HHS Public Access

Author manuscript

Osteoarthritis Cartilage. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

Osteoarthritis Cartilage. 2016 March ; 24(3): 465–472. doi:10.1016/j.joca.2015.09.015.

The relationship between smoking and knee osteoarthritis in the Osteoarthritis Initiative

Catherine E. Dubé, EdD[1], **Shao-Hsien Liu, MPH**[1], **Jeffrey B. Driban, PhD**[2], **Timothy E. McAlindon, MD, MPH**[2], **Charles B. Eaton, MD, MS**[3,4], and **Kate L. Lapane, PhD, MS**[1]

Catherine E. Dubé: Catherine.Dube@umassmed.edu; Shao-Hsien Liu: ShaoHsien.Liu@umassmed.edu; Jeffrey B. Driban: Jeffrey.Driban@tufts.edu; Timothy E. McAlindon: tmcalindon@tuftsmedicalcenter.org; Charles B. Eaton: CEaton@careNE.org; Kate L. Lapane: Kate.Lapane@umassmed.edu

[1]Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA 01655, USA

[2]Division of Rheumatology, Tufts Medical Center, Boston, MA 02111, USA

[3]Center for Primary Care and Prevention, Memorial Hospital of Rhode Island, Pawtucket, RI 02860, USA

[4]Departments of Family Medicine and Epidemiology, Warren Alpert Medical School, School of Public Health, Brown University, Providence, RI 02912, USA

Abstract

Objective—To estimate the extent that smoking history is associated with symptoms and disease progression among individuals with radiographically confirmed knee OA.

Method—Both cross-sectional (baseline) and longitudinal studies employed data from the Osteoarthritis Initiative (n= 2,250 participants). Smoking history was assessed at baseline with 44% current or former smokers. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) was used to measure knee pain, stiffness, and physical function. Disease progression was measured using joint space width (JSW). We used adjusted multivariable linear models to examine the relationship between smoking status and exposure in pack years (PY) with symptoms and JSW at baseline. Changes in symptoms and JSW over time were further assessed.

Corresponding author: Catherine Dubé EdD, Department of Quantitative Health Sciences, University of Massachusetts Medical School, 368 Plantation Street, Worcester, MA 01605 USA, Telephone: 774-455-3746; Fax: 508-856-8993, catherine.dube@umassmed.edu.

AUTHOR CONTRIBUTIONS

Catherine Dube conceived of the study and wrote substantial portions of this article. Shao-Hsien Liu conducted the analyses and wrote the Statistical Analysis section of this article. This research was conducted under the guidance of Kate Lapane and Charles Eaton with input from the remaining authors. All authors contributed to the preparation of the final manuscript, revising it critically for important scientific content. The final version of this manuscript was approved by all authors.

COMPETING INTERESTS

Authors have no competing interests directly related to this study. Drs. Dubé and Lapane were supported for unrelated work by Merck and Cubist Pharmaceuticals and Dr. McAlindon served as a paid consultant to Sanofi-Aventis, Samumed, Flexion, Fidia, McNeil Pharmaceutical, AbbVie, Bioventus, and Novartis on work unrelated to this research.

Results—In cross-sectional analyses, compared to never-smokers high PY (≥15 PY) was associated with slightly greater pain (beta 0.36, 95% CI: 0.01–0.71) and stiffness (beta 0.20, 95% CI: 0.03–0.37); and low PY (<15 PY) was associated with better JSW (beta 0.15, 95% CI: 0.02–0.28). Current smoking was associated with greater pain (beta 0.59, 95% CI: 0.04–1.15) compared to never-smokers. These associations were not confirmed in the longitudinal study. Longitudinally, no associations were found between high or low PY or baseline smoking status with changes in symptoms (at 72 months) or JSW (at 48 months).

Conclusion—Cross-sectional findings are likely due residual confounding. The more robust longitudinal analysis found no associations between smoking status and symptoms or JSW. Long-term smoking provides no benefits to knee OA patients while exposing them to other well-documented serious health risks.

Keywords

knee osteoarthritis; smoking; Osteoarthritis Initiative

INTRODUCTION

Osteoarthritis (OA) of the hip and knee is a leading cause of disability in the world[1]. Radiographic knee OA (Kellgren-Lawrence (K-L) grade ≥2) affects 37% of Americans adults[2]. Although approximately 9% of older adults are current smokers, this generation had the highest smoking rates in history in the 1960s when 54% of adult males reported current smoking and an additional 24% reported former smoking[3]. Smoking has been established as a risk factor for rheumatoid arthritis[4], however the relationship between OA and smoking is controversial[5].

There are at least 5 plausible mechanisms through which smoking may negatively affect knee OA: 1) effects of smoking on cartilage loss[6,7]; 2) interaction between smoking and OA genetic predisposition[8]; 3) smoking's effects on inflammation[9,10]; 4) an association between smoking and both insulin resistance and higher Body Mass Index (BMI)[11]; and 5) a relationship between smoking and metabolic syndrome[12–14]. Recent studies have uncovered a relationship between metabolic syndrome and risk and progression of knee OA[15,16] and when people quit smoking, risk for metabolic syndrome is reduced[13]. Given that smoking produces a chronic inflammatory state[9,10] and OA is a disease where inflammatory mediators play a key role[17] one might posit that smoking would have an overall negative effect on OA symptoms and disease progression.

The current study builds on previous research in several ways. We used data from the Osteoarthritis Initiative (OAI), a multi-site study which recruited a large number of persons with radiographically confirmed knee OA and evaluated participants using validated patient reported outcomes and measures of disease progression. Smoking history was collected at baseline, and symptoms and disease progression was followed for several years. Given this rich data source, our goal was to determine whether smoking was associated with more severe symptoms or disease progression among people with radiographically confirmed knee OA. We employed both cross-sectional and longitudinal study designs. Although we believe the more rigorous design is longitudinal, we also provide cross-sectional data from

the same cohort to help put findings into context within the broader literature on smoking and OA.

METHOD

This study was approved by the Institutional Review Boards of the University of Massachusetts Medical School and the Memorial Hospital of Rhode Island.

Study sample

Publicly available OAI data was used. OAI is a prospective natural history study of both men and women aimed at investigating the development and progression of knee OA. From 2004–2006, baseline data was collected from people 45 to 79 years of age and followed them annually to assess the development or progression of knee OA. Using four study sites (i.e., Baltimore, MD; Columbus, OH; Pittsburgh, PA; and Pawtucket, RI), 4,796 patients with established knee OA or at high risk for developing knee OA were enrolled. For detailed information about the OAI protocol, please see the OAI protocol for the cohort study[18]. Our study sample included participants with radiographic confirmed OA in at least one knee (defined as a K-L grade ≥2) at the time of enrollment (n=2,539). Participants without an OA diagnosis (e.g., those “at risk” in the OAI sample) were excluded (n= 2,257). For the cross-sectional study, participants with missing smoking status or smoking history data (n=134) or outcome measures (n=155) at baseline were excluded. For the sample used to evaluate changes in symptoms (baseline to 72 months) and structural progression (baseline to 48 months), participants with missing outcome measures (n=432 for changes in symptoms and n=745 for changes in JSW) were excluded, as were participants with missing smoking status or smoking history data (n=134). Participants with K-L grade 4 in both knees at baseline (n=62) were further excluded from the JSW sample to allow for assessment of structural change over time. The final analytic sample included 2,250 participants for the cross-sectional design and for longitudinal analysis, 1,973 participants to evaluate changes in symptoms over 72 months, and 1,598 participants to evaluate structural progression (JSW) over 48 months.

Smoking status and smoking history defined

Smoking history was part of a self-administered questionnaire provided to study eligible participants at the conclusion of their initial screening clinic visit. Study staff reviewed completed self-administered questionnaires with each participant at their enrollment visit and any missing responses were obtained. Never-smokers were those who responded “no” to the question “Have you smoked at least 100 cigarettes (5 packs) in your entire life?” (n=1,251) For those responding “yes” smoking history was collected (n=999). Age of initiation of fairly regular smoking, average number of cigarettes smoked per day, and current smoking status were also obtained. Those who were no longer smoking (n=859) reported the age at which they quit. Current smokers (n=140) reported the number of cigarettes they typically smoke each day. For those who reported having ever smoked fairly regularly, pack years (PY) were calculated by dividing the number of cigarettes smoked per day by 20 (the number of cigarettes in a pack) and multiplying by the number of years smoked. For this study, smoking exposure among current and former smokers was

categorized as low (<15 PY) or high (≥15 PY). This cut point was derived from our data given the distribution within our sample. Several other studies of smoking effects have used this cut point[19–22].

Outcome definitions

We evaluated two conceptually distinct outcomes: symptoms and structural disease status. Symptoms included pain, stiffness, and physical function. The OAI used the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scale to evaluate knee-specific symptoms[23] with assessments collected at annual visits. Higher WOMAC scores are suggestive of more severe symptoms (Pain: range 0 to 20; Stiffness: range 0 to 8; Physical function: range 0 to 68). We used WOMAC information from the knee having worse pain at baseline. For structural status, we used joint space width (JSW) as the primary outcome. If both knees had radiographic OA, the index knee was identified as the with the narrower joint space width in the medial tibiofemoral joint at baseline. Bilateral standing knee X-rays were collected annually using posterior anterior projection. Knees were flexed to 20–30 degrees, with feet rotated to 10 degrees[18]. Using serial knee x-rays, a customized software tool automatically delineated the margin of the femoral condyle and the tibial plateau and provided longitudinal measurements of JSW across different locations within the knee[24]. The distance from tibial plateau to tibial rim closest to femoral condyle was measured to indicate knee positioning[25]. The JSW measure at x=0.25 (in the medial compartment) was used because it was demonstrated to have best responsiveness to changes[26].

In OAI, a quantitative approach on plain radiographs was used to provide a precise measure of joint space width (JSW) in millimeters between the adjacent bones of the knee[27]. Multiple JSWs were measured at fixed locations along the joint in medial compartment, denoted as JSW(x), at 0.025 intervals for x = 0.15 – 0.30. The reproducibility of this technique and the responsiveness to change have been documented elsewhere[26,27], including one study using OAI data which demonstrated a responsiveness that compared favorably to magnetic resonance imaging (MRI)[26].

JSW measures were considered missing if the distance between plateau and rim was > 6.5mm (n=114 out of the 2364 participants in the baseline sample). Minimally important clinical differences for WOMAC Pain range from 1.2 to 4.6, for WOMAC Stiffness range from 0.5 to 1.5, for WOMAC Physical Function range from 4.1 to 9.9, and for JSW important clinical differences range from 0.12 to 0.84 mm[28–30].

Covariates

Potential covariates included age, gender, education, income, race, BMI, symptom-related multi-joint OA, KL-grade, alcohol drinking behavior, and SF-12 physical and mental component scores. OAI administered comprehensive measurements of participants' clinical characteristics, including knee alignment, symptom-related multi-joint OA, K-L grade, and history of having a knee injury or surgery. Knee malalignment was measured with goniometer. Varus or valgus deformity was recorded if malalignment was found. We considered symptom-related multi-joint OA present if participants had OA symptoms in at least two joints other than knee. Information was collected on prior knee injuries that limited

ability to walk for at least two days, and history of knee surgery including arthroscopy, ligament repair or meniscectomy. At-risk alcohol use was defined for female participants as more than 4 drinks on any single day or more than 7 drinks per week and male participants as more than 5 drinks on any single day or 14 drinks per week[31].

The 12-item Short-Form Health Survey (SF-12) was employed to assess general health status[32]. A Physical and Mental Component Summary score was calculated ranging from 0 to 100, with higher scores indicating better health status. The SF-12 Scores were missing in 11 participants. BMI is a risk factor for OA due to its potential local biomechanical effect and systemic metabolic effect[33]. BMI was calculated using measurements of height and weight [weight (kg)/height $(m)^2$]. Participants were then categorized in the following manner: normal weight (BMI 18.5–24.9 kg/m^2); overweight (BMI 25.0–29.9 kg/m^2); and obese (BMI ≥ 30 kg/m^2)[34].

Statistical analyses

A cross-sectional analysis was employed to examine associations between characteristics of smoking history and knee osteoarthritis within this population at a particular point in time (baseline) which helped generate hypotheses. We then conducted longitudinal analyses to determine whether a temporal relationship exists between smoking history and outcomes of interest (changes in symptoms and joint space width) following the natural development of this condition (radiographically confirmed knee OA) over time.

Before conducting the model-building exercise, descriptive characteristics of all variables at the baseline visit including the exposure (current smoking status), outcomes (WOMAC subscales and JSW), and the sociodemographic and clinical characteristics described above were calculated according to smoking exposure data (e.g., high PY, low PY, and never-smokers). The baseline WOMAC subscales (pain, stiffness, and function) and JSW were used as outcomes to examine the cross-sectional associations between smoking history/status and symptoms/structure of the knee at baseline. The outcomes for changes in symptoms and disease progression were calculated using differences from baseline to 72 months for each of the WOMAC subscales and differences from baseline to 48 months for JSW.

Since we had 4 outcome variables (e.g. pain, stiffness, physical function, JSW) and two operational definitions of exposure to smoking (e.g. number of pack years (PY) and current smoking status), we developed 8 models for both cross-sectional and longitudinal designs to examine the relationship between smoking status and OA symptoms of the knee and disease progression. The beta coefficients and corresponding 95% confidence intervals (CIs) were derived corresponding to smoking status (e.g. high/low PY and current/past smoker) compared to never-smokers. Positive and negative beta coefficients corresponded to higher and lower WOMAC subscale scores in pain, stiffness, and physical function. For JSW, positive and negative beta coefficients indicated better and worse JSW. Multivariable linear models were used to estimate the relationship between smoking status on the symptoms (or changes in symptoms) and structural status of the knee (or disease progression) in both designs. *Biological factors such as age and sex were forced into the model.* A change-in-estimate approach was used for model building where potential confounders whose

inclusion changed the smoking coefficients by at least 10% were retained in the adjusted model. Furthermore, BMI was also examined as a potential mediator in the relationship between smoking and outcome variables. Multicollinearity was evaluated and ruled out in all models. We originally thought that BMI may be a mediator and that adjustment for it may introduce collider-stratification bias[35]. BMI did not satisfy statistical requirements for being considered a mediator in this analysis.

RESULTS

Overall the sample was approximately 60% women and 78% non-Hispanic White (Table 1). The majority were college graduates, and more than half earned more than $50,000 annually. About half of the sample had symptom-related multi-joint OA, and about half had a history of knee injury. (Table 2). The average age of smoking initiation was 18.6 years. For former smokers, average time since quitting was 24.1 years. Those with a history of high PY had quit more recently than low PY subjects and were more likely to be male, have less education, lower income, engage in at-risk alcohol use, and were more likely to be obese.

In Tables 3 and 4 results of the baseline cross sectional analysis are presented. In table 3 we compared those with a history of high PY and low PY (current and former smokers) with never smokers. High PY participants reported slightly more pain (beta 0.36, 95% CI: 0.01 to 0.71) and stiffness (beta 0.20, 95% CI: 0.03 to 0.37) compared to never-smokers. Worse physical function and JSW were not associated with high PY compared to never smokers. Low PY was not associated with more or less symptoms of the knee but was associated with better JSW (beta 0.15, 95% CI: 0.02–0.28) compared to never smokers. Table 4 examines current smokers and smokers who have quit compared to never smokers. Among adjusted results, participants with current smoking status were associated with higher pain measures compared to never-smokers (beta 0.59, 95% CI: 0.04 to 1.15). Crude results indicated greater stiffness and worse function among current smokers, but once adjusted for confounders these findings were not sustained. Notably, JSW measures were not significantly different in crude or adjusted calculations in either group.

Tables 5 and 6 present results of longitudinal analyses examining disease progression represented by WOMAC symptom changes from baseline to 72-month and JSW from baseline to 48 month follow-up assessments. Changes were not different between either high or low PY participants when compared to never smokers (Table 5). Likewise, no differences in long-term symptom or JSW changes were observed between either those who reported current smoking at baseline or those who reported having quit smoking at baseline compared to participants who never smoked. (Table 6) Mean changes in JSW were similar for low PY, high PY, current, former and never smokers (range = −0.54 to −0.5 mm). (Tables 5 & 6)

Discussion

We examined data from a population of people enrolled in the Osteoarthritis Initiative with radiographically confirmed knee OA. Longitudinally, no associations were found between high or low PY or baseline smoking status with changes in WOMAC symptoms (at 72

months) or JSW (at 48 months). Cross-sectionally at baseline, participants with a history of low PY smoking had better JSW than never-smokers but worse function. High PY participants had worse pain and stiffness and no difference in JSW when compared to never-smokers. Current smokers had worse pain than never-smokers but those who had quit smoking did not. We consider the longitudinal analysis more robust than the cross-sectional, and we suspect that the small and conflicting findings from the cross-sectional study are due to residual confounding.

Several limitations must be considered. The OAI dataset has limitations. For example, although joint symptoms were measured at every follow-up visit, JSW was only measured for 48 months vs. joint symptoms (WOMAC) which were measured annually for a full 72 months. Thus we had to use these different follow-up periods for our outcome measures. Further, this was an observational study and the data collected on smoking history was self-reported. Although self-reported smoking history is considered reliable[36] and participant questionnaires were double checked by OAI research staff, there is potential for erroneous responses as participant recall may be skewed. For the longitudinal analysis, we are using smoking history data collected at baseline as there was no 48 or 72 month data collected. While pack years have been found to be a reasonably valid method to estimate life-time smoking exposure[37–38], there are no standard cut-points for higher versus lower exposure levels. Finally, although the OAI and its collaborators have collected longitudinal MRI assessments of cartilage morphology, we were unable to include MRI data in our analyses. OAI collected MRI data through several different vendors and projects and use of pooled data is advised against (see: https://oai.epi-ucsf.org/datarelease/docs/ImageAssessments/ImageAssessmentDataOverview.pdf). Even when using the largest available MRI project, we did not have a sample size with sufficient power to detect changes over time.

Our understanding of smoking's relationship to osteoarthritis remains in flux. While the 2001 Surgeon General's report on women and smoking concluded that "women who smoke have a modestly reduced risk for osteoarthritis of the knee[39]," the most recent Surgeon General's report on the health consequences of smoking (2014) did not mention osteoarthritis at all[40]. A recent review conducted by Felson and Zhang concluded that smokers are "modestly protected against developing radiographic OA in the knee[35]."

There are physiological mechanisms that would indicate that smoking is likely to be associated with osteoarthritis including smoking's effect on cartilage, and smoking-related generalized inflammation, insulin resistance, central adiposity and metabolic syndrome. Some studies have linked smoking to cartilage loss[6,7]. In a clinical trial of 42 surgical patients with pre-arthritic cartilage lesions, smoking was associated with worse cartilage outcomes due to inhibition of important mediators of cartilage metabolism, IGF-1 and bFGF[41]. Smokers are also at risk for reduced bone density[42] and a 2013 study of radiographcially confirmed knee OA patients (K-L grade ≥2) found that longitudinal bone mineral density loss was associated with progressive knee cartilage loss[43]. Susceptibility to knee OA may be genetic[44] and in one study an association was found between smoking and knee cartilage loss among those with a family history of knee OA while controls (smoking with no family history of knee OA) had no such association[8].

On the other hand, several studies have concluded that smoking is protective and may lead to improved OA symptoms. Two studies examining rates of total knee replacements found that smoking protects against end-stage knee OA[45,46]. Among healthy adults without current or prior knee disease, one study found a positive association between smoking history and both increased knee joint cartilage volume and lack of cartilage defects[47]. Some have hypothesized that since smoking is linked to sedentary behavior[48] and lower bone density[42], smokers exert less stress on weight-bearing joints thus reducing cartilage wear and tear[49].

It is clear that the relationship between smoking and osteoarthritis is complex. It is possible that some chemical exposures due to smoking are detrimental in OA while others may be beneficial. Determining what aspect of smoking might be beneficial is difficult due to the sheer numbers of chemicals in cigarette smoke. Indeed, cigarettes have more than 600 ingredients yielding over 69 known carcinogens and more than 7,000 chemicals when burned[50]. Because of the known health risks of smoking, clarity about any potential protective effects of smoking is important so smokers with OA do not find reason to continue smoking thereby putting other aspects of their health at risk. In our longitudinal analysis, we found no protective effects of smoking. Cross-sectionally we found a potential benefit in better JSW only among those with lower PY exposure. Although knee function is slightly worse at baseline, low PY smokers appear to have better JSW compared to never smokers. These findings are perplexing and we believe that their seemingly contradictory nature is most likely due to residual confounding. Our more robust longitudinal analysis found no differences in JSW changes over time among low PY smokers. High PY smokers have no difference in JSW at baseline and report greater pain and stiffness. Like low PY they have no differences in terms of symptom changes when compared to never smokers longitudinally. Overall, mean WOMAC scores changed for the entire sample but none of these changes were clinically significant. Mean JSW changes were clinically significant however the whole sample experienced worsening JSW. The rate of JSW change did not differ based on smoking status. (See Tables 5 & 6.) Thus we conclude that there is no evidence of a protective effect from smoking particularly for high PY smokers.

Generalizability

In the US older population (60+ years), radiographic knee OA is more prevalent among women (42%), those who identify as Black (52%), those with less than high school education (43%), and low income (43%)[2]. Our sample was also predominantly non-Hispanic white, more educated, and higher income. OAI is a multi-center observational study with participants drawn from 4 clinical sites (MD, OH, PA, and RI)[18] and recruiting a representative national sample was not an objective. Thus the nature of our sample limits the overall generalizability of our findings.

In conclusion, higher self-reports of pain and stiffness among those with a longer lifetime exposure to smoking in cross-sectional analyses is curious, and even more curious is better JSW among low PY smokers. However the longitudinal analysis found no differences in symptom changes. We believe that the longitudinal analysis is more robust and that statistically significant yet very small differences found in the cross-sectional analysis carry less weight and could be the result of residual bias. One conclusion from our study seems

clear – there is no convincing evidence of a beneficial effect of long-term smoking among knee OA patients. Other health risks associated with smoking and the dangers of longer-term addiction make even short-term smoking ill advised.

Acknowledgments

The OAI is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health. This manuscript was prepared using an OAI public use data set and does not necessarily reflect the opinions or views of the OAI investigators, the NIH, or the private funding partners.

ROLE OF FUNDING SOURCE

This study was funded by the National Institute of Arthritis and Musculoskeletal and Skin Disease (Project number 268201000020C-1-0-1 entitled TAS::75 0888::TAS to Charles Eaton).

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Table 1

Sociodemographic factors among people with radiographically confirmed OA of the knee (n= 2,250)

Characteristics	All (n=2,250)	[high] pack years (n=538)	[low] pack years (n=461)	Never Smoked Cigarettes (n=1,251)
			Percentage	
Current smokers	6.2	21.2	5.6	0
Age (in years)				
<65	56.2	53.4	55.1	57.8
65–74	33.0	34.9	34.9	31.4
≥75	10.8	11.7	10.0	10.7
Women	59.5	51.1	60.7	62.7
Ethnicity/Race				
Non-Hispanic White	77.5	78.6	76.1	77.5
Non-Hispanic Black	19.7	19.7	21.5	19.0
Other	2.8	1.7	2.4	3.5
Education				
High school or less	17.6	18.4	17.1	17.4
Some college	25.1	33.2	22.6	22.5
College graduate	20.3	21.8	21.5	19.3
Graduate school	37.0	26.6	38.8	40.8
Income ($)				
<25,000	14.9	17.7	10.4	15.4
25,000 – 50,000	28.5	30.5	30.6	26.9
>50,000	56.6	51.9	59.0	57.8

Table 2

Clinical factors among people with radiographically confirmed OA of the knee (n= 2,250)

Characteristics	All (n=2,250)	[high] pack years (n=538)	[low] pack years (n=461)	Never Smoked Cigarettes (n=1,251)
	Percentage			
KL grade				
2	53.6	51.9	55.3	53.6
3	34.9	35.3	33.0	35.5
4 (≥1 knee)	11.5	12.8	11.7	10.9
Family hx knee or hip joint replacement	21.3	20.6	20.2	21.9
Symptom-related multi-joint OA	52.1	56.7	52.1	50.2
At-risk alcohol use (f>7/wk; m>14/wk)	8.7	13.9	11.1	5.5
History of knee injury	49.2	49.0	51.0	48.7
History of knee surgery	29.8	30.1	30.4	29.4
Body Mass Index (kg/m2)				
<25	16.7	11.2	18.9	18.4
25 – <30	39.2	36.6	42.8	39.0
≥30	44.0	52.2	38.3	42.6
WOMAC Pain	4.1 (4.0)	4.6 (4.0)	4.2 (4.0)	3.9 (3.9)
WOMAC Stiffness	2.3 (1.8)	2.5 (1.8)	2.4 (1.8)	2.2 (1.8)
WOMAC Physical Function	13.0 (12.8)	13.8 (12.6)	13.5 (13.4)	12.4 (12.7)
Physical Component Scale	47.8 (9.2)	47.2 (9.4)	48.0 (9.5)	48.0 (9.1)
Mental Health Component Scale	53.8 (8.2)	52.7 (8.7)	54.2 (7.7)	54.1 (8.1)
Joint space width (mm)	5.0 (1.6)	4.9 (1.6)	5.1 (1.5)	5.0 (1.6)
Age of smoking initiation	18.6 (4.4)	17.8 (3.8)	19.5 (4.8)	NA
Years since quitting*	24.1 (12.6)	18.4 (10.5)	29.8 (11.8)	NA

*Based on information from 859 participants who reported having quit smoking (≥15 [high] pack years; <15 [low] pack years)

Table 3

Cross-sectional analysis at baseline: Current impact of cumulative lifetime smoking and OA symptoms for patients with radiographically confirmed knee OA, beta coefficients (95% confidence intervals (CI))

	Mean (Standard Deviation)	[high] pack years vs Never Smoked Beta coefficients (95%CI)	[low] pack years vs Never Smoked Beta coefficients (95%CI)	
Pain	High: 4.6 (4.0) Low: 4.2 (4.0) Never: 3.9 (3.9)			Negative beta indicates less pain
Crude		0.69 (0.29 to 1.09)	0.26 (−0.16 to 0.69)	
Multivariable-adjusted§		0.36 (0.01 to 0.71)	0.23 (−0.11 to 0.57)	
Stiffness	High: 2.5 (1.8) Low: 2.4 (1.8) Never: 2.2 (1.8)			Negative beta indicates less stiffness
Crude		0.27 (0.09 to 0.46)	0.13 (−0.06 to 0.33)	
Multivariable-adjusted§		0.20 (0.03 to 0.37)	0.14 (−0.03 to 0.30)	
Function	High: 13.8 (12.6) Low: 13.5 (13.4) Never: 12.4 (12.7)			Negative beta indicates better function
Crude		1.39 (0.09 to 2.69)	1.05 (−0.32 to 2.41)	
Multivariable-adjusted§		0.60 (−0.48 to 1.69)	0.98 (−0.08 to 2.03)	
Joint Space Width	High: 4.9 mm (1.6) Low: 5.1 mm (1.5) Never: 5.0 mm (1.6)			Positive beta indicates better JSW
Crude		−0.08 (−0.24 to 0.07)	0.16 (−0.01 to 0.32)	
Multivariable-adjusted§		−0.05 (−0.19 to 0.09)	0.15 (0.02 to 0.28)	

§Adjusted for current smoking status, age (linear term), sex, race, education, K-L grade, and SF12 physical component scores

Table 4

Cross-sectional analysis at baseline: Impact of current smoking status and OA symptoms for patients with radiographically confirmed knee OA, beta coefficients (95% confidence intervals (CI))

	Mean (Standard Deviation)	Current smoker vs Never Smoked Beta coefficients (95%CI)	Former smoker vs Never Smoked Beta coefficients (95%CI)	
Pain	*Current: 6.0 (4.7)* *Former: 4.1 (3.8)* *Never: 3.9 (3.9)*			Negative beta indicates less pain
Crude		2.14 (1.45 to 2.83)	0.22 (−0.02 to 0.57)	
Multivariable-adjusted§		0.59 (0.04 to 1.15)	0.25 (−0.02 to 0.52)	
Stiffness	*Current: 3.0 (1.8)* *Former: 2.3 (1.8)* *Never: 2.2 (1.8)*			Negative beta indicates less stiffness
Crude		0.76 (0.45 to 1.08)	0.12 (−0.04 to 0.27)	
Multivariable-adjusted§		0.26 (−0.02 to 0.53)	0.13 (−0.002 to 0.27)	
Function	*Current: 17.9 (14.7)* *Former: 13.0 (12.5)* *Never: 12.4 (12.7)*			Negative beta indicates better function
Crude		5.48 (3.25 to 7.71)	0.54 (−0.57 to 1.65)	
Multivariable-adjusted§		0.59 (−1.15 to 2.32)	0.62 (−0.23 to 1.47)	
Joint Space Width	*Current: 5.2 mm (1.4)* *Former: 5.0 mm (1.6)* *Never: 5.0 mm (1.6)*			Positive beta indicates better JSW
Crude		0.22 (−0.05 to 0.49)	−0.002 (−0.14 to 0.13)	
Multivariable-adjusted§		−0.02 (−0.25 to 0.20)	0.06 (−0.05 to 0.17)	

§Adjusted for age (linear term), sex, education, race, income, obesity, K-L grade, symptom-related multi-joint OA, K-L grade, SF12 physical and mental component scores

Table 5

Longitudinal analysis (72 months for WOMAC assessment; 48 months for JSW): Cumulative lifetime smoking and long-term changes in OA symptoms for patients with radiographically confirmed knee OA, beta coefficients (95% confidence intervals (CI))

	Mean Change (Standard Deviation)	[high] pack years vs Never Smoked Beta coefficients (95%CI)	[low] pack years vs Never Smoked Beta coefficients (95%CI)	Minimal clinically important difference (MCID)
Pain	High PY: −0.7 (4.1) Low PY: −0.5 (3.5) Never: −0.6 (3.6)			1.2 – 4.6, negative beta indicates less pain
Crude		−0.09 (−0.49 to 0.32)	0.06 (−0.37 to 0.49)	
Multivariable-adjusted[§]		0.03 (−0.39 to 0.45)	0.07 (−0.35 to 0.49)	
Stiffness	High PY: −0.4 (1.9) Low PY: −0.4 (1.8) Never: −0.3 (1.8)			0.5 – 1.5, negative beta indicates less stiffness
Crude		−0.04 (−0.23 to 0.16)	−0.10 (−0.31 to 0.11)	
Multivariable-adjusted[§]		0.02 (−0.19 to 0.23)	−0.11 (−0.31 to 0.10)	
Function	High PY: −1.0 (12.3) Low PY: −2.1 (10.2) Never: −1.3 (11.4)			4.1 – 9.9, negative beta indicates better function
Crude		0.23 (−1.00 to 1.47)	−0.85 (−2.16 to 0.46)	
Multivariable-adjusted[§]		0.78 (−0.51 to 2.08)	−0.85 (−2.13 to 0.44)	
Joint Space Width	High PY: −0.5 mm (0.8) Low PY: −0.5 mm (0.7) Never: −0.5 mm (0.8)			0.12 – 0.84, positive beta indicates better JSW
Crude		−0.03 (−0.13 to 0.06)	0.04 (−0.06 to 0.14)	
Multivariable-adjusted[§§]		−0.02 (−0.12 to 0.07)	0.03 (−0.07 to 0.13)	

[§] Adjusted for current smoking status, education, race, obesity, and SF-12 physical component scores

[§§] Adjusted for current smoking status, race, K-L grade, drinking behavior, obesity, and SF-12 physical component scores

Table 6

Longitudinal analysis (72 months for WOMAC assessment; 48 months for JSW): Current smoking status and long-term changes in OA symptoms for patients with radiographically confirmed knee OA, beta coefficients (95% confidence intervals (CI))

	Mean Change (Standard Deviation)	Current smoker vs Never Smoked Beta coefficients (95%CI)	Former smoker vs Never Smoked Beta coefficients (95%CI)	Minimal clinically important difference (MCID)
Pain	*Current: −0.9 (4.6)* *Former: −0.6 (3.7)* *Never: −0.6 (3.6)*			1.2 – 4.6, negative beta indicates less pain
Crude		−0.35 (−1.07 to 0.37)	0.03 (−0.32 to 0.38)	
Multivariable-adjusted§		−0.07 (−0.79 to 0.65)	0.07 (−0.27 to 0.41)	
Stiffness	*Current: −0.5 (2.0)* *Former: −0.4 (1.8)* *Never: −0.3 (1.8)*			0.5 – 1.5, negative beta indicates less stiffness
Crude		−0.17 (−0.52 to 0.18)	−0.05 (−0.22 to 0.12)	
Multivariable-adjusted§		−0.09 (−0.44 to 0.26)	0.02 (−0.19 to 0.14)	
Function	*Current: −2.7 (12.5)* *Former: −1.3 (11.2)* *Never: −1.3 (11.4)*			4.1 – 9.9, negative beta indicates better function
Crude		−1.42 (−3.63 to 0.79)	−0.09 (−1.15 to 0.97)	
Multivariable-adjusted§		−0.57 (−2.77 to 1.63)	0.02 (−1.02 to 1.06)	
Joint Space Width	*Current: −0.5 mm (0.7)* *Former: −0.5 mm (0.8)* *Never: −0.5 mm (0.8)*			0.12 – 0.84, positive beta indicates better JSW
Crude		0.02 (−0.14 to 0.08)	−0.003 (−0.08 to 0.08)	
Multivariable-adjusted§§		0.01 (−0.150 to 0.17)	−0.03 (−0.08 to 0.08)	

§ Adjusted for age (linear term), education, race, K-L grade, SF12 physical and mental component scores

§§ Adjusted for age (linear term), sex, race, and K-L grade