9.6	14.7 ± 9.1	17.2 ± 9.5	< 0.001
Vitamin C, mg/day	393.8 ± 443.4	298.5 ± 393.3	361.2 ± 444.3	411.9 ± 424.5	373.7 ± 356.7	0.102	387.2 ± 453.6	389.1 ± 448.5	428.3 ± 495.8	461.0 ± 466.4	0.026
Vitamin D, IU/day	364.4 ± 247.0	277.1 ± 214.0	298.5 ± 228.6	367.2 ± 243.8	450.6 ± 248.1	< 0.001	358.0 ± 250.2	357.1 ± 229.1	396.1 ± 231.0	557.3 ± 258.6	< 0.001
Vitamin E, mg/day‡	115.2 ± 168.7	66.3 ± 106.7	107.6 ± 205.8	111.0 ± 135.7	96.2 ± 132.8	0.324	114.2 ± 164.2	122.3 ± 166.4	126.6 ± 171.3	142.9 ± 185.5	0.046

(continued)

Table 1. (Cont'd)

	Total (n = 2,148)	Men (n = 888), glasses/week					Women (n = 1,260), glasses/week				
		None (n = 133)	≤3 (n = 342)	4–6 (n = 173)	≥7 (n = 240)	*P*	None (n = 238)	≤3 (n = 473)	4–6 (n = 246)	≥7 (n = 303)	*P*
Dietary calcium, mg/day	673.0 ± 352.7	508.2 ± 224.7	517.4 ± 210.9	722.5 ± 243.9	1,089 ± 371.5	< 0.001	437.7 ± 200.1	487.3 ± 196.0	676.2 ± 222.9	1,028 ± 364.2	< 0.001
Supplement calcium, mg/day	468.1 ± 472.9	205.5 ± 348.2	238.0 ± 367.3	263.0 ± 376.9	251.1 ± 361.0	0.252	617.8 ± 493.1	585.5 ± 470.8	633.6 ± 466.9	695.5 ± 470.2	0.010
Total fat, gm/day	55.4 ± 27.5	60.0 ± 29.4	57.1 ± 23.5	62.4 ± 30.3	72.0 ± 31.7	< 0.001	47.6 ± 26.1	48.4 ± 24.4	52.4 ± 23.9	53.3 ± 27.3	0.001
Total calories, kcal/day	1,422 ± 588	1,523 ± 638	1,418 ± 526	1,579 ± 591	1,906 ± 650	< 0.001	1,187 ± 532	1,210 ± 507	1,344 ± 480	1,487 ± 550	< 0.001
Total grain, servings/day	3.2 ± 1.8	3.5 ± 2.0	3.2 ± 1.8	3.9 ± 2.1	4.3 ± 2.0	< 0.001	2.4 ± 1.6	2.7 ± 1.5	3.1 ± 1.4	3.4 ± 1.7	< 0.001
Vegetable/fruit, servings/day	4.8 ± 2.8	4.4 ± 2.5	4.4 ± 3.0	4.4 ± 2.2	5.1 ± 3.2	0.010	4.5 ± 2.8	4.6 ± 2.6	5.2 ± 2.6	5.7 ± 2.9	< 0.001
Meat, servings/day	1.4 ± 1.2	2.1 ± 1.2	2.0 ± 1.1	2.0 ± 1.2	2.2 ± 1.2	0.227	1.6 ± 1.0	1.6 ± 1.0	1.7 ± 0.9	1.7 ± 0.9	0.138
Fish, servings/day	1.8 ± 1.1	1.3 ± 1.3	1.3 ± 1.1	1.4 ± 1.0	1.4 ± 1.3	0.210	1.4 ± 1.2	1.3 ± 1.2	1.4 ± 1.1	1.6 ± 1.2	0.011
Soft drink, glass/week	1.7 ± 4.2	2.1 ± 4.0	1.9 ± 3.9	1.3 ± 2.7	2.8 ± 5.5	0.106	2.1 ± 6.0	1.7 ± 4.2	1.2 ± 3.1	1.1 ± 2.7	0.002

* Values are the mean ± SD unless indicated otherwise. PASE = Physical Activity Scale for the Elderly; BMI = body mass index; K/L = Kellgren/Lawrence; NSAID = nonsteroidal antiinflammatory drug.
† NSAID (including aspirin, ibuprofen, etc.) use for joint pain or arthritis in the past 30 days.
‡ α-tocopherol equivalents.

(where 0 = no JSN, 1 = definite JSN, and 3 = severe JSN) has been widely used to measure progression of OA (19). For these analyses, we used the publically available quantitative JSW measurements (version 12/08/2011, online at http://oai.epi-ucsf.org) and the semiquantitative JSN readings (kXR_SQ_BU, version 11/07/2011, online at http://oai.epi-ucsf.org).

Assessment of milk consumption. Usual dietary intakes of foods and nutrients, including milk consumption, were assessed at baseline with a Block Brief Food Frequency Questionnaire (FFQ), including 60 food items in the OAI (20). The participants were asked how often they drank milk (any kind) in the past 12 months (coded as never, a few times per year, once per month, 2–3 times per month, once per week, twice per week, 3–4 times per week, 5–6 times per week, and every day) and how many glasses they drank each time. In this analysis, we grouped milk consumption into 4 categories, including none, 2 middle categories, and the highest category (i.e., none, ≤3, 4–6, and ≥7 glasses/week). This Brief FFQ has been validated against three 4-day records in a group of middle-aged women and against two 7-day records in a group of older men. The absolute value of macronutrients estimated by the reduced questionnaire was slightly lower than food record estimates, but most micronutrients were not underestimated (20,21).

Information on covariates. Baseline demographic and socioeconomic factors included race/ethnicity, age, sex, marital status, education level, employment status, annual income, and social support. Individuals were classified as African American, white, or other racial/ethnic group based on self-report. Education level was categorized as high school or less, college, and above college. General clinical parameters include current smoking, depression defined as a Center for Epidemiologic Studies Depression Scale (20 items) score >16 (22), history of traumatic knee injury and knee surgery, self-reported gout, baseline disease severity (K/L grade), alcohol use, body mass index (BMI), physical activity, weight change, use of nonsteroidal antiinflammatory drugs, intake of other dairy products (yogurt, cheese), and other dietary factors (quartiles; total calories, fat, grain, vegetable and fruit, meat, fish, soft drink, and dietary and supplement vitamin A, C, D, and E). BMI, defined as the individual's body mass divided by the square of his or her height (kg/m^2), was categorized into <25.0, 25.0–29.9, and ≥30 kg/m^2 using World Health Organization criteria. Physical activity was assessed using the Physical Activity Scale for the Elderly, an established questionnaire for measuring physical activity in older individuals that has also been validated in younger subjects (23,24). Alcohol consumption was assessed at baseline, including separate items for beer, wine, and liquor in the OAI (none or <5 gm/day, 5–10 gm/day, >10 gm/day). We also adjusted for changes of the beam angles and rim distances (from the tibial plateau to the tibial rim closest to the femoral condyle between followup visits and baseline) that indicated knee positioning consistency for radiographic examination.

Statistical analysis. The primary analysis was to assess the influence of milk consumption on the decrease in JSW over the study period. The primary outcomes were repeated measures of the JSW decreases from baseline to 12, 24, 36, and 48 months. The milk intake was analyzed as a categorical variable (none, ≤3, 4–6, and ≥7 glasses/week) as well as a continuous variable. The initial analyses were unadjusted comparisons of the decreases of JSW among levels of milk intake at each time point using analysis of variance. Sex-specific differences in results were noted; therefore, separate multivariate models for repeated measures by men and women were used to test the independent association between milk intake and the decrease in JSW over time, while adjusting for baseline disease severity, BMI, dietary factors, and other potential confounding factors described above. Because of the hierarchical structure of the data (3 levels: participant → knee → measures over time), we used linear mixed models to account for within-subject correlation and the correlation of repeated measures in knee level. To assess the possible differential effect of milk intake across the followup time points, we included the milk by followup time interaction in the model. The final covariance models were evaluated using Akaike's information criterion and the Bayesian information criterion.

In secondary analyses, we evaluated the associations between consumption of other dairy products (yogurt, cheese) and JSW changes after controlling for milk consumption and other covariates using separate models. Furthermore, we developed additional models to evaluate whether or not dietary and supplemental calcium intake mediated the association of milk consumption with JSW change. We also included interactions between milk intake and important covariates (race, smoking, obesity, physical activity, K/L grade, and vitamin D and calcium intake) in the model to evaluate potential effect modifications.

To test the robustness of our results, we also used the first full grade increase of the OARSI JSN grade as the end point for OA progression. We developed a Cox proportional hazards model to assess the independent association between milk intake and the JSN score change after controlling for other covariates. For each participant, the time of followup was calculated from the baseline date to the date of the first increase of JSN grade, death, or the end of the study, whichever came first. The discrete likelihood method was used for ties of the failure times in the models. We used a robust sandwich covariance estimate to account for the intraclass dependence within individual patients (25). Participants who indicated no milk intake in the past year were chosen as the reference group for all analyses. Adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) were used to evaluate the strength of the associations. The proportional hazard assumption was tested based on the smoothed plots of the scaled Schoenfeld residuals (26). Data analyses were performed using SAS, version 9.2.

RESULTS

In this study, we examined 2,148 participants from the OAI with a total of 3,064 eligible knees. The baseline characteristics of the participants are shown in Table 1 according to levels of milk intake in men and women. Compared to no milk intake, frequent milk drinkers were more likely to be non-Hispanic white and nonsmokers. In women, frequent milk drinkers were also more likely to be older and had more severe OA at baseline. Over the study period, 16.8% of participants were lost to followup. We did not observe significant differences in baseline characteristics between participants lost and not lost to followup.

Results of multivariable analyses in men and women are shown in Table 2. We observed a significant dose-response relationship between milk intake and adjusted mean decreases of JSW in women ($P = 0.014$ for trend) after controlling for the covariates listed above. With increasing levels of milk intake, the mean decreases of JSW were 0.38 mm, 0.29 mm, 0.29 mm, and 0.26 mm, respectively. When we included milk intake as a continuous variable, a 10-glass increase in milk intake per week was associated with a decrease of 0.06 mm JSW change over 48 months ($P = 0.020$). By contrast, in men, we did not observe a significant inverse association of milk intake with JSW change. We did not observe the significant interactions between milk consumption and followup time in men and women ($P = 0.372$ in women and 0.735 in men for interaction). Additional adjustment for alcohol consumption and a history of gout in the above models did not change the results. Inconsistent with milk consumption, ≥7 servings/week of cheese consumption was associated with increased JSW

Table 2. Adjusted mean decrease (SE) of joint space width (JSW) during followup by milk intake

Glasses/ week	Men				Women			
	N	ΔJSW, mm*	*P*	*P* for trend	N	ΔJSW, mm*	*P*	*P* for trend
None	133	0.32 (0.05)	Referent		238	0.38 (0.04)	Referent	
≤3	342	0.35 (0.04)	0.611		473	0.29 (0.03)	0.013	
4–6	173	0.41 (0.04)	0.130		246	0.29 (0.03)	0.025	
≥7	240	0.33 (0.04)	0.820	0.618	303	0.26 (0.03)	0.006	0.014

* Adjusted for age, race, education, marital status, household income, employment, depression, knee injury and knee surgery, smoking, physical activity, body mass index, use of nonsteroidal antiinflammatory drugs, baseline Kellgren/Lawrence grade, weight change, changes of rim distance and beam angle, other dairy products (yogurt, cheese), and intake of other dietary factors (total calories, fat, grain, vegetable and fruit, meat, fish, soft drink, and dietary and supplement vitamin A, C, D, and E).

Table 3. Association of milk intake with rate of osteoarthritis progression measured by the decrease of joint space narrowing score (Osteoarthritis Research Society International grades 0–3)

Glasses/ week	Men			Women		
	N	HR (95% CI)*	*P* for trend	N	HR (95% CI)*	*P* for trend
None	133	Referent		238	Referent	
≤3	342	0.77 (0.53–1.13)		473	0.67 (0.50–0.91)	
4–6	173	0.92 (0.60–1.40)		246	0.71 (0.50–1.00)	
≥7	240	0.61 (0.39–0.94)	0.075	303	0.56 (0.38–0.81)	0.008

* Hazard ratios (HRs) and 95% confident intervals (95% CIs) adjusted for age, race, education, marital status, household income, smoking, physical activity, employment, body mass index, depression, use of nonsteroidal antiinflammatory drugs, knee injury and knee surgery, baseline Kellgren/Lawrence grade, other dairy products (yogurt, cheese), and intake of other dietary factors (total calories, fat, grain, vegetable and fruit, meat, fish, soft drink, and dietary and supplement vitamin A, C, D, and E).

decrease compared to no cheese intake in women (P = 0.003), while combined dairy products and yogurt consumption were not associated with JSW change after adjusting for milk consumption and other covariates (data not shown).

In sensitivity analysis, we evaluated the association between calcium intake and JSW change. Consistent with milk consumption, the highest quartile of dietary calcium intake was associated with a reduced decrease of JSW compared to the lowest quartile in women (adjusted means 0.33 mm versus 0.24 mm; P = 0.025), but not in men. After including dietary calcium intake in the model, the effect of milk consumption was attenuated by 25% (the difference of JSW change between ≥7 glasses/week and no milk intake decreased from 0.12 mm to 0.09 mm). In addition, we did not observe any significant interactions between milk intake and race, smoking, obesity, physical activity, K/L grade, and vitamin D intake in men and women

Table 3 shows the multivariable-adjusted HRs of OA progression evaluated by time to the first increase of the semiquantitative OARSI score. Consistent with JSW analysis, after adjustment for covariates, we found a significant inverse association between milk intake and the risk of OA progression in women. With increasing levels of milk intake, the HRs were 0.67 (95% CI 0.50−0.91), 0.71 (95% CI 0.50−1.00), and 0.56 (95% CI 0.38−0.81), respectively, compared to no milk consumption (P = 0.008 for trend). In men, we found that only ≥7 glasses/week of milk intake reduced the risk of OA progression.

DISCUSSION

In this 48-month followup study of people with radiographic knee OA, we found an inverse dose-response relationship of milk consumption with structural progression of knee OA measured by both quantitative and semiquantitative JSN independent of other potential covariates in women, but in men, only ≥7 glasses/week of milk consumption was associated with reduced progression of knee OA.

Knee OA progression has been thought to involve multiple mechanisms besides cartilage loss, including changes in bone composition and shape, as well as proprioreception (27–29), which might be subject to the influences of macro- and micronutrients in the diet. McAlindon et al reported that a higher consumption of antioxidant micronutrients, especially vitamin C, might decrease cartilage loss and OA progression (8), and low vitamin D intake and low serum vitamin D levels might increase the risk for progression of knee OA (7). However, few studies have investigated the association of milk consumption and progression of OA. In a cross-sectional study using a face-to-face interview, the frequency of symptomatic knee OA was significantly lower in daily milk consumers (14). A 6-week, double-blind, placebo-controlled study investigated the effects of a nutritional supplement beverage containing milk-based micronutrients and fortified with vitamins and minerals on pain symptoms and activity in adults with OA. The authors found that daily consumption of a nutritional beverage containing milk-based micronutrients, vitamins, and minerals was beneficial in alleviating symptoms and dysfunction in subjects with OA (13).

Milk contains many of the nutrients that are required daily, including calcium, phosphorus, and protein, and is voluntarily fortified with vitamin D in the US. Milk components take part in metabolism in several ways: by providing essential amino acids, vitamins, minerals, and fatty acids, or by affecting absorption of nutrients (30). Several clinical trials of vitamin D and calcium supplementation showed that milk can reduce bone loss and lower the risk of bone fractures (31,32). Our results indicated that milk consumption may reduce knee OA progression partially through elevated dietary calcium intake. Nevertheless, the biologic mechanism for an effect of milk consumption on the radiographic progression of OA remains unclear.

In our analysis, we adjusted for major dietary factors, such as total calories, total fat, total grain, fish, meat, vegetable, and fruit consumption intake, and vitamin A, C, D, and E dietary intake and supplementation. It is possible that vitamins, minerals, soluble fiber, and phytochemicals in healthy beverages may have beneficial effects confounding with potential effects of milk intake. Moreover, we also adjusted for intake of other dairy products (yogurt, cheese), and the association remained. Milk intake (mainly low-fat or fat-free milk) may also be a marker of a general healthy diet, which may improve OA progression. Inconsistent with milk, our results indicated that cheese consumption may increase knee OA progression. The high

saturated fat acids contained in cheese may be associated with the pathogenesis of OA (33,34). A recent study reported that increased consumption of saturated fatty acids was associated with an increased incidence of bone marrow lesions, which may predict knee OA progression (33).

In addition, we found the effect of milk in OA progression differs in men and women. Sex differences have been noted in the prevalence, incidence, and severity of OA for many years (35). Faber and colleagues found cartilage thickness of the distal femur to be less in women than in men (36). Other evidence suggested a protective effect of exogenous estrogen on cartilage and bone turnover (37). In the current study, women had a much lower intake of dietary calcium than men (mean 715 mg/day in men and 647 mg/day in women; $P < 0.001$). If dietary calcium is a possible mediation factor to link between milk consumption and knee OA progression, women may be more sensitive for the effect of calcium intake through milk than men. However, the sex differences in the relationship of milk consumption with OA progression are not completely understood.

The strengths of this study include the prospective design, the large number of subjects with knee OA, and the state-of-the-art quantitative measures of structural change from sophisticated image processing technology. The quantitative software–based assessment provided a more precise measure of JSW in millimeters and permitted the assessor to document appreciable change in JSW in the tibiofemoral compartment (16,17). We also used the semiquantitative OARSI score as the measure of JSN to confirm our findings. In addition, we excluded knees in which the difference of rim distance between followup and baseline visits was $\geq$2 mm and adjusted for changes of rim distance and beam angle in the multivariate models to minimize the possible measurement error of radiographic data.

Because of the observational nature of the study, patients were not randomly assigned to milk intake groups. We cannot prove that the observed associations are causal because residual confounding could theoretically affect the observed associations. However, we controlled for potential confounding by most known risk factors that are plausibly associated with diet and OA progression. We did not control for any treatments, but no treatments have been proven to reduce radiographic OA progression, related to milk consumption. With only baseline dietary data, imprecise measurement potentially could have influenced our observed associations. However, random errors in dietary assessment measures would more likely account for a lack of association, but not the reverse. Although the quantitative approach provided a precise measure of JSW, there is no clinical criterion in JSW change available to evaluate the severity of knee OA progression. In addition, detailed information for the consumption of each type of milk (high-fat, low-fat, and fat-free milk) was not available. However, more than 90% of the OAI participants only drank fat-free or low-fat milk. High-fat milk may be associated with an increased risk of obesity, cardiovascular disease, or other chronic conditions. Therefore, the preferable effect of low-fat or fat-free milk on OA progression may be stronger than our current findings.

In conclusion, our study suggested that frequent milk intake may be associated with reduced OA progression in women. Replication of these novel findings in other prospective studies demonstrating the increase in milk consumption leads to delay in OA progression is needed to test this hypothesis.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Lu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lu, McAlindon, Lapane, Eaton.

Acquisition of data. Lu, McAlindon, Eaton.

Analysis and interpretation of data. Lu, Driban, Duryea, McAlindon, Lapane, Eaton.

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