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The Effect of Lipid Disorders on the Risk of Rotator Cuff Disease

A Systematic Review and Meta-Analysis

Jianyu Lai, MPH, and Joel J. Gagnier, ND, MSc, PhD

Investigation performed at the University of Michigan, Ann Arbor, Michigan

Background: Rotator cuff disease has a high prevalence and is associated with shoulder pain and disability. Dyslipidemia might be an intrinsic factor related to the development of the disease as it might increase tendon stiffness and result in tendon problems. The purposes of the present study were (1) to systematically review the association between lipid disorders and the risk of rotator cuff disease and (2) to provide physicians with guidance to prevent rotator cuff disease.

Methods: Six databases were searched through July 6, 2016: MEDLINE, Embase, CINAHL, Web of Science, SPORTDiscus, and the Cochrane Central Register of Controlled Trials. Eligible studies were assessed for risk of bias and strength of evidence. Meta-analysis was performed for the effect of dyslipidemia on the presence of rotator cuff disease, with the effect being expressed as an odds ratio. The overall effect was estimated, and heterogeneity across studies was expressed with the I^2 statistic. We used standard and contour-enhanced funnel plots as well as the Begg and Egger tests to check for publication bias.

Results: Three cross-sectional studies, 1 cohort study, and 3 case-control studies involving 505,852 participants were selected, with 6 of these studies being eligible for meta-analysis. The main-effect meta-analysis yielded a pooled odds ratio of 2.17 (95% confidence interval, 1.46 to 3.23; $p < 0.001$; $I^2 = 82.4\%$), indicating a higher rate of rotator cuff disease in patients with dyslipidemia. The sensitivity analysis was not different from the main-effect analysis. Contour-enhanced funnel plots revealed the possibility of publication bias or other small-study effects.

Conclusions: We found that dyslipidemia was associated with high occurrence of rotator cuff disease. We recommend that physicians examine tendon conditions if their patients have severe dyslipidemia.

Level of Evidence: Prognostic Level IV. See Instructions for Authors for a complete description of levels of evidence

The prevalence of rotator cuff disease is high in both asymptomatic and symptomatic individuals, with reported rates of 30% and 64%, respectively[1]. Because of the burden of disease associated with rotator cuff tears, including shoulder pain and disability[2,3], studies have been performed to explore risk factors for this condition[4-12].

The etiology of rotator cuff disease remains uncertain[13]. Some researchers have suggested that rotator cuff disease is multifactorial and is due to both extrinsic and intrinsic factors[2]. Intrinsic risk factors include degeneration, inflammation, oxidative stress, circulatory impairment, and lipid disorders[4]. For instance, Beason et al.[5] performed tensile tests on the supraspinatus tendon in mice, rats, and monkeys and found that stiffness and elastic modulus were much higher in the high-cholesterol groups than the normal groups.

Some research has focused on the relationship between lipid disorders and rotator cuff disease. Djerbi et al.[6], in a case-control study, found that patients with dyslipidemia had a higher prevalence of rotator cuff tears. Lin et al., in a large cohort study, found that hyperlipidemia was an independent risk factor for rotator cuff disease[4]. Abboud and Kim[7] found that patients with rotator cuff disease were more likely than controls to have higher total cholesterol, higher triglycerides, higher low-density lipoprotein (LDL), and lower high-density lipoprotein (HDL). Conversely, Longo et al., in a case-control study, found that serum triglyceride

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TABLE I Summary of Characteristics of Included Studies*

Study	Study Design	Study Location	Age *(yr)*	Inclusion and Exclusion Criteria	Sample Size (Cases:Controls) *(no. of patients)*	Female: Male Ratio *(no. of patients)*	Type of Rotator Cuff Disease
Abboud and Kim[7] (2010)	Case-control	U.S.	21-93	Inclusion: verified shoulder diagnosis, confirmed full- thickness rotator cuff tear (cases), confirmed intact rotator cuff (controls). Exclusion: previous shoulder surgery, smokers, shoulder infection, inflammatory arthritis, alcoholism, age <21 yr, chronic steroid/floxacin use, not undergoing surgical treatment	74:73	64:83	Full-thickness rotator cuff tear
Longo et al.[8] (2010)	Case-control	Italy	38-83	Inclusion: diagnosed rotator cuff tear (cases), diagnosed meniscal tear (controls). Exclusion: shoulder pain or diagnosed rotator cuff pathology (controls).	120:120	150:90	Rotator cuff tear
Rechardt et al.[9] (2010)	Cross-sectional	Finland	30	Inclusion: men and women ≥30 years of age residing in Finland between fall 2000 and spring 2001	6,150 (168:5,982)	3,387:2,850	Chronic rotator cuff tendinitis
Abate et al.[10] (2014)	Cross-sectional	Italy	>44	Inclusion: women >44 years of age with regular menstrual cycles (PreM group), stopped menstrual cycles for at least 2 years but no more than 7 years (PostM group).	110 (PreM):122 (PostM)	All women	Full-thickness rotator cuff tear
Djerbi et al.[6] (2015)	Case-control	France	NR	Inclusion: undergoing arthroscopic rotator cuff repair	206:100	127:179	Full-thickness rotator cuff tear
Lin et al.[4] (2015)	Cohort	Taiwan	NR	Exclusion: age <30 yr, death, previous diagnosis of rheumatoid arthritis, previous diagnosis of RCD, diagnosis of RCD	498,678 (26,664: 472,014)	NA	Rotator cuff disease
Kim et al.[11] (2016)	Cross-sectional	Korea	NR	Inclusion: diagnosis of supraspinatus tendinopathy with or without tear (as demonstrated by clinical evidence such as history, physical examination, and ultrasonography)	99 (66:33)	62:37	Supraspinatus tendinopathy, with or without tear

*NR = not reported, NA = not applicable, TC = total cholesterol, TG = triglycerides, LDL = low-density lipoprotein, HDL = high-density lipoprotein, RCD = rotator cuff disease, HR = hazard ratio, and ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification. †The values are given as the number of patients, the percentage of patients, or the number of patients along with the percentage in parentheses.

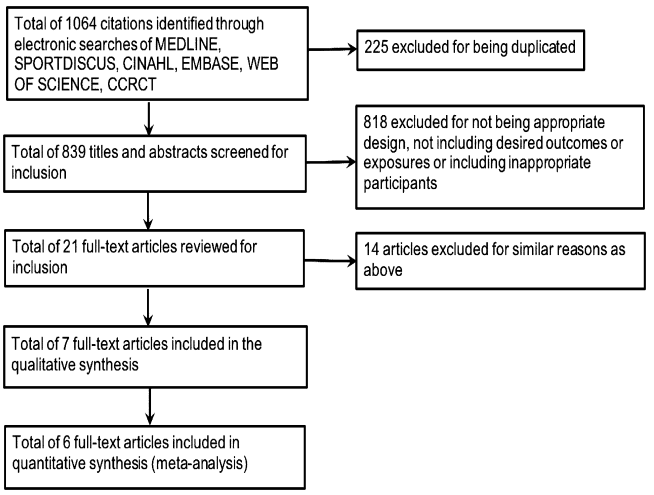

Fig. 1

Diagram showing the results of database searches as well as the final numbers of papers that were excluded and included. CINAHL = Cumulative Index to Nursing and Allied Health Literature; CCRCT = Cochrane Central Register of Controlled Trials.

and total serum cholesterol were not associated with rotator cuff tears[8].

The objectives of the present study were to perform a systematic review and meta-analysis of the association between lipid disorders and the risk of rotator cuff disease and to provide physicians with guidance to prevent rotator cuff disease. We hypothesized that hyperlipidemia would increase both the risk of occurrence and the severity of rotator cuff disease.

Materials and Methods

Criteria for Selecting Studies

Types of Studies

We included randomized experiments (clinical, laboratory, and community trials), quasi-experiments (non-randomized community, laboratory, and community trials), and observational studies (cross-sectional, cohort, and case-control studies). We considered reports (in any language) that were published in any year as well as unpublished manuscripts and reports, particularly those on ongoing studies for which preliminary findings were available.

TABLE I (*continued*)

	Lipid Disorders in Each Group		Odds Ratio		
Type of Lipid/Exposure	Defined Lipid Disorder	Disorder Present† (Cases:Controls)	Finding	Reported OR	Calculated OR Using Retrieved Data
TC, TG, LDL, HDL	Elevated serum cholesterol >240 mg/dL	63%:28%	Elevated serum cholesterol (>240 mg/dL)	NR	4.378 (95% CI, 2.412 to 7.947)
TG, TC	TG >4.5 mmol/L	1:1	TG > 4.5 mmol/L	NR	1.000 (95% CI, 0.062 to 16.174)
	TC >6.2 mmol/L	41 (34.2%):33 (27.5%)	TC > 5.2 mmol/L	NR	1.122 (95% CI, 0.652 to 1.929)
	TC 5.2-6.2 mmol/L (light hypercholesterolemia)	42 (35%):47 (39.2%)			
Metabolic syndrome (central obesity, TG, HDL, systolic blood pressure, fasting glucose)	Metabolic syndrome (3 of the following criteria present: central obesity [waist circumference >102 cm in men and >88 cm in women], TG ≥1.7 mmol/L, HDL <1.0 mmol/L in men and <1.3 mmol/L in women, systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, fasting glucose ≥6.1 mmol/L)	Male (calculated), 29: 47. Female (calculated), 30:62	Metabolic syndrome	Multivariate (men), 1.2 (95% CI, 0.7 to 1.9); multivariate (women), 0.7 (95% CI, 0.4 to 1.1)	Total, 1.233 (95% CI, 0.894 to 1.701)
TC, HDL, TG	NR	NA	NR	NA	NA
Dyslipidemia	Dyslipidemia (LDL >1.60 g/L, TG >1.50 g/L, HDL >0.40 g/L, currently taking cholesterol-lowering drugs)	74:7	Dyslipidemia	7.606 (95% CI, 3.35 to 17.25)	7.473 (95% CI, 3.131 to 17.837)
Hyperlipidemia	Hyperlipidemia (ICD-9-CM code 272, at least 3 ambulatory medical care visits, at least 1 admission course in 2000)	2,475:23,146	Hyperlipidemia	HR: 2.00 (95% CI, 1.92 to 2.08)	1.984 (95% CI, 1.900 to 2.072)
Hyperlipidemia	Hyperlipidemia (total cholesterol ≥240 mg/dL, HDL <40 mg/dL in men, HDL <50 mg/dL in women, LDL >160 mg/dL, TG >200 mg/dL)	37:12		NR	Hyperlipidemia: OR = 2.233 (95% CI, 0.945 to 5.276)

Types of Participants

Studies involving male or females of any age were included in this review.

Types of Diseases

The studied lipids included cholesterol, triglyceride, high-density lipoproteins, low-density lipoproteins, and very low-density lipoproteins. Rotator cuff disease was considered to include both rotator cuff tears (full-thickness and partial-thickness) and rotator cuff tendinitis.

Types of Outcome Measures

The primary outcome of interest was the occurrence (risk or rate) of rotator cuff disease. Secondary outcomes included the severity of rotator cuff disease and healing outcomes after treatment.

Search Methods for Identification of Studies

Six databases (MEDLINE, Embase, CINAHL, Web of Science, SPORTDiscus, and the Cochrane Central Register of Controlled Trials) were searched through July 6, 2016.

We developed the subject-specific search terms by including terms related to studied lipids and rotator cuff disease combined with keywords in relevant citations. After developing a set of preliminary search terms, we consulted an information scientist to help refine the strategies. The complete search strategies are listed in the Appendix. We also reviewed the references from retrieved studies.

Data Collection and Analysis

Administration

EndNote (Clarivate Analytics) was used to manage the retrieved records. We created a data-extraction form in a word-processing program and captured information from all articles.

Inclusion Procedure

Two investigators (including 1 of the authors [J.L.] as well as a master's student) reviewed the search results independently. Titles and abstracts were reviewed first, and the full text was reviewed if more information was needed. Reasons for excluding studies were documented. Disagreement was resolved by discussion of the investigators. Interrater agreement was assessed with raw percentage agreement and the kappa coefficient.

Data Extraction

Two reviewers (J.L. and the master's student) extracted data independently, including title, authors, contact address, publication source, publication year, country, study sponsor, study characteristics (design, setting, inclusion/exclusion criteria,

TABLE II Newcastle-Ottawa Quality Assessment: Cross-Sectional Studies

Study	Selection				Comparability	Outcome		Total Stars/ Total Possible Stars
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of exposure	Based on design and analysis	Assessment of outcome	Statistical test	
Rechardt et al.[9] (2010)	+	–	–	++	++	+	+	7/10
Abate et al.[10] (2014)	–	–	–	++	++	++	+	7/10
Kim et al.[11] (2016)	+	–	–	++	–	++	–	5/10

methodological criteria), and study population characteristics (sex, age, race, and other characteristics as appropriate). Outcome information included descriptions of the outcome event and lipid disorder, the frequency and percentage of the outcome event in each comparison group, estimates of the exposure effects (with variance estimates and 95% confidence intervals [CIs]), and p values for testing the null hypothesis. In addition, we contacted several authors of the primary studies to obtain the proportions of outcome events in each comparison group.

Assessment of Risk of Bias in Included Studies

Two reviewers (J.L. and the master's student) assessed risk of bias separately. The measurement tool was the Newcastle-Ottawa Scale[14,15], with 3 different sets of criteria (selection, comparability, and outcome/exposure) to assess the quality of cross-sectional studies, cohort studies, and case-control studies separately. Studies with more stars were less likely to suffer risk of bias.

Assessment of Evidence Strength of Included Studies

The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[16-24]. For observational studies, the quality assessments started with "Low" and were rated down for 5 factors (risk of bias, inconsistency, indirectness, imprecision, and publication bias) and rated up for 3 factors (large effect, dose response, and addressing all plausible confounding factors).

Meta-Analysis

We used STATA 14.0 (StataCorp) to analyze data. Estimates of the effects of lipids on the occurrence of rotator cuff disease were expressed as odds ratios (ORs), with the odds of rotator cuff disease in the exposure group being compared with the odds in the comparison (unexposed) group. An OR of >1 suggested an increased risk of having rotator cuff disease in the exposure group. When the OR estimates and their CIs were not presented in the articles, we calculated ORs by extracting information from the text and tables.

We first performed a fixed-effects meta-analysis and then performed an inverse-variance meta-analysis with use of a random-effects model to estimate the overall pooled effect among the studies. We also estimated a measure of the I^2 statistic, reflecting the underlying differences among the studies, with higher values indicating higher levels of heterogeneity[25].

Linear meta-regression was used to explore effect heterogeneity. The variables that were used for the meta-regression model included study type, sample size, study risk of bias, and exposure type. The outcome variable in the model was the natural logarithm of the OR. Fixed-effects and random-effects models were fitted separately with each of the covariates above.

A standard funnel plot was used to explore the existence of publication bias, with a symmetrical inverted funnel being assumed to indicate that publication bias was less possible[26]. A contour-enhanced funnel plot was also used to evaluate if studies demonstrating "significant" findings ($p < 0.05$) were more likely to be published than those demonstrating "non-significant" findings ($p > 0.05$). We also used the Egger and Begg tests to check for symmetry of the funnel plot, with p values of >0.05 indicating symmetrical distribution.

Results

Search Findings and Selected Studies

We screened 839 unduplicated articles and found 7 relevant studies[4,6-11], with 6 studies[4,6-9,11] being eligible for

TABLE III Newcastle-Ottawa Quality Assessment: Cohort Study

	Selection				Comparability	Outcome			
	Representativeness of Exposed Cohort	Selection of Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-up Long Enough for Outcomes to Occur?	Adequacy of Follow-up of Cohorts	Total Stars/ Total Possible Stars
Lin et al.[4] (2015)	+	+	+	+	++	+	+	–	8/9

TABLE IV Newcastle-Ottawa Quality Assessment: Case-Control Studies

	Selection					Outcome			
	Is the Case Definition Adequate?	Representativeness of Cases	Selection of Controls	Definition of Controls	Based on Design and Analysis	Assessment of Outcome	Same Method of Ascertainment for Cases and Controls	Non-Response Rate	Total Stars/ Total Possible Stars
Abboud and Kim[7] (2010)	+	−	−	+	−	+	+	−	4/9
Djerbi et al.[6] (2015)	+	+	−	+	++	−	+	−	6/9
Longo et al.[8] (2010)	+	−	−	+	++	+	+	−	6/9

meta-analysis (Fig. 1). The reviewers initially disagreed about the eligibility of 1.07% of the citations (raw agreement, 98.93%; Cohen kappa = 0.7042, 95% CI = 0.5201 to 0.8884), but the disagreements were resolved by discussion or by consulting the third party (J.J.G.). The 4 primary reasons for study exclusion were that (1) the analysis focused on effects other than blood lipids, (2) rotator cuff disease was not one of the outcomes on which comparisons were made and findings were presented, (3) subjects were not human, and (4) the study design was inappropriate (e.g., case study, uncontrolled cohort study).

Study Characteristics

Table I presents the details of all 7 relevant studies (505,852 participants). The meta-analysis included 6 studies (505,620 participants). All studies were observational studies, including 3 cross-sectional studies, 1 cohort study, and 3 case-control studies. Even though the study by Kim et al.[11] was longitudinal, the study design associated with the relationship of dyslipidemia and the occurrence of rotator cuff diseases was cross-sectional. Therefore, we classified it as a cross-sectional study. Three studies[7,8,10] mentioned specific lipid types (e.g., total cholesterol, triglycerides, LDL, HDL) and treated them as exposure variables. Three studies[4,6,11] used a single term such as *dyslipidemia* or *hyperlipidemia* to represent lipid disorders. Rechardt et al.[9] used the term *metabolic syndrome*, which included triglyceride and HDL disorders; however, other factors such as central obesity, systolic blood pressure, and fasting glucose were also components of the syndrome.

Risk of Bias

The assessments of risk of bias are shown in Tables II, III, and IV. The 3 cross-sectional studies fulfilled the criteria 63% of the time, whereas the case-control studies only fulfilled the criteria 59% of the time. The cohort study was better overall, fulfilling the criteria 89% of the time.

Quality of Evidence

After the evaluation with use of the GRADE criteria, the study by Djerbi et al.[6] was rated as "High" because of its complete

TABLE V GRADE Evidence Profile*

Study	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Effect (Odds Ratio)	Dose Response	Addressing All Plausible Confounding	Quality
Abboud and Kim[7] (2010)	Serious limitations (because of not adjusting for confounders)	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Large (4.38; 95% CI, 2.41 to 7.95)	Did not exist	No	⊕⊕◯◯ low
Longo et al.[8] (2010)	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Small (1.12; 95% CI, 0.65 to 1.93)	Did not exist	No	⊕⊕◯◯ low
Rechardt et al.[9] (2010)	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Small (1.23; 95% CI, 0.89 to 1.70)	Did not exist	Yes	⊕⊕⊕◯ moderate
Abate et al.[10] (2014)	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	NA	Did not exist	Yes	⊕⊕⊕◯ moderate
Djerbi et al.[6] (2015)	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Large (7.47; 95% CI, 3.13 to 17.84)	Did not exist	Yes	⊕⊕⊕⊕ high
Lin et al.[4] (2015)	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Small (1.98; 95% CI, 1.90 to 2.07)	Did not exist	Yes	⊕⊕⊕◯ moderate
Kim et al.[11] (2016)	Serious limitations (because of not adjusting for confounders)	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Small (2.23; 95% CI, 0.95 to 5.28)	Did not exist	No	⊕◯◯◯ very low

*NA = not applicable.

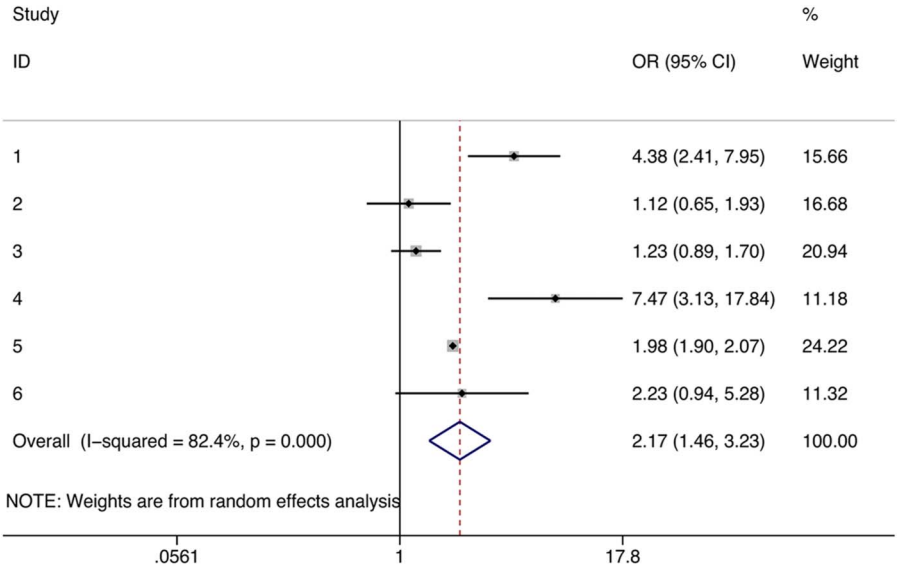

Fig. 2

Forest plot showing the results of the main-effect meta-analysis, performed with a random-effects model for the 6 studies with use of the inverse-variance method. The odds ratio (OR) indicates the odds of having rotator cuff disease when the exposure group was compared with the unexposed group. ID 1 = Abboud and Kim[7] (2010); ID 2 = Longo et al.[8] (2010); ID 3 = Rechardt et al.[9] (2010); ID 4 = Djerbi et al.[6] (2015); ID 5 = Lin et al.[4] (2015); ID 6 = Kim et al.[11] (2016).

study design and the large effect that was found. Similarly, the studies by Lin et al.[4], Abate et al.[10], and Rechardt et al.[9] were assessed as "Moderate" because they were free of serious design flaws. However, 2 studies[7,8] were rated as "Low" and 1 study[11] was rated as "Very low," revealing that these studies provided weak recommendations (Table V).

Main Effect and Sensitivity Meta-Analyses

The study by Abate et al.[10] was excluded from the meta-analysis because it failed to provide data for calculating the odds of disease in the exposure group and the comparison group. Djerbi et al.[6] reported inconsistent ORs across their study; therefore, we recalculated the OR from the data that

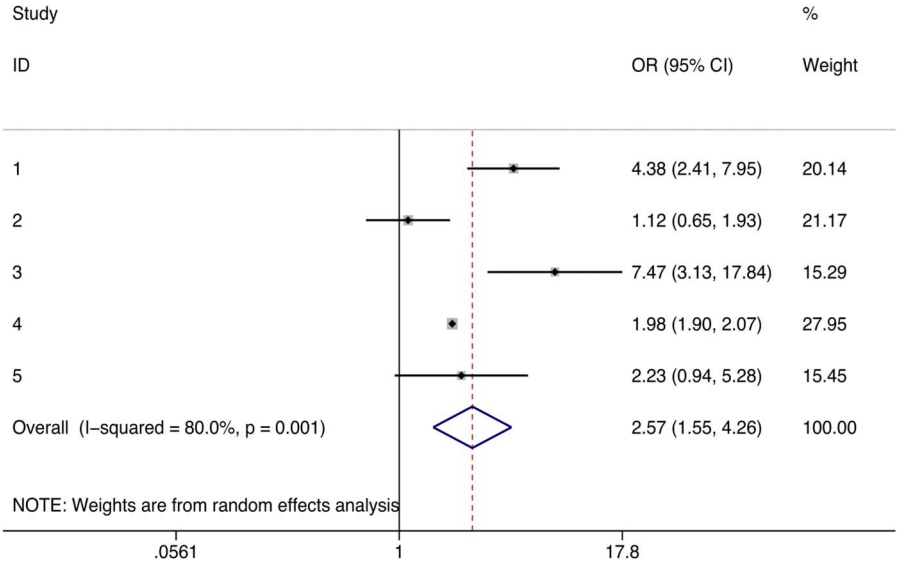

Fig. 3

Forest plot showing the results of the sensitivity meta-analysis, performed with a random-effects model for the 5 studies with use of the inverse-variance method. The odds ratio (OR) indicates the odds of having rotator cuff disease when the exposure group was compared with the unexposed group. ID 1 = Abboud and Kim[7] (2010); ID 2 = Longo et al.[8] (2010); ID 3 = Djerbi et al.[6] (2015); ID 4 = Lin et al.[4] (2015); ID 5 = Kim et al.[11] (2016).

TABLE VI Single-Variable Meta-Regression Analyses

Predictor Variable	Fixed-Effects Model			Random-Effects Model			Heterogeneity Residual I^2 (%)
	Slope (SE)*	95% CI	P Value	Slope (SE)*	95% CI	P Value	
Sample size	2.57e−07 (2.43e−07)	−2.20e−07 to 7.34e−07	0.291	−3.98e−07 (1.66e−06)	−5.00e−06 to 4.20e−06	0.822	85.34%
Study type							84.56%
Case-control (3 studies)							
Cohort (1 study)	−0.271 (0.187)	−0.638 to 0.096	0.148	−0.469 (0.904)	−3.345 to 2.407	0.640	
Cross-sectional (2 studies)	−0.674 (0.241)	−1.146 to −0.201	0.005	−0.683 (0.758)	−3.096 to 1.729	0.434	
Exposure							84.96%
Cholesterol (2 studies)							
Dyslipidemia/ hyperlipidemia (3 studies)	−0.043 (0.206)	−0.446 to 0.361	0.836	0.328 (0.735)	−2.011 to 2.666	0.686	
Metabolic syndrome (1 study)	−0.522 (0.262)	−1.036 to −0.008	0.047	−0.578 (0.946)	−3.588 to 2.433	0.585	
Study risk-of-bias scores†	−0.129 (0.445)	−1.001 to 0.744	0.772	−1.507 (2.045)	−7.186 to 4.172	0.502	85.87%

*The standard error (SE) is given in parentheses. †Lower scores represented higher risk of bias.

were reported in the article. In each study, the estimated OR was >1, independently revealing that dyslipidemia was a risk factor for the occurrence of rotator cuff disease. The fixed-effects pooled estimated OR for the 6 studies was 1.98 (95% CI, 1.89 to 2.06), whereas the random-effect pooled estimated OR was 2.17 (95% CI, 1.46 to 3.23; $p < 0.001$), both with substantial statistical heterogeneity ($I^2 = 82.4\%$; $p < 0.001$) (Fig. 2).

We also performed a sensitivity analysis with exclusion of the study by Rechardt et al.[9] as the exposure variable that was used included not only lipid disorders. The pooled estimated OR for the other 5 studies was 2.57 (95% CI, 1.55 to 4.26), also with substantial statistical heterogeneity ($I^2 = 80.0\%$; $p = 0.001$) (Fig. 3).

Meta-Regression Analyses

The results of the meta-regression analyses are summarized in Table VI. None of the 4 covariates that were included contributed substantially to the heterogeneity of the meta-analysis. Overall, case-control studies, studies with single cholesterol measurements, and studies with greater risk of bias (lower scores) tended to result in a higher estimated OR.

Publication Bias

The standard funnel plot (Fig. 4) showed a symmetrical funnel for the included 6 estimates, and the Egger and Begg tests also indicated symmetrical distribution (Egger test, $p = 0.839$; Begg test, $p = 0.260$). However, the contour-enhanced funnel plot

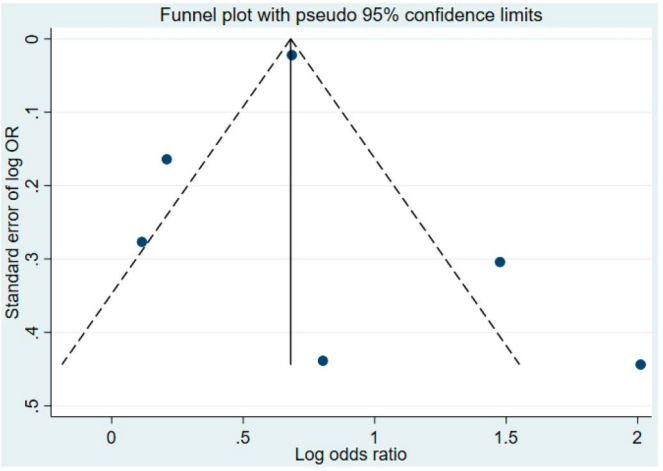

Fig. 4

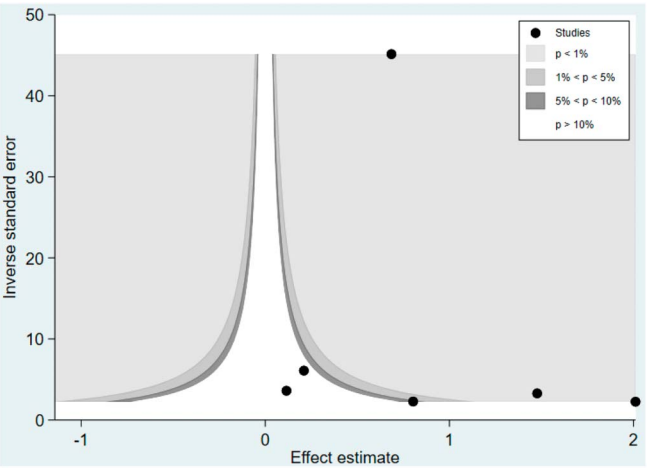

Fig. 5

Fig. 4 Funnel plot with 95% CIs about the effect estimate. Log OR = logarithm of the odds ratio. **Fig. 5** Contour-enhanced funnel plot. Effect estimates = logarithm of the odds ratio, and inverse standard error = 1/(standard error). The majority of the funnel lies in the area in which $p < 0.1$.

(Fig. 5) indicated apparent missing studies in the area in which nonsignificant studies would have been plotted. This finding suggested that publication bias was likely due to the significance of results or a small-study effect.

Discussion

We identified 7 peer-reviewed articles examining lipid disorders as related to the risk of rotator cuff disease. Among the studies in which dyslipidemia was used as an exposure variable, 3 revealed a significant association with an increased risk of rotator cuff disease (ORs and 95% CIs all >1). Overall, the odds of rotator cuff disease in patients with dyslipidemia was 2.17 (95% CI, 1.46 to 3.23) times higher than that in patients without dyslipidemia.

However, the heterogeneity of the ORs was appreciable, which was unlikely to result only from random error. After we addressed sample size, study risk of bias, exposure type, and study designs, the heterogeneity remained significant, and the limited number of studies was inadequate for the performance of further regression analysis. One important source of heterogeneity was the different definitions of dyslipidemia (Table I). Two studies used serum cholesterol levels to represent dyslipidemia, and the thresholds were different: Abboud and Kim[7] used serum cholesterol of >240 mg/dL, whereas Longo et al.[8] used total cholesterol of >5.2 mmol/L. Lin et al.[4] and Kim et al.[11] used the term *hyperlipidemia* instead of *dyslipidemia,* and Djerbi et al.[6] were the only research team that used the term *dyslipidemia*. Furthermore, all 6 studies used in the meta-analysis took place in different settings of various countries, and the inherent differences among the populations could have contributed substantial modifying or even confounding effects to the heterogeneity. However, we were unable to address these latter variables in the analyses.

The recent review study by MacDonald et al.[12] demonstrated a potential association between blood lipid levels and rotator cuff pathology. However, that study had considerable drawbacks. For example, the authors did not perform a comprehensive search of all relevant databases, they included studies with questionable observational design (e.g., a case report and an uncontrolled cohort study), they did not perform a meta-analysis or test for publication bias, and they did not use accepted methodology for qualitatively combining the evidence (e.g., the GRADE criteria[16]). Therefore, the results of that study, while informative for hypothesis generation, may be biased and do not provide a complete quantitative idea of the relationship across high-level-of-evidence study designs (randomized, cohort, or case-control studies). Hence, we performed a more comprehensive and rigorous systematic review.

Other studies demonstrated similar relationships between lipids and the occurrence of tendon diseases. The study by Abate et al.[10], which was excluded from our meta-analysis, demonstrated results consistent with the other 6 studies. In addition, that study demonstrated higher average total cholesterol, higher triglycerides, and lower HDL cholesterol in patients with tears as compared with those without tears. Rechardt et al.[27] found that the pain intensity in patients with upper-extremity soft-tissue disorders was significantly associated with low HDL cholesterol levels and high triglycerides. Several studies explored the underlying mechanism. A study involving a rabbit model[28] showed that dyslipidemia increased fat-to-muscle proportions. These increased lipids in the tendon might result in tendon xanthomas[29], thus reducing the tendon's elastic modulus and increasing stiffness and the risk of tendon rupture under tension[5,30].

With regard to our secondary outcomes, Kim et al.[11] investigated how hyperlipidemia influenced the outcomes of treatment of rotator cuff disease. Those investigators reported that, after treatment, both the hyperlipidemia and non-hyperlipidemia groups experienced a decrease in pain; however, the hyperlipidemia group had less pain reduction than the non-hyperlipidemia group did. Some animal studies have provided information to explain this association. Beason et al.[31] suggested that hypercholesterolemia has a detrimental effect on the healing of tendons, noting that they found decreased healing stiffness in hypercholesterolemic rats as compared with control rats after supraspinatus injury and repair. Moreover, fatty infiltration has been found to have an adverse effect on the healing process associated with rotator cuff disease, which might also be a result of dyslipidemia[28,32].

The present study had several strengths as well as some limitations. First, to our knowledge, this study represents the first comprehensive systematic review with meta-analysis focusing on this topic. Existing evidence suggests that hyperlipidemia is associated with multiple musculoskeletal manifestations[33], and lipid disorders tend to affect the prevalence of, and healing process associated with, rotator cuff disease. Therefore, the present study is likely to provide valuable information for future studies regarding tendon disease and metabolic disorders. Furthermore, we applied comprehensive searching strategies in several large databases and searched through reference lists, so it was unlikely that we missed relevant studies. We also assessed the risk of bias and the strength of evidence for the included studies with use of appropriate and valid criteria. However, the present study also had some drawbacks. First, a limited number of studies were found in the literature, but we included all of the available high-level observational studies on this subject. Second, there was generally a lack of studies focusing on the effects of lipid disorders on the severity and healing outcomes of rotator cuff disease; hence, we could not perform analysis for our secondary outcomes, nor could we study the effect of specific types of lipids. Third, there was high residual heterogeneity among the studies, which existed even after we fitted a random-effects model and used meta-regression to explore the influence of several variables. In general, we could not completely explain the differences across the studies. It is possible that the varying pathologies that were included in the studies contributed to these differences. But, in the end, all studies showed a similar effect (i.e., an increased risk of rotator cuff disease in association with dyslipidemia), increasing the generalizability of our findings.

Overall, our systematic review found that dyslipidemia increases the risk of rotator cuff disease, but more research is

needed to clarify this relationship and to explain the large amount of heterogeneity detected. As randomized controlled trials focusing on this topic are impossible, further rigorous prospective observational studies are needed to more clearly delineate the relationship between specific lipid profiles and rotator cuff disease as well as healing outcomes. Also, we recommend that studies be done, randomized or otherwise, to examine the role of treating lipid disorders in patients who have (or who are at risk for) rotator cuff tears. Furthermore, we recommend that, in future clinical studies of patients being treated for rotator cuff tears, lipid profiles should be carefully recorded so that this information can be used as a stratification variable. We also recommend that physicians examine tendon conditions if their patients have severe dyslipidemia as fatty infiltration may impact the success of, and recovery from, treatment.

Appendix

eA A summary of the search terms and the numbers of papers found in the databases is available with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJSOA/A64). ■

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Jianyu Lai, MPH[1]
Joel J. Gagnier, ND, MSc, PhD[1,2]

[1]Department of Orthopaedic Surgery, University of Michigan, Ann Arbor, Michigan

[2]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan

E-mail address for J. Lai: jianyul@umich.edu

ORCID iD for J. Lai: 0000-0001-5705-0138
ORCID iD for J.J. Gagnier: 0000-0002-3162-3935

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