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Interaction of obesity with smoking and inflammatory arthropathies increases the risk of periprosthetic joint infection: a propensity score matched study in a Chinese Han population

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S U M M A R Y

Background: Although a large number of studies have identified obesity as an independent risk factor for the development of periprosthetic joint infection (PJI), the synergistic impacts of obesity with other factors on PJI remain unknown. Additionally, few studies have specifically explored the risk factors of PJI within a Chinese population.
Aims: To investigate the association between obesity and PJI in a Chinese population, and identify synergistic impacts of obesity with other risk factors on the development of PJI.
Methods: Three hundred and seven patients at a single institution with a diagnosis of PJI following primary total hip or knee arthroplasty, treated from 2008 to 2015, were identified. Each case was matched with two controls who did not develop PJI after primary total hip or knee arthroplasty in the study period using propensity score matching for several important parameters. Multi-variable logistic regression models were used to estimate the association between body mass index (BMI) and the risk of developing PJI. Interaction and stratified analyses were conducted according to age, sex, type of surgery, smoking status, alcohol use, diabetes, inflammatory arthritis, liver disease and renal disease.
Findings: The multiple logistic analyses showed that obesity was associated with increased risk of PJI [odds ratio (OR) 2.48; 95% confidence interval (CI) 1.66–3.69]. When analysed as a continuous variable, BMI was also associated with increased risk of PJI (OR per 1 kg/m^2 increase in BMI 1.08; 95% CI 1.02–1.14). In the interaction analysis, patients who were obese and smoked had a higher OR of developing PJI than non-smokers who were obese (OR 3.54 vs 1.55, *P*-value for interaction=0.031). Similarly, the OR was much higher for patients with both obesity and inflammatory arthritis than for patients who were obese with no history of inflammatory arthritis (OR 3.9 vs 1.55, *P*-value for interaction=0.029). No other significant interactions were found in the association between obesity and PJI.

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Conclusion: Obesity is an independent risk factor for the development of PJI in the Chinese Han population. Surgeons should be aware that obese patients who smoke or have inflammatory arthritis are at additional increased risk of PJI.

Introduction

Despite the success of total joint arthroplasty (TJA), periprosthetic joint infection (PJI) remains an infrequent but devastating complication of this procedure. If PJI occurs, it requires multiple additional operations that may compromise functional outcomes and the health of the patient [1,2]. Furthermore, PJI places a large economic burden on the healthcare system [3]. With the increase in the number of TJA procedures being performed, particularly in elderly patients who may have underlying comorbidities, a greater number of PJI cases will be encountered [4].

Multiple modifiable and non-modifiable risk factors that contribute to the development of PJI have been identified. Several studies have found a correlation between higher body mass index (BMI) and increased risk of PJI [5–10]. However, obesity may play a role in the development of PJI not only independently but also in conjunction with other risk factors. Using a series of 3836 total knee arthroplasties (TKAs), Crowe *et al.* suggested that active tobacco use had an additive effect on risk of PJI for patients with BMI $\geq$30 kg/m^2 [11]. Identifying potential interactions between obesity and other factors on PJI is of great clinical significance as it could assist surgeons in the risk assessment aspect of the decision-making process, thus triggering closer monitoring and more aggressive management. In turn, optimizing patient weight before surgery may not only reduce the risk of PJI but also potentially improve TJA outcomes.

Few studies have specifically explored the association between obesity and PJI among a Chinese population, which is very different from Western populations in terms of BMI, lifestyle, dietary behaviours, nutrition and metabolism. The aim of this study was to investigate the association of obesity and PJI, as well as the interactions between obesity and other risk factors on the development of PJI in a Chinese population.

Methods

Study population

After institutional review board approval, a single-centre database for all patients with a diagnosis of PJI after total hip arthroplasty (THA) or TKA between 2008 and 2015 was reviewed retrospectively. Patients with missing data for BMI and follow-up were excluded. Using the aforementioned exclusion criteria, 307 patients with a diagnosis of PJI were enrolled as cases. Control subjects were patients who underwent primary TJA at the study institution over the same investigational period with a minimum one-year follow-up. The outpatient chart was cross-checked with the prospectively maintained institutional PJI database to ensure that the control subjects did not develop PJI during the study period. The exclusion criteria for control subjects were as follows: (1) patients with any evidence of PJI; (2) patients who were re-admitted for wound complications after primary TJA; and (3) patients who underwent reoperation of the index arthroplasty for any reason, aseptic or septic. To reduce the effects of selection bias and potential confounding in this observational study, propensity score matching at a 1:2 ratio was performed (detailed below).

Definition of PJI

Diagnosis of PJI was based on the Musculoskeletal Infection Society criteria for infection [12]. PJI was defined when:

- two positive periprosthetic cultures grew phenotypically identical organisms; or
- a sinus tract communicating with the joint existed; or
- three of the following five criteria were met:
  - elevated serum erythrocyte sedimentation rate and C-reactive protein
  - elevated synovial fluid white blood cell count or 2+ change on leukocyte esterase test strip
  - elevated synovial fluid polymorphonuclear neutrophil percentage
  - positive histologic analysis of periprosthetic tissue
  - a single positive culture.

Data collection

The clinical records of the patients were reviewed manually in detail to extract pertinent information that included age, BMI, sex, type of surgery (knee or hip), Charlson Comorbidity Index (CCI) score, smoking status (smoking history $\geq$100 cigarettes), alcohol use, diabetes, inflammatory arthritis (IA), chronic liver disease, renal disease, cardiovascular disease, chronic pulmonary disease, blood transfusion, operative time and hospital length of stay (LOS). As the definition of obesity varies by country, obesity was defined as BMI $\geq$28 kg/m^2 in this study using the official Chinese guidelines [13].

Statistical analysis

All analyses were performed using R software (http://www.R-project.org, The R Foundation) and EmpowerStats (X&Y Solution, Inc., Boston, MA, USA). Multiple imputation by chained equations was used for missing data on alcohol consumption, IA, cardiovascular disease and chronic pulmonary disease. In total, five data sets were imputed, and the results were pooled according to Rubin's rules [13]. The cohort was matched with a control group at a 1:2 ratio using propensity score matching based on a non-parsimonious multiple logistic regression model with respect to the following parameters: age, sex, type of surgery (knee or hip) and date of surgical procedure. The maximum difference between propensity probabilities for matching was set at 0.05.

Categorical variables were presented as frequencies and percentages, and continuous variables were presented as means and standard deviations. The clinical characteristics of

Table I
Main characteristics of the study population

Variable	Patients with PJI (*N*=307)	Control subjects (*N*=614)	*P*-value
Age (years)	64.9±12.4	64.5±13.0	0.764
Female	161 (52.4%)	328 (53.4%)	0.779
Body mass index (kg/m^2)	26.0±3.9	25.4±3.5	**0.009**
Knee surgery	192 (62.5%)	388 (63.2%)	0.847
CCI score ≥4	153 (49.8%)	240 (39.1%)	**0.002**
Smoking	70 (22.8%)	109 (17.8%)	0.068
Alcohol use	27 (8.8%)	31 (5.0%)	**0.027**
Diabetes	56 (18.2%)	85 (13.8%)	0.081
Inflammatory arthritis	60 (19.5%)	81 (13.2%)	**0.012**
Liver disease	22 (7.2%)	17 (2.8%)	**0.002**
Renal disease	13 (4.2%)	18 (2.9%)	0.301
Cardiovascular disease	14 (4.6%)	19 (3.1%)	0.259
Chronic pulmonary disease	11 (3.6%)	32 (5.2%)	0.269
Blood transfusion	232 (75.6%)	484 (78.8%)	0.263
Operative time ≥90 min	83 (27.0%)	161 (26.2%)	0.792
Length of stay	7.6±2.0	7.6±2.2	0.528

PJI, periprosthetic joint infection; CCI, Charlson Comorbidity Index. Bold type indicates significant difference.

patients and control subjects were compared using the independent *t*-test or Mann–Whitney test for continuous variables and Chi-squared test for categorical variables. The association of BMI and PJI was assessed in multi-variable logistic regression models, using BMI as both a continuous (per 1 kg/m^2 increase) and a categorical variable (≥28 kg/m^2 or not). Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated. Multi-variable logistic regression models were adjusted for all enrolled classical risk factors of PJI, with the exception of the matching variables. Adjusted smoothing spline plots were created to assess the shape of the relationship between BMI and PJI. A log likelihood ratio test was conducted to compare the one-line linear regression model with a two-piecewise linear model. Interaction and stratified analyses were conducted according to age grouping (≥ or <65 years), sex, type of surgery (knee or hip), smoking status, alcohol use, diabetes, IA, liver disease and renal disease.

Results

In total, 307 patients with a diagnosis of PJI and 614 control subjects were enrolled in this study. Table I shows the main characteristics of the study subjects and the prevalence of risk factors for PJI. No difference in sex, age or type of surgery was observed between the PJI and control groups, indicating good matching for the desired covariates. Patients with PJI had significantly higher BMI compared with the control subjects (26.0 kg/m^2±3.9 vs 25.4 kg/m^2±3.5). Additionally, there were significant differences between the PJI and control groups in CCI score [153 (49.8%) vs 240 (39.1%)], alcohol use [27 (8.8%) vs 31 (5.0%)], IA [60 (19.5%) vs 81 (13.2%)] and liver disease [22 (7.2%) vs 17 (2.8%)].

The relationship between BMI and PJI is presented in Table II. The univariate logistic regression analysis revealed that obesity was associated with increased risk of PJI (OR 1.98; 95% CI 1.46–2.7). After adjusting for confounding variables, the risk of PJI was higher in patients with obesity (OR 2.48; 95% CI 1.66–3.69). When analysed as a continuous variable, BMI was also associated with increased risk of PJI (adjusted OR per 1 kg/m^2 increase in BMI 1.08; 95% CI 1.02–1.14). The adjusted smoothing spline, represented in Figure 1, shows a non-linear relationship between BMI and PJI (*P*=0.018). When BMI was greater than the inflection point at BMI of 24–28 kg/m^2, the risk of PJI increased with the increase in BMI.

The results of the stratified analyses of the association between obesity and PJI are presented in Table III and Figure 2. The association between obesity and PJI remained generally consistent across several clinically relevant characteristics. The stratified analysis demonstrated that obesity was associated with increased risk of PJI in both age groups (<65 years: OR 1.8; 95% CI 1.19–2.74; ≥65 years: OR 2.25; 95% CI 1.42–3.56), male patients (OR 2.38; 95% CI 1.55–3.66), THA (OR 2.19; 95% CI 1.23–3.89) and TKA (OR 1.97; 95% CI 1.36–2.84), smokers (OR 3.54; 95% CI 1.85–6.78) and non-smokers (OR 1.55; 95% CI 1.05–2.29), patients without history of alcohol use (OR 2.06; 95% CI 1.49–2.84), patients without diabetes (OR 2.24; 95% CI 1.54–3.28), patients with (OR 3.9; 95% CI 1.81–8.41) and without IA (OR 1.55; 95% CI 1.06–2.25), patients without liver disease (OR 1.91; 95% CI 1.39–2.62) and patients without renal disease (OR 1.97; 95% CI 1.44–2.71).

The interaction analysis revealed that the association between obesity and PJI was modified by smoking status and history of IA (Table III and Figure 2). Patients who smoked had higher ORs between obesity and PJI than patients who did not smoke (OR 3.54 vs 1.55, *P*-value for interaction=0.031). In addition, the OR between obesity and PJI was much higher in patients with IA than in patients without IA (OR 3.9 vs 1.55, *P*-value for interaction=0.029).

Table II
Multi-variable logistic regression models evaluating the association between body mass index (BMI) and periprosthetic joint infection

Variable	*N* (%) of study participants		OR (95% CI)	
	Cases	Controls	Unadjusted	Adjusted[a]
BMI, 1 kg/m^2	307	614	1.05 (1.01–1.09)	1.08 (1.02–1.14)
BMI <28 kg/m^2	203 (66.1%)	488 (79.5%)	Ref	Ref
BMI ≥28 kg/m^2	104 (33.9%)	126 (20.5%)	1.98 (1.46–2.70)	2.48 (1.66–3.69)

OR, odds ratio; CI, confidence interval.
[a] Adjusted for Charlson Comorbidity Index score, smoking status, alcohol use, diabetes, inflammatory arthritis, liver disease, renal disease, cardiovascular disease, coronary artery disease, chronic pulmonary disease, blood transfusion, operative time and length of stay.

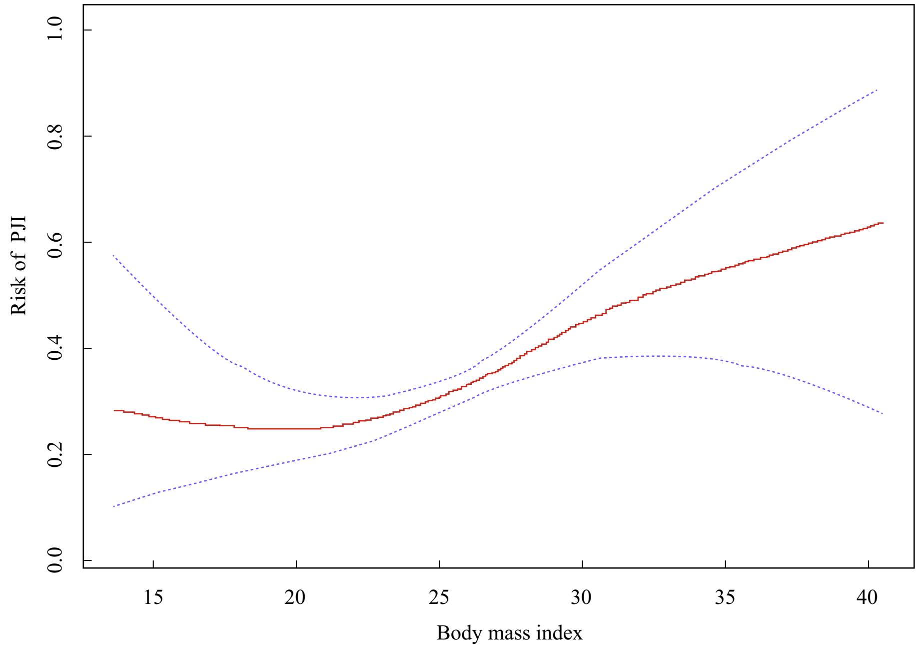

Figure 1. Relationship between body mass index and periprosthetic joint infection (PJI).

Table III
Interaction and stratified analyses between body mass index (BMI) and periprosthetic joint infection (PJI)

Subgroup	Patients with PJI		Patients without PJI		OR (95% CI)	*P*-value	*P*-value for interaction
	BMI ≥28 kg/m^2	BMI <28 kg/m^2	BMI ≥28 kg/m^2	BMI <28 kg/m^2			
Age (years)							0.49
<65	59	93	77	219	1.80 (1.19–2.74)	0.006	
≥65	45	110	49	269	2.25 (1.42–3.56)	0.001	
Sex							0.095
Female	44	117	65	263	1.52 (0.98–2.36)	0.062	
Male	60	93	61	225	2.38 (1.55–3.66)	<0.001	
Type of surgery							0.761
Knee	76	116	97	291	1.97 (1.36–2.84)	0.001	
Hip	28	87	29	197	2.19 (1.23–3.89)	0.008	
Smoking							**0.031**
Yes	51	19	47	62	3.54 (1.85–6.78)	0.001	
No	53	184	79	426	1.55 (1.05–2.29)	0.026	
Drinking							0.253
Yes	10	17	11	20	1.07 (0.37–3.13)	0.902	
No	94	186	115	468	2.06 (1.49–2.84)	<0.001	
Diabetes							0.195
Yes	40	16	56	29	1.29 (0.62–2.69)	0.49	
No	64	187	70	459	2.24 (1.54–3.28)	<0.001	
Inflammatory arthritis							**0.029**
Yes	48	12	41	40	3.90 (1.81–8.41)	0.001	
No	56	191	85	448	1.55 (1.06–2.25)	0.024	
Liver disease							0.23
Yes	9	13	2	15	5.19 (0.95–28.5)	0.058	
No	95	190	124	473	1.91 (1.39–2.62)	0.001	
Renal disease							0.922
Yes	7	6	7	11	1.83 (0.43–7.77)	0.411	
No	97	197	119	477	1.97 (1.44–2.71)	<0.001	

OR, odds ratio; CI, confidence interval.

Subgroup	Events	Total	Events	Total	Odds Ratio , 95%CI
Age					
Age <65 years	59	152	77	296	1.80 [1.19, 2.74]
Age ≥65 years	45	155	49	318	2.25 [1.42, 3.56]
Sex					
Male	60	153	61	286	2.38 [1.55, 3.66]
Female	44	161	65	328	1.52 [0.98, 2.36]
Surgical type					
Knee	76	192	97	388	1.97 [1.36, 2.84]
Hip	28	115	29	226	2.19 [1.23, 3.89]
Smoking					
Yes	51	70	47	109	3.54 [1.85, 6.78]
No	53	237	79	505	1.55 [1.05, 2.29]
Drinking					
Yes	10	27	11	31	1.07 [0.37, 3.13]
No	94	280	115	583	2.06 [1.49, 2.84]
Diabetes					
Yes	40	56	56	85	1.29 [0.62, 2.69]
No	64	251	70	529	2.24 [1.54, 3.28]
Inflammatory arthritis					
Yes	48	60	41	81	3.90 [1.81, 8.41]
No	56	247	85	533	1.55 [1.06, 2.25]
Liver disease					
Yes	9	22	2	17	5.19 [0.95, 28.50]
No	95	285	124	597	1.91 [1.39, 2.62]
Renal disease					
Yes	7	13	7	18	1.83 [0.43, 7.77]
No	97	294	119	596	1.97 [1.44, 2.71]

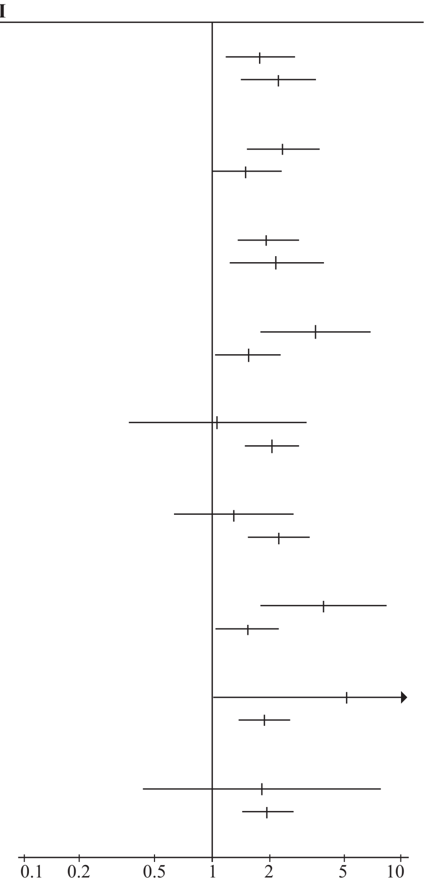

Figure 2. Odds ratios of obesity for periprosthetic joint infection in the stratified analyses.

Discussion

In the present study, obesity was identified as a significant and independent risk factor of PJI in the Chinese Han population. Obese patients had a 2.48-fold greater risk of PJI than patients with normal BMI levels. Although patients with PJI had a greater prevalence of risk factors than controls, the association between BMI and PJI remained significant after controlling for these risk factors. Each one-unit increase in BMI was associated with an 8% higher risk of PJI, further confirming the relationship between obesity and PJI. There is a non-linear relationship between BMI and PJI. When BMI was greater than the inflection point at BMI of 24–28 kg/m^2, the risk of PJI increased with increased BMI. Moreover, both smoking status and IA significantly influenced this relationship, suggesting that these two factors may interact with obesity in the pathophysiologic pathway in the development of PJI.

Although the association between obesity and PJI has been well established in Western populations, research in Asian populations, where the average BMI is lower [14,15], has been scant. The present study defined obesity as BMI $\geq$28 kg/m^2 in accordance with the official Chinese guidelines [13]. Obesity had an adjusted OR of 2.48 in the development of PJI in Chinese populations; this ratio is similar to results found in previous studies using registries and large retrospective cohorts from Europe, North America, Asia and the Pacific [5–10]. A meta-analysis by Kunutsor *et al.*, which included 29 studies, showed that a unit increase in BMI was associated with a relative risk of 1.09 for PJI; obese patients (BMI $\geq$30 kg/m^2) had a 1.6-fold higher risk of PJI compared with non-obese patients [6]. Bozic *et al.* reported that obesity was associated with a 1.73-fold increased risk of PJI using the American Medicare sample claims database of 40,919 patients who underwent primary THA [8].

Smoking, whether former or current, has been associated with increased incidence of surgical complications across various surgical disciplines [16–20]. The association between smoking, PJI and other postoperative complications is attributed to delayed wound healing as a result of nicotine-mediated vasoconstriction and impaired systemic immune response [21–24]. The present results suggest that cigarette smoking and obesity have a synergistic effect on the development of PJI, resulting in a 3.54-fold increased risk. These results are similar to those described by Crowe *et al.* [11]. They reported that smokers had a 3.07-fold risk of PJI compared with non-smokers. While tobacco use alone increased the risk of PJI, tobacco had an additive effect on risk for patients with BMI >30 kg/m^2, resulting in a higher OR for PJI (8.37; 95% CI 1.86–37.74, P=0.009). While the underlying pathology of this interaction remains unknown, it is hypothesized that the nicotine-mediated vasoconstriction and impaired systemic immune response by tobacco use may be aggravated in obese patients due to the thickness of the subcutaneous adipose tissue at the surgical site.

This study also found a positive interaction between IA and obesity on the development of PJI. Various types of IA, including rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythaematosus, psoriatic arthritis and juvenile idiopathic arthritis, can cause joint destruction, leading to pain and disability. Previous studies have shown increased risk of PJI among patients with IA [6,25–28]. These patients have often been on long-term immunosuppressive therapy, which could potentially increase the risk of wound complications and PJI [25,29,30]. Obese patients may need a larger dose of immunosuppressive drugs to control the progression of IA [31], which may be a possible explanation for the interaction between IA and obesity on the development of PJI. Another explanation may be that patients with IA are more likely to undergo intra-articular corticosteroid injection, which may play a confounding role in the association between IA and obesity on PJI.

When interpreting the findings of the present study, several limitations should be considered. First, this was a retrospective study and therefore inherently subject to selection biases and recall biases. As the history of chronic disease and social behaviours, such as alcohol consumption and smoking, was self-reported in this study, recall biases must be considered. Additionally, this was a single-institution study with a small sample size. As a result, it has limited external validity. Conclusions drawn from single-institute studies are not necessarily applicable to a wider population due to differences in institutional practices and disparate patient populations.

In conclusion, obesity is an independent risk factor for PJI in the Chinese Han population. The association between obesity and increased risk of developing PJI was modified by smoking and a history of IA. These findings suggest that known risk factors may play a role in PJI, both independently and jointly. Surgeons should not only assess BMI level, but should also consider other potential synergistic factors that may contribute to the development of PJI. A prospective clinical trial with a larger sample size is needed to detect the interaction between obesity and other risk factors for PJI.

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Conflict of interest statement
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