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Prospective associations of C-reactive protein (CRP) levels and CRP genetic risk scores with risk of total knee and hip replacement for osteoarthritis in a diverse cohort

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SUMMARY

Objective: To examine associations of high-sensitivity C-reactive protein (CRP) levels and polygenic CRP genetic risk scores (GRS) with risk of end-stage hip or knee osteoarthritis (OA), defined as incident total hip (THR) or knee replacement (TKR) for OA.

Design: This study included a cohort of postmenopausal white, African American, and Hispanic women from the Women's Health Initiative. Women were followed from baseline to date of THR or TKR, death, or December 31, 2014. Medicare claims data identified THR and TKR. Hs-CRP and genotyping data were collected at baseline. Three CRP GRS were constructed: 1) a 4-SNP GRS comprised of genetic variants representing variation in the CRP gene among European populations; 2) a multilocus 18-SNP GRS of genetic variants significantly associated with CRP levels in a meta-analysis of genome-wide association studies; and 3) a 5-SNP GRS of genetic variants significantly associated with CRP levels among African American women.

Results: In analyses conducted separately among each race and ethnic group, there were no significant associations of ln hs-CRP with risk of THR or TKR, after adjusting for age, body mass index, lifestyle characteristics, chronic diseases, hormone therapy use, and non-steroidal anti-inflammatory drug use. CRP GRS were not associated with risk of THR or TKR in any ethnic group.

Conclusions: Serum levels of ln hs-CRP and genetically-predicted CRP levels were not associated with risk of THR or TKR for OA among a diverse cohort of women.

Introduction

Osteoarthritis (OA) is a chronic, degenerative joint disease characterized by degradation of articular cartilage, thickening of subchondral bone, and synovial inflammation, leading to considerable pain, poor quality of life, and functional limitations[1]. OA is a disease of multifactorial etiology, with age, obesity, genetics, gender, and prior joint injury as major risk factors[2,3]. OA was previously considered a non-inflammatory condition, yet emerging evidence indicates that local and systemic inflammation play a role in OA pathogenesis[4–6].

Although the relationship between C-reactive protein (CRP) levels, a marker of systemic inflammation, and OA has been evaluated in several studies, findings have been conflicting[7–20].

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Furthermore, the role of systemic inflammation in advanced OA is currently unclear. In an early study, CRP levels were found to be modestly higher among women with early knee OA and significantly predicted radiographic progression, after adjustment for confounding factors including age, weight, and smoking[7]. However, others have shown that CRP levels are more closely related to OA symptoms than radiographic changes[8,9], and that CRP levels are not associated with OA independent of body mass index (BMI), a strong predictor of OA[10]. For example, increased serum levels of high-sensitivity CRP (hs-CRP) were associated with severity of pain, but not radiographic extent, among patients with severe hip or knee OA[8]. Prior studies were largely conducted among non-Hispanic white populations, restricting generalization of findings to other racial and ethnic groups. CRP levels vary by race and ethnicity and are higher among African American compared with white and Hispanic women, even after adjusting for cardiovascular risk factors[21]. Further, African Americans experience more severe hip and knee OA than whites, but it is unknown whether inflammatory processes explain racial and ethnic differences in OA risk[2]. Accordingly, the association of CRP with OA remains incompletely understood.

CRP analysis using serum is vulnerable to potential errors attributable to sampling and biological variations, confounding any associations. Genetic risk scores (GRS) comprised of genetic variants representing variations in levels of a biomarker, such as CRP or total cholesterol, have been used to circumvent issues associated with traditional biomarker measurement[22,23]. Because genetic variants are assigned at conception, they are not susceptible to measurement error, confounding, or reverse causation, thus serving as unbiased indicators of biomarker levels. Multiple genetic variants have been associated with CRP levels in genome-wide association studies (GWAS)[24,25]. However, the extent to which the accumulation of CRP level-influencing alleles from multiple genes predisposes to risk of hip or knee OA is unclear. To our knowledge, no study has evaluated the relationship between CRP GRS and OA in a racially and ethnically diverse cohort.

In this prospective study, we examined associations of serum hs-CRP levels and CRP GRS with risk of severe hip and knee OA, defined as incident total hip replacement (THR) or total knee replacement (TKR) for OA, among white, African American, and Hispanic women from the Women's Health Initiative (WHI). We constructed three literature-based GRS combining genetic markers associated with CRP in GWAS to test the hypothesis that there is an association between genetically-predicted CRP levels and risk of THR or TKR.

Methods

Study population

The WHI is an ongoing prospective study investigating major determinants of chronic diseases among women. Details of the study have been previously described[26]. Briefly, a racially and ethnically diverse cohort of 161,808 postmenopausal women aged 50–79 years old was recruited from 40 United States clinical centers between 1993 and 1998. Women participated in one or more of three clinical trials or an observational study.

Data from participants were linked to Medicare enrollment and utilization data by social security numbers, birth dates, and death dates. Medicare is the government health insurance program for US adults ages 65 years and older. The current study was exclusive to women who were continuously enrolled in fee-for-service Medicare from baseline until December 31, 2014 (the last day for which Medicare claims data were available) and who had baseline serum measurements of hs-CRP and/or genotyping data ($N = 5{,}972$) available. Detailed information on collection of hs-CRP measurements and genotyping data derived from multiple WHI GWAS are provided in the Supplementary Material. All participants provided written informed consent, and the Human Research Protections Program at the University of California, San Diego approved this study.

Identification of total knee and total hip replacement

TKR and THR for OA were identified from Medicare claims data using *International Classification of Diseases (Ninth Revision, Clinical Modification [ICD-9-CM])* procedure and diagnosis codes in the Medicare Provider Analysis and Review (MedPAR) data file, which includes hospitalization discharge data. TKR and THR for OA were identified by *ICD-9-CM* procedure codes 81.54 and 81.51, respectively, in combination with a principal diagnosis for OA (*ICD-9-CM* diagnosis code 715.xx) at the time of surgery (see Supplementary Table I for *ICD-9-CM* codes). Similar to previous studies[27], women with diagnosis codes for metastatic or bone cancer, joint infection, fractures, rheumatoid arthritis, or traumatic arthritis at the time of THR or TKR were excluded (Supplementary Table I). Furthermore, women who self-reported at baseline having a history of joint replacement or rheumatoid arthritis were excluded.

Single nucleotide polymorphism selection

Three GRS were constructed. The first GRS was comprised of four SNPs explaining variation in the *CRP* gene among European populations (Supplementary Table II): rs3093077, rs1205, rs1130864, and rs1800947[23,28]. The second GRS was comprised of 18 SNPs that were significantly associated with CRP levels at the genome-wide level ($P < 5 \times 10^{-8}$) in a meta-analysis of >80,000 individuals (Supplementary Table III): rs12037222, rs4420065, rs4129267, rs2794520, rs12239046, rs1260326, rs6734238, rs4705952, rs6901250, rs13233571, rs9987289, rs10745954, rs1183910, rs340029, rs10521222, rs2847281, rs4420638, and rs1800961[24,28]. A separate GRS for African American women only was constructed using five SNPs (rs16827466, rs6734238, rs7748513, rs7979473, and rs1160985) that were associated with CRP levels at the genome-wide level of significance in a GWAS among WHI African American women (Supplementary Table IV)[25]. Because no CRP GWAS has been conducted among Hispanic women, a separate GRS for this group could not be determined. For this analysis, it was assumed that each SNP was independently associated with the natural log of CRP levels under an additive genetic model.

Calculation of genetic risk scores

GRS were calculated by summing the number of CRP level-influencing alleles for each of the SNPs weighted by their estimated effect sizes from the original GWAS (Supplementary Tables II, III, and IV) using the following calculation: $ß_1{}^*SNP_1 + ß_2{}^*SNP_2 + ß_3{}^*SNP_3 + \ldots. ß_k{}^*SNP_k$, where $ß_k$ was the effect size, SNP_k was the allele dosage, and k was the total number of SNPs for each GRS. Effect sizes represented a one-unit increase in the natural log of CRP levels for each one-unit increase in dose of a CRP level-influencing allele. For directly-genotyped SNPs, data were coded as 0/1/2 (indicating the total number of CRP level-influencing alleles), and for imputed SNPs, the mean dosage of the allele (a value between 0 and 2) was used.

Covariates

Participants reported demographic characteristics, lifestyle behaviors, and medical history at baseline using self-administered

questionnaires. Demographic characteristics included race and ethnicity and education. Lifestyle behaviors included physical activity, smoking history, pack-years of smoking, and alcohol consumption. Trained clinic staff measured height and weight at baseline, with BMI calculated as weight in kilograms divided by height in meters squared and categorized using established cut-points[29]. Regular use of non-steroidal anti-inflammatory drugs (NSAIDs) was determined by direct examination of pill bottles brought to the clinic, and medication generic and trade names were converted into National Drug Codes from the Master Drug Data Base (Medi-Span, Indianapolis, IN). Hormone therapy use and history of major chronic diseases including coronary heart disease, cancer, diabetes, and chronic obstructive pulmonary disease were collected at the baseline visit through self-report.

Statistical analysis

Frequencies and proportions and means and standard deviations are presented for categorical and continuous variables, respectively. Descriptive characteristics were compared by ethnicity and THR or TKR using chi-square tests for categorical variables, and analysis of variance and Kruskal–Wallis tests for normally distributed and non-normally distributed continuous variables, respectively.

Associations between the natural logarithm (ln) of hs-CRP and risk of THR or TKR were determined using multivariable Cox proportional hazards regression models, with results presented as hazard ratios (HR) and 95% confidence intervals (CI). Separate analyses were conducted for white, African American, and Hispanic women, and for THR and TKR. Survival time was calculated from the date of the baseline study visit to the date of THR or TKR, date of death, or December 31, 2014, whichever came first. Women who received a THR or TKR for reasons other than OA were censored. Women whose hs-CRP levels were >10 mg/l (i.e., potentially indicating an acute infection) and those with missing data on covariates were excluded from multivariable models. Progressively-adjusted models were fit adjusting for age, education, BMI, pack-years of smoking, alcohol consumption, physical activity, chronic diseases, hormone therapy use, and NSAID use. Linear trend associations between hs-CRP and risk of THR or TKR are presented. The proportional hazards assumption was tested using Schoenfeld residuals and an interaction between CRP and time; however, violations of the assumption did not occur.

Associations between the three GRS and risk of THR or TKR were examined using Cox proportional hazards regression models adjusted for age, BMI, and the first five principal components to control for population stratification (see Supplementary Material). Analyses were conducted among each ethnic group separately. The African American and Hispanic cohorts are shown for comparison but were not sufficiently powered for GRS analysis due to small number of THR and TKR. Models were not adjusted for GWAS data source, as this factor did not appreciably alter the findings (data not shown). All GRS were divided into race-specific quartiles for analysis. Linear trend associations were tested by including GRS as continuous predictors in the multivariable models.

Statistical analyses were performed using Statistical Analysis Software (SAS) Version 9.3 (SAS Institute, Cary, NC). *P*-values were two-sided and considered statistically significant at $P < 0.05$.

Results

Descriptive characteristics

Women had a mean age of 70.3 (SD 3.9; range 64–79) years at baseline, and 80.8%, 15.6%, and 3.5% were white, African American, and Hispanic, respectively. Median follow-up time was 16.6 (interquartile range [IQR] 10.6–17.8) years for THR analyses and 16.2 (IQR 9.4–17.7) years for TKR analyses. During follow-up, 311 (6.4%) white, 35 (3.8%) African American, and 7 (3.3%) Hispanic women underwent THR for OA, and 608 (12.6%), 71 (7.6%), and 32 (15.2%) underwent TKR for OA, respectively.

At baseline, compared with other racial/ethnic groups, white women were more likely to be older, drink alcohol, and have greater pack-years of smoking (Table I). African American women were more likely than other racial/ethnic groups to be obese, have never used hormone therapy, and have a history of CHD, cancer, or diabetes. Mean baseline serum levels of ln hs-CRP were higher among African American and Hispanic compared with white women (1.1 vs 1.1 vs 0.8 mg/dl, respectively). Women with THR compared with those who did not undergo THR were more likely to be white, drink alcohol, and use NSAIDs (Supplementary Table V). Women with TKR compared with those who did not undergo TKR were more likely to be white, obese, and current hormone therapy users, and use NSAIDs (Supplementary Table VI).

Based on the 4-SNP GRS, the mean (SD; range) number of CRP level-influencing alleles among white, African American, and Hispanic women was 2.2 (1.1; 0–4.0), 2.5 (1.1; 0–5.0), and 2.2 (1.1; 0–4.0), respectively (Table I). The 4-SNP weighted GRS explained 2.4%, 0.8%, and 1.5% of ln hs-CRP variation in white, African American, and Hispanic women, respectively. According to the 18-SNP GRS, the mean (SD; range) number of CRP level-influencing alleles was 21.8 (2.6; 12.0–30.0), 21.6 (2.2; 15.2–29.0), and 20.7 (2.8; 10.0–29.0), respectively, among the ethnic groups. The 18-SNP weighted GRS explained 7.2%, 2.1%, and 10.8% of ln hs-CRP variation in white, African American, and Hispanic women, respectively. Finally, the mean (SD; range) number of CRP level-influencing alleles for the 5-SNP GRS among African American women was 4.6 (1.5; 0–10.0). The 5-SNP weighted GRS explained 4.2% of the variation in ln hs-CRP among African American women.

Associations between ln hs-CRP and risk of total hip and total knee replacement

In all models, there were no significant associations between ln hs-CRP and risk of THR among white or African American women (Table II). There were no significant linear trend associations between ln hs-CRP and risk of THR in either ethnic group.

Among white women, there was a significant linear association between ln hs-CRP and risk of TKR ($P = 0.02$) in the age-adjusted model (Table III); however, after additional adjustment for BMI, findings were no longer significant. A similar pattern was observed among African American women. Among Hispanic women, there were no associations of ln hs-CRP with risk of TKR in any models.

Associations between GRS and risk of total hip and total knee replacement

There were no significant associations of the 4-SNP GRS combining SNPs covering *CRP* variation with risk of THR among white (Table IV) or African American (Supplementary Table VII) women, and linear trend associations were not significant. The 4-SNP GRS was not significantly associated with risk of TKR in white (Table IV), African American (Supplementary Table VII), or Hispanic women (Supplementary Table VII). Similarly, the 18-SNP GRS combining significant SNPs from a published CRP meta-analysis was not significantly associated with risk of THR or TKR in any ethnic group, and linear trend associations were not significant (Table V and Supplementary Table VIII). Finally, the five-SNP GRS using SNPs from a CRP GWAS among WHI African American

Table I
Baseline characteristics by race/ethnicity ($N = 5972$)

	White ($N = 4827$)	African American ($N = 934$)	Hispanic ($N = 211$)	*P*-value
Age, years	70.5 ± 3.9	69.6 ± 3.8	68.7 ± 3.5	<0.001
Education				
Less than high school	194 (4.0)	106 (11.5)	32 (15.4)	<0.001
High school	955 (19.8)	123 (13.3)	35 (16.8)	
Some college	1930 (40.1)	320 (34.6)	71 (34.1)	
College graduate	1735 (36.0)	375 (40.6)	70 (33.7)	
Pack years of smoking				
Never smoker	2481 (53.5)	454 (51.2)	133 (64.6)	<0.001
<5	545 (11.7)	122 (13.8)	33 (16.0)	
5-<20	591 (12.7)	136 (15.4)	23 (11.2)	
≥20	1024 (22.1)	174 (19.6)	17 (8.3)	
Alcohol consumption				
Non-drinker	530 (11.1)	150 (16.4)	32 (15.5)	<0.001
Past drinker	827 (17.2)	312 (34.2)	40 (19.3)	
Current drinker	3439 (71.7)	451 (49.4)	135 (65.2)	
Body mass index, kg/m^2				
Normal	1611 (33.6)	185 (20.0)	61 (28.9)	<0.001
Overweight	1788 (37.3)	340 (36.8)	93 (44.1)	
Obese	1391 (29.0)	398 (43.1)	57 (27.0)	
Total physical activity, MET-h/wk	11.7 ± 12.8	10.1 ± 12.6	13.8 ± 14.9	<0.001
Hormone therapy use				
Never used hormones	2333 (49.5)	493 (53.4)	88 (42.9)	<0.001
Past hormone user	1597 (33.9)	260 (28.1)	45 (22.0)	
Current hormone user	780 (16.6)	171 (18.5)	72 (35.1)	
NSAID use	877 (18.2)	178 (19.1)	37 (17.5)	0.78
History of chronic diseases				
CHD	223 (4.7)	65 (7.2)	7 (3.4)	0.005
Cancer	289 (6.1)	91 (9.9)	12 (5.7)	<0.001
Diabetes	259 (5.4)	168 (18.0)	14 (6.6)	<0.001
COPD	202 (4.5)	42 (4.7)	4 (2.0)	0.21
Natural logarithm serum CRP, mg/dl	0.8 (1.0)	1.1 (1.1)	1.1 (1.0)	<0.001
Unweighted genetic risk score from CRP SNPs among European populations	2.2 ± 1.1	2.5 ± 1.1	2.1 ± 1.1	<0.001
Unweighted genetic risk score from published meta-analysis of CRP	21.8 ± 2.6	21.6 ± 2.2	20.7 ± 2.8	<0.001

Note. Data are presented as n (%) or mean (SD).

women was not significantly associated with risk of THR or TKR in this group (Supplementary Table IX).

Discussion

In a prospective study among a racially and ethnically diverse cohort of postmenopausal women, CRP GRS did not significantly predict risk of incident THR or TKR for OA during a median 16 years of follow-up. Specifically, a 4-SNP GRS composed of SNPs representing variation in the *CRP* gene in European populations, and an 18-SNP polygenic GRS composed of SNPs significantly associated with CRP levels in a meta-analysis of GWAS, were not significantly associated with risk of THR or TKR. Finally, serum levels of ln hs-CRP were not associated with risk of THR or TKR.

Our findings are in accord with previous studies showing no associations between serum CRP levels and hip or knee OA[8,10,13,16]. A population-based study among Europeans did not observe any

Table II
Multivariable associations of serum ln hs-CRP with risk of THR for osteoarthritis

	ln hs-CRP, mg/l HR (95% CI)	*P* for trend
White Women		
Model 1*	1.02 (0.87–1.19)	0.85
Model 2†	0.96 (0.80–1.14)	0.62
Model 3‡	0.97 (0.81–1.17)	0.76
Model 4§	0.96 (0.80–1.16)	0.67
African American Women		
Model 1*	0.82 (0.57–1.18)	0.28
Model 2†	0.71 (0.48–1.04)	0.08
Model 3‡	0.68 (0.45–1.02)	0.07
Model 4§	0.69 (0.45–1.07)	0.09

* Adjusted for age.
† Adjusted for model 2 + body mass index.
‡ Adjusted for model 3 + education, pack-years of smoking, alcohol consumption, and physical activity.
§ Adjusted for model 4 + chronic diseases (coronary heart disease, cancer, diabetes, and COPD), hormone therapy use, and non-steroidal anti-inflammatory drug use.

Table III
Multivariable associations of serum ln hs-CRP with risk of TKR for osteoarthritis

	ln hs-CRP, mg/l HR (95% CI)	*P* for trend
White Women		
Model 1*	1.16 (1.03–1.30)	0.02
Model 2†	0.91 (0.80–1.04)	0.16
Model 3‡	0.93 (0.81–1.07)	0.31
Model 4§	0.94 (0.82–1.09)	0.42
African American Women		
Model 1*	1.39 (1.05–1.85)	0.02
Model 2†	1.12 (0.82–1.51)	0.48
Model 3‡	1.14 (0.83–1.58)	0.41
Model 4§	1.21 (0.85–1.72)	0.29
Hispanic Women		
Model 1*	1.25 (0.78–1.99)	0.35
Model 2†	0.93 (0.55–1.56)	0.78
Model 3‡	0.69 (0.37–1.26)	0.22
Model 4§	0.66 (0.33–1.31)	0.23

* Adjusted for age.
† Adjusted for model 2 + body mass index.
‡ Adjusted for model 3 + education, pack-years of smoking, alcohol consumption, and physical activity.
§ Adjusted for model 4 + chronic diseases (coronary heart disease, cancer, diabetes, and COPD), hormone therapy use, and non-steroidal anti-inflammatory drug use.

Table IV
Multivariable associations of a genetic risk score of SNPs covering *CRP* gene variation with risk of total joint replacement for hip or knee osteoarthritis among white women

	Genetic risk score quartile				*P* for trend
	Quartile 1 HR (95% CI)	Quartile 2 HR (95% CI)	Quartile 3 HR (95% CI)	Quartile 4 HR (95% CI)	
Total hip replacement					
Model 1*	1 [Ref]	0.99 (0.66–1.46)	1.22 (0.83–1.78)	1.14 (0.76–1.72)	0.25
Model 2†	1 [Ref]	0.97 (0.65–1.44)	1.21 (0.83–1.76)	1.13 (0.75–1.69)	0.28
Total knee replacement					
Model 1*	1 [Ref]	1.00 (0.80–1.25)	1.10 (0.89–1.37)	1.04 (0.82–1.31)	0.47
Model 2†	1 [Ref]	1.01 (0.80–1.26)	1.09 (0.88–1.36)	1.00 (0.79–1.27)	0.66

* Adjusted for age + population stratification.
† Adjusted for model 1 + body mass index.

Table V
Multivariable associations of a genetic risk score of significant SNPs from a published meta-analysis of CRP with risk of total joint replacement for hip or knee osteoarthritis among white women

	Genetic risk score quartile				*P* for trend
	Quartile 1 HR (95% CI)	Quartile 2 HR (95% CI)	Quartile 3 HR (95% CI)	Quartile 4 HR (95% CI)	
Total hip replacement					
Model 1*	1 [Ref]	0.87 (0.63–1.21)	1.02 (0.75–1.41)	1.17 (0.86–1.60)	0.63
Model 2†	1 [Ref]	0.87 (0.63–1.20)	1.02 (0.74–1.41)	1.14 (0.84–1.56)	0.76
Total knee replacement					
Model 1*	1 [Ref]	0.93 (0.75–1.17)	0.89 (0.71–1.13)	1.04 (0.83–1.30)	0.43
Model 2†	1 [Ref]	0.91 (0.72–1.14)	0.86 (0.68–1.08)	1.02 (0.82–1.28)	0.54

* Adjusted for age + population stratification.
† Adjusted for model 1 + body mass index.

associations of CRP levels, including no threshold effect, with the prevalence, incidence, or progression of radiographic hip or knee OA, after accounting for BMI[10]. Another study among a European population did not observe any associations of CRP levels with risk of THR or TKR for OA, after adjusting for age, gender, BMI, and lifestyle factors[16]. In contrast, a study among white and African American women observed that CRP levels were higher among those with incident knee OA and were strongest among obese women[14]; however, findings were not adjusted for or stratified by race. A study among middle-aged to older white and African American adults observed no association between hs-CRP and incident radiological knee OA, osteophyte formation, or joint space narrowing[13]. Similarly, our findings suggest that CRP levels are not associated with risk of THR or TKR in white or African American women and do not support a role of systemic inflammation, as measured by CRP, in predicting end-stage hip or knee OA.

Only one prior study examined the relationship between CRP GRS and OA[28]. In this Mendelian randomization study among 5,755 knee OA cases and 18,505 controls, there was no association between the 4-SNP CRP GRS and risk of knee OA, but there was a 17% (HR, 1.17; 95% CI, 1.01–1.36) increased risk of knee OA per 1 mg/l increase in ln CRP for the 18-SNP polygenic GRS[28]. However, this previous study did not examine hip OA; was exclusive to European populations; employed a case-control design; used summary- rather than individual-level data; and examined knee OA overall, without consideration of different OA phenotypes. Given that OA is a heterogeneous disease with many clinical phenotypes[30], it is necessary to distinguish different OA outcomes, such as early knee OA or end-stage knee OA as indicated by TKR. We specifically examined total joint replacement as a marker of severe OA; nevertheless, we cannot rule out the possibility that CRP GRS may predict other OA phenotypes that manifest throughout the disease course, such as radiographic progression.

In a study among white men and women from the Rotterdam Study, CRP haplotypes representing genetic variation in the *CRP* gene were not associated with the prevalence, incidence, or radiographic progression of hip or knee OA[10]. These studies were conducted in white populations and did not examine racial and ethnic differences. Racial and ethnic minorities have not been adequately represented in studies examining GRS as predictors of adverse health outcomes. Due to heterogeneity in genetic architecture between individuals of varying ancestry[31], further studies of CRP GRS derived using significant genetic variants from ancestry-specific GWAS are currently needed to determine their utility in OA prediction. We did not observe any association between CRP GRS and risk of THR or TKR in any racial or ethnic group. However, the African American and Hispanic cohorts were not sufficiently powered to draw conclusive results at a population level.

There is evidence that both local and systemic inflammation contribute to OA pathogenesis[5,32]. Specifically, interleukin 1β (IL-1β), tumor necrosis factor (TNF), and interleukin 6 (IL-6) are the main proinflammatory cytokines that play major roles in OA[33]. Levels of IL-1β and TNF are elevated in the synovial fluid, synovial membrane, subchondral bone, and cartilage in OA patients[33]. Furthermore, IL-1β and TNF induce the production of many proinflammatory cytokines, such as IL-6, leading to OA disease progression[33]. Higher levels of systemic hs-CRP may reflect local inflammatory findings in the joints of OA patients. For example, a previous study observed a significant correlation between synovial fluid IL-6 levels and systemic hs-CRP levels, suggesting that systemic hs-CRP reflects synovial inflammation[34]. Some have observed that inflammation plays a greater role early in the disease course than in end-stage OA[5]. This may partly explain the lack of association between ln hs-CRP and CRP GRS with hip or knee OA in our study, as we only examined end-stage disease as reflected by TKR and THR.

Our study has some limitations. There was a smaller number of African American and Hispanic compared with white women with THR or TKR. We used THR and TKR as proxies for severe hip and knee OA, respectively, and, because we were not able to assess

radiographic OA status at baseline or during follow-up, we may have missed other severe cases of OA. We only used a single measurement of hs-CRP measured at baseline and did not have repeated measurements. While all women had access to Medicare coverage, African American women have been shown to undergo total joint replacement less frequently than white women[35], despite experiencing higher incidence and prevalence of OA. Therefore, unmeasured health service and cultural factors may have contributed to the overall lack of associations and direction of non-significant associations in African-American women.

Major strengths of our study include the prospective design and diverse cohort of white, African American, and Hispanic women, allowing us to examine CRP-OA associations in each ethnic group separately. We evaluated the association between genetically-predicted CRP and risk of THR or TKR for OA, an important consideration given that serum levels of CRP are vulnerable to confounding and reverse causation.

In summary, serum levels of ln hs-CRP and multilocus CRP GRS were not associated with risk of THR or TKR among older white, African American, or Hispanic women. Additional studies in diverse cohorts with longitudinal hs-CRP measurements and other serum inflammatory markers are needed to confirm our findings. Further studies that follow patients without OA from baseline are also needed to determine whether CRP is a stronger predictor of early compared with end-stage disease and to define how this biomarker relates to changes in radiographic severity over time. Finally, GWAS of CRP need to be conducted in diverse populations to enable construction of ethnic-specific CRP GRS. We conclude that the evidence reported to date suggests no association of low-grade systemic inflammation as measured by CRP levels or genetic risk of higher CRP levels with incident THR or TKR among women.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.joca.2018.05.002.

Author contributions

A.H.S. wrote the manuscript and conducted the statistical analysis. A.H.S. and A.Z.L. designed the study and were involved in the acquisition of data. All authors were involved in the interpretation of the data, revised it critically for important intellectual content, and approved the final version. A.H.S (email: aladdinhs@yahoo.com). takes responsibility for the integrity of the work as a whole.

Conflict of interest statement

The authors declare no conflicts of interest.

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