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Statin Use and MRI Subchondral Bone Marrow Lesion Worsening in Generalized Osteoarthritis: Longitudinal Analysis from Osteoarthritis Initiative Data

Article type: Original research

Abstract

1   ***Objectives.*** To determine the association between statin therapy and knee MRI-detected

2   subchondral bone marrow lesion (BML) longitudinal worsening in patients with Heberden's nodes

3   (HNs) as the hallmark of generalized osteoarthritis (OA) phenotype.

4   ***Methods.*** All participants gave informed consent, and IRB approved HIPAA-compliant protocol.

5   We assessed worsening in BMLs volume and number of affected subregions in the Osteoarthritis

6   Initiative (OAI) participants with HNs at baseline clinical examination (HN$^+$), using the semi-

7   quantitative MRI Osteoarthritis Knee Scores at baseline and 24-month. Participants were classified

8   according to baseline BML involvement as "no/minimal" ($\leq$2/14 knee subregions affected and

9   maximum BML score$\leq$1) or "moderate/severe." Statin users and non-users were selected using

10   1:1 propensity-score (PS) matching for OA and cardiovascular disease (CVD)-related potential

11   confounding variables. We assessed the association between statin use and increasing BML score

12   and affected subregions using adjusted mixed-effect regression models.

13   ***Results.*** The PS-matched HN$^+$ participants (63% female, aged 63.5±8.5-year-old) with no/minimal

14   and moderate/severe BML cohorts consisted of 332 (166:166, statin users: non-users) and 380

15   (190:190) knees, respectively. In the HN$^+$ participants with no/minimal BML, statin use was

16   associated with lower odds of both BML score worsening (odds ratio, 95%confidence

17   interval:0.62, 0.39–0.98) and increased number of affected subregions (0.54, 0.33–0.88). There

18   was no such association in HN$^-$ participants or those HN$^+$ participants with baseline

19   moderate/severe BML.

20   ***Conclusion.*** In patients with CVD indications for statin therapy and generalized OA phenotype

21   (HN$^+$), statin use may be protective against the OA-related subchondral bone damage only in the

22   subgroup of participants with no/minimal baseline BML.

23   **Keywords**: Magnetic Resonance Imaging, Bone Marrow, Hydroxymethylglutaryl-CoA

24   Reductase Inhibitors, Osteoarthritis, Knee, Propensity Score

25

26   **Key points:**

27   • Statin use may reduce the risk of subchondral bone damage in specific osteoarthritis

28   patients with a generalized phenotype, minimal subchondral bone damage, and

29   cardiovascular statin indications.

30   **Abbreviations and Acronyms**:

31   1) BML: Bone marrow lesion

32   2) CVD: Cardiovascular disease

33   3) DMOAD: Disease-modifying osteoarthritis drug

34   4) HN: Heberden's node

35   5) MIF: Medication inventory form

36   6) MOAKS: MRI Osteoarthritis Knee Score

37   7) OA: Osteoarthritis

38   8) OAI: Osteoarthritis Initiative

39   9) PS: Propensity-score

40   10) SMAS: Statin-associated muscle symptoms

41   11) SMD: Standardized mean difference

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Introduction:

Knee osteoarthritis (OA) is the most common debilitating disease of the peripheral joints. Despite its high prevalence, to date, no disease-modifying OA drug (DMOAD) has been approved for use in clinical practice.[1] There have been investigations on the potential DMOAD role for statins, a group of first-line lipid-lowering medications. Despite the well-established experimental evidence for the protective effect of statins against knee OA progression and subchondral bone damage in animal models,[2] previous observational studies on human OA patients have been inconclusive.[3-13] Such discrepancy could be due to heterogeneous subject selection related to different OA phenotypes, degree of baseline joint structural damage, and most importantly, presence vs. absence of cardiovascular disease (CVD) indications for statin use among participants. While there are controversial reports on the causal relationship between CVD and OA,[14-18] previous studies have shown OA is strongly associated with CVDs and CVD risk factors such as obesity and dyslipidemia.[15; 19-21] Therefore, the presence of CVD indications of statins can possibly confound or intermediate statins' DMOAD assessment.

Experimental studies have shown a protective effect of statins on the subchondral bone.[2] In human OA patients, subchondral bone marrow lesions (BMLs) are known as the imaging hallmark of OA-related subchondral bone damage in MRI examinations.[22] To date, no study has assessed the effect of statins on BMLs, and only one trial on the statins' DMOAD effect on cartilage loss has been conducted.[23; 24] In this trial, authors used a 2-year follow-up Magnetic Resonance Imaging (MRI) and included participants had no CVD indications for statin use and had heterogeneous OA etiologies.[23; 24] While authors reported that overall statins had no protective effects against OA progression, they stated that statin might reduce cartilage loss only in the subgroup of OA patients with no subchondral BMLs.[23; 24] Moreover, it has been recently shown

4

66   that statin use is associated with decreased radiographic knee OA radiographic progression

67   compared to non-use, only in those OA participants with Heberden's nodes (HN[+]).[25] HNs are

68   bony enlargements of the distal interphalangeal joints (DIPs) detectable in clinical examination

69   and are considered a hallmark of generalized OA phenotype.[26-28]

70   Using the results of the only available clinical trial and recent observational data on HN[+]

71   patients, as potential responders to the DMOAD effects of statin, we hypothesized that statins

72   potential DMOAD role might be through their protective effect on early subchondral BML

73   formation and worsening in a distinct subgroup of OA patients with generalized OA (HN[+]),

74   no/minimal BMLs, and CVD indications for statin use. Using propensity-score (PS) matching for

75   CVD factors and potential confounding by indication (OA and CVD) covariates, we tested this

76   hypothesis in participants of the Osteoarthritis Initiative (OAI) ancillary studies with tailored

77   selection criteria for assessing worsening of MRI-based subchondral bone OA-related damage

78   over 24 months follow-up.

79

Materials and Methods

Study population

In this study, we used data from the longitudinal multi-center Osteoarthritis Initiative (OAI) study (2004-2015, clinicaltrials.gov identifier: NCT00080171, details can be found at https://nda.nih.gov/oai/). All enrolled patients filled written informed consent and institutional review boards of four OAI collaborating centers have approved the Health Insurance Portability and Accountability Act-compliant protocol of this study. We collected and pooled all previously conducted MRI-based measurements of participants from nested ancillary studies performed inside OAI to assess OA-related subchondral bone damage. (Figure 1) These studies' design and selection criteria are specially tailored to assess MRI-based OA structural damage worsening in a specific subset from all OAI participants (details are explained in the OAI online repository[29]). Following deletion of duplicate measurements (753 cases between different projects), MRI Osteoarthritis Knee Score (MOAKS) measurements for 1677 knees were included from the following OAI ancillary studies: 1) Foundation for the National Institute of Health (FNIH) Consortium Osteoarthritis Biomarkers Project[30] (473 knees, project no. 22), 2) project no. 30 (125 knees) 3) projects no. 63A-63F (328 knees) 4) Pivotal OAI MRI Analyses (POMA) study (751 knees).[31] The same OAI team centrally performed all measurements according to the validated semi-quantitative MOAKS.[32]

Since it is difficult to assess structural OA damage in patients with advanced knee OA due to 'ceiling' effects on the scores, knees with end-stage knee OA on baseline X-ray were excluded. (Exclusion #1 in Figure 1) These consist of knees with replacement surgery (63 knees) and baseline radiographic Kellgren-Lawrence (KL) grade of 4 (302 knees). Moreover, knees without available baseline and 24-month follow-up evaluation of BMLs in the mentioned OAI ancillary studies were

103 excluded (7641 knees, Exclusion #2 Figure 1). Both knees were included in a minority of

104 participants (N:36, 5% of included knees).

105   To assess the potential skewness of our sampling and risk of selection bias, we compared the

106 baseline characteristics of OAI participants included in the ancillary studies and the rest of the OAI

107 participants. There was no significant difference in neither of the potential confounders.

108 (Supplementary Table 1)

109 ***Assessment of HNs***

110   At the baseline visit, trained OAI nurse staff examined whether HNs on the DIP joints of the

111 2nd-5th digits and first interphalangeal joint were present by palpation. Participants with at least one

112 HN in either hand were categorized as HN^+; whereas, participants free of HN in both hands were

113 categorized as HN^- and were separately assessed in the sensitivity analysis (Sensitivity analysis

114 #1 in Figure 1)

115 ***MRI acquisition and outcome measures***

116   MRI acquisition was performed using 3T MRI systems (Trio, Siemens Healthcare, Erlangen,

117 Germany). Parameters and pulse sequence protocol of OAI MRIs have been previously

118 reported.[32] The validated semi-quantitative MOAKS method was used to assess BMLs at

119 baseline, and follow-up MRIs and features of BML size and number of affected subregions in all

120 14 anatomical knee joint sub-regions were extracted.[32] BMLs volume was scored based on the

121 percentage of the total subregion volume occupied as 0: none, 1: <33%, 2: 33-66%, and 3: >66%

122 of joint/sub-region volume. To categorize knees according to baseline BML status, we considered

123 both the BML score and the number of affected knee joint subregions. Knees with both criteria of

124 a) ≤2 knee subregions with BMLs and b) maximum BML score ≤1 were considered no/minimal

125 BML involvement. Subsequently, knees with either a) >2 knee subregions with BMLs or b)

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126 maximum BML score >1 were considered with moderate/severe BML involvement. A 24-month

127 BML score worsening was defined as a whole- or within-grade change, where within-grade was

128 defined as a definite visual change while not fulfilling a whole-grade change definition. BML

129 worsening for longitudinal analysis (i.e., outcome to the models) was defined according to

130 previously validated measures[33] as follows: 1) worsening in the number of affected subregions

131 with BML (ranged from improvement to no change, worsening in 1 subregion, and worsening in

132 ≥2 subregions), 2) maximum worsening in BML score (ranged from no change, within-grade

133 worsening, to worsening by 1 grade, and worsening by ≥2 grades), and 3) worsening in either of

134 BML score (whole or within-grade) or the number of affected subregions (yes/no).[33]

135 *Definition of statin use:*

136   According to the OAI protocol, participants were asked to bring their medications at baseline

137 and annual visits. Staff recorded all information on statin type, frequency, and duration of use at

138 each visit, and data were recorded in the OAI Medication Inventory forms (MIFs). To determine

139 the accuracy of self-reported dosage, type, and duration of statin use, in statin users, we extracted

140 and used all available data about the indication of treatment (e.g., primary dyslipidemia, diabetes,

141 heart disease, or cerebrovascular accident), type of statin (including atorvastatin, lovastatin,

142 fluvastatin, simvastatin, pravastatin, and rosuvastatin), and duration of statin use from the OAI

143 MIF dataset. Participants who reported at least one year (equal to 50% of follow-up duration) statin

144 use in OAI MIF forms were considered statin users. Participants who had <1 year of statin use

145 (two participants in the PS-matched cohorts) or did not report statin use were regarded as statin

146 non-users.

147 *Statistical analysis:*

148   ***Propensity Score Matching:*** To minimize the confounding by indication bias, we matched

149   study subcohorts for potential confounders (CVD-related factors: indications of statin use) using

150   baseline clinical characteristics. Potential confounders were investigated using a Direct Acyclic

151   Graph to assess causal inference.[34] (Supplementary figure 1) The missing data pattern was

152   evaluated, and missing covariate data were imputed. A list of confounding variables and details of

153   the imputation method is presented in the supplementary material.

154   The matching process was performed using the 1:1 PS-matching method separately in HN$^+$

155   with no/minimal BMLs and HN$^+$ with moderate/severe BMLs subcohorts; For every knee of statin

156   users, one best-matched knee of the referent (non-users) was selected. We used the nearest

157   neighbor method with a caliper distance of 0.1 calculated with a logistic regression model. We

158   calculated the Standardized Mean Difference (SMD) before and after PS-matching to examine the

159   balance of covariate distribution between the statin users and non-users subcohorts and defined

160   imbalance as an SMD ≥ 0.1.

161   ***Regression models***: All statistical analyses were separately performed in the HN$^+$ subcohorts

162   with no/minimal BMLs and with moderate/severe BMLs to further assess our hypothesis on

163   statin's effect on the HN$^+$ statin users with no/minimal baseline BML. We used logistic mixed-

164   effect regression models while considering random intercept for each cluster of matched statin

165   user:non-user and within-subject similarities (due to the inclusion of both knees in a minority

166   (N:36, 5%) of included knees). Statin use was the independent predictor, and BML worsening

167   variables were the dependent outcomes. All models were adjusted for participants' propensity

168   scores, baseline KL grade, medial joint space narrowing grade, and knees' BML status.

169   ***Sensitivity analysis:*** We performed the same PS-matched analyses mentioned above on all

170   eligible participants (irrespective of OA phenotype) and the HN$^-$ participants to assess whether

171   our results were sensitive to stratification for OA phenotype (Sensitivity analysis #1 in Figure 1).

172   We also evaluated the sensitivity of our results to data imputation with the exclusion of participants

173   with imputed missing data (Sensitivity analysis #2 in Figure 1). Moreover, we assessed sensitivity

174   to PS-matching by performing the analyses on the entire cohort of eligible HN$^+$ OAI participants

175   without PS-matching (Sensitivity analysis #3 in Figure 1). Finally, we evaluated sensitivity to the

176   random exclusion of one of the two knees of participants with both knees included (Sensitivity

177   analysis #4).

178   The open-source R software version 4.0.3 (*MASS*, *haven*, *survival*, *MatchIt*, *mice, lme4*,

179   *lmerTest*, and *tableone* packages) was used for statistical analysis.

Results

Participants' characteristics: After the implementation of exclusion criteria and PS-matching, from a total of 9592 knees in the OAI, 332 (statin user: non-user, 166:166) matched knees of HN[+] with no/minimal BMLs and 380 (190:190) matched knees of HN[+] with moderate/severe BMLs were included in the analysis. (Figure 1) The baseline characteristics of included knees before and after PS-matching are shown in Table 1. The SMD was less than 0.1 for all variables included in the PS-matching model. Participants in all PS-matched cohorts were on average±standard deviation 63.5±8.5-year-old, were 63% women, and had an average BMI of 29±4.5 kg/m^2.

Outcome measures: In HN[+] with no/minimal baseline BML subcohort, statin use was associated with lower odds of an increasing number of affected subregions with BML (odds ratio, 95% confidence interval:0.54, 0.33–0.88), BML score worsening (0.62, 0.39–0.98), and worsening in either BML score or the number of affected subregions (0.60, 0.37–0.99). (Table 2) There was no such association in the HN[+] with moderate/severe baseline BML subcohort (worsening in the number of affected subregions:1.04, 0.70–1.53, BML score worsening:0.96, 0.65–1.42, and worsening in either BML score or the number of affected subregions:0.85, 0.50–1.47). (Table 2)

Sensitivity analysis: Our sensitivity analysis showed that without stratification for OA phenotype (all HN[+] and HN[−]s) or in HN[−] subcohort, there was no association between statin use and BML worsening. (Supplementary table 2 & 3) Furthermore, our results were not sensitive to using the PS-matching method, data imputation, or random exclusion of one knee of participants with both knees included. (Supplementary Table 2)

Discussion

Using the available data from the previously published paper on HN[+] participants and the recent trial, we have tested the hypothesis that statin use is associated with reduced BML worsening over two years in the knee joint, only in a specific OA phenotype with HNs, no/minimal BMLs, and with CVD indications for statin use. Our finding suggests that the protective effect of statins against OA-related subchondral bone damage, which is not seen in all OA patients and is exclusive to patients with HNs (as the hallmark of a generalized OA phenotype),[25] may be associated with a reduction in early OA-related subchondral damage.

The current data on statins' effects against OA-related outcomes is controversial and limited to observational studies.[3-13] The reasons for the overall inconclusive results of previous observational clinical studies could be due to the inclusion of heterogeneous OA populations in terms of OA phenotype, degree of baseline structural damage in the joint, and underlying comorbidities (e.g., CVDs) that may mediate or confound the potential DMOAD role of statins. We, therefore, carefully formed our hypothesis and selected participants using findings of a previous observational study on HN[+] patients (generalized OA)[25] and the only conducted clinical trial (minimal/no BML),[23; 24] while trying to address potential limitations of these studies (e.g., excluding patients with CVD indications for statin use in the trial). Considering the inclusion of patients with generalized OA, a large body of literature supports HNs as the hallmark of generalized OA and a strong predictor of knee OA progression.[26; 35] Previous studies have shown generalized OA and HNs in DIPs are also strongly associated with CVD risk factors such as elevated serum cholesterol and lipid dysregulation.[36]. Moreover, it has been shown HN[+] OA patients have 40% higher odds of OA MRI-detected subchondral damage during 24-months of follow-up compared to HN[−] patients.[37] *Valdes et al*., using a cross-sectional design,

224 demonstrated a significant association between statin use and less severe hip and knee OA –

225 assessed by the Kellgren-Lawrence grading system– exclusively in patients with generalized

226 OA.[7] It has been recently shown that statin use is associated with a 46% reduced risk of

227 radiographic progression of OA over 8-years compared to no use, only in HN$^+$ patients and not

228 HN$^-$s.[25]

229   On the other hand, from the only clinical trial on statins with a 2-year follow-up,[23; 24] the

230 authors reported a protective effect for statins on OA progression, but only in participants with no

231 baseline subchondral BMLs, another finding that helped to form our hypothesis and selecting

232 participants. However, according to the trial inclusion criteria, authors excluded patients with CVD

233 indications of statin use, and participants used statins purely for OA progression.[23; 24] This may

234 have resulted in excluding the population who could benefit from statins' effects on subchondral

235 bone. More importantly, the authors did not consider OA phenotypes (e.g., generalized OA) in the

236 subject selection. Our sensitivity analysis showed that when assessing all OA patients irrespective

237 of their phenotype (both HN$^+$ and HN$^-$), similar to this trial, we observed no protective association

238 with statin use.

239   While showing beneficial effects of statins in an OA population who already have statin use

240 indication may first seem only incremental in clinical practice, a considerable beneficial

241 epidemiologic impact of DMOAD role for statins can be expected in two distinct patient

242 populations. The first population is current statin users for CVD and its risk factors. Statins are

243 among the most prescribed medications in the elderly, mainly indicated for dyslipidemia and other

244 CVD risk factors.[38] One of the main challenges for statin use is the disappointing long-term

245 adherence rate of as low as 25%[39] due to reasons like perceived lack of efficacy of statins and

246 subjective musculoskeletal pain or its related subjective concerns (also known as statin-associated

247 muscle symptoms or SAMS).[40] Furthermore, older patients[41] (also more affected by OA) and

248 those with debilitating comorbidities like OA[42; 43] are among the groups with the least

249 adherence to statins.[44; 45] the second population who benefit are generalized OA statin "non-

250 users" with a CVD indication for statin use. Reports show that a third of the adults in developed

251 countries like the U.S. meet statin CVD indications, but nearly half of this population have never

252 initiated stain use.[46] If the potential DMOAD role for statins is proven, it can improve both

253 initiation of and adherence to one of the world's most commonly prescribed medications.[44; 45]

254 As for the strengths of the current study, we studied a hypothesis-driven selected large sample

255 of PS-matched participants from the validated OAI cohort. Also, we used MOAKS scorings which

256 have been shown to closely correlate with pain and structural damage or the progression of

257 OA.[33] Previous studies on the OAI data reported intra- and inter-observer reliability of 90% for

258 longitudinal BML MOAKS measurement, suggesting a low risk of measurement error for

259 influencing outcome results.[47] Moreover, we uniquely selected and PS-matched participants

260 based on previous evidence and performed several stratification and sensitivity analyses to OA

261 phenotype (HN⁻, moderate/severe BMLs) and selected methods (PS-matching, missing data

262 imputation, the inclusion of both knees) to assess the robustness of our results.

263 However, our study has several limitations. First, we lacked precise data on the duration,

264 dosage, and intensity of statin use. OAI examiners confirmed the prescription for statins according

265 to medications participants brought with them during visits. This approach may not be as valid as

266 the exact pill count and cannot be used for exploring the dose-dependent effects of statins, but it

267 may be more reliable than a self-report of medication use. A similar approach has been

268 implemented in previous OAI studies.[8; 13; 25], and it has been shown that these measures of

269 statin use are relatively accurate.[48] Second, we have included all statin users with different statin

270 use duration before the baseline visit (both prevalent and incident users). This will increase the

271 risk of Neyman bias in our results, which is a selection bias in which very sick/healthy participants

272 (because of chronic disease) are excluded from enrolment.[49] Third, our defined subcohorts were

273 not pre-specified in the OAI data collection process because of the retrospective analysis of the

274 prospectively collected data. We were limited by including participants with available MRI

275 scorings from previously conducted nested case-control studies within OAI (e.g., FNIH, POMA),

276 which have specific inclusion-exclusion criteria. We tried to tailor our study sample to address this

277 limitation using detailed selection criteria and the PS-matching method, and we assessed the

278 sensitivity of our results to using the PS-matching method. Forth, in assessing CVD statin

279 indications, lipid profile was not available in the OAI dataset, and dyslipidemia is among the most

280 common indications of statin prescription for primary CVD prevention.[50] While we tried to

281 match our participants according to other statin CVD statin indications and the majority (>70%)

282 of our participants had statin indications (all statin users, 40% of non-users according to PS-

283 matching results), it is not possible to thoroughly address this issue in studies with an observational

284 design where exposure (statin use) was not considered in selection criteria. Finally, we have not

285 assessed SAMS and muscle strength and quality in this study, a matter that can potentially

286 complicate the implementation of statin DMOAD role in routine clinical practice. Given the high

287 prevalence of SAMS, detecting any deterioration of muscle quality will raise a critical concern for

288 statins' DMOAD role in clinical practice, a matter left for future studies.

289   In conclusion, our results suggest that statin use may be protective against BML worsening

290 only in a specific OA phenotype with HNs and no/minimal baseline BMLs and with CVD statin

291 indications, which is in line with the recent observational data[25] and the only available clinical

292 trial.[23; 24] While our exploratory study results cannot be directly translated to clinical use, future

293   studies focusing on the repurposing of widely available statins as DMOADs[51] with proper

294   patient selection may produce clinical and potential cost-saving benefits compared to designing

295   new DMOAD compounds.

296

297   **Patient consent**

298   Subjects have given informed consent before participating in the Osteoarthritis Initiative

299 (OAI) project.

300   **Ethics approval**

301   The medical ethics review boards of the University of California, San Francisco (Approval

302 Number: 10-00532) and the four clinical centers of osteoarthritis initiative project recognized the

303 project as Health Insurance Portability and Accountability Act (HIPAA)-compliant.

304   **Data sharing statement**

305   The de-identified clinical and demographic information and knee MRI read of subjects is

306 publicly available at the osteoarthritis initiative project data repository at https://oai.nih.gov. All

307 dataset and the R codes used in this work are available from the corresponding author upon

308 reasonable requests.

309   **References:**

310

311   1   Bijlsma JWJ, Berenbaum F, Lafeber FPJG (2011) Osteoarthritis: an update with

312   relevance for clinical practice. The Lancet 377:2115-2126

313   2   Farnaghi S, Prasadam I, Cai G et al (2017) Protective effects of mitochondria-targeted

314   antioxidants and statins on cholesterolinduced osteoarthritis. FASEB Journal 31:356-367

315   3   Kadam UT, Blagojevic M, Belcher J (2013) Statin Use and Clinical Osteoarthritis in the

316   General Population: A Longitudinal Study. Journal of General Internal Medicine 28:943-

317   949

318   4   Makris UE, Alvarez CA, Mortensen EM, Mansi IA (2018) Association of Statin Use with

319   Increased Risk of Musculoskeletal Conditions: A Retrospective Cohort Study. Drug Saf

320   41:939-950

321   5   Clockaerts S, Van Osch GJVM, Bastiaansen-Jenniskens YM et al (2012) Statin use is

322   associated with reduced incidence and progression of knee osteoarthritis in the Rotterdam

323   study. Annals of the Rheumatic Diseases 71:642-647

324   6   Wang J, Dong J, Yang J, Wang Y, Liu J (2020) Association between statin use and

325   incidence or progression of osteoarthritis: meta-analysis of observational studies.

326   Osteoarthritis and cartilage 28:1170-1179

327   7   Valdes AM, Zhang W, Muir K, Maciewicz RA, Doherty S, Doherty M (2014) Use of

328   statins is associated with a lower prevalence of generalised osteoarthritis. Annals of the

329   Rheumatic Diseases 73:943-945

330 8 Riddle DL, Moxley G, Dumenci L (2013) Associations between Statin use and changes

331 in pain, function and structural progression: A longitudinal study of persons with knee

332 osteoarthritis. Annals of the Rheumatic Diseases 72:196-203

333 9 Michaëlsson K, Lohmander LS, Turkiewicz A, Wolk A, Nilsson P, Englund M (2017)

334 Association between statin use and consultation or surgery for osteoarthritis of the hip or

335 knee: a pooled analysis of four cohort studies. Osteoarthritis and Cartilage 25:1804-1813

336 10 Mansi IA, Mortensen EM, Pugh MJ, Wegner M, Frei CR (2013) Incidence of

337 musculoskeletal and neoplastic diseases in patients on statin therapy: results of a

338 retrospective cohort analysis. The American journal of the medical sciences 345:343-348

339 11 Eymard F, Parsons C, Edwards MH et al (2017) Statin use and knee osteoarthritis

340 progression: Results from a post-hoc analysis of the SEKOIA trial. Joint Bone Spine

341 85:609-614

342 12 Chodick G, Amital H, Shalem Y et al (2010) Persistence with Statins and Onset of

343 Rheumatoid Arthritis: A Population-Based Cohort Study. PLoS Medicine 7:e1000336-

344 e1000336

345 13 Veronese N, Koyanagi A, Stubbs B et al (2019) Statin Use and Knee Osteoarthritis

346 Outcomes: A Longitudinal Cohort Study. Arthritis Care Res (Hoboken) 71:1052-1058

347 14 Kuusalo L, Felson DT, Wang N et al (2021) Metabolic osteoarthritis - relation of diabetes

348 and cardiovascular disease with knee osteoarthritis. Osteoarthritis Cartilage 29:230-234

349 15 Hall AJ, Stubbs B, Mamas MA, Myint PK, Smith TO (2016) Association between

350 osteoarthritis and cardiovascular disease: Systematic review and meta-analysis. European

351 Journal of Preventive Cardiology 23:938-946

352   16   Corti MC, Rigon C (2003) Epidemiology of osteoarthritis: Prevalence, risk factors and

353   functional impact. Aging Clinical and Experimental Research 15:359-363

354   17   Fernandes GS, Valdes AM (2015) Cardiovascular disease and osteoarthritis: common

355   pathways and patient outcomes. European Journal of Clinical Investigation 45:405-414

356   18   Ong KL, Wu BJ, Cheung BMY, Barter PJ, Rye K-A (2013) Arthritis: its prevalence, risk

357   factors, and association with cardiovascular diseases in the United States, 1999 to 2008.

358   Annals of Epidemiology 23:80-86

359   19   Plumb MS, Aspden RM (2004) High levels of fat and (n-6) fatty acids in cancellous bone

360   in osteoarthritis. Lipids Health Dis 3:12

361   20   Findlay DM (2007) Vascular pathology and osteoarthritis. Rheumatology 46:1763-1768

362   21   Kadam UT (2004) Clinical comorbidity in patients with osteoarthritis: a case-control

363   study of general practice consulters in England and Wales. Annals of the Rheumatic

364   Diseases 63:408-414

365   22   Dore D, Quinn S, Ding C et al (2010) Natural history and clinical significance of MRI-

366   detected bone marrow lesions at the knee: a prospective study in community dwelling

367   older adults. Arthritis Research & Therapy 12:R223

368   23   Wang Y, Jones G, Hill C et al (2020) Effect of atorvastatin on knee structure and pain in

369   patients with knee osteoarthritis: a randomised controlled trial. Osteoarthritis and

370   Cartilage 28:S478-S479

371   24   Wang Y, Jones G, Hill C et al (2021) Effect of atorvastatin on knee cartilage volume in

372   patients with symptomatic knee osteoarthritis: results from a randomised placebo-

373   controlled trial. Arthritis Rheumatol. 10.1002/art.41760

374 25 Haj-Mirzaian A, Mohajer B, Guermazi A et al (2019) Statin Use and Knee Osteoarthritis

375   Outcome Measures according to the Presence of Heberden Nodes: Results from the

376   Osteoarthritis Initiative. Radiology 293:190557

377 26 Kellgren JH, Moore R (1952) Generalized osteoarthritis and Heberden's nodes. British

378   medical journal 1:181-187

379 27 Irlenbusch U, Dominick G (2006) Investigations in generalized osteoarthritis. Part 2:

380   Special histological features in generalized osteoarthritis (histological investigations in

381   Heberden's nodes using a histological score). Osteoarthritis and Cartilage 14:428-434

382 28 Nelson AE, Smith MW, Golightly YM, Jordan JM (2014) "Generalized osteoarthritis": A

383   systematic review. Seminars in Arthritis and Rheumatism 43:713-720

384 29 (2016) Overview and Description of Central Image Assessments. Available via

385   https://nda.nih.gov/binaries/content/documents/ndacms/resources/oai/oai-image-

386   assessment-overview/oai-image-assessment-overview/ndacms:resource. Accessed

387   04/25/2021 2021

388 30 Aboulenain S, Saber AY (2021) Primary OsteoarthritisStatPearls. StatPearls Publishing

389 Copyright © 2021, StatPearls Publishing LLC., Treasure Island (FL)

390 31 Hoaglund FT (2013) Primary osteoarthritis of the hip: a genetic disease caused by

391   European genetic variants. J Bone Joint Surg Am 95:463-468

392 32 Hunter DJ, Guermazi A, Lo GH et al (2011) Evolution of semi-quantitative whole joint

393   assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis and

394   Cartilage 19:990-1002

395 33 Collins JE, Losina E, Nevitt MC et al (2016) Semiquantitative Imaging Biomarkers of

396   Knee Osteoarthritis Progression: Data From the Foundation for the National Institutes of

397   Health Osteoarthritis Biomarkers Consortium. Arthritis Rheumatol 68:2422-2431

398 34 Schisterman EF, Cole SR, Platt RW (2009) Overadjustment Bias and Unnecessary

399   Adjustment in Epidemiologic Studies. Epidemiology 20:488-495

400 35 Blagojevic M, Jinks C, Jeffery A, Jordan KP (2010) Risk factors for onset of

401   osteoarthritis of the knee in older adults: a systematic review and meta-analysis.

402   Osteoarthritis and Cartilage 18:24-33

403 36 Kovari E, Kaposi A, Bekes G et al (2020) Comorbidity clusters in generalized

404   osteoarthritis among female patients: A cross-sectional study. Seminars in Arthritis and

405   Rheumatism 50:183-191

406 37 Haj-Mirzaian A, Mohajer B, Guermazi A et al (2019) Heberden's Nodes and Knee

407   Osteoarthritis–Related Osseous Structural Damage: Exploratory Study From the

408   Osteoarthritis Initiative. Arthritis & Rheumatology 71:935-940

409 38 Smith DA, Galin I (2006) Statin therapy for native and peri-interventional coronary heart

410   disease. Curr Mol Med 6:589-602

411 39 Jackevicius CA, Mamdani M, Tu JV (2002) Adherence with statin therapy in elderly

412   patients with and without acute coronary syndromes. ACC Current Journal Review 11:36

413 40 Wei MY, Ito MK, Cohen JD, Brinton EA, Jacobson TA (2013) Predictors of statin

414   adherence, switching, and discontinuation in the USAGE survey: Understanding the use

415   of statins in America and gaps in patient education. Journal of Clinical Lipidology 7:472-

416   483

417 41 Warren JR, Falster MO, Fox D, Jorm L (2013) Factors influencing adherence in long-

418   term use of statins. Pharmacoepidemiology and Drug Safety 22:1298-1307

419 42 Mauskop A, Borden WB (2011) Predictors of Statin Adherence. Current Cardiology

420   Reports 13:553

421 43 Parkinson L, Waters DL, Franck L (2017) Systematic review of the impact of

422   osteoarthritis on health outcomes for comorbid disease in older people. Osteoarthritis and

423   Cartilage 25:1751-1770

424 44 Mann DM, Allegrante JP, Natarajan S, Halm EA, Charlson M (2007) Predictors of

425   Adherence to Statins for Primary Prevention. Cardiovascular Drugs and Therapy 21:311-

426   316

427 45 Vinker S, Shani M, Baevsky T, Elhayany A (2008) Adherence with statins over 8 years

428   in a usual care setting. The American journal of managed care 14:388-392

429 46 Mercado C, DeSimone AK, Odom E et al (2015) Prevalence of cholesterol treatment

430   eligibility and medication use among adults—United States, 2005–2012. 64:1305-1311

431 47 Roemer FW, Guermazi A, Collins JE et al (2016) Semi-quantitative MRI biomarkers of

432   knee osteoarthritis progression in the FNIH biomarkers consortium

433   cohort − Methodologic aspects and definition of change. BMC Musculoskeletal Disorders

434   17:466

435 48 Boudreau DM, Daling JR, Malone KE, Gardner JS, Blough DK, Heckbert SR (2004) A

436   Validation Study of Patient Interview Data and Pharmacy Records for Antihypertensive,

437   Statin, and Antidepressant Medication Use among Older Women. Am J Epidemiol

438   159:308-317

439 49 Danaei G, Tavakkoli M, Hernan MA (2012) Bias in observational studies of prevalent

440   users: lessons for comparative effectiveness research from a meta-analysis of statins. Am

441   J Epidemiol 175:250-262

442 50 Force USPST (2016) Statin Use for the Primary Prevention of Cardiovascular Disease in

443   Adults: US Preventive Services Task Force Recommendation Statement. JAMA

444   316:1997-2007

445 51 (2015) New Indications and a Sense of (Re)purpose. EBioMedicine 2:1257-1258

446

447 **Figure and Table Legends**
448
449

450 **Figure 1.** Flowchart of study participants and exclusion criteria

451 *** Figure 1 ***

452 BML: Bone marrow lesion, HN: Heberden's node, KL: Kellgren-Lawrence, OAI: Osteoarthritis

453 initiative, PS: Propensity-score.

454   **Table 1.** Baseline characteristics of the study population before and after propensity score matching for statin use according to baseline

455   BML in MRI.

| Characteristic | HN+ participant with no/minimal BMLs | | | | | | HN+ participant with moderate/severe BMLs | | | | | |
| | Before matching | | | Propensity score-matched | | | Before matching | | | Propensity score-matched | | |
	Statin (-)	Statin (+)	SMD	Statin (-)	Statin (+)	SMD	Statin (-)	Statin (+)	SMD	Statin (-)	Statin (+)	SMD
No. of knees	339	175		166	166		386	203		190	190	
Variables in the P.S matching (Potential confounders)												
Age (year) [mean (SD)]	60.99 (8.69)	63.82 (7.87)	**0.342**	63.66 (8.41)	63.61 (7.93)	0.006	62.91 (8.65)	64.91 (7.75)	**0.244**	63.94 (7.54)	64.75 (7.80)	0.098
No. of women [N (%)]	239 (70.5)	109 (62.3)	**0.175**	110 (66.3)	104 (62.7)	0.076	251 (65.0)	125 (61.6)	0.072	120 (63.2)	118 (62.1)	0.022
BMI (kg/m²) [mean (SD)]	28.10 (4.69)	28.40 (3.84)	0.069	28.15 (3.94)	28.31 (3.91)	0.04	28.92 (4.46)	30.05 (4.19)	**0.261**	29.50 (4.67)	29.72 (3.97)	0.049
Statin CVD indications except dyslipidemia[N(%)]♦	76 (22.4)	52 (29.7)	**0.167**	48 (28.9)	50 (30.1)	0.026	119 (30.8)	89 (43.8)	**0.272**	76 (40.0)	78 (41.1)	0.021
Alcohol use, ≥1/week [N (%)]	167 (49.3)	75 (42.9)	**0.129**	76 (45.8)	75 (45.2)	0.012	174 (45.1)	83 (40.9)	0.085	78 (41.1)	81 (42.6)	0.032
Smoking, Current or past [N (%)]	151 (44.5)	92 (52.6)	**0.161**	84 (50.6)	87 (52.4)	0.036	170 (44.0)	101 (49.8)	**0.115**	90 (47.4)	91 (47.9)	0.011
PASE score [mean (SD)]	166.32 (79.40)	155.45 (70.78)	**0.145**	156.54 (74.01)	155.16 (72.30)	0.019	164.61 (82.81)	150.55 (72.49)	**0.181**	152.93 (78.22)	152.84 (73.36)	0.001
Race, non-white [N (%)]†	42 (12.4)	19 (10.9)	0.048	17 (10.2)	17 (10.2)	0.001	66 (17.1)	34 (16.7)	0.009	32 (16.8)	32 (16.8)	0.001
Other variables not in the P.S matching												
Hx of knee Injury, [N (%)]	80 (23.6)	36 (20.6)	0.07	37 (22.3)	35 (21.1)	0.03	121 (31.3)	72 (35.5)	0.09	59 (31.1)	65 (34.2)	0.07
Statin type			–			–			–			–
atorvastatin	–	79 (60.3)		–	73 (59.3)		–	82 (48.2)		–	77 (49.0)	

26

fluvastatin	–	2 (1.5)		–	2 (1.6)		–	3 (1.8)		–	2 (1.3)	
lovastatin	–	6 (4.6)		–	6 (4.9)		–	9 (5.3)		–	7 (4.5)	
pravastatin	–	9 (6.9)		–	8 (6.5)		–	14 (8.2)		–	14 (8.9)	
rosuvastatin	–	6 (4.6)		–	6 (4.9)		–	7 (4.1)		–	6 (3.8)	
simvastatin	–	29 (22.1)		–	28 (22.8)		–	55 (32.4)		–	51 (32.5)	
Statin use duration, years, [mean (SD)]	0.00 (0.00)	3.92 (2.05)	**2.7**	0.00 (0.00)	3.90 (2.06)	**2.68**	0.00 (0.00)	4.23 (2.06)	**2.9**	0.00 (0.00)	4.18 (2.08)	**2.85**
Number of affected subregions with BML			0.07			0.05			**0.2**			**0.32**
0	206 (60.8)	101 (57.7)		95 (57.2)	94 (56.6)		75 (19.4)	39 (19.2)		37 (19.5)	37 (19.5)	
1	83 (24.5)	44 (25.1)		45 (27.1)	43 (25.9)		24 (6.2)	18 (8.9)		7 (3.7)	17 (8.9)	
2	50 (14.7)	30 (17.1)		26 (15.7)	29 (17.5)		51 (13.2)	34 (16.7)		22 (11.6)	34 (17.9)	
3	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		99 (25.6)	55 (27.1)		56 (29.5)	51 (26.8)	
4	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		64 (16.6)	29 (14.3)		32 (16.8)	25 (13.2)	
≥5	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		73 (18.9)	28 (13.8)		36 (18.9)	26 (13.7)	
Maximum BML grade in knee			**0.16**			0.03			0.02			0.09
0	148 (43.7)	63 (36.0)		63 (38.0)	61 (36.7)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
1	191 (56.3)	112 (64.0)		103 (62.0)	105 (63.3)		58 (15.0)	30 (14.8)		34 (17.9)	28 (14.7)	
2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		217 (56.2)	116 (57.1)		107 (56.3)	109 (57.4)	
3	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		111 (28.8)	57 (28.1)		49 (25.8)	53 (27.9)	
Baseline KL grade			0.21			0.235			0.062			0.166

Grade 0	111 (32.7)	49 (28.0)	53 (31.9)	45 (27.1)	54 (14.0)	28 (13.8)	22 (11.6)	28 (14.7)
Grade 1	102 (30.1)	68 (38.9)	50 (30.1)	64 (38.6)	92 (23.8)	50 (24.6)	43 (22.6)	48 (25.3)
Grade 2	94 (27.7)	39 (22.3)	49 (29.5)	38 (22.9)	137 (35.5)	76 (37.4)	65 (34.2)	67 (35.3)
Grade 3	32 (9.4)	19 (10.9)	14 (8.4)	19 (11.4)	103 (26.7)	49 (24.1)	60 (31.6)	47 (24.7)

456 Data are presented as numbers of knees. Statin (+) and Statin (-) corresponds to statin users and non-users, respectively. Knees with

457 both ≤2 knee subregions with BMLs and maximum BML score ≤1 were regarded with no/minimal BML involvement, while knees

458 either having >2 knee subregions with BMLs or maximum BML score >1 were considered with moderate/severe BML involvement.

459 BMI: Body mass index, BML: Bone Marrow Lesion, HN: Heberden's node, PASE: physical activity scale for the elderly, SMD:

460 Standardized mean difference, SD: Standard deviation, N: Number of knees

461 A significant difference for SMD was defined as ≥ 0.1.

462 ♦ Statin CVD indications except dyslipidemia were indicated as the presence of either history of coronary artery disease, cerebrovascular

463 accident, diabetes (any stage of diabetes vs. no medical history of diabetes), or hypertension in clinical examination systolic blood

464 pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg at OAI visit clinical examination).

465 † race of participants was categorized as white and non-white considering the small number of participants in each non-white race group.

466

Table 2. Longitudinal 24-month assessment of subchondral BML worsening in MRI between propensity-score matched HN[+] statin users vs. non-users, according to BML involvement of the knee joint in the baseline visit MRI examination.

Statin user: non-user	HN[+]	
	No/minimal BML in baseline MRI	**Moderate/severe BML in baseline MRI**
	N: 332 (166:166)	N: 380 (190:190)
Worsening in number of affected subregions with BML	**0.54 (0.33 - 0.88), P:0.015**	1.04 (0.7 - 1.53), P:0.859
Maximum worsening in BML score	**0.62 (0.39 - 0.98), P:0.041**	0.96 (0.65 - 1.42), P:0.841
Worsening in BML score or number of affected subregions	**0.60 (0.37 - 0.99), P:0.044**	0.85 (0.50 - 1.47), P:0.566

Participants in the HN[+] subcohort were separately matched for possible confounders with the 1:1 PS matching method. Longitudinal measures of BML worsening were compared between matched statin users: non-users using logistic mixed-effect linear models. Previously validated longitudinal 24-month BML dependent variables (i.e., outcome to the models) included 1) worsening in the number of affected subregions with BML (ranged from Improvement to no change, worsening in 1 subregion, and worsening in ≥2 subregions), 2) maximum worsening in BML score (ranged from no change, within-grade worsening, to worsening by 1 grade, and worsening by ≥2 grades), and 3) worsening in either of BML score (whole or within-grade) or the number of affected subregions (yes/no). All models were adjusted for participants propensity score, baseline Kellgren-Lawrence grade, medial Joint Space Narrowing (JSN) grade, and BML status (two variables of 1. number of affected subregions affected by BMLs, and 2. max BML score in the joint) while considering random intercept for each cluster of matched statin user: non-user and random intercept considering within-subject similarities (due to the inclusion of both knees in a minority of participants, 5%) where the knee is nested within participant ID. All analyses were categorized

484 according to baseline BML involvement in MRI. Knees with both ≤2 knee subregions with BMLs

485 and maximum BML score ≤1 were regarded with no/minimal BML involvement, while knees

486 either having >2 knee subregions with BMLs or maximum BML score >1 were considered with

487 moderate/severe BML involvement. BML: Bone marrow lesions, HN: Heberden's node.

488

Supplementary Material

490 **List of confounding variables**

491   The selected covariates include age (years, quartiles), sex (male vs. female), body mass index

492 (BMI, quartiles) (kg/m^2), physical activity for elderly scale (PASE) score, race (categorized as

493 Caucasian, African Americans, Asians, others), smoking status (classified as "never smoked,"

494 "current or past smoker"), alcohol consumption in the past 12 months <1unit/week or

495 ≥1unit/week), having diabetes (any stages of diabetes vs. no medical history of diabetes), history

496 of heart attack (positive vs. negative), cerebrovascular accident (positive vs. negative), or

497 hypertension (systolic blood pressure ≥140 or diastolic blood pressure ≥90). Comorbid diabetes,

498 history of heart attack, cerebrovascular accident, and hypertension were all categorized together,

499 making a binomial variable indicating the presence of either of these comorbid statin CVD

500 indications. Units, levels, and categories of variables are listed in Table 1 in the main text.

501 **Little's test**

502 The pattern of missing data was assessed using the test of missing completely at random (Little's

503 test), visual representation, and logistic regression models, which resulted in a missing not at the

504 random pattern (1) in the OAI dataset, with fewer than 1.5% of values missing for all matching

505 variables except for combined variable of statin cardiovascular disease (CVD) indications except

506 dyslipidemia (2.9%). Despite the missing not at random pattern of data, multiple imputation

507 models were used according to previous studies trying to reduce the possible associated bias (2).

508

509 **Supplementary Figure 1.** Directed acyclic graphs visual representations of causal assumptions

510 variables potentially contributing to confounding by indication bias.
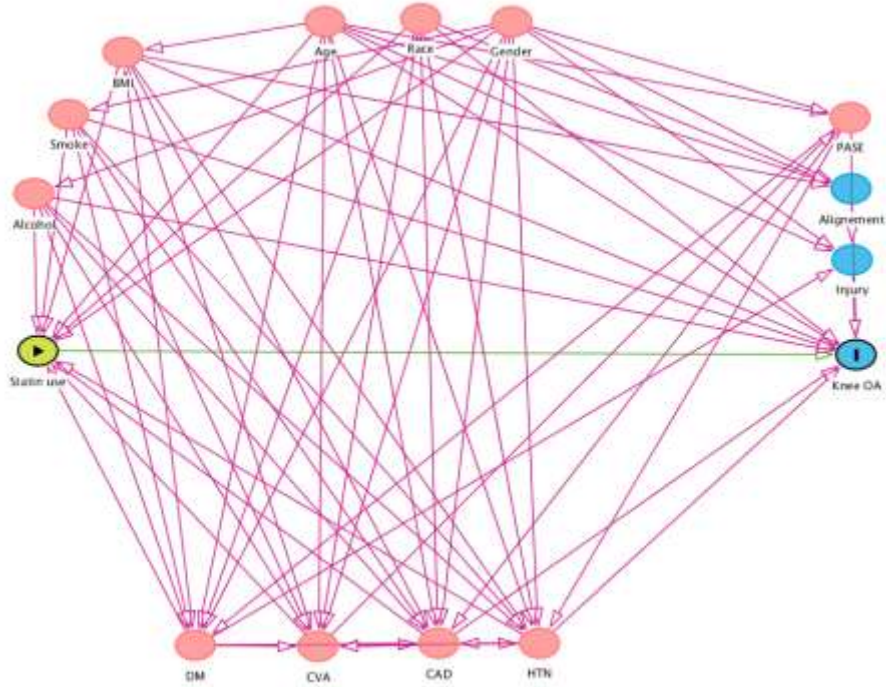
511

512 Selection of the variables potentially contributing to confounding by indication bias (red circles)

513 for covariate adjustments. Exposure was statin use, and the outcome was knee OA structural and

514 symptomatic measures. Variables marked as blue circles were regarded as ancestors of the

515 outcome, which have no causal relationship with exposure and outcome variables and were not

516 included in the model adjustment. History of knee injury was defined as a positive response to the

517 question "Knee ever injured badly enough to limit the ability to walk for at least two days?"

518 Despite that history of knee injury might have causal relationship with knee OA BML damage, it

519 is unlikely to have causal effect on the statin use. Therefore, it has not been included as a

520 confounder in the propensity-score matching model.

521   OA: Osteoarthritis, BMI: Body mass index, PASE: physical activity for elderly scale, CVA:

522   Cerebrovascular accident, DM: Diabetes Mellitus, HTN: Hypertension, CAD: Coronary artery

523   disease. Injury: a history of knee injury, Alignment: knee alignment.

524

Supplementary Table 1. Comparison of baseline characteristics between the participants of OAI

ancillary studies on MRI-based worsening of the OA structural damage and all OAI participants.

<u>Relevant to Exclusion #3 in the methods and Figure 1 of study</u>.

Characteristic	OAI participants not included in the ancillary studies	Participants of OAI ancillary studies on MRI-based worsening of the OA structural damage	SMD
No. of knees	7641	1586	
Variables in the P.S matching (Potential confounders)			
Age (year) [mean (SD)]	61.16 (9.19)	61.36 (8.83)	0.023
No. of women [N (%)]	5608 (58.5)	1021 (60.9)	0.049
No. of obese patients [N (%)]	3534 (36.9)	703 (41.9)	0.098
Statin CVD indications except dyslipidemia [N(%)]♦	2812 (30.2)	493 (30.2)	0.002
Alcohol use, ≥1/week [N (%)]	4088 (43.0)	739 (44.5)	0.03
Smoking, Current or past [N (%)]	4462 (47.1)	780 (47.2)	0.001
PASE score [mean (SD)]	160.84 (82.48)	166.33 (82.01)	0.067
Race, non-white [N (%)]†	2002 (20.9)	280 (16.7)	0.97
Variables not included in the P.S matching			
Hx. of knee Injury, [N (%)]	2584 (27.2)	509 (30.7)	0.077
Statin use at baseline, [N (%)]	2424 (25.3)	439 (26.2)	0.021
Statin type, [N (%)]			0.052
atorvastatin	1282 (52.9)	235 (53.5)	
fluvastatin	40 (1.7)	8 (1.8)	
lovastatin	108 (4.5)	18 (4.1)	
pravastatin	240 (9.9)	44 (10.0)	
rosuvastatin	102 (4.2)	22 (5.0)	
simvastatin	652 (26.9)	112 (25.5)	
OAI subcohort assignment, [N (%)]			0.197
Incidence	6568 (68.5)	1041 (62.1)	
Non-exposed	244 (2.5)	17 (1.0)	
Progression	2780 (29.0)	619 (36.9)	
Baseline X-ray KL grade, [N (%)]			0.385
Grade 0	3354 (37.5)	359 (21.5)	
Grade 1	1592 (17.8)	470 (28.2)	
Grade 2	2468 (27.6)	489 (29.3)	
Grade 3	1224 (13.7)	273 (16.4)	
Grade 4	302 (3.4)	77 (4.6)	
Baseline X-ray medial JSN grade, [N (%)]			0.242

Grade 0	5706 (63.8)	870 (52.2)
Grade 1	2090 (23.4)	497 (29.8)
Grade 2	948 (10.6)	240 (14.4)
Grade 3	196 (2.2)	61 (3.7)

528   Data are presented as numbers of knees. BML: Bone Marrow Lesion, HN: Heberden's node, JSN:

529   Joint Space Narrowing (according to OARSI criteria), KL: Kellgren-Lawrence, PASE: physical

530   activity scale for the elderly, SMD: Standardized mean difference, SD: Standard deviation, N:

531   Number of knees. According to OAI protocol, participants were assigned to three Progression,

532   incidence, and non-exposed subcohorts based on the baseline assessment of radiographic knee OA

533   and its risk factors. Participants with terminal knee OA (including knee replacement or KL grade

534   of 4 in the baseline X-ray) were excluded. Obesity was defined as BMI ≥30 kg/m2.

535   A significant difference for SMD was defined as ≥ 0.1.

536   ♦ Statin CVD indications except dyslipidemia were indicated as the presence of either history of

537   coronary artery disease, cerebrovascular accident, diabetes (any stage of diabetes vs. no medical

538   history of diabetes), or hypertension in clinical examination systolic blood pressure ≥140 mm Hg

539   or diastolic blood pressure ≥90 mm Hg at OAI visit clinical examinations).

540   † Race of participants was categorized as white and non-white considering the small number of

541   participants in each non-white race group.

542

543 **Supplementary Table 2.** Sensitivity analysis of the 24-month assessment of subchondral BML

544 worsening results to #1) stratification for OA phenotype (HN$^-$ vs. HN$^+$), #2) exclusion of

545 participants with imputed missing data, #3) inclusion of entire HN$^+$ cohort of eligible OAI

546 participants without PS-matching, and #4) random exclusion of one knee of participants whose

547 both knees were included in HN$^+$ statin users vs. non-users.

Statin user: non-user	#1) Sensitivity to stratification for OA phenotype	
	All PS-matched participants (HN$^+$ & HN$^-$)	**HN$^-$ PS-matched participants**
Worsening in number of affected subregions with BML (0-3)	0.92 (0.72 - 1.18), P:0.505	1.05 (0.67 - 1.64), P:0.844
Maximum worsening in BML score (0-3)	0.95 (0.75 - 1.21), P:0.697	1.21 (0.79 - 1.86), P:0.390
Worsening in BML score or number of affected subregions (Y/N)	0.81 (0.61 - 1.07), P:0.143	1.06 (0.65 - 1.74), P:0.814
Statin user: non-user	**#2) Sensitivity to the exclusion of participants with imputed missing data**	
	No/minimal BML involvement	**Moderate/severe BML involvement**
Worsening in number of affected subregions with BML (0-3)	**0.58 (0.35 - 0.96), P:0.036**	0.98 (0.66 - 1.46), P:0.912
Maximum worsening in BML score (0-3)	0.67 (0.42 - 1.06), P:0.09	0.99 (0.67 - 1.47), P:0.961
Worsening in BML score or number of affected subregions (Y/N)	**0.58 (0.34 - 0.97), P:0.039**	0.84 (0.48 - 1.45), P:0.521
Statin user: non-user	**#3) Sensitivity to the inclusion of the entire cohort of eligible OAI HN$^+$ participants without PS-matching**	
	No/minimal BML involvement	**Moderate/severe BML involvement**
Worsening in number of affected subregions with BML (0-3)	**0.65 (0.42 - 0.98), P:0.042**	1.13 (0.81 - 1.57), P:0.46
Maximum worsening in BML score (0-3)	**0.65 (0.43 - 0.95), P:0.029**	1.06 (0.76 - 1.46), P:0.737
Worsening in BML score or number of affected subregions (Y/N)	**0.67 (0.45 - 0.98), P:0.042**	0.80 (0.52 - 1.24), P:0.313
	#4) Sensitivity to the random exclusion of one knee of participants whose both knees were included	

Statin user: non-user	No/minimal BML involvement	Moderate/severe BML involvement
Worsening in number of affected subregions with BML (0-3)	**0.55 (0.32 - 0.91), P:0.021**	1.00 (0.66 - 1.50), P:0.987
Maximum worsening in BML score (0-3)	**0.56 (0.35 - 0.89), P:0.015**	0.87 (0.58 - 1.30), P:0.494
Worsening in BML score or number of affected subregions (Y/N)	**0.57 (0.34 - 0.97), P:0.038**	0.79 (0.45 - 1.38), P:0.407

548 Previously validated longitudinal 24-month BML dependent variables (i.e., outcome to the

549 models) included 1) worsening in the number of affected subregions with BML (ranged from

550 Improvement to no change, worsening in 1 subregion, and worsening in 2+ subregions), 2)

551 maximum worsening in BML score (ranged from no change, within-grade worsening, to

552 worsening by 1 grade, and worsening by 2+ grades), and 3) worsening in either of BML score

553 (whole or within-grade) or the number of affected subregions (yes/no). Longitudinal measures of

554 BML worsening were compared between statin users: non-users using logistic mixed-effect

555 regression models while considering random intercept for each cluster of matched statin user: non-

556 user and random intercept considering within-subject similarities (due to the inclusion of both

557 knees in a minority of participants, 5%) where the knee is nested within participant ID (except for

558 sensitivity analysis regarding the random exclusion of one knee of participants who their both

559 knees were included). All analyses were categorized according to baseline BML involvement in

560 MRI. Knees with both ≤2 knee subregions with BMLs and maximum BML score ≤1 were regarded

561 with no/minimal BML involvement, while knees either having >2 knee subregions with BMLs or

562 maximum BML score >1 were considered with moderate/severe BML involvement.

563 Models were adjusted for participants' propensity score calculated for variables potentially

564 contributing to confounding by indication bias and baseline KL grade, medial JSN grade, and

565 BML status.

566 **Supplementary Table 3.** Baseline characteristics of the Heberden's nodes negative (HN⁻) participants before and after propensity score

567 matching according to statin use.

	HN⁻ participant with no/minimal BMLs						HN⁻ participant with moderate/severe BMLs					
	Before matching			Propensity score-matched			Before matching			Propensity score-matched		
	Statin (-)	Statin (+)	SMD	Statin (-)	Statin (+)	SMD	Statin (-)	Statin (+)	SMD	Statin (-)	Statin (+)	SMD
	164	69		65	65		164	86		75	75	
Variables in the matching												
Age (year) [mean (SD)]	55.52 (7.36)	60.20 (9.36)	**0.555**	59.09 (7.50)	59.48 (9.12)	0.046	57.21 (8.39)	60.95 (8.20)	**0.45**	59.83 (9.65)	59.79 (8.03)	0.01
No. of women [N (%)]	91 (55.5)	31 (44.9)	**0.212**	28 (43.1)	29 (44.6)	0.031	100 (61.0)	38 (44.2)	**0.34**	32 (42.7)	35 (46.7)	0.08
BMI (kg/m²) [mean (SD)]	28.56 (4.79)	30.49 (4.61)	**0.411**	29.71 (4.93)	30.34 (4.68)	**0.133♣**	30.81 (5.54)	31.19 (4.64)	0.08	30.93 (5.66)	31.26 (4.86)	0.06
Statin CVD indications except dyslipidemia [N (%)]	31 (18.9)	26 (37.7)	**0.426**	19 (29.2)	22 (33.8)	0.099	54 (32.9)	29 (33.7)	0.02	28 (37.3)	22 (29.3)	**0.17♣**
Alcohol use, ≥1/week [N (%)]	66 (40.2)	23 (33.3)	**0.144**	24 (36.9)	21 (32.3)	0.097	72 (43.9)	41 (47.7)	0.08	34 (45.3)	34 (45.3)	0.01
Smoking, Current or past [N (%)]	72 (43.9)	42 (60.9)	**0.345**	42 (64.6)	39 (60.0)	0.095	72 (43.9)	30 (34.9)	**0.19**	31 (41.3)	28 (37.3)	0.08
PASE score [mean (SD)]	179.71 (90.36)	175.42 (91.93)	0.047	163.78 (81.52)	173.69 (93.07)	**0.113♣**	171.52 (89.75)	179.15 (84.98)	0.09	174.49 (84.20)	181.47 (88.71)	0.08
Race, non-white [N (%)]	23 (14.0)	6 (8.7)	**0.169**	5 (7.7)	6 (9.2)	0.055	57 (34.8)	23 (26.7)	**0.17**	25 (33.3)	23 (30.7)	0.06
Variables not in the matching												
Hx of knee Injury, [N (%)]*	47 (28.7)	22 (31.9)	0.07	15 (23.1)	21 (32.3)	**0.21**	56 (34.1)	40 (46.5)	**0.25**	22 (29.3)	36 (48.0)	**0.39**
Statin type*			–			–			–			–

atorvastatin	–	31 (60.8)		–	30 (63.8)		–	26 (41.3)		–	21 (38.9)	
fluvastatin	–	1 (2.0)		–	1 (2.1)		–	2 (3.2)		–	2 (3.7)	
lovastatin	–	1 (2.0)		–	1 (2.1)		–	2 (3.2)		–	2 (3.7)	
pravastatin	–	6 (11.8)		–	6 (12.8)		–	11 (17.5)		–	10 (18.5)	
rosuvastatin	–	4 (7.8)		–	3 (6.4)		–	4 (6.3)		–	4 (7.4)	
simvastatin	–	8 (15.7)		–	6 (12.8)		–	18 (28.6)		–	15 (27.8)	
Statin use duration, years, [mean (SD)]	0.00 (0.00)	3.67 (1.92)	**2.7**	0.00 (0.00)	3.62 (1.96)	**2.61**	0.00 (0.00)	3.63 (1.84)	**2.79**	0.00 (0.00)	3.53 (1.86)	**2.68**
Number of knee subregions with BML*			**0.15**			**0.15**			**0.47**			**0.59**
0	103 (62.8)	43 (62.3)		40 (61.5)	43 (66.2)		44 (26.8)	10 (11.6)		23 (30.7)	8 (10.7)	
1	40 (24.4)	14 (20.3)		16 (24.6)	12 (18.5)		10 (6.1)	7 (8.1)		3 (4.0)	6 (8.0)	
2	21 (12.8)	12 (17.4)		9 (13.8)	10 (15.4)		30 (18.3)	13 (15.1)		16 (21.3)	12 (16.0)	
3	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		39 (23.8)	21 (24.4)		13 (17.3)	18 (24.0)	
4	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		16 (9.8)	15 (17.4)		8 (10.7)	13 (17.3)	
≥5	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		25 (15.2)	20 (23.3)		12 (16.0)	18 (24.0)	
Maximum BML grade in knee*			**0.14**			**0.42**			0.08			0.07
0	65 (39.6)	32 (46.4)		19 (29.2)	32 (49.2)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
1	99 (60.4)	37 (53.6)		46 (70.8)	33 (50.8)		15 (9.1)	7 (8.1)		5 (6.7)	6 (8.0)	
2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		89 (54.3)	50 (58.1)		43 (57.3)	41 (54.7)	

| 3 | | 0 (0.0) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | | 60 (36.6) | 29 (33.7) | | 27 (36.0) | 28 (37.3) |

568 Data are presented as numbers of knees. Statin (+) and Statin (-) corresponds to statin users and non-users, respectively. BMI: Body

569 mass index, BML: Bone Marrow Lesion, HN: Heberden's node, PASE: physical activity scale for the elderly, SMD: Standardized mean

570 difference, SD: Standard deviation, N: Number of knees

571 A significant difference for SMD was defined as ≥ 0.1.

572 ♦ Statin CVD indications except dyslipidemia were indicated as the presence of either history of coronary artery disease, cerebrovascular

573 accident, diabetes (any stage of diabetes vs. no medical history of diabetes), or hypertension in clinical examination systolic blood

574 pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg at OAI visit clinical examination).

575 † race of participants was categorized as white and non-white considering the small number of participants in each non-white race group.

576 ♣ Variables that had an SMD ≥ 0.1 between matched groups after PS-matching were included as a covariate in the statistical models for

577 further adjustment.

578 **Supplementary data references**

579 1. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation

580 for missing data in epidemiological and clinical research: Potential and pitfalls. BMJ

581 2009;339:157–160.

582 2. Resseguier N, Giorgi R, Paoletti X. Sensitivity analysis when data are missing not-at-random.

583 Epidemiology 2011;22:282–283.