Cardiovascular risk markers in patients with psoriatic arthritis: A meta-analysis of literature studies

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**Introduction.** Several studies reported an increased cardiovascular (CV) morbidity and mortality in patients with psoriatic arthritis (PsA). We performed a meta-analysis on the impact of PsA on major markers of CV risk.

**Methods.** Studies on the relationship between PsA and common carotid artery intima-media thickness (CCA-IMT), prevalence of carotid plaques, flow-mediated dilation (FMD), nitrate-mediated dilation (NMD), pulse wave velocity (PWV), augmentation index (AIx), and ankle-brachial index (ABI) were systematically searched in the PubMed, Web of Science, Scopus, and EMBASE databases.

**Results.** Sixteen case-control studies (898 cases, 1,140 controls) were included. Compared to controls, PsA patients showed a higher CCA-IMT (MD 0.07 mm; 95% CI 0.04, 0.11; \(P < 0.0001\)), and a higher frequency of carotid plaques (OR 3.12; 95% CI 1.03, 9.39; \(P = 0.04\)). Moreover, a lower FMD was found in PsA subjects than in controls (MD \(-2.56\%\); 95% CI \(-4.17, -0.94\); \(P = 0.002\)), with no differences in NMD (MD \(-0.40\%\); 95% CI \(-1.19, 0.39\); \(P = 0.32\)). Because of the low number of studies, no meta-analytical evaluation was performed for PWV, AIx, and ABI. Despite heterogeneity among studies, PsA appears significantly associated with markers of subclinical atherosclerosis and CV risk.

**Discussion.** These findings could help to establish more specific CV prevention strategies in this clinical setting.

**Key words:** Carotid plaques, flow-mediated dilation, intima-media thickness, psoriatic arthritis, subclinical atherosclerosis

**Key messages**

- Psoriatic arthritis (PsA) is characterized by high prevalence of co-morbidities, including metabolic syndrome and its major features (obesity, hypertension, impaired fasting glucose, hyperlipidemia).
- The association of PsA with markers of cardiovascular risk is widely discussed.
- We found that PsA is associated with an increased subclinical atherosclerosis and with impaired endothelial function, both being recognized as markers of cardiovascular risk.
During recent years, a series of case-control studies reported accelerated atherosclerosis (18,19), impaired endothelial function (20,21), and increased arterial stiffness (22,23) in patients with PsA. However, these data have been challenged in other studies (24,25), and no meta-analytical data providing an overall information about this issue are currently available.

In order to provide a comprehensive overview of the relationship between PsA and subclinical atherosclerosis, we performed a systematic review with meta-analysis of literature studies evaluating the impact of PsA on the major markers of CV risk.

Methods
A protocol for this review was prospectively developed, detailing the specific objectives, the criteria for study selection, the approach to assess study quality, the outcomes, and the statistical methods.

Search strategy
To identify all available studies, a detailed search pertaining to PsA and the markers of CV risk (i.e. IMT, FMD, NMD, PWV, AIx, and ABI) was conducted according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (26). A systematic search was performed in the electronic databases (PubMed, Web of Science, Scopus, EMBASE), using the following search terms in all possible combinations: psoriatic arthritis, intima-media thickness, carotid plaques, atherosclerosis, flow-mediated dilation, nitrate-mediated dilation, endothelium-dependent dilation, endothelium-independent dilation, endothelial dysfunction, pulse wave velocity, augmentation index, arterial stiffness, ankle-brachial index. The last search was performed on 10 November 2014. The search strategy was developed without any language or publication year restriction.

In addition, the reference lists of all retrieved articles were manually reviewed. In case of missing data, study authors were contacted by e-mail to try to retrieve original data. Two of the authors (M.N.D.D.M. and P.A.) analyzed each article and performed the data extraction independently. In case of disagreement, a third investigator was consulted (R.L.). Discrepancies were resolved by consensus. Selection results showed a high inter-reader agreement (κ = 0.97) and have been reported according to the PRISMA flow chart (Supplementary Appendix 1, to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2015.1031822).

Data extraction and quality assessment
According to the pre-specified protocol, all studies evaluating the impact of PsA on the markers of CV risk were included. Case-reports, case-series without a control group, reviews, and animal studies were excluded. To be included in the analysis, a study had to provide values (means with standard deviation) of at least one variable among the following: common carotid artery IMT (CCA-IMT), brachial artery FMD or NMD, carotid-femoral or carotid-radial PWV, aortic AIx, and ABI. Studies reporting the prevalence of carotid plaques were also included.

In each study, data regarding sample size, major clinical and demographic variables, values of IMT, FMD, NMD, PWV, AIx, and ABI, and prevalence of carotid plaques in PsA patients and healthy controls were extracted.

Given the characteristics of the included studies, the evaluation of methodological quality of each study was performed with the Newcastle–Ottawa Scale (NOS), which is specifically developed to assess the quality of non-randomized observational studies (27). The scoring system encompasses three major domains (selection, comparability, exposure) and the resulting score ranges between 0 and 8, a higher score representing a better methodological quality. Results of the NOS quality assessment are reported in Supplementary Appendix 2 (to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2015.1031822).

Statistical analysis and risk of bias assessment
Statistical analysis was carried out using Review Manager (Version 5.2, The Cochrane Collaboration, Copenhagen, Denmark) provided by The Cochrane Collaboration.

Differences among cases and controls were expressed as mean difference (MD) with pertinent 95% confidence intervals (95% CI) for continuous variables, and as odds ratio (OR) with pertinent 95% CI for dichotomous variables.

IMT has been expressed in millimeters (mm), FMD, NMD, and AIx as percentage (%), PWV as mm per second (mm/s), and ABI as an absolute number.

The overall effect was tested using Z scores, and significance was set at P < 0.05. Statistical heterogeneity between studies was assessed with chi-square, Cochran’s Q test, and with I² statistic, which measures the inconsistency across study results and describes the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. In detail, an I² value of 0% indicates no heterogeneity, 25% low, 25%–50% moderate, and 50% high heterogeneity (28).

Publication bias was assessed by Egger’s test and represented graphically by funnel plots of the standard difference in means versus the standard error. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect, and Egger’s test was used to assess publication bias, over and above any subjective evaluation. P < 0.10 was considered statistically significant (29). In order to be as conservative as possible, the random effect method was used for all analyses to take into account the variability among included studies.

Sensitivity analyses
We repeated analyses by including only the studies judged as ‘high quality’ according to NOS (i.e. NOS ≥ the median value found among included studies).

A further analysis was performed after excluding studies providing a composite IMT, calculated by averaging the CCA with the internal carotid artery (ICA) and/or the carotid bifurcation (BIF) measurements.

Meta-regression analyses
We hypothesized that differences among included studies may be affected by demographic variables (mean age, male gender) and clinical data related to disease activity (disease activity score in 28 joints (DAS28), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), disease duration), anti-rheumatic treatment (therapy with non-steroidal anti-inflammatory drugs (NSAIDs), sulfasalazine (SSZ), corticosteroids (CSs), methotrexate (MTX), or TNFα-blockers), and coexistence of traditional CV risk factors (hypertension, smoking habit, diabetes mellitus, obesity, hyperlipidemia). To assess the possible effect of such variables in explaining different results observed across studies, we planned to perform meta-regression analyses after implementing a regression model with changes in IMT, FMD, NMD, PWV, AIx, and ABI values, or presence of carotid plaques as dependent variables (γ) and the above-mentioned covariates as independent variables (α). This analysis was performed with Comprehensive Meta-analysis (Version 2, Biostat, Englewood NJ, USA; 2005).
Results

After excluding duplicate results, the search retrieved 786 articles. Of these studies, 414 were excluded because they were off the topic after scanning the title and/or the abstract, 352 because they were reviews/comments/case reports or they lacked of data of interest. For 1 study the online full-length version was not available, and another 3 studies were excluded after full-length paper evaluation.

Thus, 16 articles (on 898 PsA patients and 1,140 healthy controls) were included in the final analysis (Supplementary Appendix 1, to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2015.1031822). In detail, 12 studies with data on CCA-IMT (13 data sets on 759 cases and 937 controls), 9 studies reporting on the prevalence of carotid plaques (10 data sets on 648 cases and 787 controls, 6 studies on FMD (7 data sets on 229 patients and 279 controls), and 4 on NMD (5 data sets on 173 cases and 192 controls) were included. PWV and AIx have been evaluated in one study each (22,23), while no study tested ABI in PsA patients and healthy controls. Thus, these outcomes were not included in the meta-analytical evaluation.

Study characteristics

All included studies had a case-control design. Major characteristics of populations are shown in Table I, and further data about

Table I. Demographic and clinical data of psoriatic arthritis patients and healthy controls in included studies.

| Author            | PsA (n) | M/F | Age (y) | HT (%) | Smoking (%) | DM (%) | Ob (%) | HL (%) | BMI (kg/m²) | TC (mg/dL) | LDLc (mg/dL) | HDLc (mg/dL) | TGs (mg/dL) |
|-------------------|---------|-----|---------|--------|-------------|--------|--------|--------|-------------|------------|--------------|-------------|-------------|
| Atzeni, 2011      | 22      | 12/10 | 54.9    | 9.1    |             | 27.6   | 197.1  | 109.9  | 44.6        | 175.5      |              |              |             |
| Healthy           | 35      | 19/16 | 55.4    | 0      |             | 26.1   | 176.3  |        |             |            |              |              |             |
| Bilgen, 2013a     | 32      |      |         |        |             |        |        | 28.4   |             |            |              |              |             |
| Healthy           | 37      |      |         |        |             |        |        |        |             |            |              |              |             |
| Contessa, 2009    | 41      | 31/10 | 51.9    | 24.4   | 12.2        | 14.6   | 26.5   |        |             |            |              |              |             |
| Healthy           | 41      | 31/10 | 52.1    | 21.9   | 0           | 31.7   | 25.6   |        |             |            |              |              |             |
| Di Minno, 2011    | 224     | 104/120 | 52.6   | 41.1   | 8.9         | 62.5   | 51.8   |        |             |            |              |              |             |
| Healthy           | 305     | 132/173 | 51.9  | 35.4   | 9.2         | 64.6   | 55.1   |        |             |            |              |              |             |
| Eder, 2008        | 40      | 12/28 | 57.8    | 47.5   | 12.5        | 37.5   | 28.0   | 194.0  | 122.0       | 46.0       | 150.0        |              |             |
| Healthy           | 40      | 12/28 | 57.0    | 47.5   | 17.5        | 37.5   | 27.0   | 211.0  | 131.0       | 53.0       | 149.0        |              |             |
| Gentile, 2011a    | 50      | 26/24 | 49.5    | 21.6   |             |        |        | 27.7   | 200.9       | 47.4       | 119.3        |              |             |
| Healthy           | 100     | 44/56 | 47.3    | 21.6   |             |        |        | 25.9   | 190.7       | 50.5       | 90.7         |              |             |
| Gonzalez-Juanatey, 2007 | 59 | 31/28 | 48.8 | –  | –  | –  | 25.6 | 194.7 | 116.8 | 53.8 | 90.0 |
| Healthy           | 59      | 31/28 | 48.8    | –      | –           |        |        | 25.4   | 185.9       | 51.9       | 97.4         |              |             |
| Karadag, 2010     | 24      | –      | –       | –      | –           |        |        | –      | –           | –         | –            |              |             |
| Healthy           | 50      | –      | –       | –      | –           |        |        | –      | –           | –         | –            |              |             |
| Kimhi, 2007       | 47      | 23/24 | 50.0    | 25.0   | 34.0        | 10.6   | 29.0   | 277.0  | 128.0       | 54.0       | 126.0        |              |             |
| Healthy           | 100     | 49/51 | 34.9    | 3.0    | 28.0        | 1.0    | 13.0   | 183.0  | 105.0       | 60.0       | 95.0         |              |             |
| Magro-Checa, 2013a | 77 | 40/37 | 47.3 | –  | –  | –  | –  | –  | –  | – | – |
| Healthy           | 77      | 40/37 | 47.3    | –      | –           | –      | –      | –      | –           | –         | –            |              |             |
| Peluso, 2009b     | 50      | 19/31 | 37.6    | 0      | 0           | 0      | 0      | 0      | –           | –         | –            |              |             |
| Healthy           | 50      | 21/29 | 36.8    | 0      | 0           | 0      | 0      | 0      | –           | –         | –            |              |             |
| Profumo, 2012     | 25      | 17/8  | 8.0     | 28.0   |             | –      | –      | –      | –           | –         | –            |              |             |
| Healthy           | 13      | –      | –       | –      | 0           | –      | 0      | –      | –           | –         | –            |              |             |
| Puato, 2014 (NT)  | 19      | 12/7  | 47.8    | 0      | 32.0        | 0      | –      | 24.8   | 193.0       | 47.0       | 128.0        |              |             |
| Healthy           | 38      | 20/18 | 48.8    | 0      | 26.0        | 0      | –      | 25.0   | 209.0       | 51.0       | 131.0        |              |             |
| Puato, 2014 (HT)  | 23      | 19/4  | 54.3    | 100    | 17.0        | 0      | –      | 26.0   | 220.0       | 55.0       | 119.0        |              |             |
| Healthy           | 23      | 16/6  | 48.1    | 100    | 26.0        | 0      | –      | 26.0   | 217.0       | 52.0       | 118.0        |              |             |
| Shang, 2012       | 43      | 23/20 | 53.0    | –      | –           | 0      | –      | 24.2   | –           | –         | –            |              |             |
| Healthy           | 50      | 28/22 | 44.0    | –      | 0           | –      | –      | 22.8   | –           | –         | –            |              |             |
| Sharma, 2014     | 40      | 23/17 | 42.0    | 0      | 0           | 0      | –      | –      | 153.0       | 41.2       | 143.2        |              |             |
| Healthy           | 40      | 27/13 | 39.0    | 0      | 0           | 0      | –      | –      | 142.0       | 36.8       | 134.0        |              |             |
| Tam, 2008         | 82      | 42/40 | 49.0    | 50.0   | 10.0        | 23.2   | 15.0   | 14.6   | 23.4        | 113.0      | 55.0         | 118.0        |             |
| Healthy           | 82      | 42/40 | 49.0    | 50.0   | 10.0        | 23.2   | 15.0   | 25.7   | –           | –         | –            |              |             |

Age, BMI, TC, LDLc, HDLc, and TGs are expressed as mean values.
BMI = body mass index; DM = diabetes mellitus; HDLc = HDL-cholesterol; HL = hyperlipidemia; HT = hypertension; LDLc = LDL-cholesterol; M/F = male/female; NT = normotension; Ob = obesity; Pop = population; PsA = psoriatic arthritis; TC = total cholesterol; TGs = triglycerides.

a Only abstract available.
b Only abstract available; age is expressed as median value.
disease activity and ongoing anti-rheumatic treatment of PsA patients are reported in Table II.

The number of patients varied from 19 to 224, the mean age from 37.6 to 57.8 years, and the prevalence of male gender from 37.6% to 82.6%.

The presence of hypertension was reported by 0%–100% of patients, smoking habit by 0%–34%, diabetes mellitus by 0%–30% to 82.6%, obesity by 0%–62.5%, and hyperlipidemia by 0%–37.5%.

Mean body mass index (BMI) varied from 23.4 kg/m² to 28.4 kg/m². Mean values of total cholesterol (TC) ranged from 193 to 220 mg/dL, of LDL-cholesterol (LDLc) from 109.9 to 142 mg/dL, of triglycerides (TGs) from 90 to 175.5 mg/dL.

Mean values of DAS28 varied from 2.4 to 5.9, BASDAI from 4.6 to 35, CRP from 0.46 to 2.73 mg/dL, ESR from 15.1 to 38 mm/h, and disease duration from 3.4 to 12.1 years. An ongoing treatment with methotrexate; NSAIDs -blockers by 0%–69%.

One study (25) provided separate data for PsA patients and healthy controls stratified for the presence of hypertension. The two groups were evaluated as two different data sets.

The NOS for quality assessment of included studies showed a median value of 7.

Common carotid artery IMT (CCA-IMT) and carotid plaques

In 12 studies (13 data sets) (18,19,23,24,25,30–36), we found a significantly higher CCA-IMT in 759 PsA patients than in 937 controls (MD 0.07 mm; 95% CI 0.04, 0.11; P < 0.00001) (Figure 1). The heterogeneity among studies was significant (I² = 75%; P < 0.00001), but, after excluding one study (24), similar results were obtained without heterogeneity (MD 0.08 mm; 95% CI 0.07, 0.10; P < 0.00001, I² = 2%; P < 0.00001). A total of 9 studies (10 data sets) (24,25,31,32,34–38), showed an increased prevalence of carotid plaques in 648 PsA patients as compared to 787 controls (28.3% versus 10.9%), with a corresponding OR of 3.12 (95% CI 1.03, 9.39; P = 0.04) (Figure 2).

Significant heterogeneity among studies was found (I² = 91%; P < 0.00001). Of interest, after excluding one study (24), we found similar results without heterogeneity (OR 3.51; 95% CI 2.33, 5.29; P < 0.00001, I² = 0%; P = 0.67).

Figure 1. Common carotid artery intima-media thickness (CCA-IMT) in psoriatic arthritis (PsA) patients and controls.
Flow-mediated dilation (FMD) and nitrate-mediated dilation (NMD)

Six studies (7 data sets) (19,20,21,25,30,32), evaluating a total of 229 cases and 279 controls, showed a significantly lower FMD in PsA subjects as compared to controls (MD – 2.56%; 95% CI – 4.17, –0.94; P = 0.002) (Figure 3). Significant heterogeneity among studies was found (P = 0.92; P < 0.00001), and it was not reduced by excluding one study at a time.

In contrast, no difference in the NMD was found in 4 studies (5 data sets) (19,20,25,32) evaluating a total of 173 PsA subjects and 192 controls (MD –0.40%; 95% CI –1.19, 0.39, P = 0.32) (Figure 4).

Publication bias

Because it is recognized that publication bias can affect the results of meta-analyses, we attempted to assess this potential bias using funnel plots analysis.

Funnel plots of effect size versus standard error for studies evaluating CCA-IMT, FMD, and NMD were rather symmetrical, suggesting the absence of publication bias and of small-study effect (Supplementary Appendix 3, to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2015.1031822), confirmed by Egger’s test (P = 0.45, P = 0.11, and P = 0.86, respectively).

In contrast, studies on the prevalence of carotid plaques showed an asymmetric distribution and were affected by publication bias (Egger’s P = 0.0009).

Sensitivity analyses

The median value of NOS quality assessment was 7. Thus, the analyses were repeated by including only studies classified as ‘high quality’ (NOS ≥ 7) (18,20,21,23,31–33,36) (Supplementary Appendix 2, to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2015.1031822). For 4 studies (30,34,35,37) data of interest were extracted by the abstract, thus no quality assessment could be performed.

Of interest, after excluding studies classified as ‘low quality’ (19,24,25,38) and those with only abstract available (30,34,35,37), all results were confirmed (Table III).

Similar results were confirmed also after excluding 5 studies (19,23,25,31,36) providing a composite IMT, calculated by averaging the CCA-IMT with the internal carotid artery-IMT and/or the IMT at the level of the carotid bifurcation (Table IV).

Meta-regression analyses

Since meta-regression is effective when a covariate is reported by at least 10 studies (39) and several items of information were missing from each included study, a meta-regression approach could be performed only to test the impact of age and male gender on CCA-IMT, and these demographic covariates did not impact on the evaluated outcome (P = 0.39 and P = 0.92, respectively).

Discussion

Results of the present meta-analysis consistently show that PsA is associated with subclinical atherosclerosis and endothelial dysfunction. In particular, we reported an increased carotid IMT with a high prevalence of carotid plaques and impaired FMD in patients with PsA. Our findings are strengthened by sensitivity analyses. Moreover, regression models were able to refine the results further, providing the evidence that demographic variables (age and gender) did not impact on carotid IMT.

Overall, these data clearly show an increased CV risk in patients with PsA and suggest the need for a strict monitoring of CV risk factors and of signs of subclinical atherosclerosis in PsA patients. Accordingly, previous published studies reported an increased risk of major CV events and CV death in patients with PsA (7–9) and other autoimmune (40) or rheumatic diseases (41).
Many CV risk factors are thought to have a causal role in the atherosclerotic process (42). Although PsA patients exhibit an increased prevalence of these CV risk factors (6), the relationship between subclinical atherosclerosis and PsA seems to be more complex, and the presence of traditional risk factors might not entirely explain the accelerated atherosclerotic process in this clinical setting (43). Thus, other mechanisms (i.e. inflammatory and immunological) have been proposed to explain the relationship between PsA and atherosclerosis (6).

Immune-mediated inflammation seems to play a pivotal role in the pathogenesis of atherosclerosis, being involved in endothelial dysfunction, plaque rupture, and thrombosis (44). In keeping with this, some common markers of inflammation (i.e. CRP, fibrinogen) are emerging predictors of CV disease (45,46), and patients with PsA exhibit elevated levels of these acute-phase proteins (47). ESR, another marker of inflammation, is commonly found increased in PsA (33), and high ESR has been associated with increased overall mortality in this clinical setting (48). The strong correlation between these markers of inflammation and those of platelet activation (CD62P, CD63) suggests that disease activity is involved in platelet hyperreactivity in rheumatic diseases (49). In line with these data, a direct correlation between inflammatory status (as expressed by CRP levels) and increasing quartiles of maximal platelet aggregation has also been documented in PsA (50).

Overall, our findings are in line with several experimental and clinical evidences, supporting the hypothesis that premature atherosclerosis may be one of the main features of PsA and that chronic inflammation plays an important role in its pathogenesis, acting independently and/or synergistically with traditional CV risk factors.

In order to provide a comprehensive overview of the relationship between PsA and subclinical atherosclerosis, all the major recognized markers of CV risk were taken into account in the current meta-analysis. Thus, we reported an increased carotid IMT with a high prevalence of carotid plaques and impaired FMD in patients with PsA as compared with controls, but we did not find a significant difference in the NMD. However, when interpreting the latter result, we should consider the limited number of studies (n = 4) evaluating this outcome. Although no meta-analytical evaluation was possible for arterial stiffness parameters and ABI, it is relevant that higher values of PWV and AIx have also been documented in PsA patients (22,23).

To strengthen our results, it would have been useful to assess also the prevalence of CV events among PsA subjects and healthy controls, but most included studies excluded patients with clinically proven coronary artery disease or history of myocardial infarction or cerebrovascular accidents. The clinical relevance of our results can be better understood when we consider that the risk of myocardial infarction increases by 43% every 0.163 mm increase in carotid IMT (51), and that the prevalence of carotid plaques is an even more reliable predictor of CV events than IMT (15,52).

In addition, our results on FMD further confirm the presence of accelerated atherosclerosis in patients with PsA. The rationale for the association between FMD and CV prognosis is the assumption that it reflects endothelium-dependent dilation and, in turn, NO bioavailability (53). Endothelium-derived NO possesses several anti-atherogenic and plaque-stabilizing properties, including inhibition of cell growth and proliferation, regulation of vascular tone and arterial wall stress, inhibition of leukocyte and platelet adhesion, and anti-thrombotic and fibrinolytic properties (54). In keeping with this, it has been documented that each 1% decrease in FMD is associated with a 12% increase of CV events (55).

In line with these findings, the European League Against Rheumatism (EULAR) recently proposed the application of a 1.5 multiplier to the CV risk calculated in rheumatic patients through the scores currently used for the general population (e.g. the Framingham score) (56). However, this approach still requires a long-term validation.

Our results further support the need for large long-term interventional trials with CV end-points to investigate whether benefits in articular disease achieved by aggressive suppression of inflammation may translate into reduced CV risk in PsA.

Some potential limitations of our study need to be discussed.

First, studies included in our meta-analysis have different inclusion and exclusion criteria, and most of the patients included in the analysis had comitant CV risk factors (hypertension, smoking, obesity, diabetes mellitus, hyperlipidemia), different disease activity status (DAS28, BASDAI, BASFI, CRP levels, ESR, disease duration), and different anti-rheumatic treatment (NSAIDs, SSZ, CS, RA, MTX, and others). Some studies excluded patients with obesity, diabetes, or hypertension, but this approach still requires a long-term validation.

Second, most of the included studies treated PsA patients with conventional DMARDs and biologics, and more studies are needed to evaluate the long-term consequences of these treatments on cardiovascular outcomes.

Third, a large number of included studies used CE-MRA, a technique with lower spatial and temporal resolution compared to CE-CTA, and more studies are needed to confirm the results of this meta-analysis.

Table III. Sensitivity analyses on ‘high quality’ studies (i.e. Newcastle–Ottawa Scale ≥7).

| Study or Subgroup | Mean Difference | Mean Difference |
|-------------------|----------------|----------------|
|                   |                 |                 |
| CCA-IMT           |                 |                 |
| Contodora 2001    | 0.33 ± 0.39     | 293 patients; 366 controls | MD: 0.09 [0.07, 0.12]; P < 0.000001 |
|                   |                 |                 |
| Carotoid plaques  |                 |                 |
| Pauco 2014 (HF)   | 0.81 ± 0.23     | 181 patients; 181 controls | OR: 4.53 [1.63, 12.62]; P = 0.004 |
|                   |                 |                 |
| FMD               |                 |                 |
| Sharma 2014       | 1.35 ± 0.41     | 114 patients; 140 controls | MD: –3.45 [–6.12, –0.77]; P = 0.01 |
|                   |                 |                 |
| NMD               |                 |                 |
| Total (95% CI)    |                 |                 |

95% CI = 95% confidence intervals; CCA-IMT = common carotid artery intima-media thickness; FMD = flow-mediated dilation; MD = mean difference; n = number; NMD = nitrate-mediated dilation; OR = odds ratio.
MTX, or TNFα-blockers). However, based on Cochrane’s collaboration guidelines, a meta-regression approach is effective when a covariate is reported by at least 10 studies (39), and several items of information were missing from each included study. Thus, a meta-regression approach could be performed only to test the impact of some demographic variables (age and gender) on CCA-IMT, and caution is necessary in overall results interpretation.

Second, heterogeneity among the studies was generally significant. However, all results have been confirmed without heterogeneity after the exclusion of one study (24) which has been specifically designed to compare the effect of different treatments (TNFα-blockers versus traditional disease modifying anti-rheumatic drugs) on the CCA-IMT. In addition, results were also confirmed by sensitivity analyses. Thus, although we were not able conclusively to ascertain all potential sources of heterogeneity, we are confident that the impact on results can be considered minimal.

Third, we should consider that five disease patterns are documented in PsA patients (distal joint disease, oligoarthritis, spondylarthropathy, polyarthritis, arthritis mutilans) but none of the included studies reported data on IMT, FMD, and NMD stratified according to PsA clinical subset. Similarly, no information on the type of psoriasis could be extracted from the included studies. Thus, we could not evaluate how the clinical presentation of the disease may impact on our results.

Finally, caution is necessary in the interpretation of the results on FMD and on the prevalence of carotid plaques. While IMT is a somehow reproducible parameter, FMD measurement may be influenced by many confounding factors (57), significantly limiting reproducibility of FMD assessment and, in turn, the relevance of results. In particular, some studies indicate that cuff placement (58) or duration of cuff occlusion (59) may affect results. Moreover, we have to consider that the definition of carotid plaques varied widely among studies. However, it is interesting to highlight that the effect of PsA was consistently confirmed for all evaluated outcomes, strongly suggesting an increased CV risk in these patients.

In conclusion, in our meta-analysis PsA appeared significantly associated with subclinical atherosclerosis and endothelial dysfunction and, in turn, with an increased CV risk. Thus, patients with PsA may benefit from a periodic assessment of surrogate markers of CV risk. This could help to establish more specific CV prevention strategies for these patients.

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Table IV. Sensitivity analyses after exclusion of studies providing a composite IMT.

| n of studies | n of patients | Effect size; MD [95% CI] |
|--------------|---------------|-------------------------|
| CCA-IMT      | 7 (7 data sets) | 511 patients; 663 controls | MD: 0.06 [0.01, 0.11]; P = 0.03 |

95% CI = 95% confidence intervals; CCA-IMT = common carotid artery intima-media thickness; MD = mean difference; n = number.
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