Radiology

Statin Use and Knee Osteoarthritis Outcome Measures according to the Presence of Heberden Nodes: Results from the Osteoarthritis Initiative

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Background: The exact contribution of statins to knee osteoarthritis (OA) radiographic outcomes and the characteristics of patients with OA as potential responders to statins remain unclear.

Purpose: To evaluate the effect of statin use on the incidence of radiographic knee OA (development of Kellgren-Lawrence grade ≥2) and progression of joint space narrowing (JSN) according to the nodal OA status defined according to the presence of Heberden nodes (HNs).

Materials and Methods: Institutional review boards approved this HIPAA-compliant protocol, and all participants gave informed consent. The Osteoarthritis Initiative (OAI) cohort, which began in 2004 and is ongoing (*https://clinicaltrials.gov* identifier, NCT00080171), was used to conduct a longitudinal 1:1 propensity score–matched retrospective analysis of prospectively collected data. Participants were classified as having HN-positive or HN-negative findings according to the presence of HNs at baseline physical examination. In each cohort, per-protocol and new-user design were used to match statin initiators (participants who reported ≤1 year of statin use before enrollment) and nonusers (participants who reported no statin use before enrollment) for variables that potentially contributed to confounding by indication bias. Participants were followed up annually over 8 years. Any associations between statin use and longitudinal knee OA radiographic incidence, JSN progression, or nonacceptable symptomatic state incidence was assessed by using hazard ratios (HRs) of Cox regression.

Results: In the longitudinal analysis, there were 832 knees of 602 participants (pair-matched knees of statin initiators and nonusers) in the HN-positive cohort (mean age, 64.7 years ± 8.0 [standard deviation]; 377 patients were female [62.6%]) and 386 knees of 285 participants in the HN-negative cohort (mean age, 58.9 years ± 8.2; 144 patients were female [50.5%]). In the HN-positive cohort, statin users had 46% lower risk of JSN progression in comparison with matched nonusers (HR, 0.54; 95% confidence interval [CI]: 0.36, 0.93; $P = .02$). In contrast, in the HN-negative cohort, statin use had no association with radiographic JSN progression (HR, 1.37; [95% CI: 0.74, 2.53]; $P = .32$).

Conclusion: Statin use was associated with reduced risk of radiographic knee osteoarthritis joint space narrowing progression in patients with nodal osteoarthritis.

Online supplemental material is available for this article.

Statins are widely prescribed to asymptomatic and symptomatic patients as a prevention therapy for cardiovascular disorders (1). In addition to their lipid-lowering capabilities, statins are believed to have pleiotropic effects that may be mediated by antioxidant properties and inhibition of inflammatory processes (2).

Despite research focusing on developing disease-modifying osteoarthritis (OA) drugs, to our knowledge, no disease-modifying OA drugs have been proven to be effective in slowing OA-related structural damage progression (3,4). There has been recent interest in the potential role of statins as a disease-modifying knee OA drug. Some studies suggested a protective role for statin use against knee OA outcomes (5–7). In this regard, to date, one cross-sectional study from the Osteoarthritis Initiative (OAI) has shown an association between statin use and lower prevalence of knee OA in a subgroup of 238 patients with generalized OA (8); however, two other studies found no significant association with the longitudinal risk of radiographic knee OA progression in all OAI participants (9,10). These

Abbreviations

CI = confidence interval, HN = Heberden node, HR = hazard ratio, JSN = joint space narrowing, NASS = nonacceptable symptom state, OA = osteoarthritis, OAI = Osteoarthritis Initiative, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Summary

This observational analysis shows that statin use may reduce the risk of radiographic knee joint space narrowing progression in patients with nodal (Heberden node–positive) knee osteoarthritis, indicative of a distinct pleiotropic statin effect.

Key Results

- In a longitudinal analysis, the risk of radiographic joint space narrowing progression in statin initiators (ie, incident users with ≤1 year of statin use before enrollment) with nodal (Heberden node [HN]-positive) osteoarthritis (OA) was 46% lower than that in nonusers (hazard ratio, 0.54; $P = .02$).
- No significant association between statin use and radiographic incidence or symptom outcomes was detected in the HN-positive or HN-negative cohorts.
- In a cross-sectional analysis, the baseline Kellgren-Lawrence grade in participants with nodal OA and history of statin use for more than 1 year (ie, prevalent users) was lower than that in matched nonusers (odds ratio, 0.89; 95% confidence interval: 0.80, 0.98; $P = .02$).

overall disparate results could be due to several factors, including the possibility of biases in these observational studies (ie, confounding by indication and Neyman bias) and perhaps most importantly, heterogeneous patient selection considering OA causes and phenotypes.

With regard to heterogeneity of OA phenotypes, nodal OA has been described in several reports. Heberden nodes (HNs) are bony enlargements in the distal interphalangeal joints and are clinically characteristic of nodal OA and are a hallmark of generalized OA (11). It has been shown that nodal OA, with a heritability rate of 42% and a prevalence of 13.9%–42% among all patients with knee OA, has distinct pathophysiology when compared with other causes of knee OA (eg, posttraumatic OA) (12,13). Despite the relatively limited evidence around the pathophysiology of generalized OA, it has been reported that a combination of elevated inflammatory mediators (eg, matrix metalloproteinases), oxidative stress, and lipid dysregulation may be involved (14,15)—all of which could be potentially modulated with statin use. Accordingly, we hypothesized that statin use might have protective effects against knee OA progression in patients with nodal OA phenotype. Thus, we evaluated the effect of statin use on radiographic knee osteoarthritis incidence and progression over 8 years according to nodal osteoarthritis status defined as the presence of Heberden nodes.

Materials and Methods

Data Source

We used all available data from participants in the ongoing longitudinal multicenter OAI study (clinicaltrials.gov identifier: NCT00080171). From February 2004 to May 2006, 4796 participants (9592 knees) with or at risk for knee OA were recruited and observed until the time of this writing. All enrolled patients gave written informed consent (16). Details of the study can be found at the online portal (17). The Health Insurance Portability and Accountability Act–compliant protocol of the OAI study was approved by the institutional review boards of four OAI collaborating centers. The OAI dataset files used in our study are listed in Table E1 (online). All previously published studies that used the OAI dataset are listed at the online portal (18).

Study Design and Subgroups

We performed a secondary analysis on prospectively collected data. During the baseline physical examination, a trained clinical examiner assessed the presence of HNs in the distal interphalangeal joints on the second through fifth digits and the interphalangeal joint of the first digit according to the OAI physical examination protocol (16). We used these data to define two separate subgroups based on the presence or absence of at least one HN (Fig 1). Because of the retrospective analysis of the prospectively collected data, subgroups were not prespecified during data acquisition. Within each subgroup, all available relevant data were extracted (17). Study design and analysis were performed by a musculoskeletal radiologist (S.D., 8 years of experience) and two medical graduate postdoctoral fellows (B.M., A.H.M.; each with 2 years of experience).

Statin Exposure

According to the OAI protocol, participants were asked to bring their medications to each visit; staff recorded information on statin type and frequency and duration of use. Statin types included were atorvastatin, lovastatin, fluvastatin, simvastatin, pravastatin, and rosuvastatin.

At the baseline visit, participants who reported regular statin use before enrollment were categorized as statin users; participants with no history of statin use were categorized as nonusers. Among the participants who used statins, those with 1 year or less of regular use before enrollment were termed *statin initiators* (ie, incident users), while participants with more than 1 year of regular use were termed *prevalent users* (Fig 1).

At follow-up visits, reporting regular use of statins during the past 12 months was coded as statin use for that year. To account for incident-prevalent bias in the longitudinal analysis, only statin initiators and their matched nonusers were included. Statin initiators (≤1 year of use before enrollment) and nonusers (no statin use before enrollment) were assessed in the longitudinal analysis until their last annual follow-up visit during the 8 years of follow-up (1st-, 2nd-, 3rd-, 4th-, 6th-, 7th- [only symptoms in 7th year], and 8th-year visits). Also, per the per-protocol approach used by Danaie et al (19), participants classified as nonusers who started statin use during follow-up and those classified as initiators who discontinued statin use during follow-up were censored from longitudinal analysis at that time point.

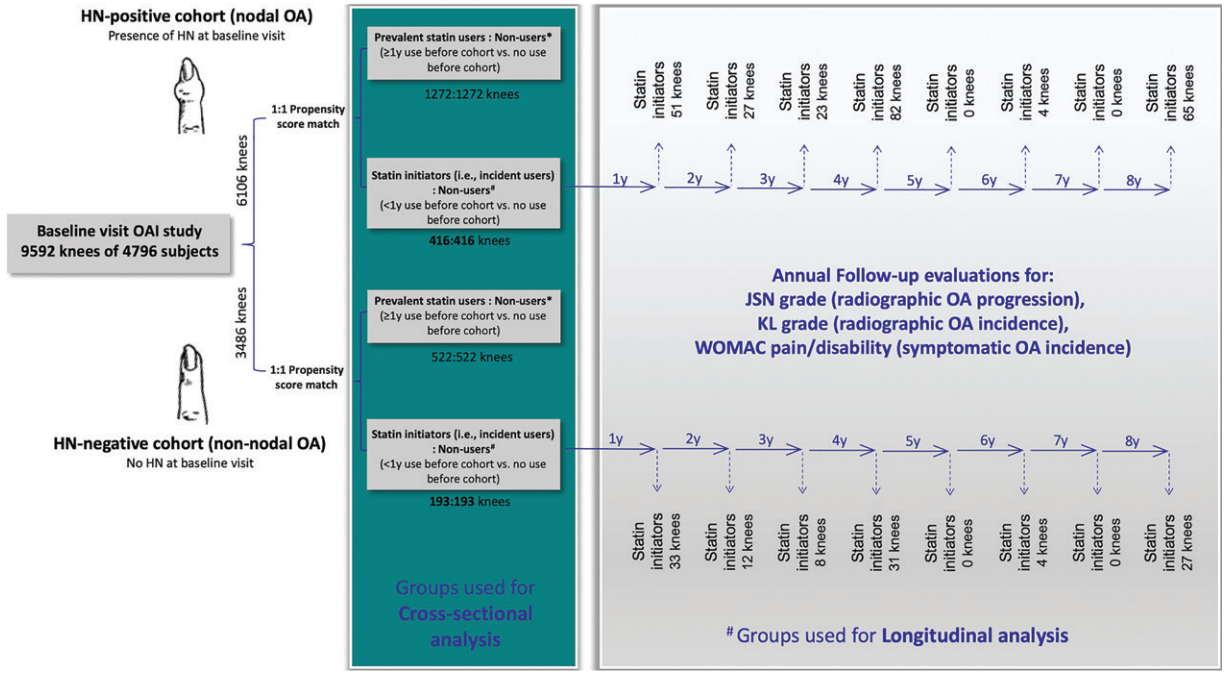

Figure 1: Flow diagram of study knees and their categorization according to the presence of Heberden node (HN) and statin use. Presented numbers in each follow-up visit are the number of knees (statin users) censored annually during follow-up Osteoarthritis Initiative (OAI) visits due to per-protocol design or last visit available data or incidence of the outcome, osteoarthritis (OA) radiographic joint space narrowing (JSN) progression. All numbers were presented for statin initiators and JSN progression as an outcome. Numbers of excluded knees or knees with JSN progression at each annual visit are slightly different for the matched nonusers and other outcomes including radiographic OA incidence and symptomatic incidence. KL = Kellgren-Lawrence, KOA = knee osteoarthritis, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Propensity Score Matching

Possible confounders were investigated by using a direct acyclic graph to assess causal inference (20) (Fig E1 [online]). The pattern of missing data was assessed by using the test of missing completely at random (Little test) (20,21). A list of confounding variables and details of the Little test are presented in Appendix E1 (online). On the basis of the per-protocol approach (19), we matched statin users (both incident and prevalent users) to nonusers by using the 1:1 propensity score matching method on the imputed dataset, using logistic regression and the nearest neighbor matching method. Standardized mean difference was used to evaluate matching between groups, with a value of 0.1 or higher indicating an imbalance.

Outcomes and Follow-Up

Primary outcomes were defined to cover radiographic knee OA incidence and progression. Radiographic outcomes were assessed by using posteroanterior radiographs with a fixed-flexion (15°) protocol (16). Knee radiographs were read at one OAI center and were scored with semiquantitative Kellgren-Lawrence grades and medial joint space narrowing (JSN) Osteoarthritis Research Society International methods at baseline and annual follow-up (22). The reliability of the central OAI readings was evaluated and confirmed previously (23). According to the OAI predefined outcomes, radiographic OA incidence was defined as development of Kellgren-Lawrence grade of 2 or higher in follow-up assessments of knees with baseline Kellgren-Lawrence grades of 0–1. Radiographic progression of JSN was defined as definite full-grade progression of tibiofemoral JSN score of 1 or higher during the annual follow-up assessments of knees with JSN grade 0–2 at baseline (22).

A secondary outcome of the study was patient-reported symptomatic incidence of knee OA, which was assessed by using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire for pain and disability. WOMAC pain and disability scores were standardized to a range of 0–100 and were summed, resulting in a standardized combined WOMAC score. Nonacceptable symptom state (NASS) incidence was defined as a combined standardized WOMAC pain or disability score of 80 or higher in 2 consecutive years in knees with a baseline score of less than 80 (24).

Statistical Analysis

All statistical analyses were performed separately in the HN-positive and HN-negative cohorts. In the cross-sectional analysis, we evaluated the association between statin use and knee OA radiographic features (Kellgren-Lawrence grade, JSN grade) and symptoms (WOMAC scores) by using linear mixed models to include clusters of matched participants and address within-participant similarity caused by the inclusion of both knees in a minority of participants. Both prevalent and incident users were separately compared with matched nonusers.

Table 1: Baseline Characteristics of the Study Population before and after Propensity Score Matching according to Presence of Heberden Nodes and Statin Use in the Heberden Node–positive Group

Characteristic	All OAI Participants			Propensity Score–matched Participants		
	Statin Users	Statin Nonusers	SMD	Statin Users	Statin Nonusers	SMD
No. of knees	1698	4408	...	1686 (416 + 1270)*	1686	...
	Variables Included in the Propensity Score Matching Model					
Age (y)†	66.0 ± 7.6	62.3 ± 9.0	0.44	65.9 ± 7.6	65.5 ± 8.4	0.05
Women†‡	65.8 ± 7.2	62.7 ± 8.8	0.31	65.7 ± 7.2	66.0 ± 8.1	0.03
Men†‡	66.3 ± 8.1	61.6 ± 9.3	0.54	66.1 ± 8.1	64.8 ± 8.7	0.16
No. of women	980 (57.7)	2812 (63.8)	0.13	978 (58.0)	1009 (59.8)	0.04
BMI (kg/m²)†	29.2 ± 4.40	28.0 ± 4.7	0.28	29.2 ± 4.4	29.2 ± 4.7	0.01
PASE score†	143.6 ± 73.1	161.1 ± 81.3	0.23	144.2 ± 73.0	148.0 ± 79.3	0.05
Smoking history	...	...	0.15	...	...	0.08
Never smoked	835 (49.2)	2405 (54.6)	NA	833 (49.4)	867 51.4)	NA
Past smoker	785 (46.2)	1732 (39.3)	NA	775 (46.0)	730 (43.3)	NA
Smoker <14 cigarettes per day	52 (3.1)	156 (3.5)	NA	52 (3.1)	48 (2.8)	NA
Smoker ≥14 cigarettes per day	26 (1.5)	115 (2.6)	NA	26 (1.5)	41 (2.4)	NA
Alcohol use	...	...	0.07	...	...	0.02
<1 drink per week	965 (56.8)	2488 (56.4)	NA	960 (56.9)	970 (57.5)	NA
1–3 drinks per week	215 (12.7)	656 (14.9)	NA	215 (12.8)	214 (12.7)	NA
4–7 drinks per week	267 (15.7)	666 (15.1)	NA	265 (15.7)	256 (15.2)	NA
8–14 drinks per week	163 (9.6)	404 (9.2)	NA	160 (9.5)	165 (9.8)	NA
>15 drinks per week	88 (5.2)	194 (4.4)	NA	86 (5.1)	81 (4.8)	NA
Comorbid condition§	702 (41.3)	1197 (27.2)	0.30	690 (40.9)	690 (40.9)	<0.01
White race‖	280 (16.5)	701 (15.9)	0.02	275 (16.3)	267 (15.8)	0.01
	Variables Not Included in the Propensity Score Matching Model					
Knee injury	429 (25.3)	1187 (26.9)	0.04	428 (25.4)	438 (26.0)	0.01
NSAID use	146 (8.6)	408 (9.3)	0.02	146 (8.7)	158 (9.4)	0.03
Hyaluronic acid IA injection	14 (0.8)	22 (0.5)	0.04	12 (0.7)	7 (0.4)	0.04
Steroid IA injection	70 (1.6)	36 (2.1)	0.04	36 (2.1)	28 (1.7)	0.04
Statin name						
Atorvastatin	884 (52.1)	NA	NA	877 (52.0)	NA	NA
Fluvastatin	28 (1.6)	NA	NA	28 (1.7)	NA	NA
Lovastatin	88 (5.2)	NA	NA	88 (5.2)	NA	NA
Pravastatin	172 (10.1)	NA	NA	172 (10.2)	NA	NA
Rosuvastatin	64 (3.8)	NA	NA	64 (3.8)	NA	NA
Simvastatin	462 (27.2)	NA	NA	457 (27.1)	NA	NA
Hydrophilic statin type**	236 (13.9)	NA	NA	236 (14.0)	NA	NA

Note.—Unless otherwise indicated, data are number of knees, with the percentage in parentheses. BMI = body mass index, IA = intra-articular injection, NA = not applicable, NSAID = nonsteroidal anti-inflammatory drug, OAI = Osteoarthritis Initiative, PASE = Physical Activity Scale for the Elderly, SMD = standardized mean difference. Significant difference for SMD was defined as ≥ 0.1.

* Data in parenthesis are numbers of incident and prevalent statin users, respectively.

† Data are mean ± standard deviation.

‡ There was no significant difference between age of men and age of women after matching.

§ Comorbid condition was defined as presence of either history of coronary artery disease, cerebrovascular accident, diabetes (any stage of diabetes vs no medical history of diabetes), or hypertension in physical examination systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg at OAI physical examinations).

‖ Race was categorized as white or nonwhite, considering the small number of participants in each nonwhite race group.

** Statin type was defined based on hydrophilic affinity. Pravastatin and rosuvastatin were classified as hydrophilic agents, and the remaining statins were classified as lipophilic drugs.

In the longitudinal analysis, we conducted Cox proportional hazards regression to examine associations between statin use and outcome. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. All regression modeling was conducted by using complex sample analysis in which matched users and nonusers and same-participant knees were included in the specific clusters with equal weight. On the basis of a per-protocol approach (19), matched statin

Table 2: Baseline Characteristics of the Study Population before and after Propensity Score Matching according to Presence of Heberden Nodes and Statin Use in the Heberden Node–negative Group

Characteristic	All OAI Participants			Propensity score–matched Participants		
	Statin Users	Statin Nonusers	SMD	Statin Users	Statin Nonusers	SMD
No. of knees	726	2760	...	715 (193 + 522)*	715	...
	Variables Included in the Propensity Score Matching Model					
Age (y)†	60.6 ± 8.8	56.5 ± 8.4	0.48	60.5 ± 8.7	60.4 ± 8.8	0.01
Women†‡	60.6 ± 8.7	56.0 ± 7.7	0.56	60.6 ± 8.7	59.9 ± 7.9	0.07
Men†‡	60.6 ± 8.7	57.1 ± 9.0	0.39	60.4 ± 8.7	60.8 ± 9.3	0.05
No. of women	308 (42.4)	1508 (54.6)	0.24	306 (42.8)	303 (42.4)	0.01
BMI (kg/m²)†	30.4 ± 4.7	28.8 ± 5.1	0.31	30.3 ± 4.7	30.4 ± 4.9	0.01
PASE score†	154.4 ± 79.5	173.16 ± 88.6	0.22	154.0 ± 79.7	159.6 ± 85.7	0.07
Smoking history	...	...	0.14	...	...	0.05
Never smoked	355 (48.9)	1471 (53.3)	NA	350 (49.0)	360 (50.3)	NA
Past smoker	317 (43.7)	103 (37.3)	NA	315 (44.1)	301 (42.1)	NA
Smoker <14 cigarettes per day	34 (4.7)	147 (5.3)	NA	33 (4.6)	33 (4.6)	NA
Smoker ≥14 cigarettes per day	20 (2.8)	112 (4.1)	NA	17 (2.4)	21 (2.9)	NA
Alcohol use	...	...	0.12	...	...	0.096
<1 drink per week	409 (56.3)	1607 (58.2)	NA	407 (56.9)	408 (57.1)	NA
1–3 drinks per week	114 (15.7)	425 (15.4)	NA	109 (15.2)	108 (15.1)	NA
4–7 drinks per week	91 (12.5)	398 (14.4)	NA	90 (12.6)	104 (14.5)	NA
8–14 drinks per week	78 (10.7)	207 (7.5)	NA	76 (10.6)	59 (8.3)	NA
>15 drinks per week	34 (4.7)	123 (4.5)	NA	33 (4.6)	36 (5.0)	NA
Comorbid condition§	282 (38.8)	735 (26.6)	0.26	275 (37.5)	268 (37.5)	0.02
White race‖	178 (24.5)	844 (30.6)	0.19	178 (24.9)	189 (26.4)	0.03
	Variables Not Included in the Propensity Score Matching Model					
Knee injury	209 (28.8)	787 (28.5)	0.14	207 (29.0)	184 (25.7)	0.07
NSAID use	86 (11.8)	282 (10.2)	0.05	84 (11.7)	79 (11.0)	0.02
Hyaluronic acid IA injection	12 (1.7)	20 (0.7)	0.09	9 (1.3)	10 (1.4)	0.01
Steroid IA injection	20 (2.8)	60 (2.2)	0.04	18 (2.5)	15 (2.1)	0.03
Statin name						
Atorvastatin	398 (54.8)	NA	NA	393 (55.0)	NA	NA
Fluvastatin	12 (1.7)	NA	NA	12 (1.7)	NA	NA
Lovastatin	20 (2.8)	NA	NA	19 (2.7)	NA	NA
Pravastatin	68 (9.4)	NA	NA	67 (9.4)	NA	NA
Rosuvastatin	38 (5.2)	NA	NA	38 (5.3)	NA	NA
Simvastatin	190 (26.2)	NA	NA	186 (26.0)	NA	NA
Hydrophilic statin type**	106 (14.6)	NA	NA	105 (14.7)	NA	NA

Note.—Unless otherwise indicated, data are number of knees, with the percentage in parentheses. BMI = body mass index, IA = intra-articular injection, NA = not applicable, NSAID = nonsteroidal anti-inflammatory drug, OAI = Osteoarthritis Initiative, PASE = Physical Activity Scale for the Elderly, SMD = standardized mean difference. Significant difference for SMD was defined as ≥ 0.1.

* Data in parenthesis are numbers of incident and prevalent statin users, respectively.

† Data are mean ± standard deviation.

‡ There was no significant difference between age of men and age of women after matching.

§ Comorbid condition was defined as presence of either history of coronary artery disease, cerebrovascular accident, diabetes (any stage of diabetes vs no medical history of diabetes), or hypertension in physical examination systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg at OAI physical examinations).

‖ Race was categorized as white or nonwhite, considering the small number of participants in each nonwhite race group.

** Statin type was defined based on hydrophilic affinity. Pravastatin and rosuvastatin were classified as hydrophilic agents, and the remaining statins were classified as lipophilic drugs.

initiator and nonuser pairs were excluded (right censored) from subsequent analyses if either the initiator or the nonuser had not met the criteria to remain in the longitudinal analysis (Fig E2 [online]).

Finally, participants were stratified into subgroups according to each possible mediator of the effect of statins (Appendix E1 [online]). The Cox model was fitted on each subgroup of data, and a homogeneity test was used to assess

Table 3: Cross-sectional Analysis of the Association between Statin Use and Knee Osteoarthritis Structural and Symptomatic Measures based on Duration of Statin Use and Heberden Node Presence

	HN-positive Group Odds Ratio		HN-negative Group Odds Ratio	
OA Measure	Prevalent Users vs Matched Nonusers (n = 1270)	Incident Users (Initiators) vs Matched Nonusers (n = 416)*	Prevalent Users vs Matched Nonusers (n = 522)	Incident Users (Initiators) vs Matched Nonusers (n = 193)*
Kellgren-Lawrence grade	0.89 (0.80, 0.98) [.02]	0.91 (0.75, 1.10) [.34]	0.96 (0.83, 1.11) [.54]	0.86 (0.69, 1.08) [.19]
Medial JSN	0.95 (0.89, 1.02) [.17]	0.92 (0.81, 1.05) [.22]	1.02 (0.93, 1.13) [.62]	0.97 (0.83, 1.12) [.63]
WOMAC pain	0.72 (0.55, 0.95) [.02]	1.36 (0.84, 2.20) [.21]	0.94 (0.58, 1.51) [.79]	2.59 (1.26, 5.34) [.01]
WOMAC disability	0.32 (0.12, 0.85) [.02]	3.02 (0.54, 16) [.21]	0.63 (0.12, 3.22) [.58]	11.52 (0.98, 135) [.05]
WOMAC total	0.19 (0.05, 0.71) [.01]	5.16 (0.48, 55) [.18]	0.57 (0.06, 5.52) [.63]	32.07 (1.03, 1003) [.048]

Note.—Data are odds ratios, with 95% confidence intervals in parentheses and *P* values in brackets. Association was assessed by using regression models for continuous or categorical outcomes and exposure of statin use–based prevalent or incidence use. The "*n*" corresponds to total number of knees included in each analysis and the number of matched statin users and nonusers. HN = Heberden node, JSN = joint space narrowing, OA = osteoarthritis, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

* These participants were included in the subsequent longitudinal analysis.

Table 4: Longitudinal Assessment of Knee Osteoarthritis Incidence and Progression between Statin Users and Nonusers

OA Measure	HN-positive Group Hazard Ratio	HN-negative Group Hazard Ratio	Homogeneity Test *P* Value
Primary outcome			
Radiographic knee OA incidence	0.86 (0.36, 1.93) [0.66]	0.80 (0.19, 3.44), [0.76]	.97
Radiographic knee OA JSN progression	0.54 (0.36, 0.93) [0.02]	1.37 (0.74, 2.53) [0.32]	.047
Secondary outcome			
Knee OA symptomatic incidence	0.93 (0.57, 1.53) [0.78]	1.33 (0.62, 2.84) [0.46]	.39

Note.–Longitudinal assessment of primary and secondary outcomes between statin users and nonusers in Heberden node (HN)-positive and HN-negative cohorts was performed with Cox proportional hazards. Data are hazard ratios, with 95% confidence intervals in parentheses, and *P* values in brackets. Knee osteoarthritis (OA) incidence is defined as Kellgren-Lawrence grade of 2 or higher in participants who had a Kellgren-Lawrence grade of 0–1 at baseline (198 knees, including 99 statin users and 99 nonusers were included in knee OA incidence assessment). Knee OA joint space narrowing (JSN) progression is defined as whole-grade progression in medial JSN grade (734 knees, including 367 statin users and 367 nonusers included in knee OA progression assessment), and knee OA symptomatic incidence is measured with nonacceptable symptomatic state (856 knees, including 428 statin users and 428 nonusers included in knee OA symptomatic incidence assessment).

the difference between estimates of two models between subgroups.

All analyses were performed by using the R platform (version 3.4.3; *https://www.r-project.org*) or SPSS software (version 24; SPSS, Chicago, Ill). A two-tailed *P* value less than .05 was considered indicative of a significant difference.

Results

Participant Characteristics

A total of 9592 knees (4796 participants) in the OAI were categorized based on the presence of HN and statin use at the baseline visit. Subsequently, statin users (both prevalent and incidence users) were matched with nonusers. After matching, 1270 prevalent users and 416 incident users (knees) were selected for the HN-positive cohort, while 522 prevalent users and 193 incident users (knees) were chosen for the HN-negative cohort. Details regarding the selection of study groups and the matching process are given in Figure 1, Appendix E1 (online), and Figure E3 (online).

Tables 1 and 2 summarize the baseline characteristics of included participants before and after applying propensity score matching. The mean age of matched participants in the HN-positive cohort was 65.7 years ± 9.5 (standard deviation) (65.9 years ± 7.6 in statin users, 65.5 years ± 8.4 in nonusers). The mean age of participants in the HN-negative cohort was 60.4 years ± 8.8 (60.5 years ± 8.7 in statin users, 60.4 years ± 8.8 in nonusers). Participant age ranged from 45 to 79 years in both cohorts. In the HN-positive and HN-negative cohorts, 58.9% (n = 1987) and 42.5% (n = 609) of knees belonged to women, respectively. Mean follow-up in the HN-positive and HN-negative cohorts was 4.0 and 4.2 years, respectively (range, 1–8 years), and the study included a total of 3560 person-years of follow-up. Matching results showed a standardized mean difference of less than 0.1 for all confounding variables. Although conventional nonsurgical treatment of knee OA, including use of nonsteroidal anti-inflammatory drugs or intra-articular injection of steroids and hyaluronic acid, was not included in the matching model, matched participants in both the HN-negative and HN-positive cohorts showed a similar rate of using these interventions with a standardized mean difference of less than 0.1 (Tables 1, 2).

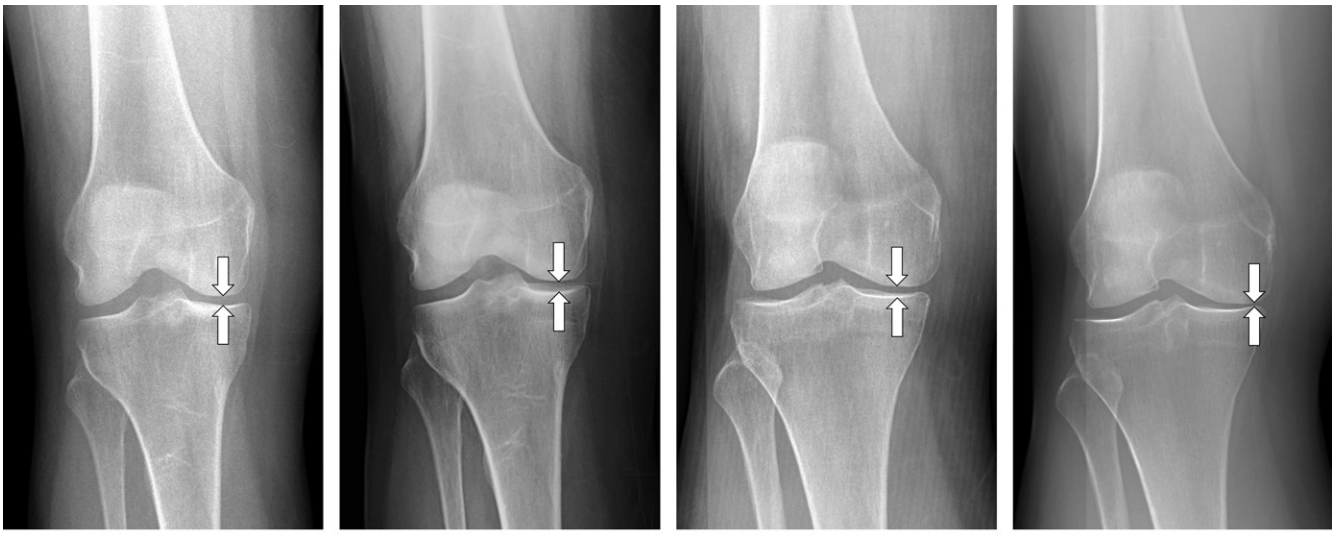

Figure 2: Baseline and follow-up radiographs of propensity score–matched statin initiator and nonuser. Both participants had Heberden nodes. **(a)** Baseline weight-bearing posteroanterior radiograph of the right knee obtained with the fixed-flexion protocol in a 71-year-old woman using statins shows grade 0 medial joint space narrowing (JSN) (arrows), as determined with the Osteoarthritis Research Society International grading method. **(b)** Follow-up radiograph of the same knee in **a** obtained 48 months later shows no progression in medial JSN, as evidenced by no interval change in JSN grading (grade 0) (arrows). **(c)** Baseline posteroanterior radiograph of the right knee in a 68-year-old propensity-score matched woman who did not use statins shows a JSN grade of 1 (arrows). **(d)** Follow-up posteroanterior radiograph of the same knee as in **c** obtained 48 months later shows JSN progression, as evidenced by an interval change in JSN grading (grade 2) (arrows).

Both prevalent users and statin initiators were entered into cross-sectional analysis with corresponding matched nonusers. The latter 416 pairs of knees of statin initiators and nonusers (total of 832 knees in 602 participants) were included in longitudinal analyses of the HN-positive cohort. Similarly, in the HN-negative cohort, we entered 522 and 193 knees of prevalent and incident users (from a total of 715 knees), respectively, into cross-sectional analysis with their nonuser match. As in the HN-positive cohort, 193 pairs of knees of statin initiators and nonusers (total of 386 knees of 285 participants) from the HN-negative cohort were entered into longitudinal analyses. In the HN-positive and HN-negative longitudinal cohorts, mean age was 64.7 years ± 8.0 and 58.9 years ± 8.2, respectively, and 62.6% (n = 377) and 50.5% (n = 144) of participants were women, respectively.

Cross-sectional Analysis

In the HN-positive cohort, prevalent statin users (but not initiators) had lower Kellgren-Lawrence grades (odds ratio, 0.89; 95% CI: 0.80, 0.98; P = .02) and lower WOMAC pain (odds ratio, 0.72; 95% CI: 0.55, 0.95; P = .02) and disability (odds ratio, 0.32; 95% CI: 0.12, 0.85; P = .02) scores compared with the matched nonusers (Table 3). In the HN-negative cohort, there was no significant relationship between statin use and knee OA radiographic outcomes; however, WOMAC pain, disability, and total scores were higher in incident users than in nonusers (Table 3).

Longitudinal Analysis

Table 4 shows the results of Cox regression complex sample analysis for the association between statin use and primary and secondary knee OA outcomes. In the HN-positive cohort, we found that statin use was associated with the decreased longitudinal risk of radiographic JSN progression over 8 years (HR, 0.54; 95% CI: 0.36, 0.93; P = .02), resulting in a 42% lower risk of JSN progression compared with nonusers (Fig 2). The number to treat for radiographic JSN progression was equal to 14 knees. In the HN-negative cohort, there was no decreased risk of radiographic OA incidence or JSN progression associated with statin exposure (Fig E4 [online]). Furthermore, as presented in Table 4, results of the homogeneity test revealed that the HR for the association between statin use and radiographic JSN progression was significantly higher in the HN-positive OA cohort than in the HN-negative cohort (P = .047) (Table 4). Statin use was not associated with radiographic knee OA incidence in either the HN-positive cohort (HR, 0.86; 95% CI: 0.36, 1.93; P = .66) or the HN-negative cohort (HR, 0.80; 95% CI: 0.19, 3.44; P = .76).

In consideration of the secondary outcome, statin use was not associated with symptomatic pain incidence measured with NASS in either the HN-positive group (HR, 0.93; 95% CI: 0.57, 1.53; P = .78) or the HN-negative group (HR, 0.33; 95% CI: 0.62, 2.84; P = .46).

Subgroup Analyses

In the HN-positive cohort, participants were stratified according to OA- and statin use–related factors, and the association between statin use and longitudinal JSN progression was assessed in each subgroup (Table 5). Results showed that number of HNs could be a predictor of the therapeutic effects of statins. Statin use was associated with a lower risk of radiographic JSN progression only in the subgroup of participants with two or more HNs (HR, 0.54; 95% CI: 0.31, 0.93; P = .01) when compared with participants with one HN (HR,

Table 5: Subgroup Analysis of Radiographic Knee Joint Space Narrowing Progression in Heberden Node–positive Cohort

Subgroup Level	JSN Progression	*P* Value
No. of HNs	…	<.01
≥2	0.54 (0.31, 0.93)	…
1	7.02 (0.9, 54.92)	…
Family history of knee OA	…	.28
Yes	1.62 (0.32, 8.11)	…
No	0.57 (0.32, 1.02)	…
Back or neck OA	…	.88
Yes	0.58 (0.11, 3.16)	…
No	0.72 (0.39, 1.31)	…
Hip, hand, neck, or back OA	…	.87
Yes	0.52 (0.09, 2.92)	…
No	0.68 (0.37, 1.23)	…
Knee injury history	…	.97
Yes	0.47 (0.09, 2.39)	…
No	0.44 (0.22, 0.87)	…
Statin type	…	.89
Lipophilic	0.52 (0.19, 1.4)	…
Hydrophilic	0.6 (0.35, 1.02)	…
Insurance full coverage	…	NC
Yes	0.77 (0.45, 1.29)	…
No	NC (inadequate sample size)	…
Occupational status	…	.90
Currently working or self employed	0.53 (0.21, 1.32)	…
Unemployed	0.62 (0.26, 1.48)	…
Income	…	.49
≥$50 000	0.6 (0.29, 1.21)	…
<$50 000	1.31 (0.2, 8.8)	…
Education level	…	.83
Completed 2-year college degree or higher	0.58 (0.27, 1.26)	…
No education or high school education	0.78 (0.17, 3.63)	…

Note.—Data are hazard ratios, with 95% confidence intervals in parentheses. Cox proportional hazard models were used to assess whole-grade progression in medial joint space narrowing (JSN). Possible contributing factors were considered to perform subgroup analysis. Homogeneity test was used to assess significant difference between subgroups. HN = Heberden node, OA = osteoarthritis, NC = not converged.

7.02; 95% CI: 0.90, 54.92; $P = .19$) (homogeneity test, $P < .01$) (Table 5). However, the small number of participants in this subgroup (ie, the one-HN subgroup) resulted in a wide CI for the estimate. No other significant difference was seen in the remaining subgroups (Table 5).

Discussion

The contribution of statins to knee osteoarthritis (OA) radiographic outcome has been unclear, and characteristics of patients with potential OA who may benefit from statin therapy are not defined. Here, we used a longitudinal matched design to assess the effect of statin use on long-term radiographic knee outcomes according to the presence of Heberden nodes (HNs). We showed that statin use was associated with a 46% lower risk of radiographic knee joint space narrowing (JSN) progression over 8 years in only HN-positive participants (hazard ratio, 0.54; $P = .02$). However, statin use was not associated with radiographic knee OA incidence in either HN-positive or HN-negative participants.

From the previously published works with conflicting results regarding the association between statin use and OA, a recent study by Veronese et al on the OAI dataset showed no association between statin use and radiographic OA incidence. Results of the Veronese et al study may be criticized because of the inclusion of prevalent statin users, which subjects the design to incident-prevalent bias (10). Valdes et al suggested a possible cross-sectional relationship between statin use and less severe hip and knee OA in only HN-positive patients as a marker for generalized OA (8).

In comparison with the previous report, the major strength of our study was a consideration of the presence of HNs as a hallmark of generalized OA and a distinct clinical biomarker for the protective effect of statins using a cohort design (6,9,10,25–27). We used the OAI dataset and were able to match our cohorts for the confounders and minimize the possibility of confounding by indication and incidence-prevalent bias (6,8–10,25–27). Details about the variables used for the matching process (ie, associated medical conditions to statin use and knee OA) are discussed in Appendix E1 (online). Moreover, knee-based sampling gave us the advantage of assessing knee-specific outcomes (6,8–10,25–27). With a mean follow-up of more than 4 years in both HN-positive and HN-negative cohorts, we were able to investigate chronic exposure to statins, considering the unclear role of duration of statin use in previous studies. Further, we addressed both symptomatic and radiographic outcomes of knee OA (6,8–10,25–27). We used a per-protocol approach instead of intention-to-treat analysis (6,8,9,25–27). In the intention-to-treat approach, the magnitude of effect depends on how closely participants adhere to the treatment assigned at the start of the study; however, in the per-protocol approach, participants who did not adhere to their assigned treatment in each visit were right censored from that visit. Therefore, we implemented the per-protocol approach to consider nonadherence to treatment (19). Unlike radiographic JSN progression, our longitudinal analysis of knee OA symptom outcomes did not show any protective effect of statin use. One possible explanation would be muscle pain, which can occur in approximately 20% of statin users (28), masking the protective effect of statins on OA-related NASS outcome.

Our study had several limitations. First, we lacked precise data on duration, dosage, and intensity of statin use. OAI examiners confirmed the prescription for statins by checking the medications participants brought to visits. This approach may not be as valid as exact pill count and cannot be used to explore the dose-dependent effects of statins, but it may be more reliable than asking patients to self-report their medication use. A similar approach has been implemented in previous OAI studies (5,7–10,29). Second, our sample size in longitudinal assessment was restricted to participants included in matching with available data at follow-up, decreasing the

power. Third, given the OAI design for annual radiographic assessments, the 1-year interval between visits may not be adequate for precise assessment of the effect of statins in participants with rapid JSN progression. Fourth, we used a per-protocol approach, which led to artificial censoring in case of change in statin use status during the study, which could lead to time-varying selection bias. However, we were unable to address potential risk of mentioned bias due to the propensity score–matched design (19). Fifth, statin use has been associated with muscle pain (30), which not only affects WOMAC-based outcomes but also can result in muscle weakness—a potential predisposing factor of knee OA itself. Since the Physical Activity Scale for the Elderly score was the only general measure of muscle endurance in the OAI dataset, we have matched these participants accordingly. Finally, because of retrospective analysis of the prospectively collected data, our defined subgroups were not prespecified in the OAI data collection process.

In conclusion, statin use may reduce radiographic knee joint space narrowing progression in Heberden node–positive patients. Future investigations that use advanced MRI-based metrics, novel serum biomarkers of inflammation and cartilage degradation, and serum lipid profile are warranted to explore underlying mechanisms for such a pleiotropic effect of statins against osteoarthritis progression (4).

Author contributions: Guarantors of integrity of entire study, A.H., B.M., S.D.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, A.H., B.M., P.G.C., J.A.C.L., S.D.; clinical studies, A.H., A.G., F.W.R., X.C., S.D.; statistical analysis, A.H., B.M., S.D.; and manuscript editing, A.H., B.M., A.G., P.G.C., J.A.C.L., M.J.B., F.W.R., S.D.

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