

BMJ Open Associations of cigarette smoking, betel quid chewing and alcohol consumption with high-sensitivity C-reactive protein in early radiographic knee osteoarthritis: a cross-sectional study

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ABSTRACT

Objectives: High-sensitivity C-reactive protein (hsCRP) is possibly related to osteoarthritis (OA) progression and a variety of OA-related symptoms. This study aimed to examine associations between cigarette smoking, betel quid chewing and alcohol consumption and hsCRP in early radiographic knee OA.

Design: Cross-sectional health examination survey.

Setting: This primary study was conducted in a health examination centre in China.

Participants: 936 (656 men and 280 women) patients with early radiographic knee OA were included in this cross-sectional study.

Primary and secondary outcome measures:

Smoking status was classified into four levels based on daily smoking habit: 0/day, 1–10/day, 11–20/day and >20/day. Betel quid chewing and alcohol consumption status was divided into 'Yes' or 'No'. Early radiographic knee OA was defined as Kellgren Lawrence (K-L) grade 1 or 2 in at least one leg, and elevated hsCRP was assessed as ≥ 3.0 mg/L.

Results: After adjustment for a number of potential confounding factors, a significant positive association between cigarette smoking and hsCRP was observed in the multivariable model. The multivariable-adjusted ORs (95% CI) of elevated hsCRP (≥ 3.0 mg/L) in the second (1–10/day, n=133), third (11–20/day, n=59) and highest (>20/day, n=104) cigarette smoking categories were 1.54 (95% CI 0.91 to 2.61), 1.27 (95% CI 0.57 to 2.79) and 2.09 (95% CI 1.20 to 3.64), respectively, compared with the non-smoker category (n=640). In addition, there was a positive dose–response relationship between cigarette smoking and elevated hsCRP (p for trend=0.01). No significant associations between betel quid chewing and alcohol consumption and hsCRP were observed in the multivariable model.

Conclusions: This study indicated that cigarette smoking was positively associated with serum hsCRP level in patients with early radiographic knee OA. However, in view of the nature of cross-sectional designs, the results need to be confirmed by further prospective studies.

Strengths and limitations of this study

- This is the first study to examine associations between cigarette smoking, betel quid chewing and alcohol consumption and serum high-sensitivity C-reactive protein (hsCRP) level in patients with early radiographic knee osteoarthritis (OA).
- In order to ensure that all examined associations were independent of confounders, a large number of potentially confounding factors were adjusted for, including age, body mass index, gender, educational level, activity level, diabetes, hypertension, high density lipoprotein cholesterol, low density lipoprotein cholesterol and triglyceride.
- The positive association between cigarette smoking and hsCRP found in previous studies has been extended to early radiographic knee OA.
- The cross-sectional design precludes causal relationships.
- The results of this study may provide new insights for the treatment of knee OA.

INTRODUCTION

Osteoarthritis (OA) is a common degenerative disease of the joints characterised by articular cartilage loss, osteophyte formation, subchondral bony sclerosis and synovial inflammation causing disability and pain.¹ Nowadays, there is growing interest in OA prevention and early treatment.² Early management of OA may result in healthcare cost savings, improvements in quality of life and a reduction in OA-related disability and morbidity. Current joint-preserving interventions include lifestyle modification, as well as pharmaceutical and surgical treatment. However, very few of these approaches have been shown to arrest or delay OA progression.²

C-reactive protein (CRP) is an acute phase protein produced by hepatocytes and adipocytes and regulated by pro-inflammatory cytokines.³ High-sensitivity CRP (hsCRP) was first measured by Montagne *et al*⁴ in 1992. A recently published systematic review and meta-analysis suggested that the serum hsCRP level in OA subjects was modestly but statistically significantly higher than that in control subjects, and that a high serum hsCRP level may be related to a variety of OA-related symptoms, such as pain and loss of physical function.⁵ Moreover, other studies indicated that a higher level of CRP may be a predictive factor for OA progression^{6,7} and is also associated with a lower gain in muscle strength over time in patients with knee OA.⁸ Consequently, OA development might be delayed and OA-associated symptoms improved by lowering the serum CRP level.

Cigarette smoking, betel quid chewing and alcohol consumption are the most common substance abuse habits worldwide.^{9–12} Some studies conducted on healthy populations reported that cigarette smoking was positively correlated with serum hsCRP concentration.^{13–16} Our previous study showed that cigarette smoking was inversely associated with the prevalence of radiographic knee OA,¹⁷ which was consistent with the results of other research.^{18–22} In addition, associations between alcohol consumption and OA and CRP have been observed for decades,^{23–28} although they are still controversial and inconclusive. In contrast, few studies have explored the associations between betel quid chewing and OA and CRP.^{29,30} To the best of our knowledge, no study has yet investigated the associations between cigarette smoking, betel quid chewing and alcohol consumption and serum hsCRP level in patients with early OA. Thus, the purpose of this study was to clarify these associations in patients with early radiographic knee OA in order to provide new insights into the early treatment of knee OA.

MATERIALS AND METHODS

Study population

A total of 1268 patients over 40 years of age with early radiographic knee OA were selected for this cross-sectional study based on their characteristics and blood biochemical assessment. Information on health-related habits was available for 936 (70.1% male) patients and these were included in the study. Participants were selected according to the following inclusion criteria: (1) aged 40 years or older; (2) early radiographic knee OA; (3) hsCRP measurements available; (4) availability of data on all basic characteristics, including age, gender and body mass index (BMI); and (5) availability of data on health-related habits, such as smoking status, alcohol consumption, activity level, etc. The present study was conducted at the Department of Health Examination Center in Xiangya Hospital between October 2013 and November 2014. The protocol of this study was reviewed and approved by the Ethics and Research Committee at Xiangya Hospital, Central South University. The study

design has been published previously.^{17,31–33} Registered nurses interviewed all participants during the examination using a standard questionnaire in order to collect information on demographic characteristics and health-related habits.

Assessment of radiographic knee OA

All subjects underwent weight-bearing bilateral antero-posterior radiography of the knee. Two orthopaedists, without knowing participants' clinical symptoms, independently evaluated and graded all radiographs using the Kellgren-Lawrence (K-L) scale.³⁴ All inconsistencies were resolved by discussion. If at least one knee joint was graded as K-L 1 or 2, the participant was diagnosed with early radiographic knee OA. The reliability of measurement was examined with an intra-class correlation coefficient (ICC), and inter-rater and intra-rater reliability were both high ($\kappa=0.86$ and 0.87 , respectively).

Blood biochemistry

All blood samples were drawn after a 12 h overnight fast and were kept at 4°C until analysis. hsCRP was measured by a latex turbidimetric method. Fasting plasma glucose concentration was measured using the glucose oxidase enzyme method. Subjects with a fasting glucose ≥ 7.0 mmol/L or who were currently undergoing drug treatment for blood glucose control were regarded as having diabetes mellitus. Laboratory tests were performed with a Beckman Coulter AU 5800 analyser (Beckman Coulter, Brea, California, USA).

Assessment of other exposures

The weight and height of each subject was measured in order to calculate BMI. Participants were also asked about their average frequency of physical activity (never, one to two times per week, three to four times per week, five times and above per week) and average duration of physical activity (half an hour or less, half an hour to 1 h, 1–2 h, more than 2 h). Smoking, alcohol consumption and betel quid chewing status were ascertained by interview. Blood pressure was measured with an electronic sphygmomanometer. Subjects with systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or who were currently undergoing drug treatment for blood pressure control were regarded as having hypertension.

Statistical analysis

Continuous data are expressed as means (SD), and category data are expressed in percentages. Differences in continuous data were evaluated by Student's *t* test (normally distributed data) or the Mann-Whitney *U* test (non-normally distributed data), while differences in category data were assessed by the χ^2 test. The associations between cigarette smoking, alcohol consumption and betel quid chewing and elevated hsCRP (≥ 3.0 mg/L)^{35,36} in patients with early OA were examined by logistic regression. Cigarette smoking status was divided into four

categories: 0/day, 1–10/day, 11–20/day and >20/day, with the 0/day category regarded as reference. First, a simply adjusted model (age, gender and BMI adjusted) was adopted for evaluating the associations. Then a multivariable model, including variables for age (continuous data), BMI (≥ 25 kg/m², <25 kg/m²), gender (male, female), educational level (high school or above, lower than high school), activity level (continuous data), diabetes (yes, no), hypertension (yes, no), high density lipoprotein cholesterol (HDL-cholesterol, continuous data),³⁷ low density lipoprotein cholesterol (LDL-cholesterol, continuous data)³⁸ and triglyceride (continuous data),³⁹ was used to estimate the ORs and related 95% CIs for the associations between cigarette smoking, alcohol consumption and betel quid chewing and hsCRP, respectively. Sensitivity analysis was conducted by excluding patients with chronic renal failure (diagnosed by serum creatinine ≥ 133 μ mol/L).⁴⁰ Tests for linear trend were conducted by inserting cigarette smoking status as ranked data into the logistic regression model. All data analyses were performed using SPSS V.19.0; $p \leq 0.05$ was considered to be statistically significant. All tests were two tailed.

RESULTS

The baseline characteristics of the participants according to hsCRP level (≥ 3.0 mg/L or <3.0 mg/L) are shown in table 1. The mean age was 51.8 \pm 6.9 years, and 656 (70.1%) of the participants were men. Of the 936 patients with early radiographic knee OA, 111 (11.9%) had diabetes mellitus and 335 (35.8%) had hypertension. Significant differences were observed in age, HDL cholesterol, physical activity level, diabetes ratio and hypertension ratio between the two groups with different hsCRP levels.

Unadjusted associations were evaluated using the χ^2 test. Smoking status was positively associated with hsCRP level according to the results of the χ^2 trend test ($p=0.002$). The results did not support a significant relationship between elevated hsCRP and alcohol consumption ($p=0.68$) or betel quid chewing ($p=0.14$). The results of multivariable adjusted analysis of associations between cigarette smoking, alcohol consumption, betel quid chewing and elevated hsCRP (≥ 3.0 mg/L) in patients with early stage OA are listed in table 2. The results showed that hsCRP level was positively correlated with smoking status. There were 1.09 times more subjects with elevated hsCRP in the highest smoking category (>20/day) compared to the non-smoking category (OR 2.09, 95% CI 1.20 to 3.64, $p=0.01$); the p value for trend was 0.01. Neither betel quid chewing (OR 0.37, 95% CI 0.11 to 1.23, $p=0.11$) nor alcohol consumption (OR 1.10, 95% CI 0.73 to 1.68, $p=0.64$) was correlated with hsCRP. Sensitivity analysis suggested similar results after the exclusion of patients with chronic renal failure.

DISCUSSION

The results of the present study suggest that cigarette smoking, but not betel quid chewing or alcohol consumption, is positively associated with serum hsCRP in patients with early radiographic knee OA. In order to control for potential confounders, patients with conditions that may impact on serum hsCRP levels should be excluded from analysis. In the present study multivariable logistic regression analysis performed after adjustment for a series of factors, including age, BMI, gender, educational level, activity level, diabetes, hypertension, high density lipoprotein, low density lipoprotein and triglyceride, revealed that the positive association between cigarette smoking and serum hsCRP level remained

Table 1 Characteristics of the 936 participants according to hsCRP level (≥ 3.0 mg/L or <3.0 mg/L)

Characteristics	Subjects with hsCRP ≥ 3.0 mg/L	Subjects with hsCRP <3.0 mg/L	p Value
Participants (n)	148	788	–
Median hsCRP (mg/L)	5.78	0.70	–
Age (years)	51.58 (6.73)	53.2 (7.89)	0.03
Female (%)	23.6	31.1	0.07
BMI (kg/m ²)	25.02 (3.12)	25.45 (3.82)	0.24
HDL-cholesterol (mmol/L)	1.47 (0.37)	1.39 (0.37)	0.01
LDL-cholesterol (mmol/L)	2.93 (0.93)	3.03 (0.94)	0.36
Triglyceride (mmol/L)	2.07 (1.83)	2.34 (2.36)	0.09
Physical activity level (h/week)	1.56 (2.66)	1.14 (2.52)	0.02
High school diploma (%)	50.0	54.3	0.33
Alcohol consumption (%)	44.6	42.8	0.68
Betel quid chewing (%)	2.0	4.7	0.14
Diabetes (%)	20.9	10.2	0.00
Hypertension (%)	47.3	33.6	0.00
Smoker (n, %)	62, 41.9	234, 29.7	0.00
Non-smoker (n, %)	86, 58.1	554, 70.3	–

Data are mean (SD) unless otherwise indicated.

BMI, body mass index; HDL-cholesterol, high density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-cholesterol, low density lipoprotein cholesterol; n, number.

Table 2 Multivariable-adjusted ORs of elevated hsCRP (≥ 3.0 mg/L) according to cigarette smoking, alcohol consumption and betel quid chewing in patients with early stage OA

Variable	No. of subjects	No. of cases	Age, sex, BMI-adjusted OR (95% CI)	p Value	Multivariable-adjusted OR (95% CI)	p Value
Smoking				<0.01*		0.01*
0/day	640	86	Reference	–	Reference	–
1–10/day	133	26	1.55 (0.92 to 2.61)	0.10	1.54 (0.91 to 2.61)	0.11
11–20/day	59	9	1.23 (0.57 to 2.68)	0.60	1.27 (0.57 to 2.79)	0.56
>20/day	104	27	2.29 (1.34 to 3.90)	<0.01	2.09 (1.20 to 3.64)	0.01
Alcohol consumption	403	66	1.00 (0.67 to 1.48)	0.99	1.10 (0.73 to 1.68)	0.64
Betel quid chewing	40	3	0.42 (0.13 to 1.41)	0.16	0.37 (0.11 to 1.23)	0.11

The multi-variable model was adjusted for age (continuous data), BMI (≥ 25 kg/m², <25 kg/m²), gender (male, female), educational level (high school or above, lower than high school), activity level (continuous data), diabetes (yes, no), hypertension (yes, no), high density lipoprotein (continuous data), low density lipoprotein (continuous data) and triglyceride (continuous data).

*p Value for trend.

BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; No., number; OA, osteoarthritis.

significant. Therefore, the acute-phase response evidenced by an increase in serum hsCRP level, seems to be predominantly affected by knee OA. This finding could support the hypothesis that a positive relationship exists between cigarette smoking and inflammation in patients with early knee OA.

Our previous study revealed a negative association between cigarette smoking and the prevalence of radiographic knee OA,¹⁷ but the present research indicated that cigarette smoking was positively correlated with serum hsCRP in patients with early radiographic knee OA. This seeming contradiction may be attributed to the different outcomes since incidence is not equal to progression. In addition, OA incidence and progression can be caused by different mechanisms triggered by smoking.^{41–42} Interestingly, hsCRP may play a greater role in OA symptoms compared to radiographic changes.⁵ A prospective cohort study showed that, of male subjects with knee OA, smokers experience more severe knee pain and greater cartilage loss than non-smokers.⁴³ Moreover, Hanna *et al*⁴⁴ showed that serum hsCRP was independently and negatively associated with the volume of tibial cartilage. Serum hsCRP is also closely related to the level of pain in patients with OA.⁵ Accordingly, the impact of cigarette smoking on the level of pain and the volume of cartilage in patients with OA might be mediated by hsCRP. Several studies have demonstrated that cigarette smoking is significantly associated with increased hsCRP in subjects with other health problems.^{45–47} A cross-sectional study revealed that cigarette smoking was the most important independent predictor of serum hsCRP level in patients with OA.⁴⁸ The results of this study extended the findings to patients with early radiographic knee OA, who may have low grade inflammation since previous studies have indicated that serum hsCRP level is associated with OA symptoms and progression.^{5–8} Smoking cessation, in addition to possibly reducing hsCRP levels, may relieve OA-related symptoms and delay the progression of knee OA. More attention should be given to the relationship

between cigarette smoking and hsCRP in patients with early knee OA.

There are approximately 600 million betel quid chewers worldwide.^{10–11} The major constituents of betel quid include carbohydrates, lipids, proteins, alkaloids and polyphenols. As far as we know, very few studies have investigated the relationship between betel quid chewing and OA, although betel quid chewing is associated with some well-known disorders.^{12–49–51} In vivo data revealed that betel quid extract could intensify the inflammatory response as well as the expression of tumour necrosis factor- α in mice models.⁵² Tsai *et al*⁴⁹ indicated that betel quid chewing was not significantly associated with CRP concentration, which agrees with our findings. Subsequently, Shafique *et al*³⁰ found that the CRP levels of betel quid chewers were significantly elevated. However, it is necessary to highlight the fact that the number of betel quid chewers in our cohort was very small and much lower than in other Hunan studies.^{53–54} Our findings may be due to the following reasons. First, the participants in this study may represent a more affluent group of people in the general population who can afford health screening. Second, the sample size of this study was relatively small (936 subjects). Third, we were only concerned with current chewers, so ex-chewers were ignored. As a consequence, it might be difficult to confirm the association between betel quid chewing and hsCRP in patients with early radiographic knee OA. Thus, further high-quality research based on a larger sample is needed.

Most previous studies suggested that a moderate level of alcohol consumption could significantly decrease plasma C-reactive protein^{25–26} in a U-shaped association.^{27–28} Unfortunately, this study only classified the alcohol status of patients into drinkers or non-drinkers, so the impact of alcohol consumption on hsCRP might have been overlooked. In addition, alcohol consumption was assessed as a combined intake of beer, wine and spirits. A recent study by Muthuri *et al*²⁴ (the first study to explore the relationship between alcohol and OA

with alcohol consumption as the primary exposure) suggested that the associations between beer, wine and spirits and OA differ. According to existing evidence, the impact of beer, wine and spirits on the hsCRP level of patients with OA might be different as well. Therefore, the pooled effects of these three subtypes of alcohol on hsCRP might have influenced our outcomes.

The strengths of this cross-sectional study are as follows. First, this is the first study to examine the associations between cigarette smoking, betel quid chewing and alcohol consumption and serum hsCRP level in patients with early radiographic knee OA. The findings of this study may provide new insights into the treatment of knee OA. Second, in order to ensure that all examined associations were independent of confounders, a considerable number of potentially confounding factors were adjusted for, including age, BMI, gender, educational level, activity level, diabetes, hypertension, HDL-cholesterol, LDL-cholesterol and triglyceride. Third, the significant positive association between cigarette smoking and hsCRP found in previous major studies has been extended to subjects with early radiographic knee OA.

The limitations of the present study should also be acknowledged. First, the cross-sectional design precludes causal relationships, and thus further prospective studies and intervention trials should be undertaken to establish causal associations between cigarette smoking, betel quid chewing and alcohol consumption and hsCRP in patients with knee OA. However, despite the cross-sectional design, this study is still important since the examined associations in patients with knee OA have not been investigated previously. Second, the sample size and the number of betel quid chewers in this study are relatively small, which might have hindered some subgroup analyses and reduced the accuracy of our findings. Consequently, more high-quality and large-scale studies are needed for further investigation. Third, the results of the present study might be complicated by the nature of hsCRP (universally recognised as a marker for inflammation or even pre-inflammation) and its associations with a number of human physiological and pathological states. Fourth, the population of this study may represent a more affluent group of people in the general population who can afford health screening. Last but not least, the present study was only concerned with subjects' current status regarding the three lifestyle habits, and ignored their history. In addition, the betel quid chewing and alcohol consumption were qualitative data, but the dose or duration of these habits might impact on the hsCRP level in subjects with OA. Consequently, some potential factors cannot be addressed.

In conclusion, the present study indicated that cigarette smoking was positively correlated with serum hsCRP in patients with early radiographic knee OA. In contrast, betel quid chewing and alcohol consumption were not significantly associated with serum hsCRP in this

population. The findings of this study need to be confirmed by further prospective research.

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Contributors All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. YZ, CZ and GL conceived the study. YZ and CZ participated in study design. TY, HL, ZD and XD coordinated data collection. JW and YY performed the statistical analysis and interpreted the results. All authors helped to plan the manuscript. YZ and CZ drafted the manuscript. All authors read and approved the final version.

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Competing interests None declared.

Ethics approval The ethics committee of Xiangya Hospital, Central South University approved this study.

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