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Smoking, body weight, physical exercise and risk of lower limb total joint replacement in a population-based cohort of men

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Abstract (word count 250)

***Objective*:** To assess the associations of smoking, body weight and physical activity with risk of undergoing total joint replacement (TJR) in a population-based cohort of men.

***Methods*:** A cohort study of 11,388 men that integrated clinical data with hospital morbidity data and mortality records. In three separate age groups we modelled the risk of TJR on baseline weight, height, co-morbidity, injury, socioeconomic status, years of smoking and exercise, using Cox proportional hazards regressions and competing risk regressions (CRR).

***Results*:** A dose-response relationship between both weight and smoking, and risk of TJR was observed. Being overweight independently increased the risk of TJR, while smoking lowered the risk. The decreased risk among smokers was demonstrated in both Cox and CRR models and became apparent after 23 years of exposure. Men who were in the highest quartile (48+ years of smoking) were 42% to 51% less likely to undergo TJR than never-smokers. Tests for trend in the log hazard-ratios across both smoking and weight quantiles yielded $P<0.05$. Vigorous exercise increased the hazard of TJR, however, the association reached statistical significance only in the 70-74 year-old age-group (adjusted-hazard ratio: 1.64, 95% CI: 1.19 - 2.24). Adjusting for Deyo-Charlson Index or Elixhauser's co-morbidities did not eliminate these associations.

***Conclusion*:** Being overweight and reporting vigorous physical activity increased the risk of TJR. This study is the first to demonstrate a strong inverse dose-response relationship of duration of smoking and TJR. More research is needed to better understand the role of smoking in the pathogenesis of osteoarthritis.

Introduction

Total hip replacement (THR) and total knee replacement (TKR) are among the most common elective surgical procedures performed in developed countries (1-4). The most common indicator for total joint replacement (TJR) is severe osteoarthritis (OA) (5,6); TJR is often considered an acceptable surrogate indicator of severe OA (7-9). Factors associated with OA (e.g., age, female gender, obesity) are predictors of TJR (7,10).

In the ageing population, OA is the most common form of arthritis (5), causing much disability and impairing quality of life (11). Independent risk factors for this disorder include older age (12), female gender (13), obesity (13-16), physical activity (12-14), and never-smoking (9,13,15). However, the reported association of some of these factors with an increased risk of OA or subsequent TJR has not been consistent. Being overweight shows the most consistent association with OA (9,13,15,16) and with TJR (7,8,14) while the results for physical activity and smoking have been the most inconsistent (7,9,12-15,17-26). Smoking has variously shown a negative association with OA (9,13,15,19,20,26) or TJR (21), a positive association with OA (22,23) or TJR (7), and no significant association with OA (12,17,24). Similarly, the association of physical activity with the risk of OA is unclear. An example of contradictory findings was demonstrated in two studies based on the population-based Framingham cohort. In the first publication on this topic, based on a sub-population from the first cohort enrolled, patients in the highest quartile of physical activity had 3.3 times the odds of developing OA compared with those in the lowest quartile of physical activity (13). However, in a second publication, based on a sub-population of the first cohort's children and their spouses, the association between physical activity and radiographic

OA was weaker and did not reach statistical significance (Adjusted OR=1.20, 95% CI 0.65 - 2.21) (18). Inconsistencies in the findings of these and other studies reflect: sampling biases or unrepresentative cases; a lack of, or incomplete adjustment for, co-morbidities and other confounders; inconsistencies in definitions of disease; or inaccuracies in definition of exposure (7,12,16,23). Some studies did not make appropriate distinction between current and past smoking (16,23), while others disregarded duration of smoking (7,12).

The purpose of this study was to assess the predictors of undergoing a lower limb total joint replacement in a large population-based cohort of elderly men while focusing on the modifiable factors of body weight, duration of smoking, and physical activity.

Methods

Data sources and study population

The study population is drawn from the Health In Men Study (HIMS) (27,28) which arose from a randomized population-based trial of ultrasound screening for abdominal aortic aneurysm (AAA) in men aged 65-83 living in Perth, Western Australia (WA). A total of 41,000 men was identified via the electoral roll (voting is compulsory in Australia) and was randomized into invited and control groups of equal size. Of the 19,352 men who were invited, 12,203 attended the baseline screening in 1996-9. At baseline the participants provided detailed health and other information including a comprehensive smoking history, and details of vigorous exercise activity (defined in the questionnaire as 'exercise that makes you breathe harder - e.g. jogging, aerobics, tennis, football, squash, etc.') a yes/no question or non-vigorous exercise (defined as

'exercise that does not make you breathe harder - e.g. slow walking or cycling, yoga, Tai Chi etc.') a yes/no question in a usual week. In addition, study nurses recorded weight, height, and waist and hip circumferences. Electronic record linkage was used to identify admissions to hospital (hospital morbidity data) for TJR in the target population. All-cause mortality was ascertained through linkage to WA Health Department mortality records. Follow-up for study end points started at baseline screening and ended in March, 2007.

The hospital morbidity data (HMD) system is a core part of the WA Linked Data System (29) and includes demographic, diagnostic, and procedural information on all patients discharged from all public and private hospitals in WA. The HMD, which has been validated (30), allows the inclusion of up to 21 diagnoses and 11 procedure codes for each hospitalization in every hospital department. The validation analysis of the HMD showed good to acceptable sensitivities and positive predictive values (PPV) for major operations (e.g., TJR: sensitivity and PPV of 0.92), and major morbidity (e.g., any cancer: sensitivity of 0.90 and PPV of 0.78; past myocardial infarction: sensitivity of 0.69 and PPV of 0.80; diabetes mellitus: sensitivity of 0.68 and PPV of 0.88) (30).

Definitions

The Deyo-Charlson Co-morbidity Index (31) and Elixhauser's co-morbidities (32) which were used to adjust for co-morbidity were based on all reported conditions in admissions that preceded baseline screening. The Deyo-Charlson Index was built using the original Charlson weights (33), and the corresponding International Statistical Classification of Disease, 9th Revision, ICD-9-CM (Clinical Modification) algorithms were used as delineated in the authors' original publication (31). We further used an ICD-10-AM (Australian Modification) adaptation of the Deyo-

Charlson Index as developed and validated using population-based hospital data from Australia (34). The coding algorithms defining Elixhauser's co-morbidities were based on definitions by Quan et al (35).

The Socio-Economic Index For Areas (SEIFA) (36) was used to define the participants' socioeconomic status. SEIFA indices indicate relative social disadvantage of populations living in different geographic areas with low scores reflecting disadvantage. Since most of the participants were recruited before 1999 (30), we used the 1996 census to calculate the index. At baseline screening the participants provided their residential postcode, thus lowering the chances of misclassification of SEIFA due to incorrect postcode. Presence of traumatic fracture of the lower limb on day of surgery was also identified from the HMD. Body mass index (BMI) was defined as body weight in kilograms divided by height in meters squared.

The ICD codes used to detect primary total hip or total knee replacement (Appendix 1) were checked by a professional clinical coder.

Statistical analysis

Attending men who had had a lower limb TJR before baseline screening were excluded from this analysis. The remaining eligible participants were followed from baseline screening until they experienced their *first* TJR or died or were right censored at the end of follow-up (March, 2007). Since the focus of the study was elective TJR, all patients who experienced a fracture of the lower limb (among those who had and did not have a TJR) were excluded from the analysis.

In three separate age groups (65-69 years, 70-74 years, and 75+ years), we modelled time to TJR on weight, height, socioeconomic status, Deyo-Charlson Co-morbidity

Index (or Elixhauser's co-morbidities), vigorous or non-vigorous physical exercise and years of smoking using Cox proportional hazards regressions and competing risk regressions (CRR) as defined by Fine and Gray (37). The latter analyses assessed the effect of predictors on the hazard of the subdistribution for TJR (the "subhazard") while accounting for the competing risk of death, since the study population was elderly and death represented a competing risk that reduced the number of individuals at risk of the event of interest, TJR (38,39). We also used the cumulative incidence function (CIF) (39), to estimate the overall risks of TJR and of death in the study population.

Tests for trend in the log hazard ratios across quantiles of duration of smoking and body weight were performed by introducing each of the ordered variables in the multivariable Cox models. The Cox proportional hazard assumptions were tested in each of the age groups using Schoenfeld residuals.

The crude attributable risk of dying among heavy-smokers (48+ years of smoking) was defined as incidence of death among the heavy-smokers minus incidence of death among the never-smokers divided by the incidence of death among the heavy-smokers (40).

All analyses were performed using Stata statistical program (version 11, Stata-Corp.).

Ethical approval was obtained from the Human Research Ethics Committees of Health Department of Western Australia and The University of Adelaide prior to commencement of study. All analyses used de-identified data.

Results

Of the total 12,203 men (mean age ± SD 72.1 ± 4.4 years, range 65 to 84 years) who participated in the baseline AAA screening study, 815 men (6.7%) were excluded as they already had undergone a TJR prior to baseline screening leaving a total of 11,388 participants for the current analysis. Of these remaining eligible participants, a total of 857 men (7.5%) had a TJR after screening, with 510 (59.5%) having a TKR and 347 (40.5%) a THR. The baseline characteristics of these 857 men differed significantly from participants who never had a TJR. The former were significantly younger, had less co-morbidity (defined by Deyo-Charlson Index), had higher mean BMI, belonged to a higher socioeconomic status, and smoked less years than those who did not undergo TJR after baseline (Table 1). A total of 486 men (with fracture of lower limb) were excluded, thus leaving 10,902 men for the study analysis.

To meet the proportionality assumptions of time-to-event models, the cohort was divided into three age groups (based on the actual age distribution in the cohort: 65-69 years, 70-74 years, and 75+ years) and the subsequent analyses were done separately on each of the age-groups.

We stratified TJR by weight quintiles and found that within each age category, the crude proportion of men undergoing TJR increased with weight, while within quintiles of weight the proportion was relatively constant across age groups (Table 2). We further stratified TJR by years of smoking, age and BMI categories and found an inverse association of duration of smoking and TJR (Table 3). To verify whether more deaths occurred among the smokers compared to never-smokers and whether this "selective mortality" (41) contributed to the inverse association of smoking and TJR, we assessed the crude and age-adjusted death rates as shown in Table 4. The crude mortality rate in each of the age-groups increased as the years of smoking increased. In the younger men (65-69 age-group), 72.4% of the crude mortality among the heavy

smokers (48+ years of smoking) was attributable to smoking. This attributable risk fell to 40.5% in the 75+ age-group. The overall age-adjusted and crude mortality rates were similar, showing an increased risk of death as years of smoking increased (Table 4).

To investigate the etiological associations of the study covariates with TJR, we calculated the cause-specific relative hazards (42) using multivariable Cox proportional hazards regressions (Table 5). After adjustment for other covariates in the models, being overweight was significantly associated with an increased hazard of TJR, showing a dose-response relationship across quintiles of the distribution of weight (P<0.001) in all three age strata. In the middle age group (70-74 years), men weighing ≥ 87.9 kg were 4.4 times more likely to undergo TJR compared to men weighing <68.4 kg (HR= 4.36, CI 95% 2.58-7.36). Vigorous exercise reported at baseline increased the hazard of undergoing TJR but this association was only statistically significant in the 70-74 age-group, (HR:1.64, CI 95% 1.19-2.24). Belonging to a higher socioeconomic status was positively associated with TJR in the 70-74 age-group, (HR:1.50, CI 95% 1.14-1.97). Smoking had an inverse association with TJR, showing a dose-response relationship across quartiles of the distribution of years of smoking in all three age strata (65-69 age-group P<0.001, 70-74 age-group P=0.002, 75+ age-group P=0.05). Compared to never-smokers, men who had smoked 48 years or more were 42% to 51% less likely to undergo TJR (HR= 0.49, CI 95% 0.32-0.74 in the 65-69 age-group; HR= 0.58, CI 95% 0.41-0.82 in the 70-74 age-group; HR= 0.51, CI 95% 0.30-0.85 in the 75+ age-group). Similar results were found after modelling time to TJR using competing risk regression (CRR) to account for the competing risk of death. However, the CRR modelling strengthened the significant associations of weight and of smoking with TJR (results not shown).

To control for potential confounding from other co-morbidities not accounted for in the Deyo-Charlson Index, the CRR models were run using Elixhauser's method (instead of Deyo-Charlson Index) and this produced findings almost identical to those of the first models (results not shown).

To assess the association of weight with different joints, we further modelled THR and TKR separately and found that the association of weight was stronger with TKR than with THR; however the dose-response relationship across quintiles of the distribution of weight was maintained in both TKR and THR. Patients weighing 87.9+ kg were 5.7 times more likely to have a TKR (adjusted HR=5.72, CI 95% 3.74-8.75), and 2.7 times more likely to have a THR (adjusted HR=2.74, CI 95% 1.75-4.29), compared with patients who weighed 68.4 kg and less.

No statistically significant interactions were found between body weight and smoking or physical activity, nor with smoking and physical activity.

Discussion

This study, involving a large population-based cohort of men, is the first to report an independent dose-response relationship of duration of smoking on the reduction of the risk of undergoing subsequent TJR.

In addition and consistent with other studies, we also demonstrated that being overweight (7,8,14) and engaging in vigorous exercise (14) significantly increased the risk of TJR.

Smoking and TJR

The association of smoking with decreased risk of OA (9,13,15,19,20,26), or subsequent TJR (21), has been reported previously. One of the earliest reports came from the cross sectional population-based first Health and Nutrition Examination

Survey (HANES I) in the United States (43) which found an age-adjusted significant inverse association of number of cigarettes smoked per day and radiographic knee OA among both men and women. To test for confounding, researchers from the Framingham Study controlled for age, sex, BMI, physical activity and past knee injury and found a similar negative association in two separate studies (13,15). In the first prevalence analysis of 1,424 participants, the adjusted OR for knee OA was 0.74 ($P<0.05$) among the smokers (15). The second analysis investigated the incidence of radiographic knee OA and showed that heavy smokers had significantly lower risk of developing new knee OA among a cohort of 598 participants initially free of OA (OR=0.4; 95% CI: 0.2-0.8) (13). A similar decrease in risk was reported in a large longitudinal population-based cohort of construction workers (9). Never-smokers had an increased relative risk of about 40% of undergoing hip replacement due to OA, while ex-smokers had an increased risk of 20% compared with smokers (9). Our study confirms the inverse association of smoking with risk of TJR. However, smokers were more likely to die than never-smokers, but even accounting for this competing risk of death, men who smoked for more years were less likely to undergo TJR compared to never-smokers.

The mechanisms behind this decrease in risk are not clear. There is some evidence that smoking may directly reduce the severity of OA. An *in vitro* study found a relationship between nicotine and stimulation of the anabolic activity of the chondrocytes (cells found in joint cartilage) (44). This was supported by a population-based prospective cohort study that showed a positive dose-response between pack-years of smoking and knee cartilage volume among healthy individuals (26).

The decrease in risk may have other explanations. Our study retrieved co-morbid conditions from the HMD and since this dataset was not originally formed for the

purpose of health research, some co-morbid conditions may have been under-reported. If co-morbidity were underestimated, the risk of TJR among never-smokers could have been overestimated (given that the ever-smokers had more co-morbidities than the never-smokers). However, we have shown that the HMD is a valid tool to assess major health-care outcomes (30). The validation analysis showed good to acceptable sensitivities and positive predictive values for serious conditions such as major co-morbidities and major surgical procedures. Another explanation is the possibility of confounding by factors not accounted for in this analysis or by selection biases prior to surgery. A survey that sought to find indications for THR or TKR as perceived by orthopedic surgeons showed that the decision against surgery was mainly affected by patient age, co-morbidity, obesity, alcohol use, technical difficulties and lack of motivation among the patients. Smoking was not indicated as a factor that would sway the decision against TKR or THR (45).

Overweight and TJR

Body weight is one of the most investigated factors in the study of OA or TJR. In many studies, being overweight and measures of relative body mass have been associated with an increased risk of OA (9,13,15,16,46) and TJR (7,8,14), with some showing a stronger association in knee OA (16), suggesting a biomechanical component in the relationship between body weight and OA. However, more studies are showing a positive relationship between being overweight and OA at different body sites including knee and hip (8,16), and non-weight bearing joints such as small joints of the hands (47,48) suggesting a connection between OA and metabolically active adipose tissue.

After controlling for physical activity, smoking, socioeconomic status, height, and co-morbidities, our study found a dose-response relationship of body weight on the risk

of undergoing THR and TKR. However, the association of weight with TKR was stronger than that with THR.

Furthermore, we found that in the older age groups, the probability of undergoing TJR was similar in the highest body weight quintiles. A possible explanation could be selection prior to surgery. Morbid obesity in these advanced ages may have swayed the decision against surgery (45), thus lowering the HR in the highest weight categories.

Vigorous exercise and TJR

This study found a positive association between vigorous exercise and TJR (14). This association could have been underestimated since the participants were relatively old when asked about their weekly exercise habits and one would assume that old age might have naturally limited their physical activity. Nevertheless, these findings suggest that those who were physically active in their younger ages stayed active as they got older and this activity was positively related to an increased risk of TJR.

This study has several strengths including its longitudinal follow-up design, accurate clinical data on body weight and many years of past exposure to smoking. Moreover, the linkage of participants' records to the HMD allowed us to account for major co-morbidities for each individual. However, the study has limitations. Although we considered TJR a surrogate indicator of severe OA, we did not directly ascertain OA status among study participants. The SEIFA indices ranked socio-economic well-being of the populations within areas rather than individuals themselves. Any area can include both relatively advantaged and disadvantaged people. Using the postcode may have introduced some misclassifications (49), however, since the postcode was provided by the participants, any misclassifications were minimized. Information on

the physical activity of the participants was self-reported and not validated. The clinical data presented in the study were collected at baseline screening and, except for age, the study did not account for changes in patient characteristics (e.g., change in body weight, physical activity) that could have occurred over time. However, the mean time from baseline screening to TJR was not long (4.6 + 2.7 years) and one may assume that in this relatively elderly cohort, OA (a degenerative disease that takes long to develop) was probably present at baseline but this was not assessed in this study. Finally, our longitudinal study is observational and a causal relationship between smoking and OA cannot necessarily be inferred.

Conclusion

This population-based cohort study has shown an increased risk for TJR with body weight and vigorous exercise, and an inverse association with smoking. Our study is the first to report a strong, inverse, dose-response relationship between duration of smoking and risk of TJR. More research is needed to better understand the role of smoking in the pathogenesis of OA, but also into the selection pathways for patients for whom TJR is indicated. Notwithstanding the findings, this study reinforces the overwhelming excess risk of premature mortality associated with smoking.

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Corrected Tables

Smoking, body weight, physical exercise and risk of lower limb total joint replacement in a population-based cohort of men

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Appendix 1: ICD-9 and ICD-10 codes used to detect primary total hip or total knee replacement

ICD version	Code	Description of procedure
ICD-9-CM	81.51	Total hip replacement
	81.54	Total knee replacement
ICD-10-AM*	49318-00	Total arthroplasty of hip, unilateral
	49319-00	Total arthroplasty of hip, bilateral
	49518-00	Total arthroplasty of knee, unilateral
	49519-00	Total arthroplasty of knee, bilateral
	49521-00	Total arthroplasty of knee with bone graft to femur, unilateral
	49521-01	Total arthroplasty of knee with bone graft to femur, bilateral
	49521-02	Total arthroplasty of knee with bone graft to tibia, unilateral
	49521-03	Total arthroplasty of knee with bone graft to tibia, bilateral
	49524-00	Total arthroplasty of knee with bone graft to femur and tibia, unilateral
	49524-01	Total arthroplasty of knee with bone graft to femur and tibia, bilateral
	49534-01	Total replacement arthroplasty of patellofemoral joint of knee

*The ICD-10 codes were based on those listed in the database

Table 1: Baseline characteristics of study population by TJR status after baseline screening

Characteristics	Had TJR N=857	Did not have TJR N=10,531	*P*-value
Age, mean ± SD, (range)	71.6 ± 4.2 (65 - 84)	72.0 ± 4.4 (65 - 84)	0.026
Deyo Charlson Index, mean ± SD, (range)	0.69 ± 1.2 (0 - 8)	0.89 ± 1.4 (0 - 11)	<0.001
BMI, mean ± SD, (range)	28.1 ± 3.5 (19.3 - 41.0)	26.7 ± 3.7 (14.0 - 67.1)	<0.001
Vigorous exercise (during a usual week), %	27.4	25.3	0.175
Ever smoked, %	67.8	71.3	0.030
Years of smoking, mean ± SD, (range)	21.8 ± 19.8 (0 - 70)	24.7 ± 20.6 (0 - 73)	<0.001
Socioeconomic status as SEIFA distribution, %			
Lower tertile (Low SES)	29.9	33.3	
Middle tertile	32.1	33.0	
Higher tertile (High SES)	38.0	33.7	0.024
Fracture of lower limb, %	4.4	4.2	0.802

Abbreviations: TJR (total joint replacement), BMI (body mass index)

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Table 2: Crude [1] rate of TJR by age and body weight categories[2]

Age categories, years	**1st quintile (weight ≤68.4 kg) N=2,181**	**2nd quintile N=2,240**	**3rd quintile N=2,186**	**4th quintile N=2,118**	**5th quintile (weight 87.9+ kg) N=2,177**	**Total N=10,902**
65-69	3.2%	5.9%	6.8%	8.2%	11.6%	**7.5%**
70-74	2.6%	7.3%	8.9%	11.9%	10.7%	**8.3%**
75-84	2.2%	6.0%	7.6%	9.6%	9.8%	**6.4%**
Total	**2.6%**	**6.4%**	**7.8%**	**9.9%**	**10.9%**	**7.5%**

[1] Not accounting for censoring
[2] Excluding those who had fracture of lower limb
Abbreviation: TJR (total joint replacement)

Table 3: Crude [1] rate of TJR by age, BMI, and years of smoking categories[2]

	BMI <30				**BMI 30+**			
	Never smoking	1st tertile of smoking 1-28yrs	2nd tertile of smoking 29-43 yrs	3rd tertile of smoking 44+ yrs	Never smoking	1st tertile of smoking 1-28yrs	2nd tertile of smoking 29-43 yrs	3rd tertile of smoking 44+ yrs
65-69 years	7.4%	7.6%	6.5%	4.6%	15.2%	11.4%	8.6%	9.0%
70-74 years	8.8%	7.5%	8.1%	6.2%	10.2%	12.9%	8.8%	12.9%
75+ years	5.8%	6.6%	6.7%	3.8%	13.5%	10.0%	8.6%	9.3%

[1] Not accounting for censoring
[2] Excluding those who had fracture of lower limb
Abbreviations: TJR (total joint replacement), BMI (body mass index)

Table 4: Crude and age-adjusted death[1] rates by years of smoking categories

	Never smoked	**1st quartile 1-23 yrs of smoking**	**2nd quartile 24-36 yrs of smoking**	**3rd quartile 37-47 yrs of smoking**	**4th quartile 48+ yrs of smoking**
65-69	64/1281= 5.0%	40/632= 6.3%	60/701= 8.6%	71/669= 10.6%	103/569= 18.1%
70-74	111/1119= 9.9%	80/731= 10.9%	113/721= 15.7%	130/693= 18.8%	186/765= 24.3%
75-84	191/896= 21.3%	123/570= 21.6%	137/503= 27.2%	136/507= 26.8%	195/545= 35.8%
Crude total death rate	366/3296= **11.1%**	243/1933= **12.6%**	310/1925= **16.1%**	337/1869= **18.0%**	484/1879= **25.8%**
Age-standardized death rates[2]	**11.3%**	**12.2%**	**16.4%**	**18.1%**	**25.3%**

[1] Deaths that preceded TJR
[2] Adjusted for age by direct standardisation method (using total population as standard)

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Table 5: Hazard ratios for TJR by age categories: Multivariable Cox proportional hazards models[1]

	Age group: 65-69 years N=3852 Had TJR, N=290 (7.5%)		**Age group: 70-74 years N=4029 Had TJR, N=336 (8.3%)**		**Age group: 75-84 years N=3021 Had TJR, N=193 (6.4%)**	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
DC Index, (cont)	0.69 (0.61-0.78)	0.000	0.77 (0.70-0.85)	0.000	0.67 (0.59-0.76)	0.000
SEIFA distribution, %						
Lower tertile (Low SES) ref	1.00		1.00		1.00	
Middle tertile	0.94 (0.69-1.27)	0.696	1.19 (0.89-1.59)	0.244	1.01 (0.70-1.46)	0.952
Higher tertile (High SES)	1.00 (0.74-1.37)	0.951	1.50 (1.14-1.97)	0.004	0.81 (0.56-1.17)	0.269
Height, cm (cont)	1.00 (0.98-1.02)	0.760	0.98 (0.97-1.00)	0.111	0.98 (0.96-1.00)	0.207
Weight, kg						
1st quintile (≤68.4kg), ref	1.00		1.00		1.00	
2nd quintile (68.5-74.8 kg)	1.69 (0.97-2.95)	0.061	2.98 (1.78-4.99)	0.000	2.98 (1.69-5.27)	0.000
3rd quintile (74.9-80.6 kg)	2.23 (1.29-3.85)	0.004	4.65 (2.79-7.75)	0.000	3.34 (1.90-5.86)	0.000
4th quintile (80.7-87.8 kg)	2.68 (1.56-4.60)	0.000	5.09 (3.08-8.42)	0.000	4.53 (2.56-7.98)	0.000
5th quintile (87.9+ kg)	3.17 (1.88-5.35)	0.000	4.36 (2.58-7.36)	0.000	4.09 (2.26-7.40)	0.000
Exercise						
None, ref	1.00		1.00		1.00	
Non-vigorous exercise	1.33 (0.97-1.81)	0.078	1.04 (0.79-1.38)	0.763	1.27 (0.89-1.81)	0.191
Vigorous exercise	1.29 (0.91-1.82)	0.145	1.64 (1.19-2.24)	0.002	1.29 (0.82-2.03)	0.261
Years of smoking						
Never smoked, ref	1.00		1.00		1.00	
1st quartile (1-23 yrs)	1.06 (0.75-1.49)	0.756	0.88 (0.64-1.22)	0.453	0.89 (0.59-1.35)	0.587
2nd quartile (24-36 yrs)	0.79 (0.56-1.11)	0.177	0.76 (0.54-1.07)	0.123	1.10 (0.72-1.69)	0.653
3rd quartile (37-47 yrs)	0.52 (0.35-0.76)	0.001	0.65 (0.45-0.95)	0.024	1.11 (0.72-1.71)	0.637
4th quartile (48+ yrs)	0.49 (0.32-0.74)	0.001	0.58 (0.41-0.82)	0.002	0.51 (0.30-0.85)	0.009

[1] The Cox model in each age group represents a multivariable analysis that assesses the association of each covariate with TJR while controlling for all other covariates listed in table.

Abbreviations: TJR (total joint replacement); DC Index (Deyo Charlson Index); SEIFA (Socio Economic Index For Areas); SES (Socioeconomic Status)