**SUBCINICIAL ATHEROSCLEROSIS IN BEHCET’S DISEASE AND ITS INVERSE RELATION TO AZATHIOPRINE USE: AN UPDATED META-ANALYSIS**

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**ABSTRACT**

**Objectives.** To evaluate the intima media thickness of carotid arteries (IMT) and its clinical, laboratory and treatment correlates in Behcet’s disease (BD). **Methods**. Systematic search of EMBASE and PubMed databases from January 2016 to October 2022; we employed random effect meta-analyses for continuous outcomes and Peto’s odds ratio for rare events**.** **Results.** The meta-analysis included 36 case control studies: the IMT was greater in BD (n=1103) than in controls (n=832) (p<0.0001) with wide heterogeneity (I*2*=86.9%); a sensitivity analysis that included mean age of BD participants, gender, disease duration and activity, atherogenic index of plasma, blood pressure, C-reactive protein, ethnicity, smoking status, anti-inflammatory and immune suppressive agents, revealed that male gender, mean age of participants and azathioprine use (the latter two in inverse fashion) partly explained the heterogeneity variance (p=0.02, p=0.005, and p=0.01). The IMT was greater in vascular (n=114) than in non-vascular BD (n=214) (p=0.006). BD patients (n=782) had a greater pooled prevalence of carotid plaques than controls (n=537) (13.1% vs 2.97%, p<0.0001). **Conclusion.** Subclinical carotid artery atherosclerosis represents a vascular feature of BD, independently of the traditional risk factors but for male gender; the inverse relations with age and azathioprine use suggest that carotid arteries are thicker at disease onset but do not progress over time, eventually dampened by immune suppressive treatment: this assumption needs verification on adequately designed clinical trials.

**Key words:** Behcet’s disease, intima media thickness, atherosclerosis, azathioprine

**INTRODUCTION**

Behcet’s disease (BD) is an autoinflammatory disease with protean clinical manifestations affecting mucous membranes, eyes, bowels, lungs, heart, brain and joints; from the vascular point of view, recurrent thrombophlebitis, thromboembolism involving upper and lower limbs, superior and inferior vena cava, splanchnic and cerebral veins are frequent [1]. Moreover, vasculitis of the *vasa vasorum* induces medial destruction and fibrosis, leading to the formation of aneurysms, stenoses and occlusions, mostly in the aorta and in the pulmonary vessels. This vascular involvement is responsible for severe morbidity and long-term mortality [2]. The inflammatory nature of BD lead to the evaluation of premature atherosclerosis via functional assessments such as flow mediated and endothelial mediated vasodilation that rely on the biological activity of endogenous and exogenous nitric oxide respectively, and morphological assessment that rely on ultrasound measurement of the intima media thickness (IMT) of the carotid arteries. An earlier metanalysis suggested impaired flow mediated vasodilatation and subclinical atherosclerosis of carotid arteries in BD, offset however by wide heterogeneity, unexplained by the sensitivity analysis [3]. Given that endothelial dysfunction, detected as impaired pulse wave velocity, was confirmed by a later meta-analysis [4], we performed an updated systematic review and meta-analysis to reassess subclinical atherosclerosis by IMT of carotid arteries and to identify explanatory variables that were not detected in the previous meta-analysis possibly due to the limited number of studies available at the time.

**MATERIAL AND METHODS**

**Research hypothesis and outcome measures**

To assess the presence of subclinical atherosclerosis in BD and in its different subsets we calculated the standardized mean IMT differences and the pooled prevalence of carotid plaques between BD patients and healthy controls and between BD subgroups without or with certain clinical features and these represented our outcome measures.

**Search strategy**

Because our previous meta-analysis was performed on articles deriving from a systematic search that was carried out from inception to January 2016 [3], on this occasion the Medline database was screened from January 2016 to October 2022 using the Medical Subject Headings (“Behcet’s disease” [All fields] AND (“atherosclerosis”) [All fields] AND (“intima media thickness”) [All fields]; likewise the EMBASE database was screened between the same dates with “Behcet’s disease” OR “atherosclerosis” AND “intima media thickness”. The searches were done on the 17th of October 2022. To reduce the effect of possible publication bias, we used the same search terms in natural language to screen the Grey Literature via theDANS EASY Data Archive, as well as Google, looking for additional citations. We finally hand searched the reference list of all papers subsequently included in the systematic review to ensure we had not missed any relevant articles.

**Inclusion criteria:** 1) IMT measured by validated and published methods; 2) retrospective, cross-sectional and prospective case-control or cohort studies addressing the difference in mean plasma IMT between BD patients and controls (CTR) or between patients with and without different clinical manifestations BD; 3) articles written in any language.

**Exclusion criteria**: 1) IMT not measured with validated methods; 2) case studies, prevalence studies and reviews; 3) articles not comparing BD patients with healthy CTR. Two investigators (PRJA and AA) checked independently the resulting citations for relevancy and removed duplicates (via EndNote); AA and MM screened all titles and abstracts, excluded the irrelevant ones and applied the eligibility criteria to the relevant ones in order to include the appropriate studies. PRJA resolved any disagreements developing at this stage. PRJA and FG also screened the reference list of retrieved papers for papers that could have been missed. Eventual articles not written in English were translated.

**Data extraction/protocol**

AA and MM independently extracted data from the articles that considered: year of publication, study design, sample size, demographic data, disease duration, clinical features of BD, inflammatory markers, outcome means and corresponding dispersion measures (standard deviations or confidence intervals). In addition, and where study allowed, we calculated and charted the male/female ratio, the cardiovascular and cerebrovascular histories, the atherogenic index of plasma, the diastolic and systolic blood pressures, the use of anti-inflammatory and immune suppressive medication (expressed as the ratio of users/non-users) and the smoking status, that were all used for the sensitivity analysis. The 2020 PRISMA guideline was followed to ensure transparency of identification, selection, appraisal and synthesis of the studies included in the systematic review and meta-analysis (5). We did not subscribe the systematic review to a registry because our data derive from case-control and observational studies with no intervention, with data extracted as described above. The electronic sheets with collected data will be available on request.

### **Evaluation of the quality of the studies**

The quality of the studies included in the meta-analysis [6] was determined by the Newcastle Ottawa Quality Assessment Scale for observational case-control studies; two investigators, MM and FG, scored the studies independently and PRJA resolved any discrepancies. The inter-rater agreement between the two assessors was high (Cohen kappa 0.7412, 95% CI 0.589, 0.921).

### **Statistical analysis**

The statistical analysis was carried out via Comprehensive Meta-analysis (Version 3, Englewood, NJ 2013, USA). Random effect meta-analysis for continuous outcomes was employed because our estimates derived from cross-sectional observational studies and not from clinical trials [7]. Peto’s odds ratio for rare events was used to compare pooled frequencies between groups [8]. The heterogeneity across study results was assessed by the I2 statistics: a value of 0% indicated no heterogeneity; values less than 25% indicated low, between 25% and 50% moderate and over 50% high heterogeneity [9]. A [Funnel plot](https://www.sciencedirect.com/topics/medicine-and-dentistry/funnel-plot) (Supplementary Figure 1) was employed for publication bias [10,11]. Sensitivity analyses were performed by meta-regression and by subgroup according to results, clinical plausibility and judgement.

**RESULTS**

**Study Number**

The database search between January 2016 and October 2022 yielded 38 records; following the screening and exclusion processes indicated in Figure 1 we evaluated 21 new cross-sectional case-control studies, that were added to the 15 articles used in our previous meta-analysis [3], for a total of 36 articles that examined the relationship between BD and atherosclerosis [12-47] ([Table 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8020102/table/table1-10760296211002914/)).

**Reporting and calculation of disease activity**

The studies varied in their disease activity scoring systems: twelve studies [24, 26, 28, 31, 35, 36, 40, 41, 42, 44-46] adopted the Behçet`s Disease Current Activity Form [48]; three studies [33, 42, 47] adopted the Behcet’s Syndrome Activity Score [49]; six studies adopted [16, 18, 19, 20, 21, 34] earlier scoring systems [50, 51]; thirteen studies calculated and reported disease activity [18, 20, 24, 26, 28, 30, 31, 33, 36, 40, 41, 44, 46], 5 studies included patients with variable degrees of disease activity without calculating it [21-23, 30, 34, 45, 47] and the remaining 12 studies never quoted disease activity.

**Varied characteristics of the studies**

One study did not report the male to female ratio [37] and four did not report the disease duration [12, 14, 23, 37]; vascular involvement was an exclusion criterion in seven studies [19, 21, 25, 30, 34, 37, 38] while it affected variable numbers of BD patients in the remaining studies; a history of cardiovascular disease (myocardial infarction, ischemic stroke) and chronic kidney disease was an exclusion criterion for twenty six studies [12,13, 15-20, 22, 24, 25, 27-30, 34-36, 38-40, 41, 43, 44, 46, 47], it was not in six studies [14, 21, 23, 31, 32, 37] and was not defined in the remaining studies; three studies differentiated muco-cutaneous disease from disease with major organ involvement [20, 30, 39] and one differentiated active versus inactive lesions [29] and we analysed the data from these four studies together. Steroid treatment was an exclusion criterion in eight studies [19, 28-31, 36, 38, 39], it was reported in fourteen studies [13, 19, 21, 23, 24, 26, 27, 33, 40, 41, 44-47] but not quoted in the remaining studies; only five studies reported plasma homocysteine [13, 17, 18, 22, 38, 41]. Smoking status was reported in sixteen studies [13-16, 18-20, 22, 23, 30, 33, 38, 41, 42-44], it was an exclusion criterion in seven studies [17, 25, 27, 28, 31, 34, 35] and it was not reported in the remaining studies. As one paper reported the atherogenic index of plasma [31] we calculated this parameter according to the formula “log (triglycerides/high density lipoprotein)” [30] for all the articles that contained the required variables and used it in our analyses. C-reactive protein (CRP) was reported in twenty-two studies, ten of which expressed the results in milligrams per litre [19-22, 29, 34, 38-40, 42, 43] that were transformed into milligrams per decilitre to harmonize the results for the sensitivity analysis (Table 1).

**Intima media thickness of carotid arteries in Behcet’s disease and normal controls**

Pooled data from 33 case-control studies comprised 1103 patients with BD and 832 controls: the effect size favoured BD (p<0.0001) with wide heterogeneity (I*2*=86.9%, p<0.0001) (Figure 2). A sensitivity analysis by meta-regression evaluated article quality, mean age of BD participants, male to female ratio, disease duration and activity, atherogenic index, diastolic and systolic blood pressure, C-reactive protein (CRP), colchicine, cyclosporin A and azathioprine as moderator variables: part of the heterogeneity variance was positively explained by gender and negatively by age and by azathioprine use (Table 2A). In the control group age and IMT were positively correlated (n=36, r=0.376, 95% CI 0.054 to 0.627, p=0.02), even more so after excluding participants younger than 35 years of age (n=28, r=0.589, 95% CI 0.277 to 0.789, p=0.001). A sensitivity analysis by subgroups assessing ethnicity (Mediterranean versus non-Mediterranean), disease activity, smoking status, vascular involvement and immune suppressive agents failed to explain any heterogeneity variance but for a slight effect of ethnicity (Table 2B).

**Prevalence of carotid plaques in Behcet’s disease**

Twelve studies investigated the presence of carotid plaques but one found plaques neither in BD nor in controls so the data from 11 case–control studies comprising 782 BD patients and 537 controls were pooled for this effect size: the prevalence of carotid plaques was higher in BD patients than in controls (13.1% vs 2.97%, p<0.0001) with no heterogeneity (Figure 3). Plaque prevalence was similar in male and females (13% vs 12.8%).

**Intima media thickness of carotid arteries in Bechet’s disease and disease controls**

Pooled data from four studies employing disease controls, one with systemic lupus erythematosus [13] and three rheumatoid arthritis [20, 21, 33] comprised 430 patients with BD and 266 with disease controls: the effect size favoured disease controls (p<0.0001) with no heterogeneity (Figure 4).

**Intima media thickness of carotid arteries by vascular involvement**

Six studies explored the relation between vascular involvement and IMT: these comprised 114 BD patients with vascular involvement and 214 patients without such involvement; the effect size favoured vascular involvement (p=0.006) with no heterogeneity (Figure 5).

**Intima media thickness of carotid arteries by systemic/mucocutaneous involvement**

Four studies compared IMT in patients with systemic versus mucocutaneous involvement: we pooled their data comprising 216 BD participants with systemic involvement and 117 with muco-cutaneous involvement: the effect size was neutral (p=0.74) with no heterogeneity (Figure 6).

**DISCUSSION**

**Intima media thickness and its explanatory variables in Behcet’s disease**

Our meta-analysis reveals that subclinical atherosclerosis of the carotid arteries is a vascular feature of BD, in that the effect size of IMT favoured BD, though offset by high heterogeneity that was extensively investigated: the traditional atherogenic risk factors such as blood pressure, lipid profile, smoking and inflammatory status (expressed as CRP) as well as a history of cardiovascular or cerebrovascular disease failed to explain any of the heterogeneity variance. That said, the studies included in the meta-analysis were carried out on BD patients too young to develop essential hypertension (52) and premature cardiovascular disease (53) and whose lipid profiles were mostly normal.

Instead, the meta-regression revealed an inverse correlation between age of BD participants and IMT: the risk of either venous or arterial thrombosis is higher in the early stages of BD [54] and decreases with immune suppressive treatment in subsequent years [55, 56]. Given that 64.5% of the studies included in the metanalysis investigated patients with a disease duration ranging between 5 and 10 years and 19.3% investigated patients with a disease duration greater than 10 years, it is possible that ongoing immune suppressive treatments attenuated or reduced the risk of atherosclerosis in later years from diagnosis. Indeed, the inverse and significant relation between azathioprine and IMT and the non-significant but inverse trends for disease duration, colchicine and cyclosporin A would be in keeping with these concepts.

The meta-regression also revealed an association between male gender and IMT: it is known that vascular disease is more likely to occur in male BD patients [57] and males are more at risk of carotid atherosclerosis in the general population [58]. Furthermore, pooled studies performed on BD patients outside the Mediterranean basin showed a slightly lower heterogeneity, suggesting that certain ethnic backgrounds with inherent dietary and lifestyle patterns [59-61] coupled with the genetic variability of atherosclerosis [62] may influence the IMT.

**Intima media thickness in subsets of Behcet’s disease**

Of relevance, IMT was greater in BD with vascular disease than without, in agreement with the notion that venous thromboembolism may associate with atherosclerosis [63, 64] and its complications [65], notion indirectly confirmed by the observation that IMT was similar in studies comparing BD patients with muco-cutaneous and systemic manifestations (of which only 4 patients had a vessel involvement). On the other hand, IMT was lower in BD than in rheumatoid arthritis and systemic lupus erythematosus patients: this means that the atherogenic potential of an relapsing/remitting auto-inflammatory disease like BD is inferior to that of two chronic systemic inflammatory diseases, though the ages and the disease durations of the lupus and rheumatoid arthritis patients were greater than those of BD (13, 20, 21, 33). Anyhow, the strong effect size for carotid plaques suggests that atherosclerosis may develop in BD, though IMT progression and plaque formation/growth follow different biological pathways [66].

**Limitations of the study**

The current meta-analysis has several limitations: 1) all studies were cross-sectional and not prospective; 2) the lack of reporting disease activity and/or of the different disease activity scoring systems, as this would have given a better understanding of the relation between disease activity and IMT; 3) the lack of reporting number and length of inflammatory flares since diagnosis, as this would have better informed the relation with IMT; 4) owing to the involvement of plasma HC in BD [67], the relation with the IMT could not be adequately assessed as HC was reported in five studies only; 5) only four studies reported the use of anti-tumour necrosis factor agents [29, 40, 42, 46] precluding an appreciation of their effect on the IMT; 6) the inverse relation between azathioprine use and IMT derived from 19 studies, half of those included in the meta-analysis; 7) the use of an empirical graphical method to evaluate publication bias can be misleading [10,11] and inappropriate for observational studies [5].

**CONCLUSION**

**Relevant points**

The results of our meta-analysis indicate that: 1) subclinical atherosclerosis is a vascular feature of BD; 2) age (in an inverse fashion) and male gender relate to IMT; 3) azathioprine use associates with a lower IMT. This unreported observation is not unexpected: monocytes are involved in the pathogenesis of BD (68) and atherosclerosis (69) and 6-mercaptopurine (the pro-drug of azathioprine) induces monocyte apoptosis (70) whereas colchicine is believed to provide cardiovascular protection (71).

**Prospects for future research**

The hazard ratios for ischemic heart disease and mortality in BD are 3.09 and 1.40 respectively [72]: further research is required to identify other auto-inflammatory markers, possibly related to free radical overproduction [73], inflammasome activation [74] and inhibitory RNA modulation [75] that may be more relevant [76] to vascular damage in BD; equally, randomized clinical trials are needed to better define whether immune suppressive or anti-inflammatory agents (such as colchicine) may reduce the vascular risk of BD.

**Statements and Declarations**

None of the authors has any financial or non-financial competing interest to declare.

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**Legend to figures**

Figure 1. flowchart indicating the screening and exclusion of articles up to final inclusion in

qualitative and quantitative analysis

Figure 2: forest plot of studies comparing intima media thickness in Behcet’s disease and controls.

Figure 3: forest plot of studies comparing the pooled prevalence of carotid plaques in Behcet’s disease and controls

Figure 4: forest plot of studies comparing intima media thickness in Bechet’s disease and disease controls

Figure 5: forest plot of studies comparing intima media thickness in vascular versus non-vascular Behcet’s disease

Figure 6: forest plot of studies comparing intima media thickness in muco-cutaneous versus systemic Behcet’s disease

Table 1. Demographics, clinical and laboratory variables of control and Behcet’s disease participants

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref** | **Author** |  | **CTR** | **M/F** | **Age** | **IMT** | **BD** | **M/F** | **Age** | **IMT** | **DD** | **DA** | **CRP** | **NOS** |
| **No** | **Year** |  | **No** |  | **years** | **mm** | **No** |  | **years** | **mm** | **years** |  | **mg/dl** |  |
|  |  | **Country** |  |  | ***x̅* ± *σ*** | ***x̅ ± σ*** |  |  | ***x̅ ± σ*** | ***x̅ ± σ*** | ***x̅ ± σ*** | ***x̅ ± σ*** | ***x̅ ± σ*** |  |
| 11 | Sait, 2004 | Turkey | 42 | 25/17 | 40±9 | 0.59±0.12 | 40 | 19/21 | 39.8±8 | 0.81±0.12 |  |  |  | 5 |
| 12 | Keser, 2005 | Turkey | 77 | 46/31 | 37±7.8 | 0.48±0.09 | 114 | 68/46 | 38±9.4 | 0.55±0.14 | 10±6.58 |  | 1.1 ± 2.0 | 6 |
| 13 | Oflaz, 2005 | Turkey | 46 | 37/9 | 36±9.3 | 0.55±0.14 | 50 | 41/9 | 38±9.3 | 0.69±0.15 |  |  |  | 6 |
| 14 | Ozturk 2006 | Turkey | 34 | 21/13 | 34±8.5 | 0.54±0.13 | 34 | 21/13 | 34±8.5 | 0.81±0.17 | 0.57±0.43 | 5.8±2.0. | 27.4±50 | 5 |
| 15 | Rhee, 2007 | Korea | 53 | 26/27 | 37±7.2 | 0.52±0.06 | 41 | 20/21 | 37±7.9 | 0.52±0.09 | 6.5±0.6 |  |  | 6 |
| 16 | Caliskan, 2008 | Turkey | 35 | 19/16 | 38±7.9 | 0.46±0.18 | 53 | 24/29 | 36±.3 | 0.51±0.01 | 4.13±4.5 |  | 3.91±5.1 | 4 |
| 17 | Hong, 2008 | Korea | 20 | 13/7 | 40±5.1 | 0.59±0.11 | 40 | 24/16 | 39±8.5 | 0.71±0.17 | 5.2±4 | 1.3±1.3 | 0.5±0.5 | 6 |
| 18 | Ozturk, 2008 | Turkey | 21 | 15/6 | 35±8 | 0.57±0.14 | 21 | 15/6 | 35±8.6 | 0.86±0.18 | 7.3±5.8 |  | 1.07±1.3 | 5 |
| 19 | Seyahi, 2008 | Turkey | 156 | 83/73 | 39±6.6 | 0.68±0.08 | 239 | 162/77 | 40±8.7 | 0.71±0.09 | 12 | 8.1± 4.0 | 3.4±4.0 | 7 |
| 20 | Ozgen, 2010 | Turkey | 29 | 6/23 | 38±10 | 0.54±0.04 | 37 | 18/19 | 35±10 | 0.67±0.07 | 3.9±4.7 |  | 2.8 ±3.6 | 5 |
| 21 | Messedi, 2011 | Tunisia | 50 | 35/15 | 46±7 | 0.58±0.08 | 50 | 35/15 | 48±6 | 0.65±0.11 | 12.8±8.7 |  | 0.22±0.1 | 6 |
| 22 | Can 2012 | Turkey | 51 | 23/28 | 34±7.2 | 0.39±.09 | 36 | 14/22 | 39±6.4 | 0.56±0.12 |  |  |  | 4 |
| 23 | Hassan, 2012 | Egypt | 20 | 10/10 | 34±4.2 | 0.4±0.1 | 30 | 25/5 | 35±8.7 | 0.72±0.04 | 8.7±5.9 | 2.2±1.5 |  | 5 |
| 24 | Yurdakul, 2012 | Turkey | 20 | 12/8 | 45±8.2 | 0.59±0.09 | 40 | 24/16 | 44±5.4 | 0.69±0.15 | 5.9 |  |  | 6 |
| 25 | Caldas, 2013 | Brazil | 23 | 11/12 | 35±4.6 | 0.56±0.13 | 23 | 11/12 | 35±7.6 | 0.59±0.13 | 8.9±5.6 | 5.7±5.5 | 7.5 ± 12 | 6 |
| 26 | Uyar 2015 | Turkey | 25 | 12/13 | 32±9.2 | 0.6±0.16 | 26 | 12/14 | 35±9 | 1.02±0.3 | 7±5 |  | 0.65 ±4.2 | 8 |
| 27 | Icli 2016 | Turkey | 50 | 29/21 | 36±12 | 0.41±0.23 | 48 | 31/17 | 36±11.5 | 0.68±0.26 | 7.8±6.2 | 3.5±1.7 | 12.1±12.2 | 6 |
| 28 | Sereflican 2016 | Turkey | 26 | 5/21 | 31±5.3 | 0.56±0.11 | 31 | 12/19 | 35±9 | 0.48±0.08 | 8.1±6.7 | 1.3±1.4 | 1.24±1.8 | 6 |
| 29 | Yildirim 2016 | Turkey | 30 | 18/12 | 37±12 | 0.62±0.06 | 30 | 17/13 | 39±12.3 | 0.64±0.07 | 9.2±9.4 |  |  | 8 |
| 30 | Cure 2017 | Turkey | 84 | 58/26 | 36±9.5 | 0.48±0.11 | 84 | 60/24 | 37±10.5 | 0.61±0.14 | 12.5±9.8 | 4±2.3 | 5.7 ± 8.5 | 6 |
| 31 | El-Gazzar 2017 | Egypt | 38 | 30/8 | 35±6.5 | 0.42±0.12 | 38 | 30/8 | 36±7.8 | 0.78±0.32 | 7.6±5.1 | 2.5 ± 1.4 |  | 7 |
| 32 | Yolbas 2017 | Turkey | 40 | 29/11 | 43±13 | 0.64±0.08 | 49 | 28/21 | 37±11 | 0.62±0.09 | 7.0±6.0 | 14.8±17.2 | 1.37±2.2 | 5 |
| 33 | Alis 2018 | Turkey | 28 | 15/13 | 36±8.2 | 0.41±0.07 | 34 | 18/16 | 40±10 | 0.5±0.12 | 9.2±9.8 |  | 0.93±0.2 | 6 |
| 34 | Elden 2018 | Egypt | 20 | 15/5 | 36±9.4 | 0.47±0.04 | 20 | 17/3 | 32±9.9 | 0.64±0.03 | 9.6 ±6.0 | 3.8±1.55 | 1.35±1.7 | 5 |
| 35 | Icli 2018 | Turkey | 30 | 24/6 | 38±12 | 0.43±0.09 | 48 | 32/16 | 37±11.2 | 0.62±0.13 | 8±6.3 | 2.75±2 | 3.9 ± 4.3 | 6 |
| 36 | Kancilic 2018 | Turkey | 16 |  | 39±7.7 | 0.47±0.11 | 24 |  | 38±11 | 0.49±0.16 |  |  |  | 5 |
| 37 | Ozdemir 2018 | Turkey | 40 | 25/15 | 41±8 | 0.59±0.1 | 68 | 42/26 | 42.1±9 | 0.7±0.07 | 11.8±3.9 |  | 0.77 ± 0.2 | 7 |
| 38 | Ozisler 2019 | Turkey | 33 | 14/19 | 40±8 | 0.52±0.11 | 33 | 14/19 | 40±8.8 | 0.52±0.10 | 11.3 ± 6.5 |  | 0.42 ± 0.3 | 6 |
| 39 | Hassan 2020 | Egypt | 42 | 23/19 | 37±8 | 0.64±0.17 | 42 | 25/17 | 35±7.8 | 0.85±0.3 | 3.5±1.18 | 2.7±0.6 | 2.6±0.7 | 6 |
| 40 | El-Najjari 2020 | Egypt | 50 | 32/18 | 32±8 | 0.57±0.32 | 50 | 37/13 | 35±8.5 | 0.75±0.71 | 6.8±3.8 | 2.37±1.5 |  | 0.19 |
| 41 | Kaymaz 2021 | Turkey | 30 | 14/16 | 40±11 | 0.47±0.07 | 63 | 41/22 | 41±14 | 0.56±0.11 | 9 ± 4.4 | 1.7±1.07 |  | 8 |
| 42 | Uslu-Y 2021 | Turkey | 30 | 12/18 | 41±12 | 0.69±0.13 | 100 | 38/62 | 46±12 | 0.78±0.21 |  |  | 0.70±1.4 | 5 |
| 43 | Rodrigues 2022 | Brasil | 12 | 3/9 | 50±8 | 0.74±0.08 | 12 | 5/7 | 46±5.9 | 0.73±0.10 | 15±4.4 |  | 5.15±4.4 | 6 |
| 44 | Hussein 2022 | Egypt | 30 | 23/30 | 31±11 | 0.6±0.1 | 40 | 35/5 | 30.9±9.2 | 0.8±0.1 | 5.35 ±4.8 |  | 0.05±0.22 | 5 |
| 45 | Baykara 2022 | Turkey | 58 | 30/28 | 37± 6 | 0.41±0.1 | 58 | 32/26 | 40±10 | 0.51±0.1 | 10.3±8.03 | 3.5±1.7 | 12.5±11.9 | 7 |
| 46 | Ismail 2022 | Egypt | 50 | 38/12 | 29±5 | 0.56±0.25 | 50 | 38/12 | 30±6 | 0.80±0.29 | 2.32±1.1 | 5.8±1.7 |  | 5 |

Abbreviations. Ref: reference CTR: control; M/F male/female; IMT: intima media thickness; BD: Behcet’s disease; DD: disease duration; DA: disease activity; CRP: C-reactive protein; NOS: Newcastle Ottawa Score; No: number; mm: millimetre; x̅ ± σ: mean±standard deviation.

Table 2. Sensitivity analysis in the Behcet’s disease/control comparison

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 1. **Sensitivity analysis by meta-regression** | | | | |
|  |  |  |  |  |
|  | **Studies No** | **CC** | **95% CI** | **p-value** |
|  |  |  |  |  |
| NOQAS | 36 | -0.168 | -0.394, 0.058 | 0.14 |
|  |  |  |  |  |
| Mean age of BD | 36 | -0.077 | -0.130, -0.023 | 0.004 |
|  |  |  |  |  |
| Male/female ratio | 35 | 0.198 | 0.041, 0.355 | 0.01 |
|  |  |  |  |  |
| Disease duration | 27 | -0.056 | -0.146, 0.034 | 0.22 |
|  |  |  |  |  |
| Disease activity | 17 | -0.053 | -0.121, 0.013 | 0.19 |
|  |  |  |  |  |
| Atherogenic index | 23 | -0.086 | -2.512, 2.343 | 0.94 |
|  |  |  |  |  |
| Diastolic blood pressure | 22 | -0.005 | -0.074, 0.063 | 0.87 |
|  |  |  |  |  |
| Systolic blood pressure | 22 | 0.006 | -0.031, 0.044 | 0.74 |
|  |  |  |  |  |
| C-reactive protein | 23 | 0.024 | -0.023, 0.073 | 0.33 |
|  |  |  |  |  |
| Colchicine | 20 | -0.030 | -0.069, 0.086 | 0.12 |
|  |  |  |  |  |
| Cyclosporin A | 19 | -0.969 | -2.364, 0.895 | 0.33 |
|  |  |  |  |  |
| Azathioprine | 19 | -0.547 | -0.984, -0.110 | 0.01 |
| Azathioprine (minus outlier) | 18 | -1.176 | -2.049, -0.304 | 0.008 |
|  |  |  |  |  |
| 1. **Sensitivity analysis by subgroups** | | | | |
|  |  |  | |  |
|  | **Studies** | **Heterogeneity** | | **Effect size** |
|  |  |  |  |  |
| **By ethnicity** | **No** | **%** | **p-value** | **p-value** |
| Turkey + Egypt +Tunisia | 31 | 87.7 | <0.0001 | <0.0001 |
| Brazil + Korea | 5 | 64.2 | 0.02 | 0.07 |
|  |  |  |  |  |
| **By disease activity** |  |  |  |  |
| Reported | 17 | 87.8 | <0.0001 | <0.0001 |
| Not Reported | 19 | 87.7 | <0.0001 | <0.0001 |
|  |  |  |  |  |
| **By smoking status** |  |  |  |  |
| Reported | 16 | 83.2 | <0.0001 | <0.0001 |
| Excluded | 7 | 76.7 | 0.001 | <0.0001 |
| Not reported | 13 | 82.1 | <0.0001 | <0.0001 |
|  |  |  |  |  |
| **By vascular involvement** |  |  |  |  |
| Reported | 28 | 85.3 | <0.0001 | <0.0001 |
| Not reported | 8 | 86.6 | <0.0001 | <0.0001 |
|  |  |  |  |  |
| **By MI, IS, CKD** |  |  |  |  |
| Reported | 8 | 92.0 | <0.0001 | <0.0001 |
| Excluded | 26 | 84.1 | <0.0001 | <0.0001 |
| Not reported | 2 | 33.4 | 0.2 | <0.0001 |
|  |  |  |  |  |
| **By steroid intake** |  |  |  |  |
| Reported | 14 | 89.5 | <0.0001 | <0.0001 |
| Excluded | 8 | 84.7 | <0.0001 | <0.0001 |
| Not reported | 14 | 81.1 | 0.0001 | <0.0001 |
|  |  |  |  |  |
| **By any immune suppression\*** |  |  |  |  |
| Reported | 20 | 86.3 | <0.0001 | <0.0001 |
| Not reported | 16 | 87.8 | <0.0001 | <0.0001 |
|  |  |  |  |  |

Abbreviations. C: correlation coefficient; CI: confidence interval; BD: Behcet’s disease; NOQAS: Newcastle Ottawa Quality Assessment Score; MI: myocardial infarction; IS: ischaemic stroke; CKD: chronic kidney disease;

\*includes colchicine, cyclosporin A, azathioprine and anti-tumor necrosis factor-α

**Identification of new studies via other methods**

**Identification of new studies via databases and registers**

**Previous studies**

Records identified from:

Websites n = 3

Organisations n = 0

Citation searching n = 2

Records removed *before screening*: 0

Duplicate records removed n=10

Records marked as ineligible by automation tools n = 0

Records removed for other reasons n = 0

Records identified from databases:

Medline n=12

Embase n=26

Registers n=0

Studies included in previous version of review n =15

Reports of studies included in previous version of review n = 0

**Identification**

Records excluded by a human n=1

Records screened n=28

Reports not retrieved

n = 0

Reports sought for retrieval

n = 5

Reports not retrieved n=0

Reports sought for retrieval n=27

**Screening**

Reports excluded:

Paper without extractable data n=1

Abstracts incomplete data n=6

Paper on femoral arteries n=1

Paper on paediatric Behcet’s n=1

Review paper n=1

Reports excluded:

Prevalence data n = 1

Reports assessed for eligibility n = 4

Reports assessed for eligibility n=27

New studies included in review

n = 17

**Included**

Figure 1

Total studies included in review

n = 36



Figure 2



Figure 3



Figure 4



Figure 5



Figure 6