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Soft Drink Intake and Progression of Radiographic Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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ARTICLE SUMMARY

Article focus

- To examine the prospective association of soft drink consumption with radiographic progression of knee osteoarthritis
- To examine gender differences in effect of soft drink on OA progression

Key messages

- There is a significant dose-response relationship between soft drink intake and radiographic knee osteoarthritis progression in men, but not in women.
- A stronger relationship was found in non-obese men.

Strengths and limitations of this study

- The prospective design, large number of patients with knee OA, and the state-of-the-art quantitative measures of structural change from sophisticated image processing technology.
- Consistent findings using both semi-quantitative and quantitative measures of OA progression.
- Residual confounding may exist for this observational study.
- Soft drink consumption was based on self-report.

ABSTRACT

Objectives: We examine the prospective association of soft drink consumption with radiographic progression of knee OA.

Design: Prospective cohort study.

Setting: This study used data from the Osteoarthritis Initiative (OAI).

Participants: In OAI, 2,149 participants (3,066 knees) with radiographic knee OA and having dietary data at baseline were followed up to 12, 24, 36 and 48 months.

Measures: The soft drink consumption was assessed with a Block Brief Food Frequency Questionnaire completed at baseline. To evaluate knee OA progression, we used quantitative joint space width based on plain radiographs. The multivariate linear models for repeated measures were used to test the independent association between soft drink intake and the change in JSW over time, while adjusting for body mass index and other potential confounding factors.

Results: In stratified analyses by gender, we observed a significant dose-response relationship between baseline soft drink intake and adjusted mean change of JSW in men. With increasing levels of soft drink intake (none, ≤1, 2-4, and ≥5 times/week), the mean decreases of JSW were 0.31mm, 0.39mm, 0.34mm and 0.60mm respectively. When we further stratified by obesity, a stronger dose-response relationship was found in non-obese men. In obese men, only the highest soft drink level (≥5 times/week) was associated with increased change in JSW compared to no use. In women, no significant association was observed.

Conclusions: Our results suggest that frequent consumption of soft drinks may be associated with increased OA progression in men. Replication of these novel findings in other studies demonstrating the reduction in soft drink consumption leads to delay in OA progression is needed.

Key words soft drink consumption, osteoarthritis progression, diet.

Introduction

Osteoarthritis (OA), a slowly progressing disease characterized by pain, deformity, and loss of function, is the major cause physical disability in older people.[1] Nearly 27 million have clinical osteoarthritis in the United States.[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 OA progression over time in patients with OA. It is, therefore, 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 incident knee OA. [4, 5] However, findings on risk factors for OA progression have been inconclusive. Except for the level of serum hyaluronic acid and generalized OA, no other risk factor has been consistently associated with the risk of OA progression. [6 7]

Soft drink consumption has increased rapidly across the globe in recent decades.[8] Sugar sweetened beverages intake is a significant contributor to weight-gain and has been associated with increased risk of obesity, type 2 diabetes, cardiovascular disease and poor bone health. [9, 10 11] Soft drinks may displace essential nutrients and contribute to overall poorer diets, [12] while low consumption of vitamin D and anti-oxidant micronutrients may increase the risk for progression of knee OA. [13 14] To our knowledge, no study has linked soft drink consumption to OA progression. We examined the prospective association between consumption of soft drinks and progression of knee OA using data from the Osteoarthritis Initiative (OAI).

Methods

Subjects

OAI was launched in 2002 by the National Institute of Health (NIH) 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 aged 45 through 79 years in 2004 and followed them annually for the development or progression of OA. The clinical sites involved were located in Baltimore, MD; Columbus, OH; Pittsburgh, PA; and Pawtucket, RI. 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.[15] The follow-up rate was >90% over the first 48 months. The detailed OAI protocol can be found elsewhere. [16]

For the current study, we included individuals with medial radiographic knee OA in at least one knee at baseline. We excluded knees with severe radiographic OA defined as the baseline Kellgren and Lawrence (KL) grade of 4 or those with primarily lateral joint space narrowing (JSN), and knees in which the difference of rim distance (from tibial plateau to tibial rim closest to femoral condyle) between follow-up and baseline visits were ≥2mm to minimize possible measurement error of radiographic data. The 2,149 participants (3,066 knees) with KL grade of 2 or 3 and having dietary data at baseline constituted the study sample. Follow-up at 12, 24, 36 and 48 months were included in this analysis.

Radiographic progression of OA

In OAI, current radiographic assessment techniques on plain radiographs involved both semi-quantitative and quantitative assessment of JSN. For the semi-quantitative approach, the Osteoarthritis Research Society International grade (OARSI grade: 0=no JSN, 1=definite JSN to 3=severe JSN) has been widely used to measure progression of OA.[17] For these analyses, we used the publically available semi-quantitative JSN readings (kXR_SQ_BU, version 11/07/2011, http://oai.epi-ucsf.org). Recently, a quantitative approach has been used to provide a precise measure of joint space width (JSW) in millimeters between the adjacent bones of the knee. [18, 19] Multiple JSWs were measured at fixed locations along the joint in medial compartment, denoted as JSW(x), at 0.025 intervals for x = 0.15 - 0.30. The reproducibility of this technique and the responsiveness to change have been documented elsewhere,[18 20] including one study using OAI data which demonstrated a responsiveness that compared favorably to magnetic

resonance imaging (MRI).[20] We used medial JSW at x=0.25 with the best responsiveness of change to quantify the progression of OA. [20] We define the repeated measures of the decreases of JSW from baseline to 12, 24, 36 and 48 months as the outcome variable.

Assessment of soft drink consumption

Usual dietary intakes of foods and nutrients including soft drink consumption were assessed at baseline with a Block Brief Food Frequency Questionnaire (FFQ) including 60 food items in OAI.[21] The participants were asked how often they had consumed regular soft drinks/bottled drinks (not diet drinks) 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). In this analysis, we grouped these into 4 categories: none, ≤1, 2-4, and ≥5 times/week. Similar questionnaires were used to collect the frequencies of other beverages intake, such as, milk, juice, tea and coffee, etc. This brief FFQ has been validated against three four-day records in a group of middle-aged women, and against two seven-day records in a group of older men. The absolute value of macronutrients estimated by the reduced questionnaire was a slightly lower than food-record estimates, but most micronutrients were not underestimated. [21, 22]

Information on covariates

Baseline demographic and socioeconomic factors include 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, history of traumatic knee injury and knee surgery, body mass index (BMI), physical activity, weight change, milk and juice intake, total energy intake and baseline disease severity (KL grade). Physical activity was assessed by using the Physical Activity Scale for the Elderly (PASE), an established questionnaire for measuring physical activity in older individuals that has also been validated in younger subjects.[23, 24] In addition, we also adjusted for changes of the beam angles and rim distances (from tibial plateau

to tibial rim closest to femoral condyle between follow-up visits and baseline) which indicate knee-positioning consistency for x-ray exam.

Statistical analysis

First we performed exploratory analyses of all variables of interest including the exposure (frequency of soft drink intake), radiographic structural measures (K-L grade, JSN score and JSW) and potential confounders described above. Descriptive statistics such as the minimum, maximum, median and mean for each continuous variable and frequency table for each categorical variable was used to summarize the data as well as detect outliers, data entry mistakes, and missing values.

The primary analysis was to assess the influence of soft drink consumption on the change 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 respectively. The initial analyses were unadjusted comparisons of the changes of JSW over time among levels of soft drink intake using Analysis of Variance (ANOVA) and Multivariate Analysis of Variance (MANOVA). Then separate multivariate models for repeated measures by men and women were used to test the independent association between soft drink intake and the decrease in JSW over time, while adjusting for BMI, physical activity, baseline disease severity and potential confounding factors described above. Due to the hierarchical structure of the data (each subject has 2 knees over multiple time points), we used general linear mixed models (GLMM) to account for within subject correlation. The final covariance models were evaluated using Akaike's information criterion (AIC) and Bayesian information criterion (BIC). BMI has been an important factor related to both soft drink intake and OA progression.[9, 25] To examine the possible effect modifications, we further performed stratified analyses by obesity (BMI≥30.0 kg/m^2) and also adjusted BMI within each category to reduce the possible residual confounding bias. In addition, the association of soft drink consumption with JSW change may also be mediated through BMI. The indirect effect of BMI was evaluated using Sobel test [26]

In addition, we also used the first increase of the OARSI JSN grade as the endpoint. We developed a Cox proportional hazards model to assess independent association between soft drink intake and the JSN score change after controlling for other covariates. For each participant, the time of follow-up was calculated from the baseline date to the date of the first increase of JSN grade, death, or 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. [27] Participants who indicated no soft drink consumption in the past year were chosen as the reference group for all analyses. Adjusted hazard ratios with 95% confidence intervals 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. Data analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

Results

In this study, we studied 2,149 participants from OAI having a total of 3,066 eligible knees. Participants were representative of all categories of soft drink intake at baseline (none, n=687; ≤1 times/week, n=976; 2-4 times/week, n=285; ≥5 times/week, n=201). Baseline characteristics of participants are shown in Table 1 according to levels of soft drink intake. Compared to no soft drink use, high soft drink users were more likely to be men, between 45 and 54 years, not married, not employed, current smokers, and have lower education and household income and higher BMI.

Results of multivariable analyses are shown in Table 2 in men and women. We observed a significant dose-response relationship in men between soft drink intake and adjusted mean decreases of JSW in men (p trend<0.001) after controlling for age, race, education, marital status, household income, employment, BMI, physical activity, follow-up time, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline KL grade, weight change, the changes of rim distance and beam angle. With increasing levels of soft drink intake (none, ≤1, 2-4, and ≥5 times/week), the mean decreases of JSW were 0.31mm, 0.39mm,

0.34mm and 0.60mm respectively. When we stratified by obesity, a stronger dose-response relationship was found (decreases of JSW were 0.24mm, 0.38mm, 0.32mm, 0.62mm respectively) in non-obese men. In obese men, only the highest soft drink level (≥5 times/week) was associated with increased JSW change compared to no use. The effect of soft drink consumption was different between men and women (p for interaction =0.003). No significant association was observed In women. Table 3 shows the multivariable adjusted hazard ratios (HR) of OA progression evaluated by time to the first increase of semi- quantitative OARSI score. Consistent with JSW analyses, we found that the increasing soft drink intake was associated with the increasing rate of OA progression in men but not in women. Compared to no soft drink intake, the HR for ≤1, 2-4, and ≥5 times/week were 1.56 (95% CI, 1.13-2.16), 1.55 (95% CI, 1.02-2.35) and 2.05 (95% CI, 1.32-3.19) respectively in men (p trend=0.002). When we stratified by obesity, a dose-response relationship was observed in both non-obese and obese men. The hazard ratios were 2.30 (95% CI, 1.22-4.34) and 1.90 (95% CI, 1.03-3.52) respectively with the soft drink intake ≥5 times/week compared to no intake. However, no significant association was found in women. In addition, our mediation analysis indicated a modest (3.2%) indirect effect through BMI (p for Sobel test=0.098)

Discussion

In this 48-month follow-up study of people with radiographic knee OA, we found a positive association with a significant dose-response relationship between soft drink consumption and structural progression of knee OA measured by both semi-quantitative and quantitative JSN independent of BMI and other potential risk factors in men, but not in women.

Knee OA progression has been thought to involve multiple mechanisms besides cartilage loss including changes in bone composition, shape, as well as proprioreception,[28, 29] which might be subject to the influences of macro and micronutrients in the diet. McAlindon et al. reported that a higher consumption of anti-oxidant micronutrients, especially vitamin C, might decrease cartilage loss and OA progression, [14] and low vitamin D intake and low serum vitamin D levels might increase the risk for progression of knee OA. [13] However, no study investigated

the association of soft drink consumption and progression of OA. Sugar sweetened beverages intake is a significant contributor to weight-gain and has been associated with increased risk of obesity, type 2 diabetes, cardiovascular disease and poor bone health. [10 11, 30] Nevertheless, the biologic mechanism for soft drinks in the progression of OA remains unclear. One explanation for the observed findings is that soft drinks may substitute for healthy diet. Soft drink consumption may be associated with decreased intakes of protein, milk and dairy products, fruit juice, fruit and a variety of vitamins and nutrients. [12, 31] One study reported a negative association between soft drink consumption and an overall healthy eating index.[32] However, in our analysis, the observed effects remained after adjustment for milk and juice intake supports the likelihood that this is not only due to displacement of other healthy beverages in the diet. We considered the extent to which the sugar in soft drinks leads to OA progression. To further evaluate this, we evaluated the relation between fruit juice consumption and OA progression. Fruit juice consumption was not associated with OA progression in our study (results are not shown). It is possible that vitamins, minerals, soluble fiber, and phytochemicals in fruit juices may have beneficial effects counterbalancing potential adverse effects of sugars.

Previous studies demonstrated that weight gain and obesity may increase risk of joint space loss, suggestive of cartilage loss, as visualized on radiographs, [7, 33, 34] though these findings are not universally reported. Nevertheless, our mediation analysis indicated that the indirect effect through BMI was modest and the association between soft drinks and OA progression remained after adjustment for BMI, weight change and total energy intake suggestive of independent effects of soft drinks. Soft drinks may contain phosphoric acid, which was shown to interfere with calcium absorption and to contribute to imbalances that lead to additional loss of calcium.[35] It has also been suggested that the high fructose corn syrup used to sweeten carbonated beverages may negatively affect bone.[36] Long-term effects of soft drinks on osteoarthritis have not been studied in experimental settings so far, and further research is warranted.

Sex differences have been noted in the prevalence, incidence, and severity of OA for many years. [37] Faber and colleagues found cartilage thickness of the distal femur to be less in women than in men. [38] Other evidences suggested a protective effect of exogenous estrogen on cartilage and bone turnover. [39] However the gender differences in the relationship of soft drink consumption with OA progression are not understood. We found a stronger association between soft drink consumption and JSW change in non-obese men than in obese men. One possible reason is that the effect of soft drink consumption may not be strong enough to provide additional effect beyond obesity.

The strengths of this study include the prospective design, large number of patients with knee OA, and the state-of-the-art quantitative measures of structural change from sophisticated image processing technology. The quantitative software based assessment provides a more precise measure of JSW in millimeters and permits the assessor to document appreciable change in JSW in the tibiofemoral compartment [18, 19] In contrast, the semi-quantitative approach, for example, the KL grading or the OARSI score, has limitations that lead to insensitivity to changes in status.[40] The consistent findings from both quantitative and semi-quantitative measures of OA progression increase the reliablity of the study. In addition, we excluded knees in which the difference of rim distance between follow-up and baseline visits ≥2mm 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 soft drink 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 soft drink consumption and changes in these variables over time. Imprecise dietary measurement could potentially have influenced our observed associations. However, random errors in dietary assessment measures might have accounted for a lack of association but not the reverse.

In conclusion, our study suggested that frequent consumption of sweetened soft drinks may be associated with increased OA progression in men. Replication of these novel findings in other prospective studies demonstrating the reduction in soft drink consumption leads to delay in OA progression are needed to test this hypothesis.

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Contributors All authors listed above have made substantial contributions to the conception and design of the study, or data analysis and interpretation of data, drafting the article and final approval.

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Conflict of interest None

Ethics approval OAI was approved by the Institutional Review Board, the University of California, San Francisco (UCSF), and its affiliates. UCSF holds Office of Human Research Protections Federalwide Assurance number FWA00000068.

Data sharing statement: There are no additional data available.

Table 1. Baseline characteristics of participants with radiographic knee OA according to levels of soft drink intake

Variables	Total N=2,149	Soft drink intake, times/week				
		None n=687	≤1 n=976	2-4 n=285	≥5 n=201	P value
Age in years, mean (SD)	62.4(9.0)	63.9 (8.9)	62.7 (8.8)	61.6 (9.1)	58.0 (8.0)	<0.001
Men, %	41.32	29.40	44.98	49.12	53.23	<0.001
Race/ethnicity, %						
Non-hispanic White	76.04	83.70	77.36	62.46	62.69	
Non-hispanic Black	20.75	12.95	19.36	34.74	34.33	
Others	3.21	3.35	3.28	2.81	2.99	<0.001
Education, %						
≤high school	18.44	14.12	17.21	27.72	26.00	
College	45.90	46.00	46.31	44.56	45.50	
Above college	35.66	39.88	36.48	27.72	28.50	<0.001
Household Income, %						
<25k	15.17	11.51	15.04	18.42	23.56	
25k-49k	27.85	27.06	27.77	31.20	26.18	
50k-99k	36.00	37.17	36.99	34.96	28.80	
100k+	20.98	24.26	20.20	15.41	21.47	<0.001
Married, %	65.02	64.77	67.90	59.65	59.50	0.075
Employed, %	58.21	53.31	57.89	58.60	69.15	0.002
Smoke, %						
Never	54.07	51.53	53.79	59.65	56.22	
Current	6.38	4.51	5.43	7.02	16.42	
Past	39.55	43.96	40.78	33.33	27.36	<0.001
PASE, mean (SD)[a]	157 (82)	147 (77)	161 (82)	165 (90)	163 (83)	0.001
BMI (kg/m^2), %						

<25	15.68	20.23	16.09	9.82	6.47	
25-29	38.39	36.83	39.34	40.70	35.82	
30+	45.93	42.94	44,57	49.47	57.71	<0.001
K-L grade [c] (index knee), %						
2	63.47	65.07	63.52	57.89	65.67	
3	36.53	34.93	36.48	42.11	34.33	<0.001
Milk, times/week						
None	17.19	22.27	12.62	17.31	21.89	
≤1	30.52	28.09	32.41	29.33	31.34	
2-4	21.39	20.52	22.87	20.49	18.41	
≥5	30.89	29.11	32.10	32.86	28.36	0.657

a. Physical Activity Scale for the Elderly (PASE) score

b. Body mass index

c. Kellgren-Lawrence Scale

Table 2. Adjusted mean (SE) decreases of Joint Space Width (JSW) by soft drink intake*

	Soft drinks, times / week	Men				Women			
		N	ΔJSW, mm*	P value	P trend	N	ΔJSW, mm*	P value	P trend
Overall	None	202	0.31(0.03)	Referent		485	0.32(0.02)	Referent	
	≤1	439	0.39(0.02)	0.055		537	0.33(0.02)	0.626	
	2-4	140	0.34(0.04)	0.540		145	0.36(0.04)	0.331	
	≥5	107	0.60(0.05)	<0.001	<0.001	94	0.30(0.05)	0.751	0.756
Non-obese	None	113	0.24(0.04)	Referent		279	0.30(0.03)	Referent	
	≤1	266	0.38(0.03)	0.010		277	0.30(0.03)	0.946	
	2-4	85	0.32(0.05)	0.236		60	0.35(0.06)	0.395	
	≥5	53	0.62(0.07)	<0.001	<0.001	32	0.30(0.07)	0.955	0.681
Obese	None	89	0.40(0.05)	Referent		206	0.34(0.03)	Referent	
	≤1	173	0.41(0.03)	0.993		260	0.37(0.03)	0.471	
	2-4	55	0.38(0.06)	0.749		85	0.38(0.05)	0.518	
	≥5	54	0.57(0.06)	0.032	0.064	62	0.33(0.06)	0.900	0.829

* Adjusted for age, race, education, marital status, household income, employment, follow-up time, BMI, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline K-L grade and JSW, weight change, the changes of rim distance and beam angle.

Table 3. Soft drink consumption and rate of OA progression measured by the change of medial compartment Joint space narrowing score (JSN, OARSI grades 0-3)

	Soft drinks times / week	Men			Women		
		N	Hazard Ratio (95% CI)	P trend	N	Hazard Ratio (95% CI)	P trend
Overall	None	202	Referent		485	Referent	
	≤1	439	1.56(1.13,2.16)		537	0.80(0.62,1.02)	
	2-4	140	1.55(1.02,2.35)		145	1.09(0.77,1.54)	
	≥5	107	2.05(1.32,3.19)	0.002	94	0.81(0.52,1.26)	0.539
Non-obese	None	113	Referent		279	Referent	
	≤1	266	1.66(1.05,2.63)		277	0.71(0.49,1.03)	
	2-4	85	1.45(0.80,2.60)		60	1.03(0.59,1.80)	
	≥5	53	2.30(1.22,4.34)	0.025	32	0.86(0.41,1.84)	0.559
Obese	None	89	Referent		206	Referent	
	≤1	173	1.58(0.99,2.52)		260	0.88(0.63,1.25)	
	2-4	55	1.77(0.96,3.28)		85	1.17(0.74,1.84)	
	≥5	54	1.90(1.03,3.52)	0.033	62	0.87(0.50,1.52)	0.965

*Adjusted for age, race, education, marital status, household income, employment, follow-up time, BMI, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline K-L grade.

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Our manuscript has compliance to all items of the STROBE Statement for cohort study.

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a

		meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Soft Drink Intake and Progression of Radiographic Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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ARTICLE SUMMARY

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Article focus

- To examine the prospective association of soft drink consumption with radiographic progression of knee osteoarthritis
- To examine gender differences in effect of soft drink on OA progression

Key messages

- There is a significant dose-response relationship between soft drink intake and radiographic knee osteoarthritis progression in men, but not in women.
- A stronger relationship was found in non-obese men.

Strengths and limitations of this study

- The prospective design, large number of patients with knee OA, and the quantitative measures of structural change from sophisticated image processing technology.
- Consistent findings using both semi-quantitative and quantitative measures of OA progression.
- Residual confounding may exist for this observational study.
- Soft drink consumption was based on self-report.

ABSTRACT

Objectives: We examine the prospective association of soft drink consumption with radiographic progression of knee OA.

Design: Prospective cohort study.

Setting: This study used data from the Osteoarthritis Initiative (OAI).

Participants: In OAI, 2,149 participants with radiographic knee OA and having dietary data at baseline were followed up to 12, 24, 36 and 48 months.

Measures: The soft drink consumption was assessed with a Block Brief Food Frequency Questionnaire completed at baseline. To evaluate knee OA progression, we used quantitative medial tibiofemoral joint space width (JSW) based on plain radiographs. The multivariate linear models for repeated measures were used to test the independent association between soft drink intake and the change in JSW over time, while adjusting for body mass index and other potential confounding factors.

Results: In stratified analyses by gender, we observed a significant dose-response relationship between baseline soft drink intake and adjusted mean change of JSW in men. With increasing levels of soft drink intake (none, ≤1, 2-4, and ≥5 times/week), the mean decreases of JSW were 0.31mm, 0.39mm, 0.34mm and 0.60mm respectively. When we further stratified by obesity, a stronger dose-response relationship was found in non-obese men. In obese men, only the highest soft drink level (≥5 times/week) was associated with increased change in JSW compared to no use. In women, no significant association was observed.

Conclusions: Our results suggest that frequent consumption of soft drinks may be associated with increased OA progression in men. Replication of these novel findings in other studies demonstrating the reduction in soft drink consumption leads to delay in OA progression is needed.

Key words soft drink consumption, osteoarthritis progression, diet.

Introduction

Osteoarthritis (OA), a slowly progressing disease characterized by pain, deformity, and loss of function, is the major cause physical disability in older people.[1] Nearly 27 million have clinical osteoarthritis in the United States.[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 OA progression over time in patients with OA. It is, therefore, 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 incident knee OA. [4, 5] However, findings on risk factors for OA progression have been inconclusive. Except for the level of serum hyaluronic acid and generalized OA, no other risk factor has been consistently associated with the risk of OA progression. [6 7]

Soft drink consumption has increased rapidly across the globe in recent decades.[8] Sugar sweetened beverages intake is a significant contributor to weight-gain and has been associated with increased risk of obesity, type 2 diabetes, cardiovascular disease and poor bone health. [9, 10 11] Soft drinks may displace essential nutrients and contribute to overall poorer diets, [12] while low consumption of vitamin D and anti-oxidant micronutrients may increase the risk for progression of knee OA. [13 14] To our knowledge, no study has linked soft drink consumption to OA progression. We examined the prospective association between consumption of soft drinks and progression of knee OA using data from the Osteoarthritis Initiative (OAI).

Methods

Subjects

OAI was launched in 2002 by the National Institute of Health (NIH) 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 aged 45 through 79 years in 2004 and followed them annually for the development or progression of OA. The clinical sites involved were located in Baltimore, MD; Columbus, OH; Pittsburgh, PA; and Pawtucket, RI. 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.[15] The follow-up rate was >90% over the first 48 months. The detailed OAI protocol can be found elsewhere. [16]

For the current study, we included individuals with medial radiographic knee OA in at least one knee at baseline. We excluded knees with severe radiographic OA defined as the baseline Kellgren and Lawrence (KL) grade of 4 or those with primarily lateral joint space narrowing (JSN), and knees in which the difference of rim distance (from tibial plateau to tibial rim closest to femoral condyle) between follow-up and baseline visits were ≥2mm to minimize possible measurement error of radiographic data. The 2,149 participants (3,066 knees) with KL grade of 2 or 3 and having dietary data at baseline constituted the study sample. Follow-up at 12, 24, 36 and 48 months were included in this analysis. The overall loss to follow up rate was 16.8% over the study period.

Radiographic progression of OA

In OAI, current radiographic assessment techniques on plain radiographs involved both semi-quantitative and quantitative assessment of JSN. For the semi-quantitative approach, the Osteoarthritis Research Society International grade (OARSI grade: 0=no JSN, 1=definite JSN to 3=severe JSN) has been widely used to measure progression of OA.[17] For these analyses, we used the publically available semi-quantitative JSN readings (kXR_SQ_BU, version 11/07/2011, http://oai.epi-ucsf.org). Recently, a quantitative approach has been used to provide a precise measure of joint space width (JSW) in millimeters between the adjacent bones of the knee. [18, 19] Multiple JSWs were measured at fixed locations along the joint in medial compartment, denoted as JSW(x), at

0.025 intervals for x = 0.15 - 0.30. The reproducibility of this technique and the responsiveness to change have been documented elsewhere,[18 20] including one study using OAI data which demonstrated a responsiveness that compared favorably to magnetic resonance imaging (MRI).[20] We used medial JSW at x=0.25 with the best responsiveness of change to quantify the progression of OA. [20] We define the repeated measures of the decreases of JSW from baseline to 12, 24, 36 and 48 months as the outcome variable.

Assessment of soft drink consumption

Usual dietary intakes of foods and nutrients including soft drink consumption were assessed at baseline with a Block Brief Food Frequency Questionnaire (FFQ) including 60 food items in OAI.[21] The participants were asked how often they had consumed regular soft drinks/bottled drinks (not diet drinks) 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). Based on previous studies [9,10,11], we grouped these into 4 categories: none, ≤1, 2-4, and ≥5 times/week. Similar questionnaires were used to collect the frequencies of other beverages intake, such as, milk, juice, tea and coffee, etc. This brief FFQ has been validated against three four-day records in a group of middle-aged women, and against two seven-day records in a group of older men. The absolute value of macronutrients estimated by the reduced questionnaire was a slightly lower than food-record estimates, but most micronutrients were not underestimated. [21, 22]

Information on covariates

Baseline demographic and socioeconomic factors include 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, alcohol consumption, history of

traumatic knee injury and knee surgery, self-reported gout, body mass index (BMI), physical activity, weight change, milk and juice intake, total energy intake and baseline disease severity (KL grade). Physical activity was assessed by using the Physical Activity Scale for the Elderly (PASE), an established questionnaire for measuring physical activity in older individuals that has also been validated in younger subjects.[23, 24] Alcohol consumption (pure alcohol in grams /day) was assessed at baseline including separate items for beer, wine, and liquor in OAI. In addition, we also adjusted for changes of the beam angles and rim distances (from tibial plateau to tibial rim closest to femoral condyle between follow-up visits and baseline) which indicate knee-positioning consistency for x-ray exam.

Statistical analysis

First we performed exploratory analyses of all variables of interest including the exposure (frequency of soft drink intake), radiographic structural measures (K-L grade, JSN score and JSW) and potential confounders described above. Descriptive statistics such as the minimum, maximum, median and mean for each continuous variable and frequency table for each categorical variable was used to summarize the data as well as detect outliers, data entry mistakes, and missing values.

The primary analysis was to assess the influence of soft drink consumption on the change 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 respectively. The initial analyses were unadjusted comparisons of the changes of JSW over time among levels of soft drink intake using Analysis of Variance (ANOVA) and Multivariate Analysis of Variance (MANOVA). Then separate multivariate models for repeated measures by men and women were used to test the independent association between soft drink intake and the decrease in JSW over time, while adjusting for BMI, physical activity, baseline disease severity and potential confounding factors described above. Due to the hierarchical structure of the data (each subject has 2 knees over multiple time points), we used

general linear mixed models (GLMM) to account for within subject correlation. The final covariance models were evaluated using Akaike's information criterion (AIC) and Bayesian information criterion (BIC). BMI has been an important factor related to both soft drink intake and OA progression.[9, 25] To examine the possible effect modifications, we further performed stratified analyses by obesity (BMI≥30.0 kg/m^2) and also adjusted BMI within each category to reduce the possible residual confounding bias. In addition, the association of soft drink consumption with JSW change may also be mediated through BMI. The indirect effect of BMI was evaluated using Sobel test [26]

In addition, we also used the first increase of the OARSI JSN grade as the endpoint. We developed a Cox proportional hazards model to assess independent association between soft drink intake and the JSN score change after controlling for other covariates. For each participant, the time of follow-up was calculated from the baseline date to the date of the first increase of JSN grade, death, or 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. [27] Participants who indicated no soft drink consumption in the past year were chosen as the reference group for all analyses. Adjusted hazard ratios with 95% confidence intervals 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. Data analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

Results

In this study, we studied 2,149 participants from OAI having a total of 3,066 eligible knees. All categories of soft drink intake were represented in participants at baseline (none, n=687; ≤1 times/week, n=976; 2-4 times/week, n=285; ≥5 times/week, n=201). Baseline characteristics of participants are shown in Table 1 according to levels of soft drink intake. Compared to no soft drink use, high soft drink users were more likely to be men, between

45 and 54 years, not married, not employed, current smokers, and have lower education and household income and higher BMI.

Results of multivariable analyses are shown in Table 2 in men and women. We observed a significant dose-response relationship in men between soft drink intake and adjusted mean decreases of JSW in men (p trend<0.001) after controlling for age, race, education, marital status, household income, employment, BMI, physical activity, follow-up time, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline KL grade, weight change, the changes of rim distance and beam angle. With increasing levels of soft drink intake (none, ≤1, 2-4, and ≥5 times/week), the mean decreases of JSW were 0.31mm, 0.39mm, 0.34mm and 0.60mm respectively. When we stratified by obesity, a stronger dose-response relationship was found (decreases of JSW were 0.24mm, 0.38mm, 0.32mm, 0.62mm respectively) in non-obese men. In obese men, only the highest soft drink level (≥5 times/week) was associated with increased JSW change compared to no use. The effect of soft drink consumption was different between men and women (p for interaction =0.003). No significant association was observed In women. Table 3 shows the multivariable adjusted hazard ratios (HR) of OA progression evaluated by time to the first increase of semi- quantitative OARSI score. Consistent with JSW analyses, we found that the increasing soft drink intake was associated with the increasing rate of OA progression in men but not in women. Compared to no soft drink intake, the HR for ≤1, 2-4, and ≥5 times/week were 1.56 (95% CI, 1.13-2.16), 1.55 (95% CI, 1.02-2.35) and 2.05 (95% CI, 1.32-3.19) respectively in men (p trend=0.002). When we stratified by obesity, a dose-response relationship was observed in both non-obese and obese men. The hazard ratios were 2.30 (95% CI, 1.22-4.34) and 1.90 (95% CI, 1.03-3.52) respectively with the soft drink intake ≥5 times/week compared to no intake. However, no significant association was found in women. In addition, our mediation analysis indicated a modest (3.2%) indirect effect through BMI (p for Sobel test=0.098). In

sensitivity analyses, additional adjustment for alcohol consumption and a history of gout in the above models did not change the results.

Discussion

In this 48-month follow-up study of people with radiographic knee OA, we found a positive association with a significant dose-response relationship between soft drink consumption and structural progression of knee OA measured by both semi-quantitative and quantitative JSN independent of BMI and other potential risk factors in men, but not in women.

Knee OA progression has been thought to involve multiple mechanisms besides cartilage loss including changes in bone composition, shape, as well as proprioreception,[28, 29] which might be subject to the influences of macro and micronutrients in the diet. McAlindon et al. reported that a higher consumption of anti-oxidant micronutrients, especially vitamin C, might decrease cartilage loss and OA progression, [14] and low vitamin D intake and low serum vitamin D levels might increase the risk for progression of knee OA. [13] However, no study investigated the association of soft drink consumption and progression of OA. Sugar sweetened beverages intake is a significant contributor to weight-gain and has been associated with increased risk of obesity, type 2 diabetes, cardiovascular disease and poor bone health. [10, 11, 30] Nevertheless, the biologic mechanism for soft drinks in the progression of OA remains unclear. One explanation for the observed findings is that soft drinks may substitute for healthy diet. Soft drink consumption may be associated with decreased intakes of protein, milk and dairy products, fruit juice, fruit and a variety of vitamins and nutrients. [12, 31] One study reported a negative association between soft drink consumption and an overall healthy eating index.[32] However, in our analysis, the observed effects remained after adjustment for milk and juice intake supports the likelihood that this is not only due to displacement of other healthy beverages in the diet. We considered the extent to which the sugar in soft drinks leads to OA progression. To further evaluate this, we evaluated the relation between fruit

juice consumption and OA progression. Fruit juice consumption was not associated with OA progression in our study (results are not shown). It is possible that vitamins, minerals, soluble fiber, and phytochemicals in fruit juices may have beneficial effects counterbalancing potential adverse effects of sugars.

Previous studies demonstrated that weight gain and obesity may increase risk of joint space loss, suggestive of cartilage loss, as visualized on radiographs, [7, 33, 34] though these findings are not universally reported. Nevertheless, our mediation analysis indicated that the indirect effect through BMI was modest and the association between soft drinks and OA progression remained after adjustment for BMI, weight change and total energy intake suggestive of independent effects of soft drinks. Soft drinks may contain phosphoric acid, which was shown to interfere with calcium absorption and to contribute to imbalances that lead to additional loss of calcium.[35] It has also been suggested that the high fructose corn syrup used to sweeten carbonated beverages may negatively affect bone.[36] Long-term effects of soft drinks on osteoarthritis have not been studied in experimental settings so far, and further research is warranted.

Sex differences have been noted in the prevalence, incidence, and severity of OA for many years. [37] Faber and colleagues found cartilage thickness of the distal femur to be less in women than in men. [38] Other evidences suggested a protective effect of exogenous estrogen on cartilage and bone turnover. [39] However the gender differences in the relationship of soft drink consumption with OA progression are not understood. We found a stronger association between soft drink consumption and JSW change in non-obese men than in obese men. One possible reason is that the effect of soft drink consumption may not be strong enough to provide additional effect beyond obesity.

The strengths of this study include the prospective design, large number of patients with knee OA, and the state-of-the-art quantitative measures of structural change from sophisticated image processing technology. The quantitative software based assessment provides a more precise measure of JSW in millimeters and permits the assessor to

document appreciable change in JSW in the tibiofemoral compartment [18, 19] In contrast, the semi-quantitative approach, for example, the KL grading or the OARSI score, has limitations that lead to insensitivity to changes in status.[40] The consistent findings from both quantitative and semi- quantitative measures of OA progression increase the reliablity of the study. In addition, we excluded knees in which the difference of rim distance between follow-up and baseline visits ≥2mm 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 soft drink 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 soft drink consumption and changes in these variables over time. Imprecise dietary measurement could potentially have influenced our observed associations. However, random errors in dietary assessment measures might have accounted for a lack of association but not the reverse.

In conclusion, our study suggested that frequent consumption of sweetened soft drinks may be associated with increased OA progression in men. Replication of these novel findings in other prospective studies demonstrating the reduction in soft drink consumption leads to delay in OA progression are needed to test this hypothesis.

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Contributors All authors listed above have made substantial contributions to the conception and design of the study, or data analysis and interpretation of data, drafting the article and final approval.

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Conflict of interest None

Ethics approval OAI was approved by the Institutional Review Board, the University of California, San Francisco (UCSF), and its affiliates. UCSF holds Office of Human Research Protections Federalwide Assurance number FWA00000068.

Data sharing statement: There are no additional data available.

Table 1. Baseline characteristics of participants with radiographic knee OA according to levels of soft drink intake

Variables	Total N=2,149	Soft drink intake, times/week				
		None n=687	≤1 n=976	2-4 n=285	≥5 n=201	P value
Age in years, mean (SD)	62.4(9.0)	63.9 (8.9)	62.7 (8.8)	61.6 (9.1)	58.0 (8.0)	<0.001
Men, %	41.32	29.40	44.98	49.12	53.23	<0.001
Race/ethnicity, %						
Non-hispanic White	76.04	83.70	77.36	62.46	62.69	
Non-hispanic Black	20.75	12.95	19.36	34.74	34.33	
Others	3.21	3.35	3.28	2.81	2.99	<0.001
Education, %						
≤high school	18.44	14.12	17.21	27.72	26.00	
College	45.90	46.00	46.31	44.56	45.50	
Above college	35.66	39.88	36.48	27.72	28.50	<0.001
Household Income, %						
<25k	15.17	11.51	15.04	18.42	23.56	
25k-49k	27.85	27.06	27.77	31.20	26.18	
50k-99k	36.00	37.17	36.99	34.96	28.80	
100k+	20.98	24.26	20.20	15.41	21.47	<0.001
Married, %	65.02	64.77	67.90	59.65	59.50	0.075
Employed, %	58.21	53.31	57.89	58.60	69.15	0.002
Smoke, %						
Never	54.07	51.53	53.79	59.65	56.22	
Current	6.38	4.51	5.43	7.02	16.42	
Past	39.55	43.96	40.78	33.33	27.36	<0.001
Alcohol, gm/day						
0-<5	66.08	63.75	66.19	68.77	69.65	

5-<10	10.80	11.21	10.45	12.98	7.96	
10+	23.12	25.04	23.36	18.25	22.39	0.056
PASE, mean (SD)[a]	157 (82)	147 (77)	161 (82)	165 (90)	163 (83)	0.001
BMI (kg/m^2), %						
<25	15.68	20.23	16.09	9.82	6.47	
25-29	38.39	36.83	39.34	40.70	35.82	
30+	45.93	42.94	44,57	49.47	57.71	<0.001
Gout, %	3.63	2.77	4.00	5.26	2.49	0.447
K-L grade [c] (index knee), %						
2	63.47	65.07	63.52	57.89	65.67	
3	36.53	34.93	36.48	42.11	34.33	<0.001
Milk, times/week						
None	17.19	22.27	12.62	17.31	21.89	
≤1	30.52	28.09	32.41	29.33	31.34	
2-4	21.39	20.52	22.87	20.49	18.41	
≥5	30.89	29.11	32.10	32.86	28.36	0.657

a. Physical Activity Scale for the Elderly (PASE) score

b. Body mass index

c. Kellgren-Lawrence Scale

Table 2. Adjusted mean (SE) decreases of Joint Space Width (JSW) by soft drink intake*

	Soft drinks, times / week	Men				Women			
		N	ΔJSW, mm*	P value	P trend	N	ΔJSW, mm*	P value	P trend
Overall	None	202	0.31(0.03)	Referent		485	0.32(0.02)	Referent	
	≤1	439	0.39(0.02)	0.055		537	0.33(0.02)	0.626	
	2-4	140	0.34(0.04)	0.540		145	0.36(0.04)	0.331	
	≥5	107	0.60(0.05)	<0.001	<0.001	94	0.30(0.05)	0.751	0.756
Non-obese	None	113	0.24(0.04)	Referent		279	0.30(0.03)	Referent	
	≤1	266	0.38(0.03)	0.010		277	0.30(0.03)	0.946	
	2-4	85	0.32(0.05)	0.236		60	0.35(0.06)	0.395	
	≥5	53	0.62(0.07)	<0.001	<0.001	32	0.30(0.07)	0.955	0.681
Obese	None	89	0.40(0.05)	Referent		206	0.34(0.03)	Referent	
	≤1	173	0.41(0.03)	0.993		260	0.37(0.03)	0.471	
	2-4	55	0.38(0.06)	0.749		85	0.38(0.05)	0.518	
	≥5	54	0.57(0.06)	0.032	0.064	62	0.33(0.06)	0.900	0.829

* Adjusted for age, race, education, marital status, household income, employment, follow-up time, BMI, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline K-L grade and JSW, weight change, the changes of rim distance and beam angle.

Table 3. Soft drink consumption and rate of OA progression measured by the change of medial compartment Joint space narrowing score (JSN, OARSI grades 0-3)

	Soft drinks times / week	Men			Women		
		N	Hazard Ratio (95% CI)	P trend	N	Hazard Ratio (95% CI)	P trend
Overall	None	202	Referent		485	Referent	
	≤1	439	1.56(1.13,2.16)		537	0.80(0.62,1.02)	
	2-4	140	1.55(1.02,2.35)		145	1.09(0.77,1.54)	
	≥5	107	2.05(1.32,3.19)	0.002	94	0.81(0.52,1.26)	0.539
Non-obese	None	113	Referent		279	Referent	
	≤1	266	1.66(1.05,2.63)		277	0.71(0.49,1.03)	
	2-4	85	1.45(0.80,2.60)		60	1.03(0.59,1.80)	
	≥5	53	2.30(1.22,4.34)	0.025	32	0.86(0.41,1.84)	0.559
Obese	None	89	Referent		206	Referent	
	≤1	173	1.58(0.99,2.52)		260	0.88(0.63,1.25)	
	2-4	55	1.77(0.96,3.28)		85	1.17(0.74,1.84)	
	≥5	54	1.90(1.03,3.52)	0.033	62	0.87(0.50,1.52)	0.965

*Adjusted for age, race, education, marital status, household income, employment, follow-up time, BMI, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline K-L grade.

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Soft Drink Intake and Progression of Radiographic Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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ARTICLE SUMMARY

Article focus

- To examine the prospective association of soft drink consumption with radiographic progression of knee osteoarthritis
- To examine gender differences in effect of soft drink on OA progression

Key messages

- There is a significant dose-response relationship between soft drink intake and radiographic knee osteoarthritis progression in men, but not in women.
- A stronger relationship was found in non-obese men.

Strengths and limitations of this study

- The prospective design, large number of patients with knee OA, and the quantitative measures of structural change from sophisticated image processing technology.
- Consistent findings using both semi-quantitative and quantitative measures of OA progression.
- Residual confounding may exist for this observational study.
- Soft drink consumption was based on self-report.

ABSTRACT

Objectives: We examine the prospective association of soft drink consumption with radiographic progression of knee OA.

Design: Prospective cohort study.

Setting: This study used data from the Osteoarthritis Initiative (OAI).

Participants: In OAI, 2,149 participants with radiographic knee OA and having dietary data at baseline were followed up to 12, 24, 36 and 48 months.

Measures: The soft drink consumption was assessed with a Block Brief Food Frequency Questionnaire completed at baseline. To evaluate knee OA progression, we used quantitative medial tibiofemoral joint space width (JSW) based on plain radiographs. The multivariate linear models for repeated measures were used to test the independent association between soft drink intake and the change in JSW over time, while adjusting for body mass index and other potential confounding factors.

Results: In stratified analyses by gender, we observed a significant dose-response relationship between baseline soft drink intake and adjusted mean change of JSW in men. With increasing levels of soft drink intake (none, ≤1, 2-4, and ≥5 times/week), the mean decreases of JSW were 0.31mm, 0.39mm, 0.34mm and 0.60mm respectively. When we further stratified by obesity, a stronger dose-response relationship was found in non-obese men. In obese men, only the highest soft drink level (≥5 times/week) was associated with increased change in JSW compared to no use. In women, no significant association was observed.

Conclusions: Our results suggest that frequent consumption of soft drinks may be associated with increased OA progression in men. Replication of these novel findings in other studies demonstrating the reduction in soft drink consumption leads to delay in OA progression is needed.

Key words soft drink consumption, osteoarthritis progression, diet.

Introduction

Osteoarthritis (OA), a slowly progressing disease characterized by pain, deformity, and loss of function, is the major cause physical disability in older people.[1] Nearly 27 million have clinical osteoarthritis in the United States.[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 OA progression over time in patients with OA. It is, therefore, 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 incident knee OA. [4, 5] However, findings on risk factors for OA progression have been inconclusive. Except for the level of serum hyaluronic acid and generalized OA, no other risk factor has been consistently associated with the risk of OA progression. [6 7]

Soft drink consumption has increased rapidly across the globe in recent decades.[8] Sugar sweetened beverages intake is a significant contributor to weight-gain and has been associated with increased risk of obesity, type 2 diabetes, cardiovascular disease and poor bone health. [9, 10 11] Soft drinks may displace essential nutrients and contribute to overall poorer diets, [12] while low consumption of vitamin D and anti-oxidant micronutrients may increase the risk for progression of knee OA. [13 14] To our knowledge, no study has linked soft drink consumption to OA progression. We examined the prospective association between consumption of soft drinks and progression of knee OA using data from the Osteoarthritis Initiative (OAI).

Methods

Subjects

OAI was launched in 2002 by the National Institute of Health (NIH) 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 aged 45 through 79 years in 2004 and followed them annually for the development or progression of OA. The clinical sites involved were located in Baltimore, MD; Columbus, OH; Pittsburgh, PA; and Pawtucket, RI. 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.[15] The follow-up rate was >90% over the first 48 months. The detailed OAI protocol can be found elsewhere. [16]

For the current study, we included individuals with medial radiographic knee OA in at least one knee at baseline. We excluded knees with severe radiographic OA defined as the baseline Kellgren and Lawrence (KL) grade of 4 or those with primarily lateral joint space narrowing (JSN), and knees in which the difference of rim distance (from tibial plateau to tibial rim closest to femoral condyle) between follow-up and baseline visits were ≥2mm to minimize possible measurement error of radiographic data. The 2,149 participants (3,066 knees) with KL grade of 2 or 3 and having dietary data at baseline constituted the study sample. Follow-up at 12, 24, 36 and 48 months were included in this analysis. The overall loss to follow up rate was 16.8% over the study period.

Radiographic progression of OA

In OAI, current radiographic assessment techniques on plain radiographs involved both semi-quantitative and quantitative assessment of JSN. For the semi-quantitative approach, the Osteoarthritis Research Society International grade (OARSI grade: 0=no JSN, 1=definite JSN to 3=severe JSN) has been widely used to measure progression of OA.[17] For these analyses, we used the publically available semi-quantitative JSN readings (kXR_SQ_BU, version 11/07/2011, http://oai.epi-ucsf.org). Recently, a quantitative approach has been used to provide a precise measure of joint space width (JSW) in millimeters between the adjacent bones of the knee. [18, 19] Multiple JSWs were measured at fixed locations along the joint in medial compartment, denoted as JSW(x), at

0.025 intervals for x = 0.15 - 0.30. The reproducibility of this technique and the responsiveness to change have been documented elsewhere,[18 20] including one study using OAI data which demonstrated a responsiveness that compared favorably to magnetic resonance imaging (MRI).[20] We used medial JSW at x=0.25 with the best responsiveness of change to quantify the progression of OA. [20] We define the repeated measures of the decreases of JSW from baseline to 12, 24, 36 and 48 months as the outcome variable.

Assessment of soft drink consumption

Usual dietary intakes of foods and nutrients including soft drink consumption were assessed at baseline with a Block Brief Food Frequency Questionnaire (FFQ) including 60 food items in OAI.[21] The participants were asked how often they had consumed regular soft drinks/bottled drinks (not diet drinks) 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). Based on previous studies [9,10,11], we grouped these into 4 categories: none, ≤1, 2-4, and ≥5 times/week. Similar questionnaires were used to collect the frequencies of other beverages intake, such as, milk, juice, tea and coffee, etc. This brief FFQ has been validated against three four-day records in a group of middle-aged women, and against two seven-day records in a group of older men. The absolute value of macronutrients estimated by the reduced questionnaire was a slightly lower than food-record estimates, but most micronutrients were not underestimated. [21, 22]

Information on covariates

Baseline demographic and socioeconomic factors include 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, alcohol consumption, history of

traumatic knee injury and knee surgery, self-reported gout, body mass index (BMI), physical activity, weight change, milk and juice intake, total energy intake and baseline disease severity (KL grade). Physical activity was assessed by using the Physical Activity Scale for the Elderly (PASE), an established questionnaire for measuring physical activity in older individuals that has also been validated in younger subjects.[23, 24] Alcohol consumption (pure alcohol in grams /day) was assessed at baseline including separate items for beer, wine, and liquor in OAI. In addition, we also adjusted for changes of the beam angles and rim distances (from tibial plateau to tibial rim closest to femoral condyle between follow-up visits and baseline) which indicate knee-positioning consistency for x-ray exam.

Statistical analysis

First we performed exploratory analyses of all variables of interest including the exposure (frequency of soft drink intake), radiographic structural measures (K-L grade, JSN score and JSW) and potential confounders described above. Descriptive statistics such as the minimum, maximum, median and mean for each continuous variable and frequency table for each categorical variable was used to summarize the data as well as detect outliers, data entry mistakes, and missing values.

The primary analysis was to assess the influence of soft drink consumption on the change 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 respectively. The initial analyses were unadjusted comparisons of the changes of JSW over time among levels of soft drink intake using Analysis of Variance (ANOVA) and Multivariate Analysis of Variance (MANOVA). Then separate multivariate models for repeated measures by men and women were used to test the independent association between soft drink intake and the decrease in JSW over time, while adjusting for BMI, physical activity, baseline disease severity and potential confounding factors described above. Due to the hierarchical structure of the data (each subject has 2 knees over multiple time points), we used

general linear mixed models (GLMM) to account for within subject correlation. The final covariance models were evaluated using Akaike's information criterion (AIC) and Bayesian information criterion (BIC). BMI has been an important factor related to both soft drink intake and OA progression.[9, 25] To examine the possible effect modifications, we further performed stratified analyses by obesity (BMI≥30.0 kg/m^2) and also adjusted BMI within each category to reduce the possible residual confounding bias. In addition, the association of soft drink consumption with JSW change may also be mediated through BMI. The indirect effect of BMI was evaluated using Sobel test [26]

In addition, we also used the first increase of the OARSI JSN grade as the endpoint. We developed a Cox proportional hazards model to assess independent association between soft drink intake and the JSN score change after controlling for other covariates. For each participant, the time of follow-up was calculated from the baseline date to the date of the first increase of JSN grade, death, or 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. [27] Participants who indicated no soft drink consumption in the past year were chosen as the reference group for all analyses. Adjusted hazard ratios with 95% confidence intervals 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. Data analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

Results

In this study, we studied 2,149 participants from OAI having a total of 3,066 eligible knees. All categories of soft drink intake were represented in participants at baseline (none, n=687; ≤1 times/week, n=976; 2-4 times/week, n=285; ≥5 times/week, n=201). Baseline characteristics of participants are shown in Table 1 according to levels of soft drink intake. Compared to no soft drink use, high soft drink users were more likely to be men, between

45 and 54 years, not married, not employed, current smokers, and have lower education and household income and higher BMI.

Results of multivariable analyses are shown in Table 2 in men and women. We observed a significant dose-response relationship in men between soft drink intake and adjusted mean decreases of JSW in men (p trend<0.001) after controlling for age, race, education, marital status, household income, employment, BMI, physical activity, follow-up time, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline KL grade, weight change, the changes of rim distance and beam angle. With increasing levels of soft drink intake (none, ≤1, 2-4, and ≥5 times/week), the mean decreases of JSW were 0.31mm, 0.39mm, 0.34mm and 0.60mm respectively. When we stratified by obesity, a stronger dose-response relationship was found (decreases of JSW were 0.24mm, 0.38mm, 0.32mm, 0.62mm respectively) in non-obese men. In obese men, only the highest soft drink level (≥5 times/week) was associated with increased JSW change compared to no use. The effect of soft drink consumption was different between men and women (p for interaction =0.003). No significant association was observed In women. Table 3 shows the multivariable adjusted hazard ratios (HR) of OA progression evaluated by time to the first increase of semi- quantitative OARSI score. Consistent with JSW analyses, we found that the increasing soft drink intake was associated with the increasing rate of OA progression in men but not in women. Compared to no soft drink intake, the HR for ≤1, 2-4, and ≥5 times/week were 1.56 (95% CI, 1.13-2.16), 1.55 (95% CI, 1.02-2.35) and 2.05 (95% CI, 1.32-3.19) respectively in men (p trend=0.002). When we stratified by obesity, a dose-response relationship was observed in both non-obese and obese men. The hazard ratios were 2.30 (95% CI, 1.22-4.34) and 1.90 (95% CI, 1.03-3.52) respectively with the soft drink intake ≥5 times/week compared to no intake. However, no significant association was found in women. In addition, our mediation analysis indicated a modest (3.2%) indirect effect through BMI (p for Sobel test=0.098). In

sensitivity analyses, additional adjustment for alcohol consumption and a history of gout in the above models did not change the results.

Discussion

In this 48-month follow-up study of people with radiographic knee OA, we found a positive association with a significant dose-response relationship between soft drink consumption and structural progression of knee OA measured by both semi-quantitative and quantitative JSN independent of BMI and other potential risk factors in men, but not in women.

Knee OA progression has been thought to involve multiple mechanisms besides cartilage loss including changes in bone composition, shape, as well as proprioreception,[28, 29] which might be subject to the influences of macro and micronutrients in the diet. McAlindon et al. reported that a higher consumption of anti-oxidant micronutrients, especially vitamin C, might decrease cartilage loss and OA progression, [14] and low vitamin D intake and low serum vitamin D levels might increase the risk for progression of knee OA. [13] However, no study investigated the association of soft drink consumption and progression of OA. Sugar sweetened beverages intake is a significant contributor to weight-gain and has been associated with increased risk of obesity, type 2 diabetes, cardiovascular disease and poor bone health. [10 11, 30] Nevertheless, the biologic mechanism for soft drinks in the progression of OA remains unclear. One explanation for the observed findings is that soft drinks may substitute for healthy diet. Soft drink consumption may be associated with decreased intakes of protein, milk and dairy products, fruit juice, fruit and a variety of vitamins and nutrients. [12, 31] One study reported a negative association between soft drink consumption and an overall healthy eating index.[32] However, in our analysis, the observed effects remained after adjustment for milk and juice intake supports the likelihood that this is not only due to displacement of other healthy beverages in the diet. We considered the extent to which the sugar in soft drinks leads to OA progression. To further evaluate this, we evaluated the relation between fruit

juice consumption and OA progression. Fruit juice consumption was not associated with OA progression in our study (results are not shown). It is possible that vitamins, minerals, soluble fiber, and phytochemicals in fruit juices may have beneficial effects counterbalancing potential adverse effects of sugars.

Previous studies demonstrated that weight gain and obesity may increase risk of joint space loss, suggestive of cartilage loss, as visualized on radiographs, [7, 33, 34] though these findings are not universally reported. Nevertheless, our mediation analysis indicated that the indirect effect through BMI was modest and the association between soft drinks and OA progression remained after adjustment for BMI, weight change and total energy intake suggestive of independent effects of soft drinks. Soft drinks may contain phosphoric acid, which was shown to interfere with calcium absorption and to contribute to imbalances that lead to additional loss of calcium.[35] It has also been suggested that the high fructose corn syrup used to sweeten carbonated beverages may negatively affect bone.[36] Long-term effects of soft drinks on osteoarthritis have not been studied in experimental settings so far, and further research is warranted.

Sex differences have been noted in the prevalence, incidence, and severity of OA for many years. [37] Faber and colleagues found cartilage thickness of the distal femur to be less in women than in men. [38] Other evidences suggested a protective effect of exogenous estrogen on cartilage and bone turnover. [39] However the gender differences in the relationship of soft drink consumption with OA progression are not understood. We found a stronger association between soft drink consumption and JSW change in non-obese men than in obese men. One possible reason is that the effect of soft drink consumption may not be strong enough to provide additional effect beyond obesity.

The strengths of this study include the prospective design, large number of patients with knee OA, and the state-of-the-art quantitative measures of structural change from sophisticated image processing technology. The quantitative software based assessment provides a more precise measure of JSW in millimeters and permits the assessor to

document appreciable change in JSW in the tibiofemoral compartment [18, 19] In contrast, the semi-quantitative approach, for example, the KL grading or the OARSI score, has limitations that lead to insensitivity to changes in status.[40] The consistent findings from both quantitative and semi- quantitative measures of OA progression increase the reliablity of the study. In addition, we excluded knees in which the difference of rim distance between follow-up and baseline visits ≥2mm 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 soft drink 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 soft drink consumption and changes in these variables over time. Imprecise dietary measurement could potentially have influenced our observed associations. However, random errors in dietary assessment measures might have accounted for a lack of association but not the reverse.

In conclusion, our study suggested that frequent consumption of sweetened soft drinks may be associated with increased OA progression in men. Replication of these novel findings in other prospective studies demonstrating the reduction in soft drink consumption leads to delay in OA progression are needed to test this hypothesis.

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Contributors All authors listed above have made substantial contributions to the conception and design of the study, or data analysis and interpretation of data, drafting the article and final approval.

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Conflict of interest None

Ethics approval OAI was approved by the Institutional Review Board, the University of California, San Francisco (UCSF), and its affiliates. UCSF holds Office of Human Research Protections Federalwide Assurance number FWA00000068.

Data sharing statement: There are no additional data available.

Table 1. Baseline characteristics of participants with radiographic knee OA according to levels of soft drink intake

Variables	Total N=2,149	Soft drink intake, times/week				
		None n=687	≤1 n=976	2-4 n=285	≥5 n=201	P value
Age in years, mean (SD)	62.4(9.0)	63.9 (8.9)	62.7 (8.8)	61.6 (9.1)	58.0 (8.0)	<0.001
Men, %	41.32	29.40	44.98	49.12	53.23	<0.001
Race/ethnicity, %						
Non-hispanic White	76.04	83.70	77.36	62.46	62.69	
Non-hispanic Black	20.75	12.95	19.36	34.74	34.33	
Others	3.21	3.35	3.28	2.81	2.99	<0.001
Education, %						
≤high school	18.44	14.12	17.21	27.72	26.00	
College	45.90	46.00	46.31	44.56	45.50	
Above college	35.66	39.88	36.48	27.72	28.50	<0.001
Household Income, %						
<25k	15.17	11.51	15.04	18.42	23.56	
25k-49k	27.85	27.06	27.77	31.20	26.18	
50k-99k	36.00	37.17	36.99	34.96	28.80	
100k+	20.98	24.26	20.20	15.41	21.47	<0.001
Married, %	65.02	64.77	67.90	59.65	59.50	0.075
Employed, %	58.21	53.31	57.89	58.60	69.15	0.002
Smoke, %						
Never	54.07	51.53	53.79	59.65	56.22	
Current	6.38	4.51	5.43	7.02	16.42	
Past	39.55	43.96	40.78	33.33	27.36	<0.001
Alcohol, gm/day						
0-<5	66.08	63.75	66.19	68.77	69.65	

5-<10	10.80	11.21	10.45	12.98	7.96	
10+	23.12	25.04	23.36	18.25	22.39	0.056
PASE, mean (SD)[a]	157 (82)	147 (77)	161 (82)	165 (90)	163 (83)	0.001
BMI (kg/m^2), %						
<25	15.68	20.23	16.09	9.82	6.47	
25-29	38.39	36.83	39.34	40.70	35.82	
30+	45.93	42.94	44,57	49.47	57.71	<0.001
Gout, %	3.63	2.77	4.00	5.26	2.49	0.447
K-L grade [c] (index knee), %						
2	63.47	65.07	63.52	57.89	65.67	
3	36.53	34.93	36.48	42.11	34.33	<0.001
Milk, times/week						
None	17.19	22.27	12.62	17.31	21.89	
≤1	30.52	28.09	32.41	29.33	31.34	
2-4	21.39	20.52	22.87	20.49	18.41	
≥5	30.89	29.11	32.10	32.86	28.36	0.657

a. Physical Activity Scale for the Elderly (PASE) score

b. Body mass index

c. Kellgren-Lawrence Scale

Table 2. Adjusted mean (SE) decreases of Joint Space Width (JSW) by soft drink intake*

	Soft drinks, times / week	Men				Women			
		N	ΔJSW, mm*	P value	P trend	N	ΔJSW, mm*	P value	P trend
Overall	None	202	0.31(0.03)	Referent		485	0.32(0.02)	Referent	
	≤1	439	0.39(0.02)	0.055		537	0.33(0.02)	0.626	
	2-4	140	0.34(0.04)	0.540		145	0.36(0.04)	0.331	
	≥5	107	0.60(0.05)	<0.001	<0.001	94	0.30(0.05)	0.751	0.756
Non-obese	None	113	0.24(0.04)	Referent		279	0.30(0.03)	Referent	
	≤1	266	0.38(0.03)	0.010		277	0.30(0.03)	0.946	
	2-4	85	0.32(0.05)	0.236		60	0.35(0.06)	0.395	
	≥5	53	0.62(0.07)	<0.001	<0.001	32	0.30(0.07)	0.955	0.681
Obese	None	89	0.40(0.05)	Referent		206	0.34(0.03)	Referent	
	≤1	173	0.41(0.03)	0.993		260	0.37(0.03)	0.471	
	2-4	55	0.38(0.06)	0.749		85	0.38(0.05)	0.518	
	≥5	54	0.57(0.06)	0.032	0.064	62	0.33(0.06)	0.900	0.829

* Adjusted for age, race, education, marital status, household income, employment, follow-up time, BMI, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline K-L grade and JSW, weight change, the changes of rim distance and beam angle.

Table 3. Soft drink consumption and rate of OA progression measured by the change of medial compartment Joint space narrowing score (JSN, OARSI grades 0-3)

	Soft drinks times / week	Men			Women		
		N	Hazard Ratio (95% CI)	P trend	N	Hazard Ratio (95% CI)	P trend
Overall	None	202	Referent		485	Referent	
	≤1	439	1.56(1.13,2.16)		537	0.80(0.62,1.02)	
	2-4	140	1.55(1.02,2.35)		145	1.09(0.77,1.54)	
	≥5	107	2.05(1.32,3.19)	0.002	94	0.81(0.52,1.26)	0.539
Non-obese	None	113	Referent		279	Referent	
	≤1	266	1.66(1.05,2.63)		277	0.71(0.49,1.03)	
	2-4	85	1.45(0.80,2.60)		60	1.03(0.59,1.80)	
	≥5	53	2.30(1.22,4.34)	0.025	32	0.86(0.41,1.84)	0.559
Obese	None	89	Referent		206	Referent	
	≤1	173	1.58(0.99,2.52)		260	0.88(0.63,1.25)	
	2-4	55	1.77(0.96,3.28)		85	1.17(0.74,1.84)	
	≥5	54	1.90(1.03,3.52)	0.033	62	0.87(0.50,1.52)	0.965

*Adjusted for age, race, education, marital status, household income, employment, follow-up time, BMI, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline K-L grade.

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Our manuscript has compliance to all items of the STROBE Statement for cohort study.

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a

		meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Soft Drink Intake and Progression of Radiographic Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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Soft Drink Intake and Progression of Radiographic Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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ARTICLE SUMMARY

AARTICLE SUMMARY

Article focus

- To examine the prospective association of soft drink consumption with radiographic progression of knee osteoarthritis
- To examine gender differences in effect of soft drink on OA progression

Key messages

- There is a significant dose-response relationship between soft drink intake and radiographic knee osteoarthritis progression in men, but not in women.
- A stronger relationship was found in non-obese men.

Strengths and limitations of this study

- The prospective design, large number of patients with knee OA, and the quantitative measures of structural change from sophisticated image processing technology.
- Consistent findings using both semi-quantitative and quantitative measures of OA progression.
- Residual confounding may exist for this observational study.
- Soft drink consumption was based on self-report.

ABSTRACT

Objectives: We examine the prospective association of soft drink consumption with radiographic progression of knee OA.

Design: Prospective cohort study.

Setting: This study used data from the Osteoarthritis Initiative (OAI).

Participants: In OAI, 2,149 participants with radiographic knee OA and having dietary data at baseline were followed up to 12, 24, 36 and 48 months.

Measures: The soft drink consumption was assessed with a Block Brief Food Frequency Questionnaire completed at baseline. To evaluate knee OA progression, we used quantitative medial tibiofemoral joint space width (JSW) based on plain radiographs. The multivariate linear models for repeated measures were used to test the independent association between soft drink intake and the change in JSW over time, while adjusting for body mass index and other potential confounding factors.

Results: In stratified analyses by gender, we observed a significant dose-response relationship between baseline soft drink intake and adjusted mean change of JSW in men. With increasing levels of soft drink intake (none, ≤1, 2-4, and ≥5 times/week), the mean decreases of JSW were 0.31mm, 0.39mm, 0.34mm and 0.60mm respectively. When we further stratified by obesity, a stronger dose-response relationship was found in non-obese men. In obese men, only the highest soft drink level (≥5 times/week) was associated with increased change in JSW compared to no use. In women, no significant association was observed.

Conclusions: Our results suggest that frequent consumption of soft drinks may be associated with increased OA progression in men. Replication of these novel findings in other studies demonstrating the reduction in soft drink consumption leads to delay in OA progression is needed.

Key words soft drink consumption, osteoarthritis progression, diet.

Introduction

Osteoarthritis (OA), a slowly progressing disease characterized by pain, deformity, and loss of function, is the major cause physical disability in older people.[1] Nearly 27 million have clinical osteoarthritis in the United States.[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 OA progression over time in patients with OA. It is, therefore, 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 incident knee OA. [4, 5] However, findings on risk factors for OA progression have been inconclusive. Except for the level of serum hyaluronic acid and generalized OA, no other risk factor has been consistently associated with the risk of OA progression. [6 7]

Soft drink consumption has increased rapidly across the globe in recent decades.[8] Sugar sweetened beverages intake is a significant contributor to weight-gain and has been associated with increased risk of obesity, type 2 diabetes, cardiovascular disease and poor bone health. [9, 10 11] Soft drinks may displace essential nutrients and contribute to overall poorer diets, [12] while low consumption of vitamin D and anti-oxidant micronutrients may increase the risk for progression of knee OA. [13 14] To our knowledge, no study has linked soft drink consumption to OA progression. We examined the prospective association between consumption of soft drinks and progression of knee OA using data from the Osteoarthritis Initiative (OAI).

Methods

Subjects

OAI was launched in 2002 by the National Institute of Health (NIH) 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 aged 45 through 79 years in 2004 and followed them annually for the development or progression of OA. The clinical sites involved were located in Baltimore, MD; Columbus, OH; Pittsburgh, PA; and Pawtucket, RI. 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.[15] The follow-up rate was >90% over the first 48 months. The detailed OAI protocol can be found elsewhere. [16]

For the current study, we included individuals with medial radiographic knee OA in at least one knee at baseline. We excluded knees with severe radiographic OA defined as the baseline Kellgren and Lawrence (KL) grade of 4 or those with primarily lateral joint space narrowing (JSN), and knees in which the difference of rim distance (from tibial plateau to tibial rim closest to femoral condyle) between follow-up and baseline visits were ≥2mm to minimize possible measurement error of radiographic data. The 2,149 participants (3,066 knees) with KL grade of 2 or 3 and having dietary data at baseline constituted the study sample. Follow-up at 12, 24, 36 and 48 months were included in this analysis. The overall loss to follow up rate was 16.8% over the study period.

Radiographic progression of OA

In OAI, current radiographic assessment techniques on plain radiographs involved both semi-quantitative and quantitative assessment of JSN. For the semi-quantitative approach, the Osteoarthritis Research Society International grade (OARSI grade: 0=no JSN, 1=definite JSN to 3=severe JSN) has been widely used to measure progression of OA.[17] For these analyses, we used the publically available semi-quantitative JSN readings (kXR_SQ_BU, version 11/07/2011, http://oai.epi-ucsf.org). Recently, a quantitative approach has been used to provide a precise measure of joint space width (JSW) in millimeters between the adjacent bones of the knee. [18, 19] Multiple JSWs were measured at fixed locations along the joint in medial compartment, denoted as JSW(x), at

0.025 intervals for x = 0.15 - 0.30. The reproducibility of this technique and the responsiveness to change have been documented elsewhere,[18 20] including one study using OAI data which demonstrated a responsiveness that compared favorably to magnetic resonance imaging (MRI).[20] We used medial JSW at x=0.25 with the best responsiveness of change to quantify the progression of OA. [20] We define the repeated measures of the decreases of JSW from baseline to 12, 24, 36 and 48 months as the outcome variable.

Assessment of soft drink consumption

Usual dietary intakes of foods and nutrients including soft drink consumption were assessed at baseline with a Block Brief Food Frequency Questionnaire (FFQ) including 60 food items in OAI.[21] The participants were asked how often they had consumed regular soft drinks/bottled drinks (not diet drinks) 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) (variable name: V00FFQ69, http://oai.epi-ucsf.org). Based on previous studies [9,10,11], we grouped these into 4 categories: none, ≤1, 2-4, and ≥5 times/week. Similar questionnaires were used to collect the frequencies of other beverages intake, such as, milk, juice, tea and coffee, etc. This brief FFQ has been validated against three four-day records in a group of middle-aged women, and against two seven-day records in a group of older men. The absolute value of macronutrients estimated by the reduced questionnaire was a slightly lower than food-record estimates, but most micronutrients were not underestimated. [21, 22]

Information on covariates

Baseline demographic and socioeconomic factors include 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, alcohol consumption, history of

traumatic knee injury and knee surgery, self-reported gout, body mass index (BMI), physical activity, weight change, milk and juice intake, total energy intake and baseline disease severity (KL grade). Physical activity was assessed by using the Physical Activity Scale for the Elderly (PASE), an established questionnaire for measuring physical activity in older individuals that has also been validated in younger subjects.[23, 24] Alcohol consumption (pure alcohol in grams /day) was assessed at baseline including separate items for beer, wine, and liquor in OAI. In addition, we also adjusted for changes of the beam angles and rim distances (from tibial plateau to tibial rim closest to femoral condyle between follow-up visits and baseline) which indicate knee-positioning consistency for x-ray exam.

Statistical analysis

First we performed exploratory analyses of all variables of interest including the exposure (frequency of soft drink intake), radiographic structural measures (K-L grade, JSN score and JSW) and potential confounders described above. Descriptive statistics such as the minimum, maximum, median and mean for each continuous variable and frequency table for each categorical variable was used to summarize the data as well as detect outliers, data entry mistakes, and missing values.

The primary analysis was to assess the influence of soft drink consumption on the change 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 respectively. The initial analyses were unadjusted comparisons of the changes of JSW over time among levels of soft drink intake using Analysis of Variance (ANOVA) and Multivariate Analysis of Variance (MANOVA). Then separate multivariate models for repeated measures by men and women were used to test the independent association between soft drink intake and the decrease in JSW over time, while adjusting for BMI, physical activity, baseline disease severity and potential confounding factors described above. Due to the hierarchical structure of the data (each subject has 2 knees over multiple time points), we used

general linear mixed models (GLMM) to account for within subject correlation. The final covariance models were evaluated using Akaike's information criterion (AIC) and Bayesian information criterion (BIC). BMI has been an important factor related to both soft drink intake and OA progression.[9, 25] To examine the possible effect modifications, we further performed stratified analyses by obesity (BMI≥30.0 kg/m^2) and also adjusted BMI within each category to reduce the possible residual confounding bias. In addition, the association of soft drink consumption with JSW change may also be mediated through BMI. The indirect effect of BMI was evaluated using Sobel test [26]

In addition, we also used the first increase of the OARSI JSN grade as the endpoint. We developed a Cox proportional hazards model to assess independent association between soft drink intake and the JSN score change after controlling for other covariates. For each participant, the time of follow-up was calculated from the baseline date to the date of the first increase of JSN grade, death, or 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. [27] Participants who indicated no soft drink consumption in the past year were chosen as the reference group for all analyses. Adjusted hazard ratios with 95% confidence intervals 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. Data analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

Results

In this study, we studied 2,149 participants from OAI having a total of 3,066 eligible knees. All categories of soft drink intake were represented in participants at baseline (none, n=687; ≤1 times/week, n=976; 2-4 times/week, n=285; ≥5 times/week, n=201). Baseline characteristics of participants are shown in Table 1 according to levels of soft drink intake. Compared to no soft drink use, high soft drink users were more likely to be men, between

45 and 54 years, not married, not employed, current smokers, and have lower education and household income and higher BMI.

Results of multivariable analyses are shown in Table 2 in men and women. We observed a significant dose-response relationship in men between soft drink intake and adjusted mean decreases of JSW in men (p trend<0.001) after controlling for age, race, education, marital status, household income, employment, BMI, physical activity, follow-up time, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline KL grade, weight change, the changes of rim distance and beam angle. With increasing levels of soft drink intake (none, ≤1, 2-4, and ≥5 times/week), the mean decreases of JSW were 0.31mm, 0.39mm, 0.34mm and 0.60mm respectively. When we stratified by obesity, a stronger dose-response relationship was found (decreases of JSW were 0.24mm, 0.38mm, 0.32mm, 0.62mm respectively) in non-obese men. In obese men, only the highest soft drink level (≥5 times/week) was associated with increased JSW change compared to no use. The effect of soft drink consumption was different between men and women (p for interaction =0.003). No significant association was observed In women. Table 3 shows the multivariable adjusted hazard ratios (HR) of OA progression evaluated by time to the first increase of semi- quantitative OARSI score. Consistent with JSW analyses, we found that the increasing soft drink intake was associated with the increasing rate of OA progression in men but not in women. Compared to no soft drink intake, the HR for ≤1, 2-4, and ≥5 times/week were 1.56 (95% CI, 1.13-2.16), 1.55 (95% CI, 1.02-2.35) and 2.05 (95% CI, 1.32-3.19) respectively in men (p trend=0.002). When we stratified by obesity, a dose-response relationship was observed in both non-obese and obese men. The hazard ratios were 2.30 (95% CI, 1.22-4.34) and 1.90 (95% CI, 1.03-3.52) respectively with the soft drink intake ≥5 times/week compared to no intake. However, no significant association was found in women. In addition, our mediation analysis indicated a modest (3.2%) indirect effect through BMI (p for Sobel test=0.098). In

sensitivity analyses, additional adjustment for alcohol consumption and a history of gout in the above models did not change the results.

Discussion

In this 48-month follow-up study of people with radiographic knee OA, we found a positive association with a significant dose-response relationship between soft drink consumption and structural progression of knee OA measured by both semi-quantitative and quantitative JSN independent of BMI and other potential risk factors in men, but not in women.

Knee OA progression has been thought to involve multiple mechanisms besides cartilage loss including changes in bone composition, shape, as well as proprioreception,[28, 29] which might be subject to the influences of macro and micronutrients in the diet. McAlindon et al. reported that a higher consumption of anti-oxidant micronutrients, especially vitamin C, might decrease cartilage loss and OA progression, [14] and low vitamin D intake and low serum vitamin D levels might increase the risk for progression of knee OA. [13] However, no study investigated the association of soft drink consumption and progression of OA. Sugar sweetened beverages intake is a significant contributor to weight-gain and has been associated with increased risk of obesity, type 2 diabetes, cardiovascular disease and poor bone health. [10, 11, 30] Nevertheless, the biologic mechanism for soft drinks in the progression of OA remains unclear. One explanation for the observed findings is that soft drinks may substitute for healthy diet. Soft drink consumption may be associated with decreased intakes of protein, milk and dairy products, fruit juice, fruit and a variety of vitamins and nutrients. [12, 31] One study reported a negative association between soft drink consumption and an overall healthy eating index.[32] However, in our analysis, the observed effects remained after adjustment for milk and juice intake supports the likelihood that this is not only due to displacement of other healthy beverages in the diet. We considered the extent to which the sugar in soft drinks leads to OA progression. To further evaluate this, we evaluated the relation between fruit

juice consumption and OA progression. Fruit juice consumption was not associated with OA progression in our study (results are not shown). It is possible that vitamins, minerals, soluble fiber, and phytochemicals in fruit juices may have beneficial effects counterbalancing potential adverse effects of sugars.

Previous studies demonstrated that weight gain and obesity may increase risk of joint space loss, suggestive of cartilage loss, as visualized on radiographs, [7, 33, 34] though these findings are not universally reported. Nevertheless, our mediation analysis indicated that the indirect effect through BMI was modest and the association between soft drinks and OA progression remained after adjustment for BMI, weight change and total energy intake suggestive of independent effects of soft drinks. Soft drinks may contain phosphoric acid, which was shown to interfere with calcium absorption and to contribute to imbalances that lead to additional loss of calcium.[35] It has also been suggested that the high fructose corn syrup used to sweeten carbonated beverages may negatively affect bone.[36] Long-term effects of soft drinks on osteoarthritis have not been studied in experimental settings so far, and further research is warranted.

Sex differences have been noted in the prevalence, incidence, and severity of OA for many years. [37] Faber and colleagues found cartilage thickness of the distal femur to be less in women than in men. [38] Other evidences suggested a protective effect of exogenous estrogen on cartilage and bone turnover. [39] However the gender differences in the relationship of soft drink consumption with OA progression are not understood. We found a stronger association between soft drink consumption and JSW change in non-obese men than in obese men. One possible reason is that the effect of soft drink consumption may not be strong enough to provide additional effect beyond obesity.

The strengths of this study include the prospective design, large number of patients with knee OA, and the state-of-the-art quantitative measures of structural change from sophisticated image processing technology. The quantitative software based assessment provides a more precise measure of JSW in millimeters and permits the assessor to

document appreciable change in JSW in the tibiofemoral compartment [18, 19] In contrast, the semi-quantitative approach, for example, the KL grading or the OARSI score, has limitations that lead to insensitivity to changes in status.[40] The consistent findings from both quantitative and semi- quantitative measures of OA progression increase the reliablity of the study. In addition, we excluded knees in which the difference of rim distance between follow-up and baseline visits ≥2mm 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 soft drink groups. We cannot prove that the observed associations are causal because residual confounding could theoretically affect the observed associations. We controlled for potential confounding by most known risk factors that are plausibly associated with soft drink consumption and changes in these variables over time. However, adjustment for baseline covariates may not completely remove the confounding influence. For example, effect of BMI may be lagged, and the cumulative exposure to overweight/obesity may not be perfectly correlated with baseline BMI. Imprecise dietary measurement could potentially have influenced our observed associations. However, random errors in dietary assessment measures might have accounted for a lack of association but not the reverse. Regarding physical activity, PASE can potentially capture all types of activities and allow grading by intensity for elderly. However, questionnaires have obvious weaknesses considering recall and reporting bias. Also PASE may not be sufficient for assessing PA levels and intensity in younger patients with OA. [41]

In conclusion, our study suggested that frequent consumption of sweetened soft drinks may be associated with increased OA progression in men. Replication of these novel findings in other prospective studies demonstrating the reduction in soft drink consumption leads to delay in OA progression are needed to test this hypothesis.

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Contributors All authors listed above have made substantial contributions to the conception and design of the study, or data analysis and interpretation of data, drafting the article and final approval.

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Conflict of interest None

Ethics approval OAI was approved by the Institutional Review Board, the University of California, San Francisco (UCSF), and its affiliates. UCSF holds Office of Human Research Protections Federal wide Assurance number FWA00000068.

Data sharing statement: There are no additional data available.

Table 1. Baseline characteristics of participants with radiographic knee OA according to levels of soft drink intake

Variables	Total N=2,149	Soft drink intake, times/week				
		None n=687	≤1 n=976	2-4 n=285	≥5 n=201	P value
Age in years, mean (SD)	62.4(9.0)	63.9 (8.9)	62.7 (8.8)	61.6 (9.1)	58.0 (8.0)	<0.001
Men, %	41.32	29.40	44.98	49.12	53.23	<0.001
Race/ethnicity, %						
Non-hispanic White	76.04	83.70	77.36	62.46	62.69	
Non-hispanic Black	20.75	12.95	19.36	34.74	34.33	
Others	3.21	3.35	3.28	2.81	2.99	<0.001
Education, %						
≤high school	18.44	14.12	17.21	27.72	26.00	
College	45.90	46.00	46.31	44.56	45.50	
Above college	35.66	39.88	36.48	27.72	28.50	<0.001
Household Income, %						
<25k	15.17	11.51	15.04	18.42	23.56	
25k-49k	27.85	27.06	27.77	31.20	26.18	
50k-99k	36.00	37.17	36.99	34.96	28.80	
100k+	20.98	24.26	20.20	15.41	21.47	<0.001
Married, %	65.02	64.77	67.90	59.65	59.50	0.075
Employed, %	58.21	53.31	57.89	58.60	69.15	0.002
Smoke, %						
Never	54.07	51.53	53.79	59.65	56.22	
Current	6.38	4.51	5.43	7.02	16.42	
Past	39.55	43.96	40.78	33.33	27.36	<0.001
Alcohol, gm/day						
0-<5	66.08	63.75	66.19	68.77	69.65	

5-<10	10.80	11.21	10.45	12.98	7.96	
10+	23.12	25.04	23.36	18.25	22.39	0.056
PASE, mean (SD)[a]	157 (82)	147 (77)	161 (82)	165 (90)	163 (83)	0.001
BMI (kg/m^2), %						
<25	15.68	20.23	16.09	9.82	6.47	
25-29	38.39	36.83	39.34	40.70	35.82	
30+	45.93	42.94	44,57	49.47	57.71	<0.001
Gout, %	3.63	2.77	4.00	5.26	2.49	0.447
K-L grade [c] (index knee), %						
2	63.47	65.07	63.52	57.89	65.67	
3	36.53	34.93	36.48	42.11	34.33	<0.001
Milk, times/week						
None	17.19	22.27	12.62	17.31	21.89	
≤1	30.52	28.09	32.41	29.33	31.34	
2-4	21.39	20.52	22.87	20.49	18.41	
≥5	30.89	29.11	32.10	32.86	28.36	0.657

a. Physical Activity Scale for the Elderly (PASE) score

b. Body mass index

c. Kellgren-Lawrence Scale

Table 2. Adjusted mean (SE) decreases of Joint Space Width (JSW) by soft drink intake*

	Soft drinks, times / week	Men				Women			
		N	ΔJSW, mm*	P value	P trend	N	ΔJSW, mm*	P value	P trend
Overall	None	202	0.31(0.03)	Referent		485	0.32(0.02)	Referent	
	≤1	439	0.39(0.02)	0.055		537	0.33(0.02)	0.626	
	2-4	140	0.34(0.04)	0.540		145	0.36(0.04)	0.331	
	≥5	107	0.60(0.05)	<0.001	<0.001	94	0.30(0.05)	0.751	0.756
Non-obese	None	113	0.24(0.04)	Referent		279	0.30(0.03)	Referent	
	≤1	266	0.38(0.03)	0.010		277	0.30(0.03)	0.946	
	2-4	85	0.32(0.05)	0.236		60	0.35(0.06)	0.395	
	≥5	53	0.62(0.07)	<0.001	<0.001	32	0.30(0.07)	0.955	0.681
Obese	None	89	0.40(0.05)	Referent		206	0.34(0.03)	Referent	
	≤1	173	0.41(0.03)	0.993		260	0.37(0.03)	0.471	
	2-4	55	0.38(0.06)	0.749		85	0.38(0.05)	0.518	
	≥5	54	0.57(0.06)	0.032	0.064	62	0.33(0.06)	0.900	0.829

* Adjusted for age, race, education, marital status, household income, employment, follow-up time, BMI, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline K-L grade and JSW, weight change, the changes of rim distance and beam angle.

Table 3. Soft drink consumption and rate of OA progression measured by the change of medial compartment Joint space narrowing score (JSN, OARSI grades 0-3)

	Soft drinks times / week	Men			Women		
		N	Hazard Ratio (95% CI)	P trend	N	Hazard Ratio (95% CI)	P trend
Overall	None	202	Referent		485	Referent	
	≤1	439	1.56(1.13,2.16)		537	0.80(0.62,1.02)	
	2-4	140	1.55(1.02,2.35)		145	1.09(0.77,1.54)	
	≥5	107	2.05(1.32,3.19)	0.002	94	0.81(0.52,1.26)	0.539
Non-obese	None	113	Referent		279	Referent	
	≤1	266	1.66(1.05,2.63)		277	0.71(0.49,1.03)	
	2-4	85	1.45(0.80,2.60)		60	1.03(0.59,1.80)	
	≥5	53	2.30(1.22,4.34)	0.025	32	0.86(0.41,1.84)	0.559
Obese	None	89	Referent		206	Referent	
	≤1	173	1.58(0.99,2.52)		260	0.88(0.63,1.25)	
	2-4	55	1.77(0.96,3.28)		85	1.17(0.74,1.84)	
	≥5	54	1.90(1.03,3.52)	0.033	62	0.87(0.50,1.52)	0.965

*Adjusted for age, race, education, marital status, household income, employment, follow-up time, BMI, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline K-L grade.

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Soft Drink Intake and Progression of Radiographic Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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ARTICLE SUMMARY

Article focus

- To examine the prospective association of soft drink consumption with radiographic progression of knee osteoarthritis
- To examine gender differences in effect of soft drink on OA progression

Key messages

- There is a significant dose-response relationship between soft drink intake and radiographic knee osteoarthritis progression in men, but not in women.
- A stronger relationship was found in non-obese men.

Strengths and limitations of this study

- The prospective design, large number of patients with knee OA, and the quantitative measures of structural change from sophisticated image processing technology.
- Consistent findings using both semi-quantitative and quantitative measures of OA progression.
- Residual confounding may exist for this observational study.
- Soft drink consumption was based on self-report.

ABSTRACT

Objectives: We examine the prospective association of soft drink consumption with radiographic progression of knee OA.

Design: Prospective cohort study.

Setting: This study used data from the Osteoarthritis Initiative (OAI).

Participants: In OAI, 2,149 participants with radiographic knee OA and having dietary data at baseline were followed up to 12, 24, 36 and 48 months.

Measures: The soft drink consumption was assessed with a Block Brief Food Frequency Questionnaire completed at baseline. To evaluate knee OA progression, we used quantitative medial tibiofemoral joint space width (JSW) based on plain radiographs. The multivariate linear models for repeated measures were used to test the independent association between soft drink intake and the change in JSW over time, while adjusting for body mass index and other potential confounding factors.

Results: In stratified analyses by gender, we observed a significant dose-response relationship between baseline soft drink intake and adjusted mean change of JSW in men. With increasing levels of soft drink intake (none, ≤1, 2-4, and ≥5 times/week), the mean decreases of JSW were 0.31mm, 0.39mm, 0.34mm and 0.60mm respectively. When we further stratified by obesity, a stronger dose-response relationship was found in non-obese men. In obese men, only the highest soft drink level (≥5 times/week) was associated with increased change in JSW compared to no use. In women, no significant association was observed.

Conclusions: Our results suggest that frequent consumption of soft drinks may be associated with increased OA progression in men. Replication of these novel findings in other studies demonstrating the reduction in soft drink consumption leads to delay in OA progression is needed.

Key words soft drink consumption, osteoarthritis progression, diet.

Introduction

Osteoarthritis (OA), a slowly progressing disease characterized by pain, deformity, and loss of function, is the major cause physical disability in older people.[1] Nearly 27 million have clinical osteoarthritis in the United States.[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 OA progression over time in patients with OA. It is, therefore, 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 incident knee OA. [4, 5] However, findings on risk factors for OA progression have been inconclusive. Except for the level of serum hyaluronic acid and generalized OA, no other risk factor has been consistently associated with the risk of OA progression. [6 7]

Soft drink consumption has increased rapidly across the globe in recent decades.[8] Sugar sweetened beverages intake is a significant contributor to weight-gain and has been associated with increased risk of obesity, type 2 diabetes, cardiovascular disease and poor bone health. [9, 10 11] Soft drinks may displace essential nutrients and contribute to overall poorer diets, [12] while low consumption of vitamin D and anti-oxidant micronutrients may increase the risk for progression of knee OA. [13 14] To our knowledge, no study has linked soft drink consumption to OA progression. We examined the prospective association between consumption of soft drinks and progression of knee OA using data from the Osteoarthritis Initiative (OAI).

Methods

Subjects

OAI was launched in 2002 by the National Institute of Health (NIH) 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 aged 45 through 79 years in 2004 and followed them annually for the development or progression of OA. The clinical sites involved were located in Baltimore, MD; Columbus, OH; Pittsburgh, PA; and Pawtucket, RI. 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.[15] The follow-up rate was >90% over the first 48 months. The detailed OAI protocol can be found elsewhere. [16]

For the current study, we included individuals with medial radiographic knee OA in at least one knee at baseline. We excluded knees with severe radiographic OA defined as the baseline Kellgren and Lawrence (KL) grade of 4 or those with primarily lateral joint space narrowing (JSN), and knees in which the difference of rim distance (from tibial plateau to tibial rim closest to femoral condyle) between follow-up and baseline visits were ≥2mm to minimize possible measurement error of radiographic data. The 2,149 participants (3,066 knees) with KL grade of 2 or 3 and having dietary data at baseline constituted the study sample. Follow-up at 12, 24, 36 and 48 months were included in this analysis. The overall loss to follow up rate was 16.8% over the study period.

Radiographic progression of OA

In OAI, current radiographic assessment techniques on plain radiographs involved both semi-quantitative and quantitative assessment of JSN. For the semi-quantitative approach, the Osteoarthritis Research Society International grade (OARSI grade: 0=no JSN, 1=definite JSN to 3=severe JSN) has been widely used to measure progression of OA.[17] For these analyses, we used the publically available semi-quantitative JSN readings (kXR_SQ_BU, version 11/07/2011, http://oai.epi-ucsf.org). Recently, a quantitative approach has been used to provide a precise measure of joint space width (JSW) in millimeters between the adjacent bones of the knee. [18, 19] Multiple JSWs were measured at fixed locations along the joint in medial compartment, denoted as JSW(x), at

0.025 intervals for x = 0.15 - 0.30. The reproducibility of this technique and the responsiveness to change have been documented elsewhere,[18 20] including one study using OAI data which demonstrated a responsiveness that compared favorably to magnetic resonance imaging (MRI).[20] We used medial JSW at x=0.25 with the best responsiveness of change to quantify the progression of OA. [20] We define the repeated measures of the decreases of JSW from baseline to 12, 24, 36 and 48 months as the outcome variable.

Assessment of soft drink consumption

Usual dietary intakes of foods and nutrients including soft drink consumption were assessed at baseline with a Block Brief Food Frequency Questionnaire (FFQ) including 60 food items in OAI.[21] The participants were asked how often they had consumed regular soft drinks/bottled drinks (not diet drinks) 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) (variable name: V00FFQ69, http://oai.epi-ucsf.org). Based on previous studies [9,10,11], we grouped these into 4 categories: none, ≤1, 2-4, and ≥5 times/week. Similar questionnaires were used to collect the frequencies of other beverages intake, such as, milk, juice, tea and coffee, etc. This brief FFQ has been validated against three four-day records in a group of middle-aged women, and against two seven-day records in a group of older men. The absolute value of macronutrients estimated by the reduced questionnaire was a slightly lower than food-record estimates, but most micronutrients were not underestimated. [21, 22]

Information on covariates

Baseline demographic and socioeconomic factors include 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, alcohol consumption, history of

traumatic knee injury and knee surgery, self-reported gout, body mass index (BMI), physical activity, weight change, milk and juice intake, total energy intake and baseline disease severity (KL grade). Physical activity was assessed by using the Physical Activity Scale for the Elderly (PASE), an established questionnaire for measuring physical activity in older individuals that has also been validated in younger subjects.[23, 24] Alcohol consumption (pure alcohol in grams /day) was assessed at baseline including separate items for beer, wine, and liquor in OAI. In addition, we also adjusted for changes of the beam angles and rim distances (from tibial plateau to tibial rim closest to femoral condyle between follow-up visits and baseline) which indicate knee-positioning consistency for x-ray exam.

Statistical analysis

First we performed exploratory analyses of all variables of interest including the exposure (frequency of soft drink intake), radiographic structural measures (K-L grade, JSN score and JSW) and potential confounders described above. Descriptive statistics such as the minimum, maximum, median and mean for each continuous variable and frequency table for each categorical variable was used to summarize the data as well as detect outliers, data entry mistakes, and missing values.

The primary analysis was to assess the influence of soft drink consumption on the change 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 respectively. The initial analyses were unadjusted comparisons of the changes of JSW over time among levels of soft drink intake using Analysis of Variance (ANOVA) and Multivariate Analysis of Variance (MANOVA). Then separate multivariate models for repeated measures by men and women were used to test the independent association between soft drink intake and the decrease in JSW over time, while adjusting for BMI, physical activity, baseline disease severity and potential confounding factors described above. Due to the hierarchical structure of the data (each subject has 2 knees over multiple time points), we used

general linear mixed models (GLMM) to account for within subject correlation. The final covariance models were evaluated using Akaike's information criterion (AIC) and Bayesian information criterion (BIC). BMI has been an important factor related to both soft drink intake and OA progression.[9, 25] To examine the possible effect modifications, we further performed stratified analyses by obesity (BMI≥30.0 kg/m^2) and also adjusted BMI within each category to reduce the possible residual confounding bias. In addition, the association of soft drink consumption with JSW change may also be mediated through BMI. The indirect effect of BMI was evaluated using Sobel test [26]

In addition, we also used the first increase of the OARSI JSN grade as the endpoint. We developed a Cox proportional hazards model to assess independent association between soft drink intake and the JSN score change after controlling for other covariates. For each participant, the time of follow-up was calculated from the baseline date to the date of the first increase of JSN grade, death, or 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. [27] Participants who indicated no soft drink consumption in the past year were chosen as the reference group for all analyses. Adjusted hazard ratios with 95% confidence intervals 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. Data analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

Results

In this study, we studied 2,149 participants from OAI having a total of 3,066 eligible knees. All categories of soft drink intake were represented in participants at baseline (none, n=687; ≤1 times/week, n=976; 2-4 times/week, n=285; ≥5 times/week, n=201). Baseline characteristics of participants are shown in Table 1 according to levels of soft drink intake. Compared to no soft drink use, high soft drink users were more likely to be men, between

45 and 54 years, not married, not employed, current smokers, and have lower education and household income and higher BMI.

Results of multivariable analyses are shown in Table 2 in men and women. We observed a significant dose-response relationship in men between soft drink intake and adjusted mean decreases of JSW in men (p trend<0.001) after controlling for age, race, education, marital status, household income, employment, BMI, physical activity, follow-up time, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline KL grade, weight change, the changes of rim distance and beam angle. With increasing levels of soft drink intake (none, ≤1, 2-4, and ≥5 times/week), the mean decreases of JSW were 0.31mm, 0.39mm, 0.34mm and 0.60mm respectively. When we stratified by obesity, a stronger dose-response relationship was found (decreases of JSW were 0.24mm, 0.38mm, 0.32mm, 0.62mm respectively) in non-obese men. In obese men, only the highest soft drink level (≥5 times/week) was associated with increased JSW change compared to no use. The effect of soft drink consumption was different between men and women (p for interaction =0.003). No significant association was observed In women. Table 3 shows the multivariable adjusted hazard ratios (HR) of OA progression evaluated by time to the first increase of semi- quantitative OARSI score. Consistent with JSW analyses, we found that the increasing soft drink intake was associated with the increasing rate of OA progression in men but not in women. Compared to no soft drink intake, the HR for ≤1, 2-4, and ≥5 times/week were 1.56 (95% CI, 1.13-2.16), 1.55 (95% CI, 1.02-2.35) and 2.05 (95% CI, 1.32-3.19) respectively in men (p trend=0.002). When we stratified by obesity, a dose-response relationship was observed in both non-obese and obese men. The hazard ratios were 2.30 (95% CI, 1.22-4.34) and 1.90 (95% CI, 1.03-3.52) respectively with the soft drink intake ≥5 times/week compared to no intake. However, no significant association was found in women. In addition, our mediation analysis indicated a modest (3.2%) indirect effect through BMI (p for Sobel test=0.098). In

sensitivity analyses, additional adjustment for alcohol consumption and a history of gout in the above models did not change the results.

Discussion

In this 48-month follow-up study of people with radiographic knee OA, we found a positive association with a significant dose-response relationship between soft drink consumption and structural progression of knee OA measured by both semi-quantitative and quantitative JSN independent of BMI and other potential risk factors in men, but not in women.

Knee OA progression has been thought to involve multiple mechanisms besides cartilage loss including changes in bone composition, shape, as well as proprioreception,[28, 29] which might be subject to the influences of macro and micronutrients in the diet. McAlindon et al. reported that a higher consumption of anti-oxidant micronutrients, especially vitamin C, might decrease cartilage loss and OA progression, [14] and low vitamin D intake and low serum vitamin D levels might increase the risk for progression of knee OA. [13] However, no study investigated the association of soft drink consumption and progression of OA. Sugar sweetened beverages intake is a significant contributor to weight-gain and has been associated with increased risk of obesity, type 2 diabetes, cardiovascular disease and poor bone health. [10 11, 30] Nevertheless, the biologic mechanism for soft drinks in the progression of OA remains unclear. One explanation for the observed findings is that soft drinks may substitute for healthy diet. Soft drink consumption may be associated with decreased intakes of protein, milk and dairy products, fruit juice, fruit and a variety of vitamins and nutrients. [12, 31] One study reported a negative association between soft drink consumption and an overall healthy eating index.[32] However, in our analysis, the observed effects remained after adjustment for milk and juice intake supports the likelihood that this is not only due to displacement of other healthy beverages in the diet. We considered the extent to which the sugar in soft drinks leads to OA progression. To further evaluate this, we evaluated the relation between fruit

juice consumption and OA progression. Fruit juice consumption was not associated with OA progression in our study (results are not shown). It is possible that vitamins, minerals, soluble fiber, and phytochemicals in fruit juices may have beneficial effects counterbalancing potential adverse effects of sugars.

Previous studies demonstrated that weight gain and obesity may increase risk of joint space loss, suggestive of cartilage loss, as visualized on radiographs, [7, 33, 34] though these findings are not universally reported. Nevertheless, our mediation analysis indicated that the indirect effect through BMI was modest and the association between soft drinks and OA progression remained after adjustment for BMI, weight change and total energy intake suggestive of independent effects of soft drinks. Soft drinks may contain phosphoric acid, which was shown to interfere with calcium absorption and to contribute to imbalances that lead to additional loss of calcium.[35] It has also been suggested that the high fructose corn syrup used to sweeten carbonated beverages may negatively affect bone.[36] Long-term effects of soft drinks on osteoarthritis have not been studied in experimental settings so far, and further research is warranted.

Sex differences have been noted in the prevalence, incidence, and severity of OA for many years. [37] Faber and colleagues found cartilage thickness of the distal femur to be less in women than in men. [38] Other evidences suggested a protective effect of exogenous estrogen on cartilage and bone turnover. [39] However the gender differences in the relationship of soft drink consumption with OA progression are not understood. We found a stronger association between soft drink consumption and JSW change in non-obese men than in obese men. One possible reason is that the effect of soft drink consumption may not be strong enough to provide additional effect beyond obesity.

The strengths of this study include the prospective design, large number of patients with knee OA, and the state-of-the-art quantitative measures of structural change from sophisticated image processing technology. The quantitative software based assessment provides a more precise measure of JSW in millimeters and permits the assessor to

document appreciable change in JSW in the tibiofemoral compartment [18, 19] In contrast, the semi-quantitative approach, for example, the KL grading or the OARSI score, has limitations that lead to insensitivity to changes in status.[40] The consistent findings from both quantitative and semi- quantitative measures of OA progression increase the reliablity of the study. In addition, we excluded knees in which the difference of rim distance between follow-up and baseline visits ≥2mm 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 soft drink groups. We cannot prove that the observed associations are causal because residual confounding could theoretically affect the observed associations. We controlled for potential confounding by most known risk factors that are plausibly associated with soft drink consumption and changes in these variables over time. However, adjustment for baseline covariates may not completely remove the confounding influence. For example, effect of BMI may be lagged, and the cumulative exposure to overweight/obesity may not be perfectly correlated with baseline BMI. Imprecise dietary measurement could potentially have influenced our observed associations. However, random errors in dietary assessment measures might have accounted for a lack of association but not the reverse. Regarding physical activity, PASE can potentially capture all types of activities and allow grading by intensity for elderly. However, questionnaires have obvious weaknesses considering recall and reporting bias. Also PASE may not be sufficient for assessing PA levels and intensity in younger patients with OA. [41]

In conclusion, our study suggested that frequent consumption of sweetened soft drinks may be associated with increased OA progression in men. Replication of these novel findings in other prospective studies demonstrating the reduction in soft drink consumption leads to delay in OA progression are needed to test this hypothesis.

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Contributors All authors listed above have made substantial contributions to the conception and design of the study, or data analysis and interpretation of data, drafting the article and final approval.

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Conflict of interest None

Ethics approval OAI was approved by the Institutional Review Board, the University of California, San Francisco (UCSF), and its affiliates. UCSF holds Office of Human Research Protections Federal wide Assurance number FWA00000068.

Data sharing statement: There are no additional data available.

Table 1. Baseline characteristics of participants with radiographic knee OA according to levels of soft drink intake

Variables	Total N=2,149	Soft drink intake, times/week				
		None n=687	≤1 n=976	2-4 n=285	≥5 n=201	P value
Age in years, mean (SD)	62.4(9.0)	63.9 (8.9)	62.7 (8.8)	61.6 (9.1)	58.0 (8.0)	<0.001
Men, %	41.32	29.40	44.98	49.12	53.23	<0.001
Race/ethnicity, %						
Non-hispanic White	76.04	83.70	77.36	62.46	62.69	
Non-hispanic Black	20.75	12.95	19.36	34.74	34.33	
Others	3.21	3.35	3.28	2.81	2.99	<0.001
Education, %						
≤high school	18.44	14.12	17.21	27.72	26.00	
College	45.90	46.00	46.31	44.56	45.50	
Above college	35.66	39.88	36.48	27.72	28.50	<0.001
Household Income, %						
<25k	15.17	11.51	15.04	18.42	23.56	
25k-49k	27.85	27.06	27.77	31.20	26.18	
50k-99k	36.00	37.17	36.99	34.96	28.80	
100k+	20.98	24.26	20.20	15.41	21.47	<0.001
Married, %	65.02	64.77	67.90	59.65	59.50	0.075
Employed, %	58.21	53.31	57.89	58.60	69.15	0.002
Smoke, %						
Never	54.07	51.53	53.79	59.65	56.22	
Current	6.38	4.51	5.43	7.02	16.42	
Past	39.55	43.96	40.78	33.33	27.36	<0.001
Alcohol, gm/day						
0-<5	66.08	63.75	66.19	68.77	69.65	

5-<10	10.80	11.21	10.45	12.98	7.96	
10+	23.12	25.04	23.36	18.25	22.39	0.056
PASE, mean (SD)[a]	157 (82)	147 (77)	161 (82)	165 (90)	163 (83)	0.001
BMI (kg/m^2), %						
<25	15.68	20.23	16.09	9.82	6.47	
25-29	38.39	36.83	39.34	40.70	35.82	
30+	45.93	42.94	44,57	49.47	57.71	<0.001
Gout, %	3.63	2.77	4.00	5.26	2.49	0.447
K-L grade [c] (index knee), %						
2	63.47	65.07	63.52	57.89	65.67	
3	36.53	34.93	36.48	42.11	34.33	<0.001
Milk, times/week						
None	17.19	22.27	12.62	17.31	21.89	
≤1	30.52	28.09	32.41	29.33	31.34	
2-4	21.39	20.52	22.87	20.49	18.41	
≥5	30.89	29.11	32.10	32.86	28.36	0.657

a. Physical Activity Scale for the Elderly (PASE) score

b. Body mass index

c. Kellgren-Lawrence Scale

Table 2. Adjusted mean (SE) decreases of Joint Space Width (JSW) by soft drink intake*

	Soft drinks, times / week	Men				Women			
		N	ΔJSW, mm*	P value	P trend	N	ΔJSW, mm*	P value	P trend
Overall	None	202	0.31(0.03)	Referent		485	0.32(0.02)	Referent	
	≤1	439	0.39(0.02)	0.055		537	0.33(0.02)	0.626	
	2-4	140	0.34(0.04)	0.540		145	0.36(0.04)	0.331	
	≥5	107	0.60(0.05)	<0.001	<0.001	94	0.30(0.05)	0.751	0.756
Non-obese	None	113	0.24(0.04)	Referent		279	0.30(0.03)	Referent	
	≤1	266	0.38(0.03)	0.010		277	0.30(0.03)	0.946	
	2-4	85	0.32(0.05)	0.236		60	0.35(0.06)	0.395	
	≥5	53	0.62(0.07)	<0.001	<0.001	32	0.30(0.07)	0.955	0.681
Obese	None	89	0.40(0.05)	Referent		206	0.34(0.03)	Referent	
	≤1	173	0.41(0.03)	0.993		260	0.37(0.03)	0.471	
	2-4	55	0.38(0.06)	0.749		85	0.38(0.05)	0.518	
	≥5	54	0.57(0.06)	0.032	0.064	62	0.33(0.06)	0.900	0.829

* Adjusted for age, race, education, marital status, household income, employment, follow-up time, BMI, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline K-L grade and JSW, weight change, the changes of rim distance and beam angle.

Table 3. Soft drink consumption and rate of OA progression measured by the change of medial compartment Joint space narrowing score (JSN, OARSI grades 0-3)

	Soft drinks times / week	Men			Women		
		N	Hazard Ratio (95% CI)	P trend	N	Hazard Ratio (95% CI)	P trend
Overall	None	202	Referent		485	Referent	
	≤1	439	1.56(1.13,2.16)		537	0.80(0.62,1.02)	
	2-4	140	1.55(1.02,2.35)		145	1.09(0.77,1.54)	
	≥5	107	2.05(1.32,3.19)	0.002	94	0.81(0.52,1.26)	0.539
Non-obese	None	113	Referent		279	Referent	
	≤1	266	1.66(1.05,2.63)		277	0.71(0.49,1.03)	
	2-4	85	1.45(0.80,2.60)		60	1.03(0.59,1.80)	
	≥5	53	2.30(1.22,4.34)	0.025	32	0.86(0.41,1.84)	0.559
Obese	None	89	Referent		206	Referent	
	≤1	173	1.58(0.99,2.52)		260	0.88(0.63,1.25)	
	2-4	55	1.77(0.96,3.28)		85	1.17(0.74,1.84)	
	≥5	54	1.90(1.03,3.52)	0.033	62	0.87(0.50,1.52)	0.965

*Adjusted for age, race, education, marital status, household income, employment, follow-up time, BMI, knee injury and knee surgery, smoking, milk and juice intake, total energy intake, baseline K-L grade.

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Our manuscript has compliance to all items of the STROBE Statement for cohort study.

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a

		meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.