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Subclinical atherosclerosis in Behcet's disease: A systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate subclinical atherosclerosis in Behcet disease (BD), we performed a systematic review and meta-analysis of studies where atherosclerosis was determined by flow-mediated dilatation (FMD) and endothelial-mediated dilatation (EMD) and by measurement of intima media thickness (IMT) of carotid arteries.

Methods: Systematic search of EMBASE and PubMed databases from January 2000 to January 2014 according to PRISMA guidelines.

Results: Nine studies met the inclusion criteria on FMD/EMD, 11 on IMT and 4 on both. BD had lower FMD than controls (SMD = −0.89, 95% CI: −0.660 to −1.11, $p < 0.001$), which was confirmed by subgroup analyses on active and inactive patients (SMD = −1.17, 95% CI: −1.45 to −0.89 and SMD = −0.72, 95% CI: −0.97 to −0.46, $p = 0.0001$ for both). EMD was lower in BD but with a large estimate (SMD = 0.38, 95% CI: −0.79 to −0.03, $p = 0.06$, $I^2 = 82.2\%$). IMT was greater in BD and the large estimate (SMD = 0.95, 95% CI: 0.63–1.28, $p < 0.0001$, $I^2 = 87.6\%$) persisted after subgroup analysis on active and inactive patients ($I^2 = 88.4\%$ and 86.7%, respectively). Pooling IMT studies by a Newcastle Ottawa Scale of 5 and 6/7 yielded lower estimates (SMD = 0.54, 95% CI: 0.32–0.75, $p < 0.0001$, $I^2 = 58.7\%$ and SMD = 1.72, 95% CI: 1.35–2.09 $p < 0.05$, $I^2 = 48.6\%$).

Conclusions: FMD is impaired in BD even in inactive state and IMT is greater despite a degree of statistical heterogeneity that reflects the clinical heterogeneity of BD. Future prospective studies should account for risk stratification of atherosclerosis in BD.

Introduction

Behcet's disease (BD) is a systemic vasculitis characterised by recurrent oral and genital aphthosis, ophthalmic, cutaneous, articular, intestinal, urogenital, neurological, pulmonary and vascular manifestations [1]. The prevalence of vascular involvement may be as high as 40% according to the ethnicity of the population under study [2] and superficial thrombophlebitis accompanies vascular occlusion in almost 13% of patients [3]. The vascular manifestations are prevalently venous thrombosis as well as aneurysm formation; occlusions in the superior and inferior vena cava, in the supra-hepatic vein and in the cerebral vein range between 3% and 41% [4]; aneurysms commonly develop in the pulmonary arteries but do not spare femoral, popliteal, subclavian and common carotid arteries [2]. Arterial disease ranges from 0.5% to 17% [2] and though the prevalence of myocardial is only 1.1%, it occurs in relatively young BD patients in their third decade of life [5] and may be silent in up to 25% of cases [6]. The standardized mortality ratio calculated from 428 BD patients was 10-fold higher than the reference population in the age group of 14–24 years, with pulmonary artery aneurysms and Budd–Chiari syndrome the leading cause of death followed by arterial disease, though the standardized mortality ratio decreased in older age groups [7]. Given the chronic inflammatory background of BD, the issue of premature atherosclerosis was addressed over the last decades with conflicting evidence [8]. We therefore assessed the available data by performing a systematic review and a meta-analysis of the studies where atherosclerosis was assessed by flow-mediated vasodilation (FMD) and endothelial-mediated vasodilation (EMD) and by measurement of the intima media thickness (IMT) of carotid arteries, noninvasive markers of endothelial health in

Abbreviations: FMD, flow-mediated dilatation; EMD, endothelial-mediated dilatation; IMT, intima media thickness; NOQAS, Newcastle Ottawa Quality Assessment Scale.

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humans [9,10]. Our designated outcomes were the difference in FMD/EMD measured at the brachial artery and IMT measured at the carotid arteries derived from studies comparing BD patients with groups of individuals deemed as healthy controls.

Methods

Search strategy and selection criteria

A systematic review according to the PRISMA guidelines was carried out [11]; the PubMed and EMBASE databases were searched with the following terms: BD, atherosclerosis, flow-mediated vasodilatation and endothelial dysfunction, intima media thickness and carotid. A preliminary search had not revealed any articles on the topic before January 2000 therefore, the final search spanned from January 2000 up to January 2014. Review articles, case reports and surveys on aneurysms regardless of the vascular districts were excluded. The reference list of retrieved papers was checked for references that could have been missed.

Criteria for selecting articles

Two investigators (M.M. and P.R.J.A.) independently assessed all the papers generated for relevancy and considered those observational case–control studies addressing the difference in mean brachial artery FMD and EMD and mean carotid artery IMT between BD patients and matched healthy controls. To be included in the review, the articles had to meet the following criteria: (1) BD patients and matched healthy controls had to be compared for FMD/EMD at the brachial artery and IMT at the common carotid artery and (2) the technique for brachial artery and carotid artery IMT measurement had to be based on similar published protocols [9,10]. Exclusion criteria were the following: (1) articles not written in English, (2) studies not comparing BD patients with healthy controls and (3) measurement of IMT of carotid arteries and of brachial artery FMD/EMD that deviated substantially from predefined protocols [9,10]. M.M. and P.R.J.A. screened all abstracts and applied the eligibility criteria in order to identify studies that were appropriate for inclusion. They independently extracted data using predefined criteria, which included date of publication, population, language, study design, participant data and results.

Evaluation of the quality of the studies

The quality of the studies identified was assessed by the Newcastle Ottawa Quality Assessment Scale (NOQAS) for case–control studies specifically developed to assess quality of observational studies; however, all the studies evaluated and included in the meta-analysis are simply comparing two different groups because they had no real exposure to qualify as true case–control [12]. The scoring system covers three major domains (selection of cases and controls, comparability of selected groups and ascertainment of either the exposure or outcome of interest) and the resulting score may range between 0 and 8, a higher score representing a better methodological quality. Data were independently extracted into a standard electronic form and averaged and any discrepancies were resolved by consensus.

Outcome measures

The primary outcomes were the mean differences of FMD/EMD measured at the brachial artery and of IMT measured at the common carotid arteries. Data on mean values in both BD patients and matched healthy groups were collected to investigate the extent to which a pooled standardized mean difference between groups can be derived and considered as representative for BD patients. The secondary outcome was the difference of the pooled prevalence of subjects with carotid plaques derived from the BD and the healthy group.

Statistical analysis

Statistical analysis was carried out using STATA (StataCorp. 2013; Stata Statistical Software: Release 13; College Station, TX: StataCorp LP). Random effects meta-analyses for continuous outcomes (FMD, EMD and IMT) were employed as the estimates were the result of observational studies rather than planned experiments such as clinical trials. Besides clinical rich information, each study contained information on outcomes means, standard deviations and number of individuals in each group. The aim of the analysis was to investigate the average effect of the outcomes attributable to BD group; that is a standardized mean difference between BD patients and normal healthy individuals. Statistical heterogeneity among studies was assessed with chi square Cochran's Q test and with I^2 statistics, which measures the inconsistency across study results and describes the proportion of total variation in study estimates that are due to heterogeneity rather than sampling error. More specifically, an I^2 value of 0% indicates absence of heterogeneity and values less than 25% indicate low, between 25% and 50% moderate and over 50% high heterogeneity [13]. Subgroup analyses were based on clinical judgment, similarity of circumstances in which the studies have been conducted and the publication index. Whilst empirical methods such as Funnel plots [14,15] were part of preliminary investigations, the final estimates for an average effect on the BD outcomes relied on robust clinical and statistical compatibility, i.e., with evidence consistent with studies homogeneity [16]. Peto's method for pooled odds ratios was used to compare subjects with carotid artery plaques within BD and control groups because of its good performance when events are very rare [17].

Results

After completion of the screening process (Fig. 1), 24 studies met the criteria for inclusion in the analysis: 9 investigated FMD and/or EMD [18–26], 11 IMT [8,27–36] and 4 investigated both [37–40].

Quality of the studies

A score of ≥ 7 on the NOQAS was arbitrarily taken as a threshold for a good quality study: in the FMD/EMD section four studies ranked at ≥ 7 [19,21,23,26] (Table 1). In the IMT section part of the study only one study achieved a high score [8] (Table 2). Reasons for achieving a low score were poor selection criteria, poor documentation of patient and/or control inclusion/exclusion criteria, inadequate matching, poor comparability and failure to report disease duration and/or disease activity. The inter-rater reliability agreement of the two investigators (M.A. and P.R.J.A.) for NOQAS was 0.41 (95% CI: 0.0836–0.745) calculated by Cohen's kappa.

Analysis of flow-mediated vasodilatation

Data from 13 case–control studies comprising 554 patients with BD and 472 controls were pooled for the effect size of this outcome (Table 1). Random effect meta-analysis revealed wide heterogeneity amongst the studies ($I^2 = 95.6\%$, $p < 0.0001$) suggesting poor prospects for average pooled estimates. Having explored the causes for this heterogeneity, four studies [18,19,21,24] deviated slightly from the FMD methodology in that the cuff of the sphygmomanometer was applied at the forearm, a technique that yields a lower value than applying the cuff at the upper arm [41]. Removal of the four studies

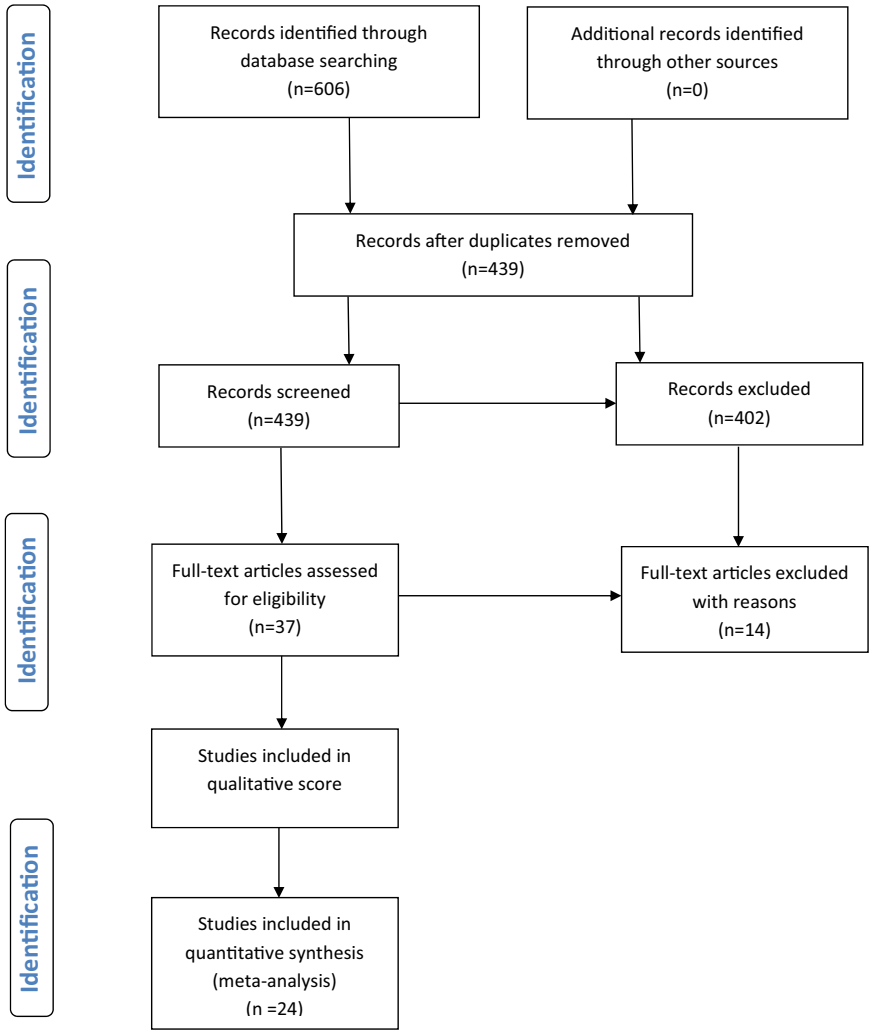

Fig. 1. Summary of literature search according to the Prisma flow chart. Full text excluded $n = 6$ investigated pulse wave velocity, $n = 3$ investigated coronary artery disease, $n = 1$ did not provide intima media thickness measurements, $n = 2$ repeated study on same patients in same year and $n = 1$ had no control group.

evidenced impaired FMD in the overall BD group (SMD = −0.89, 95% CI: −1.11 to −0.66, $p = 0.0001$, $I^2 = 45.3\%$) (Fig. 2A).

BD patients were then split according to active and inactive disease where possible: we arbitrarily considered patients with vascular involvement [20,37,38] as having active disease and pooled them with active disease patients proper [20,22,23,25,26,40]: FMD was significantly lower with moderate heterogeneity (SMD = −1.17, 95% CI: −1.45 to −0.89, $p = 0.0001$, $I^2 = 37.5\%$) (Fig. 2B). Pooled data from inactive disease patients [20,22,23,25,26,37–39] also revealed impaired FMD with moderate heterogeneity (SMD = −0.74, 95% CI: −0.97 to −0.51, $p = 0.0001$, $I^2 = 35.5\%$) (Fig. 2C).

Analysis of endothelial-mediated vasodilatation

Of the 13 case–control studies evaluating FMD, eight also evaluated EMD (Table 1). Data of these eight case–control studies comprising 360 BD patients and 306 controls were pooled for this outcome. Random effect meta-analysis showed some evidence for impaired EMD in BD (SMD = 0.380, 95% CI: −0.027 to 0.788, $p = 0.06$) but with elevated heterogeneity ($I^2 = 82.2\%$).

Analysis of intima media thickness of carotid arteries

Data from 15 case–control studies comprising 848 patients with BD and 677 controls were pooled for the effect size of this outcome (Table 2). Random effect meta-analysis revealed wide heterogeneity ($I^2 = 87.6\%$, $p < 0.0001$ for both) invalidating the pooled estimate (Fig. 3A). All investigators measured IMT at the common carotid artery but for one study where the authors presented the average IMT taken at the distal common carotids, at the far wall of the carotid bulbs and at the far wall of the internal carotid artery [8]. Indeed studies varied with regards to inclusion criteria: $n = 3$ compared patients with and without vascular involvement and provided separate measurements [27,37,38], $n = 1$ provided separate data for patients with and without systemic involvement (mucocutaneous only) [36], $n = 3$ studies included a mixture of active and inactive disease [32,34,40] of which one provided separate data for active and inactive disease [32], $n = 3$ studies were carried out on patients with low or inactive disease [31,33,35], $n = 2$ were carried out on patients without vascular and/or systemic involvement [38,39] and $n = 2$ were carried out in patients without cardiovascular risk factors [28,30].

To reduce heterogeneity, we arbitrarily aligned patients according to (1) inactive disease, (2) no vascular involvement and (3) no systemic involvement. We therefore extracted data of patients without vascular involvement from the three studies where these data were provided separately [27,37,38], we extracted the data of the patients without systemic involvement [36], we maintained the data of the patients with inactive disease [32] and we excluded the only study where inactive and active disease patients could not

Table 1
Demographics, flow and endothelial-mediated vasodilatation and Newcastle Ottawa Scale for controls and Behcet's disease

Study	Controls					Behcet's Disease						NOS
	N	M/F	Age	FMD	EMD	*N*	M/F	Age	Disease status	FMD	EMD	
Ozuguz et al. [26]	20	8/12	37 ± 10.3	14.3 ± 5.52		40	15/25	39.6 ± 9.9	AD/ID	9.4 ± 3.5		7
Yurdakul et al. [39]	20	12/8	45.4 ± 8.2	16.36 ± 4.62	20.05 ± 1.57	40	24/16	44.9 ± 5.4	Non vasc/non S	13.34 ± 4.92	16.31 ± 2.45	6
Yuksekkaya et al. [25]	25	15/10	35 ± 10	26 ± 18		30	16/14	39 ± 12	AD/ID	10.83 ± 12.62		5
Can et al. [40]	51	23/28	34.5 ± 7.2	9.04 ± 4.8		36	14/22	39.6 ± 6.4	AD/ID	5.2 ± 3.8		5
Acigoz et al. [24]	40	22/18	35.2 ± 9.8	15.5 ± 1.6	18.1 ± 1.3	40	24/16	34.7 ± 8.6	AD	5.2 ± 1.4	17.7 ± 1.3	6
Caliskan et al. [38]	35	19/16	38.1 ± 7.9	18.5 ± 8		53	24/29	36.75 ± 6.35	VD/non V	16.4 ± 8.05		4
Ulusoy et al. [23]	29	24/5	29.5 ± 5.8	21.4 ± 6.4	19.2 ± 5.3	28	24/4	31.1 ± 7.1	MC	15.7 ± 2.4	18.4 ± 6.2	7
Caliskan et al. [22]	35		35.9 ± 4.6	15.83 ± 5.29		35		36.5 ± 6.8	AD/ID	11.21 ± 7.96		6
Protogerou et al. [21]	90	58/32	40.1 ± 1.2	5.7 ± 0.4	13.4 ± 0.7	87	29/58	39.5 ± 2.7	AD/ID	4.1 ± 0.4	12.8 ± 0.5	7
Kayikcioglu et al. [20]	30	18/12	41 ± 8	20.4 ± 9.1	25.3 ± 10.5	65	40/25	38 ± 9	ID/V/non V	11.4 ± 6.3	21.6 ± 20.5	6
Oflaz et al. [37]	46	37/9	36.2 ± 9.3	14.41 ± 3.39	17.82 ± 5.27	50	41/9	38.7 ± 9.3	V/non V	10.41 ± 3.85	18.8 ± 6.06	6
Ozdemir et al. [19]	30	20/10	36 ± 8	4.4 ± 3.4	16.1 ± 3.9	31	19/12	37 ± 7	ID/no CVD	1.4 ± 3	16.4 ± 3.7	7
Chambers et al. [18]	21	10/11	40 ± 2	5.7 ± 0.9	19.7 ± 1.9	19	9/10	41 ± 2	AD	0.7 ± 0.9	19.7 ± 1.7	6

N: numbers; M/F: male/female; AD: active disease; ID: inactive disease; V: vascular; CVD: cardiovascular risk disease.

Table 2
Demographics, intima media thickness and Newcastle Ottawa Scale for controls and Bechet's disease patients

Study	Country	Controls					Behcet's disease							NOS
		N	M/F	Age	IMT	Pl%	*N*	M/F	Age	Disease status	IMT	Pl %	Dis Dur	
Caldas et al. [36]	Brasil	23	11/12	35.4 ± 6	0.561 ± 0.134	NM	23	11/12	35 ± 7.6	Sys/MC	0.594 ± 0.138	NM	8.9 ± 5.6	6
Can et al. [40]	Turkey	51	23/28	34.5 ± 7.2	0.39 ± 0.09	NM	36	14/22	39.6 ± 6.4	AD/ID	0.56 ± 0.122	NM		4
Hassan et al. [35]	Egypt	20	NA	34.5 ± 4.2	0.4 ± 0.1	0	30	25/5	35.8 ± 8.7	ID	0.72 ± 0.4	16.7	8.7 ± 5.9	5
Yurdakul et al. [39]	Turkey	20	12/8	45.4 ± 8.2	0.59 ± 0.09	NM	40	24/16	44.9 ± 5.4	Non sys/non V	0.69 ± 0.15	NM	5.9	6
Ozgen et al. [34]	Turkey	29	6/23	38 ± 10	0.547 ± 0.04	NM	37	18/19	35.3 ± 10	AD/ID	0.675 ± 0.07	NM	3.9 ± 4.7	5
Messedi et al. [33]	Tunisia	50	35/15	46 ± 7	0.581 ± 0.087	2	50	35/15	48 ± 6	ID	0.658 ± 0.112	10	12.8 ± 8.7	6
Hong et al. [32]	Korea	20	13/7	40.2 ± 5.1	0.59 ± 0.11	0	40	24/16	39.1 ± 8.5	AD/ID	0.71 ± 0.17	2.5	5.2 ± 4	6
Caliskan et al. [38]	Turkey	35	19/16	38.1 ± 7.9	0.46 ± 0.82	NM	53	24/29	36.75 ± 6.35	V/non V	0.515 ± 0.012	NM	4.08 ± 4.5	4
Ozturk et al. [31]	Turkey	21	15/6	35 ± 8	0.57 ± 0.14	NM	21	15/6	35.8 ± 8.6	ID	0.86 ± 0.18	NM	7.3 ± 5.8	5
Seyahi et al. [8]	Turkey	156	83/73	39 ± 6.6	0.68 ± 0.08	15.38	239	162/27	40 ± 6.6		0.71 ± 0.09	26.36	12	7
Rhee et al. [30]	Korea	53	26/27	37.1 ± 7.2	0.52 ± 0.06	0	41	20/21	37.6 ± 7.9	No CVD risk	0.52 ± 0.09	0	6.5 ± 0.6	6
Ozturk et al. [29]	Turkey	34	21/13	34.6 ± 8.5	0.54 ± 0.13	0	34	21/13	34.6 ± 8.5	Non V	0.81 ± 0.17	17.6	7 ± 5.2	5
Oflaz et al. [37]	Turkey	46	37/9	36.2 ± 9.3	0.55 ± 0.14	NM	50	41/9	38.7 ± 9.3	V/non V	0.69 ± 0.15	NM		6
Keser et al. [28]	Turkey	77	46/31	37.2 ± 7.8	0.48 ± 0.09	0	114	68/46	38.1 ± 9.4	No CVD risk	0.55 ± 0.14	4.38	10.08 ± 6.58	6
Alan et al. [27]	Turkey	42	25/17	40 ± 9	0.59 ± 0.12	5	40	19/21	39.8 ± 8	V/non V	0.81 ± 0.12	10		5

N: numbers; M/F: male/female; IMT: intima media thickness carotid; Pl%: plaque percentage; Dis Dur: disease duration; NOS: Newcastle Ottawa Scale; NA: not available; AD: active disease; ID: inactive disease; V: vascular; CVD: cardiovascular risk disease; NM: not mentioned.

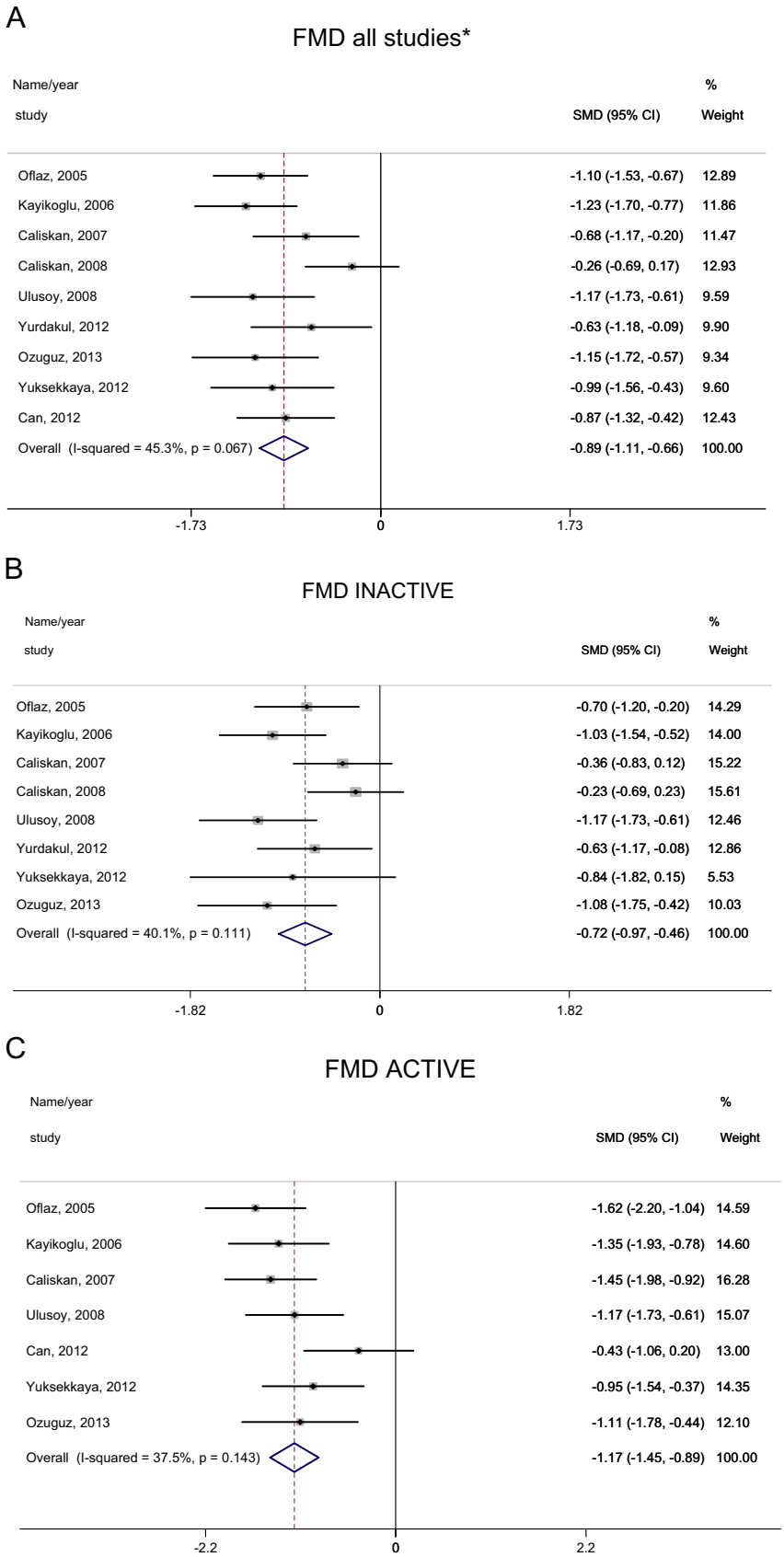

Fig. 2. Forest plots of flow-mediated dilation (FMD) on (A) all studies, (B) on inactive Behcet's disease and (C) on active Behcet's disease.

be separated [34] and repeated the analysis alongside with the remaining studies. The random effect meta-analysis showed significant heterogeneity ($I^2 = 80.1\%$, $p < 0.0001$). Therefore, we analysed separately patients with no vascular involvement and no cardiovascular risk factors [27–30,37–40] and still attained wide heterogeneity ($I^2 = 82\%$, $p < 0.0001$).

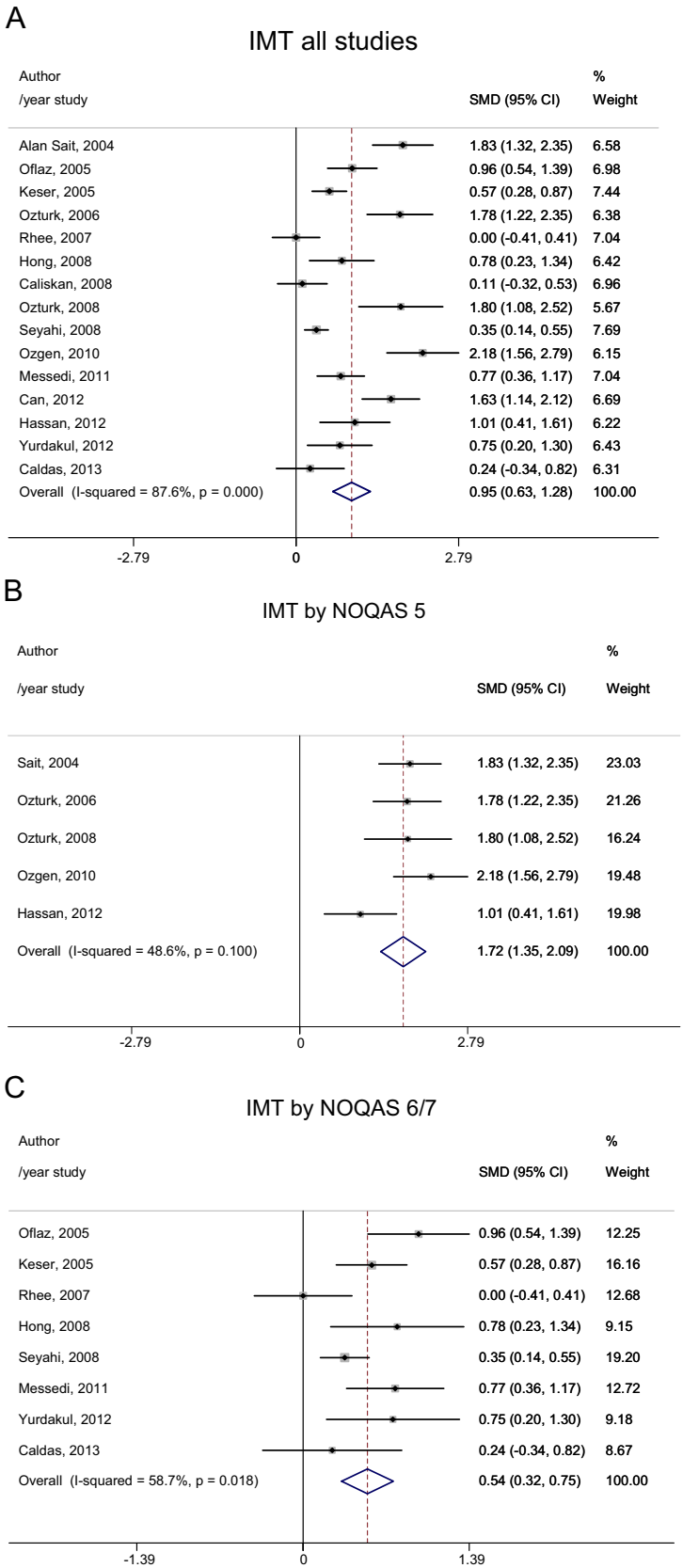

Fig. 3. Forest plots of the intima media thickness (IMT) of carotid arteries on (A) all studies, (B) on studies with a NOQAS of 5 and (C) on studies with a NOQAS of 6/7.

To reduce heterogeneity in an opposite fashion, we arbitrarily pooled patients according to (1) active disease, (2) vascular involvement and (3) systemic involvement. We extracted data from patients with systemic involvement [36] and with vascular disease [27,37,38] on the assumption they implied active disease, we removed two studies with a mixture of active and inactive

patients [34,40] and repeated the random effect analysis that yielded again wide heterogeneity (I^2 = 86.8%).

We finally re-approached the meta-analysis according to the NOQAS: pooled data from studies with a NOQAS of 5 revealed larger IMT in BD patients than controls (SMD = 0.54, 95% CI: 0.32–0.75, $p < 0.0001$) with moderate to high heterogeneity (I^2 = 58.7%) (Fig. 3B) and pooled data from studies with a NOQAS of 6/7 also revealed moderate heterogeneity (I^2 = 58.7)(Fig. 3C).

Analysis of carotid plaque frequency

The presence of carotid plaques was investigated in eight studies [8,27–30,32,33,35] but we pooled only 7 case–control studies comprising 547 BD patients and 397 controls for the effect size of this outcome because one study had found plaques neither in BD subjects nor in controls [30]. The pooled prevalence of subjects with carotid plaques was 12% in the BD population (range from 4% to 18%) and 3.7% (range from 2% to 9%) in the control group. Peto's meta-analysis revealed an OR of 2.853 (95% CI: 1.814–4.487; $p = 0.0001$) with no heterogeneity (I^2 = 4.18) (Fig. 4), indicative of a strong prevalence of patients with plaques in the BD populations under consideration.

Discussion

This meta-analysis shows that FMD is impaired in BD patients: in keeping with the possibility that incident disease activity would have a major impact on FMD at the time of the endothelial investigations we found a greater degree of FMD impairment in patients with higher disease activity; however, FMD impairment during inactive disease means that BD patients are at risk of arterial damage in the long term. Some of the FMD studies also assessed EMD but the apparent difference between BD and controls was offset by wide statistical heterogeneity. While EMD depends on exogenous nitric oxide for the relaxation of smooth muscle cells within the vasculature, FMD relies mostly on the biological activity of endogenous nitric oxide which may be impaired both in relation to disease activity [42] and to type vascular involvement [43] in BD and shows age and sex dependency [44].

In an "inflammatory vascular disease" such as Behcet's [1], the endothelium may be acutely affected in active disease and chronically affected in apparently inactive disease eventually contributing to atherosclerosis: in cross-sectional studies incident disease status, and drug intake may have more immediate impact on functional measurements such as FMD/EMD than a more "static" measurement such as IMT. Several inflammatory, immunological and metabolic factors may contribute to early FMD dysfunction in BD: elevated plasma concentration of homocysteine [19,26] C-reactive protein [22,26], enhanced oxidative [24] and nitrative stress [45], impaired biological activity of nitric oxide [42,43] and an abnormal lipid profile [19,22,43]. However, because these data were not uniformly present in the studies included in the meta-analysis we could not perform a meta-regression that would have explained to what extent the abovementioned factors contributed to the FMD difference between BD and controls.

Nevertheless, given the independent predictive value of impaired FMD on cardiovascular risk [46] most of the BD patients in this meta-analysis were diseased long enough to have accrued arterial wall damage expressed as a greater IMT and or as plaque. In fact our meta-analysis revealed overall thicker intima media in BD patients in keeping with the atherosclerosis hypothesis though pooled data from all studies revealed high statistical heterogeneity. We were not surprised of this result as we know that BD is a very heterogeneous disease in itself. On the other hand, the data we obtained on the prevalence of BD patients with plaques were devoid of heterogeneity and very convincing in terms of significance. The studies included in this part of the meta-analysis were carried out on small cohorts of BD patients that varied according to disease activity, presence or absence of systemic disease, of vascular involvement and of cardiovascular risk factors. Moreover, BD patients were on different pharmacological treatments for varied lengths of time and the gender difference so relevant in atherosclerosis was poorly accounted for but in one large study where IMT was unaffected by sex [8].

Additionally, some sociocultural atherosclerotic risk factors such as diet and physical activity can vary according to different geographical regions, though most of the studies of this meta-

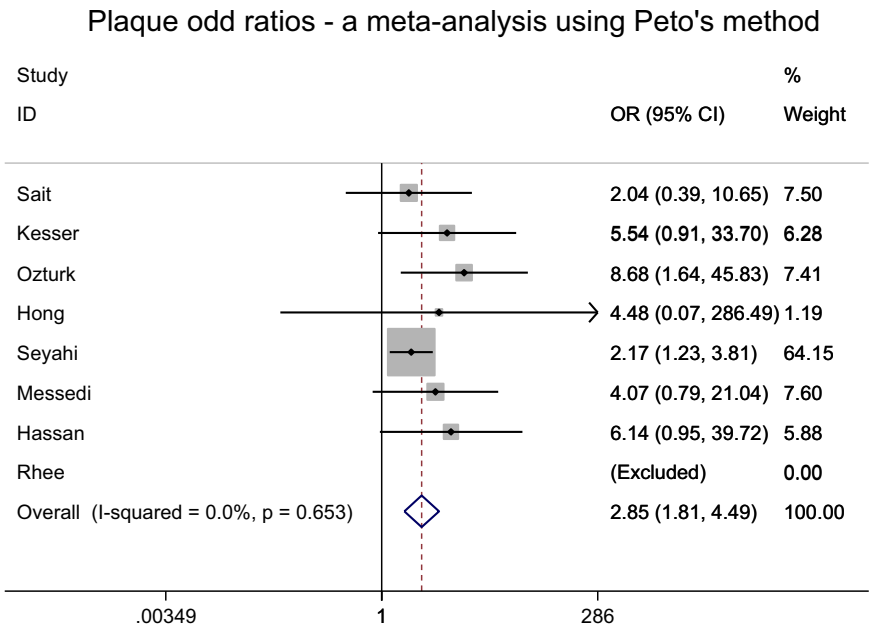

Fig. 4. Individual study contribution to the pooled odds ratio for the presence of plaque in patients with Behcet's disease.

analysis were from Turkey and unlikely to introduce an ethnic bias. Interestingly, however, when the meta-analysis was re-run on the same studies pooled by the NOQAS there was less variance than pooling by subgroups of disease activity: this suggests that quality, reflected also in the small size of the studies that inherit large variability, represents a major determinant of our IMT meta-analysis. Nevertheless, we present robust statistics based on clinically compatible and comparable papers that rule against the possibility of publication bias evaluated by an often misleading empirical graphical method; on the other hand, the results may suffer from aggregation bias because the analysis was not based on the individual data of the participants [47]. The risk of venous thrombosis is 14-fold higher and that of arterial thrombosis 5.4-fold higher in BD [48]: immune suppression decreases the risk of recurrent venous occlusion by a hazard ratio of 0.27 [49] and the annual incidence of arterial disease by almost fourfold [50], though the presence of venous and arterial involvement is negatively associated with complete remission [50].

In the general population, there is some evidence that subjects who suffer idiopathic venous thrombosis have a 60% higher risk of developing atherosclerotic disease [51], confirmed by a cohort study from Denmark where a 20–40% risk persisted 20 years after the thrombotic event [52]. The patients in these studies are at least a decade older than the BD patients of our meta-analysis, and although not all of the BD patients in our meta-analysis suffered venous thrombosis, the issue of atherosclerosis in BD should be evaluated also in older BD populations.

Conclusion

Atherosclerosis expressed as impaired FMD, greater IMT and plaque frequency represents a clinical feature of BD in their fourth decade; however, as cross-sectional studies cannot prove causality, future studies should be adequately powered and prospectively designed with serial FMD and carotid ultrasound measurements to understand which subgroups of BD patients are at greater risk of developing atherosclerosis and define whether they should receive risk factor modifications and/or preventative measures at an early stage of endothelial dysfunction to retard the development of additional cardiovascular disease.

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