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Cigarette smoking and risk of total knee replacement for severe osteoarthritis among Chinese in Singapore - The Singapore Chinese Health Study

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Abstract

Purpose—Data on the effects of cigarette smoking with osteoarthritis (OA) are inconsistent and no study has examined the effect of smoking cessation. We examined smoking status, duration, dosage and cessation in association with risk of total knee replacement (TKR) for severe knee OA among elderly Chinese in Singapore.

Methods—We used data from the Singapore Chinese Health Study, a population-based prospective cohort of 63,257 Chinese men and women aged 45 to 74 years during enrolment between 1993 and 1998. Detailed information on smoking, current diet and lifestyle factors were obtained through in-person interviews. As of 31 December 2011, 1,973 incident TKR cases for

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Conflict of Interest

All authors (LYY, ALW, JT, WR, YJM and KWP) have no financial disclosures or notable competing interests.

Contributions

The authors declare the following contributions to the preparation of the manuscript: study conception and design (LYY and KWP), acquisition of data (LYY, ALW and KWP), data analysis (WR, KWP), interpretation of data (all authors), drafting of manuscript (LYY and KWP), critical revision of the manuscript for important intellectual content (all authors) and final approval of the manuscript (all authors). LYY (katyccc@hotmail.com) and KWP (woonpuay.koh@duke-nus.edu.sg) take responsibility for the integrity of the work as a whole.

severe knee OA had been identified via linkage with nationwide hospital discharge database. We used Cox regression methods to examine smoking in relation to TKR risk with adjustment for age, gender, education, body mass index, comorbidities and physical activity level.

Results—Compared to never smokers, current smokers had a 51% decrease in risk of TKR [Hazards ratio (HR) =0.49; 95% confidence interval (CI) =0.40-0.60]. Among current smokers, there was a very strong dose-dependent association between increasing duration and dosage of smoking with decreasing risk of TKR (p for trend<0.0001). Among former smokers, there was a dose-dependent response between decrease in duration of smoking cessation and reduction in TKR risk (p for trend=0.034).

Conclusion—Our findings strongly implicate smoking as a protective factor for total knee replacement indicated for severe knee OA. This concurs with experimental data that nicotine promotes proliferation and collagen synthesis in chondrocytes.

Keywords

Knee osteoarthritis; smoking; Chinese; cohort study

Introduction

Osteoarthritis (OA) of the knee is one of the leading causes of disability among non-institutionalized adults in the elderly population, and the risk of disability attributable to knee OA alone is greater than any other medical condition in people aged 65 years and over [1]. The consequence of severe knee OA includes loss of function and independence, and imposes a great economic burden to individuals as well as to society. With the global problem of aging in both developed and developing regions on the rise, the global burden incurred by knee OA has been increasing. According to the World Health Organization (WHO) Global Burden of Disease Study across 21 epidemiological regions across the world, there was a 26.6% increase in the burden of knee OA as measured by years lived with disability (YLDs) per 100,000 from 1990 to 2010 [2].

While non-steroidal anti-inflammatory therapy, exercise and control of body weight remain the main options [3], there is no effective treatment for severe knee OA, and total knee replacement (TKR) is often the last and only effective solution in relieving the pain and disability associated with severe disease. Hence, identification of potentially modifiable risk or protective factors could lead to the development of effective strategy in retarding the progression of knee OA. There was an unexpected finding of a modest, inverse association between smoking and prevalence of x-ray-diagnosed knee OA during the analysis of the first Health and Nutrition Examination Survey (HANES 1) in the United States [4]. Subsequently, although a few other population-based studies have also demonstrated reduced risk of knee OA among smokers [5-7], the association between smoking and risk of knee OA remains conflicting and inconsistent. In a meta-analysis of 48 studies, the inverse association between smoking and development of OA was observed only in case-control studies but did not reach statistical significance in cohort studies and cross-sectional studies [8]. Of interest to our study, in this meta-analysis, significant inverse association was reported only in knee OA [odds ratio (OR) 0.86; 95% confidence interval (CI) 0.77-0.96]

but not in hip, hand or spine OA. Another meta-analysis that examined studies on smoking and progression of OA also concluded that there was no compelling evidence that smoking had a protective effect on the progression of disease [9]. However, the authors acknowledged that there was moderate heterogeneity among these studies due to diversity in the study design, OA site and definition of smoking, which may make the overall meta-analysis suboptimal. Again, of relevance to our study, meta-analysis of results from four studies that specifically examined smoking and risk of TKR for knee OA showed significant inverse association in smokers compared to non-smokers (OR 0.86; 95% CI 0.78-0.96). These two meta-analyses suggest that the effect of smoking on development and progression of OA could indeed be limited only to the knee joint. Furthermore, few studies have examined in detail the dose-dependent association with dosage and duration of smoking; and none has examined the effect of smoking cessation. There is sparse information on the association between smoking and severe knee OA in non-white populations, especially from prospective studies. The current study therefore, examined the effects of smoking and smoking cessation on the risk of total knee replacement (TKR) for severe knee OA using prospective data from The Singapore Chinese Health Study, a population-based cohort study of elderly Chinese in Singapore.

MATERIAL AND METHODS

Study population

We used data from the Singapore Chinese Health Study, a population-based prospective cohort of 63,257 Chinese men (n=27,959) and women (n=35,298) of ages 45 to 74 years during enrolment between 1993 and 1998 [10]. All subjects were recruited from the public housing estates, where about 85% of the Singapore population resided at the time of recruitment, and about 85% of those invited to participate responded positively. The study subjects were restricted to two major dialect groups in Singapore: Hokkiens and Cantonese, who originated from Fujian and Guangdong Provinces in Southern China, respectively. This study was approved by the Institutional Review Boards at the National University of Singapore and the University of Pittsburgh.

Baseline exposure assessment

At recruitment, each study subject was interviewed in person by a trained interviewer using a structured questionnaire, which focused on history of tobacco and alcohol use, current diet, level of physical activity, medical history, and detailed menstrual and reproductive history (women only). Current diet was assessed using a validated 165-item, semi-quantitative food frequency questionnaire, and the development of a Singapore Food Composition Table based on raw and cooked foods allowed for the computation of personal intakes of 96 nutritive/non-nutritive dietary ingredients in study subjects [10]. For cigarette smoking, the subjects were asked, “Have you ever smoked at least one cigarette a day for one year or longer”; and defined as “never-smokers” for those who answered “no”, “former smokers” for those who answered “yes, but I quit smoking”, and “current smokers” for those who answered “yes, and I currently smoke”. Ever smokers were then asked about number of cigarettes smoked per day (six pre-determined categories: 6 or less, 7-12, 13-22, 23-32, 33-42, and 43 or more) and number of years of smoking (four pre-determined categories:

<10, 10-19, 20-39, 40+). Former smokers were asked about the duration of cessation (seven pre-determined categories: less than 1 year, 1-2 years, 3-4 years, 5-9 years, 10-14 years, 15-19 years, 20 years or more).

Body weight and height at baseline were self-reported during the interview; and body mass index (BMI) was calculated as current weight in kilograms divided by height in meters squared (kg/m^2). There were 9,781 cohort subjects with unknown weight, 97 with unknown height, and 192 with both unknown weight and height. For those with missing weight and/or height, BMI were calculated using imputed weight and/or height derived from the linear regression equation: Weight = y-intercept + gradient × height, where values for the y-intercept and gradient were derived from gender-specific weight-height regression lines obtained from all cohort subjects with known heights and weights. This method of imputed BMI was reported in detail previously [11]. For the assessment of physical activity, subjects were asked to estimate the number of hours spent per day sleeping, sitting to watch TV or work, and the numbers of hours per week spent on moderate activities such as brisk walking, bowling, bicycling on level ground, tai chi or chi kung, vigorous activities such as moving heavy furniture, loading or unloading trucks, shoveling or equivalent manual labor, and on strenuous sports such as jogging, bicycling on hills, tennis, squash, swimming laps or aerobics.

Identification of incident cases of TKR for severe knee OA

TKR were identified via record linkage analysis with hospital discharge databases of the MediClaim System, which has captured the surgical procedure and up to three diagnoses according to the International Classification of Disease (ICD-9) coding system 9 for all inpatient discharges from all public and private hospitals in Singapore since 1990 [12]. We first identified subjects in our cohort who have been admitted to the hospitals for TKR. Since TKR may be bilateral or repeated, only first-time TKR cases were included. All TKR cases were then verified by checking the diagnosis code to confirm that severe knee OA (ICD-9 code 715) was the reason for the surgery. We excluded all cases with any mention of diagnoses that included septic arthritis, gonarthrosis, osteomyelitis, villonodular synovitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and other inflammatory arthritis, or a secondary cause for OA such as avascular or aseptic necrosis of joint, meniscus or ligament injuries, old tear or rupture or injuries, delay in development, other acquired deformities of knee and neuritis. There were a total of 2,101 cases of TKR for severe knee OA identified within the cohort after excluding 89 cases of TKR done for other diagnoses listed above. We excluded from statistical analysis 128 prevalent cases of TKR, which occurred before enrollment to the cohort for these subjects. Thus, 1,973 incident TKR cases and 61,156 subjects without TKR as of December 31, 2011 were included in the final analysis. The causes and date of death and immigration information of all cohort subjects were ascertained through record linkage analysis with the population-based Singapore Registry of Births and Deaths. As of December 31, 2011, only 47 subjects from this cohort were known to be lost to follow-up due to migration out of Singapore or for other reasons.

Statistical analysis

For each study subject, person-years were counted from the date of baseline interview to the date of TKR operation, date of death or lost to follow-up, or 31 December 2011, whichever occurred first. We used the Chi-square test (for categorical variables) or the Student's t-test (for continuous variables) to examine the difference in distributions of baseline characteristics by smoking status as well as TKR status. We used Cox proportional hazard model to examine the association between cigarette smoking and risk of TKR. The magnitude of the associations was assessed by the hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). All Cox regression models included the following covariates: age at recruitment (years), year of recruitment (1993-1995, 1995-1998), dialect group (Hokkien, Cantonese), body mass index (kg/m^2), level of education in categories (no formal education, primary school, secondary school or higher), self-reported diabetes mellitus, ischemic heart disease and stroke, hours per day sleeping, hours per week in moderate activity, hours per week in vigorous work, hours per week in strenuous sports, hours per day sitting at work, and hours per day watching TV. To examine linear trend, ordinal values of the categories in number of years of smoking, number of cigarettes smoked per day and number of years of smoking cessation were entered as continuous variables in the Cox proportional hazards model. All statistical analysis was conducted using SAS Version 9.2 (SAS Institute, Inc., Cary, North Carolina). All reported p values are two-sided; $p< 0.05$ was considered statistically significant.

RESULTS

After a mean follow-up time of 14.5 (±4.3) years, there were 1,973 incident cases of TKR for severe OA knee among the 63,129 subjects included in the analyses. The mean age at TKR was 67.8 (± 6.6) years. The mean time of follow-up for smokers and non-smokers were 13.6 years and 14.9 years, respectively. Women accounted for 83.4% of all TKR cases. The age-adjusted incident rate for TKR was 216.2 per 100,000 person-years (95% CI = 206.6-225.7) for both sexes combined, and 83.4 (95% CI=74.4-92.4) for men and 316.8 (95% CI=301.4-332.1) for women per 100,000 person-years, respectively. Compared to never smokers, former and current smokers were more likely to be males, older at recruitment and less educated (Table 1). Comparing to non-cases, TKR cases were older at recruitment, less educated and had significantly higher BMI (Table 1).

Table 2 presents the association between cigarette smoking and TKR risk for all cohort subjects and separately among men and women. With never smokers as the referent group, after adjusting for age, BMI, educational level, comorbidities and other confounders related to level of physical activity and sedentary behavior, current smokers had a statistically significant, reduced risk of TKR (HR =0.49; 95% CI=0.40-0.60), while former smokers had an attenuated reduction of TKR risk that was of borderline significance (HR=0.85, 95% CI=0.70-1.05). Compared to never smokers, current smokers also had a statistically significant and dose-dependent inverse association for years of smoking and number of cigarettes smoked per day with TKR risk (both *P*s for trend <0.0001). When subjects were placed in ordinal categories by smoking status and dosage per day, the risk was lowest in current smokers with the highest dose (HR=0.40, 95% CI=0.30-0.54). Results remained

essentially the same in men and women separately (Table 2); there was no suggestion of any interaction between smoking status and gender on TKR risk (p for interaction=0.13). Finally, among former smokers, compared to never smokers, there was a dose-dependent response between decrease in duration of smoking cessation and reduction in TKR risk (p for trend=0.034), and with the lowest relative risk observed in those who quit recently within a year (Table 2). This effect was mainly driven by the association observed among men. In women, although former smokers also had reduced TKR risk, this dose-dependent response with duration of smoking cessation did not reach statistical significance due to small number of former smokers among women. However, the associations with smoking cessation were not statistically different by gender (p for interaction=0.58). Subjects were divided by age at recruitment into those below 55 years, 55-64 years and 65 years or older. Compared to never-smokers, current smokers had the lowest risk of TKR in all three age groups; HRs (95% CIs) for smokers versus never smokers were 0.66 (0.48-0.92) for <55 years of age at recruitment, 0.47 (0.36-0.63) for 55-64 years of age at recruitment, and 0.35 (0.22-0.56) for 65 years or older at recruitment. The reduction in HR with increasing age at recruitment was expected since older smokers were more likely to have smoked for a longer period of time than younger smokers. Since smokers generally have higher mortality rate than non-smokers, including in our own findings from this cohort [13], to exclude premature death as a potential competing outcome with TKR, we further excluded from the analyses subjects who died before the censored date of 31 December 2011, and this comprised 14,875 subjects (23.6% of cohort), including 173 cases of TKR (8.8% of TKR cases). The results remained essentially unchanged. Compared to never smokers, former smokers had a relative risk of 0.89 (95% CI=0.71-1.10) and current smokers had a relative risk of 0.57 (95% CI=0.46-0.70).

Since obesity is a strong risk factor for severe knee OA [14], we were interested to see if obesity modified the effects of smoking on TKR risk. We used BMI ≥25 kg/m^2 as the cut-off to divide the subjects into those with normal range of BMI and who were overweight according to the current WHO recommendation [15]. In this analysis, we only included 52,780 subjects with self-reported body weight and height at baseline. The associations between various measures of smoking and TKR risk were essentially the same for individuals with BMI <25 and 25+ kg/m^2 (*p* for interaction between smoking status and BMI group=0.14) (Table 3). Finally, we examined if the association of smoking with risk of TKR was different by length of follow-up. We divided the cohort into two groups by the median interval between recruitment and the date of TKR for the cases, which was 10 years. The results remained essentially the same in showing lowest relative risk in current smokers in both groups. For the group with follow-up duration less than 10 years, compared to never smokers, HR for former and current smokers were 0.69 (95% CI=0.52-0.93) and 0.40 (95% CI=0.30-0.53), respectively. The corresponding figures for individuals with follow-up of ten or more years were 1.04 (95% CI=0.78-1.38) and 0.58 (95% CI=0.44-0.75), respectively.

DISCUSSION

The present study represents to date the most comprehensive examination of the effect of smoking, including dosage, duration and cessation, using prospective data from a population-based cohort in Asia. The results showed that dosage and duration of smoking

were inversely associated in a dose-dependent manner with risk of TKR for severe knee OA. This strong inverse association between smoking and risk of TKR was similar by gender and BMI category, and was attenuated with increasing duration of smoking cessation.

The strength of this study is the large number of TKR cases identified from a population-based prospective cohort with a long follow-up time. Another strength is the presumed lack of recall bias in exposure since they were obtained prior to disease diagnosis. Our case ascertainment of TKR for severe knee OA through linkage with the comprehensive, nationwide hospital database can be considered complete. In Singapore, a study in a public hospital reviewed over 1,600 medical records and reported that primary knee OA accounted for 96% of the TKR cases [16]. In our study we had included only the first incident TKR for each case, and verified that the surgical indication was primary knee OA. Obesity is an established risk factor for knee OA [14] and a major confounding factor in the smoking-OA association as smokers are generally thinner than non-smokers [17], and therefore are at lower risk for knee OA. Hence, a unique strength of this study is the relative leanness (mean BMI of 23.2 kg/m^2) and the low prevalence of overweight (only 26% subjects with BMI ≥ 25 kg/m^2) in this study population compared to the more obese counterparts in Western populations, where an apparent inverse association between smoking and knee OA may be confounded by obesity [8]. Hence, this cohort is ideal for the examination of the effect of smoking on knee OA. The presence of a statistically significant inverse association between smoking and TKR risk after adjustment for BMI, and also among individuals with BMI <25 kg/m^2, suggests that the inverse association between smoking and severe knee OA is independent of obesity. In this cohort, despite very different prevalence of smoking between men and women (36% in men were current smokers versus 6% in women), the inverse associations between duration and dosage of smoking and risk of TKR for knee OA in men were comparable to the associations in women, thus substantiating the robustness of our findings. Finally, we included all established and other possible risk factors for severe knee OA as covariates in our regression-based risk models to minimize the likelihood of spurious associations resulting from insufficient control of confounding.

One limitation of the study is the use of TKR as the surrogate outcome for severe knee OA, as this would exclude subjects who had severe knee OA but did not undergo surgery due to medical, financial or other reasons. Smokers in this study had lower education level and this may result in lower health literacy and access to health service. However, Singapore is a small city-state with a system for easy access to specialized medical care at relatively affordable cost, and the comparatively high incidence of TKR in this cohort suggests that there is relatively adequate accessibility to TKR for severe knee OA. Another potential bias in our study is that smokers may be less likely to undergo surgery even if they have severe OA. However, a survey among orthopedic surgeons in New York City in the United States showed that the decision against total knee replacement surgery was mainly affected by patient's age, comorbidity, obesity, alcohol use, technical difficulties and lack of motivation, while patient's smoking status was not a consideration [18]. Another limitation of the study is the single assessment of exposure at baseline, which may result in underestimation of the effect of smoking if subjects changed their smoking habits subsequently. As matter of fact, approximately 22% smokers of the cohort study participants at baseline quit their smoking habit at the first follow-up interview about 5.8 years after recruitment. Therefore, the true

effect of smoking on the risk reduction of TKR would be larger than the observed one in the present study. Moreover, since non-smokers generally have lower mortality rate than smokers [13], the incidence of TKR in non-smokers could be higher due to survival advantage. However, in this study, the inverse association between smoking and TKR remained essentially unchanged when all subjects who died before the censored date were excluded from analysis. The association between smoking and knee OA has remained conflicting from prospective studies conducted among Western populations. Following the report of an inverse association between smoking and risk of knee OA based on a cross-sectional analysis from the first Health and Nutrition Examination Survey (HANES 1) in the United States [4], the population-based prospective Framingham OA study also reported significantly reduced risk of incident radiographic knee OA in smokers [19]. Furthermore a cohort of male construction workers in Sweden also found a reduced risk of knee arthroplasty in current smokers [20]. However, there were also other cohort studies that failed to report an inverse association between smoking and knee OA risk [21-25]. In a US cohort, the inverse smoking – knee OA risk association was attenuated and become statistically non-significant after adjustment for potential confounding factors [7]. In a meta-analysis that evaluated 48 observational studies of smoking in relation to development of OA, a statistically significant inverse association with smoking was reported in case-control studies (OR=0.82, 95% CI=0.70 to 0.95) but did not reach statistical significance for cross-sectional studies (OR=0.89, 95% CI=0.78-1.01) or cohort studies (OR=0.92, 95% CI=0.81-1.06). Nevertheless, in the subgroup analysis, significant inverse association was reported in knee OA [odds ratio (OR) 0.86; 95% confidence interval (CI) 0.77-0.96] although not in hip, hand or spine OA [8].

There could be several reasons for the null findings from some of the cohort studies. First, our study demonstrated that the inverse association between smoking and risk of TKR was rapidly lost with smoking cessation. Hence, studies that categorized current and former smokers in the same group would attenuate the effect of current smoking [24,25]. In the subgroup analysis of current and past smokers in the meta-analysis involving 48 studies, statistically significant 15% reduction in risk of OA was reported in current smokers but the association was null in past smokers [8]. Studies with a predominance of men and/ or younger subjects may over-represent secondary OA resulting from joint injuries and where smoking may not be implicated [21] [26]. Osteoarthritis of joints at different sites may have different mechanisms at play and hence have different predisposition with the same factor [27,28]. For example, it has been suggested that while overweight is a risk factor predisposing to OA in the knee and hand joints, the hip joint may benefit from being surrounded by robust anatomical structures in obese individuals [23]. Similarly, in a study that examined the association of smoking with arthritis of the knee, hand, foot and spine, the unadjusted risk estimate was lowest for OA of the hand and knee compared to the other two sites [7]. In a meta-analysis of 48 studies examining OA at four different anatomic sites, only knee OA had statistically significant inverse association with smoking [8]. Hence, studies on OA that combined knee with other joints could diminish the overall association between smoking and risk of outcome of interest [21]. In our study, we studied severe knee OA that required TKR, which represented a clinically relevant end-point. TKR is a surrogate for severe knee OA and has also been used as the outcome of interest in other population-

based cohort studies [20,29,30]. It is possible that smoking is implicated in the progression but not onset of disease. Hence, cohort studies that have used early radiographic signs of knee OA as the study outcome may not show the effect of smoking on progression of OA [22,31]. In fact, in a recent meta-analysis that included 16 observational studies on the association of smoking and progression of OA, there was a significant inverse association of 0.86 between ever-smoking and TKR (95% CI=0.78-0.96) [9].

A population-based cohort of men in Australia recently demonstrated a dose-response relationship between duration of smoking and reduction in risk of undergoing subsequent total joint replacement [30]. Our study is the first to show dose-response relationship between increasing dosage of smoking and decreasing risk of severe knee OA requiring TKR in both genders, and also the first to show stepwise attenuation of risk reduction with increasing duration of smoking cessation. These results have added to the strength of evidence for an association between smoking and reduced risk of severe knee OA.

The inverse association between smoking and risk of severe knee OA is biologically plausible. Recent experimental studies have shown that nicotine in cigarettes up-regulated collagen synthesis in chondrocytes isolated from normal human femoral head [32], and also promoted the proliferation of articular chondrocytes isolated from the knee joints of both normal and OA patients in a concentration-dependent manner [33]. In addition, nicotine also enhanced the expression of cartilage-specific type II collagen in both types of chondrocytes. Since articular cartilage is avascular, it is conceivable that the effect of smoking is directly mediated by circulating levels of nicotine on articular chondrocytes, and is hence rapidly reversed with smoking cessation.

In conclusion, this study provided strong epidemiologic evidence for an inverse association between cigarette smoking and the risk of TKR for severe knee OA. While we certainly do not advocate smoking as a means of preventing onset or progression of OA, our observation have practical implications in understanding the biological effect of nicotine present in cigarette smoke on chondrocytes. More importantly, the development of chemo-preventive agents from nicotine analogues may provide an effective means to reduce the progression and lessen the burden of severe knee OA.

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TABLE 1

Description of selected demographic and lifestyle characteristics by smoking status and total knee replacement (TKR), The Singapore Chinese Health Study 1993-2011

	Smoking status			TKR for severe OA knee	
	Never	**Former**	**Current**	**Yes**	**No**
Number of subjects (%)	43,814 (69.4)	6,986 (11.1)	12,329 (19.5)	1,973 (3.1)	61,156 (96.9)
Gender, n (%)					
Male	11,721 (26.8)	6,091 (87.2)	10,126 (82.1)	328 (16.6)	27,610 (45.2)
Female	32,093 (73.3)	895 (12.8)	2,203 (17.9)	1,645 (83.4)	33,546 (54.9)
Dialect, n (%)					
Cantonese	21,175 (48.3)	3,429 (49.1)	4,612 (37.4)	864 (43.8)	28,352 (46.4)
Hokkien	22,639 (51.7)	3,557 (50.9)	7,717 (62.6)	1,109 (56.2)	32,804 (53.6)
Age at recruitment ± SD	55.7 (7.9)	59.7 (8.1)	57.5 (7.9)	57.3 (6.9)	56.5 (8.0)
Body mass index ± SD (kg/m^2)	23.3 (3.3)	23.3 (3.4)	22.5 (3.2)	25.1 (3.5)	23.1 (3.3)
Level of education, n (%)					
No formal education	13,173 (30.1)	1,141 (16.3)	2,943 (23.9)	822 (41.7)	16,435 (26.9)
Primary	17,767 (40.6)	3,759 (53.8)	6,480 (52.6)	832 (42.2)	27,174 (44.4)
Secondary or above	12,874 (29.4)	2,086 (29.9)	2,906 (23.6)	319 (16.2)	17,547 (28.7)
Weekly vigorous work, n (%)					
No	41,476 (94.7)	6,375 (91.3)	10,661 (86.5)	1,880 (95.3)	56,632 (92.6)
0.5-3 hours/week	1,390 (3.2)	341 (4.9)	761 (6.2)	58 (2.9)	2,434 (4.0)
4-6 hours/week	327 (0.8)	71 (1.0)	290 (2.4)	18 (0.9)	670 (1.1)
7+ hours/week	621 (1.4)	199 (2.9)	617 (5.0)	17 (0.9)	1,420 (2.3)
Weekly strenuous sports, n (%)					
No	40,711 (92.9)	6,364 (91.1)	11,694 (94.9)	1,901 (96.4)	56,868 (93.0)
0.5-1 hours/week	1,438 (3.3)	264 (3.8)	269 (2.2)	29 (1.5)	1,942 (3.2)
2-3 hours/week	1,013 (2.3)	218 (3.1)	218 (1.8)	27 (1.4)	1,422 (2.3)
4+ hours/week	652 (1.5)	140 (2.0)	148 (1.2)	16 (0.8)	924 (1.5)
Weekly moderate activity, n (%)					
No	33,912 (77.4)	5,082 (72.8)	10,173 (82.5)	1,532 (77.7)	47,635 (77.9)
0.5-3 hours/week	6,288 (14.4)	1,150 (16.5)	1,333 (10.8)	242 (12.3)	8,529 (14.0)

	Smoking status			TKR for severe OA knee	
	Never	**Former**	**Current**	**Yes**	**No**
4+ hours/week	3,614 (8.3)	754 (10.8)	823 (6.7)	199 (10.1)	4,992 (8.2)
Hours of sleep/day ± SD	7.0 (1.1)	7.0 (1.2)	7.1 (1.2)	6.8 (1.1)	7.0 (1.1)

All differences among never, former and current smokers were statistically significant ($p<0.0001$).

All differences between TKR cases and non-cases were statistically significant ($p<0.02$).

Table 2

Cigarette smoking in relation to risk of total knee replacement, The Singapore Chinese Health Study, 1993-2011

	Total (n=63,129)		Men (n=27,938)		Women (n=35,191)	
	Cases	**HR (95% CI)**	**Cases**	**HR (95% CI)**	**Cases**	**HR (95% CI)**
Smoking status						
Never smoker	1,731	1.00	187	1.00	1544	1.00
Former smoker	119	0.85 (0.70-1.05)	82	0.81 (0.62-1.06)	37	0.84 (0.60-1.17)
Current smoker	123	0.49 (0.40-0.60)	59	0.40 (0.30-0.54)	64	0.57 (0.44-0.73)
P for trend		<0.0001		<0.0001		<0.0001
Years of smoking among current smokers						
Never smoker	1731	1.00	187	1.00	1544	1.00
< 19 years	14	0.87 (0.51-1.47)	4	0.69 (0.25-1.86)	10	0.95 (0.51-1.76)
20-39 years	68	0.57 (0.44-0.74)	38	0.49 (0.34-0.70)	30	0.66 (0.46-0.95)
40+ years	41	0.35 (0.25-0.48)	17	0.25 (0.15-0.41)	24	0.42 (0.28-0.64)
p for trend		<0.0001		<0.0001		<0.0001
Number of cigarettes per day among current smokers						
Never smoker	1731	1.00	187	1.00	1544	1.00
1-12 cig/day	73	0.56 (0.44-0.71)	25	0.46 (0.30-0.71)	48	0.60 (0.45-0.81)
13-22 cig/day	36	0.40 (0.29-0.57)	22	0.33 (0.21-0.51)	14	0.52 (0.31-0.88)
23+ cig/day	14	0.42 (0.24-0.71)	12	0.39 (0.22-0.70)	2	0.37 (0.09-1.48)
p for trend		<0.0001		<0.0001		<0.0001
Smoking status in combination with number of cigarettes/day						
Never smoker	1,731	1.00	187	1.00	1544	1.00
Former 1-12 cig/day	65	1.02 (0.79-1.31)	39	1.20 (0.84-1.70)	26	0.81 (0.55-1.20)
Former 13+ cig/day	54	0.69 (0.52-0.92)	43	0.63 (0.45-0.88)	11	0.92 (0.51-1.67)
Current 1-12 cig/day	73	0.56 (0.44-0.71)	25	0.48 (0.31-0.73)	48	0.60 (0.45-0.81)
Current 13+ cig/day	50	0.40 (0.30-0.54)	34	0.36 (0.25-0.52)	16	0.49 (0.30-0.81)
p for trend		<0.0001		<0.0001		<0.0001
Number of years of smoking cessation among former smokers						
Never smoker	1,731	1.00	187	1.00	1544	1.00
20+ years	39	0.93 (0.67-1.29)	29	0.97 (0.65-1.45)	10	0.76 (0.41-1.41)

	Total (n=63,129)		Men (n=27,938)		Women (n=35,191)	
	Cases	**HR (95% CI)**	**Cases**	**HR (95% CI)**	**Cases**	**HR (95% CI)**
5-19 years	54	0.82 (0.62-1.10)	38	0.78 (0.55-1.11)	16	0.89 (0.54-1.46)
1-4 years	19	0.71 (0.45-1.13)	12	0.68 (0.38-1.23)	7	0.77 (0.36-1.61)
< 1 year	7	0.67 (0.32-1.41)	3	0.49 (0.16-1.54)	4	0.91 (0.34-2.42)
p for trend		0.034		0.039		0.338

Adjusted for age at recruitment (years), year of recruitment (1993-1995, 1995-1998), dialect group (Hokkien, Cantonese), body mass index (kg/m^2), level of education in categories (no formal education, primary school, secondary school or higher), self-reported diabetes mellitus, ischemic heart disease, stroke, hours per day sleeping, hours per week in moderate activity, hours per week in vigorous work, hours per week in strenuous sports, hours per day sitting at work, hours per day watching TV; CI, confidence interval.

Table 3

Cigarette smoking in relation to risk of total knee replacement stratified by body mass index (BMI) level, The Singapore Chinese Health Study, 1993-2011

	BMI < 25 kg/m^2 (n=39,056)		BMI ≥25 kg/m^2 (n=13,724)	
	Cases	**HR[a] (95% CI)**	**Cases**	**HR[a] (95% CI)**
Smoking status				
Never smoker	702	1.00	740	1.00
Former smoker	51	0.90 (0.66-1.23)	60	0.99 (0.74-1.32)
Current smoker	49	0.43 (0.32-0.59)	47	0.58 (0.43-0.80)
P for trend		<0.0001		0.0015
Years of smoking among current smokers				
Never smoker	702	1.00	740	1.00
<19 years	6	0.85 (0.38-1.90)	4	0.63 (0.24-1.70)
20-39 years	29	0.53 (0.36-0.78)	31	0.73 (0.50-1.07)
40+ years	14	0.27 (0.15-0.46)	12	0.39 (0.22-0.69)
p for trend		<0.0001		0.0004
Smoking status in combination with number of cigarettes/day				
Never smoker	702	1.00	740	1.00
Former 1-12 cig/day	28	1.08 (0.73-1.60)	31	1.19(0.82-1.72)
Former 13+ cig/day	23	0.72 (0.46-1.12)	29	0.81 (0.54-1.21)
Current 1-12 cig/day	30	0.52 (0.36-0.75)	25	0.64 (0.43-0.96)
Current 13+ cig/day	19	0.33 (0.20-0.53)	22	0.52 (0.33-0.80)
p for trend		<0.0001		0.0004

Adjusted for age at recruitment (years), year of recruitment (1993-1995, 1995-1998), dialect group (Hokkien, Cantonese), level of education in categories (no formal education, primary school, secondary school or higher), self-reported diabetes mellitus, ischemic heart disease, stroke, hours per day sleeping, hours per week in moderate activity, hours per week in vigorous work, hours per week in strenuous sports, hours per day sitting at work, hours per day watching TV; CI, confidence interval.