Association between osteoarthritis and dyslipidaemia: a systematic literature review and meta-analysis

Pauline Baudart,1,2 Karine Louati,1,3,4 Christian Marcelli,5,6,7 Francis Berenbaum,1,3,4,8 Jérémie Sellam1,3,4,8

ABSTRACT

Objectives We aimed to investigate the prevalence of dyslipidaemia in patients with osteoarthritis (OA) and whether OA and dyslipidaemia are associated.

Methods We performed a systematic literature review and a meta-analysis, including cross-sectional, cohort and case–control studies, to assess the number of patients with OA and/or dyslipidaemia. We calculated the mean (±SD) prevalence of dyslipidaemia in patients with and without OA and the risk of dyslipidaemia (OR, 95% CI) among patients with OA.

Results From 605 articles screened, 48 were included in the analysis (describing 29 cross-sectional, 10 cohort and 9 case–control studies). The mean prevalence of dyslipidaemia was 30.2%±0.6% among 14,843 patients with OA and 8.0%±0.1% among 196,168 without OA. The risk of dyslipidaemia was greater than without OA overall (OR 1.98, 95% CI 1.43 to 2.75, p<0.0001) and with knee OA (OR 2.27, 1.33 to 3.89, p=0.003) and hand OA (OR 2.12, 1.46 to 3.07, p<0.0001).

Conclusion The risk of dyslipidaemia was twofold greater than without OA, so lipid disturbances could be a risk factor for OA. Such a result supports the individualisation of the metabolic syndrome-associated OA phenotype.

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease and a major cause of pain and disability. It is currently considered a disease with multiple distinguishable phenotypes: post-traumatic, ageing-related, genetic and metabolic syndrome (MetS)-associated OA.1 Metabolic OA, the most commonly studied phenotype, is defined by the association between OA and MetS, associating obesity, hyperglycaemia with insulin resistance, dyslipidaemia and hypertension.2 Metabolic OA mainly affects middle-aged people (45–65 years) and leads to knee, hand and generalised OA. The association between OA and MetS has been reported in several epidemiological studies.3 4 The pathophysiological link between both diseases could be chronic low-grade systemic inflammation occurring in both conditions.5

The association of OA with each MetS component has been investigated.6 Obesity and overweight are independently linked to hand OA, with a twofold increased risk.7 This association suggests the release of inflammatory mediators by adipose tissue adipokines. We recently reported an association between OA and diabetes mellitus, with a 1.46-fold increased risk of OA with diabetes mellitus and a 1.41-fold increased risk of diabetes mellitus with OA.8 The link between both pathologies could be explained by the action of pro-inflammatory cytokines and oxidative stress occurring in both diseases.9 10

The link between OA and the other components of MetS remains debated. Experimental studies have suggested that lipid disturbances could be involved in OA pathophysiology,11 but epidemiological studies revealed heterogeneous results.

With a systematic literature review and meta-analysis, we aimed to investigate the prevalence of dyslipidaemia in patients with
OA and assess whether OA and dyslipidemia are associated.

**METHODS**

The systematic review was registered on PROSPERO (CRD: 42016037290).

**Literature search**

We performed a systematic search of articles in MEDLINE via PubMed, EMBASE and the Cochrane library. The keywords used for the PubMed search were (((Dyslipidemias)[Mesh] OR ‘Hypertriglyceridemia’[Mesh]) OR ‘Hypercholesterolemia’[Mesh]) OR ‘HDL’[All Fields] OR ‘LDL’[All Fields] OR ‘Triglycerides’[All Fields] OR ‘Hyperlipidemias’[Mesh]) OR ‘Cholesterol’[Mesh] OR ‘Metabolic Syndrome X’[Mesh] AND ‘Osteoarthritis’[Mesh] AND ‘humans’[MeSH Terms] AND (English[lang] OR French[lang])). No time limit was set for publication date, and articles published up to 1 January 2016 were searched. We also searched the abstracts from international meetings of the American College of Rheumatology (ACR), European League Against Rheumatism, Société Française de Rhumatologie, European Society of Cardiology, Endocrine Society’s Annual Meeting and European Congress of Endocrinology.

**Study selection**

We selected articles published in English or French that described observational studies of adults (>18 years of age) with cohort, case–control and cross-sectional designs. Studies were included if they specified the number of patients with OA and dyslipidemia and/or the prevalence or incidence of OA in patients with dyslipidemia and/or dyslipidemia in patients with OA, and/or the mean values of parameters of dyslipidemia in patients with and without OA and/or the existence or not of an association between OA and dyslipidemia. We excluded non-observational studies (therapeutic trials, reviews, letters and case reports). Articles that did not mention the number of patients with OA or dyslipidemia and those that did not evaluate the link between the two diseases were excluded. The selection of articles was based on titles and abstracts, then full texts.

**Data synthesis**

We extracted the following data: publication data (title of the article, first author, journal and publication date), study design (type of study, year(s) of inclusion, study quality score), population (total number of patients included, mean age and sex of patients), methodology of articles (the definition used for OA and dyslipidemia, OA location) and data needed for statistical analysis (number of patients with OA and/or dyslipidemic patients; mean total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglyceride (TG) levels (mg/dL or mmol/L); and number of patients receiving statins.
### Table 1 Description of the 48 articles studies selected for analysis

| Osteoarthritis population | General population |
|---------------------------|---------------------|
| **Type of study**         | **Author Year**     | **Author Year** |
| Cross-selectional         | Stürmer et al 25 1998 | Davis et al 26 1988 |
|                           | Racaza et al 2012    | Han et al 2013    |
|                           | Erb et al 2004       | Dahaghin et al 2007 |
|                           | Eymard et al 2015    | Haugen et al 2015 |
|                           | Shea et al 2015      | Inoue et al 2011  |
|                           | Salamon et al 2015   | Cemeroglu et al 2014 |
|                           | Abourazzak et al 2015| Meek et al 2014   |
|                           | Juge et al 2015      | Al-Arfaj 2003     |
|                           | Rolefstad et al 2014 | Suri et al 2010   |
|                           | Saunders et al 2013  | Puenpatom et al 2009 |
|                           | Nuñez et al 2012     | Hart et al 1995   |
|                           | Shukurova et al 2014 | Maddah et al 2015 |
|                           | Salaru et al 2013    | Engström et al 2009 |
|                           | Kemta Lekpa et al 2014| Yoshimura et al 2012 |
|                           | Niu et al 2015       | Nielen et al 2012 |
|                           | Haugen et al 2013    | Marshall et al 2015 |
|                           | Courties et al 2014  | Hussain et al 2014 |
|                           | Cohort               | Sowers et al 2009 |
|                           | Gandhi et al 2014    | Massengale et al 2012 |
|                           | Laires et al 2015    |                 |
|                           | Thelier–Deloison et al 2012 |               |
|                           | Case–control         | Soran et al 2008  |
|                           |                     | Cheras et al 1997 |
|                           | Mishra et al 2012    | Oliviero et al 2012 |
|                           | Addimanda et al 2012 | Philbin et al 1996 |
|                           |                       | Irshad et al 2014 |
|                           |                       | Zayed et al 2013  |
|                           |                       | Cheng et al 2013  |

*Data from a congress.

number with MetS and number with obesity or mean body mass index (BMI) in kg/cm²). The quality of the study was estimated by using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) scale, the score expressed in percentage of positive answers in relation to the number of items selected.14

**Statistical analysis**

First, we performed a descriptive analysis of the prevalence of dyslipidemia in patients with and without OA and used the number of patients with dyslipidemia and total number with and without OA. To estimate this prevalence from cohort longitudinal prospective studies, we used baseline data. Prevalence was expressed as mean±SD Second, we calculated the mean TC, LDL, HDL and TG levels in patients with and without OA. Third, for studies examining an association between OA and dyslipidemia, we calculated the risk of dyslipidemia with OA by estimating the overall OR with 95% CIs. The data were extracted from studies examining the number of dyslipemic patients with and without OA. We used Revman V.5.3 for the meta-analysis with a fixed-effects model. Heterogeneity was assessed by the I² index; with I²>50% (high heterogeneity), we used a random-effects model, and with I² <50% (low heterogeneity), we used a fixed-effects model. With strong heterogeneity, we used a randomised-effects analysis. To investigate potential publication bias, we have performed the funnel plot. The association was considered positive with OR >1, and the result was considered statistically significant with p≤0.05. We performed sensitivity and subgroup analyses.
RESULTS
Characteristics of studies included

The selection of articles is reported in the flow chart (figure 1). We identified 605 publications; 48 articles (including 13 abstracts) from 43 studies were included (2 articles from the SEKOIA study, 4 from the FRAMINGHAM study and 2 from the National Health and Nutrition Examination Survey III). One abstract was obtained from the EMBASE database and not from screening congress abstracts. The 48 articles described 29 cross-sectional, 10 cohort and 9 case–control studies. Among them, 29 articles involved the OA population and 19 the general population (table 1). We did not find any studies based on a cohort of patients with dyslipidemia, which explains why the prevalence or relative risk of OA in patients with dyslipidemia was not calculated. Table 2 shows the definitions of OA and dyslipidemia in selected studies.

The median STROBE quality score was 69.1% (range 42%–91%). Nine articles had a STROBE quality score <60% (table 3).

In total, 30 articles assessed the association of OA and dyslipidemia, 30 assessed the prevalence of dyslipidemia among patients with OA and 22 assessed mean lipid level values among patients with OA (table 3).

Patient characteristics

This study involved 306,044 patients. The mean age range was 39.0±4.7 to 77.5±9.0 years.17 The mean proportion of females was 53.2% (range 40.6% to 100% [18–22]). The localisation was the knee in 23 articles,3 15 16 19–21 24–40 hand in 9,13 22 41–47 generalised OA in 3,25 31 47 hip in 3,25 34 57 spine in 2,48 49 and shoulder in 1.17 MetS was reported in nine articles,1 20 24 28 30 36 40 45 50 the prevalence of MetS ranged from 5% to 97.5%.40 The prevalence of obesity ranged from 7.8% to 100%15 40 and BMI from 22.3±2.7 to 37.3±5.9 g/cm².46 Seven articles described the use of statin treatment (table 3).

Prevalence of dyslipidemia among patients with and without OA (table 4)

The mean prevalence of dyslipidemia among 14,843 patients with OA and 8.0±0.1% among 196,168 without OA. The mean prevalence with knee OA was 27.6%±1.4%,15 20 24 25 28 30–35 37 38 hand OA 37.6%±1.6%,22 43–47 generalised OA 30.5%±3.9%,25 31 47 hip OA 20%±2.1%25 55 37 and symptomatic OA was 21%.28 44

Mean lipid-level values with and without OA (table 4)

The mean lipid-level values for patients with and without OA were for TC, 245±25.1 and 233.1±17.5 mg/dL; LDL, 126.5±20.7 and 136.9±15.9 mg/dL; HDL, 54.4±8.9 and 53.1±7.5 mg/dL; and TG, 137.3±80.3 and 131±27.5 mg/dL.

Association between dyslipidemia and OA

Overall, 30 articles indicated the presence or the absence of an association between OA and dyslipidemia; 21 (70%) showed a positive association between OA and dyslipidemia 3 4 15 18 21 23 24 30 31 39 40 47 48 52 57; 12/18 articles (67%) with STROBE score >60% found a positive association.3 4 18 19 21 23 40 47 48 52 54 55 In addition, 4/7 articles19–22 that reported an OR adjusted on age and BMI found a positive association. Among the three with negative association findings after adjustment, two had a STROBE score >60%.34 37

Overall risk of dyslipidemia with OA: meta-analysis

Among 204,148 patients from 13 articles,4 15 22 24 30 31 34 37 47 48 54–56 the overall OR was 1.98 (95% CI 1.43 to 2.75, p<0.0001; I²=94%), evaluated by a random-effects model (figure 2).

Risk of dyslipidemia with OA: sensitivity analyses

To strengthen our results, we performed four sensitivity analyses. First, we removed the studies that did not use ACR criteria or Kellgren-Lawrence grading for OA diagnosis: among 2568 patients from the six remaining articles,22 24 30 31 47 56 the risk of dyslipidemia was increased with than without OA (OR 2.64, 95% CI 2.14 to 3.26, p<0.0001, I²=0%). Second, we excluded studies with a STROBE score <60%: among 203,629 patients from the nine remaining articles,4 24 30 34 37 47 48 54 55 the risk of dyslipidemia remained increased with than without OA (OR 1.63, 1.13 to 2.36, p=0.009, I²=95%). Third, we excluded studies that specified the use of statin treatment because the definition of dyslipidemia in these studies was based on only lipid values and did not account for statin treatment. Among 41,539 patients from the 10 remaining articles,4 15 24 30 31 34 37 47 54 56 the risk of dyslipidemia remained increased with than without OA (OR 1.95, 1.42 to 2.61, p<0.0001, I²=87%). Fourth, we pooled the results of the articles that reported an age-adjusted and BMI-adjusted OR. Among 31,764 patients, from the four articles,31 34 37 47 there was no association between dyslipidemia and OA (OR 1.31, 95% CI 0.88 to 1.95, p<0.0001; I²=83%).

Risk of dyslipidemia with OA: subgroup analyses

We performed a subgroup analysis by OA localisation. The increased risk of dyslipidemia with OA persisted with OA localisation. Among 805 patients, OR 2.27, 1.33 to 3.69, p=0.0003, I²=88%); 34 37 48 50 hand OA (among 233 patients, OR 1.08, 0.69 to 1.71, p=0.78, I²=0%); 51 52 but not hip OA (among 24,934 patients, OR 0.86, 0.69 to 1.08, p=0.18, I²=0%); 34 37

DISCUSSION

We investigated the potential association between OA and dyslipidemia with a systematic review and meta-analysis and found a 30% prevalence of dyslipidemia with OA, which seems much higher than in the non-OA population (8.0%). Furthermore, the meta-analysis revealed an increased risk of dyslipidemia, by 1.98, than with than without OA and was observed with knee as well as hand OA.

The mean prevalence of dyslipidemia in hand OA was 37.6%±1.6%, much higher than the mean prevalence...
Table 2  Characteristics of the 48 included articles: definitions of osteoarthritis (OA) and dyslipidemia, outcomes and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) study quality

| Author                | OA definition         | Dyslipidemia definition       | Outcome                               | STROBE study quality (%) |
|-----------------------|-----------------------|--------------------------------|---------------------------------------|--------------------------|
| Stürmer et al⁵⁵        | Arthroplasty or KL≥2   | TC≥240mg/dL and/or statin therapy | MV in OA+ Association of OA and dyslipidemia | 53                       |
| Racaza et al⁵⁵         | ACR or Cq and Rx       | –                              | NPD in OA+                            | 42                       |
| Erb et al⁶⁶            | Cq and Rx              | –                              | MV in OA+                             | 50                       |
| Eymard et al⁶⁸         | ACR Cq and Rx KL scale | History of dyslipidemia        | NPD in OA+                            | 82                       |
| Shea et al⁶⁹           | Cq and Rx              | –                              | NPS in OA+ MV in OA+                  | 78                       |
| Salamon et al⁵⁰        | ACR                   | –                              | NPD in OA+ MV in OA+                  | 72                       |
| Abourazzak et al⁵⁵     | KL≥2                  | HDL<50mg/dL TG≥150mg/dL         | NPD in OA+                            | 66                       |
| Juge et al¹⁷*          | Rx                    | –                              | NPD in OA+                            | NA                       |
| Rollefstad et al²³*    | History of OA         | –                              | MV in OA+ and OA− Association of OA and dyslipidemia | NA                       |
| Saunders et al³³*      | KL scale              | TC>4mmol/L                      | NPD in OA+ Association of MV and KL scale | NA                       |
| Nuñez et al³⁵*         | –                     | Hypercholesterolemia (ND)       | NPD in OA+                            | NA                       |
| Shukurova et al³⁷*     | -                     | Hypercholesterolemia (ND)       | NPD in OA+                            | NA                       |
| Salaru et al³³*        | ACR                   | –                              | NPD in OA+                            | NA                       |
| Kemta Lekpa et al²⁵*   | ACR                   | –                              | NPD in OA+                            | NA                       |
| Niu et al³⁶*           | Arthroplasty or KL≥2   | HDL<40mg/dL in M;<50mg/dL in W TG≥150mg/dL | Association of OA and dyslipidemia | NA                       |
| Haugen et al¹³*        | KL≥2                  | Low HDL and HTG (ND)            | NPD in OA+ Association of OA and dyslipidemia | NA                       |
| Courties et al⁴⁵*      | KL≥2                  | –                              | NPD in OA+                            | NA                       |
| Gandhi et al⁴⁹         | Cq and Rx              | HDL<35mg/dL in M;<40mg/dL in W; TG≥150mg/dL | NPD in OA+                            | 52                       |
| Laires et al³⁸*        | –                     | –                              | NPD in OA+                            | NA                       |
| Thelier–Deloison et al¹⁵* | History of OA    | –                              | NPD in OA+ and OA− Association of OA and dyslipidemia | NA                       |
| Soran et al¹⁶          | Cq and Rx              | –                              | MV in OA+ and OA− Association of OA and dyslipidemia | 65                       |
| Cheras et al¹⁶         | Cq and Rx              | –                              | MV in OA+ and OA− Association of OA and dyslipidemia | 75                       |
| Mishra et al³⁹         | KL scale ACR           | –                              | MV in OA+ and OA− Association of OA and dyslipidemia | 58                       |
| Oliviero et al⁵²       | ACR                   | –                              | MV in OA+ and OA− Association OA and dyslipidemia | 67                       |

Continued
| Author             | OA definition | Dyslipidemia definition                                                                 | Outcome                                                                 | STROBE study quality (%) |
|--------------------|---------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------|
| Addimanda et al    | Cq            | LDL≥130 mg/dL and/or CT≥240 mg/dL and/or statin therapy                                    | NPD in OA+ and OA– Association of OA and dyslipidemia                     | 75                       |
| Philbin et al      | Questionnaire Radiological Danielson scale | LDL≥160 mg/dL and/or HDL≤35 mg/dL                                                       | NPD in OA+ and OA– NPS in OA+ and OA– Association of OA and dyslipidemia MV in OA+ and OA– | 73                       |
| Irshad et al       | KL scale      | TC≥200 mg/dL and/or TG≥150 mg/dL                                                          | NPD in OA+ and OA– Association of OA and dyslipidemia                     | 47                       |
| Zayed et al        | ACR           | –                                                                                        | MV in OA+ and OA– NPS in OA+ and OA– Association of OA and dyslipidemia    | 56                       |
| Cheng et al        | –             | –                                                                                        | Association of OA and dyslipidemia                                         | NA                       |
| Davis et al        | Rx            | –                                                                                        | MV in OA+ and OA– Association of OA and dyslipidemia                       | 67                       |
| Han et al          | History of OA by physician | HDL<40 mg/dL in M,<50 mg/dL in W; TG≥150 mg/dL                                             | MV in OA+ and OA– Association of OA and dyslipidemia                       | 84                       |
| Dahaghin et al     | KL≥2, ACR, Cq | –                                                                                        | MV in OA+ and OA– Association of OA and dyslipidemia                       | 69                       |
| Haugen et al       | KL≥2          | –                                                                                        | NPS in OA+ MV in OA+                                                      | 84                       |
| Inoue et al        | KL≥2          | HDL<40 mg/dL in M,<50 mg/dL in W; TG≥150 mg/dL                                             | NPD in OA+ and OA– Association of OA and dyslipidemia                     | 69                       |
| Cemeroglu et al    | ≥3 articulations with KL≥2 | TC>200 mg/dL LDL>100 mg/dL HDL<40 mg/dL TG>150 mg/dL | NPD in OA+ and OA– MV in OA+ and OA– NPS in OA+ and OA– Association of OA and dyslipidemia | 59                       |
| Meek et al         | Codes         | –                                                                                        | MV in OA+ NPS in OA+                                                      | 78                       |
| Al-Arfaj et al     | KL≥2          | TC≥220 mg/dL                                                                             | NPD in OA+ and OA– Association of OA and dyslipidemia                     | 50                       |
| Suri et al         | Pathria and Weishaupt scale | TC≥240 mg/dL                                                                           | NPD in OA+ and OA– Association of OA and dyslipidemia                     | 72                       |
| Puenpatom et al    | Codes Rx History of OA by physician | Codes or HDL<40 mg/dL in M,<50 mg/dL in W; or TG≥150 mg/dL | NPD in OA+ and OA– Association of OA and dyslipidemia                     | 69                       |
| Hart et al         | KL≥2          | –                                                                                        | Association of OA and dyslipidemia                                         | 78                       |
of 30.2%±0.6% with OA overall. Moreover, the risk of dyslipidemia was increased twofold with hand OA (OR 2.12, 95% CI 1.46 to 3.07). These results again confirm the systemic metabolic component of hand OA, as recently reported in the NEO study. The pathophysiological link between hand OA and MetS might be explained by the action of the adipose-tissue source of proinflammatory cytokines and the action of visceral fat.

Hip OA, defined by joint replacement, was not associated with dyslipidemia possibly because of a selection bias of patients: cardiovascular comorbidities often associated with dyslipidemia might have restricted the indication for surgery due to the perioperative period. Furthermore, mechanical stress is more involved than metabolic stress in this joint.

For knee OA, the mean prevalence of dyslipidemia was 27.6%±1.4% and the association between knee OA and dyslipidemia was confirmed with increased risk of dyslipidemia (OR 2.27, 95% CI 1.33 to 3.89). The association between knee OA and MetS is sometimes conflicting. Han et al., Inoue et al., and Hussain et al. did not find any positive association possibly because of different OA definitions. A recent study showed that the most important risk factor of knee OA was mechanical stress (before and after adjustment for metabolic factors), which limits the identification of a systemic metabolic component in knee OA.

Our meta-analysis has some limitations. The heterogeneity between studies was high, probably because of differences in OA localisations, definition of OA and dyslipidemia, statin therapy could not have been taken into account, and types and quality of studies.

Our meta-analysis has some limitations. The heterogeneity between studies was high, probably because of differences in OA localisations, definition of OA and dyslipidemia, statin therapy could not have been taken into account, and types and quality of studies. Dyslipidemia referred to lipid abnormalities such as hypercholesterolemia, low HDL level, high LDL level or hypertriglyceridemia. Because of the different definitions of dyslipidemia, we chose to define dyslipidemia first by high LDL level, then low HDL level, then hypercholesterolemia and hypertriglyceridemia. To counteract this heterogeneity, we performed sensitivity analyses to check whether the association between OA and dyslipidemia persisted after removing studies with poor methodology and found that the association persisted in all sensitivity analyses. Moreover, the heterogeneity of the studies was assessed by the I² index and we adapted the method to its value. The results of the meta-analysis are not modified by removing the most heterogeneous studies (data not shown). We were not able to integrate confounding factors such as age, BMI, HTA, smoking and physical activity in the overall statistical analysis. Obesity is a major risk

### Table 2

| Author            | OA definition | Dyslipemia definition | Outcome                          | STROBE study quality (%) |
|-------------------|---------------|-----------------------|----------------------------------|--------------------------|
| Maddah et al      | KL≥2          | TC≥5 mmol/L and TG≥2 mmol/L and HDL≤1 mmol/L in M, ≤1.1 mmol/L in W | NPD in OA+ and OA− Association of OA and dyslipidemia MV in OA+ and OA− | 72                       |
| Engström et al    | Codes: arthroplasty for hip or knee OA | HDL<1.03 mmol/L in M, <1.29 mmol/L in W; TG≥1.7 mmol/L or statin therapy | NPD in OA+ and OA− Association of OA and dyslipidemia | 79                       |
| Yoshimura et al   | KL≥2          | HDL≤40 mg/dL          | MV in OA+ and OA− Association of OA and dyslipidemia | 91                       |
| Nielen et al      | Codes         | Codes: hypercholesterolemia | NPD in OA+ and OA− NPS in OA+     | 81                       |
| Marshall et al    | KL scale      | Codes                | NPD in OA+ and NPS in OA− | 74                       |
| Hussain et al     | Joint replacement | HDL<1.03 mmol/L in M, <1.29 mmol/L in W; HTG≥1.7 mmol/L | NPD in OA+ and OA− Association of OA and dyslipidemia | 85                       |
| Sowers et al      | KL≥2          | HDL≤45 mg/dL or LDL≤160 mg/dL or TG≥200 mg/dL | MV in OA+ and OA− Association of OA and dyslipidemia | 70                       |
| Massengale et al  | –             | TC≥240 mg/dL          | NPD in OA+ and OA− | 78                       |

ACR, American College of Rheumatology; Cq, clinical; HDL, high-density lipoprotein; HTG, hypertriglyceridemia; KL, Kellgren and Lawrence; LDL, low-density lipoprotein; M, men; MV, mean values of lipid profile; NA, if the data were issued only from congress; ND, not defined; NPD, number of patients with dyslipidemia; NPS, number of patients with statin therapy; OA+, patients with osteoarthritis; OA−, patients without osteoarthritis; Rx, radiography; TC, total cholesterol; TG, triglycerides; W, women.

*Data from a congress.
Table 3  Characteristics of the population on the 48 included articles: number, age, gender, overweight proportion

| Author                  | Sample size (N = number of total patients; n= number of patients with OA) | Mean age (years) in OA+ and OA– patients | Gender in OA+ and OA– patients (% of F) | Overweight proportion (%) or BMI (kg/m²) in OA+ and OA– patients |
|-------------------------|-------------------------------------------------------------------------|------------------------------------------|----------------------------------------|------------------------------------------------------------------|
| Stürmer et al[25]       | n=809                                                                   | –                                        | OA+: F: 62.3%                          | –                                                                |
| Racaza et al[25]        | n=859                                                                   | OA+: 62.9                                | OA+: F: 74.5%                          | –                                                                |
| Erb et al[26]           | N=250, n=64                                                             | OA+: 57.3±10.1                           | OA+: F: 62.5%                          | OA+: 30.9±7.6 kg/m²                                               |
| Eymard et al[28]        | n=559                                                                   | OA+: 62.8                                | OA+: F: 70.1%                          | –                                                                |
| Shea et al[29]          | n=791                                                                   | OA+: 74.25±4.5                           | OA+: F: 62.3%                          | OA+: 27.28 kg/m²                                                  |
| Salamon et al[30]       | N=927, n=344                                                            | –                                        | OA+: F: 83.4%                          | OA+: 29.5 kg/m²                                                   |
| Abourazzak et al[31]    | n=130                                                                   | OA+: 56.7±8.1                            | OA+: F: 100%                           | OA+: 32.54±2.9 kg/m²                                             |
| Juge et al[32] *        | n=147                                                                   | OA+: 75.8±10                             | OA+: F: 68.7%                          | OA+: 27.2 kg/m²                                                   |
| Rollefstad et al[33]    | N=1243                                                                  | OA+: 64.1±8.6                            | OA+: F: 73.1%                          | –                                                                |
| Nuñez et al[34] *       | n=147                                                                   | OA+: 56.1±7.9                            | –                                      | OA+: 61.6% of OP                                                  |
| Shukurova et al[35]     | n=791                                                                   | OA+: 69.8±8                              | OA+: F: 79.2%                          | –                                                                |
| Salaru et al[36] *      | n=61                                                                    | OA+: 69.6±8                              | OA+: F: 90%                            | –                                                                |
| Kemta Lekpa et al[37]   | n=148                                                                   | OA+: 57±10.6                             | OA+: F: 75%                            | OA+: 53% of OP 30.8±5.6 kg/m²                                    |
| Niu et al[38] *         | n=1091                                                                  | OA+: 62                                  | OA+: F: 55.5%                          | –                                                                |
| Haugen et al[39] *      | n=748                                                                   | OA+ : 58.1                               | –                                      | OA+65.7% of OP                                                   |
| Courties et al[40] *    | n=869                                                                   | OA+: 54±7                                | OA+: F : 72%                           | –                                                                |
| Gandhi et al[41]        | n=1502                                                                  | OA+: 55.3±15.5                           | OA+: F: 48.8%                          | OA+: 27.3 kg/m²                                                   |
| Laires et al[42] *      | n=197                                                                   | OA+: 67±8.6                              | OA+: F: 79.2%                          | –                                                                |
| Thelier–Deloison et al[43] * | n=112, n=26               | –                                        | –                                      | OA+100% of OP                                                   |
| Soran et al[44]         | N=66, n=36                                                              | OA+: 40.9±2.5                            | OA+: F: 72.2%                          | OA+: 29.9±3.3 kg/m²                                             |
| CHERAS et al[45]        | N=96, n=44                                                              | OA+: 69±9                                | OA+: F 40.9%                           | OA+: 25.8 kg/m²                                                   |
| Mishra et al[46]        | N=100, n=28                                                             | OA+: 49.1±1.4                            | OA+: F: 71.4%                          | OA+: 24.8 kg/m²                                                   |
| Oliviero et al[47]      | N=77, n=16                                                              | OA+: 54.7±11.5                           | OA+: F: 68.7%                          | –                                                                |
| Addimanda et al[48]     | N=753, n=44                                                              | OA+: 68±8                                | OA+: F: 92.8%                          | OA+: 25.1±3.8 kg/m²                                             |
| Philbin et al[49]       | N=69, n=46                                                               | OA+: 65.8±9.3                            | OA+: F: 97.4%                          | OA+: 24.9±3.9 kg/m²                                             |
| Irshad et al[50]        | N=100, n=50                                                             | –                                        | –                                      | –                                                                |
| Zayed et al[51]         | N=80, n=40                                                              | OA+: 43.5±3.7                            | OA+: F: 87.5%                          | OA+: 37.3±5.9 kg/m²                                             |
| Cheng et al[52] *       | N=56,060, n=23,530                                                      | –                                        | –                                      | –                                                                |
| Davis et al[53]         | N=3885, n=301                                                           | –                                        | –                                      | –                                                                |
| Han et al[54]           | N=10,839, n=270                                                         | OA+: 64.5±10.1                           | OA+: F: 84.8%                          | –                                                                |

Continued
### Table 3

Continued

| Author           | Sample size (N = number of total patients; n = number of patients with OA) | Mean age (years) in OA+ and OA− patients | Gender in OA+ and OA− patients (% of F) | Overweight proportion (%) or BMI (kg/m²) in OA+ and OA− |
|------------------|--------------------------------------------------------------------------|------------------------------------------|----------------------------------------|-------------------------------------------------------|
| Dahaghin et al²¹ | n=3585                                                                   | --                                       | --                                     | OA+26.3±3.5 kg/m²                                      |
| Haugen et al²²   | N=1348 n=726                                                             | --                                       | --                                     | --                                                    |
| Inoue et al³⁰    | N=795 n=251                                                               | OA+: 66.3                                | OA+: F: 79.3%                           | OA+23.8 kg/m²                                         |
|                  |                                                                          | OA−: 55.5                                | OA−: F: 54.7%                           | OA−: 22.8 kg/m²                                       |
| Cemeroglu et al²²| N=61 n=39                                                                | --                                       | OA+: F: 100%                            | --                                                   |
| Meek et al⁵¹     | N=858 n=206                                                               | OA+: 59.2±11                             | OA+: F: 79.1%                           | --                                                   |
| Al-Arfaj²¹       | N=246 n=122                                                              | --                                       | --                                     | --                                                   |
| Suri et al⁴⁶     | N=441 n=310                                                               | OA+: 57.8±10.6                           | OA+: F: 49%                             | OA−: 39%                                             |
| Puenpatom et al⁴⁴| N=7714 n=975                                                              | OA+: 69.6                                | OA+: F: 61.3%                           | OA+: 66.9% of OP                                       |
|                  |                                                                          | OA−: 41.3                                | OA−: F: 51.3%                           | OA−: 34.8% of OP                                       |
| Hart et al¹⁹     | N=979 n=118                                                              | --                                       | OA+: F: 100%                            | --                                                   |
| Maddah et al²⁴   | N=625 n=244                                                               | OA+: 61.2                                | OA+: F: 89.8%                           | OA−: 73.8%                                           |
| Engström et al²⁴ | N=5194 n=209                                                             | OA+: 59.9                                | OA+: F: 66.5%                           | OA+: 27.9 kg/m²                                        |
|                  |                                                                          | OA−: 57.6                                | OA−: F: 58.4%                           | OA−: 25.37 kg/m²                                       |
| Yoshimura et al³²| N=1690 n=71                                                               | OA+: 67.3±8.2                            | OA+: F: 74.6%                           | OA+: 23.6±2.9 kg/m²                                    |
|                  |                                                                          | OA−: 58.2±11.8                           | OA−: F: 58.6%                           | OA−: 22.4±3.2 kg/m²                                    |
| Nielen et al⁶⁴   | N=175 956 n=4040                                                          | OA+: 59.8                                | OA+: F: 68.7%                           | --                                                   |
|                  |                                                                          | OA−: 51                                  | OA−: F: 50.4%                           | --                                                   |
| Marshall et al⁴⁴ | N=1076 n=341                                                              | OA+: 69.0                                | OA+: F: 80.4%                           | --                                                   |
| Hussain et al³⁷  | N=20 430 n=1222                                                           | OA+: 68.3±7.7                            | OA+: F: 66.2                            | OA+: 76.8% of OP                                       |
|                  |                                                                          | OA−: 64.8±8.6                            | OA−: F: 59.5%                           | OA−: 28.6±5.0 kg/m²                                    |
| Sowers et al²¹   | N=664 n=53                                                                | OA+: 50±5                                | OA+: F: 100%                            | OA+: 35.6±11.1 kg/m²                                   |
|                  |                                                                          | OA−: 47±8                                | OA−: F: 100%                            | OA−: 27.3±8.4 kg/m²                                    |
| Massengale et al⁴⁶| N=2477 n=466                                                              | --                                       | OA+: F: 58.2%                           | --                                                   |
|                  |                                                                          | OA−: F: 46.6%                            | --                                     | --                                                   |

*Data from a congress. BMI, body mass index; F, female; M, male; OA, osteoarthritis.

### Table 4

Main results of prevalence of dyslipidemia and mean lipid-level values in patients with osteoarthritis (OA) and non-OA patients

|                      | Prevalence of dyslipidemia | Mean CT level (mg/dL) | Mean high-density lipoprotein level (mg/dL) | Mean low-density lipoprotein level (mg/dL) | Mean triglyceride level (mg/dL) |
|----------------------|---------------------------|-----------------------|---------------------------------------------|-------------------------------------------|---------------------------------|
| **OA+ population**   |                           |                       |                                             |                                           |                                |
| 30.2±0.7%            |                           | 245±25.1              | 54.4±8.9                                    | 126.5±20.7                                | 137.3±80.3                     |
| n=14 823 n=28        |                           | n=6037 n=14           | n=5856 n=18                                 | n=656 n=9                                 | n=2406 n=15                    |
| **OA− population**   |                           |                       |                                             |                                           |                                |
| 8.0%±0.1%            |                           | 233.1±17.5            | 53.1±7.5                                    | 136.9±15.9                                | 131±27.3                      |
| n=196 168 n=13       |                           | n=3763 n=3            | n=412 n=7                                   | n=451 n=2                                 | n=3460 n=6                     |

Baudart P, et al. RMD Open 2017;3:e000442, doi:10.1136/rmdopen-2017-000442
factor of development and progression of OA. Obesity increases the risk of OA of the weightbearing joints due to excessive mechanical stress but is also associated with dyslipidemia in MetS. We identified seven articles accounting for confounding factors of dyslipidemia and OA: four showed a positive association after adjustment on age and BMI. However, when we meta-analysed the seven articles that reported an age-adjusted and BMI-adjusted OR, there was no association between dyslipidemia and OA, but raw data before adjustment on age and BMI are used. Finally, the impact of statin treatment could not be assessed because of the lack of data concerning its prescription. In fact, we have no details about statin use in dyslipidemic and non-dyslipidemic patients. However, Riddle et al did not find beneficial effect of statins on the structural progress at patients monitored for a knee osteoarthritis.

In this funnel plot, the distribution of common values is not heterogeneous. Likewise, we can consider that there is no major publication bias in our meta-analysis.

We demonstrated an association between dyslipidemia and OA, but the pathophysiological explanation for the causal relationship has not been clearly defined. Experimental studies suggest the existence of lipid metabolism dysfunction in OA. Mice with altered HDL metabolism showed knee OA despite abnormal weight gain. Gierman et al showed that dietary cholesterol intake increased spontaneous cartilage damage in mice. High LDL levels promote synovial inflammation and ectopic bone formation in mouse OA models. Oxidised-LDL (oxLDL) could be involved in the development and progression of OA by stimulating synovial cells (macrophages, synovial fibroblasts and endothelial cells) and chondrocytes. A treatment strategy that lowers the level of oxLDL could be interesting.

In conclusion, this is the first systematic review and meta-analysis demonstrating an association between OA and dyslipidemia, which illustrates the role of metabolic disturbances beyond glucose metabolism in OA pathophysiology. Such a study emphasises the need to screen and manage cardiovascular comorbidities in patients with OA in clinical practice.
8. Louati K, Vidal C, Berenbaum F, et al. Association between Diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. RMD Open 2015;1:e000077.

9. Berenbaum F. Diabetes-induced osteoarthritis: from a new paradigm to a new phenomenon: towards pathophysiological delineation of diabetes mellitus-related osteoarthritis. Osteoarthritis Cartilage 2015;23:1513–22.

10. Hamada D, Maynard R, Schott E, et al. Suppressive effects of insulin on tumor necrosis Factor-Dependent early osteoarthritis changes associated with obesity and type 2 Diabetes Mellitus. Arthritis Rheumatol 2016;68:1392–402.

11. Brouwers H, van Hegedu J, Toes R, et al. Lipid mediators of inflammation in rheumatoid arthritis and osteoarthritis. Best Pract Res Clin Rheumatol 2015;29:741–55.

12. von Elm E, Altman DG, Egger M, et al. The strengthening of Reporting of Observational studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–9.

13. Thelier-Deloinson N, Chevalier X, Oppert J-M, et al. Prevalence of clinical digital osteoarthritis (Heberden and Bouchard nodes) in a selected population of patients with severe obesity: a prospective study. Osteoarthritis Cartilage 2012;20:S174–S296.

14. Soran N, Altindag O, Cakir H, et al. Assessment of paraxonase activities in patients with knee osteoarthritis. Redox Rep 2008;13:194–8.

15. Juge S, Poinot M, Eymar S, et al. The relationship between co-morbidity and knee osteoarthritis - Data from the Framingham Study [abstract 243]. ACR Congr 2010.

16. Cherasa PA, Whitaker AN, Blackwell EA, et al. Hypercoagulability and hypofibrinolysis in primary osteoarthritis. Clin Orthop Relat Res 1997;57:67–77.

17. Hart DJ, Doyle DV, Specter TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford Study. J Rheumatol 1995;22:118–23.

18. Abdourrazak F, Talbi S, Lazrak F, et al. Does metabolic syndrome or its individual components affect pain function in knee osteoarthritis women? Curr Rheumatol Rev 2015;8:1–14.

19. Sowers M, Karvonen-Gutierrez CA, Palmieri-Smith R, et al. Knee osteoarthritis in obese women with cardiometabolic abnormalities. Arthritis Rheum 2009;61:1328–38.

20. Cemergolu G, Aydin H, Yasar ZS, et al. Hand and heart, hand in hand: is radiological hand osteoarthritis associated with atherosclerosis? Int J Rheum Dis 2014;17:299–303.

21. Rolfesfstad S, et al. Patients with Osteoarthritis DO NOT have increased risk of Cardiovascular Disease in Ullensaker Community in Norway [abstract 274]. ACR Congr 2014.

22. Mok K, Mahdizadeh J. Association of metabolic syndrome and its Components with Knee Osteoarthritis. Acta Med Iran 2015;53:327–32.

23. Davia AV, Entinger WH, Neuhaus JM. The role of metabolic factors and blood pressure in the association of obesity with osteoarthritis of the knee. J Rheumatol 1989;16:851–7.

24. Han CD, Yang HI, Lee WS, et al. Correlation between metabolic syndrome and knee osteoarthritis: data from the Korean National Health and Nutrition Examination survey (KHANES). BMC Public Health 2013;13:603.

25. Eybard F, Parsons C, Edwards MH, et al. Diabetes is a risk factor for knee osteoarthritis progression. Osteoarthritis Cartilage 2015;23:851–9.

26. Shek MK, Britchewsky SB, Hsu FC, et al. The association between vitamin K status and knee osteoarthritis features in older adults: the Health, Aging and Body Composition Study. Osteoarthritis Cartilage 2015;23:370–8.

27. Inoue R, Ishibashi Y, Tuda E, et al. Medical problems and risk factors of metabolic syndrome among radiographic knee osteoarthritis patients in the Japanese general population. J Orthop Sci 2011;16:704–9.

28. Al-Arfaj AS. Radioisotopic osteoarthritis and serum cholesterol. Saudi Med J 2003;24:745–7.

29. Nuhez M, et al. Locus of control of pain in patients with knee osteoarthritis [abstract]. Ann Rheum Dis 2012;71:633.

30. Salaru V, et al. The relationship between co-morbidity and quality of life in patients with knee osteoarthritis [abstract 248]. Eur J Intern Med 2013.
60. Riddle DL, Moxley G, Dumenci L. Associations between statin use and changes in pain, function and structural progression: a longitudinal study of persons with knee osteoarthritis. *Ann Rheum Dis* 2013;72:196–203.

61. Triantaphyllidou IE, Kalvioti E, Karavia E, et al. Perturbations in the HDL metabolic pathway predispose to the development of osteoarthritis in mice following long-term exposure to western-type diet. *Osteoarthritis Cartilage* 2013;21:322–30.

62. Gierman LM, Kühnast S, Kouidi S, et al. Osteoarthritis development is induced by increased dietary cholesterol and can be inhibited by atorvastatin in APOE*3leiden.CETP mice—a translational model for atherosclerosis. *Ann Rheum Dis* 2014;73:921–7.

63. de Munter W, van den Bosch MH, Slöetjes AW, et al. High LDL levels lead to increased synovial inflammation and accelerated ectopic bone formation during experimental osteoarthritis. *Osteoarthritis Cartilage* 2016;24:844–55.

64. de Munter W, van der Kraan PM, van den Berg WB, et al. High systemic levels of low-density lipoprotein cholesterol: fuel to the flames in inflammatory osteoarthritis? *Rheumatology* 2016;55:16–24.

65. Racaza GZ, Salido EO, Penserga EG. Clinical profile of Filipino patients with osteoarthritis seen at two arthritis clinics. *Int J Rheum Dis* 2012;15:399–406.

66. Erb N, Pace AV, Douglas KM, et al. Risk assessment for coronary heart disease in rheumatoid arthritis and osteoarthritis. *Scand J Rheumatol* 2004;33:293–9.

67. Shukurova S. Osteoarthritis place in rheumatic diseases hospitalization structure [abstract P-260]. *MCR Congr* 2014.