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Association between body mass index and risk of total knee replacement, the Singapore Chinese Health Study

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SUMMARY

Purpose: Data on the association between body mass index (BMI) and risk of knee osteoarthritis (KOA) are sparse for Asian populations who are leaner than Western populations. We evaluated the association between BMI and risk of total knee replacement (TKR) due to severe KOA among Chinese in Singapore.
Methods: We used data from the Singapore Chinese Health Study (SCHS), a population-based prospective cohort of 63,257 Chinese men and women, aged 45–74 years at enrollment from 1993 to 1998. Information on height, weight, diet and lifestyle factors were obtained *via* in-person interviews. TKR cases for severe KOA were identified *via* linkage with the nationwide hospital discharge database through 2011. Cox regression and weighted least squares regression were used in the analysis.
Results: The mean BMI among cohort participants was 23.1 kg/m^2, and more than two-thirds had BMI below 25 kg/m^2. A total of 1649 had TKR attributable to severe KOA. Risk of TKR increased in a strong dose-dependent manner with increasing BMI throughout the 15–32 kg/m^2 range and became less clear at BMI >32 kg/m^2. In the BMI range 16–27 kg/m^2, there was a 27% increase in TKR risk for each unit increase in BMI (P for trend < 0.001). Compared to BMI 19–20 kg/m^2, the risk estimates of TKR were all statistically significant with increasing unit of BMI ≥21 kg/m^2. Results were similar for men and women.
Conclusion: Our results provided evidence for a constant mechanical mechanism underlying BMI and KOA initiation and/or progression.
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Introduction

Knee osteoarthritis (KOA) is a leading cause of disability among the aged population worldwide[1]. A positive association between obesity or being overweight and increased risk of KOA has been shown in numerous studies[2–4]. Hence, the global prevalence of KOA will continue to rise in tandem with the increasing prevalence of obesity worldwide. Guidelines for managing KOA recommend weight loss for body mass index (BMI) ≥25 kg/m^2[5,6]. However, there is a paucity of data on risk of initiation and progression of KOA among people with BMI lower than 25 kg/m^2. It is unknown whether there is a threshold effect of BMI on risk of KOA or a critical level of BMI above which risk of KOA rises dramatically. The identification of these BMI levels may serve as a weight reduction target in managing patients with KOA.

In this study we characterize the association between BMI and risk of total knee replacement (TKR) due to severe KOA using prospective data from the Singapore Chinese Health Study (SCHS), a population with a relatively lower BMI than western populations. This population-based cohort of middle-aged to elderly Chinese in Singapore provided ample data to investigate BMI as a risk factor

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for TKR attributable to severe KOA over a wide range of BMI values and in particular for BMI <25 kg/m^2.

Research methods

Study population

The SCHS recruited 27,959 Chinese men and 35,298 women (n = 63,257) of ages 45–74 years between 1993 and 1998 in Singapore[7]. Subjects were recruited from public housing estates, where 86% of Singapore's population lived at the time of recruitment. Study subjects were restricted to the two major dialect groups in Singapore: Hokkien and Cantonese, originating from the 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

The baseline assessment was conducted *via* in-person interview at recruitment using a structured questionnaire. Information was obtained on educational level, height, weight, cigarette smoking, habitual physical activity, sleep hours, self-reported medical history (e.g., physician-diagnosed hypertension, diabetes, coronary artery disease and stroke), alcohol consumption and habitual dietary intake (using a validated 165-item food frequency questionnaire). Body weight and height at baseline were self-reported during the interview. There were 10,054 cohort participants with unknown weight, 99 with unknown height, and 196 with both unknown weight and height. Their BMIs 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 obtained from gender-specific weight-height regression lines drawn from all cohort participants with known heights and weights. If only weight or height was missing, the linear regression equation was used to estimate the missing value. If both weight and height were both missing, the missing height was assigned the sex-specific median value and missing weight value calculated from the linear regression equation. We analyzed data for participants with known body weight and height in the main models, and for the whole cohort that included imputed values for those with missing BMI in secondary models.

For cigarette smoking, current smokers were asked about the number of cigarettes smoked per day and the number of years of smoking, and former smokers were asked about the number of years since quitting. In assessing physical activity, subjects were asked to estimate the number of hours per week spent on moderate activities (such as brisk walking, bowling, bicycling on level ground, tai chi or chi kung), vigorous work (such as moving heavy furniture, loading and unloading trucks, shoveling or equivalent manual labor) and strenuous sports (such as jogging, bicycling on hills, tennis, squash, swimming laps or aerobics). This section of the questionnaire was adapted from the physical activity questionnaire in the European Prospective Investigation in Cancer (EPIC) Study[8]. Participants were also asked for the number of hours per day spent watching TV and sleeping.

Identification of incident cases of TKR for severe KOA

Identification of TKR for severe KOA was accomplished *via* record linkage analysis using the MediClaim System hospital discharge database through 31 December 2011. The system has been in use in Singapore since 1990 and records surgical procedures and up to three diagnoses per patient for inpatient discharges from public and private hospitals based on the ninth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-9)[9]. Since TKR may be bilateral or repeated, only first-time TKR cases were included. All TKR cases were verified by checking diagnosis code, and only subjects who underwent TKR for severe KOA (ICD-9 code 715) were counted as cases. A total of 128 prevalent cases of TKR which occurred prior to subject enrollment into the cohort were excluded from analysis. We also excluded those who underwent TKR for diagnoses such as septic arthritis, osteomyelitis, villonodular synovitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and other inflammatory arthritis, or secondary causes of KOA such as avascular or aseptic necrosis of joint, meniscus or ligament injuries, and other congenital or acquired deformities of the knee (n = 89)[10]. Deaths were identified through record linkage with the Singapore Registry of Births and Deaths. As of December 2011, only 47 subjects were known to be lost to follow-up due to migration out of Singapore or for other reasons, suggesting the ascertainment of vital status for cohort participants is virtually complete.

Statistical analysis

For each study subject, person-years were counted from the baseline interview to the date of TKR operation, death, lost to follow-up, or 31 December 2011, whichever occurred first. Association between BMI and risk of TKR was investigated using multivariable Cox proportional hazards models. The hazards ratio (HR) of TKR and its 95% confidence interval (CI) were estimated using the Cox model with BMI (kg/m^2) per unit change. We set BMI of 19–<20 kg/m^2 as the reference category to have a relatively large sample size and thus relatively stable estimates of HR. In all analyses, HRs were adjusted for the following variables: age at recruitment (years); year of recruitment (1993–1995, 1995–1998); dialect group (Hokkien, Cantonese), level of education (no formal education, primary school, secondary school or higher); self-reported histories of physician-diagnosed diabetes mellitus, ischemic heart disease, and stroke; number of hours per day of sleeping, sitting at work, and watching TV; numbers of hours per week spent in moderate physical activity, vigorous work, and strenuous sports; and smoking status (never, former, or current), number of cigarettes per day, and number of years of smoking for current smokers; and for former smokers, number of years since quitting smoking. The association between BMI and risk of TKR was investigated separately for men and women. The proportional hazards assumption was found to be tenable. The potential for interaction effects between BMI and age, gender, and physical activities or smoking on TKR risk was also examined.

In a graphical approach to investigate the relationship between BMI and risk of TKR, BMI was partitioned into one-unit intervals, and the natural logarithm of the hazards ratio (*ln* HR) was plotted against the median value of each interval. It was immediately apparent that in the BMI range 16–27 kg/m^2, the relationship between BMI and *ln* HR was represented very well by a straight line. A line was fitted using weighted least squares regression with interval sample size as the weight. Exponentiating the slope of the fitted line (b) gives the multiplicative factor for change in risk (i.e., HR) per unit change in BMI. In addition, we calculated the change in HR per unit change in BMI within the range 16–27 kg/m^2 in a separate Cox regression model with BMI as a continuous variable.

All hypothesis tests performed were two-sided and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS Version 9.2 (SAS Institute, Inc., Cary, North Carolina).

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