BMI Polygenic Risk Score Modifies the Association between Prior Joint Surgery and End Stage Osteoarthritis of the Knee and Hip

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Disclosures: Patrick M. Carry (editor for medical/orthopaedic publication), Jyothi Lokanadham (N), Mike Zuscik (N), Cheryl Ackert-Bicknell (on the editorial or governing board of any medical-related company and/or orthopaedic publication)

INTRODUCTION: Osteoarthritis (OA) is influenced by environmental and genetic factors. The identification of modifiable environmental risk factors in observational studies is challenging due to the presence confounding variables. Genetic based measures of environmental exposures allow for unbiased and causal estimates of the association between these exposures and disease. Body mass index (BMI) has been identified as a strong risk factor in prior work[1]. However, the relationship between this modifiable exposure and other strong risk factors such as prior joint injury has been evaluated. The purpose of this study was to test the interrelationship between genetically predicted BMI, prior surgery, and osteoarthritis (OA).

METHODS: This study was performed in the UK Biobank (UKB), a population-based cohort of genetic and phenotypic data from half a million UK participants. Genotyping in the UKB was performed using two custom designed arrays that cover 805,426 markers across the genome. An additional ~96 million genotypes were imputed using the Haplotype Reference Consortium and the UK10K haplotype resource[2]. We queried the UK Biobank (UKB) to identify n=365,337 individuals with surgical, interview, hospital record, primary care, and genetic data. We excluded individuals with missing or poor-quality genetic data as well as individuals with autoimmune and/or parathyroid hormone disorders. End stage OA (hip or knee) was defined as the need for total joint arthroplasty (TJA) and one or more OA diagnosis codes (ICD9 or ICD10) for hip and knee OA, respectively. A prior joint surgery was determined based on surgical codes and/or self-reported surgical history. A prior hip surgery was defined as a hip surgery that occurred prior to the first occurrence of a hip OA diagnosis code. A prior knee surgery was defined as a knee surgery that occurred prior to the first occurrence of a knee OA ICD code. Genetically predicted BMI was based on a BMI polygenic risk score. The BMI polygenic risk score (PRS) for the UKB was developed by Thompson et al[3] based on a meta-analysis of multiple external genetic wide association studies. Multi-variable logistic regression models were used to test the association between OA and the BMI PRS. We included an interaction term (BMI*prior surgery) to test whether a prior joint surgery modified the association between BMI PRS and end stage OA. Hip and knee OA were modelled separately. All logistic models were adjusted for age, sex, the first 10 principal components representing genetic ancestry, genotyping array, as well as the Townsend deprivation index, a community level measure of socioeconomic status.

RESULTS SECTION: BMI genetic risk score and prior surgery were significantly associated with increased risk of both hip and knee OA, see Table 1 below. The relationship between BMI and hip OA risk was modified by prior surgery. Risk of knee OA per 1 standard deviation (stdv.) increase in BMI genetic risk score was higher in the hip surgery group (Odds Ratio (OR) per 1 stdv. increase in BMI: 1.23, 95% CI: 1.11-1.36) compared to the non-surgical group (OR per 1 stdv. increase in BMI: 1.12, 95% CI: 1.10-1.15). The relationship between BMI and knee OA risk was also modified by prior knee surgery. However, BMI was a stronger risk factor for knee OA in the non-surgical group (OR per 1 stdv. increase in BMI: 1.23, 95% CI: 1.21-1.25, p<.0001) compared to the prior knee surgical group (OR per 1 stdv. increase in BMI: 1.16, 95% CI: 1.11-1.21, p <.0001).

DISCUSSION: BMI, age, sex, and prior surgery were confirmed as strong risk factors for the development of both hip and knee OA. The relationship between BMI genetic risk score and OA risk differed by joint (hip vs knee) and history of prior surgery. Our results support the notion that OA environmental risk factors are interdependent and joint specific.

SIGNIFICANCE/CLINICAL RELEVANCE: OA lacks effective treatment or prevention strategies. Understanding the unique, joint specific mechanisms connecting elevated BMI, a modifiable risk factor, to OA may yield insight into novel treatment strategies.

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IMAGES AND TABLES:

Table 1. Risk factors for knee and hip OA

Contrast	Odds Ratio	Lower 95% CI	Upper 95% CI	P value
Knee OA				
Prior knee surgery vs no knee surgery	3.37	3.20	3.53	<.0001
BMI per 1 standard deviation increase in PRS	1.22	1.20	1.24	<.0001
Male vs female	1.11	1.07	1.15	<.0001
Age per 1-year increase	1.11	1.11	1.11	<.0001
Townsend deprivation index per 1-unit increase	1.01	1.01	1.02	<.0001
Hip OA				
Prior hip surgery vs no hip surgery	3.34	3.02	3.70	<.0001
BMI per 1 standard deviation increase in PRS	1.13	1.11	1.15	<.0001
Male vs female	1.28	1.23	1.33	<.0001
Age per 1-year increase	1.09	1.09	1.10	<.0001
Townsend deprivation index per 1-unit increase	1.00	0.99	1.00	0.4917

CI = confidence interval, PRS = polygenic risk score