



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

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2 **Soft Drink Intake and Progression of Radiographic Knee Osteoarthritis: Data from the**  
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4 **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,  $\leq 1$ , 2-4, and  $\geq 5$  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 ( $\geq 5$  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.<sup>1</sup> Nearly 27 million have clinical osteoarthritis in the United States.<sup>2</sup> With the aging of the population, the health care burden from OA is expected to increase dramatically during the next few decades.<sup>3</sup> 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.<sup>4,5</sup> 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.<sup>6,7</sup>

Soft drink consumption has increased rapidly across the globe in recent decades.<sup>8</sup> 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.<sup>9,10,11</sup> Soft drinks may displace essential nutrients and contribute to overall poorer diets,<sup>12</sup> while low consumption of vitamin D and anti-oxidant micronutrients may increase the risk for progression of knee OA.<sup>13,14</sup> 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

1  
2 biospecimens from those at risk for or with knee OA. The OAI began enrolling people aged 45  
3  
4 through 79 years in 2004 and followed them annually for the development or progression of OA.  
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6 The clinical sites involved were located in Baltimore, MD; Columbus, OH; Pittsburgh, PA; and  
7  
8 Pawtucket, RI. OAI has been a longitudinal study of 4,796 subjects with either established knee  
9  
10 OA or significant risk factors for the development of knee OA followed over an 8-year period.<sup>15</sup>  
11  
12 The follow-up rate was >90% over the first 48 months. The detailed OAI protocol can be found  
13  
14 elsewhere.<sup>16</sup>  
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18 For the current study, we included individuals with medial radiographic knee OA in at least  
19  
20 one knee at baseline. We excluded knees with severe radiographic OA defined as the baseline  
21  
22 Kellgren and Lawrence (KL) grade of 4 or those with primarily lateral joint space narrowing  
23  
24 (JSN), and knees in which the difference of rim distance (from tibial plateau to tibial rim closest  
25  
26 to femoral condyle) between follow-up and baseline visits were  $\geq 2$ mm to minimize possible  
27  
28 measurement error of radiographic data. The 2,149 participants (3,066 knees) with KL grade of  
29  
30 2 or 3 and having dietary data at baseline constituted the study sample. Follow-up at 12, 24, 36  
31  
32 and 48 months were included in this analysis.  
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### 35 **Radiographic progression of OA**

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37 In OAI, current radiographic assessment techniques on plain radiographs involved both semi-  
38  
39 quantitative and quantitative assessment of JSN. For the semi-quantitative approach, the  
40  
41 Osteoarthritis Research Society International grade (OARSI grade: 0=no JSN, 1=definite JSN to  
42  
43 3=severe JSN) has been widely used to measure progression of OA.<sup>17</sup> For these analyses, we  
44  
45 used the publically available semi-quantitative JSN readings (kXR\_SQ\_BU, version 11/07/2011,  
46  
47 <http://oai.epi-ucsf.org>). Recently, a quantitative approach has been used to provide a precise  
48  
49 measure of joint space width (JSW) in millimeters between the adjacent bones of the knee.<sup>18, 19</sup>  
50  
51 Multiple JSWs were measured at fixed locations along the joint in medial compartment, denoted  
52  
53 as JSW(x), at 0.025 intervals for  $x = 0.15 - 0.30$ . The reproducibility of this technique and the  
54  
55 responsiveness to change have been documented elsewhere,<sup>18, 20</sup> including one study using  
56  
57 OAI data which demonstrated a responsiveness that compared favorably to magnetic  
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1  
2 resonance imaging (MRI).<sup>20</sup> We used medial JSW at x=0.25 with the best responsiveness of  
3  
4 change to quantify the progression of OA. <sup>20</sup> We define the repeated measures of the decreases  
5  
6 of JSW from baseline to 12, 24, 36 and 48 months as the outcome variable.  
7

### 8 9 **Assessment of soft drink consumption**

10 Usual dietary intakes of foods and nutrients including soft drink consumption were assessed at  
11  
12 baseline with a Block Brief Food Frequency Questionnaire (FFQ) including 60 food items in  
13  
14 OAI.<sup>21</sup> The participants were asked how often they had consumed regular soft drinks/bottled  
15  
16 drinks (not diet drinks) in the past 12 months (coded as: never, a few times per year, once per  
17  
18 month, 2-3 times per month, once per week, twice per week, 3-4 times per week, 5-6 times per  
19  
20 week, and every day). In this analysis, we grouped these into 4 categories: none,  $\leq 1$ , 2-4, and  
21  
22  $\geq 5$  times/week. Similar questionnaires were used to collect the frequencies of other beverages  
23  
24 intake, such as, milk, juice, tea and coffee, etc. This brief FFQ has been validated against three  
25  
26 four-day records in a group of middle-aged women, and against two seven-day records in a  
27  
28 group of older men. The absolute value of macronutrients estimated by the reduced  
29  
30 questionnaire was a slightly lower than food-record estimates, but most micronutrients were not  
31  
32 underestimated. <sup>21, 22</sup>  
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35

### 36 37 **Information on covariates**

38 Baseline demographic and socioeconomic factors include race/ethnicity, age, sex, marital  
39  
40 status, education level, employment status, annual income and social support. Individuals were  
41  
42 classified as African American, white, or other racial/ethnic group based on self report.  
43  
44 Education level was categorized as high school or less, college and above college. General  
45  
46 clinical parameters include current smoking, history of traumatic knee injury and knee surgery,  
47  
48 body mass index (BMI), physical activity, weight change, milk and juice intake, total energy  
49  
50 intake and baseline disease severity (KL grade). Physical activity was assessed by using the  
51  
52 Physical Activity Scale for the Elderly (PASE), an established questionnaire for measuring  
53  
54 physical activity in older individuals that has also been validated in younger subjects.<sup>23, 24</sup> In  
55  
56 addition, we also adjusted for changes of the beam angles and rim distances (from tibial plateau  
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1  
2 to tibial rim closest to femoral condyle between follow-up visits and baseline) which indicate  
3  
4 knee-positioning consistency for x-ray exam.  
5

### 6 7 **Statistical analysis**

8  
9 First we performed exploratory analyses of all variables of interest including the exposure  
10 (frequency of soft drink intake), radiographic structural measures (K-L grade, JSN score and  
11 JSW ) and potential confounders described above. Descriptive statistics such as the minimum,  
12  
13 maximum, median and mean for each continuous variable and frequency table for each  
14  
15 categorical variable was used to summarize the data as well as detect outliers, data entry  
16  
17 mistakes, and missing values.  
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20  
21 The primary analysis was to assess the influence of soft drink consumption on the change in  
22  
23 JSW over the study period. The primary outcomes were repeated measures of the JSW  
24  
25 decreases from baseline to 12, 24, 36 and 48 months respectively. The initial analyses were  
26  
27 unadjusted comparisons of the changes of JSW over time among levels of soft drink intake  
28  
29 using Analysis of Variance (ANOVA) and Multivariate Analysis of Variance (MANOVA). Then  
30  
31 separate multivariate models for repeated measures by men and women were used to test the  
32  
33 independent association between soft drink intake and the decrease in JSW over time, while  
34  
35 adjusting for BMI, physical activity, baseline disease severity and potential confounding factors  
36  
37 described above. Due to the hierarchical structure of the data (each subject has 2 knees over  
38  
39 multiple time points), we used general linear mixed models (GLMM) to account for within subject  
40  
41 correlation. The final covariance models were evaluated using Akaike's information criterion  
42  
43 (AIC) and Bayesian information criterion (BIC). BMI has been an important factor related to  
44  
45 both soft drink intake and OA progression.<sup>9, 25</sup> To examine the possible effect modifications, we  
46  
47 further performed stratified analyses by obesity ( $\text{BMI} \geq 30.0 \text{ kg/m}^2$ ) and also adjusted BMI within  
48  
49 each category to reduce the possible residual confounding bias. In addition, the association of  
50  
51 soft drink consumption with JSW change may also be mediated through BMI. The indirect effect  
52  
53 of BMI was evaluated using Sobel test<sup>26</sup>  
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2 In addition, we also used the first increase of the OARSI JSN grade as the endpoint. We  
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4 developed a Cox proportional hazards model to assess independent association between soft  
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6 drink intake and the JSN score change after controlling for other covariates. For each  
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8 participant, the time of follow-up was calculated from the baseline date to the date of the first  
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10 increase of JSN grade, death, or end of the study, whichever came first. The discrete  
11  
12 likelihood method was used for ties of the failure times in the models. We used a robust  
13  
14 sandwich covariance estimate to account for the intraclass dependence within individual  
15  
16 patients.<sup>27</sup> Participants who indicated no soft drink consumption in the past year were chosen  
17  
18 as the reference group for all analyses. Adjusted hazard ratios with 95% confidence intervals  
19  
20 were used to evaluate the strength of the associations. The proportional hazard assumption  
21  
22 was tested based on the smoothed plots of the scaled Schoenfeld residuals. Data analyses  
23  
24 were performed using SAS 9.2 (SAS Institute, Cary, NC).  
25  
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27

## 28 **Results**

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30 In this study, we studied 2,149 participants from OAI having a total of 3,066 eligible knees.  
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32 Participants were representative of all categories of soft drink intake at baseline (none, n=687;  
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34 ≤1 times/week, n=976; 2-4 times/week, n=285; ≥5 times/week, n=201). Baseline characteristics  
35  
36 of participants are shown in Table 1 according to levels of soft drink intake. Compared to no soft  
37  
38 drink use, high soft drink users were more likely to be men, between 45 and 54 years, not  
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40 married, not employed, current smokers, and have lower education and household income and  
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42 higher BMI.  
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46 Results of multivariable analyses are shown in Table 2 in men and women. We observed a  
47  
48 significant dose-response relationship in men between soft drink intake and adjusted mean  
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50 decreases of JSW in men (p trend<0.001) after controlling for age, race, education, marital  
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52 status, household income, employment, BMI, physical activity, follow-up time, knee injury and  
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54 knee surgery, smoking, milk and juice intake, total energy intake, baseline KL grade, weight  
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56 change, the changes of rim distance and beam angle. With increasing levels of soft drink intake  
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58 (none, ≤1, 2-4, and ≥5 times/week), the mean decreases of JSW were 0.31mm, 0.39mm,  
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60

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 ( $\geq 5$  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  $\leq 1$ , 2-4, and  $\geq 5$  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  $\geq 5$  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 proprioception,<sup>28, 29</sup> 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,<sup>14</sup> and low vitamin D intake and low serum vitamin D levels might increase the risk for progression of knee OA.<sup>13</sup> However, no study investigated

1  
2 the association of soft drink consumption and progression of OA. Sugar sweetened beverages  
3  
4 intake is a significant contributor to weight-gain and has been associated with increased risk of  
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6 obesity, type 2 diabetes, cardiovascular disease and poor bone health.<sup>10 11,30</sup> Nevertheless,  
7  
8 the biologic mechanism for soft drinks in the progression of OA remains unclear. One  
9  
10 explanation for the observed findings is that soft drinks may substitute for healthy diet. Soft  
11  
12 drink consumption may be associated with decreased intakes of protein, milk and dairy  
13  
14 products, fruit juice, fruit and a variety of vitamins and nutrients.<sup>12,31</sup> One study reported a  
15  
16 negative association between soft drink consumption and an overall healthy eating index.<sup>32</sup>  
17  
18 However, in our analysis, the observed effects remained after adjustment for milk and juice  
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20 intake supports the likelihood that this is not only due to displacement of other healthy  
21  
22 beverages in the diet. We considered the extent to which the sugar in soft drinks leads to OA  
23  
24 progression. To further evaluate this, we evaluated the relation between fruit juice consumption  
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26 and OA progression. Fruit juice consumption was not associated with OA progression in our  
27  
28 study (results are not shown). It is possible that vitamins, minerals, soluble fiber, and  
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30 phytochemicals in fruit juices may have beneficial effects counterbalancing potential adverse  
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32 effects of sugars.  
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37 Previous studies demonstrated that weight gain and obesity may increase risk of joint space  
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39 loss, suggestive of cartilage loss, as visualized on radiographs,<sup>7,33,34</sup> though these findings are  
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41 not universally reported. Nevertheless, our mediation analysis indicated that the indirect effect  
42  
43 through BMI was modest and the association between soft drinks and OA progression remained  
44  
45 after adjustment for BMI, weight change and total energy intake suggestive of independent  
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47 effects of soft drinks. Soft drinks may contain phosphoric acid, which was shown to interfere  
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49 with calcium absorption and to contribute to imbalances that lead to additional loss of calcium.<sup>35</sup>  
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51 It has also been suggested that the high fructose corn syrup used to sweeten carbonated  
52  
53 beverages may negatively affect bone.<sup>36</sup> Long-term effects of soft drinks on osteoarthritis have  
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55 not been studied in experimental settings so far, and further research is warranted.  
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2 Sex differences have been noted in the prevalence, incidence, and severity of OA for many  
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4 years.<sup>37</sup> Faber and colleagues found cartilage thickness of the distal femur to be less in women  
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6 than in men.<sup>38</sup> Other evidences suggested a protective effect of exogenous estrogen on  
7  
8 cartilage and bone turnover.<sup>39</sup> However the gender differences in the relationship of soft drink  
9  
10 consumption with OA progression are not understood. We found a stronger association  
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12 between soft drink consumption and JSW change in non-obese men than in obese men. One  
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14 possible reason is that the effect of soft drink consumption may not be strong enough to provide  
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16 additional effect beyond obesity.  
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18  
19 The strengths of this study include the prospective design, large number of patients with knee  
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21 OA, and the state-of-the-art quantitative measures of structural change from sophisticated  
22  
23 image processing technology. The quantitative software based assessment provides a more  
24  
25 precise measure of JSW in millimeters and permits the assessor to document appreciable  
26  
27 change in JSW in the tibiofemoral compartment<sup>18, 19</sup> In contrast, the semi-quantitative  
28  
29 approach, for example, the KL grading or the OARSI score, has limitations that lead to  
30  
31 insensitivity to changes in status.<sup>40</sup> The consistent findings from both quantitative and semi-  
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33 quantitative measures of OA progression increase the reliability of the study. In addition, we  
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35 excluded knees in which the difference of rim distance between follow-up and baseline visits  
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37  $\geq 2$ mm and adjusted for changes of rim distance and beam angle in the multivariate models to  
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39 minimize the possible measurement error of radiographic data.  
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43 Because of the observational nature of the study, patients were not randomly assigned to soft  
44  
45 drink groups. We cannot prove that the observed associations are causal because residual  
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47 confounding could theoretically affect the observed associations. However, we controlled for  
48  
49 potential confounding by most known risk factors that are plausibly associated with soft drink  
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51 consumption and changes in these variables over time. Imprecise dietary measurement could  
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53 potentially have influenced our observed associations. However, random errors in dietary  
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55 assessment measures might have accounted for a lack of association but not the reverse.  
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2 In conclusion, our study suggested that frequent consumption of sweetened soft drinks may  
3 be associated with increased OA progression in men. Replication of these novel findings in  
4 other prospective studies demonstrating the reduction in soft drink consumption leads to delay  
5 in OA progression are needed to test this hypothesis.  
6  
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33 and design of the study, or data analysis and interpretation of data, drafting the article and final  
34 approval.  
35  
36  
37

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41 report; or in the decision to submit the paper for publication.  
42  
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47 **Conflict of interest** None  
48

49 **Ethics approval** OAI was approved by the Institutional Review Board, the University of  
50 California, San Francisco (UCSF), and its affiliates. UCSF holds Office of Human Research  
51 Protections Federalwide Assurance number FWA00000068.  
52  
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56 **Data sharing statement:** There are no additional data available.  
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**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				P value
		None n=687	≤1 n=976	2-4 n=285	≥5 n=201	
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) <sup>a</sup>	157 (82)	147 (77)	161 (82)	165 (90)	163 (83)	0.001
BMI (kg/m <sup>2</sup> ), %						

<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 <sup>c</sup> (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.							

## References

1. Dunlop DD, Manheim LM, Yelin EH, Song J, Chang RW. The costs of arthritis. *Arthritis Rheum*. Feb 15 2003;49(1):101-113.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum*. Jan 2008;58(1):26-35.
3. Reginster JY. The prevalence and burden of arthritis. *Rheumatology (Oxford)*. Apr 2002;41 Suppl 1:3-6.
4. Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. *Radiol Clin North Am*. Jan 2004;42(1):1-9, v.
5. Garstang SV, Stitik TP. Osteoarthritis: epidemiology, risk factors, and pathophysiology. *Am J Phys Med Rehabil*. Nov 2006;85(11 Suppl):S2-11; quiz S12-14.
6. Zhang Y, Niu J, Felson DT, Choi HK, Nevitt M, Neogi T. Methodologic challenges in studying risk factors for progression of knee osteoarthritis. *Arthritis Care Res (Hoboken)*. Nov 2010;62(11):1527-1532.
7. Felson DT, Goggins J, Niu J, Zhang Y, Hunter DJ. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. *Arthritis Rheum*. Dec 2004;50(12):3904-3909.
8. Nielsen SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. *Am J Prev Med*. Oct 2004;27(3):205-210.
9. Malik VS, Popkin BM, Bray GA, Despres JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation*. Mar 23 2010;121(11):1356-1364.
10. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care*. Nov 2010;33(11):2477-2483.
11. Wyszak G. Teenaged girls, carbonated beverage consumption, and bone fractures. *Arch Pediatr Adolesc Med*. Jun 2000;154(6):610-613.
12. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health*. Apr 2007;97(4):667-675.
13. McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med*. Sep 1 1996;125(5):353-359.
14. McAlindon TE, Jacques P, Zhang Y, et al. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? *Arthritis Rheum*. Apr 1996;39(4):648-656.
15. Simard JF, Karlson EW, Costenbader KH, et al. Perinatal factors and adult-onset lupus. *Arthritis Rheum*. Aug 15 2008;59(8):1155-1161.
16. The osteoarthritis initiative protocol for the cohort study. <<http://oai.epi-csf.org/datarelease/docs/StudyDesignProtocol.pdf>>; [accessed 04.25.2012]
17. Guermazi A, Hunter DJ, Roemer FW. Plain radiography and magnetic resonance imaging diagnostics in osteoarthritis: validated staging and scoring. *J Bone Joint Surg Am*. Feb 2009;91 Suppl 1:54-62.

18. Duryea J, Zaim S, Genant HK. New radiographic-based surrogate outcome measures for osteoarthritis of the knee. *Osteoarthritis Cartilage*. Feb 2003;11(2):102-110.
19. Sharp JT, Angwin J, Boers M, et al. Computer based methods for measurement of joint space width: update of an ongoing OMERACT project. *J Rheumatol*. Apr 2007;34(4):874-883.
20. Duryea J, Neumann G, Niu J, et al. Comparison of radiographic joint space width with magnetic resonance imaging cartilage morphometry: analysis of longitudinal data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)*. Jul 2010;62(7):932-937.
21. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. *Epidemiology*. Jan 1990;1(1):58-64.
22. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol*. Sep 1986;124(3):453-469.
23. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*. Feb 1993;46(2):153-162.
24. Johansen KL, Painter P, Kent-Braun JA, et al. Validation of questionnaires to estimate physical activity and functioning in end-stage renal disease. *Kidney Int*. Mar 2001;59(3):1121-1127.
25. Issa SN, Sharma L. Epidemiology of osteoarthritis: an update. *Curr Rheumatol Rep*. Feb 2006;8(1):7-15.
26. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. Dec 1986;51(6):1173-1182.
27. Lin DY. Cox regression analysis of multivariate failure time data: the marginal approach. *Stat Med*. Nov 15 1994;13(21):2233-2247.
28. Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis*. Jan 2011;70(1):60-67.
29. Driban JB, Lo GH, Lee JY, et al. Quantitative bone marrow lesion size in osteoarthritic knees correlates with cartilage damage and predicts longitudinal cartilage loss. *BMC Musculoskelet Disord*. 2011;12:217.
30. Tucker KL. Dietary intake and bone status with aging. *Curr Pharm Des*. 2003;9(32):2687-2704.
31. Marshall TA, Eichenberger Gilmore JM, Broffitt B, Stumbo PJ, Levy SM. Diet quality in young children is influenced by beverage consumption. *J Am Coll Nutr*. Feb 2005;24(1):65-75.
32. Rodriguez-Artalejo F, Garcia EL, Gorgojo L, et al. Consumption of bakery products, sweetened soft drinks and yogurt among children aged 6-7 years: association with nutrient intake and overall diet quality. *Br J Nutr*. Mar 2003;89(3):419-429.
33. Wolfe F, Lane NE. The longterm outcome of osteoarthritis: rates and predictors of joint space narrowing in symptomatic patients with knee osteoarthritis. *J Rheumatol*. Jan 2002;29(1):139-146.
34. Dougados M, Gueguen A, Nguyen M, et al. Longitudinal radiologic evaluation of osteoarthritis of the knee. *J Rheumatol*. Mar 1992;19(3):378-384.

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35. Amato D, Maravilla A, Montoya C, et al. Acute effects of soft drink intake on calcium and phosphate metabolism in immature and adult rats. *Rev Invest Clin*. May-Jun 1998;50(3):185-189.
36. Milne DB, Nielsen FH. The interaction between dietary fructose and magnesium adversely affects macromineral homeostasis in men. *J Am Coll Nutr*. Feb 2000;19(1):31-37.
37. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage*. Sep 2005;13(9):769-781.
38. Faber SC, Eckstein F, Lukasz S, et al. Gender differences in knee joint cartilage thickness, volume and articular surface areas: assessment with quantitative three-dimensional MR imaging. *Skeletal Radiol*. Mar 2001;30(3):144-150.
39. Linn S, Murtaugh B, Casey E. Role of sex hormones in the development of osteoarthritis. *Pm R*. May 2012;4(5 Suppl):S169-173.
40. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage*. 2007;15 Suppl A:A1-56.

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

	Item No	Recommendation
<b>Title and abstract</b>	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
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
<b>Methods</b>		
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
<b>Results</b>		
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
<b>Discussion</b>		
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
<b>Other information</b>		
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>.



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

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2 1 **Soft Drink Intake and Progression of Radiographic Knee Osteoarthritis: Data from**  
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4 2 **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,  $\leq 1$ , 2-4, and  $\geq 5$  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 ( $\geq 5$  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.

## 85 Introduction

86 Osteoarthritis (OA), a slowly progressing disease characterized by pain, deformity, and loss  
87 of function, is the major cause physical disability in older people.<sup>1</sup> Nearly 27 million have  
88 clinical osteoarthritis in the United States.<sup>2</sup> With the aging of the population, the health care  
89 burden from OA is expected to increase dramatically during the next few decades.<sup>3</sup>  
90 However, little is known about the course of OA progression over time in patients with OA.  
91 It is, therefore, of great importance to identify modifiable risk factors for OA progression.  
92 Over the past few decades, many observational studies have examined risk factors for the  
93 incidence and progression of knee OA. Several risk factors (i.e., obesity, joint injury, and  
94 certain sports) have been found to be strongly associated with an increased risk for  
95 incident knee OA.<sup>4,5</sup> However, findings on risk factors for OA progression have been  
96 inconclusive. Except for the level of serum hyaluronic acid and generalized OA, no other  
97 risk factor has been consistently associated with the risk of OA progression.<sup>6,7</sup>

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

## 107 Methods

### 108 Subjects

109 OAI was launched in 2002 by the National Institute of Health (NIH) to develop resources for  
110 the identification of new biomarkers and treatment targets for knee OA. The objective of the  
111 OAI was to pool public and private scientific expertise and funding to collect, analyze, and

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2 112 make widely available the largest research resource to date of clinical data, radiologic  
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4 113 information, and biospecimens from those at risk for or with knee OA. The OAI began  
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6 114 enrolling people aged 45 through 79 years in 2004 and followed them annually for the  
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8 115 development or progression of OA. The clinical sites involved were located in Baltimore,  
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10 116 MD; Columbus, OH; Pittsburgh, PA; and Pawtucket, RI. OAI has been a longitudinal study  
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12 117 of 4,796 subjects with either established knee OA or significant risk factors for the  
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14 118 development of knee OA followed over an 8-year period.<sup>15</sup> The follow-up rate was >90%  
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16 119 over the first 48 months. The detailed OAI protocol can be found elsewhere.<sup>16</sup>  
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19 120 For the current study, we included individuals with medial radiographic knee OA in at  
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21 121 least one knee at baseline. We excluded knees with severe radiographic OA defined as  
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23 122 the baseline Kellgren and Lawrence (KL) grade of 4 or those with primarily lateral joint  
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25 123 space narrowing (JSN), and knees in which the difference of rim distance (from tibial  
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27 124 plateau to tibial rim closest to femoral condyle) between follow-up and baseline visits were  
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29 125  $\geq 2$ mm to minimize possible measurement error of radiographic data. The 2,149  
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31 126 participants (3,066 knees) with KL grade of 2 or 3 and having dietary data at baseline  
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33 127 constituted the study sample. Follow-up at 12, 24, 36 and 48 months were included in this  
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35 128 analysis. The overall loss to follow up rate was 16.8% over the study period.  
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### 38 129 **Radiographic progression of OA**

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40 130 In OAI, current radiographic assessment techniques on plain radiographs involved both  
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42 131 semi-quantitative and quantitative assessment of JSN. For the semi-quantitative  
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44 132 approach, the Osteoarthritis Research Society International grade (OARSI grade: 0=no  
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46 133 JSN, 1=definite JSN to 3=severe JSN) has been widely used to measure progression of  
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48 134 OA.<sup>17</sup> For these analyses, we used the publically available semi-quantitative JSN  
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50 135 readings (kXR\_SQ\_BU, version 11/07/2011, <http://oai.epi-ucsf.org>). Recently, a  
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52 136 quantitative approach has been used to provide a precise measure of joint space width  
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54 137 (JSW) in millimeters between the adjacent bones of the knee.<sup>18,19</sup> Multiple JSWs were  
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56 138 measured at fixed locations along the joint in medial compartment, denoted as JSW(x), at  
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2 139 0.025 intervals for  $x = 0.15 - 0.30$ . The reproducibility of this technique and the  
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4 140 responsiveness to change have been documented elsewhere,<sup>18 20</sup> including one study  
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6 141 using OAI data which demonstrated a responsiveness that compared favorably to  
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8 142 magnetic resonance imaging (MRI).<sup>20</sup> We used medial JSW at  $x=0.25$  with the best  
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10 143 responsiveness of change to quantify the progression of OA.<sup>20</sup> We define the repeated  
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12 144 measures of the decreases of JSW from baseline to 12, 24, 36 and 48 months as the  
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14 145 outcome variable.

### 146 **Assessment of soft drink consumption**

147 Usual dietary intakes of foods and nutrients including soft drink consumption were  
148 assessed at baseline with a Block Brief Food Frequency Questionnaire (FFQ) including 60  
149 food items in OAI.<sup>21</sup> The participants were asked how often they had consumed regular  
150 soft drinks/bottled drinks (not diet drinks) in the past 12 months (coded as: never, a few  
151 times per year, once per month, 2-3 times per month, once per week, twice per week, 3-4  
152 times per week, 5-6 times per week, and every day). Based on previous studies<sup>9,10,11</sup>, we  
153 grouped these into 4 categories: none,  $\leq 1$ , 2-4, and  $\geq 5$  times/week. Similar  
154 questionnaires were used to collect the frequencies of other beverages intake, such as,  
155 milk, juice, tea and coffee, etc. This brief FFQ has been validated against three four-day  
156 records in a group of middle-aged women, and against two seven-day records in a group  
157 of older men. The absolute value of macronutrients estimated by the reduced  
158 questionnaire was a slightly lower than food-record estimates, but most micronutrients  
159 were not underestimated.<sup>21, 22</sup>

### 160 **Information on covariates**

161 Baseline demographic and socioeconomic factors include race/ethnicity, age, sex, marital  
162 status, education level, employment status, annual income and social support. Individuals  
163 were classified as African American, white, or other racial/ethnic group based on self  
164 report. Education level was categorized as high school or less, college and above college.  
165 General clinical parameters include current smoking, alcohol consumption, history of

1  
2 166 traumatic knee injury and knee surgery, self-reported gout, body mass index (BMI),  
3  
4 167 physical activity, weight change, milk and juice intake, total energy intake and baseline  
5  
6 168 disease severity (KL grade). Physical activity was assessed by using the Physical Activity  
7  
8  
9 169 Scale for the Elderly (PASE), an established questionnaire for measuring physical activity  
10  
11 170 in older individuals that has also been validated in younger subjects.<sup>23, 24</sup> Alcohol  
12  
13 171 consumption (pure alcohol in grams /day) was assessed at baseline including separate  
14  
15 172 items for beer, wine, and liquor in OAI. In addition, we also adjusted for changes of the  
16  
17 173 beam angles and rim distances (from tibial plateau to tibial rim closest to femoral condyle  
18  
19 174 between follow-up visits and baseline) which indicate knee-positioning consistency for x-  
20  
21 175 ray exam.

## 23 176 **Statistical analysis**

25  
26 177 First we performed exploratory analyses of all variables of interest including the exposure  
27  
28 178 (frequency of soft drink intake), radiographic structural measures (K-L grade, JSN score  
29  
30 179 and JSW ) and potential confounders described above. Descriptive statistics such as the  
31  
32 180 minimum, maximum, median and mean for each continuous variable and frequency table  
33  
34 181 for each categorical variable was used to summarize the data as well as detect outliers,  
35  
36 182 data entry mistakes, and missing values.

37  
38  
39 183 The primary analysis was to assess the influence of soft drink consumption on the  
40  
41 184 change in JSW over the study period. The primary outcomes were repeated measures of  
42  
43 185 the JSW decreases from baseline to 12, 24, 36 and 48 months respectively. The initial  
44  
45 186 analyses were unadjusted comparisons of the changes of JSW over time among levels of  
46  
47 187 soft drink intake using Analysis of Variance (ANOVA) and Multivariate Analysis of  
48  
49 188 Variance (MANOVA). Then separate multivariate models for repeated measures by men  
50  
51 189 and women were used to test the independent association between soft drink intake and  
52  
53 190 the decrease in JSW over time, while adjusting for BMI, physical activity, baseline disease  
54  
55 191 severity and potential confounding factors described above. Due to the hierarchical  
56  
57 192 structure of the data (each subject has 2 knees over multiple time points), we used  
58  
59  
60

1  
2 193 general linear mixed models (GLMM) to account for within subject correlation. The final  
3  
4 194 covariance models were evaluated using Akaike's information criterion (AIC) and  
5  
6 195 Bayesian information criterion (BIC). BMI has been an important factor related to both  
7  
8 196 soft drink intake and OA progression.<sup>9, 25</sup> To examine the possible effect modifications, we  
9  
10 197 further performed stratified analyses by obesity ( $BMI \geq 30.0 \text{ kg/m}^2$ ) and also adjusted BMI  
11  
12 198 within each category to reduce the possible residual confounding bias. In addition, the  
13  
14 199 association of soft drink consumption with JSW change may also be mediated through  
15  
16 200 BMI. The indirect effect of BMI was evaluated using Sobel test<sup>26</sup>

17  
18  
19 201 In addition, we also used the first increase of the OARSI JSN grade as the endpoint.  
20  
21 202 We developed a Cox proportional hazards model to assess independent association  
22  
23 203 between soft drink intake and the JSN score change after controlling for other covariates.  
24  
25 204 For each participant, the time of follow-up was calculated from the baseline date to the  
26  
27 205 date of the first increase of JSN grade, death, or end of the study, whichever came first.  
28  
29 206 The discrete likelihood method was used for ties of the failure times in the models.  
30  
31 207 We used a robust sandwich covariance estimate to account for the intraclass dependence  
32  
33 208 within individual patients.<sup>27</sup> Participants who indicated no soft drink consumption in the  
34  
35 209 past year were chosen as the reference group for all analyses. Adjusted hazard ratios  
36  
37 210 with 95% confidence intervals were used to evaluate the strength of the associations. The  
38  
39 211 proportional hazard assumption was tested based on the smoothed plots of the scaled  
40  
41 212 Schoenfeld residuals. Data analyses were performed using SAS 9.2 (SAS Institute, Cary,  
42  
43 213 NC).

## 44 214 **Results**

45  
46  
47 215 In this study, we studied 2,149 participants from OAI having a total of 3,066 eligible knees.  
48  
49 216 All categories of soft drink intake were represented in participants at baseline (none,  
50  
51 217  $n=687$ ;  $\leq 1$  times/week,  $n=976$ ; 2-4 times/week,  $n=285$ ;  $\geq 5$  times/week,  $n=201$ ). Baseline  
52  
53 218 characteristics of participants are shown in Table 1 according to levels of soft drink intake.  
54  
55 219 Compared to no soft drink use, high soft drink users were more likely to be men, between  
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1  
2 220 45 and 54 years, not married, not employed, current smokers, and have lower education  
3  
4 221 and household income and higher BMI.

5  
6 222 Results of multivariable analyses are shown in Table 2 in men and women. We  
7  
8 223 observed a significant dose-response relationship in men between soft drink intake and  
9  
10 224 adjusted mean decreases of JSW in men ( $p$  trend<0.001) after controlling for age, race,  
11  
12 225 education, marital status, household income, employment, BMI, physical activity, follow-up  
13  
14 226 time, knee injury and knee surgery, smoking, milk and juice intake, total energy intake,  
15  
16 227 baseline KL grade, weight change, the changes of rim distance and beam angle. With  
17  
18 228 increasing levels of soft drink intake (none,  $\leq 1$ , 2-4, and  $\geq 5$  times/week), the mean  
19  
20 229 decreases of JSW were 0.31mm, 0.39mm, 0.34mm and 0.60mm respectively. When we  
21  
22 230 stratified by obesity, a stronger dose-response relationship was found (decreases of JSW  
23  
24 231 were 0.24mm, 0.38mm, 0.32mm, 0.62mm respectively) in non-obese men. In obese men,  
25  
26 232 only the highest soft drink level ( $\geq 5$  times/week) was associated with increased JSW  
27  
28 233 change compared to no use. The effect of soft drink consumption was different between  
29  
30 234 men and women ( $p$  for interaction =0.003). No significant association was observed in  
31  
32 235 women. Table 3 shows the multivariable adjusted hazard ratios (HR) of OA progression  
33  
34 236 evaluated by time to the first increase of semi- quantitative OARSI score. Consistent with  
35  
36 237 JSW analyses, we found that the increasing soft drink intake was associated with the  
37  
38 238 increasing rate of OA progression in men but not in women. Compared to no soft drink  
39  
40 239 intake, the HR for  $\leq 1$ , 2-4, and  $\geq 5$  times/week were 1.56 (95% CI, 1.13-2.16), 1.55 (95%  
41  
42 240 CI, 1.02-2.35) and 2.05 (95% CI, 1.32-3.19) respectively in men ( $p$  trend=0.002). When  
43  
44 241 we stratified by obesity, a dose-response relationship was observed in both non-obese  
45  
46 242 and obese men. The hazard ratios were 2.30 (95% CI, 1.22-4.34) and 1.90 (95% CI, 1.03-  
47  
48 243 3.52) respectively with the soft drink intake  $\geq 5$  times/week compared to no intake.  
49  
50 244 However, no significant association was found in women. In addition, our mediation  
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52 245 analysis indicated a modest (3.2%) indirect effect through BMI ( $p$  for Sobel test=0.098). In  
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2 246 sensitivity analyses, additional adjustment for alcohol consumption and a history of gout in  
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4 247 the above models did not change the results.  
5

## 6 248 **Discussion**

7  
8 249 In this 48-month follow-up study of people with radiographic knee OA, we found a positive  
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10 250 association with a significant dose-response relationship between soft drink consumption  
11  
12 251 and structural progression of knee OA measured by both semi-quantitative and  
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14 252 quantitative JSN independent of BMI and other potential risk factors in men, but not in  
15  
16 253 women.  
17

18  
19 254 Knee OA progression has been thought to involve multiple mechanisms besides  
20  
21 255 cartilage loss including changes in bone composition, shape, as well as  
22  
23 256 proprioception,<sup>28,29</sup> which might be subject to the influences of macro and micronutrients  
24  
25 257 in the diet. McAlindon et al. reported that a higher consumption of anti-oxidant  
26  
27 258 micronutrients, especially vitamin C, might decrease cartilage loss and OA progression,<sup>14</sup>  
28  
29 259 and low vitamin D intake and low serum vitamin D levels might increase the risk for  
30  
31 260 progression of knee OA.<sup>13</sup> However, no study investigated the association of soft drink  
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33 261 consumption and progression of OA. Sugar sweetened beverages intake is a significant  
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35 262 contributor to weight-gain and has been associated with increased risk of obesity, type 2  
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37 263 diabetes, cardiovascular disease and poor bone health.<sup>10 11,30</sup> Nevertheless, the biologic  
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39 264 mechanism for soft drinks in the progression of OA remains unclear. One explanation for  
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41 265 the observed findings is that soft drinks may substitute for healthy diet. Soft drink  
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43 266 consumption may be associated with decreased intakes of protein, milk and dairy  
44  
45 267 products, fruit juice, fruit and a variety of vitamins and nutrients.<sup>12,31</sup> One study reported a  
46  
47 268 negative association between soft drink consumption and an overall healthy eating  
48  
49 269 index.<sup>32</sup> However, in our analysis, the observed effects remained after adjustment for milk  
50  
51 270 and juice intake supports the likelihood that this is not only due to displacement of other  
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53 271 healthy beverages in the diet. We considered the extent to which the sugar in soft drinks  
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55 272 leads to OA progression. To further evaluate this, we evaluated the relation between fruit  
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2 273 juice consumption and OA progression. Fruit juice consumption was not associated with  
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4 274 OA progression in our study (results are not shown). It is possible that vitamins, minerals,  
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6 275 soluble fiber, and phytochemicals in fruit juices may have beneficial effects  
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8 276 counterbalancing potential adverse effects of sugars.

10 277 Previous studies demonstrated that weight gain and obesity may increase risk of joint  
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12 278 space loss, suggestive of cartilage loss, as visualized on radiographs,<sup>7, 33, 34</sup> though these  
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14 279 findings are not universally reported. Nevertheless, our mediation analysis indicated that  
15  
16 280 the indirect effect through BMI was modest and the association between soft drinks and  
17  
18 281 OA progression remained after adjustment for BMI, weight change and total energy intake  
19  
20 282 suggestive of independent effects of soft drinks. Soft drinks may contain phosphoric acid,  
21  
22 283 which was shown to interfere with calcium absorption and to contribute to imbalances that  
23  
24 284 lead to additional loss of calcium.<sup>35</sup> It has also been suggested that the high fructose corn  
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26 285 syrup used to sweeten carbonated beverages may negatively affect bone.<sup>36</sup> Long-term  
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28 286 effects of soft drinks on osteoarthritis have not been studied in experimental settings so  
29  
30 287 far, and further research is warranted.

34 288 Sex differences have been noted in the prevalence, incidence, and severity of OA for  
35  
36 289 many years.<sup>37</sup> Faber and colleagues found cartilage thickness of the distal femur to be  
37  
38 290 less in women than in men.<sup>38</sup> Other evidences suggested a protective effect of  
39  
40 291 exogenous estrogen on cartilage and bone turnover.<sup>39</sup> However the gender differences  
41  
42 292 in the relationship of soft drink consumption with OA progression are not understood. We  
43  
44 293 found a stronger association between soft drink consumption and JSW change in non-  
45  
46 294 obese men than in obese men. One possible reason is that the effect of soft drink  
47  
48 295 consumption may not be strong enough to provide additional effect beyond obesity.

51 296 The strengths of this study include the prospective design, large number of patients  
52  
53 297 with knee OA, and the state-of-the-art quantitative measures of structural change from  
54  
55 298 sophisticated image processing technology. The quantitative software based assessment  
56  
57 299 provides a more precise measure of JSW in millimeters and permits the assessor to  
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1  
2 300 document appreciable change in JSW in the tibiofemoral compartment<sup>18, 19</sup> In contrast,  
3  
4 301 the semi-quantitative approach, for example, the KL grading or the OARSI score, has  
5  
6 302 limitations that lead to insensitivity to changes in status.<sup>40</sup> The consistent findings from  
7  
8 303 both quantitative and semi- quantitative measures of OA progression increase the  
9  
10 304 reliability of the study. In addition, we excluded knees in which the difference of rim  
11  
12 305 distance between follow-up and baseline visits  $\geq 2$ mm and adjusted for changes of rim  
13  
14 306 distance and beam angle in the multivariate models to minimize the possible  
15  
16 307 measurement error of radiographic data.

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18  
19 308 Because of the observational nature of the study, patients were not randomly assigned  
20  
21 309 to soft drink groups. We cannot prove that the observed associations are causal because  
22  
23 310 residual confounding could theoretically affect the observed associations. However, we  
24  
25 311 controlled for potential confounding by most known risk factors that are plausibly  
26  
27 312 associated with soft drink consumption and changes in these variables over time.  
28  
29 313 Imprecise dietary measurement could potentially have influenced our observed  
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31 314 associations. However, random errors in dietary assessment measures might have  
32  
33 315 accounted for a lack of association but not the reverse.

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35  
36 316 In conclusion, our study suggested that frequent consumption of sweetened soft drinks  
37  
38 317 may be associated with increased OA progression in men. Replication of these novel  
39  
40 318 findings in other prospective studies demonstrating the reduction in soft drink consumption  
41  
42 319 leads to delay in OA progression are needed to test this hypothesis.  
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45 320

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14  
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16  
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18  
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26  
27 339 the writing of the report; or in the decision to submit the paper for publication.

28  
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31  
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33  
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35  
36 343 Research  
37  
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39  
40 345 **Data sharing statement:** There are no additional data available.  
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**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				P value
		None n=687	≤1 n=976	2-4 n=285	≥5 n=201	
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) <sup>a</sup>	157 (82)	147 (77)	161 (82)	165 (90)	163 (83)	0.001
BMI (kg/m <sup>2</sup> ), %						
<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 <sup>c</sup> (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

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

355 b. Body mass index

356 c. Kellgren-Lawrence Scale

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**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.							



## References

1. Dunlop DD, Manheim LM, Yelin EH, Song J, Chang RW. The costs of arthritis. *Arthritis Rheum*. Feb 15 2003;49(1):101-113.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum*. Jan 2008;58(1):26-35.
3. Reginster JY. The prevalence and burden of arthritis. *Rheumatology (Oxford)*. Apr 2002;41 Suppl 1:3-6.
4. Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. *Radiol Clin North Am*. Jan 2004;42(1):1-9, v.
5. Garstang SV, Stitik TP. Osteoarthritis: epidemiology, risk factors, and pathophysiology. *Am J Phys Med Rehabil*. Nov 2006;85(11 Suppl):S2-11; quiz S12-14.
6. Zhang Y, Niu J, Felson DT, Choi HK, Nevitt M, Neogi T. Methodologic challenges in studying risk factors for progression of knee osteoarthritis. *Arthritis Care Res (Hoboken)*. Nov 2010;62(11):1527-1532.
7. Felson DT, Goggins J, Niu J, Zhang Y, Hunter DJ. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. *Arthritis Rheum*. Dec 2004;50(12):3904-3909.
8. Nielsen SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. *Am J Prev Med*. Oct 2004;27(3):205-210.
9. Malik VS, Popkin BM, Bray GA, Despres JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation*. Mar 23 2010;121(11):1356-1364.
10. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care*. Nov 2010;33(11):2477-2483.
11. Wyszak G. Teenaged girls, carbonated beverage consumption, and bone fractures. *Arch Pediatr Adolesc Med*. Jun 2000;154(6):610-613.
12. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health*. Apr 2007;97(4):667-675.
13. McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med*. Sep 1 1996;125(5):353-359.
14. McAlindon TE, Jacques P, Zhang Y, et al. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? *Arthritis Rheum*. Apr 1996;39(4):648-656.
15. Simard JF, Karlson EW, Costenbader KH, et al. Perinatal factors and adult-onset lupus. *Arthritis Rheum*. Aug 15 2008;59(8):1155-1161.
16. The osteoarthritis initiative protocol for the cohort study. <<http://oai.epi-csf.org/datarelease/docs/StudyDesignProtocol.pdf>>; [accessed 04.25.2012]
17. Guermazi A, Hunter DJ, Roemer FW. Plain radiography and magnetic resonance imaging diagnostics in osteoarthritis: validated staging and scoring. *J Bone Joint Surg Am*. Feb 2009;91 Suppl 1:54-62.

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18. Duryea J, Zaim S, Genant HK. New radiographic-based surrogate outcome measures for osteoarthritis of the knee. *Osteoarthritis Cartilage*. Feb 2003;11(2):102-110.
19. Sharp JT, Angwin J, Boers M, et al. Computer based methods for measurement of joint space width: update of an ongoing OMERACT project. *J Rheumatol*. Apr 2007;34(4):874-883.
20. Duryea J, Neumann G, Niu J, et al. Comparison of radiographic joint space width with magnetic resonance imaging cartilage morphometry: analysis of longitudinal data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)*. Jul 2010;62(7):932-937.
21. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. *Epidemiology*. Jan 1990;1(1):58-64.
22. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol*. Sep 1986;124(3):453-469.
23. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*. Feb 1993;46(2):153-162.
24. Johansen KL, Painter P, Kent-Braun JA, et al. Validation of questionnaires to estimate physical activity and functioning in end-stage renal disease. *Kidney Int*. Mar 2001;59(3):1121-1127.
25. Issa SN, Sharma L. Epidemiology of osteoarthritis: an update. *Curr Rheumatol Rep*. Feb 2006;8(1):7-15.
26. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. Dec 1986;51(6):1173-1182.
27. Lin DY. Cox regression analysis of multivariate failure time data: the marginal approach. *Stat Med*. Nov 15 1994;13(21):2233-2247.
28. Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis*. Jan 2011;70(1):60-67.
29. Driban JB, Lo GH, Lee JY, et al. Quantitative bone marrow lesion size in osteoarthritic knees correlates with cartilage damage and predicts longitudinal cartilage loss. *BMC Musculoskelet Disord*. 2011;12:217.
30. Tucker KL. Dietary intake and bone status with aging. *Curr Pharm Des*. 2003;9(32):2687-2704.
31. Marshall TA, Eichenberger Gilmore JM, Broffitt B, Stumbo PJ, Levy SM. Diet quality in young children is influenced by beverage consumption. *J Am Coll Nutr*. Feb 2005;24(1):65-75.
32. Rodriguez-Artalejo F, Garcia EL, Gorgojo L, et al. Consumption of bakery products, sweetened soft drinks and yogurt among children aged 6-7 years: association with nutrient intake and overall diet quality. *Br J Nutr*. Mar 2003;89(3):419-429.
33. Wolfe F, Lane NE. The longterm outcome of osteoarthritis: rates and predictors of joint space narrowing in symptomatic patients with knee osteoarthritis. *J Rheumatol*. Jan 2002;29(1):139-146.
34. Dougados M, Gueguen A, Nguyen M, et al. Longitudinal radiologic evaluation of osteoarthritis of the knee. *J Rheumatol*. Mar 1992;19(3):378-384.

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35. Amato D, Maravilla A, Montoya C, et al. Acute effects of soft drink intake on calcium and phosphate metabolism in immature and adult rats. *Rev Invest Clin*. May-Jun 1998;50(3):185-189.
36. Milne DB, Nielsen FH. The interaction between dietary fructose and magnesium adversely affects macromineral homeostasis in men. *J Am Coll Nutr*. Feb 2000;19(1):31-37.
37. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage*. Sep 2005;13(9):769-781.
38. Faber SC, Eckstein F, Lukasz S, et al. Gender differences in knee joint cartilage thickness, volume and articular surface areas: assessment with quantitative three-dimensional MR imaging. *Skeletal Radiol*. Mar 2001;30(3):144-150.
39. Linn S, Murtaugh B, Casey E. Role of sex hormones in the development of osteoarthritis. *Pm R*. May 2012;4(5 Suppl):S169-173.
40. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage*. 2007;15 Suppl A:A1-56.

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2 1 **Soft Drink Intake and Progression of Radiographic Knee Osteoarthritis: Data from**  
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4 2 **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,  $\leq 1$ , 2-4, and  $\geq 5$  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 ( $\geq 5$  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.

## 85 Introduction

86 Osteoarthritis (OA), a slowly progressing disease characterized by pain, deformity, and loss  
87 of function, is the major cause physical disability in older people.<sup>1</sup> Nearly 27 million have  
88 clinical osteoarthritis in the United States.<sup>2</sup> With the aging of the population, the health care  
89 burden from OA is expected to increase dramatically during the next few decades.<sup>3</sup>  
90 However, little is known about the course of OA progression over time in patients with OA.  
91 It is, therefore, of great importance to identify modifiable risk factors for OA progression.  
92 Over the past few decades, many observational studies have examined risk factors for the  
93 incidence and progression of knee OA. Several risk factors (i.e., obesity, joint injury, and  
94 certain sports) have been found to be strongly associated with an increased risk for  
95 incident knee OA.<sup>4,5</sup> However, findings on risk factors for OA progression have been  
96 inconclusive. Except for the level of serum hyaluronic acid and generalized OA, no other  
97 risk factor has been consistently associated with the risk of OA progression.<sup>6,7</sup>

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

## 107 Methods

### 108 Subjects

109 OAI was launched in 2002 by the National Institute of Health (NIH) to develop resources for  
110 the identification of new biomarkers and treatment targets for knee OA. The objective of the  
111 OAI was to pool public and private scientific expertise and funding to collect, analyze, and

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2 112 make widely available the largest research resource to date of clinical data, radiologic  
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4 113 information, and biospecimens from those at risk for or with knee OA. The OAI began  
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6 114 enrolling people aged 45 through 79 years in 2004 and followed them annually for the  
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8 115 development or progression of OA. The clinical sites involved were located in Baltimore,  
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10 116 MD; Columbus, OH; Pittsburgh, PA; and Pawtucket, RI. OAI has been a longitudinal study  
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12 117 of 4,796 subjects with either established knee OA or significant risk factors for the  
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14 118 development of knee OA followed over an 8-year period.<sup>15</sup> The follow-up rate was >90%  
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16 119 over the first 48 months. The detailed OAI protocol can be found elsewhere.<sup>16</sup>  
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19 120 For the current study, we included individuals with medial radiographic knee OA in at  
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21 121 least one knee at baseline. We excluded knees with severe radiographic OA defined as  
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23 122 the baseline Kellgren and Lawrence (KL) grade of 4 or those with primarily lateral joint  
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25 123 space narrowing (JSN), and knees in which the difference of rim distance (from tibial  
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27 124 plateau to tibial rim closest to femoral condyle) between follow-up and baseline visits were  
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29 125  $\geq 2$ mm to minimize possible measurement error of radiographic data. The 2,149  
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31 126 participants (3,066 knees) with KL grade of 2 or 3 and having dietary data at baseline  
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33 127 constituted the study sample. Follow-up at 12, 24, 36 and 48 months were included in this  
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35 128 analysis. **The overall loss to follow up rate was 16.8% over the study period.**  
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### 38 129 **Radiographic progression of OA**

39 130 In OAI, current radiographic assessment techniques on plain radiographs involved both  
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41 131 semi-quantitative and quantitative assessment of JSN. For the semi-quantitative  
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43 132 approach, the Osteoarthritis Research Society International grade (OARSI grade: 0=no  
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45 133 JSN, 1=definite JSN to 3=severe JSN) has been widely used to measure progression of  
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47 134 OA.<sup>17</sup> For these analyses, we used the publically available semi-quantitative JSN  
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49 135 readings (kXR\_SQ\_BU, version 11/07/2011, <http://oai.epi-ucsf.org>). Recently, a  
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51 136 quantitative approach has been used to provide a precise measure of joint space width  
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53 137 (JSW) in millimeters between the adjacent bones of the knee.<sup>18,19</sup> Multiple JSWs were  
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55 138 measured at fixed locations along the joint in medial compartment, denoted as JSW(x), at  
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2 139 0.025 intervals for  $x = 0.15 - 0.30$ . The reproducibility of this technique and the  
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4 140 responsiveness to change have been documented elsewhere,<sup>18 20</sup> including one study  
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6 141 using OAI data which demonstrated a responsiveness that compared favorably to  
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8 142 magnetic resonance imaging (MRI).<sup>20</sup> We used medial JSW at  $x=0.25$  with the best  
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10 143 responsiveness of change to quantify the progression of OA.<sup>20</sup> We define the repeated  
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12 144 measures of the decreases of JSW from baseline to 12, 24, 36 and 48 months as the  
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14 145 outcome variable.

### 146 **Assessment of soft drink consumption**

147 Usual dietary intakes of foods and nutrients including soft drink consumption were  
148 assessed at baseline with a Block Brief Food Frequency Questionnaire (FFQ) including 60  
149 food items in OAI.<sup>21</sup> The participants were asked how often they had consumed regular  
150 soft drinks/bottled drinks (not diet drinks) in the past 12 months (coded as: never, a few  
151 times per year, once per month, 2-3 times per month, once per week, twice per week, 3-4  
152 times per week, 5-6 times per week, and every day). **Based on previous studies**<sup>9,10,11</sup>, we  
153 grouped these into 4 categories: none,  $\leq 1$ , 2-4, and  $\geq 5$  times/week. Similar  
154 questionnaires were used to collect the frequencies of other beverages intake, such as,  
155 milk, juice, tea and coffee, etc. This brief FFQ has been validated against three four-day  
156 records in a group of middle-aged women, and against two seven-day records in a group  
157 of older men. The absolute value of macronutrients estimated by the reduced  
158 questionnaire was a slightly lower than food-record estimates, but most micronutrients  
159 were not underestimated.<sup>21, 22</sup>

### 160 **Information on covariates**

161 Baseline demographic and socioeconomic factors include race/ethnicity, age, sex, marital  
162 status, education level, employment status, annual income and social support. Individuals  
163 were classified as African American, white, or other racial/ethnic group based on self  
164 report. Education level was categorized as high school or less, college and above college.  
165 General clinical parameters include current smoking, alcohol consumption, history of

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2 166 traumatic knee injury and knee surgery, self-reported gout, body mass index (BMI),  
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4 167 physical activity, weight change, milk and juice intake, total energy intake and baseline  
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6 168 disease severity (KL grade). Physical activity was assessed by using the Physical Activity  
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9 169 Scale for the Elderly (PASE), an established questionnaire for measuring physical activity  
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11 170 in older individuals that has also been validated in younger subjects.<sup>23, 24</sup> Alcohol  
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13 171 consumption (pure alcohol in grams /day) was assessed at baseline including separate  
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15 172 items for beer, wine, and liquor in OAI. In addition, we also adjusted for changes of the  
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17 173 beam angles and rim distances (from tibial plateau to tibial rim closest to femoral condyle  
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19 174 between follow-up visits and baseline) which indicate knee-positioning consistency for x-  
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21 175 ray exam.

## 23 176 **Statistical analysis**

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26 177 First we performed exploratory analyses of all variables of interest including the exposure  
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28 178 (frequency of soft drink intake), radiographic structural measures (K-L grade, JSN score  
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30 179 and JSW ) and potential confounders described above. Descriptive statistics such as the  
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32 180 minimum, maximum, median and mean for each continuous variable and frequency table  
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34 181 for each categorical variable was used to summarize the data as well as detect outliers,  
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36 182 data entry mistakes, and missing values.

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39 183 The primary analysis was to assess the influence of soft drink consumption on the  
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41 184 change in JSW over the study period. The primary outcomes were repeated measures of  
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43 185 the JSW decreases from baseline to 12, 24, 36 and 48 months respectively. The initial  
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45 186 analyses were unadjusted comparisons of the changes of JSW over time among levels of  
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47 187 soft drink intake using Analysis of Variance (ANOVA) and Multivariate Analysis of  
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49 188 Variance (MANOVA). Then separate multivariate models for repeated measures by men  
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51 189 and women were used to test the independent association between soft drink intake and  
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53 190 the decrease in JSW over time, while adjusting for BMI, physical activity, baseline disease  
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55 191 severity and potential confounding factors described above. Due to the hierarchical  
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57 192 structure of the data (each subject has 2 knees over multiple time points), we used  
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2 193 general linear mixed models (GLMM) to account for within subject correlation. The final  
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4 194 covariance models were evaluated using Akaike's information criterion (AIC) and  
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6 195 Bayesian information criterion (BIC). BMI has been an important factor related to both  
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8 196 soft drink intake and OA progression.<sup>9, 25</sup> To examine the possible effect modifications, we  
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10 197 further performed stratified analyses by obesity ( $BMI \geq 30.0 \text{ kg/m}^2$ ) and also adjusted BMI  
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12 198 within each category to reduce the possible residual confounding bias. In addition, the  
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14 199 association of soft drink consumption with JSW change may also be mediated through  
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16 200 BMI. The indirect effect of BMI was evaluated using Sobel test<sup>26</sup>

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18  
19 201 In addition, we also used the first increase of the OARSI JSN grade as the endpoint.  
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21 202 We developed a Cox proportional hazards model to assess independent association  
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23 203 between soft drink intake and the JSN score change after controlling for other covariates.  
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25 204 For each participant, the time of follow-up was calculated from the baseline date to the  
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27 205 date of the first increase of JSN grade, death, or end of the study, whichever came first.  
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29 206 The discrete likelihood method was used for ties of the failure times in the models.  
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31 207 We used a robust sandwich covariance estimate to account for the intraclass dependence  
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33 208 within individual patients.<sup>27</sup> Participants who indicated no soft drink consumption in the  
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35 209 past year were chosen as the reference group for all analyses. Adjusted hazard ratios  
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37 210 with 95% confidence intervals were used to evaluate the strength of the associations. The  
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39 211 proportional hazard assumption was tested based on the smoothed plots of the scaled  
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41 212 Schoenfeld residuals. Data analyses were performed using SAS 9.2 (SAS Institute, Cary,  
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43 213 NC).

## 44 214 **Results**

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47 215 In this study, we studied 2,149 participants from OAI having a total of 3,066 eligible knees.  
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49 216 **All categories of soft drink intake were represented in participants at baseline** (none,  
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51 217  $n=687$ ;  $\leq 1$  times/week,  $n=976$ ; 2-4 times/week,  $n=285$ ;  $\geq 5$  times/week,  $n=201$ ). Baseline  
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53 218 characteristics of participants are shown in Table 1 according to levels of soft drink intake.  
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55 219 Compared to no soft drink use, high soft drink users were more likely to be men, between  
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2 220 45 and 54 years, not married, not employed, current smokers, and have lower education  
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4 221 and household income and higher BMI.

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6 222 Results of multivariable analyses are shown in Table 2 in men and women. We  
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8 223 observed a significant dose-response relationship in men between soft drink intake and  
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10 224 adjusted mean decreases of JSW in men ( $p$  trend<0.001) after controlling for age, race,  
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12 225 education, marital status, household income, employment, BMI, physical activity, follow-up  
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14 226 time, knee injury and knee surgery, smoking, milk and juice intake, total energy intake,  
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16 227 baseline KL grade, weight change, the changes of rim distance and beam angle. With  
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18 228 increasing levels of soft drink intake (none,  $\leq 1$ , 2-4, and  $\geq 5$  times/week), the mean  
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20 229 decreases of JSW were 0.31mm, 0.39mm, 0.34mm and 0.60mm respectively. When we  
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22 230 stratified by obesity, a stronger dose-response relationship was found (decreases of JSW  
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24 231 were 0.24mm, 0.38mm, 0.32mm, 0.62mm respectively) in non-obese men. In obese men,  
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26 232 only the highest soft drink level ( $\geq 5$  times/week) was associated with increased JSW  
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28 233 change compared to no use. The effect of soft drink consumption was different between  
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30 234 men and women ( $p$  for interaction =0.003). No significant association was observed in  
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32 235 women. Table 3 shows the multivariable adjusted hazard ratios (HR) of OA progression  
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34 236 evaluated by time to the first increase of semi- quantitative OARSI score. Consistent with  
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36 237 JSW analyses, we found that the increasing soft drink intake was associated with the  
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38 238 increasing rate of OA progression in men but not in women. Compared to no soft drink  
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40 239 intake, the HR for  $\leq 1$ , 2-4, and  $\geq 5$  times/week were 1.56 (95% CI, 1.13-2.16), 1.55 (95%  
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42 240 CI, 1.02-2.35) and 2.05 (95% CI, 1.32-3.19) respectively in men ( $p$  trend=0.002). When  
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44 241 we stratified by obesity, a dose-response relationship was observed in both non-obese  
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46 242 and obese men. The hazard ratios were 2.30 (95% CI, 1.22-4.34) and 1.90 (95% CI, 1.03-  
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48 243 3.52) respectively with the soft drink intake  $\geq 5$  times/week compared to no intake.  
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50 244 However, no significant association was found in women. In addition, our mediation  
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52 245 analysis indicated a modest (3.2%) indirect effect through BMI ( $p$  for Sobel test=0.098). In  
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2 246 sensitivity analyses, additional adjustment for alcohol consumption and a history of gout in  
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4 247 the above models did not change the results.  
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## 6 248 Discussion

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8 249 In this 48-month follow-up study of people with radiographic knee OA, we found a positive  
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10 250 association with a significant dose-response relationship between soft drink consumption  
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12 251 and structural progression of knee OA measured by both semi-quantitative and  
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14 252 quantitative JSN independent of BMI and other potential risk factors in men, but not in  
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16 253 women.  
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19 254 Knee OA progression has been thought to involve multiple mechanisms besides  
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21 255 cartilage loss including changes in bone composition, shape, as well as  
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23 256 proprioception,<sup>28,29</sup> which might be subject to the influences of macro and micronutrients  
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25 257 in the diet. McAlindon et al. reported that a higher consumption of anti-oxidant  
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27 258 micronutrients, especially vitamin C, might decrease cartilage loss and OA progression,<sup>14</sup>  
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29 259 and low vitamin D intake and low serum vitamin D levels might increase the risk for  
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31 260 progression of knee OA.<sup>13</sup> However, no study investigated the association of soft drink  
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33 261 consumption and progression of OA. Sugar sweetened beverages intake is a significant  
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35 262 contributor to weight-gain and has been associated with increased risk of obesity, type 2  
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37 263 diabetes, cardiovascular disease and poor bone health.<sup>10 11,30</sup> Nevertheless, the biologic  
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39 264 mechanism for soft drinks in the progression of OA remains unclear. One explanation for  
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41 265 the observed findings is that soft drinks may substitute for healthy diet. Soft drink  
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43 266 consumption may be associated with decreased intakes of protein, milk and dairy  
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45 267 products, fruit juice, fruit and a variety of vitamins and nutrients.<sup>12,31</sup> One study reported a  
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47 268 negative association between soft drink consumption and an overall healthy eating  
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49 269 index.<sup>32</sup> However, in our analysis, the observed effects remained after adjustment for milk  
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51 270 and juice intake supports the likelihood that this is not only due to displacement of other  
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53 271 healthy beverages in the diet. We considered the extent to which the sugar in soft drinks  
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55 272 leads to OA progression. To further evaluate this, we evaluated the relation between fruit  
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2 273 juice consumption and OA progression. Fruit juice consumption was not associated with  
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4 274 OA progression in our study (results are not shown). It is possible that vitamins, minerals,  
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6 275 soluble fiber, and phytochemicals in fruit juices may have beneficial effects  
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8 276 counterbalancing potential adverse effects of sugars.

10 277 Previous studies demonstrated that weight gain and obesity may increase risk of joint  
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12 278 space loss, suggestive of cartilage loss, as visualized on radiographs,<sup>7, 33, 34</sup> though these  
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14 279 findings are not universally reported. Nevertheless, our mediation analysis indicated that  
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16 280 the indirect effect through BMI was modest and the association between soft drinks and  
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18 281 OA progression remained after adjustment for BMI, weight change and total energy intake  
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20 282 suggestive of independent effects of soft drinks. Soft drinks may contain phosphoric acid,  
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22 283 which was shown to interfere with calcium absorption and to contribute to imbalances that  
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24 284 lead to additional loss of calcium.<sup>35</sup> It has also been suggested that the high fructose corn  
25  
26 285 syrup used to sweeten carbonated beverages may negatively affect bone.<sup>36</sup> Long-term  
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28 286 effects of soft drinks on osteoarthritis have not been studied in experimental settings so  
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30 287 far, and further research is warranted.

34 288 Sex differences have been noted in the prevalence, incidence, and severity of OA for  
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36 289 many years.<sup>37</sup> Faber and colleagues found cartilage thickness of the distal femur to be  
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38 290 less in women than in men.<sup>38</sup> Other evidences suggested a protective effect of  
39  
40 291 exogenous estrogen on cartilage and bone turnover.<sup>39</sup> However the gender differences  
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42 292 in the relationship of soft drink consumption with OA progression are not understood. We  
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44 293 found a stronger association between soft drink consumption and JSW change in non-  
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46 294 obese men than in obese men. One possible reason is that the effect of soft drink  
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48 295 consumption may not be strong enough to provide additional effect beyond obesity.

51 296 The strengths of this study include the prospective design, large number of patients  
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53 297 with knee OA, and the state-of-the-art quantitative measures of structural change from  
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55 298 sophisticated image processing technology. The quantitative software based assessment  
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57 299 provides a more precise measure of JSW in millimeters and permits the assessor to  
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1  
2 300 document appreciable change in JSW in the tibiofemoral compartment<sup>18, 19</sup> In contrast,  
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4 301 the semi-quantitative approach, for example, the KL grading or the OARSI score, has  
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6 302 limitations that lead to insensitivity to changes in status.<sup>40</sup> The consistent findings from  
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8 303 both quantitative and semi- quantitative measures of OA progression increase the  
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10 304 reliability of the study. In addition, we excluded knees in which the difference of rim  
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12 305 distance between follow-up and baseline visits  $\geq 2$ mm and adjusted for changes of rim  
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14 306 distance and beam angle in the multivariate models to minimize the possible  
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16 307 measurement error of radiographic data.

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19 308 Because of the observational nature of the study, patients were not randomly assigned  
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21 309 to soft drink groups. We cannot prove that the observed associations are causal because  
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23 310 residual confounding could theoretically affect the observed associations. However, we  
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25 311 controlled for potential confounding by most known risk factors that are plausibly  
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27 312 associated with soft drink consumption and changes in these variables over time.  
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29 313 Imprecise dietary measurement could potentially have influenced our observed  
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31 314 associations. However, random errors in dietary assessment measures might have  
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33 315 accounted for a lack of association but not the reverse.

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36 316 In conclusion, our study suggested that frequent consumption of sweetened soft drinks  
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38 317 may be associated with increased OA progression in men. Replication of these novel  
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40 318 findings in other prospective studies demonstrating the reduction in soft drink consumption  
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42 319 leads to delay in OA progression are needed to test this hypothesis.

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15  
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17  
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25  
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27  
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29  
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31  
32 342 California, San Francisco (UCSF), and its affiliates. UCSF holds Office of Human  
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38 345 **Data sharing statement:** There are no additional data available.  
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**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				P value
		None n=687	≤1 n=976	2-4 n=285	≥5 n=201	
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) <sup>a</sup>	157 (82)	147 (77)	161 (82)	165 (90)	163 (83)	0.001
BMI (kg/m <sup>2</sup> ), %						
<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 <sup>c</sup> (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

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

355 b. Body mass index

356 c. Kellgren-Lawrence Scale

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**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.							

## References

1. Dunlop DD, Manheim LM, Yelin EH, Song J, Chang RW. The costs of arthritis. *Arthritis Rheum*. Feb 15 2003;49(1):101-113.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum*. Jan 2008;58(1):26-35.
3. Reginster JY. The prevalence and burden of arthritis. *Rheumatology (Oxford)*. Apr 2002;41 Suppl 1:3-6.
4. Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. *Radiol Clin North Am*. Jan 2004;42(1):1-9, v.
5. Garstang SV, Stitik TP. Osteoarthritis: epidemiology, risk factors, and pathophysiology. *Am J Phys Med Rehabil*. Nov 2006;85(11 Suppl):S2-11; quiz S12-14.
6. Zhang Y, Niu J, Felson DT, Choi HK, Nevitt M, Neogi T. Methodologic challenges in studying risk factors for progression of knee osteoarthritis. *Arthritis Care Res (Hoboken)*. Nov 2010;62(11):1527-1532.
7. Felson DT, Goggins J, Niu J, Zhang Y, Hunter DJ. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. *Arthritis Rheum*. Dec 2004;50(12):3904-3909.
8. Nielsen SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. *Am J Prev Med*. Oct 2004;27(3):205-210.
9. Malik VS, Popkin BM, Bray GA, Despres JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation*. Mar 23 2010;121(11):1356-1364.
10. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care*. Nov 2010;33(11):2477-2483.
11. Wyszak G. Teenaged girls, carbonated beverage consumption, and bone fractures. *Arch Pediatr Adolesc Med*. Jun 2000;154(6):610-613.
12. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health*. Apr 2007;97(4):667-675.
13. McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med*. Sep 1 1996;125(5):353-359.
14. McAlindon TE, Jacques P, Zhang Y, et al. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? *Arthritis Rheum*. Apr 1996;39(4):648-656.
15. Simard JF, Karlson EW, Costenbader KH, et al. Perinatal factors and adult-onset lupus. *Arthritis Rheum*. Aug 15 2008;59(8):1155-1161.
16. The osteoarthritis initiative protocol for the cohort study. <<http://oai.epi-csf.org/datarelease/docs/StudyDesignProtocol.pdf>>; [accessed 04.25.2012]
17. Guermazi A, Hunter DJ, Roemer FW. Plain radiography and magnetic resonance imaging diagnostics in osteoarthritis: validated staging and scoring. *J Bone Joint Surg Am*. Feb 2009;91 Suppl 1:54-62.

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18. Duryea J, Zaim S, Genant HK. New radiographic-based surrogate outcome measures for osteoarthritis of the knee. *Osteoarthritis Cartilage*. Feb 2003;11(2):102-110.
19. Sharp JT, Angwin J, Boers M, et al. Computer based methods for measurement of joint space width: update of an ongoing OMERACT project. *J Rheumatol*. Apr 2007;34(4):874-883.
20. Duryea J, Neumann G, Niu J, et al. Comparison of radiographic joint space width with magnetic resonance imaging cartilage morphometry: analysis of longitudinal data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)*. Jul 2010;62(7):932-937.
21. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. *Epidemiology*. Jan 1990;1(1):58-64.
22. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol*. Sep 1986;124(3):453-469.
23. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*. Feb 1993;46(2):153-162.
24. Johansen KL, Painter P, Kent-Braun JA, et al. Validation of questionnaires to estimate physical activity and functioning in end-stage renal disease. *Kidney Int*. Mar 2001;59(3):1121-1127.
25. Issa SN, Sharma L. Epidemiology of osteoarthritis: an update. *Curr Rheumatol Rep*. Feb 2006;8(1):7-15.
26. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. Dec 1986;51(6):1173-1182.
27. Lin DY. Cox regression analysis of multivariate failure time data: the marginal approach. *Stat Med*. Nov 15 1994;13(21):2233-2247.
28. Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis*. Jan 2011;70(1):60-67.
29. Driban JB, Lo GH, Lee JY, et al. Quantitative bone marrow lesion size in osteoarthritic knees correlates with cartilage damage and predicts longitudinal cartilage loss. *BMC Musculoskelet Disord*. 2011;12:217.
30. Tucker KL. Dietary intake and bone status with aging. *Curr Pharm Des*. 2003;9(32):2687-2704.
31. Marshall TA, Eichenberger Gilmore JM, Broffitt B, Stumbo PJ, Levy SM. Diet quality in young children is influenced by beverage consumption. *J Am Coll Nutr*. Feb 2005;24(1):65-75.
32. Rodriguez-Artalejo F, Garcia EL, Gorgojo L, et al. Consumption of bakery products, sweetened soft drinks and yogurt among children aged 6-7 years: association with nutrient intake and overall diet quality. *Br J Nutr*. Mar 2003;89(3):419-429.
33. Wolfe F, Lane NE. The longterm outcome of osteoarthritis: rates and predictors of joint space narrowing in symptomatic patients with knee osteoarthritis. *J Rheumatol*. Jan 2002;29(1):139-146.
34. Dougados M, Gueguen A, Nguyen M, et al. Longitudinal radiologic evaluation of osteoarthritis of the knee. *J Rheumatol*. Mar 1992;19(3):378-384.

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35. Amato D, Maravilla A, Montoya C, et al. Acute effects of soft drink intake on calcium and phosphate metabolism in immature and adult rats. *Rev Invest Clin*. May-Jun 1998;50(3):185-189.
  36. Milne DB, Nielsen FH. The interaction between dietary fructose and magnesium adversely affects macromineral homeostasis in men. *J Am Coll Nutr*. Feb 2000;19(1):31-37.
  37. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage*. Sep 2005;13(9):769-781.
  38. Faber SC, Eckstein F, Lukasz S, et al. Gender differences in knee joint cartilage thickness, volume and articular surface areas: assessment with quantitative three-dimensional MR imaging. *Skeletal Radiol*. Mar 2001;30(3):144-150.
  39. Linn S, Murtaugh B, Casey E. Role of sex hormones in the development of osteoarthritis. *Pm R*. May 2012;4(5 Suppl):S169-173.
  40. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage*. 2007;15 Suppl A:A1-56.

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

	Item No	Recommendation
<b>Title and abstract</b>	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
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
<b>Methods</b>		
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
<b>Results</b>		
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
<b>Discussion</b>		
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
<b>Other information</b>		
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>.



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

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Secondary Subject Heading:	Rheumatology, Nutrition and metabolism
Keywords:	Epidemiology < TROPICAL MEDICINE, RHEUMATOLOGY, NUTRITION & DIETETICS

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2 1 **Soft Drink Intake and Progression of Radiographic Knee Osteoarthritis: Data from**  
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8 4 Bing Lu<sup>1</sup>, Oneeb Ahmad<sup>2</sup>, Fang-Fang Zhang<sup>3</sup>, Jeffrey B. Driban<sup>4</sup>, Jeffrey Duryea<sup>1</sup>, Kate L.  
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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,  $\leq 1$ , 2-4, and  $\geq 5$  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 ( $\geq 5$  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.

## 85 Introduction

86 Osteoarthritis (OA), a slowly progressing disease characterized by pain, deformity, and loss  
87 of function, is the major cause physical disability in older people.<sup>1</sup> Nearly 27 million have  
88 clinical osteoarthritis in the United States.<sup>2</sup> With the aging of the population, the health care  
89 burden from OA is expected to increase dramatically during the next few decades.<sup>3</sup>  
90 However, little is known about the course of OA progression over time in patients with OA.  
91 It is, therefore, of great importance to identify modifiable risk factors for OA progression.  
92 Over the past few decades, many observational studies have examined risk factors for the  
93 incidence and progression of knee OA. Several risk factors (i.e., obesity, joint injury, and  
94 certain sports) have been found to be strongly associated with an increased risk for  
95 incident knee OA.<sup>4,5</sup> However, findings on risk factors for OA progression have been  
96 inconclusive. Except for the level of serum hyaluronic acid and generalized OA, no other  
97 risk factor has been consistently associated with the risk of OA progression.<sup>6,7</sup>

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

## 107 Methods

### 108 Subjects

109 OAI was launched in 2002 by the National Institute of Health (NIH) to develop resources for  
110 the identification of new biomarkers and treatment targets for knee OA. The objective of the  
111 OAI was to pool public and private scientific expertise and funding to collect, analyze, and

1  
2 112 make widely available the largest research resource to date of clinical data, radiologic  
3  
4 113 information, and biospecimens from those at risk for or with knee OA. The OAI began  
5  
6 114 enrolling people aged 45 through 79 years in 2004 and followed them annually for the  
7  
8 115 development or progression of OA. The clinical sites involved were located in Baltimore,  
9  
10 116 MD; Columbus, OH; Pittsburgh, PA; and Pawtucket, RI. OAI has been a longitudinal study  
11  
12 117 of 4,796 subjects with either established knee OA or significant risk factors for the  
13  
14 118 development of knee OA followed over an 8-year period.<sup>15</sup> The follow-up rate was >90%  
15  
16 119 over the first 48 months. The detailed OAI protocol can be found elsewhere.<sup>16</sup>  
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19 120 For the current study, we included individuals with medial radiographic knee OA in at  
20  
21 121 least one knee at baseline. We excluded knees with severe radiographic OA defined as  
22  
23 122 the baseline Kellgren and Lawrence (KL) grade of 4 or those with primarily lateral joint  
24  
25 123 space narrowing (JSN), and knees in which the difference of rim distance (from tibial  
26  
27 124 plateau to tibial rim closest to femoral condyle) between follow-up and baseline visits were  
28  
29 125  $\geq 2$ mm to minimize possible measurement error of radiographic data. The 2,149  
30  
31 126 participants (3,066 knees) with KL grade of 2 or 3 and having dietary data at baseline  
32  
33 127 constituted the study sample. Follow-up at 12, 24, 36 and 48 months were included in this  
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35 128 analysis. The overall loss to follow up rate was 16.8% over the study period.  
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### 38 129 **Radiographic progression of OA**

39  
40 130 In OAI, current radiographic assessment techniques on plain radiographs involved both  
41  
42 131 semi-quantitative and quantitative assessment of JSN. For the semi-quantitative  
43  
44 132 approach, the Osteoarthritis Research Society International grade (OARSI grade: 0=no  
45  
46 133 JSN, 1=definite JSN to 3=severe JSN) has been widely used to measure progression of  
47  
48 134 OA.<sup>17</sup> For these analyses, we used the publically available semi-quantitative JSN  
49  
50 135 readings (kXR\_SQ\_BU, version 11/07/2011, <http://oai.epi-ucsf.org>). Recently, a  
51  
52 136 quantitative approach has been used to provide a precise measure of joint space width  
53  
54 137 (JSW) in millimeters between the adjacent bones of the knee.<sup>18,19</sup> Multiple JSWs were  
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56 138 measured at fixed locations along the joint in medial compartment, denoted as JSW(x), at  
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1  
2 139 0.025 intervals for  $x = 0.15 - 0.30$ . The reproducibility of this technique and the  
3  
4 140 responsiveness to change have been documented elsewhere,<sup>18 20</sup> including one study  
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6 141 using OAI data which demonstrated a responsiveness that compared favorably to  
7  
8 142 magnetic resonance imaging (MRI).<sup>20</sup> We used medial JSW at  $x=0.25$  with the best  
9  
10 143 responsiveness of change to quantify the progression of OA.<sup>20</sup> We define the repeated  
11  
12 144 measures of the decreases of JSW from baseline to 12, 24, 36 and 48 months as the  
13  
14 145 outcome variable.

### 17 146 **Assessment of soft drink consumption**

19 147 Usual dietary intakes of foods and nutrients including soft drink consumption were  
20  
21 148 assessed at baseline with a Block Brief Food Frequency Questionnaire (FFQ) including 60  
22  
23 149 food items in OAI.<sup>21</sup> The participants were asked how often they had consumed regular  
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25 150 soft drinks/bottled drinks (not diet drinks) in the past 12 months (coded as: never, a few  
26  
27 151 times per year, once per month, 2-3 times per month, once per week, twice per week, 3-4  
28  
29 152 times per week, 5-6 times per week, and every day) (variable name: V00FFQ69,  
30  
31 <http://oai.epi-ucsf.org>). Based on previous studies<sup>9,10,11</sup>, we grouped these into 4  
32  
33 153 categories: none,  $\leq 1$ , 2-4, and  $\geq 5$  times/week. Similar questionnaires were used to collect  
34  
35 154 the frequencies of other beverages intake, such as, milk, juice, tea and coffee, etc. This  
36  
37 155 brief FFQ has been validated against three four-day records in a group of middle-aged  
38  
39 156 women, and against two seven-day records in a group of older men. The absolute value  
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41 157 of macronutrients estimated by the reduced questionnaire was a slightly lower than food-  
42  
43 158 record estimates, but most micronutrients were not underestimated.<sup>21, 22</sup>

### 47 160 **Information on covariates**

49 161 Baseline demographic and socioeconomic factors include race/ethnicity, age, sex, marital  
50  
51 162 status, education level, employment status, annual income and social support. Individuals  
52  
53 163 were classified as African American, white, or other racial/ethnic group based on self  
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55 164 report. Education level was categorized as high school or less, college and above college.  
56  
57 165 General clinical parameters include current smoking, alcohol consumption, history of  
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1  
2 166 traumatic knee injury and knee surgery, self-reported gout, body mass index (BMI),  
3  
4 167 physical activity, weight change, milk and juice intake, total energy intake and baseline  
5  
6 168 disease severity (KL grade). Physical activity was assessed by using the Physical Activity  
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8  
9 169 Scale for the Elderly (PASE), an established questionnaire for measuring physical activity  
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11 170 in older individuals that has also been validated in younger subjects.<sup>23, 24</sup> Alcohol  
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13 171 consumption (pure alcohol in grams /day) was assessed at baseline including separate  
14  
15 172 items for beer, wine, and liquor in OAI. In addition, we also adjusted for changes of the  
16  
17 173 beam angles and rim distances (from tibial plateau to tibial rim closest to femoral condyle  
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19 174 between follow-up visits and baseline) which indicate knee-positioning consistency for x-  
20  
21 175 ray exam.

### 23 176 **Statistical analysis**

25  
26 177 First we performed exploratory analyses of all variables of interest including the exposure  
27  
28 178 (frequency of soft drink intake), radiographic structural measures (K-L grade, JSN score  
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30 179 and JSW ) and potential confounders described above. Descriptive statistics such as the  
31  
32 180 minimum, maximum, median and mean for each continuous variable and frequency table  
33  
34 181 for each categorical variable was used to summarize the data as well as detect outliers,  
35  
36 182 data entry mistakes, and missing values.

37  
38  
39 183 The primary analysis was to assess the influence of soft drink consumption on the  
40  
41 184 change in JSW over the study period. The primary outcomes were repeated measures of  
42  
43 185 the JSW decreases from baseline to 12, 24, 36 and 48 months respectively. The initial  
44  
45 186 analyses were unadjusted comparisons of the changes of JSW over time among levels of  
46  
47 187 soft drink intake using Analysis of Variance (ANOVA) and Multivariate Analysis of  
48  
49 188 Variance (MANOVA). Then separate multivariate models for repeated measures by men  
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51 189 and women were used to test the independent association between soft drink intake and  
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53 190 the decrease in JSW over time, while adjusting for BMI, physical activity, baseline disease  
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55 191 severity and potential confounding factors described above. Due to the hierarchical  
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57 192 structure of the data (each subject has 2 knees over multiple time points), we used  
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1  
2 193 general linear mixed models (GLMM) to account for within subject correlation. The final  
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4 194 covariance models were evaluated using Akaike's information criterion (AIC) and  
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6 195 Bayesian information criterion (BIC). BMI has been an important factor related to both  
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8 196 soft drink intake and OA progression.<sup>9, 25</sup> To examine the possible effect modifications, we  
9  
10 197 further performed stratified analyses by obesity ( $\text{BMI} \geq 30.0 \text{ kg/m}^2$ ) and also adjusted BMI  
11  
12 198 within each category to reduce the possible residual confounding bias. In addition, the  
13  
14 199 association of soft drink consumption with JSW change may also be mediated through  
15  
16 200 BMI. The indirect effect of BMI was evaluated using Sobel test<sup>26</sup>

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18  
19 201 In addition, we also used the first increase of the OARSI JSN grade as the endpoint.  
20  
21 202 We developed a Cox proportional hazards model to assess independent association  
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23 203 between soft drink intake and the JSN score change after controlling for other covariates.  
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25 204 For each participant, the time of follow-up was calculated from the baseline date to the  
26  
27 205 date of the first increase of JSN grade, death, or end of the study, whichever came first.  
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29 206 The discrete likelihood method was used for ties of the failure times in the models.  
30  
31 207 We used a robust sandwich covariance estimate to account for the intraclass dependence  
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33 208 within individual patients.<sup>27</sup> Participants who indicated no soft drink consumption in the  
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35 209 past year were chosen as the reference group for all analyses. Adjusted hazard ratios  
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37 210 with 95% confidence intervals were used to evaluate the strength of the associations. The  
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39 211 proportional hazard assumption was tested based on the smoothed plots of the scaled  
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41 212 Schoenfeld residuals. Data analyses were performed using SAS 9.2 (SAS Institute, Cary,  
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43 213 NC).

## 44 214 **Results**

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47 215 In this study, we studied 2,149 participants from OAI having a total of 3,066 eligible knees.  
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49 216 All categories of soft drink intake were represented in participants at baseline (none,  
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51 217  $n=687$ ;  $\leq 1$  times/week,  $n=976$ ; 2-4 times/week,  $n=285$ ;  $\geq 5$  times/week,  $n=201$ ). Baseline  
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53 218 characteristics of participants are shown in Table 1 according to levels of soft drink intake.  
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55 219 Compared to no soft drink use, high soft drink users were more likely to be men, between  
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2 220 45 and 54 years, not married, not employed, current smokers, and have lower education  
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4 221 and household income and higher BMI.  
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6 222 Results of multivariable analyses are shown in Table 2 in men and women. We  
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8 223 observed a significant dose-response relationship in men between soft drink intake and  
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10 224 adjusted mean decreases of JSW in men ( $p$  trend<0.001) after controlling for age, race,  
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12 225 education, marital status, household income, employment, BMI, physical activity, follow-up  
13  
14 226 time, knee injury and knee surgery, smoking, milk and juice intake, total energy intake,  
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16 227 baseline KL grade, weight change, the changes of rim distance and beam angle. With  
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18 228 increasing levels of soft drink intake (none,  $\leq 1$ , 2-4, and  $\geq 5$  times/week), the mean  
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20 229 decreases of JSW were 0.31mm, 0.39mm, 0.34mm and 0.60mm respectively. When we  
21  
22 230 stratified by obesity, a stronger dose-response relationship was found (decreases of JSW  
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24 231 were 0.24mm, 0.38mm, 0.32mm, 0.62mm respectively) in non-obese men. In obese men,  
25  
26 232 only the highest soft drink level ( $\geq 5$  times/week) was associated with increased JSW  
27  
28 233 change compared to no use. The effect of soft drink consumption was different between  
29  
30 234 men and women ( $p$  for interaction =0.003). No significant association was observed in  
31  
32 235 women. Table 3 shows the multivariable adjusted hazard ratios (HR) of OA progression  
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34 236 evaluated by time to the first increase of semi- quantitative OARSI score. Consistent with  
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36 237 JSW analyses, we found that the increasing soft drink intake was associated with the  
37  
38 238 increasing rate of OA progression in men but not in women. Compared to no soft drink  
39  
40 239 intake, the HR for  $\leq 1$ , 2-4, and  $\geq 5$  times/week were 1.56 (95% CI, 1.13-2.16), 1.55 (95%  
41  
42 240 CI, 1.02-2.35) and 2.05 (95% CI, 1.32-3.19) respectively in men ( $p$  trend=0.002). When  
43  
44 241 we stratified by obesity, a dose-response relationship was observed in both non-obese  
45  
46 242 and obese men. The hazard ratios were 2.30 (95% CI, 1.22-4.34) and 1.90 (95% CI, 1.03-  
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48 243 3.52) respectively with the soft drink intake  $\geq 5$  times/week compared to no intake.  
49  
50 244 However, no significant association was found in women. In addition, our mediation  
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52 245 analysis indicated a modest (3.2%) indirect effect through BMI ( $p$  for Sobel test=0.098). In  
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2 246 sensitivity analyses, additional adjustment for alcohol consumption and a history of gout in  
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4 247 the above models did not change the results.  
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## 6 248 **Discussion**

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8 249 In this 48-month follow-up study of people with radiographic knee OA, we found a positive  
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10 250 association with a significant dose-response relationship between soft drink consumption  
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12 251 and structural progression of knee OA measured by both semi-quantitative and  
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14 252 quantitative JSN independent of BMI and other potential risk factors in men, but not in  
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16 253 women.  
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19 254 Knee OA progression has been thought to involve multiple mechanisms besides  
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21 255 cartilage loss including changes in bone composition, shape, as well as  
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23 256 proprioception,<sup>28,29</sup> which might be subject to the influences of macro and micronutrients  
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25 257 in the diet. McAlindon et al. reported that a higher consumption of anti-oxidant  
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27 258 micronutrients, especially vitamin C, might decrease cartilage loss and OA progression,<sup>14</sup>  
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29 259 and low vitamin D intake and low serum vitamin D levels might increase the risk for  
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31 260 progression of knee OA.<sup>13</sup> However, no study investigated the association of soft drink  
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33 261 consumption and progression of OA. Sugar sweetened beverages intake is a significant  
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35 262 contributor to weight-gain and has been associated with increased risk of obesity, type 2  
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37 263 diabetes, cardiovascular disease and poor bone health.<sup>10 11,30</sup> Nevertheless, the biologic  
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39 264 mechanism for soft drinks in the progression of OA remains unclear. One explanation for  
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41 265 the observed findings is that soft drinks may substitute for healthy diet. Soft drink  
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43 266 consumption may be associated with decreased intakes of protein, milk and dairy  
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45 267 products, fruit juice, fruit and a variety of vitamins and nutrients.<sup>12,31</sup> One study reported a  
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47 268 negative association between soft drink consumption and an overall healthy eating  
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49 269 index.<sup>32</sup> However, in our analysis, the observed effects remained after adjustment for milk  
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51 270 and juice intake supports the likelihood that this is not only due to displacement of other  
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53 271 healthy beverages in the diet. We considered the extent to which the sugar in soft drinks  
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55 272 leads to OA progression. To further evaluate this, we evaluated the relation between fruit  
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2 273 juice consumption and OA progression. Fruit juice consumption was not associated with  
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4 274 OA progression in our study (results are not shown). It is possible that vitamins, minerals,  
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6 275 soluble fiber, and phytochemicals in fruit juices may have beneficial effects  
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8 276 counterbalancing potential adverse effects of sugars.

10 277 Previous studies demonstrated that weight gain and obesity may increase risk of joint  
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12 278 space loss, suggestive of cartilage loss, as visualized on radiographs,<sup>7, 33, 34</sup> though these  
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14 279 findings are not universally reported. Nevertheless, our mediation analysis indicated that  
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16 280 the indirect effect through BMI was modest and the association between soft drinks and  
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18 281 OA progression remained after adjustment for BMI, weight change and total energy intake  
19  
20 282 suggestive of independent effects of soft drinks. Soft drinks may contain phosphoric acid,  
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22 283 which was shown to interfere with calcium absorption and to contribute to imbalances that  
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24 284 lead to additional loss of calcium.<sup>35</sup> It has also been suggested that the high fructose corn  
25  
26 285 syrup used to sweeten carbonated beverages may negatively affect bone.<sup>36</sup> Long-term  
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28 286 effects of soft drinks on osteoarthritis have not been studied in experimental settings so  
29  
30 287 far, and further research is warranted.

34 288 Sex differences have been noted in the prevalence, incidence, and severity of OA for  
35  
36 289 many years.<sup>37</sup> Faber and colleagues found cartilage thickness of the distal femur to be  
37  
38 290 less in women than in men.<sup>38</sup> Other evidences suggested a protective effect of  
39  
40 291 exogenous estrogen on cartilage and bone turnover.<sup>39</sup> However the gender differences  
41  
42 292 in the relationship of soft drink consumption with OA progression are not understood. We  
43  
44 293 found a stronger association between soft drink consumption and JSW change in non-  
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46 294 obese men than in obese men. One possible reason is that the effect of soft drink  
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48 295 consumption may not be strong enough to provide additional effect beyond obesity.

51 296 The strengths of this study include the prospective design, large number of patients  
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53 297 with knee OA, and the state-of-the-art quantitative measures of structural change from  
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55 298 sophisticated image processing technology. The quantitative software based assessment  
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57 299 provides a more precise measure of JSW in millimeters and permits the assessor to  
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1  
2 300 document appreciable change in JSW in the tibiofemoral compartment<sup>18, 19</sup> In contrast,  
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4 301 the semi-quantitative approach, for example, the KL grading or the OARSI score, has  
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6 302 limitations that lead to insensitivity to changes in status.<sup>40</sup> The consistent findings from  
7  
8 303 both quantitative and semi- quantitative measures of OA progression increase the  
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10 304 reliability of the study. In addition, we excluded knees in which the difference of rim  
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12 305 distance between follow-up and baseline visits  $\geq 2$ mm and adjusted for changes of rim  
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14 306 distance and beam angle in the multivariate models to minimize the possible  
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16 307 measurement error of radiographic data.

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18  
19 308 Because of the observational nature of the study, patients were not randomly assigned  
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21 309 to soft drink groups. We cannot prove that the observed associations are causal because  
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23 310 residual confounding could theoretically affect the observed associations. We controlled  
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25 311 for potential confounding by most known risk factors that are plausibly associated with soft  
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27 312 drink consumption and changes in these variables over time. However, adjustment for  
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29 313 baseline covariates may not completely remove the confounding influence. For example,  
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31 314 effect of BMI may be lagged, and the cumulative exposure to overweight/obesity may not  
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33 315 be perfectly correlated with baseline BMI. Imprecise dietary measurement could  
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35 316 potentially have influenced our observed associations. However, random errors in dietary  
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37 317 assessment measures might have accounted for a lack of association but not the reverse.  
38  
39 318 Regarding physical activity, PASE can potentially capture all types of activities and allow  
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41 319 grading by intensity for elderly. However, questionnaires have obvious weaknesses  
42  
43 320 considering recall and reporting bias. Also PASE may not be sufficient for assessing PA  
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45 321 levels and intensity in younger patients with OA.<sup>41</sup>

46  
47 322 In conclusion, our study suggested that frequent consumption of sweetened soft drinks  
48  
49 323 may be associated with increased OA progression in men. Replication of these novel  
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51 324 findings in other prospective studies demonstrating the reduction in soft drink consumption  
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53 325 leads to delay in OA progression are needed to test this hypothesis.  
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1  
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3

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9  
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17  
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27

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29  
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31  
32 341 the article and final approval.  
33

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39  
40 345 the writing of the report; or in the decision to submit the paper for publication.  
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43 346 **Conflict of interest** None  
44

45 347 **Ethics approval** OAI was approved by the Institutional Review Board, the University of  
46  
47 348 California, San Francisco (UCSF), and its affiliates. UCSF holds Office of Human  
48  
49 349 Research Protections Federal wide Assurance number FWA00000068.  
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51 350 **Data sharing statement:** There are no additional data available.  
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**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				P value
		None n=687	≤1 n=976	2-4 n=285	≥5 n=201	
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) <sup>a</sup>	157 (82)	147 (77)	161 (82)	165 (90)	163 (83)	0.001
BMI (kg/m <sup>2</sup> ), %						
<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 <sup>c</sup> (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

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

354 b. Body mass index

355 c. Kellgren-Lawrence Scale

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**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.							

## References

1. Dunlop DD, Manheim LM, Yelin EH, et al. The costs of arthritis. *Arthritis Rheum.* Feb 15 2003;49(1):101-113.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum.* Jan 2008;58(1):26-35.
3. Reginster JY. The prevalence and burden of arthritis. *Rheumatology (Oxford).* Apr 2002;41 Suppl 1:3-6.
4. Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. *Radiol Clin North Am.* Jan 2004;42(1):1-9, v.
5. Garstang SV, Stitik TP. Osteoarthritis: epidemiology, risk factors, and pathophysiology. *Am J Phys Med Rehabil.* Nov 2006;85(11 Suppl):S2-11; quiz S12-14.
6. Zhang Y, Niu J, Felson DT, et al. Methodologic challenges in studying risk factors for progression of knee osteoarthritis. *Arthritis Care Res (Hoboken).* Nov 2010;62(11):1527-1532.
7. Felson DT, Goggins J, Niu J, et al. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. *Arthritis Rheum.* Dec 2004;50(12):3904-3909.
8. Nielsen SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. *Am J Prev Med.* Oct 2004;27(3):205-210.
9. Malik VS, Popkin BM, Bray GA, et al. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation.* Mar 23 2010;121(11):1356-1364.
10. Malik VS, Popkin BM, Bray GA, et al. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care.* Nov 2010;33(11):2477-2483.
11. Wyszak G. Teenaged girls, carbonated beverage consumption, and bone fractures. *Arch Pediatr Adolesc Med.* Jun 2000;154(6):610-613.
12. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health.* Apr 2007;97(4):667-675.
13. McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med.* Sep 1 1996;125(5):353-359.
14. McAlindon TE, Jacques P, Zhang Y, et al. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? *Arthritis Rheum.* Apr 1996;39(4):648-656.
15. Simard JF, Karlson EW, Costenbader KH, et al. Perinatal factors and adult-onset lupus. *Arthritis Rheum.* Aug 15 2008;59(8):1155-1161.
16. The osteoarthritis initiative protocol for the cohort study. <<http://oai.epi-csf.org/datarelease/docs/StudyDesignProtocol.pdf>>; [accessed 04.25.2012]
17. Guermazi A, Hunter DJ, Roemer FW. Plain radiography and magnetic resonance imaging diagnostics in osteoarthritis: validated staging and scoring. *J Bone Joint Surg Am.* Feb 2009;91 Suppl 1:54-62.

18. Duryea J, Zaim S, Genant HK. New radiographic-based surrogate outcome measures for osteoarthritis of the knee. *Osteoarthritis Cartilage*. Feb 2003;11(2):102-110.
19. Sharp JT, Angwin J, Boers M, et al. Computer based methods for measurement of joint space width: update of an ongoing OMERACT project. *J Rheumatol*. Apr 2007;34(4):874-883.
20. Duryea J, Neumann G, Niu J, et al. Comparison of radiographic joint space width with magnetic resonance imaging cartilage morphometry: analysis of longitudinal data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)*. Jul 2010;62(7):932-937.
21. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. *Epidemiology*. Jan 1990;1(1):58-64.
22. Block G, Hartman AM, Dresser CM, et al. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol*. Sep 1986;124(3):453-469.
23. Washburn RA, Smith KW, Jette AM, et al. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*. Feb 1993;46(2):153-162.
24. Johansen KL, Painter P, Kent-Braun JA, et al. Validation of questionnaires to estimate physical activity and functioning in end-stage renal disease. *Kidney Int*. Mar 2001;59(3):1121-1127.
25. Issa SN, Sharma L. Epidemiology of osteoarthritis: an update. *Curr Rheumatol Rep*. Feb 2006;8(1):7-15.
26. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. Dec 1986;51(6):1173-1182.
27. Lin DY. Cox regression analysis of multivariate failure time data: the marginal approach. *Stat Med*. Nov 15 1994;13(21):2233-2247.
28. Yusuf E, Kortekaas MC, Watt I, et al. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis*. Jan 2011;70(1):60-67.
29. Driban JB, Lo GH, Lee JY, et al. Quantitative bone marrow lesion size in osteoarthritic knees correlates with cartilage damage and predicts longitudinal cartilage loss. *BMC Musculoskelet Disord*. 2011;12:217.
30. Tucker KL. Dietary intake and bone status with aging. *Curr Pharm Des*. 2003;9(32):2687-2704.
31. Marshall TA, Eichenberger Gilmore JM, Broffitt B, et al. Diet quality in young children is influenced by beverage consumption. *J Am Coll Nutr*. Feb 2005;24(1):65-75.
32. Rodriguez-Artalejo F, Garcia EL, Gorgojo L, et al. Consumption of bakery products, sweetened soft drinks and yogurt among children aged 6-7 years: association with nutrient intake and overall diet quality. *Br J Nutr*. Mar 2003;89(3):419-429.
33. Wolfe F, Lane NE. The longterm outcome of osteoarthritis: rates and predictors of joint space narrowing in symptomatic patients with knee osteoarthritis. *J Rheumatol*. Jan 2002;29(1):139-146.
34. Dougados M, Gueguen A, Nguyen M, et al. Longitudinal radiologic evaluation of osteoarthritis of the knee. *J Rheumatol*. Mar 1992;19(3):378-384.

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35. Amato D, Maravilla A, Montoya C, et al. Acute effects of soft drink intake on calcium and phosphate metabolism in immature and adult rats. *Rev Invest Clin*. May-Jun 1998;50(3):185-189.
36. Milne DB, Nielsen FH. The interaction between dietary fructose and magnesium adversely affects macromineral homeostasis in men. *J Am Coll Nutr*. Feb 2000;19(1):31-37.
37. Srikanth VK, Fryer JL, Zhai G, et al. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage*. Sep 2005;13(9):769-781.
38. Faber SC, Eckstein F, Lukasz S, et al. Gender differences in knee joint cartilage thickness, volume and articular surface areas: assessment with quantitative three-dimensional MR imaging. *Skeletal Radiol*. Mar 2001;30(3):144-150.
39. Linn S, Murtaugh B, Casey E. Role of sex hormones in the development of osteoarthritis. *Pm R*. May 2012;4(5 Suppl):S169-173.
40. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage*. 2007;15 Suppl A:A1-56.
41. Ida Svege I, Kolle E, Risberg MA. Reliability and validity of the Physical Activity Scale for the Elderly (PASE) in patients with hip osteoarthritis. *BMC Musculoskeletal Disorders*. 2012; 13:26.

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2 1 **Soft Drink Intake and Progression of Radiographic Knee Osteoarthritis: Data from**  
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4 2 **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,  $\leq 1$ , 2-4, and  $\geq 5$  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 ( $\geq 5$  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.

## 85 Introduction

86 Osteoarthritis (OA), a slowly progressing disease characterized by pain, deformity, and loss  
87 of function, is the major cause physical disability in older people.<sup>1</sup> Nearly 27 million have  
88 clinical osteoarthritis in the United States.<sup>2</sup> With the aging of the population, the health care  
89 burden from OA is expected to increase dramatically during the next few decades.<sup>3</sup>  
90 However, little is known about the course of OA progression over time in patients with OA.  
91 It is, therefore, of great importance to identify modifiable risk factors for OA progression.  
92 Over the past few decades, many observational studies have examined risk factors for the  
93 incidence and progression of knee OA. Several risk factors (i.e., obesity, joint injury, and  
94 certain sports) have been found to be strongly associated with an increased risk for  
95 incident knee OA.<sup>4,5</sup> However, findings on risk factors for OA progression have been  
96 inconclusive. Except for the level of serum hyaluronic acid and generalized OA, no other  
97 risk factor has been consistently associated with the risk of OA progression.<sup>6,7</sup>

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

## 107 Methods

### 108 Subjects

109 OAI was launched in 2002 by the National Institute of Health (NIH) to develop resources for  
110 the identification of new biomarkers and treatment targets for knee OA. The objective of the  
111 OAI was to pool public and private scientific expertise and funding to collect, analyze, and

1  
2 112 make widely available the largest research resource to date of clinical data, radiologic  
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4 113 information, and biospecimens from those at risk for or with knee OA. The OAI began  
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6 114 enrolling people aged 45 through 79 years in 2004 and followed them annually for the  
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8 115 development or progression of OA. The clinical sites involved were located in Baltimore,  
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10 116 MD; Columbus, OH; Pittsburgh, PA; and Pawtucket, RI. OAI has been a longitudinal study  
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12 117 of 4,796 subjects with either established knee OA or significant risk factors for the  
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14 118 development of knee OA followed over an 8-year period.<sup>15</sup> The follow-up rate was >90%  
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16 119 over the first 48 months. The detailed OAI protocol can be found elsewhere.<sup>16</sup>  
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19 120 For the current study, we included individuals with medial radiographic knee OA in at  
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21 121 least one knee at baseline. We excluded knees with severe radiographic OA defined as  
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23 122 the baseline Kellgren and Lawrence (KL) grade of 4 or those with primarily lateral joint  
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25 123 space narrowing (JSN), and knees in which the difference of rim distance (from tibial  
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27 124 plateau to tibial rim closest to femoral condyle) between follow-up and baseline visits were  
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29 125  $\geq 2$ mm to minimize possible measurement error of radiographic data. The 2,149  
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31 126 participants (3,066 knees) with KL grade of 2 or 3 and having dietary data at baseline  
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33 127 constituted the study sample. Follow-up at 12, 24, 36 and 48 months were included in this  
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35 128 analysis. **The overall loss to follow up rate was 16.8% over the study period.**  
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### 39 129 **Radiographic progression of OA**

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41 130 In OAI, current radiographic assessment techniques on plain radiographs involved both  
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43 131 semi-quantitative and quantitative assessment of JSN. For the semi-quantitative  
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45 132 approach, the Osteoarthritis Research Society International grade (OARSI grade: 0=no  
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47 133 JSN, 1=definite JSN to 3=severe JSN) has been widely used to measure progression of  
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49 134 OA.<sup>17</sup> For these analyses, we used the publically available semi-quantitative JSN  
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51 135 readings (kXR\_SQ\_BU, version 11/07/2011, <http://oai.epi-ucsf.org>). Recently, a  
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53 136 quantitative approach has been used to provide a precise measure of joint space width  
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55 137 (JSW) in millimeters between the adjacent bones of the knee.<sup>18,19</sup> Multiple JSWs were  
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57 138 measured at fixed locations along the joint in medial compartment, denoted as JSW(x), at  
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2 139 0.025 intervals for  $x = 0.15 - 0.30$ . The reproducibility of this technique and the  
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4 140 responsiveness to change have been documented elsewhere,<sup>18 20</sup> including one study  
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6 141 using OAI data which demonstrated a responsiveness that compared favorably to  
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8 142 magnetic resonance imaging (MRI).<sup>20</sup> We used medial JSW at  $x=0.25$  with the best  
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10 143 responsiveness of change to quantify the progression of OA.<sup>20</sup> We define the repeated  
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12 144 measures of the decreases of JSW from baseline to 12, 24, 36 and 48 months as the  
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14 145 outcome variable.

### 146 **Assessment of soft drink consumption**

147 Usual dietary intakes of foods and nutrients including soft drink consumption were  
148 assessed at baseline with a Block Brief Food Frequency Questionnaire (FFQ) including 60  
149 food items in OAI.<sup>21</sup> The participants were asked how often they had consumed regular  
150 soft drinks/bottled drinks (not diet drinks) in the past 12 months (coded as: never, a few  
151 times per year, once per month, 2-3 times per month, once per week, twice per week, 3-4  
152 times per week, 5-6 times per week, and every day) (variable name: V00FFQ69,  
153 <http://oai.epi-ucsf.org>). Based on previous studies<sup>9,10,11</sup>, we grouped these into 4  
154 categories: none,  $\leq 1$ , 2-4, and  $\geq 5$  times/week. Similar questionnaires were used to collect  
155 the frequencies of other beverages intake, such as, milk, juice, tea and coffee, etc. This  
156 brief FFQ has been validated against three four-day records in a group of middle-aged  
157 women, and against two seven-day records in a group of older men. The absolute value  
158 of macronutrients estimated by the reduced questionnaire was a slightly lower than food-  
159 record estimates, but most micronutrients were not underestimated.<sup>21, 22</sup>

### 160 **Information on covariates**

161 Baseline demographic and socioeconomic factors include race/ethnicity, age, sex, marital  
162 status, education level, employment status, annual income and social support. Individuals  
163 were classified as African American, white, or other racial/ethnic group based on self  
164 report. Education level was categorized as high school or less, college and above college.  
165 General clinical parameters include current smoking, alcohol consumption, history of

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2 166 traumatic knee injury and knee surgery, self-reported gout, body mass index (BMI),  
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4 167 physical activity, weight change, milk and juice intake, total energy intake and baseline  
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6 168 disease severity (KL grade). Physical activity was assessed by using the Physical Activity  
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9 169 Scale for the Elderly (PASE), an established questionnaire for measuring physical activity  
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11 170 in older individuals that has also been validated in younger subjects.<sup>23, 24</sup> Alcohol  
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13 171 consumption (pure alcohol in grams /day) was assessed at baseline including separate  
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15 172 items for beer, wine, and liquor in OAI. In addition, we also adjusted for changes of the  
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17 173 beam angles and rim distances (from tibial plateau to tibial rim closest to femoral condyle  
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19 174 between follow-up visits and baseline) which indicate knee-positioning consistency for x-  
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21 175 ray exam.

## 23 176 **Statistical analysis**

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26 177 First we performed exploratory analyses of all variables of interest including the exposure  
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28 178 (frequency of soft drink intake), radiographic structural measures (K-L grade, JSN score  
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30 179 and JSW ) and potential confounders described above. Descriptive statistics such as the  
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32 180 minimum, maximum, median and mean for each continuous variable and frequency table  
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34 181 for each categorical variable was used to summarize the data as well as detect outliers,  
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36 182 data entry mistakes, and missing values.

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39 183 The primary analysis was to assess the influence of soft drink consumption on the  
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41 184 change in JSW over the study period. The primary outcomes were repeated measures of  
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43 185 the JSW decreases from baseline to 12, 24, 36 and 48 months respectively. The initial  
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45 186 analyses were unadjusted comparisons of the changes of JSW over time among levels of  
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47 187 soft drink intake using Analysis of Variance (ANOVA) and Multivariate Analysis of  
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49 188 Variance (MANOVA). Then separate multivariate models for repeated measures by men  
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51 189 and women were used to test the independent association between soft drink intake and  
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53 190 the decrease in JSW over time, while adjusting for BMI, physical activity, baseline disease  
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55 191 severity and potential confounding factors described above. Due to the hierarchical  
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57 192 structure of the data (each subject has 2 knees over multiple time points), we used  
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2 193 general linear mixed models (GLMM) to account for within subject correlation. The final  
3  
4 194 covariance models were evaluated using Akaike's information criterion (AIC) and  
5  
6 195 Bayesian information criterion (BIC). BMI has been an important factor related to both  
7  
8 196 soft drink intake and OA progression.<sup>9, 25</sup> To examine the possible effect modifications, we  
9  
10 197 further performed stratified analyses by obesity ( $BMI \geq 30.0 \text{ kg/m}^2$ ) and also adjusted BMI  
11  
12 198 within each category to reduce the possible residual confounding bias. In addition, the  
13  
14 199 association of soft drink consumption with JSW change may also be mediated through  
15  
16 200 BMI. The indirect effect of BMI was evaluated using Sobel test<sup>26</sup>

17  
18  
19 201 In addition, we also used the first increase of the OARSI JSN grade as the endpoint.  
20  
21 202 We developed a Cox proportional hazards model to assess independent association  
22  
23 203 between soft drink intake and the JSN score change after controlling for other covariates.  
24  
25 204 For each participant, the time of follow-up was calculated from the baseline date to the  
26  
27 205 date of the first increase of JSN grade, death, or end of the study, whichever came first.  
28  
29 206 The discrete likelihood method was used for ties of the failure times in the models.  
30  
31 207 We used a robust sandwich covariance estimate to account for the intraclass dependence  
32  
33 208 within individual patients.<sup>27</sup> Participants who indicated no soft drink consumption in the  
34  
35 209 past year were chosen as the reference group for all analyses. Adjusted hazard ratios  
36  
37 210 with 95% confidence intervals were used to evaluate the strength of the associations. The  
38  
39 211 proportional hazard assumption was tested based on the smoothed plots of the scaled  
40  
41 212 Schoenfeld residuals. Data analyses were performed using SAS 9.2 (SAS Institute, Cary,  
42  
43 213 NC).

## 44 214 **Results**

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46  
47 215 In this study, we studied 2,149 participants from OAI having a total of 3,066 eligible knees.  
48  
49 216 **All categories of soft drink intake were represented in participants at baseline** (none,  
50  
51 217  $n=687$ ;  $\leq 1$  times/week,  $n=976$ ; 2-4 times/week,  $n=285$ ;  $\geq 5$  times/week,  $n=201$ ). Baseline  
52  
53 218 characteristics of participants are shown in Table 1 according to levels of soft drink intake.  
54  
55 219 Compared to no soft drink use, high soft drink users were more likely to be men, between  
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1  
2 220 45 and 54 years, not married, not employed, current smokers, and have lower education  
3  
4 221 and household income and higher BMI.

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6 222 Results of multivariable analyses are shown in Table 2 in men and women. We  
7  
8 223 observed a significant dose-response relationship in men between soft drink intake and  
9  
10 224 adjusted mean decreases of JSW in men ( $p$  trend $<0.001$ ) after controlling for age, race,  
11  
12 225 education, marital status, household income, employment, BMI, physical activity, follow-up  
13  
14 226 time, knee injury and knee surgery, smoking, milk and juice intake, total energy intake,  
15  
16 227 baseline KL grade, weight change, the changes of rim distance and beam angle. With  
17  
18 228 increasing levels of soft drink intake (none,  $\leq 1$ , 2-4, and  $\geq 5$  times/week), the mean  
19  
20 229 decreases of JSW were 0.31mm, 0.39mm, 0.34mm and 0.60mm respectively. When we  
21  
22 230 stratified by obesity, a stronger dose-response relationship was found (decreases of JSW  
23  
24 231 were 0.24mm, 0.38mm, 0.32mm, 0.62mm respectively) in non-obese men. In obese men,  
25  
26 232 only the highest soft drink level ( $\geq 5$  times/week) was associated with increased JSW  
27  
28 233 change compared to no use. The effect of soft drink consumption was different between  
29  
30 234 men and women ( $p$  for interaction =0.003). No significant association was observed in  
31  
32 235 women. Table 3 shows the multivariable adjusted hazard ratios (HR) of OA progression  
33  
34 236 evaluated by time to the first increase of semi- quantitative OARSI score. Consistent with  
35  
36 237 JSW analyses, we found that the increasing soft drink intake was associated with the  
37  
38 238 increasing rate of OA progression in men but not in women. Compared to no soft drink  
39  
40 239 intake, the HR for  $\leq 1$ , 2-4, and  $\geq 5$  times/week were 1.56 (95% CI, 1.13-2.16), 1.55 (95%  
41  
42 240 CI, 1.02-2.35) and 2.05 (95% CI, 1.32-3.19) respectively in men ( $p$  trend=0.002). When  
43  
44 241 we stratified by obesity, a dose-response relationship was observed in both non-obese  
45  
46 242 and obese men. The hazard ratios were 2.30 (95% CI, 1.22-4.34) and 1.90 (95% CI, 1.03-  
47  
48 243 3.52) respectively with the soft drink intake  $\geq 5$  times/week compared to no intake.  
49  
50 244 However, no significant association was found in women. In addition, our mediation  
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52 245 analysis indicated a modest (3.2%) indirect effect through BMI ( $p$  for Sobel test=0.098). In  
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2 246 sensitivity analyses, additional adjustment for alcohol consumption and a history of gout in  
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4 247 the above models did not change the results.  
5

## 6 248 Discussion 7

8 249 In this 48-month follow-up study of people with radiographic knee OA, we found a positive  
9  
10 250 association with a significant dose-response relationship between soft drink consumption  
11  
12 251 and structural progression of knee OA measured by both semi-quantitative and  
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14 252 quantitative JSN independent of BMI and other potential risk factors in men, but not in  
15  
16 253 women.  
17

18  
19 254 Knee OA progression has been thought to involve multiple mechanisms besides  
20  
21 255 cartilage loss including changes in bone composition, shape, as well as  
22  
23 256 proprioception,<sup>28,29</sup> which might be subject to the influences of macro and micronutrients  
24  
25 257 in the diet. McAlindon et al. reported that a higher consumption of anti-oxidant  
26  
27 258 micronutrients, especially vitamin C, might decrease cartilage loss and OA progression,<sup>14</sup>  
28  
29 259 and low vitamin D intake and low serum vitamin D levels might increase the risk for  
30  
31 260 progression of knee OA.<sup>13</sup> However, no study investigated the association of soft drink  
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33 261 consumption and progression of OA. Sugar sweetened beverages intake is a significant  
34  
35 262 contributor to weight-gain and has been associated with increased risk of obesity, type 2  
36  
37 263 diabetes, cardiovascular disease and poor bone health.<sup>10 11,30</sup> Nevertheless, the biologic  
38  
39 264 mechanism for soft drinks in the progression of OA remains unclear. One explanation for  
40  
41 265 the observed findings is that soft drinks may substitute for healthy diet. Soft drink  
42  
43 266 consumption may be associated with decreased intakes of protein, milk and dairy  
44  
45 267 products, fruit juice, fruit and a variety of vitamins and nutrients.<sup>12,31</sup> One study reported a  
46  
47 268 negative association between soft drink consumption and an overall healthy eating  
48  
49 269 index.<sup>32</sup> However, in our analysis, the observed effects remained after adjustment for milk  
50  
51 270 and juice intake supports the likelihood that this is not only due to displacement of other  
52  
53 271 healthy beverages in the diet. We considered the extent to which the sugar in soft drinks  
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55 272 leads to OA progression. To further evaluate this, we evaluated the relation between fruit  
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1  
2 273 juice consumption and OA progression. Fruit juice consumption was not associated with  
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4 274 OA progression in our study (results are not shown). It is possible that vitamins, minerals,  
5  
6 275 soluble fiber, and phytochemicals in fruit juices may have beneficial effects  
7  
8 276 counterbalancing potential adverse effects of sugars.

10 277 Previous studies demonstrated that weight gain and obesity may increase risk of joint  
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12 278 space loss, suggestive of cartilage loss, as visualized on radiographs,<sup>7, 33, 34</sup> though these  
13  
14 279 findings are not universally reported. Nevertheless, our mediation analysis indicated that  
15  
16 280 the indirect effect through BMI was modest and the association between soft drinks and  
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18 281 OA progression remained after adjustment for BMI, weight change and total energy intake  
19  
20 282 suggestive of independent effects of soft drinks. Soft drinks may contain phosphoric acid,  
21  
22 283 which was shown to interfere with calcium absorption and to contribute to imbalances that  
23  
24 284 lead to additional loss of calcium.<sup>35</sup> It has also been suggested that the high fructose corn  
25  
26 285 syrup used to sweeten carbonated beverages may negatively affect bone.<sup>36</sup> Long-term  
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28 286 effects of soft drinks on osteoarthritis have not been studied in experimental settings so  
29  
30 287 far, and further research is warranted.

34 288 Sex differences have been noted in the prevalence, incidence, and severity of OA for  
35  
36 289 many years.<sup>37</sup> Faber and colleagues found cartilage thickness of the distal femur to be  
37  
38 290 less in women than in men.<sup>38</sup> Other evidences suggested a protective effect of  
39  
40 291 exogenous estrogen on cartilage and bone turnover.<sup>39</sup> However the gender differences  
41  
42 292 in the relationship of soft drink consumption with OA progression are not understood. We  
43  
44 293 found a stronger association between soft drink consumption and JSW change in non-  
45  
46 294 obese men than in obese men. One possible reason is that the effect of soft drink  
47  
48 295 consumption may not be strong enough to provide additional effect beyond obesity.

51 296 The strengths of this study include the prospective design, large number of patients  
52  
53 297 with knee OA, and the state-of-the-art quantitative measures of structural change from  
54  
55 298 sophisticated image processing technology. The quantitative software based assessment  
56  
57 299 provides a more precise measure of JSW in millimeters and permits the assessor to  
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1  
2 300 document appreciable change in JSW in the tibiofemoral compartment<sup>18, 19</sup> In contrast,  
3  
4 301 the semi-quantitative approach, for example, the KL grading or the OARSI score, has  
5  
6 302 limitations that lead to insensitivity to changes in status.<sup>40</sup> The consistent findings from  
7  
8 303 both quantitative and semi- quantitative measures of OA progression increase the  
9  
10 304 reliability of the study. In addition, we excluded knees in which the difference of rim  
11  
12 305 distance between follow-up and baseline visits  $\geq 2$ mm and adjusted for changes of rim  
13  
14 306 distance and beam angle in the multivariate models to minimize the possible  
15  
16 307 measurement error of radiographic data.

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18  
19 308 Because of the observational nature of the study, patients were not randomly assigned  
20  
21 309 to soft drink groups. We cannot prove that the observed associations are causal because  
22  
23 310 residual confounding could theoretically affect the observed associations. We controlled  
24  
25 311 for potential confounding by most known risk factors that are plausibly associated with soft  
26  
27 312 drink consumption and changes in these variables over time. **However, adjustment for**  
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29 313 **baseline covariates may not completely remove the confounding influence. For example,**  
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31 314 **effect of BMI may be lagged, and the cumulative exposure to overweight/obesity may not**  
32  
33 315 **be perfectly correlated with baseline BMI.** Imprecise dietary measurement could  
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35 316 potentially have influenced our observed associations. However, random errors in dietary  
36  
37 317 assessment measures might have accounted for a lack of association but not the reverse.  
38  
39 318 **Regarding physical activity, PASE can potentially capture all types of activities and allow**  
40  
41 319 **grading by intensity for elderly. However, questionnaires have obvious weaknesses**  
42  
43 320 **considering recall and reporting bias. Also PASE may not be sufficient for assessing PA**  
44  
45 321 **levels and intensity in younger patients with OA.**<sup>41</sup>

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47  
48 322 In conclusion, our study suggested that frequent consumption of sweetened soft drinks  
49  
50 323 may be associated with increased OA progression in men. Replication of these novel  
51  
52 324 findings in other prospective studies demonstrating the reduction in soft drink consumption  
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54 325 leads to delay in OA progression are needed to test this hypothesis.  
55  
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1  
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3

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27

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29  
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31  
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33

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39  
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41  
42

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44

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46  
47 348 California, San Francisco (UCSF), and its affiliates. UCSF holds Office of Human  
48  
49 349 Research Protections Federal wide Assurance number FWA00000068.  
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51 350 **Data sharing statement:** There are no additional data available.  
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**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				P value
		None n=687	≤1 n=976	2-4 n=285	≥5 n=201	
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) <sup>a</sup>	157 (82)	147 (77)	161 (82)	165 (90)	163 (83)	0.001
BMI (kg/m <sup>2</sup> ), %						
<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 <sup>c</sup> (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

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

354 b. Body mass index

355 c. Kellgren-Lawrence Scale

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**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.							

## References

1. Dunlop DD, Manheim LM, Yelin EH, Song J, Chang RW. The costs of arthritis. *Arthritis Rheum*. Feb 15 2003;49(1):101-113.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum*. Jan 2008;58(1):26-35.
3. Reginster JY. The prevalence and burden of arthritis. *Rheumatology (Oxford)*. Apr 2002;41 Suppl 1:3-6.
4. Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. *Radiol Clin North Am*. Jan 2004;42(1):1-9, v.
5. Garstang SV, Stitik TP. Osteoarthritis: epidemiology, risk factors, and pathophysiology. *Am J Phys Med Rehabil*. Nov 2006;85(11 Suppl):S2-11; quiz S12-14.
6. Zhang Y, Niu J, Felson DT, Choi HK, Nevitt M, Neogi T. Methodologic challenges in studying risk factors for progression of knee osteoarthritis. *Arthritis Care Res (Hoboken)*. Nov 2010;62(11):1527-1532.
7. Felson DT, Goggins J, Niu J, Zhang Y, Hunter DJ. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. *Arthritis Rheum*. Dec 2004;50(12):3904-3909.
8. Nielsen SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. *Am J Prev Med*. Oct 2004;27(3):205-210.
9. Malik VS, Popkin BM, Bray GA, Despres JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation*. Mar 23 2010;121(11):1356-1364.
10. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care*. Nov 2010;33(11):2477-2483.
11. Wyszak G. Teenaged girls, carbonated beverage consumption, and bone fractures. *Arch Pediatr Adolesc Med*. Jun 2000;154(6):610-613.
12. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health*. Apr 2007;97(4):667-675.
13. McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med*. Sep 1 1996;125(5):353-359.
14. McAlindon TE, Jacques P, Zhang Y, et al. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? *Arthritis Rheum*. Apr 1996;39(4):648-656.
15. Simard JF, Karlson EW, Costenbader KH, et al. Perinatal factors and adult-onset lupus. *Arthritis Rheum*. Aug 15 2008;59(8):1155-1161.
16. The osteoarthritis initiative protocol for the cohort study. <<http://oai.epi-csf.org/datarelease/docs/StudyDesignProtocol.pdf>>; [accessed 04.25.2012]
17. Guermazi A, Hunter DJ, Roemer FW. Plain radiography and magnetic resonance imaging diagnostics in osteoarthritis: validated staging and scoring. *J Bone Joint Surg Am*. Feb 2009;91 Suppl 1:54-62.



18. Duryea J, Zaim S, Genant HK. New radiographic-based surrogate outcome measures for osteoarthritis of the knee. *Osteoarthritis Cartilage*. Feb 2003;11(2):102-110.
19. Sharp JT, Angwin J, Boers M, et al. Computer based methods for measurement of joint space width: update of an ongoing OMERACT project. *J Rheumatol*. Apr 2007;34(4):874-883.
20. Duryea J, Neumann G, Niu J, et al. Comparison of radiographic joint space width with magnetic resonance imaging cartilage morphometry: analysis of longitudinal data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)*. Jul 2010;62(7):932-937.
21. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. *Epidemiology*. Jan 1990;1(1):58-64.
22. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol*. Sep 1986;124(3):453-469.
23. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*. Feb 1993;46(2):153-162.
24. Johansen KL, Painter P, Kent-Braun JA, et al. Validation of questionnaires to estimate physical activity and functioning in end-stage renal disease. *Kidney Int*. Mar 2001;59(3):1121-1127.
25. Issa SN, Sharma L. Epidemiology of osteoarthritis: an update. *Curr Rheumatol Rep*. Feb 2006;8(1):7-15.
26. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. Dec 1986;51(6):1173-1182.
27. Lin DY. Cox regression analysis of multivariate failure time data: the marginal approach. *Stat Med*. Nov 15 1994;13(21):2233-2247.
28. Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis*. Jan 2011;70(1):60-67.
29. Driban JB, Lo GH, Lee JY, et al. Quantitative bone marrow lesion size in osteoarthritic knees correlates with cartilage damage and predicts longitudinal cartilage loss. *BMC Musculoskelet Disord*. 2011;12:217.
30. Tucker KL. Dietary intake and bone status with aging. *Curr Pharm Des*. 2003;9(32):2687-2704.
31. Marshall TA, Eichenberger Gilmore JM, Broffitt B, Stumbo PJ, Levy SM. Diet quality in young children is influenced by beverage consumption. *J Am Coll Nutr*. Feb 2005;24(1):65-75.
32. Rodriguez-Artalejo F, Garcia EL, Gorgojo L, et al. Consumption of bakery products, sweetened soft drinks and yogurt among children aged 6-7 years: association with nutrient intake and overall diet quality. *Br J Nutr*. Mar 2003;89(3):419-429.
33. Wolfe F, Lane NE. The longterm outcome of osteoarthritis: rates and predictors of joint space narrowing in symptomatic patients with knee osteoarthritis. *J Rheumatol*. Jan 2002;29(1):139-146.
34. Dougados M, Gueguen A, Nguyen M, et al. Longitudinal radiologic evaluation of osteoarthritis of the knee. *J Rheumatol*. Mar 1992;19(3):378-384.

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35. Amato D, Maravilla A, Montoya C, et al. Acute effects of soft drink intake on calcium and phosphate metabolism in immature and adult rats. *Rev Invest Clin*. May-Jun 1998;50(3):185-189.
  36. Milne DB, Nielsen FH. The interaction between dietary fructose and magnesium adversely affects macromineral homeostasis in men. *J Am Coll Nutr*. Feb 2000;19(1):31-37.
  37. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage*. Sep 2005;13(9):769-781.
  38. Faber SC, Eckstein F, Lukasz S, et al. Gender differences in knee joint cartilage thickness, volume and articular surface areas: assessment with quantitative three-dimensional MR imaging. *Skeletal Radiol*. Mar 2001;30(3):144-150.
  39. Linn S, Murtaugh B, Casey E. Role of sex hormones in the development of osteoarthritis. *Pm R*. May 2012;4(5 Suppl):S169-173.
  40. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage*. 2007;15 Suppl A:A1-56.
  41. Ida Svege I, Kolle E, Risberg MA. Reliability and validity of the Physical Activity Scale for the Elderly (PASE) in patients with hip osteoarthritis. *BMC Musculoskeletal Disorders*. 2012; 13:26.

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

	Item No	Recommendation
<b>Title and abstract</b>	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
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
<b>Methods</b>		
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
<b>Results</b>		
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
<b>Discussion</b>		
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
<b>Other information</b>		
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>.