What Are the Prognostic Factors for Radiographic Progression of Knee Osteoarthritis? A Meta-analysis

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Abstract

Background A previous systematic review on prognostic factors for knee osteoarthritis (OA) progression showed associations for generalized OA and hyaluronic acid levels. Knee pain, radiographic severity, sex, quadriceps strength, knee injury, and regular sport activities were not associated. It has been a decade since the literature search of that review and many studies have been performed since then investigating prognostic factors for radiographic knee OA progression.

Questions/purposes The purpose of this study is to provide an updated systematic review of available evidence regarding prognostic factors for radiographic knee OA progression.

Methods We searched for observational studies in MEDLINE and EMBASE. Key words were: knee, osteoarthritis (or arthritis, or arthrosis, or degenerative joint disease), progression (or prognosis, or precipitate, or predictive), and case-control (or cohort, or longitudinal, or follow-up). Studies fulfilling the inclusion criteria were assessed for methodologic quality according to established criteria for reviews on prognostic factors in musculoskeletal disorders. Data were extracted and results were pooled if possible or summarized according to a best-evidence synthesis. A total of 1912 additional articles were identified; 43 met our inclusion criteria. The previous review contained 36 articles, thus providing a new total of 79 articles. Seventy-two of the included articles were scored high quality, the remaining seven were low quality.

Results The pooled odds ratio (OR) of two determinants showed associations with knee OA progression: baseline knee pain (OR, 2.38 [95% CI, 1.74–3.27) and Heberden nodes (OR, 2.66 [95% CI, 1.46–8.84]). Our best-evidence synthesis showed strong evidence that varus alignment, serum hyaluronic acid, and tumor necrosis factor-α are associated with knee OA progression. There is strong evidence that sex, former knee injury, quadriceps strength, smoking, running, and regular performance of sports are not associated with knee OA progression. Evidence for the majority of determined associations, however, was limited, conflicting, or inconclusive.

Conclusions Baseline knee pain, presence of Heberden nodes, varus alignment, and high levels of serum markers hyaluronic acid and tumor necrosis factor-α predict knee OA progression. Sex, knee injury, and quadriceps strength, among others, did not predict knee OA progression. Large variation remains in definitions of knee OA and knee OA progression. Clinical studies should use more consistent definitions of these factors to facilitate data pooling by future meta-analyses.

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Introduction

The prevalence of osteoarthritis of the knee (OA) is increasing worldwide and this burden will continue to increase owing to aging of the general population [95]. Consequent to an increase in incidence is the rise in the number of patients with knee OA who are prone to further deterioration of the knee. It therefore is important to better understand, control, and attempt to prevent further progression of disease in patients with knee OA.

In 2007, Belo et al. [4] published the first systematic review on prognostic factors for progression of knee OA. They found that generalized OA and hyaluronic acid levels were associated with progression of knee OA. Knee pain, baseline radiographic severity, sex, quadriceps strength, knee injury, and regular sport activities were not associated. For the remaining factors the evidence was limited or conflicting. Their literature search had been performed up to December 2003; however, many articles studying radiographic progression of knee OA have been published in the decade since that review. Therefore, we performed an update of the systematic review of observational studies by Belo et al. [4] to determine the currently available evidence on prognostic factors for radiographic progression of knee OA.

Search Strategy and Criteria

Literature Search

In the review by Belo et al. [4], the search of the literature had been performed in MEDLINE and EMBASE for all available observational studies up to December 2003. We searched in MEDLINE and EMBASE from December 2003 up to February 2013. Key words were: knee, osteoarthritis (or arthritis, or arthrosis, or degenerative joint disease), progression (or prognosis, or precipitate, or predictive), and case-control (or cohort, or longitudinal, or follow-up). Articles were reviewed for inclusion independently by two authors (ANB and JNB or JR). The following inclusion criteria were used: 85% or more of participants in the analyses for OA progression had radiographic evidence of knee OA at baseline; the study investigated determinants associated with radiographic knee OA progression; radiographic progression was the outcome measure; the study had a case-control or cohort design with a minimal 1-year follow-up; full text of the article was available; the study was in English, Dutch, German, or French. Studies that observed the incidence of knee OA were excluded. A detailed description of our search strategy is available online (Appendix 1. Supplemental materials are available with the online version of CORR®). All articles were reviewed for inclusion independently by two authors (ANB and JNB or JR). Studies that used MRI features to define OA progression were excluded. However, studies determining MRI features as prognostic factors were included.

Methodologic Quality

The same methodologic quality assessment criteria as in the original review by Belo et al. [4] were used for this review (Table 1). These criteria were based on established criteria used in systematic reviews of prognostic factors for patients with musculoskeletal disorders and were described by Lievense et al. [49], Scholten-Peeters et al. [69], and Altman [1]. The criteria cover the internal validity and the informativeness of the study. All included articles were scored independently by two authors (ANB and JNB or JR). Cohen’s kappa coefficient (κ) was calculated to indicate the interrater agreement.

Data Extraction

Study population characteristics, observed risk factors, definitions of knee OA progression, and measures of association were extracted.

Table 1. Methodologic quality assessment criteria

| Study population |
|------------------|
| Description of source population |
| Valid inclusion criteria |
| Sufficient description of inclusion criteria |
| Followup |
| Followup at least 1 year |
| Prospective or retrospective data collection |
| Loss to followup ≤ 20% |
| Information about loss to followup (selective for age, sex, or severity) |
| Exposure |
| Exposure assessment blinded for the outcome |
| Exposure measured identically in the studied population at baseline and followup |
| Outcome |
| Outcome assessment blinded for exposure |
| Outcome measured identically in the studied population at baseline and followup |
| Analysis |
| Measure of association or measures of variance given |
| Adjusted for age, sex, and severity |

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Evidence Synthesis

Odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) were pooled when there was consistency in definition of study population, measured determinants, and assessed outcome (using Review Manager [RevMan], Version 5.3; Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We tested for heterogeneity with the chi-square and I-square tests. If heterogeneity was absent, a fixed effects model was applied to calculate pooled OR through the Mantel Haenszel test. In the absence of consistency among definitions for OA, a best-evidence synthesis was used to summarize the data. The level of evidence was based on the updated guidelines by Furlan et al. [34] and was divided into the following levels: (A) strong, ie, consistent (> 75%) findings among two or more high-quality studies; (B) moderate, ie, findings in one high-quality study and consistent findings in two or more low-quality studies; (C) limited, ie, findings in one high-quality study or consistent findings in three or more low-quality studies; and (D) conflicting or inconclusive evidence, ie, less than 75% of the studies reported consistent findings, or the results were based on only one study. High quality was defined as a quality score of 9 or greater (> 65% of the maximal attainable score). When performing the best-evidence synthesis, we only differentiated between high- and low-quality studies.

Studies Included

Of the 1912 articles identified using our search strategy, 43 met the inclusion criteria [2, 5, 7, 11, 13, 19, 20, 25–28, 30, 35, 38–44, 46, 48, 50–52, 55, 57–62, 64–66, 73, 74, 78, 85, 88, 91–93]. Belo et al. reviewed 36 articles [3, 8, 12, 14–16, 18, 21–24, 29, 31, 32, 37, 45, 47, 48, 52, 62, 63, 72, 74, 77, 80, 82, 85, 87, 93]; therefore the total number of included studies was 79, studying 59 different determinants for the progression of knee OA (Table 2). Three reviewers scored 559 items for the methodologic quality assessment of the 43 newly included articles and agreed on 519 items (93%; $k = 0.79$). The 50 disagreements were resolved in a single consensus meeting. Seventy-two of the 79 included articles were scored as high quality (score, 9–13), and only one article had the maximum attainable score. The remaining seven were scored as low quality, however no article was scored less than 6. Six different criteria were used for the inclusion of participants with OA and 13 definitions were applied to define radiographic OA progression. Furthermore, there were differences in how the determinants under study were measured, ie, continuous, dichotomous, or categorical with varying cut-off points.

Study Results

Because of the large number of studied determinants ($n = 59$), we pragmatically grouped our findings into five different categories: systemic factors (Table 3); disease characteristics (Table 4); intrinsic factors (Table 5); extrinsic factors (Table 6); and markers (Table 7). Some authors presented statistically significant associations to OA progression, but used p values or regression coefficients as measures of association [3, 5, 12, 14, 20, 21, 23, 31, 37, 41, 42, 44, 45, 47, 48, 52, 62, 63, 72, 74, 77, 80, 82, 85, 87, 93]. We chose to present only OR, RR, or HR as measures of associations; however, we have tabulated whether there was a significant association with OA progression in an article.

Sensitivity Analysis

For factors in which we were forced to use a best-evidence synthesis, we conducted a sensitivity analysis to check whether differences in sample size could have altered our conclusions. Additionally we checked whether large variances in followup could have led to different conclusions.

Results

Summaries of the results for systemic factors, disease characteristics, intrinsic factors, extrinsic factors, and markers are available (Appendix 2. Supplemental material is available with the online version of CORR).

Pooled Results

The presence of knee pain at baseline and Heberden nodes were associated with the progression of knee OA. The pooled ORs based on pools of studies with consistency among the definitions for OA inclusion, OA progression, and the determinant under study, were 2.38 for knee pain at baseline (95% CI,1.74–3.27; $I^2 = 52\%$) (Fig. 1) and 2.66 for the presence of Heberden nodes (95% CI, 1.46–8.84); $I^2 = 0\%$) (Fig. 2). Because of the large number of determinants with only a restricted number of studies per determinant and owing to lack of consistency between the reviewed studies regarding inclusion criteria, outcome measures, and measures of association, statistical pooling was not possible for the majority of the determinants.

Best-evidence Synthesis

For the remaining determinants, we applied a best-evidence synthesis, which showed that based on consistent findings
| Study                        | Number of participants | Followup (months) | Definition of OA for inclusion | Mean age in years ± SD | Women (%) | Quality score |
|-----------------------------|------------------------|-------------------|--------------------------------|------------------------|-----------|---------------|
| Sharma et al. [78], 2010    | 950                    | 30                | K/L                            | 63.6 ± 7.8             | 62        | 13            |
| Brouwer et al. [13], 2007   | 169                    | 72                | K/L                            | 66.4 ± 6.7             | 59        | 12            |
| Cerejo et al. [16], 2002    | 230                    | 18                | K/L                            | 64 ± 10.8              | 73        | 12            |
| Dieppe et al. [21], 1997    | 415                    | 37.6*             | K/L                            | 65.3                   | 68        | 12            |
| Felson et al. [29], 2003    | 223                    | 15 and 30         | OARSI                          | 66.2 ± 9.4             | 42        | 12            |
| Madan-Sharma et al. [50], 2008 | 186                  | 24                | ACR criteria                   | 60.2                   | 81        | 12            |
| McAlindon et al. [53], 1996 | 556                    | 120               | K/L                            | 70.3                   | 63        | 12            |
| Sharma et al. [79], 2001    | 230                    | 18                | K/L, JSW                        | 64.0 ± 11.1            | 75        | 12            |
| Spector et al. [81], 1994   | 58                     | 24                | K/L                            | 56.8 ± 5.9             | 100       | 12            |
| Vilim et al. [87], 2002     | 48                     | 36                | K/L, JSW                        | 62.8 (48–74)           | 71        | 12            |
| Bagge et al. [3], 1992      | 74                     | 48                | K/L                            | NR                     | 57        | 11            |
| Benichou et al. [5], 2010   | 67                     | 12                | OARSI                          | 60 ± 9                 | 64        | 11            |
| Botha-Scheepers et al. [11], 2008 | 86               | 24                | ACR criteria                   | 61                     | 80        | 11            |
| Brandt et al. [12], 1999    | 82                     | 31.5*             | K/L                            | 70.1                   | 70        | 11            |
| Denoble et al. [20], 2011   | 69                     | 36                | K/L                            | 64.5 ± 10.1            | 71        | 11            |
| Dieppe et al. [23], 1993    | 60                     | 60                | cOA and rOA                     | 62.2 ± 1.5             | 65        | 11            |
| Dieppe et al. [22], 2000    | 349                    | 96                | K/L                            | 65.3                   | 68        | 11            |
| Ledingham et al. [47], 1995 | 188                    | 24                | K/L                            | 71 (34–91)             | 63        | 11            |
| Miyazaki et al. [56], 2002  | 74                     | 72                | K/L, JSW                        | 69.9 ± 7.8             | 81        | 11            |
| Nevitt et al. [59], 2010    | 1754                   | 30                | K/L                            | 63 ± 8                 | 63        | 11            |
| Niu et al. [61], 2009       | 2623                   | 30                | K/L                            | 62.4 ± 8.0             | 59        | 11            |
| Sharif et al. [72], 1995    | 75                     | 60                | K/L                            | 64.2 ± 11.6            | 69        | 11            |
| Sharif et al. [75], 1995    | 57                     | 60                | JSW                            | NR                     | NR        | 11            |
| Sharif et al. [76], 2000    | 40                     | 60                | K/L                            | 65.2 ± 9.9             | 61        | 11            |
| Sharif et al. [74], 2004    | 115                    | 60                | K/L                            | 63.6 ± 9.7             | 55        | 11            |
| Sharif et al. [73], 2007    | 115                    | 60                | K/L                            | 63.6 ± 9.7             | 55        | 11            |
| Zhang et al. [96], 1998     | 551                    | 96                | K/L                            | 71 (63–91)             | 100       | 11            |
| Zhang et al. [94], 2000     | 473                    | 96                | K/L                            | 71 (63–91)             | 100       | 11            |
| Bettica et al. [8], 2002    | 216                    | 48                | Osteophytes, JSW                | NR                     | 100       | 10            |
| Cooper et al. [18], 2000    | 354                    | 61.2*             | K/L                            | 71.3                   | 72        | 10            |
| Dam et al. [19], 2009       | 138                    | 21                | ACR criteria                   | 60                     | 48        | 10            |
| Doherty et al. [24], 1996   | 134                    | 30                | K/L                            | 71 (41–88)             | 56        | 10            |
| Duncan et al. [25], 2011    | 414                    | 36                | K/L                            | 64.8 ± 8.1             | 51        | 10            |
| Felson et al. [31], 1995    | 869                    | 97.2*             | K/L                            | 70.8 ± 5.0             | 64        | 10            |
| Felson et al. [30], 2007    | 715 + 488              | 30 + 120          | NR, ACR criteria               | 53 ± 66                | 53 + 40   | 10            |
| Fraenkel et al. [32], 1998  | 423                    | 48                | K/L                            | NR                     | 67        | 10            |
| Hart et al. [37], 2002      | 830                    | 48                | Osteophytes, JSW                | 54.1 ± 5.9             | 100       | 10            |
| Kopec et al. [43], 2012     | 259                    | 72                | K/L                            | NR                     | 65        | 10            |
| Lane et al. [45], 1998      | 55                     | 108               | Osteophytes, JSW                | 66                     | 33        | 10            |
| Larsson et al. [46], 2012   | 74                     | 90                | OARSI                          | 50 (32–73)             | 18        | 10            |
| Mazzuca et al. [51], 2006   | 319                    | 30                | K/L                            | 60.0 ± 9.6             | 84        | 10            |
| McAlindon et al. [54], 1996 | 640                    | 120               | K/L                            | 70.3                   | 64        | 10            |
| Miyazaki et al. [55], 2012  | 84                     | 96                | K/L                            | 72.3 ± 3.1             | 93        | 10            |
| Muraki et al. [57], 2012    | 1313                   | 40                | K/L                            | 68.7 ± 11.3            | 75        | 10            |
| Nelson et al. [58], 2010    | 329                    | 60                | K/L                            | 61.9 ± 9.7             | 61        | 10            |
| Pavelka et al. [63], 2000   | 139                    | 60                | K/L                            | 59.1 ± 8.0             | 76        | 10            |
| Reijman et al. [66], 2007   | 532                    | 72                | K/L                            | 68.6 ± 7.0             | 68        | 10            |
| Schouten et al. [70], 1992  | 239                    | 146.4*            | K/L                            | 57.2 ± 6.1             | 59        | 10            |
in multiple high-quality studies, there seems to be strong
evidence that varus alignment, serum TNFα level, and
serum hyaluronic acid level are associated with radio-
graphic progression of knee OA. There also is strong
evidence that sex (female), former knee injury, quadriceps
strength, smoking, running, and regular performance of
sports are not associated with progression of knee OA.

There was moderate evidence showing that a higher
dietary intake of vitamin D is inversely associated with
progression of knee OA. Thus far, there is limited evidence
that ethnicity, metabolic syndrome, genetic components
adduction moment, meniscal damage, knee ROM, general
vitamin and β-carotene intake, serum levels IL-10 and
N-propeptide of type II collagen, synovial aggrecan
neoepitope amino acid sequence and IL-18, and fractal
dimension progression on radiographic fractal signature
analysis are associated with progression of knee OA. There
also is limited evidence that knee OA progression is not
associated with osteoporosis; past or present estrogen use;
uric acid concentrations; depression or anxiety; hand grip
(muscle) strength; bone marrow lesions or edema; menis-
cectomy; chondrocalcinosis; MRI-detected subchondral
bone cysts, cartilage loss, or joint effusion; AP knee laxity;
vitamin E intake; serum levels IL-1Ra and transforming
growth factor-β1; and 99mTc-MDP uptake on bone
scintigraphy.

| Study                          | Number of participants | Followup (months) | Definition of OA for inclusion | Mean age in years ± SD | Women (%) | Quality score |
|--------------------------------|------------------------|-------------------|--------------------------------|------------------------|-----------|--------------|
| Sharma et al. [77], 2003        | 171                    | 18                | K/L                            | 64.0 ± 11.1            | 74        | 10           |
| Spector et al. [80], 1992       | 63                     | 132               | K/L                            | 60 and 61              | 72        | 10           |
| Spector et al. [82], 1997       | 845                    | 48                | K/L                            | NR                     | 100       | 10           |
| Sugiyama et al. [83], 2003      | 110                    | 48                | JSW                            | 50.2 ± 6.0             | 100       | 10           |
| Wilder et al. [88], 2009        | 217                    | 67.2*             | K/L                            | 65.9 ± 9.6             | 61        | 10           |
| Yoshimura et al. [91], 2012     | 1296                   | 36                | K/L                            | 63                     | 66        | 10           |
| Zhai et al. [93], 2007          | 618                    | 84                | NR                             | 56                     | -NR       | 10           |
| Attur et al. [2], 2011          | 98                     | 24                | K/L                            | 60.7                   | 56        | 9            |
| Bergink et al. [7], 2009        | 1248                   | 72                | K/L                            | 66.2 ± 6.7             | 58        | 9            |
| Bruyere et al. [14], 2003       | 157                    | 36                | ACR criteria                   | 66.0 ± 7.3             | 76        | 9            |
| Bruyere et al. [15], 2003       | 157                    | 36                | ACR criteria                   | 66.0 ± 7.3             | 76        | 9            |
| Felson et al. [27], 2005        | 270                    | 30                | K/L                            | 66.6 ± 9.2             | 40        | 9            |
| Golightly et al. [35], 2010     | 1583                   | 72                | K/L                            | 60.9 ± 10.0            | 64        | 9            |
| Harvey et al. [38], 2010        | 2964                   | 30                | K/L                            | 62 ± 8                 | 58        | 9            |
| Haugen et al. [39], 2012        | 267                    | 12                | OARSI                          | 61.0 ± 9.5             | 55        | 9            |
| Kraus et al. [44], 2009         | 138                    | 36                | K/L                            | NR                     | 74        | 9            |
| Le Graverand et al. [48], 2009  | 141                    | 24                | K/L                            | 56                     | 100       | 9            |
| Mazzuca et al. [52], 2004       | 73                     | 30                | K/L                            | 55.2 ± 5.8             | 100       | 9            |
| Nishimura et al. [60], 2010     | 92                     | 48                | K/L                            | 71 ± 4.7               | 61        | 9            |
| Perego and Wilder [64], 2011    | 157                    | 72                | K/L                            | 66.5 ± 8.7             | 56        | 9            |
| Reijman et al. [65], 2004       | 237                    | 72                | K/L                            | 69.1 ± 6.9             | 71        | 9            |
| Schouten et al. [71], 1993      | 239                    | 146               | K/L                            | 57.4 ± 6.3             | 59        | 9            |
| Wolfe and Lane [89], 2002       | 583                    | 31 ± 102          | ACR criteria                   | 63.4 ± 11.8            | 77        | 9            |
| Yusuf et al. [92], 2011         | 155                    | 72                | K/L                            | 59.6 ± 7.5             | 85        | 9            |
| Fayfman et al. [26], 2009       | 490                    | 120               | K/L                            | 60.5                   | 62        | 8            |
| Felson et al. [28], 2004        | 227                    | 30                | K/L                            | 66.4 ± 9.4             | 41        | 8            |
| Hunter et al. [40], 2007        | 595                    | 36                | Clinical symptoms              | 73.6 ± 2.9             | 60        | 8            |
| Valdes et al. [85], 2004        | 280                    | 120               | K/L                            | 56.9                   | 100       | 8            |
| Kerkhof et al. [41], 2010       | 835                    | 72                | K/L                            | 67                     | 64        | 6            |
| Kerna et al. [42], 2009         | 141                    | 36                | NR                             | 70                     | 70        | 6            |
| Pavelka et al. [62], 2004       | 89                     | 24                | ACR criteria                   | 56.7 ± 7.2             | 66        | 6            |

OA = osteoarthritis; K/L = Kellgren-Lawrence score; OARSI = Osteoarthritis Research Society International atlas; ACR = American College of Rheumatology; JSW = joint space width, cOA = clinical OA; rOA = radiographic OA; NR = not reported; *mean followup in months; §criteria not reported for one of the cohorts.
| Determinant | Study | Instrument of measurement | Definition of knee OA progression | OR/RR/HR (95% CI) | Association with OA progression* |
|------------|-------|---------------------------|-----------------------------------|------------------|----------------------------------|
| Age        | Bagge et al. [3], 1992 | Dichotomous | Increase K/L ≥ 1 (baseline K/L not provided) | Not provided | o |
|            | Benichou et al. [5], 2010 | < 60 versus ≥ 60 years | Change in JSW (mean difference) | Not provided | o |
|            | Dieppe et al. [23], 1993 | | JSN ≥ 2 mm | Not provided | o |
|            | Felson et al. [31], 1995 | | Increase K/L ≥ 1 (baseline K/L ≥ 2) | Not provided | o |
|            | Mazzuca et al. [51], 2006 | Continuous (years) | Change in JSW (mean difference) | OR 1.13 (0.87–1.48) | o |
|            | Miyazaki et al. [56], 2002 | Continuous (years) | JSN ≥ 1 grade on a 4-grade scale | OR 1.22 (1.05–1.41) | + |
|            | Muraki et al. [57], 2012 | Per 5-year increase | Increase K/L ≥ 1 (baseline K/L ≥ 2) | OR 1.17 (1.05–1.30) | + |
|            | Nishimura et al. [60], 2010 | Continuous (years) | Increase K/L ≥ 1 (baseline K/L ≥ 2) | OR 0.93 (0.83–1.06) | o |
|            | Schouten et al. [70], 1992 | Fourth quartile versus first | Change in JSW ≥ 1 on a 9-point scale | OR 3.84 (1.10–13.4) | + |
|            | Wolfe and Lane [89], 2002 | Continuous (years) | JSN score = 3 on a 4-point scale | HR 1.00 (0.98–1.02) | o |
| Female sex | Benichou et al. [5], 2010 | | Change in JSW (mean difference) | Not provided | o |
|            | Felson et al. [31], 1995 | | JSN ≥ 2 mm | Not provided | o |
|            | Ledingham et al. [47], 1995 | | Increase K/L or JSW (cutoff not provided) | RR 1.43 (0.80–2.58) | o |
|            | Miyazaki et al. [56], 2002 | | JSN ≥ 1 grade on a 4-grade scale | OR 2.17 (1.13–4.15) | + |
|            | Nishimura et al. [60], 2010 | | Increase K/L ≥ 1 (baseline K/L ≥ 2) | OR 1.32 (0.22–7.75) | o |
|            | Schouten et al. [70], 1992 | | Change in JSW ≥ 1 on a 9-point scale | OR 0.50 (0.22–1.11) | o |
|            | Spector et al. [80], 1992 | | Change JSN ≥ 1 (4-grade scale), or ≥ 10% JSW reduction | Not provided | o |
| Ethnicity  | Wolfe and Lane [89], 2002 | Black versus white | JSN score = 3 on a 4-point scale | HR 0.73 (0.44–1.19) | o |
|            | Kopec et al. [43], 2012 | | Increase K/L ≥ 1 (baseline K/L ≥ 2) | HR 1.67 (1.05–2.67) | + |
| Low bone density | Hart et al. [37], 2002 | Low versus high | Change JSN ≥ 1 grade on a 4-grade scale | Not provided | o |
|            | Nevitt et al. [59], 2010 | High versus low | Change JSN ≥ 0.5 grade or osteophytes ≥ 1 | OR 1.3 (0.7–2.0) | o |
|            | Zhang et al. [94], 2000 | Fourth quartile (high) versus first | Increase K/L ≥ 1 (baseline K/L ≥ 2) | OR 0.1 (0.03–0.3) | + |
| Osteoporosis | Nishimura et al. [60], 2010 | Present versus absent | Increase K/L ≥ 1 (baseline K/L ≥ 2) | OR 1.67 (0.44–6.28) | o |
| IGF-1      | Fraenkel et al. [32], 1998 | Third tertile versus first in women | Increase K/L ≥ 1 (baseline K/L ≥ 2) | OR 0.9 (0.5–1.6) | o |
|            | Schouten et al. [71], 1993 | Third tertile versus first in men | Increase K/L ≥ 1 (baseline K/L ≥ 2) | OR 0.9 (0.3–3.0) | o |
|            | Schouten et al. [71], 1993 | Third tertile versus first | Change ≥ 2 on a 5-point scale for radiographic OA | OR 2.58 (1.01–6.60) | + |
| Determinant                              | Study                          | Instrument of measurement | Definition of knee OA progression | OR/RR/HR (95% CI) | Association with OA progression* |
|-----------------------------------------|-------------------------------|---------------------------|----------------------------------|------------------|----------------------------------|
| Metabolic syndrome (OW, HT, DL, IGT)    | Yoshimura et al. [91], 2012   | ≥ 3 components versus none | Increase K/L ≥ 1 (baseline K/L ≥ 2) | OR 2.80 (1.68–4.68) | +                                |
|                                         |                               | Two components versus none |                                  | OR 2.29 (1.49–3.54) | +                                |
|                                         |                               | One component versus none  |                                  | OR 1.38 (0.91–2.08) | o                                |
| Estrogen use                            | Zhang et al. [96], 1998       | Past use versus never used | Increase K/L ≥ 1 (baseline K/L ≥ 2) | OR 0.9 (0.6–1.4)  | o                                |
| (n = 551)                               |                               | Current use versus never used |                                  | OR 0.4 (0.1–1.5)  | o                                |
| Uric acid concentration                 | Schouten et al. [70], 1992    | High tertile versus low   | Change in JSW ≥ 1 on a 9-point scale | OR 1.36 (0.46–4.02) | o                                |
| (n = 239)                               |                               | Middle versus low         |                                  | OR 1.05 (0.36–3.00) | o                                |
| Plasma homocysteine                     | Fayfman et al. [26], 2009     | Third tertile versus first in men | Increase K/L ≥ 1 (baseline K/L ≥ 2) | OR 0.6 (0.1–1.1)  | o                                |
| (n = 490)                               |                               | Third tertile versus first in women |                                  | OR 1.7 (0.8–3.8)  | o                                |
| Genetic components                      | Zhai et al. [93], 2007        | Hereditability in MZ      | Change ≥ 1 in JSN or osteophyte score | Not provided     | o                                |
| (n = 618)                               |                               | Hereditability in DZ      |                                  | Not provided     | +                                |
| SNP                                     | Kerna et al. [42], 2009       | rs3740199 in women       | Increase JSN ≥ 1 or osteophyte grade | OR 2.66 (1.19–5.98) | +                                |
| (n = 421)                               |                               | rs1871054                |                                  | Not provided     | o                                |
|                                        | Valdes et al. [85], 2004      | ADAM12_48                | Increase K/L ≥ 1 (baseline K/L not provided) | Not provided     | o                                |
|                                        |                               | CILP_395                 |                                    | Not provided     | +                                |
|                                        |                               | TNA_106                  |                                    | Not provided     | o                                |
| Depression/anxiety                      | Wolfe and Lane [89], 2002     | Depression, yes versus no | JSN score = 3                     | HR 1.09 (0.93–1.28) | o                                |
| (n = 583)                               |                               | Anxiety, yes versus no   |                                    | HR 0.95 (0.84–1.08) | o                                |

* Statistically significant association of the determinant with OA progression: + = positive association, − = negative association, o = no association (adjusted for age and sex if applicable); OA = osteoarthritis; K/L = Kellgren-Lawrence score; JSW = joint space width; JSN = joint space narrowing; IGF-1 = insulin-like growth factor 1; OW = overweight; HT = hypertension; DL = dyslipidemia; IGT = impaired glucose tolerance; MZ = monozygotic; DZ = dizygotic; SNP = single nucleotide polymorphisms; ADAM = A disintegrin and matrix metalloproteinase domain 12; CILP = cartilage intermediate-layer protein, nucleotide pyrophosphohydrolase; TNA = tetranectin (plasminogen-binding protein); OR = odds ratio; RR = relative risk; HR = hazard ratio; n = combined sample size.
| Determinant                  | Study                                      | Instrument of measurement                                                                 | Definition of knee OA progression                                      | OR/RR/HR (95% CI)            | Association with OA progression |
|-----------------------------|--------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------------------|---------------------------------|
| Knee pain                   | Cooper et al. [18], 2000                   | Present versus absent                                                                      | Increase K/L ≥ 1 (baseline K/L ≥ 1)                                     | OR 0.8 (0.4–1.7)             | o                               |
|                             | Dieppe et al. [23], 1993                   | Present versus absent                                                                      | Increase K/L ≥ 1 (baseline K/L ≥ 2)                                     | OR 2.4 (0.7–8.0)             | o                               |
|                             | Miyazaki et al. [56], 2002                 | Present versus absent                                                                      | JSN ≥ 2 mm                                                              | Not provided                 | o                               |
|                             | Muraki et al. [57], 2012                   | Present versus absent                                                                      | Change JSN ≥ 1 grade on a 4-grade scale                                 | OR 0.93 (0.78–1.11)          | o                               |
|                             | Spector et al. [80], 1992                  | Present versus absent                                                                      | Increase K/L ≥ 1 (baseline K/L ≥ 2)                                     | OR 2.63 (1.81–3.81)          | +                               |
|                             | Wolfe and Lane [89], 2002                  | Present versus absent                                                                      | Change JSN ≥ 1 grade on a 4-grade scale, or ≥ 10% JSN                  | Not provided                 | o                               |
|                            | Wolfe and Lane [89], 2002                  | Present versus absent                                                                      | JSN score = 3 on a 4-point scale                                       | HR 1.55 (1.07–2.24)          | +                               |
|                            | Mazzuca et al. [51], 2006                  | JSW high versus low                                                                       | Change in JSW (mean difference)                                        | OR 0.67 (0.49–0.91)          | +                               |
|                            | Miyazaki et al. [56], 2002                 | JSW, > 3 versus < 3 mm                                                                    | Change JSN ≥ 1 grade on a 4-grade scale                                 | OR 0.74 (0.25–2.19)          | o                               |
|                            | Pavelka et al. [63], 2000                  | JSW (continuous)                                                                          | Increase K/L ≥ 1 (baseline K/L not provided)                            | Not provided                 | o                               |
|                            | Wolfe and Lane [89], 2002                  | Initial JSN, high versus low                                                               | JSN score = 3 on a 4-point scale                                       | HR 2.62 (2.03–3.40)          | +                               |
|                            | Ledingham et al. [47], 1995                | Change ≥ 1 roA                                                                            | Change in attrition (cutoff not provided)                              | OR 1.72 (1.36–1.99)          | +                               |
|                            | Schouten et al. [70], 1992                 | Multiple joints versus local joint OA                                                     | Increase K/L (cutoff not provided)                                     | OR 2.39 (1.16–4.93)          | +                               |
|                            | Haugen et al. [39], 2012                   | Score hand JSN                                                                            | Increase K/L ≥ 1 (baseline K/L ≥ 2)                                     | OR 1.00 (0.93–1.08)          | o                               |
|                            | Ledingham et al. [47], 1995                | Score hand osteophytes                                                                     | Increase K/L ≥ 1 (baseline K/L ≥ 2)                                     | OR 0.96 (0.87–1.06)          | o                               |
|                            | Schouten et al. [70], 1992                 | Generalized OA                                                                           | Change in JSW ≥ 1 on a 9-point scale                                    | OR 3.28 (1.30–8.27)          | +                               |
|                            |                                    |                                            | Change in JSW ≥ 1 on a 9-point scale                                    | OR 1.17 (0.51–2.72)          | o                               |
Conflicting evidence was found for the associations between knee OA progression and age; low bone density; serum insulin growth factor-1 level; baseline radiographic or clinical OA severity; generalized osteoarthritis; duration of symptoms; valgus alignment or malalignment in general; past knee injury; the presence of tibiofemoral osteophytes; BMI; leg length inequality; serum vitamin D level; dietary intake of vitamin C; serum C-reactive protein, IL-1β, keratan sulfate, and serum cartilage oligometric matrix protein levels, and urinary crosslinked C-telopeptide level. Inconclusive evidence was found for the determined associations between knee OA progression and the single nucleotide polymorphisms CILP_395 (cartilage intermediate-layer proteins) and rs3740199, patellofemoral alignment, and serum pentosidine levels. There also was inconclusive evidence for no associations found between knee OA progression and the single nucleotide polymorphisms rs1871054, ADAM12_48 (A disintegrin and matrix metalloproteinase domain 12), and TNA_106 (tetraneectin plasminogen-binding protein), and serum levels of YKL-40 (chitinase-3-like protein 1), MMP-9 (matrix metalloproteinase-9); and TIMP-9 (tissue inhibitors of metalloproteinase).

Sensitivity Analysis

In this analysis, we tested whether conclusions from relatively small studies (less than 200) incorrectly influenced conclusions drawn from larger studies with more statistical power studying the same determinant, or that results from studies with a relatively short followup (cutoff 24 months) altered conclusions from studies with a longer followup. Our sensitivity analysis found that our conclusions did not change across the range of clinically plausible differences in followup duration or sample size regarding the strong, moderate, or conflicting evidence we found for the various presented determinants.

Discussion

We performed an updated systematic review of available evidence regarding prognostic factors for radiographic knee OA progression. We found that there is strong evidence that baseline knee pain and Heberden nodes, varus alignment, and high baseline serum levels of hyaluronic acid and TNFα are predictive for knee OA progression. There also seems to be strong evidence that sex (female), former knee injury, quadriceps strength, smoking, running, and regular performance of sports are not predictive for progression of knee OA. For all other studied factors in our review, the evidence is limited, conflicting, or inconclusive. In the best-evidence synthesis, we considered only...
### Table 5. Intrinsic factors discussed in the reviewed studies

| Determinant       | Study                                      | Analysis of determinant | Definition of knee OA progression | OR/RR/HR (95% CI) | Association with OA progression* |
|-------------------|--------------------------------------------|-------------------------|-----------------------------------|-------------------|----------------------------------|
| Alignment         | Brouwer et al. [13], 2007                  | Varus versus neutral    | Increase K/L $\geq 1$ (baseline K/L $\geq 2$) | OR 2.90 (1.07–7.88) | +                                |
|                   |                                             | Valgus versus neutral   | Increase K/L $\geq 1$ (baseline K/L $\geq 2$) | OR 1.39 (0.48–4.05) | o                                |
|                   | Cerejo et al. [16], 2002                   | Varus versus nonvarus (K/L 0–1) | Change JSN $\geq 1$ grade on a 4-grade scale | OR 2.50 (0.67–9.39) | +                                |
|                   |                                             | Varus versus nonvarus (K/L 2) |                                  | OR 4.12 (1.92–8.82) | +                                |
|                   |                                             | Varus versus nonvarus (K/L 3) |                                  | OR 11.0 (3.10–37.8) | +                                |
|                   |                                             | Valgus versus nonvalgus (K/L 2) |                                  | OR 2.46 (0.95–6.34) | o                                |
|                   |                                             | Valgus versus nonvalgus (K/L 3) |                                  | OR 10.4 (2.76–39.5) | +                                |
|                   | Hunter et al. [40], 2007                   | Patellar tilt, fourth versus first quartile | Medial patellofemoral change JSN $\geq 1$ grade on a 4-grade scale | OR 0.19 (0.09–0.43) | –                                |
|                   |                                             | Sulcus angle, fourth versus first quart |                                  | OR 1.49 (0.60–3.73) | o                                |
|                   |                                             | Bisect offset, fourth versus first quart |                                  | OR 2.23 (1.10–4.50) | +                                |
|                   |                                             | Patellar tilt, fourth versus first quartile | Lateral patellofemoral change JSN $\geq 1$ grade on a 4-grade scale | OR 1.13 (0.57–2.24) | o                                |
|                   |                                             | Sulcus angle, fourth versus first quartile |                                  | OR 2.09 (0.99–4.41) | o                                |
|                   |                                             | Bisect offset, fourth versus first quartile |                                  | OR 0.35 (0.15–0.83) | –                                |
|                   | Miyazaki et al. [56], 2002                 | Varus versus nonvarus | Change JSN $\geq 1$ grade on a 4-grade scale | OR 0.90 (0.66–1.23) | o                                |
|                   | Schouten et al. [70], 1992                 | Malaligned, present versus absent | Change JSN $\geq 1$ grade on a 4-grade scale | OR 5.13 (1.14–23.1) | +                                |
|                   | Sharma et al. [79], 2001                   | Varus versus nonvarus | Change JSN $\geq 1$ grade on a 4-grade scale | OR 4.09 (2.20–7.62) | +                                |
|                   |                                             | Varus versus mild valgus |                                  | OR 2.98 (1.51–5.89) | +                                |
|                   |                                             | Valgus versus nonvalgus |                                  | OR 4.89 (2.13–11.2) | +                                |
|                   |                                             | Valgus versus mild varus |                                  | OR 3.42 (1.31–8.96) | +                                |
|                   | Sharma et al. [78], 2010                   | Valgus versus neutral | Change medial JSN $\geq 1$ grade on a 4-grade scale | OR 0.34 (0.21–0.55) | –                                |
|                   |                                             | Varus versus neutral |                                  | OR 3.59 (2.62–4.92) | +                                |
|                   |                                             | Valgus versus neutral | Change lateral JSN $\geq 1$ grade on a 4-grade scale | OR 4.85 (3.17–7.42) | +                                |
|                   |                                             | Varus versus neutral |                                  | OR 0.12 (0.07–0.21) | –                                |
|                   | Yusuf et al. [92], 2011                    | Varus ($<$ 182°) versus nonvarus | Change JSN $\geq 1$ grade on a 6-grade scale | RR 2.3 (1.4–3.1) | +                                |
|                   |                                             | Valgus ($>$ 184°) versus nonvalgus |                                  | RR 1.7 (0.97–2.6) | o                                |
|                   |                                             | Malaligned, BMI $>$ 25 kg/m² |                                  | RR 4.1 (1.8–6.1) | +                                |
| Adduction moment  | Miyazaki et al. [56], 2002                 | $\geq 5$ versus $<$ 5 (% weight x height) | Change JSN $\geq 1$ grade on a 4-grade scale | OR 6.46 (2.40–17.5) | +                                |
| (n = 74)          |                                            |                         |                                  |                   |                                  |
| Knee injury       | Cooper et al. [18], 2000                   | Yes versus no | Increase K/L $\geq 1$ (baseline K/L $\geq 1$) | OR 1.2 (0.5–3.0) | o                                |
| (n = 207)         |                                            |                         | Increase K/L $\geq 1$ (baseline K/L $\geq 2$) | OR 1.1 (0.3–4.4) | o                                |
|                   | Schouten et al. [70], 1992                 | Knee injury: yes versus no | Change JSN $\geq 1$ grade on a 4-grade scale | OR 2.62 (0.93–7.36) | o                                |
|                   |                                            | Sport injury: yes versus no | Change JSN $\geq 1$ grade on a 4-grade scale | OR 0.62 (0.17–2.19) | o                                |
| Determinant                        | Study                                      | Analysis of determinant | Definition of knee OA progression | OR/RR/HR (95% CI) | Association with OA progression |
|-----------------------------------|--------------------------------------------|-------------------------|-----------------------------------|------------------|---------------------------------|
| Bone marrow lesions/edema (n = 186) | Madan-Sharma et al. [50], 2008              | Present versus absent   | JSN > 1 grade on a 4-grade scale  | RR 0.9 (0.18–3.0) | o                               |
| Subchondral bone cysts (MRI) (n = 186) | Madan-Sharma et al. [50], 2008              | Present versus absent   | JSN > 1 grade on a 4-grade scale  | RR 1.6 (0.5–4.0) | o                               |
| Cartilage loss (MRI) (n = 186)    | Madan-Sharma et al. [50], 2008              | Present versus absent   | JSN > 1 grade on a 4-grade scale  | RR 3.0 (0.5–9.6) | o                               |
| Joint effusion (n = 186)          | Madan-Sharma [50], 2008                    | Present on MRI          | JSN > 1 grade on a 4-grade scale  | RR 0.6 (0.6–1.8) | o                               |
| Meniscal damage (n = 186)         | Madan-Sharma et al. [50], 2008              | Present versus absent   | JSN > 1 grade on a 4-grade scale  | RR 8.91 (1.1–22.8) | +                              |
| Meniscectomy (n = 239)            | Schouten et al. [70], 1992                 | Yes versus no           | Change JSN ≥ 1 grade on a 4-grade scale | OR 2.28 (0.57–9.03) | o                               |
| Chondrocalcinosis (n = 239)       | Schouten et al. [70], 1992                 | Yes versus no           | Change JSN ≥ 1 grade on a 4-grade scale | OR 2.01 (0.55–7.42) | o                               |
| Osteophytes tibiofemoral (n = 337) | Benichou et al. [5], 2010                  | Definite versus not     | Change in JSW (mean difference)   | Not provided     | o                               |
| Knee ROM (n = 92)                 | Nishimura et al. [60], 2010                | Mean ROM                | Increase K/L ≥ 1 (baseline K/L ≥ 2) | OR 0.94 (0.89–0.99) | –                               |

* Statistically significant association of the determinant with OA progression: + = positive association, − = negative association, o = no association (adjusted for age and sex if applicable); OA = osteoarthritis; K/L = Kellgren-Lawrence score; JSN = joint space narrowing; JSW = joint space width; OR = odds ratio; RR = relative risk; HR = hazard ratio; n = combined sample size.
| Determinant | Study | Analysis of determinant | Definition of knee OA progression | OR/RR/HR (95% CI) | Association with OA progression* |
|------------|-------|-------------------------|------------------------------------|------------------|---------------------------------|
| BMI (n = 6791) | Benichou et al. [5], 2010 | < 30 versus ≥ 30 kg/m² | Change in JSW (mean difference) | Not provided | + |
| Cooper et al. [18], 2000 | | Highest tertile versus lowest | Increase K/L ≥ 1 (baseline K/L ≥ 1) | OR 2.6 (1.0–6.8) | + |
| Dieppe et al. [23], 1993 | | Continuous | JSN ≥ 2 mm or knee surgery | Not provided | o |
| Felson et al. [28], 2004 | | Per 2-unit increase ($) | Change JSN ≥ 1 grade on a 4-grade scale | OR 0.98 (0.8–1.4) | o |
| | | As $, with 3°–6° malalignment | | OR 1.23 (1.0–1.4) | + |
| | | As $, with ≥ 7° malalignment | | OR 0.93 (0.7–1.2) | o |
| Ledingham et al. [47], 1995 | | Continuous | Change in JSW (cutoff not provided) | OR 1.07 (1.02–1.14) | + |
| | | Change in osteophytes (cutoff not provided) | | OR 1.06 (1.00–1.12) | + |
| | | Change in K/L (cutoff not provided) | | Not provided | o |
| | | | | | |
| LeGraverand et al. [48], 2009 | | < 30 versus ≥ 30 kg/m² | Change in JSW (mean difference) | Not provided | o |
| Miyazaki et al. [56], 2002 | | Continuous | JSN ≥ 1 grade on a 4-grade scale | OR 1.21 (0.91–1.61) | o |
| Muraki et al. [57], 2012 | | Per 5-unit increase | Increase K/L ≥ 1 (baseline K/L ≥ 1) | OR 1.43 (1.16–1.77) | + |
| Nishimura et al. [60], 2010 | | Continuous | Increase K/L ≥ 1 (baseline K/L ≥ 2) | OR 0.93 (0.78–1.11) | o |
| Niu et al. [61], 2009 | | < 25 versus ≥ 30 kg/m² | Increase JSN ≥ 0.5 grade | RR 1.1 (0.9–1.4) | o |
| Reijman et al. [66], 2007 | | ≤ 25 versus > 27.5 kg/m² | Increase JSN ≥ 1 mm | OR 1.4 (0.8–2.6) | o |
| | | Change in K/L (cutoff not provided) | OR 2.1 (1.2–3.7) | + |
| Schouten et al. [70], 1992 | | Second quartile versus first | Change in JSW ≥ 1 on a 9-point scale | OR 1.77 (0.48–6.50) | o |
| | | Fourth quartile versus first | | OR 5.28 (1.54–18.1) | + |
| | | Fourth quartile versus first | | OR 11.1 (3.28–37.3) | + |
| Spector et al. [81], 1994 | | Third tertile versus first | Increase K/L or JSN (cutoff not provided) | RR 4.69 (0.63–34.8) | o |
| Wolfe and Lane [89], 2002 | | Continuous | JSN score = 3 | HR 1.03 (1.00–1.06) | + |
| Yusuf et al. [92], 2011 | | BMI 25–30 versus < 25 | Change JSN ≥ 1 grade on a 6-grade scale | RR 2.4 (1.3–3.6) | + |
| | | BMI >30 versus < 25 | Change JSN ≥ 1 grade on a 6-grade scale | RR 2.9 (1.7–4.1) | + |
| Quadriceps strength (n = 253) | Brandt et al. [12], 1999 | Progressive versus nonprogressive group† | Increase K/L ≥ 1 (baseline K/L not provided) | Not provided | o |
| | Sharma et al. [77], 2003 | High versus low strength† | Increase JSN ≥ 1 | Not provided | o |
| Leg length inequality (n = 4547) | Golightly et al. [35], 2010 | Leg length inequality versus no inequality | Increase K/L ≥ 1 (baseline K/L ≥ 1) | HR 1.22 (0.82–1.80) | o |
| | Harvey et al. [38], 2010 | ≥ 1 cm versus no inequality, shorter leg | Increase K/L ≥ 1 (baseline K/L ≥ 2) | HR 1.83 (1.10–3.05) | + |
| | | ≥ 2 cm versus no inequality, shorter leg | JSN ≥ 1 grade or knee surgery | OR 1.3 (1.0–1.7) | + |
| | | | | OR 1.4 (0.5–3.7) | o |
| Determinant                  | Study                              | Analysis of determinant                     | Definition of knee OA progression                          | OR/RR/HR (95% CI) | Association with OA progression* |
|-----------------------------|------------------------------------|---------------------------------------------|-----------------------------------------------------------|------------------|----------------------------------|
| AP knee laxity (n = 84)     | Miyazaki et al. [55], 2012         | Before exercise                             | Increase K/L ≥ 1 (baseline K/L ≥ 1) or radiographic cartilage loss > 0.2 mm annually | OR 1.29 (0.54–3.08) o | 0                                |
|                            |                                    | Enhanced laxity resulting from exercise     | Increase ≥ 1 on JSW and osteophyte score                   | OR 4.15 (1.12–15.4) + | +                                |
| Running (n = 294)           | Lane et al. [45], 1998             | Dichotomous†                                | Change in JSW ≥ 1 on a 9-point scale                      | Not provided o    | o                                |
|                            | Schouten et al. [70], 1992         | Dichotomous†                                | Increase K/L ≥ 1 (baseline K/L ≥ 1)                      | OR 0.53 (0.17–1.68) o | o                                |
| Regular sports (n = 593)    | Cooper et al. [18], 2000           | Dichotomous†                                | Change in JSW ≥ 1 (baseline K/L ≥ 2)                     | OR 0.7 (0.4–1.6) o | o                                |
|                            | Schouten et al. [70], 1992         | Physical activity†                          | Change in JSW ≥ 1 on a 9-point scale                      | OR 0.9 (0.3–2.5) o | o                                |
| Nutritional variables (n = 3381) | Bergink et al. [7], 2009       | Vitamin D intake (low versus high)          | Increase K/L ≥ 1 (baseline K/L ≥ 2)                      | OR 7.7 (1.3–43.5) – | –                                |
|                            |                                    | Serum vitamin D (low versus high)           | Increase K/L ≥ 1 (baseline K/L ≥ 2)                      | OR 2.1 (0.6–7.4) o | o                                |
|                            | Felson et al. [30], 2007           | Vitamin D serum levels < 20 ng/mL           | Change JSN ≥ 1 grade on a 4-grade scale, Framingham      | OR 0.83 (0.54–1.27) o | o                                |
|                            |                                    | Vitamin D serum levels < 20 ng/mL           | Change JSN ≥ 1 grade on a 4-grade scale, BOKS study      | OR 0.63 (0.35–1.14) o | o                                |
|                            | McAlindon et al. [53], 1996        | Vitamin D intake (middle versus high)       | Increase JSN ≥ 1                                        | OR 2.99 (1.06–8.49) – | –                                |
|                            |                                    | Serum vitamin D (middle versus high)        | Increase JSN ≥ 1                                        | OR 2.83 (1.02–7.85) – | –                                |
|                            | McAlindon et al. [54], 1996        | Vitamin C intake (middle versus low)        | Increase K/L ≥ 1                                        | OR 0.32 (0.14–0.77) – | –                                |
|                            |                                    | β-carotene intake (high versus low)         | Increase K/L ≥ 1                                        | OR 0.42 (0.19–0.94) – | –                                |
|                            |                                    | Vitamin E (high versus low)                 | Increase K/L ≥ 1                                        | OR 0.68 (0.28–1.64) o | o                                |
|                            | Perego and Wilder [64], 2011       | Vitamin C intake                            | Increase K/L ≥ 1 (baseline K/L ≥ 2)                      | RR 0.94 (0.79–1.12) o | o                                |
|                            | Wilder et al. [88], 2009           | Vitamin intake in general                   | Increase K/L ≥ 1 (baseline K/L ≥ 2)                      | RR 0.93 (0.87–0.99) – | –                                |
| Smoking (n = 331)           | Nishimura et al. [60], 2010        | Yes versus no                               | Increase K/L ≥ 1 (baseline K/L ≥ 2)                      | OR 0.73 (0.09–6.15) o | o                                |
|                            | Schouten et al. [70], 1992         | Past smoker versus never                    | Change in JSW ≥ 1 on a 9-point scale                     | OR 1.07 (0.38–3.04) o | o                                |
|                            |                                    | Current smoker versus never                 | Change in JSW ≥ 1 on a 9-point scale                     | OR 0.96 (0.34–2.75) o | o                                |

* Statistically significant association of the determinant with OA progression: + = positive association, − = negative association, o = 1o association (adjusted for age and sex if applicable); † assessed at baseline; ‡ assessed at followup; OA = osteoarthritis; JSW = joint space width; K/L = Kellgren-Lawrence score; JSN = joint space narrowing; OR = odds ratio; RR = relative risk; HR = hazard ratio; n = combined sample size.
| Marker          | Study                                   | Instrument of measurement | Definition of knee OA progression                                      | OR/RR/HR (95% CI)                      | Association with OA progression* |
|-----------------|----------------------------------------|---------------------------|------------------------------------------------------------------------|----------------------------------------|----------------------------------|
| CRP (serum)     | Kerkhof et al. [41], 2010              | Continuous                | Increase K/L ≥ 1 (baseline K/L ≥ 2) or surgery                         | Not provided                          | o                                |
| (n = 1720)      | Sharif et al. [76], 2000               | Continuous                | JSN ≥ 2 mm or knee surgery                                             | OR 1.12 (0.81–1.55)                   | o                                |
|                 | Spector et al. [82], 1997              | Continuous                | Increase K/L ≥ 1 (baseline K/L not provided)                          | Not provided                          | +                                |
| IL-1β (serum)   | Attur et al. [2], 2011                 | Increased versus normal   | Increase K/L ≥ 1 or > 30% JSW reduction                               | OR 3.2 (1.2–8.7)                      | +                                |
| (n = 184)       | Botha-Scheepers et al. [11], 2008     | Fourth quartile versus first | Change JSN ≥ 1 grade on a 4-grade scale                               | RR 1.3 (0.5–2.0)                      | o                                |
| IL-10 (serum)   | Botha-Scheepers et al. [11], 2008     | Fourth quartile versus first | Change JSN ≥ 1 grade on a 4-grade scale                               | RR 4.3 (1.7–6.2)                      | +                                |
| (n = 86)        |                                        |                           |                                                                        |                                        |                                  |
| IL-1Ra (serum)  | Botha-Scheepers et al. [11], 2008     | Fourth quartile versus first | Change JSN ≥ 1 grade on a 4-grade scale                               | RR 2.1 (0.7–3.9)                      | o                                |
| (n = 86)        |                                        |                           |                                                                        |                                        |                                  |
| TNFα (serum)    | Attur et al. [2], 2011                 | Increased versus normal   | Increase K/L ≥ 1 or > 30% JSW reduction                               | OR 8.9 (2.6–30.8)                     | +                                |
| (n = 253)       | Botha-Scheepers et al. [11], 2008     | Fourth quartile versus first | Change JSN ≥ 1 grade on a 4-grade scale                               | RR 6.1 (1.4–9.8)                      | +                                |
|                 | Denoble et al. [20], 2011              | Continuous                | Change in osteophyte score                                             | Not provided                          | +                                |
| TGF-β1 (serum)  | Nelson et al. [58], 2010               | Continuous                | Increase K/L ≥ 1 (baseline K/L ≥ 1)                                   | HR 1.04 (0.41–2.65)                   | o                                |
| (n = 329)       |                                        |                           | Increase K/L ≥ 1 (baseline K/L ≥ 2)                                   | HR 1.10 (0.46–2.63)                   | o                                |
| Hyaluronic acid (serum) | Buryere et al. [14], 2003 | High level versus low | Change in mean JSW (cutoff not provided)                             | Not provided                          | +                                |
| (n = 361)       | Pavelka et al. [62], 2004              | High level versus low     | Change in mean JSW (cutoff not provided)                             | Not provided                          | +                                |
|                 | Sharif et al. [72], 1995               | High level versus low     | JSN ≥ 2 mm or knee surgery                                             | Not provided                          | o                                |
| Keratan sulfate (serum) | Buryere et al. [14], 2003 | High level versus low | Change in mean JSW (cutoff not provided)                             | Not provided                          | +                                |
| (n = 232)       | Sharif et al. [72], 1995               | High level versus low     | JSN ≥ 2 mm or knee surgery                                             | Not provided                          | o                                |
| COMP (serum)    | Buryere et al. [14], 2003              | High level versus low     | Change in mean JSW (cutoff not provided)                             | Not provided                          | o                                |
| (n = 466)       | Pavelka et al. [62], 2004              | High level versus low     | Change in mean JSW (cutoff not provided)                             | Not provided                          | o                                |
|                 | Sharif et al. [75], 1995               | High level versus low     | JSN ≥ 2 mm or knee surgery                                             | Not provided                          | o                                |
|                 | Sharif et al. [74], 2004               | OA progression versus nonprogression | JSN ≥ 2 mm or knee surgery                                              | Not provided                          | +                                |
| Pentosidine (serum) | Pavelka et al. [62], 2004 | High level versus low | Change in mean JSW (cutoff not provided)                             | Not provided                          | +                                |
| (n = 89)        | Pavelka et al. [62], 2004              | High level versus low     | Change in mean JSW (cutoff not provided)                             | Not provided                          | +                                |
| MMP-9 (serum)   | Pavelka et al. [62], 2004              | High level versus low     | Change in mean JSW (cutoff not provided)                             | Not provided                          | o                                |
| (n = 89)        | Pavelka et al. [62], 2004              | High level versus low     | Change in mean JSW (cutoff not provided)                             | Not provided                          | o                                |
| Marker          | Study                        | Instrument of measurement | Definition of knee OA progression | OR/RR/HR (95% CI) | Association with OA progression* |
|-----------------|------------------------------|---------------------------|-----------------------------------|------------------|----------------------------------|
| TIMP-9 (serum)  | Pavelka et al. [62], 2004    | High level versus low     | Change in mean JSW (cutoff not provided) | Not provided | o                                |
| (n = 89)        |                              |                           |                                   |                   |                                  |
| PIIANP (serum)  | Sharif et al. [73], 2007     | Fourth quartile versus first | JSN ≥ 2 mm or knee surgery         | RR 3.2 (1.1–9.0) | +                                |
| (n = 115)       |                              |                           |                                   |                   |                                  |
| CTX-II (urine)  | Dam et al. [19], 2009        | Third tertile versus first | Increase K/L ≥ 1 (disregarding baseline K/L) | OR 2.3 | o                                |
| (n = 490)       |                              |                           |                                   |                   |                                  |
|                 | Reijman et al. [65], 2004    | Fourth quartile versus first | JSN ≥ 2 mm                             | OR 6.0 (1.2–30.8) | +                                |
|                 |                              | Fourth quartile versus first | JSN ≥ 1.5 mm                        | OR 1.8 (0.8–4.1) | o                                |
|                 | Sharif et al. [73], 2007     | Fourth quartile versus first | JSN ≥ 1 mm                             | OR 1.1 (0.7–1.7) | o                                |
|                 | Larsson et al. [46], 2012    | Baseline level ARG5       | ≥ 1-unit increase OARSI score       | OR 6.77 (1.38–33.2) | +                                |
|                 |                              | > followup level ARG5      |                                   |                   |                                  |
|ARGS (synovial)  | Denoble et al. [20], 2011    | Continuous                | Change in osteophyte score          | Not provided | +                                |
| (n = 69)        |                              |                           |                                   |                   |                                  |
| IL-18 (synovial)| Kraus et al. [44], 2009      | FD progression versus nonprogression | Medial JSN ≥ 1 or osteophyte formation | Not provided | +                                |
| (n = 138)       |                              |                           |                                   |                   |                                  |
| Bone scintigraphy | Mazzuca et al. [52], 2004 | 99mTc-MDP uptake         | Change in JSW (mean difference) | Not provided | o                                |
| (n = 73)        |                              |                           |                                   |                   |                                  |

* Statistically significant association of the determinant with OA progression: + = positive association, − = negative association, o = no association (adjusted for age and sex if applicable); OA = osteoarthritis; K/L = Kellgren-Lawrence score; JSN = joint space narrowing; CRP = C-reactive protein; IL = interleukin; TNF = tumor necrosis factor; YKL-40 = chitinase-3-like protein 1; JSW = joint space width; TGF = transforming growth factor; C2C = collagen type II cleavage; COMP = cartilage oligomeric matrix protein; MMP = matrix metalloproteinase; TIMP = tissue inhibitors of metalloproteinase; PIANP = N-propeptide of type IIA collagen; CTX-II = crosslinked C-telopeptide; ARG5 = aggrecan neoepitope amino acid sequence; FSA = fractal signature analysis; FD = fractal dimension (horizontal and vertical); OR = odds ratio; RR = relative risk; HR = hazard ratio; n = combined sample size.
significant associations as associated prognostic factors. However, several of the included articles had small sample sizes, which consequently can lead to lower statistical power and more often to failure to detect differences that might be present.

A possible limitation to our inclusion criteria was addressed by Zhang et al. [97]. They reported that, unlike randomized trials, observational studies of patients with preexisting disease are subject to various biases that may account for discrepancies found between risk factors for disease incidence and progression. They hypothesized that risk factors actually might exist for progressive knee OA but that flaws in study design and the measure of disease progression may prevent us from detecting risk factors [97]. Having cited their article, it seems reasonable that there is the possibility that we have not determined all risk factors for progression of knee OA, because some factors might not have achieved significance in multivariable analyses in a study and thus were not included in our evidence synthesis. Nonetheless, we believe we have summarized all presently known risk factors of which a possible association with knee OA progression has been studied.

We acknowledge that when applying a best-evidence synthesis, one might unjustly conclude that there may be conflicting or strong evidence for or against an association of the determinant under study with knee OA. We would have preferred to pool the data of all included studies. However, because of large variation in criteria used in the articles for defining disease, or disease progression, pooling of the data generally was not possible. We encountered six different criteria that were used for the inclusion of OA (Table 2). Another approximately 13 different definitions were applied for OA progression (Tables 3–7). Furthermore, there were differences in how the determinants under study were measured, (continuous, dichotomous, or categorical), and varying cutoff points were used. As previously described, we pooled the results for “knee pain” and “Heberden nodes” for which both results showed associations with the progression of knee OA. This is different from the conclusions we would have drawn from a best-evidence synthesis, which would show conflicting
evidence for both determinants. In our opinion, it is likely that more of the conflicting associations we presented were attributable to the differences in definitions of knee OA or knee OA progression. For example, the conflicting evidence for BMI probably would be altered if statistical pooling was feasible; given that all 11 significant risk estimates (OR/RR/HR) regarding BMI were positive associations and that six of the 12 nonsignificant associations also were positive associations, it seems likely that if pooled, the combined overall association between BMI and knee OA would be a positive, significant one. In addition, the conflicting evidence for age, seven of the 10 presented analyses (70%) showed no significant association, falling just short for the criteria for ascertaining strong evidence (> 75%) for no association between age and OA progression.

In the original review by Belo et al. [4] and in a review by van Dijk et al. [86], the evidence for association between varus alignment and OA progression was limited. However, a couple studies have been performed since these reviews were published that have determined significant associations with varus alignment, which enabled us to conclude that there is strong evidence for this finding. The latter is in accordance with results published in later systematic reviews by Tanamas et al. [84] and Chapple et al. [17]. Except for the original review by Belo et al., there are to our knowledge no other reviews available that have determined the predictive value of serum hyaluronic acid levels and OA progression [9]. In addition, to our knowledge, no reviews have been published assessing the predictive value of serum level TNFα for knee OA progression.

We found strong evidence that sex was not associated with knee OA progression, as did Belo et al. [4]. This is in contrast to the earlier reviews published by van Dijk et al. [86] and Chapple et al. [17]. van Dijk et al. found limited evidence for the absence of an association with sex, but they included articles that used physical functioning as an outcome measure. Chapple et al. found conflicting evidence; however, their evidence was based on four analyses of three studies, which also are included in our review [21, 47, 70]. Three of the four analyses were consistent (no association); one was conflicting (significant association) [47]. Our evidence synthesis was based on 10 analyses, of which nine analyses were consistent (no association), consequently outweighing the one conflicting finding. van Dijk et al. and Chapple et al. reported limited evidence for the absence of an association between quadriceps strength and knee OA progression. This is consistent with our finding; however, our conclusion is based on more evidence. Consistent results also were found for regular performance of sports, in which van Dijk et al. reported limited and Chapple et al. reported strong evidence for absence of an association. However, in articles by Fransen and McConnell [33] and Bennell and Hinman [6] reviewing the effect of exercise therapy in patients with knee OA, the authors reported that exercise has a short-term benefit in patients with knee OA, although the magnitude of the reported benefit is small. This highlights the importance of the need to understand the working mechanism of exercise therapy.

A topic of considerable interest is the potential association between BMI and knee OA progression. Previous reviewers have established a positive association between BMI and incident knee OA [10, 95]. However, the evidence for an association between BMI and progression of knee OA remains conflicting in our review, which is consistent with the findings by Belo et al. [4] and Chapple et al. [17].

Noteworthy is the lack of overlap in evidence for prognostic factors for hip and knee OA progression. In two large reviews studying prognostic factors for hip OA, Lievense et al. [49] provided strong evidence for an association between hip OA progression with type of hip migration and with atrophic bone response. They also presented strong evidence for the absence of an association with BMI. Wright et al. [90] reported strong evidence for association of hip OA progression with age, joint space width at entry, femoral head migration, femoral osteophytes, bony sclerosis, baseline hip pain, and certain hip OA severity indexes. They also provided strong evidence for the absence of an association with acetabular osteophytes. The discrepancy between the findings for hip and knee OA is unclear but could be attributable to the difference in the number of studies available determining risk factors for progression of hip or knee OA [9].

Future research on the true relationship between prognostic factors for radiographic progression of knee OA is needed, mainly on the factors where conflicting evidence was presented (eg, age, baseline OA severity, BMI). Furthermore, we presented limited, inconclusive, or conflicting evidence on many factors with potential associations with OA progression. It would be important to investigate determinants that can be influenced or modified to reduce the risk of OA progression, perhaps including metabolic syndrome, bone marrow lesions, or osteoporosis. Moreover, there would be obvious advantages to testing the effect of new or existing disease-modifying pharmacologic or surgical interventions in patients with an established increased risk of OA progression.

We found strong evidence that baseline knee pain and Heberden nodes, varus alignment, and high baseline serum levels of hyaluronic acid and TNFα are predictive for knee OA progression. Sex (female), former knee injury, quadriceps strength, smoking, running, and regular performance of sports are not predictive for progression of
knee OA. Many studies have been performed and are being performed determining risk factors for knee OA progression, but the variability in how OA and OA progression are defined across the relevant studies remains an impediment to pooling the available evidence. We strongly recommend future researchers use uniform definitions of determinants, disease, and disease progression; it would enable more precise determination of possible risk factors for knee OA progression through meta-analyses. The majority of the included studies used the Kellgren-Lawrence classification as definition of disease and disease progression. This classification has been criticized because the criteria have been described and interpreted differently in various studies [67]. However, the Kellgren-Lawrence criteria provide a reliable classification of knee OA and OA progression, given that the original description of the criteria are applied [67, 68]. We therefore recommend that future researchers use the Kellgren-Lawrence classification to define radiographic OA and OA progression. Furthermore, considering that some MRI scoring systems have been and currently are being developed to define knee OA progression [36], it seems preferable that the same MRI scoring system would be used universally in future studies on prognostic factors for knee OA progression. We would like to call on expert committees, such as the Osteoarthritis Research Society International (OARSI) for OA Imaging to announce their recommendations on this important topic.

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