Correlation between radiographic knee osteoarthritis and lifetime cigarette smoking amount in a Korean population

A cross-sectional study

Jung Woo Kim, MD[a], Sang Yoon Lee, MD, PhD[b],*

Abstract

Although the inverse correlation between smoking and degenerative arthritis is controversial, quantitative analysis of the correlation between lifetime cigarette smoking amount and degenerative arthritis has not been performed. We investigated the correlation between knee radiographic osteoarthritis (ROA) and lifetime cigarette smoking amount in the general population.

This cross-sectional study used the Fifth and Sixth Korean National Health and Nutrition Examination Survey (2010–2013) data. Subjects included 11,638 community-dwelling adults aged ≥50 years. Knee ROA was defined as a Kellgren/Lawrence grade ≥2 on plain radiography. Lifetime cigarette smoking amount was calculated in terms of pack-year and further divided into quartile groups. Independent correlation between smoking and knee ROA was determined using odds ratios (OR) adjusted for age, sex, obesity, physical activity, and household income on multivariate logistic regression analysis.

Knee ROA prevalence was 37.3%; prevalence of lifetime cigarette smokers was 26.0%. Subjects with knee ROA had higher mean age, female sex ratio, and body mass index but lower physical activity level. The adjusted logistic regression model revealed that female sex (OR, 2.110; 95% confidence interval [CI], 1.895–2.349) was significantly associated with knee ROA. Older age, obesity, and lower household income were positively correlated with knee ROA. Second-and fourth-quartile groups of smokers had the lower ROA prevalence than never-smokers (OR, 0.800; 95% CI, 0.643–0.99; OR, 0.812; 95% CI, 0.684–0.965, respectively).

An inverse correlation with knee ROA was confirmed in mid-light to heavy smokers. Prospective studies are needed to reveal whether knee ROA involves smoking.

Abbreviations: BMI = body mass index, CI = confidence interval, IPAQ = International Physical Activity Questionnaire, K/L = Kellgren/Lawrence, KNHANES = Korea National Health and Nutrition Examination Survey, METs = metabolic equivalents, OA = osteoarthritis, OR = odds ratios, PY = pack-years, ROA = radiographic osteoarthritis.

Keywords: cigarette smoking, cross-sectional studies, knee joints, osteoarthritis

[a] Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul National University Hospital, [b] Department of Rehabilitation Medicine, Seoul National University College of Medicine, SMG-SNU Boramae Medical Center, Seoul, Republic of Korea.

* Correspondence: Sang Yoon Lee, Department of Rehabilitation Medicine, Seoul National University College of Medicine, SMG-SNU Boramae Medical Center, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Republic of Korea (e-mail: rehabilee@gmail.com).

1. Introduction

Several risk factors have been known to be associated with knee osteoarthritis (OA). Physical activity, occupation, obesity, and diabetes mellitus are modifiable and could be targets of knee OA prevention,[1,2] while age, sex, race, and genetics are non-modifiable factors. In contrast, there are protective factors against knee OA. A few studies investigating socioeconomic status such as household income or occupation found these attributes to be protective against knee OA.[3] Cigarette smoking is a known protective factor of knee OA. However, the association between cigarette smoking and incident knee OA remains controversial.

Many studies have suggested that cigarette smoking is inversely correlated with knee OA. One prospective cohort study of 598 subjects reported that smokers had a lower risk of knee OA than did nonsmokers (OR = 0.4; 95% confidence interval [CI], 0.2–0.8).[4] Felson et al reported that the adjusted risk of severe OA was lower in heavy smokers than in nonsmokers (relative risk, 0.73). A meta-analysis of 38 independent observational studies (481,744 participants) also suggested that those who had ever smoked were at a significantly decreased risk of developing knee OA relative to those who had never smoked (relative risk, 0.80; 95% CI, 0.73–0.88), a finding that was unaffected by study design.[5]

However, one recent meta-analysis of 48 studies (537,730 participants) showed that the protective effect of cigarette smoking in OA observed in some epidemiological studies is likely to be false because it may be caused by selection bias.[6] The authors suggested that hospital setting and secondary exposure to cigarette smoking were the major source of the negative association. One cross-sectional population-based study of 1003 women reported that there was no clear protective effect of smoking on OA of the hands and knees.[7] A recent meta-analysis also reported that cigarette smoking was not a statistically significant risk or protective factor (pooled OR, 0.92; 95% CI, 0.83–1.01).[3]

Most studies published to date have simply classified cigarette smoking status as a categorical variable. Based on current smoking behavior, subjects were categorized into three groups: those who currently smoked cigarettes; those who previously smoked cigarettes; and those who never smoked cigarettes.[8] Although Zhang et al classified smoking status into four levels based on the daily smoking habit in a cross-sectional study of a Chinese population, they did not identify the long-term effects of smoking because they did not analyze the accumulated data of lifetime cigarette smoking.[9] To the best of our knowledge, no quantitative analysis of lifetime cigarette smoking amount and its correlation with knee OA has been performed. Therefore, here we aimed to investigate whether there was a correlation with knee OA depending on cigarette smoking amount in the general population.

2. Materials and methods

2.1. Data source and study population

This cross-sectional study examined the public data obtained from the Fifth and Sixth Korea National Health and Nutrition Examination Survey (KNHANES) conducted from 2010 to 2013 by the Korea Centers for Disease Control and Prevention. The KNHANES used a stratified multistage probability-sampling method to select its study subjects. Sampling weights were used to represent the entire Korean population. From this pool of data, we included subjects aged ≥50 years who had completed surveys on body weight, height, area of residence, household income status, International Physical Activity Questionnaire (IPAQ), and cigarette smoking status for whom radiographs of the knee were available. With respect to the residential area, subjects dwelling in "dong" (city or downtown) were defined as urban dwellers, while subjects dwelling in "eup" or "myeon" (uptown or village) were defined as rural dwellers. Monthly household income (monthly income/$\sqrt{}$ number of family members) was divided into four quartile groups: lowest, lower middle, higher middle, and highest.[10] The present study finally included 11,638 community-dwelling subjects. All subjects provided written informed consent, and the Korea Centers for Disease Control and Prevention Institutional Review Board (ethical review committee for health survey data) approved the study protocol (IRB Nos. 2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C, and 2013-07CON-03-4C).

2.2. Anthropometric data and physical activity measurements

From the anthropometric data (height and weight), body mass index (BMI) was calculated as the body weight divided by height

squared (kg/m^2). Obesity was defined and classified using the criteria for the Asia-Pacific region as follows: normal weight (BMI 18.5–22.9 kg/m^2), overweight (BMI 23–24.9 kg/m^2), and obese (BMI ≥25 kg/m^2) groups.[11] Obese was further subdivided into obese I (BMI 25–29.9 kg/m^2) and obese II (BMI ≥30 kg/m^2) subgroups. The short version of the IPAQ in Korea,[12] which measures health-related physical activity in populations, was used to measure each subject's current physical activity. Continuous activity scores expressed as total metabolic equivalents were calculated as follows: (daily minutes of walking × days per week walking × 3.3) + (daily minutes of moderate-intensity activity × days per week with moderate-intensity activity × 4.0) + (daily minutes of vigorous activity × days per week with vigorous activity × 8.0).[13] Physical activity was also divided into four quartile groups: low, mid-low, mid-high, and high.

2.3. Radiographic examination of knee joints

Radiographic examinations of the knee, hip, and lumbar spine were performed using an SD 3000 Synchro Stand (Accele Ray SYFM Co., Seoul, Korea). Bilateral weight-bearing anteroposterior and lateral (30° flexion) plain radiographs of the knees were obtained.[14] Radiographic changes in each joint were then independently assessed by two musculoskeletal radiologists using the Kellgren/Lawrence (KL) grading system,[15] with concordant grades accepted. The higher grade was accepted if a grade differed between the two radiologists' assessments.[16] Inter-rater agreement within 1 grade of difference between the 2 radiologists was 92.8% and weighted Cohen's kappa coefficient was 0.65.[16] The presence of radiographic OA (ROA) was defined as a KL grade of at least 2 in the knee joints.

2.4. Quantification of lifetime cigarette smoking

Self-reported lifetime cigarette smoking amount was calculated in terms of pack-years (PY) as follows: (packs smoked per day) × (years as a smoker). Four quartile groups (light, mid-light, mid-heavy, and heavy smokers) were established based on the lifetime cigarette smoking amount; a fifth group (never smoker) was also included.[17] As a result of the calculation, the cut-off values were determined with the first quartile group below 3 PY, the second quartile group below 12 PY, and the third quartile group below 27 PY in this population.

2.5. Statistical analysis

The subjects' characteristics for healthy and ROA joints were compared using Student's t test for continuous variables and the χ^2 test for categorical variables. Multivariable logistic regression analyses were performed to evaluate the effects of cigarette smoking on knee ROA adjusted for age group, sex, obesity, physical activity, and household income. The adjusted model was developed using backward elimination with a significance level of 0.1 to enter and 0.05 to stay. We also evaluated possible multiple collinearities between covariables by correlation analysis and collinearity statistical tests (tolerance and variance inflation factor tests) as suggested for the regression analysis. Sampling weights were used for each participant's data to represent the entire Korean population. PASW Statistics 18 (SPSS Inc, Chicago, IL) was used for all analyses. P values < .05 were considered statistically significant.

3. Results

3.1. Characteristics of the study subjects

Of the total population, 4344 (37.3%) individuals had knee ROA and 26.0% were lifetime cigarette smokers. Subjects with knee ROA had a higher mean age (68.36 ± 8.81 years vs 61.52 ± 8.60 years, $P < .001$), female sex ratio (69.4% vs 50.2%, $P < .001$), waist circumference (84.71 ± 9.28 cm vs 82.41 ± 8.93 cm, $P < .001$), and BMI (24.66 ± 3.33 kg/m^2 vs 23.62 ± 2.95 kg/m^2, $P < .001$) than those with a healthy knee joint. The proportions of low household income (44.07% vs 24.75%, $P < .001$) and lower physical activity (33.35% vs 25.61%, $P < .001$) were higher in the knee ROA group than the healthy knee joint group. In the lifetime cigarette smoking group, the ratio of never-smokers was also higher in the knee ROA group than in the healthy knee joint group (81.94% vs 74.02%, $P < .001$) (Table 1).

3.2. Association between knee ROA and cigarette smoking

On multivariable logistic regression analysis, no significant collinearity was identified for any of the covariables in statistical tests of collinearity. The adjusted logistic regression model

revealed that female sex (OR, 2.110; 95% CI, 1.895–2.349) was significantly associated with knee ROA. Older age, obesity, and lower household income also showed positive correlations with knee ROA. The second (mid-light) and fourth (heavy) smoker quartile groups had the lower prevalence of ROA compared to the never-smoker group (OR, 0.800; 95% CI, 0.643–0.994; and OR, 0.812; 95% CI, 0.684–0.965, respectively) (Table 2).

4. Discussion

The most important finding of this study was that there was an inverse correlation between mid-light to heavy cigarette smoking and knee ROA. Since several epidemiologic variables that can affect knee ROA such as age, sex, obesity, and physical activity have been adjusted, the correlation is considered independent. To the best of our knowledge, this is the first study to investigate the association between knee ROA and quantitatively calculated lifetime cigarette smoking.

In this study, we wanted to confirm the inverse correlation between lifetime cigarette smoking and knee ROA and whether this correlation would increase as amount of smoking increased. The analysis did not confirm the linear dose–dependent relationship based on cigarette smoking amount. Compared to

Table 1

Characteristics of subjects by radiographic knee osteoarthritis.

	Control (n=7294)	Radiographic knee OA (n=4344)	P*
Age (years)	61.52 ± 8.60	68.36 ± 8.81	<.001
Sex (Female %)	50.2%	69.4%	<.001[†]
Region (Urban %)	76.5%	67.2	.001[†]
BMI (kg/m^2)	23.62 ± 2.95	24.66 ± 3.33	<.001
Waist circumference (cm)	82.41 ± 8.93	84.71 ± 9.28	<.001
Obesity (%)			<.001[†]
Low (BMI < 18.5)	3.3	1.89	
Normal (BMI 18.5–22.9)	38.73	28.89	
Overweight (BMI 23–24.9)	27.73	25.19	
Obese I (BMI 25–29.9)	28.15	38.07	
Obese II (BMI ≥ 30)	2.13	5.96	
Household income (%)			<.001[†]
1Q (low)	24.75	44.07	
2Q (mid-low)	26.38	24.92	
3Q (mid-high)	22.63	16.96	
4Q (high)	26.25	14.04	
Physical activity (METs/week)	2121.93 ± 3336.29	1848.29 ± 3380.78	<.001
Physical activity quartile (%)			<.001[†]
1Q (low)	25.61	33.35	
2Q (mid-low)	23.79	24.68	
3Q (mid-high)	24.46	20.20	
4Q (high)	26.14	21.77	
Cigarette smoking (%)			<.001[†]
Never-smoker	74.02	81.94	
1Q (light)	3.71	3.59	
2Q (mid-light)	5.45	3.42	
3Q (mid-heavy)	7.62	4.53	
4Q (heavy)	9.20	6.51	
Kellgren/Lawrence grade			
Grade 0	4390	0	
Grade 1	2904	0	
Grade 2	0	1848	
Grade 3	0	1629	
Grade 4	0	867	

BMI = body mass index, METs = metabolic equivalents, OA = osteoarthritis.
P value by [*]independent t test and [†]Chi-square test.

Table 2

Odds ratios of radiographic knee osteoarthritis.

	N	Unadjusted OR* (95% CI)	P	Adjusted OR† (95% CI)	P
Sex					
Male	4946	1.000		1.000	
Female	6692	2.249 (2.083–2.428)	<.001	2.110 (1.895–2.349)	<.001
Age					
50–59	4326	1.000		1.000	
60–69	3802	2.763 (2.504–3.047)	<.001	2.750 (2.469–3.063)	<.001
70–79	2885	5.616 (5.065–6.227)	<.001	5.844 (5.171–6.605)	<.001
≥80	625	9.886 (8.304–11.769)	<.001	11.685 (9.501–14.371)	<.001
Obesity				–	
Low	314	1.000		1.000	
Normal	4044	1.288 (1.001–1.656)	.049	2.198 (1.650–2.929)	<.001
Overweight	3126	1.568 (1.217–2.020)	.001	3.230 (2.415–4.320)	<.001
Obese I	3742	2.335 (1.816–3.001)	<.001	4.921 (3.684–6.572)	<.001
Obese II	412	4.838 (3.545–6.602)	<.001	9.637 (6.747–13.766)	<.001
Physical activity					
1Q (low)	3310	1.000		1.000	
2Q (mid-low)	2809	0.797 (0.719–0.882)	<.001	0.932 (0.831–1.046)	.231
3Q (mid-high)	2660	0.634 (0.571–0.705)	<.001	0.849 (0.753–0.956)	.007
4Q (high)	2859	0.640 (0.577–0.709)	<.001	1.044 (0.928–1.175)	.473
Household income					
1Q (low)	3677	1.000		1.000	
2Q (mid-low)	2999	0.531 (0.482–0.584)	<.001	0.799 (0.715–0.892)	<.001
3Q (mid-high)	2407	0.421 (0.379–0.468)	<.001	0.791 (0.699–0.895)	<.001
4Q (high)	2555	0.300 (0.269–0.335)	<.001	0.653 (0.574–0.742)	<.001
Cigarette smoking					
Never-smoker	8846	1.000		1.000	
1Q (light)	449	0.875 (0.719–1.064)	.179	1.035 (0827–1.294)	.764
2Q (mid-light)	569	0.566 (0.470–0.683)	<.001	0.800 (0.643–0.994)	.044
3Q (mid-heavy)	780	0.537 (0.457–0.632)	<.001	0.835 (0.688–1.013)	.068
4Q (heavy)	994	0.640 (0.556–0.736)	<.001	0.812 (0.684–0.965)	.018

CI = confidence interval, OR = odds ratio.

* Unadjusted odds ratios by logistic regression analysis.

† Adjusted odds ratios by multivariate logistic regression analysis; adjusted for all other variables.

never-smokers, light smokers did not have a different prevalence of knee OA, whereas it was clearly reduced in mid-light smokers. This means that there might be a cut-off amount of lifetime cigarette smoking where protective effects are observed. In this study, because smoking amount was roughly divided into four quartile groups, 12 PY, which corresponds to the boundary between the first and second quartile, is considered this cut-off. However, these thresholds will require further study using more detailed continuous variables.

Smoking is known to be a risk factor for various diseases, but it is rather protective against certain conditions such as Parkinson's disease and ulcerative colitis.[18] One reported that smokers are less likely to have ulcerative colitis than non-smokers and a recent meta-analysis reported a 66% reduction in the Parkinson's disease risk in current smokers compared to never smokers.[19] These preventive effects are explained by the action of nicotine on acetylcholine receptors.[20]

Several studies have explained the cartilage protection mechanism of smoking. Gullahorn et al suggested that nicotine upregulates glycosaminoglycan and collagen synthesis activity of articular chondrocytes at physiological levels seen in smokers.[21] One study also reported that nicotine promotes proliferation and collagen synthesis of human chondrocytes and that the proliferation was increased in a nicotine concentration–dependent manner.[22] Thus, the authors insisted that the positive effect of smoking in OA may be related to altered metabolism of

chondrocytes. Nicotine also prevented cartilage damage and had an anti-inflammatory effect in a rat model of early stage OA.[23]

Although smokers could be protected against OA, physicians would never advocate for it because smoking has a multitude of negative effects on health.[20] Rather, this might provide an opportunity to identify constituents of tobacco that have favorable effects on knee OA and to test them as treatments. However, toxic effects of nicotine on joint cartilage have also been reported. Deng et al showed that nicotine induced the retardation of chondrogenesis by downregulation of the insulin-like growth factor–1 signaling pathway in fetal rats.[24] Another reported that prenatal nicotine exposure induced poor articular cartilage quality in rat models.[25] Therefore, there is a problem with the suggestion that nicotine would be used to prevent or treat OA, and more in-depth basic and clinical studies are needed.

While smoking could directly affect knee OA, an indirect effect has also been suggested. Felson and Zhang reported that BMI can be a mediator between smoking and OA rather than a confounding factor.[20] They insisted that adjusting for BMI, which is done in most epidemiologic studies examining the association between smoking and the risk of OA, might block one biological mechanism through which smoking affects the risk of OA. Thus, they suggested that examining the risk of OA in smokers vs non-smokers without adjusting for BMI can better estimate the total effect of smoking on OA. However, obesity defined using BMI is one of the best documented risk factors for

knee OA.[26] Therefore, analyzing the correlation with knee OA without adjusting for BMI would be a highly confusing study.

This study was designed as a cross-sectional study using the national data. Would the inverse correlation identified in this study be consistent regardless of study design? Interestingly, two recent meta-analyses provided different answers to this question. Kong et al suggested an inverse association between cigarette smoking and risk of knee OA irrespective of study design.[5] The authors showed that the inverse correlation was not affected by study design and that the pooled relative risks were 0.71 (95% CI, 0.61–0.84), 0.83 (95% CI, 0.73–0.94), and 0.79 (95% CI, 0.65–0.96) for case–control, cross-sectional, and cohort studies, respectively. However, a meta-analysis by Blagojevic et al showed that smoking appeared to have a moderately protective effect, but this was not evident once the analysis was restricted to cohort studies.[27] Although the pooled OR suggested a small protective effect of smoking (0.84; 95% CI 0.74–0.95), the effect size was significant only in case–control studies (OR 0.60, 95% CI 0.51–0.71), not in cohort study (OR 0.97, 95% CI 0.88–1.07). Although the studies included in these two meta-analyses differed, the study by Kong et al was published more recently (in 2017) and included more recently released papers. Thus, the newly published findings appear to have strengthened this inverse correlation regardless of study design.

There are several limitations to this study. First, it was difficult to establish causality between cigarette smoking and knee ROA because of the genuine limitations of cross-sectional studies. Therefore, further longitudinal studies or controlled trials are needed to reveal the causal relationship. Furthermore, we could not analyze several comorbidities and variables which can affect knee ROA, but were not included the survey. Second, the survey on cigarette smoking amount was self-reported, and these data were used to calculate lifetime smoking amount. However, as some studies have pointed out, self-reporting of smoking status is potentially unreliable.[28] Thus, a more detailed quantitative assessment of smoking amount is required. Third, this study measured only ROA, not clinical OA. Although ROA was evaluated to include asymptomatic OA but with structural changes in joints, cigarette smoking is also known to have an analgesic effect.[29] Therefore, further studies are needed to determine whether cigarette smoking has protective and analgesic effects in symptomatic knee OA.

5. Conclusions

An inverse correlation with knee ROA was confirmed in mid-light to heavy smokers. Prospective studies are needed to reveal the causality of smoking on knee ROA, and nicotine might be used to prevent and treat OA through more in-depth basic and clinical research in the future.

Acknowledgments

The authors did not receive any writing assistance.

Author contributions

Conceptualization: Jung Woo Kim, Sang Yoon Lee.
Data curation: Jung Woo Kim, Sang Yoon Lee.
Formal analysis: Jung Woo Kim, Sang Yoon Lee.
Investigation: Jung Woo Kim, Sang Yoon Lee.
Methodology: Jung Woo Kim, Sang Yoon Lee.

Project administration: Sang Yoon Lee.
Software: Sang Yoon Lee.
Supervision: Sang Yoon Lee.
Validation: Sang Yoon Lee.
Writing – original draft: Jung Woo Kim.
Writing – review & editing: Sang Yoon Lee.

References

[1] Lohmander LS, Gerhardsson de Verdier M, Rollof J, et al. Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. Ann Rheum Dis 2009;68:490–6.

[2] Wilder FV, Hall BJ, Barrett JP. Smoking and osteoarthritis: is there an association? The clearwater osteoarthritis study osteoarthritis and cartilage/OARS. Osteoarthr Res Soc 2003;11:29–35.

[3] Silverwood V, Blagojevic-Bucknall M, Jinks C, et al. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis and cartilage /OARS. Osteoarthr Res Soc 2015;23:507–15.

[4] Felson DT, Zhang Y, Hannan MT, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. Arthritis Rheum 1997;40:728–33.

[5] Kong L, Wang L, Meng F, et al. Association between smoking and risk of knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis and cartilage /OARS. Osteoarthr Res Soc 2017;25:809–16.

[6] Hui M, Doherty M, Zhang W. Does smoking protect against osteoarthritis? Meta-analysis of observational studies. Ann Rheum Dis 2011;70:1231–7.

[7] Hart DJ, Spector TD. Cigarette smoking and risk of osteoarthritis in women in the general population: the Chingford study. Ann Rheum Dis 1993;52:93–6.

[8] Cheng Y, Macera CA, Davis DR, et al. Physical activity and self-reported, physician-diagnosed osteoarthritis: is physical activity a risk factor? J Clin Epidemiol 2000;53:315–22.

[9] Zhang Y, Zeng C, Li H, et al. Relationship between cigarette smoking and radiographic knee osteoarthritis in Chinese population: a cross-sectional study. Rheumatol Int 2015;35:1211–7.

[10] Kim SR, Han K, Choi JY, et al. Age- and sex-specific relationships between household income, education, and diabetes mellitus in Korean adults: the Korea National Health and Nutrition Examination Survey, 2008-2010. PLoS One 2015;10:e0117034.

[11] Lim JU, Lee JH, Kim JS, et al. Comparison of World Health Organization and Asia-Pacific body mass index classifications in COPD patients. Int J Chron Obstruct Pulmon Dis 2017;12:2465–75.

[12] Chun MY. Validity and reliability of Korean version of international physical activity questionnaire short form in the elderly. Korean J Fam Med 2012;33:144–51.

[13] Fogelholm M, Malmberg J, Suni J, et al. International physical activity questionnaire: validity against fitness. Med Sci Sports Exerc 2006;38:753–60.

[14] Park JH, Hong JY, Han K, et al. Prevalence of symptomatic hip, knee, and spine osteoarthritis nationwide health survey analysis of an elderly Korean population. Medicine (Baltimore) 2017;96:e6372.

[15] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.

[16] Lee S, Kim TN, Kim SH. Sarcopenic obesity is more closely associated with knee osteoarthritis than is nonsarcopenic obesity: a cross-sectional study. Arthritis Rheum 2012;64:3947–54.

[17] Glennon SG, Huedo-Medina T, Rawal S, et al. Chronic Cigarette Smoking Associates Directly and Indirectly with Self-Reported Olfactory Alterations: analysis of the 2011-2014 National Health and Nutrition Examination Survey (NHANES). Nicotine Tob Res 2017;21:818–27.

[18] Lunney PC, Leong RW. Review article: ulcerative colitis, smoking and nicotine therapy. Aliment Pharmacol Ther 2012;36:997–1008.

[19] Noyce AJ, Bestwick JP, Silveira-Moriyama L, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol 2012;72:893–901.

[20] Felson DT, Zhang Y. Smoking and osteoarthritis: a review of the evidence and its implications. Osteoarthritis and cartilage/OARS. Osteoarthr Res Soc 2015;23:331–3.

[21] Gullahorn L, Lippiello L, Karpman R. Smoking and osteoarthritis: differential effect of nicotine on human chondrocyte glycosaminoglycan and collagen synthesis. Osteoarthritis and cartilage /OARS. Osteoarthr Res Soc 2005;13:942–3.

[22] Ying X, Cheng S, Shen Y, et al. Nicotine promotes proliferation and collagen synthesis of chondrocytes isolated from normal human and osteoarthritis patients. Mol Cell Biochem 2012;359:263–9.

[23] Gu Q, Li D, Wei B, et al. Effects of nicotine on a rat model of early stage osteoarthritis. Int J Clin Exp Pathol 2015;8:3602–12.

[24] Deng Y, Cao H, Cu F, et al. Nicotine-induced retardation of chondrogenesis through down-regulation of IGF-1 signaling pathway to inhibit matrix synthesis of growth plate chondrocytes in fetal rats. Toxicol Appl Pharmacol 2013;269:25–33.

[25] Tie K, Tan Y, Deng Y, et al. Prenatal nicotine exposure induces poor articular cartilage quality in female adult offspring fed a high-fat diet and the intrauterine programming mechanisms. Reprod Toxicol 2016;60: 11–20.

[26] Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. Arthritis Rheum 1999;42:17–24.

[27] Blagojevic M, Jinks C, Jeffery A, et al. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis and cartilage/OARS. Osteoarthr Res Soc 2010;18:24–33.

[28] Bryant J, Bonevski B, Paul C, et al. Assessing smoking status in disadvantaged populations: is computer administered self report an accurate and acceptable measure? BMC Med Res Methodol 2011;11:153.

[29] Ditre JW, Heckman BW, Zale EL, et al. Acute analgesic effects of nicotine and tobacco in humans: a meta-analysis. Pain 2016;157:1373–81.