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Genomic Risk Score for Advanced Osteoarthritis in Older Adults

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Objective. Prevention of osteoarthritis (OA) remains important, as there are no disease-modifying treatments. A personalized approach has the potential to better target prevention strategies. In the present study, we used recently identified genetic risk variants from genome-wide association analysis for advanced OA to calculate polygenic risk scores (PRS) for knee and hip OA and assessed PRS performance in an independent population of older community-dwelling adults.

Methods. PRS were calculated in 12,093 individuals of European genetic descent ages ≥70 years who were enrolled in the Aspirin in Reducing Events in the Elderly trial. The outcome measure was knee and hip replacement (hospitalizations during the trial and self-reported joint replacements before enrollment). PRS were considered as continuous (per SD) and categorical (low risk [0–20%], medium risk [21–80%], high risk [81–100%]) variables. Logistic regression was used to examine associations between PRS and risk of joint replacement, adjusted for age, sex, body mass index, and socioeconomic status.

Results. Among the participants, 1,422 (11.8%) had knee replacements and 1,297 (10.7%) had hip replacements. PRS (per SD) were associated with a risk of knee replacement (odds ratio [OR] 1.13 [95% confidence interval (95% CI) 1.07–1.20]) and hip replacement (OR 1.23 [95% CI 1.16–1.30]). Participants with high PRS had an increased risk of knee replacement (OR 1.44 [95% CI 1.20–1.73]) and hip replacement (OR 1.88 [95% CI 1.56–2.26]), compared to those with low PRS. Associations were stronger for PRS and hip replacement risk in women than in men. Associations were similar in sensitivity analyses that examined joint replacements before and during the trial separately.

Conclusion. PRS have the potential to improve prevention of severe knee and hip OA by providing a personalized approach and identifying individuals who may benefit from early intervention.

INTRODUCTION

Osteoarthritis (OA), the most common form of arthritis, is estimated to affect 250 million people worldwide, with numbers continuously growing due to aging and increased obesity (1). OA is a chronic disease with no cure, and joint replacement is indicated once conservative management options have been exhausted. The majority of total knee replacement (TKR) and total hip replacement (THR) procedures (98% and 89%, respectively) are performed for OA (2), resulting in significant healthcare burden. To date, strategies to prevent and treat OA have used a "one-size-fits-all" approach with limited effectiveness, mainly focusing on obesity and physical activity. In general, these strategies do not take into consideration that OA is a heterogeneous disease with distinct phenotypes (3) influenced by genetic and environmental factors (4), with risk factors varying across different joints (5). Current risk prediction models for OA lack the ability to identify with precision those most at risk and include disease

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markers, reducing their utility for prevention and treatment of early disease.

Over the last few years, large genetic studies have enabled the discovery of common genetic risk loci associated with OA. In 2019, a large genome-wide association study (GWAS) of advanced OA was undertaken in a population of European ancestry and identified 64 associated genetic loci, 52 of them novel (6). This more than doubled the number of previously identified variants (7). In 2021, a larger multiethnic GWAS meta-analysis of 826,690 individuals from 9 populations (177,517 with OA) identified 100 independent OA-associated variants across 11 OA phenotypes, 52 of which were novel (8).

The discovery of these variants now enables the calculation of polygenic risk scores (PRS), which aggregate the effect of many common disease-associated variants to generate a combined measure of the genetic risk. However, independent validation studies for PRS for advanced OA are challenging and require large genetic studies of older populations independent of the studies used in the original GWAS to derive the PRS, where the majority of OA diagnoses and joint replacements have occurred. PRS validation studies also need to be conducted in a healthcare setting where there is access to procedures such as joint replacement when indicated. Thus, we performed a validation study of newly derived PRS for OA in a well-characterized cohort of older adults in Australia, enrolled into the Aspirin in Reducing Events in the Elderly (ASPREE) trial (9–11), in which detailed information on joint replacements was collected. It was hypothesized that PRS would be associated with the risk of knee and hip replacement in older adults. Our study represents an important step in the assessment of genomic risk scores for prediction of advanced OA in older adults, in which the burden of disease is high.

PATIENTS AND METHODS

Study design and participants. The study population comprised genotyped participants of the ASPREE trial. Study design, participant characteristics, and primary results have been previously published (9–11). Briefly, ASPREE was an international randomized placebo-controlled clinical trial to determine whether daily 100 mg aspirin extended disability-free survival in 19,114 healthy older individuals ages ≥70 years (≥65 years for US participants). ASPREE participants had no history of diagnosed cardiovascular events, serious illness, dementia, or physical disability at enrollment. The median follow-up period was 4.7 years. Participants provided written informed consent for genetic research, and the study was approved by local Ethics Committees and registered on ClinicalTrials.gov (identifier: NCT01038583). The cohort for the current analysis was drawn from the 16,703 participants from Australia.

Assessment of advanced knee and hip OA. Advanced OA was defined as knee or hip replacement for OA. Australia has a universal healthcare system that includes publicly funded access to joint replacement, so knee and hip replacement can be considered a marker of advanced OA (12). Knee and hip replacements during the ASPREE trial (median follow-up 4.7 years) were identified by review of all hospitalizations for knee and hip surgical procedures, most with the indication recorded as OA. Self-reported history of joint replacements prior to ASPREE enrollment was obtained from the ASPREE Longitudinal Study of Older Persons questionnaire (13). Participants were asked, "Have you had any of the following operations?" and to mark "Hip replacement" and "Knee replacement" as Right, Left, Both, or No. Advanced knee and hip OA were defined as any knee and hip replacement—either hospitalizations or self-reported joint replacements.

Genotyping and PRS. Genotyping was performed on 14,052 DNA samples from ASPREE participants using the Axiom 2.0 Precision Medicine Diversity Research Array (ThermoFisher Scientific) following standard protocols (14). Variant calling used a custom pipeline aligned to human reference genome hg38. We limited our study to participants with European genetic ancestry to mitigate the effect of population stratification bias in polygenic scoring. To define genetic ancestry, principal component analysis was performed using the 1000 Genomes reference population, excluding ASPREE samples that did not overlap with the Non-Finnish European 1000 Genomes cluster (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42156) (15). Samples from 12,093 participants passed the following filters: non-Finnish European genetic descent, unrelated (identity-by-descent to third-degree relative), and minimum age at randomization of 70 years. Imputation was performed using the TOPMed Imputation Panel and Server (16–18). Pre-imputation quality control filtered variants using plink 1.9 for missing genotype rates (–geno, –mind 0.1) and Hardy-Weinberg equilibrium (–hwe 10–60). Post-imputation quality control removed variants with low imputation quality scores ($r^2 < 0.3$).

Two different PRS were calculated for knee and hip replacement respectively, based on those reported in the recent GWAS meta-analysis (8). For each PRS, we selected only genome-wide significant single nucleotide polymorphisms (SNPs) specific to the trait reported in the GWAS meta-analysis (8). This can be identified in the paper with the SNPs labeled as TKR and THR, comprising 10 SNPs for TKR and 38 SNPs for THR. In our analysis, 1 THR variant was removed due to poor imputation quality, resulting in SNP counts of 10 for TKR and 37 for THR (Supplementary Table 1, https://onlinelibrary.wiley.com/doi/10.1002/art.42156). Plink version 1.9 was used to calculate the weighted sum of the log odds ratios (ORs) reported for the effect alleles for each variant.

Table 1. Baseline characteristics of the study participants based on PRS*

	Low-risk PRS (Q1, 0–20%)	Medium-risk PRS (Q2–4, 21–80%)	High-risk PRS (Q5, 81–100%)
Knee	2,422 (20.0)	7,253 (60.0)	2,418 (20.0)
Age at randomization			
Mean ± SD years	75.3 ± 4.3	75.0 ± 4.2	75. ± 4.2
Median (range) years	74.1 (70.0–94.8)	73.8 (70.0–95.9)	73.8 (70.1–92.5)
Age category			
<75 years	1,418 (58.6)	4,430 (61.1)	1,472 (60.9)
75–79 years	625 (25.8)	1,842 (25.4)	596 (24.7)
≥80 years	379 (15.7)	981 (13.5)	350 (14.5)
Female sex	1,335 (55.1)	3,904 (53.8)	1,314 (54.3)
BMI, mean ± SD kg/m^2	27.8 ± 4.5	28.0 ± 4.5	28.3 ± 4.6
BMI category			
Underweight	14 (0.6)	42 (0.6)	7 (0.3)
Normal	650 (26.8)	1,811 (25.0)	582 (24.1)
Overweight	1,115 (46.0)	3,312 (45.7)	1,090 (45.1)
Obese	634 (26.2)	2,051 (28.3)	729 (30.2)
Missing	9 (0.4)	37 (0.5)	10 (0.4)
Education >12 years	939 (38.8)	2,885 (39.8)	976 (40.4)
Index of relative socioeconomic advantage and disadvantage score, mean ± SD	1,006.2 ± 68.3	1,004.1 ± 68.4	1,006.0 ± 69.7
Aspirin group	1,226 (50.6)	3,637 (50.1)	1,171 (48.4)
Hip	2,419 (20.0)	7,256 (60.0)	2,418 (20.0)
Age at randomization			
Mean ± SD years	75.0 ± 4.2	75.0 ± 4.2	75.0 ± 4.3
Median (range) years	73.8 (70.1–92.7)	73.9 (70.0–95.9)	73.8 (70.0–93.3)
Age category			
<75 years	1,504 (62.2)	4,352 (60.0)	1,464 (60.6)
75–79 years	576 (23.8)	1,876 (25.9)	611 (25.3)
≥80 years	339 (14.0)	1,028 (14.2)	343 (14.2)
Female sex	1,292 (53.4)	3,968 (54.7)	1,293 (53.5)
BMI, mean ± SD kg/m^2	28.0 ± 4.6	28.0 ± 4.5	28.0 ± 4.5
BMI category			
Underweight	15 (0.6)	37 (0.5)	11 (0.5)
Normal	595 (24.6)	1,842 (25.4)	606 (25.1)
Overweight	1,112 (46.4)	3,317 (45.7)	1,078 (44.6)
Obese	675 (27.9)	2,027 (27.9)	712 (29.5)
Missing	12 (0.5)	33 (0.5)	11 (0.5)
Education >12 years	967 (40.0)	2,882 (39.7)	951 (39.3)
Index of relative socioeconomic advantage and disadvantage score, mean ± SD	1,006.5 ± 68.3	1,005.2 ± 68.7	1,002.5 ± 68.9
Aspirin group	1,235 (51.1)	3,586 (49.4)	1,213 (50.2)

* Except where indicated otherwise, values are the number (%) of participants. PRS = polygenic risk score; Q1 = quintile 1; BMI = body mass index.

Demographic and socioeconomic data. Height and weight were measured using standardized protocols at the ASPREE baseline visit. Body mass index (BMI) was calculated from height and weight, and obesity was defined as a BMI of ≥30 kg/m^2 (19). Age and years of education were self-reported at the baseline ASPREE clinical visit. The index of relative socioeconomic advantage and disadvantage summarizes information about the economic and social conditions of people and households within an area, including both relative advantage and disadvantage measures (20).

Statistical analysis. The PRS were analyzed as continuous variables on the SD scale and were also categorized into 3 groups based on quintiles of the PRS distribution: low-risk (quintile 1 [Q1], 0–20%), medium-risk (Q2–4, 21–80%) and high-risk (Q5, 81–100%). Multiple logistic regression was used to examine the association between PRS (either as a continuous or as a categorical variable) and risk of knee and hip replacement, with adjustment for age, sex, BMI, education, and index of relative socioeconomic advantage and disadvantage. The area under the receiver operating characteristic curve (AUC) was calculated for the multiple logistic regression analysis before and after PRS was included in the regression models. Additional adjustment for treatment group was performed. We examined the interaction between PRS and treatment group, sex, or obesity for their association with the risk of knee and hip replacement by introducing interaction terms in the regression models. In a sensitivity analysis, incident joint replacements occurring during the trial (reviewed

Table 2. Association of PRS with risk of knee and hip replacement*

	Total participants with joint replacement, no. (%)	Univariable analysis		Multivariable analysis†	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Knee replacement	1,422 (11.8)	–	–	–	–
Knee PRS, per SD	–	1.14 (1.08–1.20)	<0.001	1.13 (1.07–1.20)	<0.001
Knee PRS category	–	–	–	–	–
Low-risk PRS (Q1, 0–20%)	231 (9.5)	1.00	–	1.00	–
Medium-risk PRS (Q2–4, 21–80%)	864 (11.9)	1.28 (1.10–1.49)	0.001	1.30 (1.11–1.52)	0.001
High-risk PRS (Q5, 81–100%)	327 (13.5)	1.48 (1.24–1.77)	<0.001	1.44 (1.20–1.73)	<0.001
Hip replacement	1,297 (10.7)	–	–		
Hip PRS, per SD	–	1.23 (1.17–1.31)	<0.001	1.23 (1.16–1.30)	<0.001
Hip PRS category	–	–	–	–	–
Low-risk PRS (Q1, 0–20%)	200 (8.3)	1.00	–	1.00	–
Medium-risk PRS (Q2–4, 21–80%)	745 (10.3)	1.27 (1.08–1.49)	0.004	1.27 (1.08–1.50)	0.004
High-risk PRS (Q5, 81–100%)	352 (14.6)	1.89 (1.57–2.27)	<0.001	1.88 (1.56–2.26)	<0.001

* PRS = polygenic risk score; OR = odds ratio; 95% CI = 95% confidence interval; Q1 = quintile 1.
† Adjusted for age, sex, body mass index, education, and index of relative socioeconomic advantage and disadvantage.

hospitalizations) and prevalent joint replacements occurring before the trial (self-reported) were examined separately, using Cox proportional hazards regression and logistic regression, respectively.

The specificity of PRS was assessed by testing hip PRS against the risk of knee replacement, and knee PRS against the risk of hip replacement. Additional analysis was performed to examine the risk of knee and hip replacement against the middle half of the study population. *P* values less than 0.05 were considered significant. Analyses were performed using R version 3.6.1 (21) and Stata version 16.1.

RESULTS

Characteristics of study participants. The mean age at randomization of the 12,093 participants was 75.0 years, with the majority (86%) ages 70–79 years. The mean ± SD BMI was 28.0 ± 4.5 kg/m^2, with 3,414 participants (28.2%) classified as obese. Both knee and hip PRS showed a normal distribution (mean ± SD 0.25 ± 0.13 and mean ± SD 0.51 ± 0.34, respectively). The characteristics of study participants are presented based on PRS categories (Table 1) and joint replacement status (Supplementary Table 2, https://onlinelibrary.wiley.com/doi/10.1002/art.42156). In total, 1,422 participants (11.8%) had ≥1 knee replacement and 1,297 participants (10.7%) had ≥1 hip replacement (occurring either during the ASPREE trial or prior to enrollment) (Supplementary Table 3, https://onlinelibrary.wiley.com/doi/10.1002/art.42156). Among the participants with knee replacements, 689 had surgeries during the ASPREE trial and 948 had surgeries according to self-reported history. Among the participants with hip replacements, 529 had surgeries during the ASPREE trial and 914 had surgeries according to self-reported history (Supplementary Table 3).

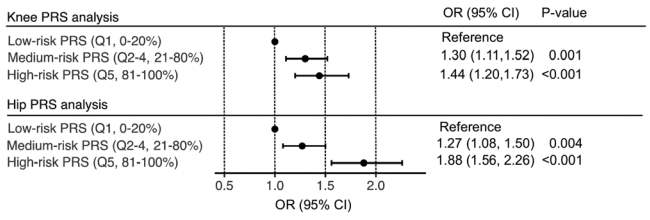

Figure 1. Association between polygenic risk scores (PRS) and risk of knee and hip replacement. Multiple logistic regression models are shown. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were adjusted for age, sex, body mass index, education, and index of relative socioeconomic advantage and disadvantage. PRS were categorized by quintiles into low-risk (quintile 1 [Q1], 0–20%), medium-risk (Q2–4, 21–80%), and high-risk (Q5, 81–100%) groups.

Association between PRS and risk of knee and hip replacement. The results for the associations between PRS and risk of knee and hip replacement are presented in Table 2 and Figure 1. Higher knee PRS was associated with an increased risk of knee replacement in univariable analysis and after adjustment for age, sex, BMI, education, and index of relative socioeconomic advantage and disadvantage (OR 1.13 [95% confidence interval (95% CI) 1.07–1.20] per SD of PRS). The frequency of participants with knee replacement surgery increased with knee PRS categories: 9.5% in the low-risk group, 11.9% in the medium-risk group, and 13.5% in the high-risk group. Compared to those in the low-risk PRS group (Q1), and after adjustment for confounders, the OR of knee replacement was 1.30 (95% CI 1.11–1.52) in the medium-risk PRS group (Q2–4) and 1.44 (95% CI 1.20–1.73) in the high-risk PRS group (Q5). The AUC was 0.666 (95% CI 0.651–0.680) for the regression model including age, sex, BMI, education, and index of relative socioeconomic advantage and disadvantage, and 0.668 (95% CI 0.654–0.683) when adding PRS to the model.

Higher hip PRS was associated with an increased risk of hip replacement in univariable analysis and after adjustment for

Table 3. Association of PRS with risk of hip replacement, stratified by sex*

	Men		Women	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Hip PRS, per SD	1.15 (1.06–1.26)	0.001	1.30 (1.20–1.40)	<0.001
Hip PRS category				
Low-risk PRS (Q1, 0–20%)	1.00		1.00	
Medium-risk PRS (Q2–4, 21–80%)	1.14 (0.90–1.45)	0.26	1.39 (1.11–1.75)	0.005
High-risk PRS (Q5, 81–100%)	1.57 (1.20–2.05)	0.001	2.19 (1.70–2.83)	<0.001

* Adjusted for age, body mass index, education, and index of relative socioeconomic advantage and disadvantage. See Table 2 for definitions.

confounders (OR 1.23 [95% CI 1.16–1.30] per SD of PRS). The frequency of participants with hip replacement surgery increased with hip PRS categories: 8.3% in the low-risk group, 10.3% in the medium-risk group, and 14.6% in the high-risk group. Compared to those in the low-risk PRS group (Q1) and after adjustment for confounders, the OR of hip replacement was 1.27 (95% CI 1.08–1.50) in the medium-risk PRS group (Q2–4), and 1.88 (95% CI 1.56–2.26) in the high-risk PRS group (Q5). The AUC was 0.570 (95% CI 0.554–0.587) for the regression model including age, sex, BMI, education, and index of relative socioeconomic advantage and disadvantage, and 0.589 (95% CI 0.572–0.605) when adding PRS to the model.

Additional adjustment for treatment group did not change the results for the association between PRS and risk of knee and hip replacement. There was no interaction between PRS and treatment group or obesity in the associations with risk of knee and hip replacement ($P > 0.32$ for all). While there was no interaction between PRS and sex in the associations with risk of knee replacement ($P > 0.25$ for all), there was some evidence of an interaction between PRS and sex in the associations with risk of hip replacement ($P = 0.045$ for PRS, $P = 0.25$ for medium-risk PRS category, and $P = 0.08$ for high-risk PRS category). Stronger associations between PRS and the risk of hip replacement were observed in women compared to men (Table 3). The OR of hip replacement in high-risk compared to low-risk PRS group was 2.19 (95% CI 1.70–2.83) in women compared to 1.57 (95% CI 1.20–2.05) in men.

Sensitivity analysis. Associations were similar when in-trial joint replacement hospitalizations and pretrial self-reported joint replacements were examined separately (Supplementary Tables 4 and 5 and Supplementary Figure 2, https://onlinelibrary.wiley.com/doi/10.1002/art.42156). The cumulative incidence of knee and hip replacement in relation to PRS categories is shown in Figure 2, considering only joint replacements occurring prospectively during the ASPREE trial and excluding participants with pretrial self-reported knee or hip replacement. The specificity of PRS was examined (Supplementary Table 6, https://onlinelibrary.wiley.com/doi/10.1002/art.42156). Higher hip PRS was associated with an increased risk of knee replacement after adjustment for confounders (OR 1.09 [95% CI 1.03–1.15] per SD of PRS), with knee replacement risk increased in the high-risk hip PRS category compared to the low-risk PRS category (OR 1.27 [95% CI 1.07–1.52]). There was no significant association between knee PRS and risk of hip replacement. The risk of knee and hip replacement against the middle half of the study population was also examined (Supplementary Table 7, https://onlinelibrary.wiley.com/doi/10.1002/art.42156). The OR of knee replacement was 0.81 (95% CI 0.70–0.93) in the low-risk PRS group (bottom 25%) and 1.09 (95% CI 0.95–1.24) in the

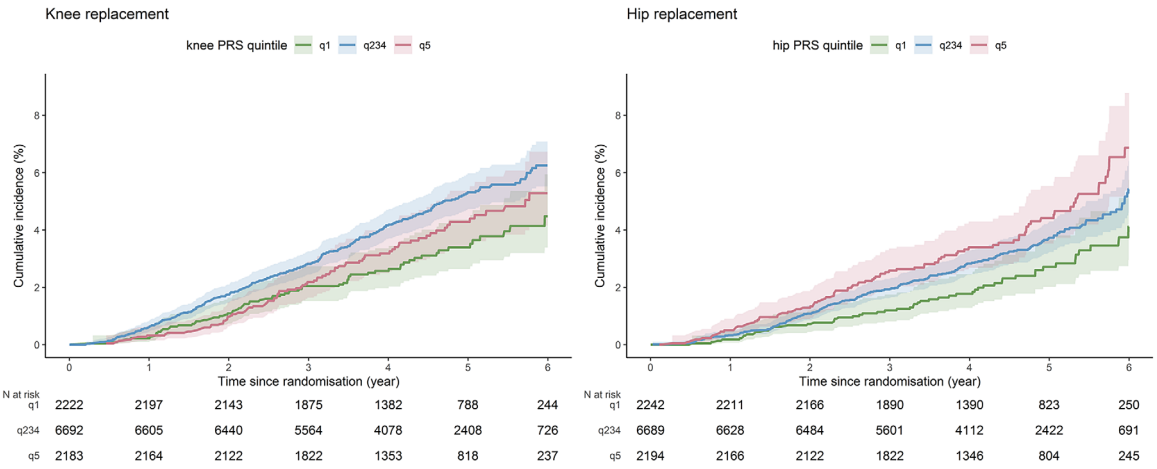

Figure 2. Cumulative incidence of knee and hip replacement in relation to categories of polygenic risk scores (PRS).

high-risk PRS group (top 25%). The OR of hip replacement was 0.80 (95% CI 0.68–0.93) in the low-risk PRS group and 1.40 (95% CI 1.22–1.60) in the high-risk PRS group.

DISCUSSION

We evaluated the performance of newly derived PRS for advanced OA requiring knee or hip replacement in a large genetic study of older community-dwelling individuals who were ambulatory and independently living at baseline. The current study is the first to present independent validation of PRS in relation to the risk of OA and demonstrated an association between specific knee and hip PRS and advanced OA, independent of age, sex, BMI, and socioeconomic status. We found meaningfully different risks of knee and hip replacement among low-risk (Q1), medium-risk (Q2–4), and high-risk (Q5) PRS groups, with stronger associations for hip replacement than knee replacement. Our results suggest that PRS have the potential to better target preventive interventions for severe OA by providing a personalized approach.

We demonstrated that specific genomic risk scores calculated separately for knee and hip OA (8) were associated with advanced OA requiring a knee or hip joint replacement in a well-characterized cohort of community-dwelling, ambulatory older adults, with data suggesting the specificity of knee PRS with less likelihood for hip PRS. We also found that the hip PRS was associated with a stronger risk for hip replacement compared to the knee PRS for knee replacement, independent of age, sex, BMI, and socioeconomic status. This was not unexpected, given that twin studies have suggested that ~70% of the variation in risk of hip OA can be attributed to genetic factors, compared to 45% for knee OA (22). These differences may reflect the stronger association of obesity, physical exertion, and injuries (strongly influenced by lifestyle factors) with knee OA, compared to hip OA (5,23,24).

Our findings are also consistent with evidence suggesting an important role of hip bone shape (strongly influenced by genetic factors) in the pathogenesis of hip OA (25). As there was a lower number of genetic variants for knee PRS compared to hip PRS (10 versus 38), the knee PRS would have lower power with a lower explained variance. The smaller number of variants that have been found for knee OA is probably due to a more heterogeneous etiology of knee OA compared to hip OA. Furthermore, we found stronger associations between hip PRS and risk of hip replacement in women than in men. Sex-specific differences in the anatomy and hip bone shape may alter the predisposition toward hip OA in men and women, and it may be that genetic factors affect the anatomy and hip bone shape or have other heterogeneous effects between sexes. The possible sex-specific association requires further investigation.

Although the overall ORs observed per SD PRS change for knee and hip replacements were modest (<1.3 per SD), individuals with a high-risk knee PRS had a 44% increased risk of knee replacement, and participants with a high-risk hip PRS had an 88% increased risk of hip replacement compared to those with a low-risk PRS. The magnitude of these associations was comparable to other PRS studies for different diseases and traits, where ORs per SD PRS typically range between 1.1 and 1.8 (e.g., ischemic stroke [26], coronary artery disease [27], and breast cancer [28]). Implementation of targeted therapy based on PRS has commenced for some conditions such as breast cancer and coronary artery disease (29). PRS associations with advanced knee OA and hip OA in our study remained significant when considering only incident joint replacements occurring prospectively during the ASPREE trial.

In the current study, we demonstrate that it is possible to develop a propensity score based on genetic risk, which is an independent risk factor for severe knee and hip OA requiring a joint replacement, independent of age, sex, BMI, and socioeconomic status. As the genotypes used to calculate a PRS do not change over the life course and are not influenced by environmental and lifestyle factors, PRS could act as an independent risk factor versus conventional clinical risk factors for OA. Access to information on genetic risk, prior to the manifestation of clinical symptoms, has the potential to improve compliance with preventive strategies and address risk factors earlier in the disease course. Genetic risk scores for OA therefore have the potential to be incorporated into decision support algorithms earlier in life, to improve targeting of interventions and clinical management. PRS could also potentially be used as part of the algorithm to identify "fast progressors" of OA for inclusion in clinical trials aimed at drug development.

Strengths of our study include the well-characterized, older study population with robust data on knee and hip replacements collected. The median age at recruitment was 75 years in a large community-based population of independently living older adults, allowing for observation of joint replacements in the most clinically relevant population and age group. Knee and hip replacements are valid measures of advanced OA in the context of the Australian healthcare system, as all Australian citizens and permanent residents have access to quality health care services including joint replacement under Australia's publicly funded universal health insurance system (Medicare). It also identifies an important OA outcome that needs to be prevented.

Limitations of our study include combining incident (hospitalizations during the trial) and prevalent (self-reported, before enrollment) joint replacements as a marker of advanced OA. The median age of TKR and THR is 69 years in Australia, with >85% of total joint replacement procedures performed in people ages >55 years (2). Therefore, including prevalent and incident joint replacements provides a more valid assessment of joint replacement as a marker of severe OA. The observed associations of the PRS were similar for incident versus prevalent joint replacements when analyzed separately, suggesting that there are not

major genetic differences with regard to risk of advanced OA between these groups. It may be that genetic influences are even higher in those who are younger and have a joint replacement. The population we examined, the ASPREE participants ages ≥70 years with a median age of 75 years at baseline, represents a significant proportion of all joint replacements, but does not include younger individuals who may be at particularly high genetic risk. Although we found a significant genetic component and validated the PRS for advanced OA in this older population, the genetic influence in younger individuals warrants further investigation.

The use of self-reported data may have overestimated the number of knee and hip replacements. Arthroscopy may have been misidentified for some self-reported joint replacements, but this is still likely to reflect OA, given that arthroscopies in this older population are most likely to have been performed for pathologic conditions such as meniscal pathology due to OA (30). The self-reported joint replacements occurred at a younger age (<70 years) when hip fracture is very uncommon. Another limitation of our study is limited details on the indication and type (primary or revision) of surgery recorded for hospitalization and/or self-reported joint replacements. However, in Australia, the majority of TKR and THR surgeries (98% and 89%, respectively) are performed in advanced OA, and a minority (10%) of joint replacement procedures are revision surgery for a primary joint replacement (2). Potential misclassifications of knee and hip replacement would most likely have been nondifferential and, if anything, may have underestimated the magnitude of observed PRS associations. Our results may not be generalizable to the general population since only relatively healthy older adults were included in the ASPREE trial, likely free of comorbid disease that is often present in OA patients.

In conclusion, our study demonstrates that genomic risk scores for advanced knee and hip OA are robustly associated with the risk of knee and hip replacement in older community-dwelling individuals, independent of age, sex, BMI, and socioeconomic status. There was a stronger association for the hip PRS than the knee PRS and for hip replacement risk in women. PRS have the potential to improve prevention of severe knee and hip OA by providing a personalized approach and identifying individuals who may benefit from early intervention.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Wang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lacaze, Wang, Cicuttini.
Acquisition of data. Lacaze, Franks.
Analysis and interpretation of data. Lacaze, Wang, Polekhina, Bakshi, Riaz, Owen, Abidi, Tiller, McNeil, Cicuttini.

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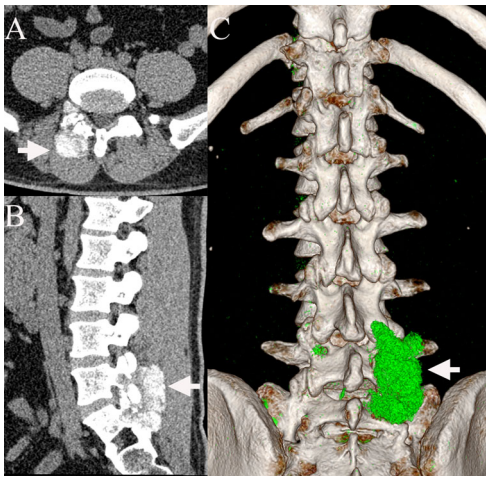
Clinical images: Gout of the spine



The patient, a 34-year-old man with a history of gout for >8 years, presented with symptoms of recurrent joint pain and lower back pain for 3 days. He had been receiving treatment with colchicine and benzbromarone starting in 2013. Laboratory tests revealed marked elevation in serum urate levels to 694 μmoles/liter (reference range 180–450 μmoles/liter). Conventional computed tomography (CT) of the axial (**A**) and sagittal (**B**) orientations revealed a hyperdense mass in the L5–S1 facet joint with bone erosion (**arrows**). Dual-energy CT revealed extensive urate crystal deposition within the lumbosacral facet joint (**arrow** in **C**). The findings were consistent with a diagnosis of spinal gout. The patient was started on colchicine, loxoprofen sodium, febuxostat, and sodium bicarbonate; the patient's symptoms were relieved within 1 week, and he was discharged from the hospital. Spinal gout is rarely encountered in clinical practice and therefore early recognition is important to allow timely diagnosis and prompt treatment, potentially averting unnecessary surgeries (1,2). Dual-energy CT may be useful in the diagnosis of spinal gout (1–3).

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