Association of Age and Sex at Onset With Glenohumeral Osteoarthritis

A Systematic Review and Meta-analysis

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Objective: The aim of the present systematic review is to synthesize existing evidence (qualitative and quantitative) regarding age- and sex-specific differences with glenohumeral osteoarthritis.

Design: The electronic databases PubMed, MEDLINE, and Web of Science were searched up to March 15, 2023. Articles reporting on the association of risk factors (age and sex) with glenohumeral osteoarthritis were considered. We used Newcastle-Ottawa Scale to assess study quality. Meta-analysis was conducted to quantitatively summarize the association of age and sex with glenohumeral osteoarthritis.

Results: A total of 24 articles were retrieved for full-text review. Of 24 articles, 8 reporting age-specific and 5 articles reporting sex-specific associations with glenohumeral osteoarthritis were included. The odds ratio for the age (odds ratio = 3.18; 95% confidence interval = 1.10–15.92) and female sex (odds ratio = 1.78; 95% confidence interval = 0.95–3.42) were increased and observed statistically significant.

Conclusions: The present systematic review and meta-analysis suggests the role of increasing age as one of the significant contributors to glenohumeral osteoarthritis. However, association of female sex with glenohumeral osteoarthritis is least convincing. Future studies are required to understand the molecular mechanisms behind the contributory role of increasing age and female sex in the establishment of glenohumeral osteoarthritis.

Key Words: Glenohumeral Osteoarthritis, Risk Factors, Osteoarthritis, Meta-analysis, Effects

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What Is Known

- The association of age- and sex-specific effects has been controversial with the establishment of glenohumeral osteoarthritis.

What Is New

- We observed that increased age and female sex have strong association with glenohumeral osteoarthritis.

Glenohumeral osteoarthritis (GH OA) is the third most common musculoskeletal disorder after hip and knee OA.[1] Glenohumeral osteoarthritis causes pain, limits the day-to-day activities of affected individuals, and leads to poor functional outcomes. The prevalence of GH OA has been estimated to be 17%–19% among individuals older than 40 and 60 yrs, respectively.[2–4] Glenohumeral osteoarthritis is characterized by the degeneration of articular cartilage of the humeral head and can be primary (degeneration of cartilage over time) and secondary (trauma, shoulder dislocation and instability, massive rotator cuff tears, and inflammatory arthropathy). The etiology of GH OA is not well understood, and various risk factors (both clinical and biological factors) are generally considered to contribute to the degeneration of the glenohumeral joint.

Multiple risk factors such as age, sex, race, obesity, smoking status, genetic predisposition, hyperlaxity, shoulder overuse, occupations involving the use of upper limbs and overhead sports activities have been associated with GH OA.[2,5–7] However, a systematic understanding on their role and association with GH OA remains elusive.[8] Earlier published systematic reviews on GH OA provided evidences on intra-articular infiltration therapy, outcomes and survivorship after arthroscopy, reverse shoulder arthroplasty, outcomes of hyaluronic acid, and critical shoulder angle.[9–14] This is to the best of our knowledge a systematic review on the association between age and sex and the presence of GH OA has not been conducted.

Hence, the primary aim of this systematic review is to synthesize existing evidence (qualitative and quantitative) regarding age- and sex-specific difference with GH OA. To achieve this, we performed a meta-analysis to elucidate the hypothesis concerning the age- and sex-specific effects on GH OA.

METHODS

Search Strategy and Criteria

The systematic review and meta-analysis were conducted as per Preferred Reporting Items for Systematic Reviews and

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The data searched, extracted, and analyzed in the present systematic review and meta-analysis are presented in the form of figures, tables, and supplementary information within the manuscript.

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Meta-Analyses guidelines and reports the required information accordingly (see supplementary checklist, Supplemental Digital Content 1, http://links.lww.com/PHM/C272).[15] A protocol was developed before starting the literature search and registered in the PROSPERO (CRD: CRD42022371283).[16] A comprehensive search was performed on the following electronic databases: MEDLINE (PubMed), EMBASE, and Web of Science up to March 15, 2023. More detailed description of key words, MeSH (Medical Subject Headings), and tiab (Title and Abstract) terms used in the literature search to or describe the risk factors for GH OA are provided in supplementary material 1 (Supplemental Digital Content 2, http://links.lww.com/PHM/C273).

Search results from each database were exported into EndNote 20 bibliographic software (Thomson Reuters, New York, NY). A total of 7073 articles were identified after reviewing manual bibliography. After removing duplicate studies 4206 articles were finally obtained. All articles were transferred into Rayyan, a free platform (http://rayyan.qcri.org) that makes an initial screening of titles and abstracts easy for the reviewers.[17] Two independent researchers (JEG and UBP) screened all the titles and abstracts based on the criteria described. In case of disagreement by the first two researchers, a third researcher (NBJ) took a final decision on the inclusion of articles. Eligibility criteria for inclusion were study design (cross-sectional, case-controls studies and retrospective review of prospectively collected data) and publication in English language. Studies that were not original article (editorials, opinions, systematic reviews, and meta-analysis), animal studies, and basic science research (biomarker studies) were excluded.

QUALITY ASSESSMENT

A methodological quality assessment was conducted for each article included by two independent researchers RP and NBJ and scored the quality of the articles as per the guidelines of Newcastle-Ottawa Quality Assessment Scale. We converted the studies into three categories based on the quality criteria (Newcastle-Ottawa Quality Assessment Scale) and categorized them as good (7–8 stars), fair (5–6 stars), and poor (4 stars).[18]

ASSESSMENT OF RISK FACTORS

We focused on age and sex as the major risk factors for GH OA.

Data Abstraction

The full-text articles for the selected studies were retrieved and data were abstracted in a spreadsheet for age- and sex-specific results along with their risk estimates and 95% confidence interval (CI). A standard approach was used to extract data from each article: study title, date of the publication, journal, first author, study design, glenohumeral osteoarthritis specifics, age, sex, number of cases and controls, risk factor, and outcome specifics (unadjusted effect estimate and multivariable adjusted effect estimates, if available). Studies represented estimates for two or more independent populations (e.g., men and women in different age groups) all the estimates were documented for sensitivity analyses.

STATISTICAL ANALYSIS

To assess the association of age and sex with GH OA, we used a conventional random-effects mixed model approach by treating the studies as a random effect.[19] The odds ratio (OR) and corresponding 95% CIs served as the effect estimate for the meta-analysis. To ensure robustness, we preferred adjusted estimates where potential confounders are controlled for over unadjusted estimates, and for any missing estimates in a study, we imputed the OR from standard error and other relevant estimates present in the study. We also preferred the OR a measure of the effect because of its favorable statistical properties, unlike the relative risk has the advantage of being invariant to the labelling of the event. Furthermore, the ORs are valid regardless of the type of sampling used, which is not the case for other comparative measures for binary data.[19] We assumed that age was distributed normally, which is a reasonable statistical assumption.[20] Therefore, in studies where age was reported as a categorical variable, we calculated weighted average age first using the midpoint age between the two threshold values as the average age and multiplying by total number of categories to get the age. Then, we sum all the numbers for each category and divided by our sample size to get the weighted average age.

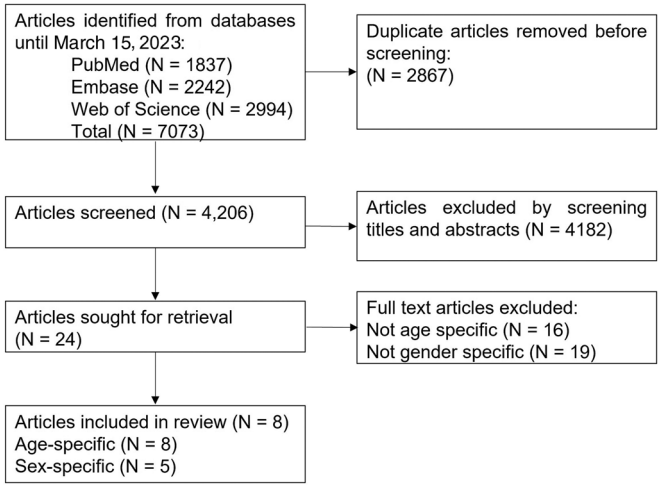

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the systematic review.

TABLE 1. Quality assessment using the Newcastle-Ottawa Quality Assessment Scale of included studies

	Selection				Comparability	Outcome/Exposure			
Articles	**1**	**2**	**3**	**4**	**1**	**1**	**2**	**3**	**Total Score**
Cameron et al.[23] (2002)	*	*			*	*	*	*	6 (F)
Cho et al.[24] (2015)	*	*	*		**	*	*	*	8 (G)
Kobayashi et al.[3] (2014)	*	*	*		**	*	*	*	8 (G)
Schoenfeldt et al.[25] (2018)	*	*	*		*	*		*	6 (F)
Shinagawa et al.[26] (2018)	*	*	*		**	*	*		7 (G)
Siviero et al.[27] (2009)	*		*		**	*	*	*	7 (G)
Oh et al.[2] (2011)	*	*	*		**	*		*	7 (G)
Zhang et al.[28] (2016)	*	*	*		**	*	*	*	8 (G)

*Represents 1 point for each numbered item in selection, comparability, and outcome/exposure categories.

**Represents 2 points for comparability category.

To test for heterogeneity, we used Cochran Q test and I^2 index. Given the presence of significant heterogeneity, we opted for a random-effect model. For statistical significance, two-sided tests were conducted, and a P value <0.05 was considered as the threshold. In addition, we addressed publication bias by conducting Begg test and Egger test, which provided valuable insights into the reliability and potential bias of the included studies. All the analyses were performed in R studio version 4.2.2 using meta and metafor package.[21,22] Through these comprehensive methodologies and statistical analyses, we aimed to generate a more comprehensive and reliable understanding of the relationship between age, sex, and GH OA.

RESULTS

Search Results

The process to search eligible studies is shown in Figure 1. A total of 7073 articles were assessed after a complete search; 2867 duplicate articles were removed before the screening. Of 4206 articles, 4182 were excluded after screening for title and abstract. Finally, 24 articles were retrieved for full-text review published since 2000. Among those, 16 articles did not report on age and 19 articles did not report on sex as one of the risk factors for GH OA. Finally, eight studies reporting age-specific and five studies reporting sex-specific estimates on risk factors for GH OA were included.

Study Characteristics and Quality Assessment

A total of eight studies with 4091 patients were reviewed. Selected studies were published between 2000 to 2023, including one cohort study, five cross-sectional studies, and two retrospective reviews of prospective studies. Six of the studies included were classified as good quality as per the assessment of the Newcastle-Ottawa Scale and three studies were classified as fair quality (Table 1).

Age and Glenohumeral Osteoarthritis

Eight studies reported age-specific risk estimates for GH OA either as a continuous variable or categorical variable.[2,3,23–28] Of these, two were retrospective studies, five were cross-sectional studies, and one was a prospective cohort study. These studies reported on the prevalence of GH OA, associated risk factors, functional limitations in upper limbs, critical shoulder angle, and arm dominance versus GH OA are displayed in supplementary table 2 (Supplemental Digital Content 3, http://links.lww.com/PHM/C274).

Two studies evaluated age as a categorical variable in establishing a relationship with GH OA.[2,3] Kobayashi et al.[3] evaluated the prevalence of GH OA in different age groups. They observed 1.8% prevalence in the age group 40–49 yrs, 9.6% in 50–59 yrs, 14.7% in 60–69 yrs, 26.9% in 70–79 yrs, and 27.5% in ≥80 yrs. In univariate analysis, an odds ratio of 9.78 (95% CI = 1.29–74.26), 19.29 (95% CI = 2.59–143.52) and

TABLE 2. Characteristics of studies included in the meta-analysis

Name of the Author	Year	Country	Total Population	Study Design	OR (95% CI) for Age	OR (95% CI) for Sex*
Cameron et al.[23]	2002	United States	422	Retrospective	1.02 (0.28–3.68)	
Siviero et al.[27]	2009	Italy	1867	Prospective	2.61 (1.57–4.35)	2.75 (1.65–4.58)
Oh et al.[2]	2011	South Korea	679	Cross-sectional	2.99 (1.76–5.08)	
Kobayashi et al.[3]	2014	Japan	541	Cross-sectional	13.81 (1.79–106.45)	
Cho et al.[24]	2015	South Korea	36	Cross-sectional	1.1 (0.7–1.6)	1.90 (0.80–4.4)
Zhang et al.[28]	2016	China	211	Cross-sectional	1.05 (1.05–1.06)	
Shinagawa et al.[26]	2018	Japan	183	Cross-sectional	1.87 (0.93–3.70)	0.71 (0.40–1.29)
Schoenfeldt et al.[25]	2018	United States	152	Retrospective	1.05 (0.75–1.46)	

*Male as a reference.

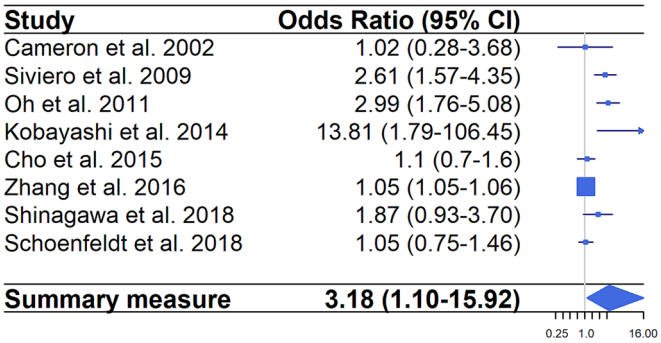

FIGURE 2. Forest plot showing association between age and glenohumeral osteoarthritis. Figure showing effect estimates (odds ratios), 95% CIs, and the summary measure of contributing studies evaluating the association between age and glenohumeral osteoarthritis.

20.43 (95% CI = 2.58–162.16) was observed for the age groups of 60–69, 70–79, and ≥80 yrs, respectively. Furthermore, multivariate analysis also reported odds ratios of 5.59 (95% CI = 1.29–74.26), 11.59 (95% CI = 152–88.29), and 10.77 (95% CI = 1.31–88.54), for the age groups of 60–69, 70–79, and ≥80 yrs, respectively, and provided evidence for increasing age and its association with GH OA. Oh et al.[2] reported an odds ratio of 2.41 (95% CI = 1.41–4.12) and 3.58 (95% CI = 2.11–6.05) for the age groups 70–74 and ≥75 yrs, respectively. A multivariate analysis again replicated the findings for the same age groups indicating an odds ratio of 2.20 (95% CI = 1.21–3.78) and 3.42 (95% CI = 1.99–5.85).

Cameron et al.[23] reported age as one of the risk factors associated with GH OA. No significant difference for age per 5 yrs in association with GH OA was observed,[24] whereas Shinagawa et al.[26] reported increasing age per 10 yrs has a significant association with GH OA. A retrospective analysis showed that females acquire GH OA at an older age than men.[25]

Meta-analysis

We pooled the results from eight studies to analyze the effects of age on GH OA (Table 2). The pooled odds ratio was 3.18 (95% CI = 1.10–15.92) with significant heterogeneity (I^2 = 84.60%) (Fig. 2, Table 3). Begg regression test did not show any publication bias (P = 0.061), while Egger test showed a significant publication bias (P = 0.036) (Table 3).

Sex and Glenohumeral Osteoarthritis

Five studies reported sex-specific risk estimates for GH OA.[24,25,27–29] Of these, four were cross-sectional studies and one was retrospective cross-sectional study. These studies also reported the prevalence of GH OA, associated risk factors and the dominance of arm *versus* GH OA are displayed in supplementary table 2 (Supplemental Digital Content 3, http://links.lww.com/PHM/C274).

Females were reported to contain large number of primary GH OA cases when compared with males.[28,29] On the contrary, another study reported that both sexes were almost equally diagnosed with GH OA.[25] Cho et al.[24] reported high prevalence for GH OA in females than males in univariate analysis, but in multivariate analysis, they did not find any association. Siviero et al.[27] reported that females ≤76 yrs are 3.3 times more at risk to develop definite GH OA and about two times more to have probable GH OA than males in the same age group. Similarly, males older than 76 yrs were observed at 3.5 times more risk to develop definite GH OA and 1.6 times more risky to have probable GH OA than young ones.[27]

Meta-analysis

We were only able to pool results of three studies (two multivariate and one univariate analysis) to analyze the effects of sex on GH OA (Table 2). The pooled odds ratio observed was 1.78 (95% CI = 0.78–3.42) indicating that female sex is more prone to develop GH OA with significant heterogeneity (I^2 = 80.68%) (Fig. 3, Table 3). Begg test and Egger test did not show any publication bias (P = 1 and P = 0.86, respectively) (Table 3).

DISCUSSION

We synthesized the evidence on association of age and sex with GH OA. Our meta-analysis results suggested that increased age and female sex have strong association with GH OA.

Increasing age had a strong association with an increased likelihood of GH OA in our study. Either as continuous or categorical variable, aging was observed consistently associated with increased odds of GH OA. The likely reason behind the association of aging with GH OA is due to degeneration of the glenohumeral joint. Cell senescence can be a possible mechanism behind aging-related osteoarthritis development. This is caused by oxidative damage that leads to age-associated deterioration of chondrocyte formation, decreases the ability of cells to maintain, and restores articular cartilage.[30–32] Systemic levels of proinflammatory cytokines such as IL-6 and TNF-α also increase along with aging.[33,34]

TABLE 3. Meta-analysis for age and sex with GH OA

Variables	No. Studies	Total Population	Pooled OR (95% CI)	Heterogeneity (I^2)	Begg Test; Egger Test
Age	8	4091	3.18 (1.10–15.92)	84.60%	0.061; 0.036
Sex	3	2086	1.78 (0.95–3.42)	80.68%	1; 0.86

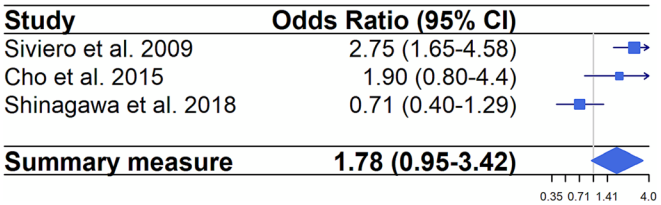

FIGURE 3. Forest plot showing association between sex and glenohumeral osteoarthritis. Figure showing effect estimates (odds ratios), 95% CIs, and the summary measure of contributing studies evaluating the association between sex and glenohumeral osteoarthritis.

The relationship between sex and GH OA was observed with inconsistency across different studies included in our systematic review. We were only able to pool results of three studies that showed that female sex had a higher odd of GH OA but could not demonstrate a statistically significant difference because of a smaller number of studies included. However, the likely reasons for female sex being more predisposed to GH OA may be related to fluctuations in hormones during menopause or host genetics. There is a growing body of evidence that estrogen affects the cartilage metabolism via molecular pathways.[35] Estrogen is considered to play an important role in maintaining stability of cartilage. Thus, a decline in the sex hormone levels after the menopause may also trigger the development of OA by inhibiting the matrix metalloproteinase (MMP) pathways in cartilage and reduced amount of type II collagen degradation markers.[35–38] Lower levels of β-estradiol and progesterone in serum may also predispose females to GH OA as is seen in knee effusion synovitis.[39]

The present study has significant strength. This is the first meta-analysis on age and sex for GH OA. The limitations of our meta-analysis include the relatively small number of studies that met eligibility. Previous published studies describing the role of female sex and among males stratifying data between older versus young males were fewer in number. This led to another limitation in establishing contribution of female sex to GH OA on large studies and if older males are developing more GH OA as compared with young males. Previous evidence available for meta-analysis was mostly from either retrospective or cross-sectional studies that limited the conclusion of association between age and sex with the GH OA. In addition, the number of studies assessing these risk factors was relatively small, which can lead to bias of statistical significance.

CONCLUSIONS

The present systematic review and meta-analysis suggests the role of increasing age as one of the significant contributors to GH OA. However, association of female sex with GH OA is least convincing. Future studies on molecular mechanisms that contribute to the effects of aging and female sex on joint degeneration are needed. In addition, considering potential association of age and female sex with GH OA, better designed studies on large sample size are needed to provide more definitive evidence. Thus, data generated will help in identifying the patients with a particular age and sex at risk after developing GH OA and stratifying them for rehabilitation approaches. This might lead to prioritize care that is age- and sex-specific centered and responsive.

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