Prognostic factors for finger interphalangeal joint osteoarthritis: A systematic review

Running Title: Prognostic factors for hand IPJ osteoarthritis

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ABSTRACT

Objective

Radiographic hand osteoarthritis affects one-in-five adults. Symptomatic hand osteoarthritis can result in functional impairment, pain, and reduced quality of life. A prevalent form of hand osteoarthritis is interphalangeal joint (IPJ) osteoarthritis, however prognostic factors for IPJ osteoarthritis remain poorly understood. This systematic review aimed to identify prognostic factors for IPJ osteoarthritis, and summarise the diagnostic criteria for IPJ osteoarthritis in prognostic studies.

Methods

EMBASE, MEDLINE, Scopus and The Cochrane Library were searched from inception until 19th February 2020 (PROSPERO CRD42019116782). Eligible studies described diagnostic criteria defining IPJ osteoarthritis, and assessed potential prognostic factors for IPJ osteoarthritis. Risk of bias was assessed using a modified QUIPS tool and a best evidence synthesis was used.

Results

Eighteen studies were included (risk of bias: 8 high, 3 moderate, 7 low). All defined osteoarthritis radiographically, and three studies incorporated clinical symptoms into their definition of osteoarthritis. Forty-nine potential prognostic factors were assessed. Eight were prognostic: older age in women, female gender (both moderate evidence); family history of Heberden's nodes, Kashin-beck-disease, older age in men, dental occupation in men, finger fracture, parity (all limited evidence). Higher BMI in women (limited evidence) was prognostic for symptomatic radiographic osteoarthritis. No prognostic factors for symptomatic osteoarthritis were identified.

59

60 **Conclusion**

61 IPJ osteoarthritis is most commonly defined radiographically, yet criteria were heterogeneous.

62 Eight prognostic factors for radiographic IPJ osteoarthritis and one for symptomatic
63 radiographic IPJ osteoarthritis were identified, all with limited or moderate evidence. Further
64 studies on causality and on prognostic pathways are needed.

65

66 **Key messages:**

- 67 • Studies assessing hand interphalangeal joint (IPJ) osteoarthritis most commonly
68 diagnose osteoarthritis using a radiographic criteria.
- 69 • There is moderate evidence that older age in women and female gender are prognostic
70 factors
- 71 • Nodes in family, Kashin-Beck's, older men, male dentists, fracture, parity have limited
72 evidence as prognosticators

INTRODUCTION

Radiographic osteoarthritis in the hand and wrist are amongst the most prevalent type of osteoarthritis in the general population (1). This year osteoarthritis is expected to be the fourth leading cause of worldwide disability (2). Currently, treatment of hand osteoarthritis is difficult and relies on symptomatic management, as there are no disease modifying drugs. However, the efficacies of such symptomatic treatments are often limited by other comorbidities and by drug toxicities (3-5). With few effective treatment options available, clinical trials evaluating new drugs and non-pharmacological therapies are needed. Guidelines for randomised control trials in hand osteoarthritis advise recruiting patients with established hand osteoarthritis (6). However, recruiting patients with an increased risk of developing hand osteoarthritis could facilitate the identification of new drug therapies to delay or prevent the development of osteoarthritis (6) and excluding these participants can limit the ability to detect a therapeutic treatment effect (7). If it were possible to predict which people are at highest risk of developing hand osteoarthritis, suitable participants could be recruited to future trials. Furthermore, if prognostic factors for hand osteoarthritis were recognised in clinical settings, clinicians could implement preventative strategies.

Diagnosing osteoarthritis in the hand can be challenging, as interphalangeal joint (IPJ) osteoarthritis is thought to be a different subset of disease to osteoarthritis at the first carpometacarpal joint (CMCJ), and is therefore considered to have different aetiology and pathology (8). There is also known disassociation between radiographic signs and symptoms (9). Research to date has mainly focused on defining CMCJ osteoarthritis and understanding its aetiology, whilst prognostic factors for the presence of IPJ osteoarthritis, and diagnostic criteria used to describe IPJ osteoarthritis are not yet well established. Therefore, the aim of

- 97 this systematic review was to identify prognostic factors for the presence of IPJ osteoarthritis,
- 98 and describe the diagnostic criteria used to define IPJ osteoarthritis in prognostic studies.

MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (10). The protocol was prospectively registered on PROSPERO (CRD42019116782).

Search strategy

A specialist healthcare librarian (EH) assisted in developing the search strategies, which retrieved articles including terms related to the hand and fingers, terms related to osteoarthritis, and terms related to development and incidence, in the abstract, title or as MeSH terms (Supplementary Data S1). Searches were undertaken in four electronic databases: i) Medline by Ovid, ii) Embase by Ovid, iii) Scopus, iv) The Cochrane Library, and search terms were amended as necessary for each database (Supplementary Data S1). The searches were initially completed on 17th October 2018 and duplicates were removed (Supplementary Data S2). All articles were imported into Rayyan QCRI Tool (11), and two groups of reviewers (Group 1: KS, Group 2: HC and JL) independently screened titles and abstracts. Potentially eligible articles including articles with insufficient title and/or abstract information proceeded to full text review. The reference lists of included articles were also reviewed by two independent reviewers for additional relevant studies, though no additional articles were identified this way. For articles where the full text was not available, a request was sent directly to the authors with a 4-month response policy. Any inter-rating disagreement was discussed at a meeting between the reviewers, and any further disagreement was resolved through discussion with a third reviewer (SRF). The searches were updated on 19th February 2020.

Inclusion Criteria

For inclusion, papers must have a) investigated the association between a factor and the presence of IPJ osteoarthritis, b) described the diagnostic criteria, either radiographic and/or symptomatic, used to define IPJ osteoarthritis, c) measured IPJ (i.e. distal IPJ (DIPJ) and/or proximal IPJ (PIPJ)) osteoarthritis separate to first CMCJ osteoarthritis, d) described the association between one or more potential prognostic factor and the presence of IPJ osteoarthritis, e) allowed for a time delay between the presence of the factor and the presence of osteoarthritis, allowing time for osteoarthritis to develop. We included cross-sectional studies if the prognostic factor was historical (for example- a history of a medical condition), as long as the prognostic factor did not change over time.

Exclusion Criteria

Excluded article types were case reports, brief reports, abstracts, reviews and letters to the editor. Ineligible articles included animal, cell, and cadaver studies, studies of inflammatory arthritis, and articles not published in English. Articles assessing genetic factors were excluded. Finally, articles for which a full text was not accessible and not provided from the author within four months of correspondence were excluded.

Risk of Bias

Risk of bias of included studies was assessed independently by two reviewers (KS and HC), using a modified Quality in Prognosis Studies (QUIPS) tool (12) (Supplementary Table S1). We excluded the ‘confounding factors’ domain, as it is difficult to define a confounder in the context of prognostic factor studies, and confounders themselves can be considered to be known prognostic factors (13). An overall score of ‘low’, ‘moderate’ or ‘high’ was given to each of the six domains (Supplementary Table S1), and then an overall risk of bias for each study was calculated. A study was defined as having an overall high risk of bias if one or more

domains was of high risk of bias (14-17); an overall moderate risk of bias if three or more domains were of moderate risk of bias (none high risk of bias) (14-16); and an overall low risk of bias if all domains were low risk of bias, or one or two domains were moderate risk of bias (18). Any discrepancies between reviewers were discussed at a consensus meeting, and any further disagreement was resolved by discussion with a third reviewer (SRF).

Data Extraction

All data was extracted by one reviewer (KS) and inputted to a Microsoft Excel spreadsheet, and independently cross-checked by a second reviewer (HC). Extracted data included participant demographics, study characteristics, the factor(s) assessed, the diagnostic criteria used to define IPJ osteoarthritis, and the effect measure. Data was extracted from all time points reported in each study.

Best evidence synthesis

All potential prognostic factors assessed for IPJ osteoarthritis were identified separately for radiographic, radiographic symptomatic and symptomatic diagnostic criteria. Subgroup analyses for DIPJ and PIPJ osteoarthritis were performed. In the absence of heterogeneity, a meta-analysis to pool factors investigated across multiple studies was planned, and quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework (19).

If studies were heterogeneous with regards to study populations, potential prognostic factors analysed, effect measures, and the methods used to define IPJ osteoarthritis, a narrative summary was used. The association between a potential prognostic factor and the presence of IPJ osteoarthritis was categorised as: a) A prognostic factor (positive association/s), b) Not a

prognostic factor (negative association/s or no statistical association), c) Mixed evidence (associations in different directions). A best evidence synthesis method was used to summarise the data, assessed in the following sequential order (20-24). If multiple analyses were performed within one study, the consistent findings approach below was applied to the analyses to determine whether the study itself showed consistent or mixed evidence, after which the study was used in calculating the overall best evidence synthesis.

a) Consistent findings ($\geq 75\%$ of studies showing associations in the same direction) for either a positive or negative/ no association

b) Mixed evidence: Inconsistent findings ($< 75\%$ of studies showing associations in the same direction)

If findings were consistent, the strength of evidence was assessed:

i. Strong evidence: > 2 studies with low risk of bias

ii. Moderate evidence: 1 study with low risk of bias and 1 other study, Or: > 2 studies with moderate or high risk of bias

iii. Limited evidence with low risk of bias: 1 study with low risk of bias

iv. Limited evidence: 1 or 2 studies with moderate or high risk of bias

RESULTS

Search Strategy

The results from the search in 2018 and the updated search in 2020 are combined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) figure below. In total, the searches produced 25,739 abstracts, and after the removal of duplicates 13,346 remained. After title and abstract screening, 178 full texts were reviewed, and 18 articles met the inclusion criteria (Figure 1). No further articles were included from screening the reference lists of other reviews.

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of study selection

Study Characteristics

Data was extracted from 18 studies (Supplementary Table S2) (25-42). Four studies were prospective cohort studies (26, 31, 35, 38), eleven studies were cross-sectional (27-30, 32-34, 36, 37, 39, 41), and three studies were case-control studies (25, 40, 42). Five studies included only women (28, 30, 34, 35, 37). Of the studies which reported mean age of participants, Fu et al. included the youngest participants (age of cases: mean 39.2 (standard deviation 3.6) years, age of controls: 38.7 (3.1) years) (40), whilst Cho et al. included the oldest participants (72 (5) years) (41).

Risk of Bias

Eight studies had an overall high risk of bias (25, 26, 29-31, 33, 38, 39), three had an overall moderate risk of bias (27, 35, 41), and seven had an overall low risk of bias (28, 32, 34, 36, 37, 39, 42) (Table 1). 'Study participation' was of high risk of bias in the studies by Jones et al.

and Fu et al. as they did not describe the source population and it is unclear whether there was 80% participation from eligible individuals (29, 40). Lehto et al. and Haara et al. did not describe ‘Study attrition’ (25, 31). Risk of bias for the ‘Prognostic factor measurement’ domain was high in the studies by Cooley et al. and Kalichman et al., as comprehensive descriptions of the factors were not provided; whilst in the study by Biermasz et al., a continuous variable was converted to a categorical variable (30, 33, 38). Chaisson et al. was found to be of high risk of bias in the ‘Outcome measurement domain’ as the radiographs were not interpreted with blinding, and some participants had missing radiographic data (26).

Table 1: Risk of bias for included studies

Diagnostic criteria used to define IPJ Osteoarthritis

All studies used radiography in their definition of osteoarthritis (25-42), including one study which specified a symptomatic radiographic definition (37) (Table 2). A version of the Kellgren Lawrence (KL) atlas (43-45) was most commonly used (25-28, 31, 33, 34, 36-41). Five studies used the Altman, also known as the Osteoarthritis Research Society International (OARSI) (40, 46) atlas (29, 30, 32, 35, 40, 42). Ding et al was the only study to include a definition of radiographic symptomatic osteoarthritis, which was defined as ‘KL grade ≥ 2 with ‘mild’ pain during the last 30 days in ≥ 1 DIPJ’. Two studies used a non-radiographic symptomatic definition of osteoarthritis, by assessing the presence of Heberden’s nodes (29, 30). Jones et al defined symptomatic IPJ osteoarthritis as the ‘total number of DIPJs with Heberden’s nodes’, whilst Cooley et al defined it as ‘Heberden’s nodes in ≥ 1 DIPJ’.

Table 2: Diagnostic criteria used to define the presence of finger interphalangeal joint osteoarthritis in included studies

239

240 **Potential prognostic factors for IPJ osteoarthritis**

241 In total, 64 potential prognostic factors for IPJ osteoarthritis were investigated across the
242 eighteen studies (Table 3). Due to heterogeneity in study populations, the methods used to
243 measure the factors and to measure osteoarthritis, and difference in statistical analyses, meta-
244 analyses could not be performed and a best evidence descriptive synthesis was used.

245

246 **Table 3: Potential prognostic factors assessed for their association with the presence of** 247 **interphalangeal joint osteoarthritis**

248

249 ***Radiographic IPJ osteoarthritis***

250 Forty-nine potential prognostic factors were assessed for their association with radiographic
251 IPJ osteoarthritis (all effect measures shown in Supplementary Table S3) (Table 4). Eight
252 prognostic factors were identified: Older age in women (moderate evidence; multiple
253 regression $\beta = 0.39$ and $\beta = 0.35$ (27), likelihood method (effect measure not given) $p < 0.001$
254 and $p < 0.001$ (33), odds ratio (OR) 1.12 (95% confidence interval (CI) 1.07 to 1.18) and 1.12
255 (1.07 to 1.67) (34), relative risk (RR) 1.0 (0.9 to 1.2), 0.9 (0.7 to 1.2), 1.0 (0.9 to 1.2), 0.9 (0.1
256 to 1.1) (35)); female gender (moderate evidence: OR 2.85 (2.28 to 3.57) (31), OR 1.3 (0.9 to
257 1.9) (32), one-way multivariate analysis of covariance (MANCOVA) (effect size not given)
258 $p = 0.011$ and $p = 0.019$ (33), OR 3.5 (2.2 to 5.8) and 2.1 (1.6 to 2.9) (41)); family history of
259 Heberden's nodes in women (limited evidence in low risk of bias study: OR 1.94 (1.15 to 3.28)
260 and 1.75 (1.04 to 2.93) (34)); Adult Kashin Beck disease (limited evidence; Fisher's exact test
261 (effect size not given) $p < 0.05$ for all analyses (40)); older age in men (limited evidence:
262 multiple regression $\beta = 0.22$ and $\beta = 0.35$ (27)), likelihood method (effect measure not given)
263 $p < 0.001$ and $p < 0.014$ (33)); dental occupation in men (limited evidence: (effect measure and

size not given) $p=0.02$ (25)); history of finger fracture (limited evidence: OR 2.42 (1.22 to 4.83) (29)); and Parity (limited evidence: OR 7.78 (1.25 to 50.0) (30)) (Table 4). Mixed evidence was found for higher body mass index (BMI) (29, 31, 32, 36), higher BMI in men (27), and higher Insulin-like growth factor-1 (IGF-1) (38); whilst 39 factors were found not be prognostic for IPJ osteoarthritis (effect measures shown in Supplementary Table S3) (Table 4).

In the subgroup analysis for DIPJ osteoarthritis, forty-four potential prognostic factors were assessed. Compared to the analysis of all IPJs, differences were found for: female gender which showed strong evidence for being a prognostic factor (OR 2.85 (2.28 to 3.57) (31), OR 1.3 (0.9 to 1.9) (32), one-way MANCOVA (effect size not given) $p=0.019$ (33), OR 2.1 (1.6 to 2.9) (41)); higher BMI in men which showed limited evidence for being a prognostic factor (multiple regression $\beta=0.25$ (27)). Older age in women (27, 33, 35), atherosclerosis in women (39), and no use of hormonal therapy (30) showed mixed evidence (effect measures shown in Supplementary Table S3) (Table 4).

In the subgroup analysis for PIPJ osteoarthritis, twenty-three potential prognostic factors were investigated. When compared to all IPJ, different results were found for: female gender which showed limited evidence for being a prognostic factor (one-way MANCOVA (effect size not given) $p=0.011$ (33), OR 3.5 (2.2 to 5.8) (41)); higher BMI in men (27) and higher BMI in women (27, 35), which both showed limited evidence for not being prognostic factors; and higher grip strength in men (26) and older age in women (27, 33-35) showed mixed results (effect measures shown in Supplementary Table S3) (Table 4).

Table 4: Best evidence synthesis for potential prognostic factors assessed for their association with the presence of radiographic finger interphalangeal joint osteoarthritis

289

290 ***Radiographic symptomatic IPJ osteoarthritis***

291 Higher BMI in women was the only potential prognostic factor assessed, and it was found to
292 have limited evidence in one low risk of bias study for being a prognostic factor (37)
293 (effect measures shown in Supplementary Table S4). The definition of osteoarthritis presence
294 used by Ding et al. was based on the DIPJs, so no subgroup analyses were performed (37).

295

296 ***Symptomatic IPJ osteoarthritis***

297 Fourteen potential prognostic factors were assessed for their association with the presence of
298 symptomatic IPJ osteoarthritis (29, 30) (effect measures shown in Supplementary Table S5).
299 Each potential prognostic factor was assessed by one high risk of bias study, and no factor was
300 found to be prognostic for IPJ osteoarthritis (Table 5). All definitions of symptomatic IPJ
301 osteoarthritis included only the DIPJ, so subgroup analysis could not be performed.

302

303 **Table 5: Best evidence synthesis for potential prognostic factors assessed for their**
304 **association with the presence of symptomatic finger interphalangeal joint osteoarthritis**

DISCUSSION

We identified 18 studies in the literature which assessed prognostic factors for the presence of IPJ osteoarthritis (25-42). All studies defined osteoarthritis radiographically (25-42). Symptomatic radiographic osteoarthritis was also defined by one study (37), and symptomatic osteoarthritis assessing Heberden's nodes was also defined by two studies (29, 30). Sixty-four potential risk factors were investigated in the literature (25-42). Of these, eight were prognostic factors for radiographic IPJ osteoarthritis, with evidence ranging from moderate to limited (25, 27, 29, 31-35, 40, 41); and one prognostic factor (limited evidence) for symptomatic radiographic osteoarthritis was found (37). Few differences were seen in the DIPJ and PIPJ subgroup analyses.

Of the radiographic definitions, the KL atlas, or a modified version of it, was most commonly used (43-45). The 2008 European League Against Rheumatism (EULAR) Standing Committee on International Clinical Studies Including Therapeutic Trials (ESCISIT) for hand osteoarthritis listed recommendations for diagnosing hand osteoarthritis (1). They also identified radiographic definitions as the most common method of diagnosing hand osteoarthritis. A systematic review assessing the use of radiography in studies of hand osteoarthritis found that the KL atlas in particular was the most commonly used radiographic scoring method for hand osteoarthritis (47). It described the KL atlas as being a composite sum score across all hand joints (47). In our review, KL sum score was used as a diagnostic criteria in only two studies (33, 38). However, these studies did not use specific a cut-off sum score above which osteoarthritis was diagnosed. It is possible that Kalichman et al. and Biermasz et al. included IPJs with a KL grade of 1 when counting the KL sum score (33, 38). However, a KL grade of 1 describes possible or doubtful joint space narrowing with possible osteophyte formation, and is often considered not to represent osteoarthritis in the joint (43-45). Kalichman

et al. used this definition when reporting older age in women as a prognostic factor for radiographic IPJ osteoarthritis (33). Despite four studies assessing the association between older age in women and IPJ osteoarthritis, this could have skewed the results, and therefore they should be interpreted with caution (27, 33-35). More commonly, studies included in this review used a threshold of KL grade ≥ 2 in a specific number of IPJs as the definition of osteoarthritis being present (25, 27, 28, 31, 34, 36, 37, 39, 41, 48). However, there was also no consensus on how the KL atlas was applied between studies. The lack of harmonisation between studies in defining the presence of radiographic osteoarthritis prevented meta-analyses, and further work is needed to identify methods of harmonisation between datasets, to allow for the pooling of data.

Diagnostic criteria to define radiographic symptomatic osteoarthritis was used by one study (37). Our results found that higher BMI in women was a prognostic factor for symptomatic radiographic IPJ osteoarthritis, but not for radiographic osteoarthritis (27, 34, 35, 37). However, only one study assessed symptomatic radiographic IPJ osteoarthritis, and it was of high risk of bias, resulting in limited evidence (37). Diagnostic criteria to define symptomatic osteoarthritis were used by two studies (29, 30). No prognostic factors were identified for symptomatic osteoarthritis, despite fourteen factors being investigated (29, 30). In the literature, there is poor correlation between radiographic and symptomatic hand osteoarthritis (9). All of the factors investigated for an association with symptomatic osteoarthritis were also investigated for an association with radiographic osteoarthritis. Twelve of these were found to have no association with either radiographic or symptomatic osteoarthritis, suggesting that although diagnostic criteria for radiographic and symptomatic osteoarthritis might not be well correlated, their aetiology and pathogenesis might be (29, 30). Additional and more robust studies are required to validate the prognostic factor findings for symptomatic radiographic and

symptomatic IPJ osteoarthritis. Similarly, further research is needed to better understand the relationship between radiographic and symptomatic IPJ osteoarthritis, particularly as patients more commonly seek medical investigations or management because of clinical symptoms rather than radiographic signs of IPJ OA. Studies investigating prognostic factors for symptomatic IPJ OA are likely to have more meaningful implications for patients than those investigating radiographic IPJ OA.

The work from the 2008 EULAR ESCISIT for hand osteoarthritis identified risk factors for hand osteoarthritis (1). They used a Delphi consensus of 21 osteoarthritis experts, and both their results and ours identified female gender as a prognostic factor (1, 31-33, 41). Zhang et al. performed a literature review and reported age over 40 as a risk factor (1). We found older age in men and women were both prognostic factors, with all studies investigating these factors reporting a mean age of participants of over 40 years' old (27, 33-35). Zhang et al. identified obesity as a prognostic factor, we found only higher BMI in women was prognostic for symptomatic radiographic osteoarthritis (1, 37). They also identified family history as a risk factor, whilst we identified only a family history of Heberden's nodes as a prognostic factor; they identified prior injury, whilst we found this was specifically finger fracture; and they listed occupation, whilst we found only dental occupation in men was prognostic (1, 25, 29, 34). Additionally, they listed higher bone density and menopausal status as risk factors, though we were not able to replicate these recommendations (1, 30, 42). However, Zhang et al. did not include a systematic review and therefore might not fully assessed all associations and lack of associations between factors and osteoarthritis (1). Furthermore, they used hand osteoarthritis as an outcome, despite some evidence suggesting IPJ and base of thumb osteoarthritis might be different subsets (49) and have different prognostic factors (1, 6). Our results suggest that older aged women (27, 33-35) and females (31-33, 41) are at increased risk of developing

radiographic IPJ osteoarthritis; whilst older age in men (27, 33), men whom are dentists (25), people with a history of finger fracture (29), those with adult Kashin Beck disease (40), and women with a family history of Heberden's nodes (34) or a history of parity (30) may also be at increased risk, though the evidence is limited. Our sub-group analyses suggest that DIPJ and PIPJ osteoarthritis have similar prognostic factors, and should be combined in future analyses. However, further studies are required to validate these findings. Prognostic pathway studies are also needed to understand the relationship between risk factors and whether multiple factors in co-existence with each other moderate the risk of radiographic IPJ osteoarthritis being present (50).

To our knowledge, this is the first systematic review to identify prognostic factors for the presence of IPJ osteoarthritis. A strength of this review is the exclusion of first CMCJ osteoarthritis, and the analysis of radiographic IPJ osteoarthritis separate to symptomatic IPJ osteoarthritis. Only one study diagnosed osteoarthritis using a symptomatic radiographic definition (37), and only two studies diagnosed symptomatic osteoarthritis (29, 30). Additional studies using non-radiographic definitions of IPJ osteoarthritis are needed. Primary studies did not assess prognostic pathways and no prognostic models for IPJ osteoarthritis were identified, highlighting that further work is needed to understand prognostic pathways and to better inform clinical decision making (50). This review is limited by the majority of studies being of moderate or high risk of bias (25-27, 29-31, 33, 35, 38, 39, 41). A meta-analysis could not be performed due to heterogeneity in methodology between studies and differences in effect measures between studies. Harmonisation between datasets is required to enable pooling of results.

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CONFLICTS OF INTEREST

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