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Mira Merashli, Tommaso Bucci, Jose Delgado-Alves, Paul R.J. Ames

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RELEVANCE OF VEIN WALL THICKNESS IN BEHCET'S DISEASE:

A SYSTEMATIC REVIEW AND META-ANALYSIS

Mira Merashli[1], Tommaso Bucci[2], Jose Delgado-Alves[3], Paul RJ Ames[3,4].

[1]Department of Rheumatology, American University of Beirut, Beirut, Lebanon; [2]Department of General Surgery, Surgical Specialties and Organ Transplantation "Paride Stefanini", Sapienza University of Rome, Rome, Italy; [3]Immune Response & Vascular Disease Unit, CEDOC, Nova University Lisbon, Rua Camara Pestana, Lisbon, Portugal; [4]Department of Haematology, Dumfries Royal Infirmary, Cargenbridge, Dumfries, UK.

Corresponding author: Dr Paul RJ Ames, Department of Haematology, Dumfries Royal Infirmary, Cargenbridge, Dumfries, DG2 7AH, Scotland, UK.

E-mail: paxmes@aol.com; phone 0044 1387 246246, fax: 0044 1387 216246;

ORCID: 0000-0003-0165-9651

Highlights

Vein wall thickness is a vascular feature of Behcet's disease

Vein wall thickness is explained by age, male gender and disease duration

Vein wall is thicker in Behcet's patients with a history of previous venous occlusion

ABSTRACT

Objectives: To perform a meta-analysis on articles evaluating the common femoral vein wall thickness (VWT) in Behcet's disease and its possible clinical, laboratory and treatment correlates (BD). **Methods**. Systematic search of EMBASE and PubMed databases from inception to October 2023; we employed random effect meta-analyses for continuous outcomes**. Results.** The meta-analysis included 9 case-control and 1 cohort study: the VWT was greater in BD (n=650) than in controls (n=396) (p<0.0001) with wide heterogeneity (I^2=94.4%); a sensitivity analysis that included mean age of BD participants, gender, disease duration and activity, C-reactive protein, smoking status, immune-suppressive and anti-inflammatory medication, revealed that the heterogeneity variance was partly explained by age (p<0.0001), male gender (p=0.03), disease duration (p<0.0001) and smoking (p=0.06). The VWT was greater in BD with thrombotic/vascular (n=189) than in non-thrombotic/vascular BD (n=140) (p=0.006) with no heterogeneity **Conclusion.** VWT is greater in BD than controls: age, male gender, disease duration and smoking relate to VWT that was greater in BD patients with a history of thrombotic/vascular disease. Prospective studies are required to assess whether VWT may be considered a vascular marker of disease activity.

Key words: Behcet's disease, venous wall thickness

1. INTRODUCTION

Behcet's disease (BD) is a vasculitis characterised by an elevated vascular burden associated with long-term morbidity and mortality [1]: on the venous side, recurrent thrombophlebitis, occlusions affecting upper and lower limbs, superior and inferior vena cava, splanchnic and cerebral circulation are frequent and often recurrent; on the arterial side, aneurysms, stenoses and occlusions can be seen, mostly in the aorta and in the pulmonary vessels [2]; thickening of the intima media of carotid arteries is consistent with premature atherosclerosis particularly in the earlier years of BD [3] whereas thickening of veins had been investigated

for the first time in 2014 as a means of detecting venous inflammation that could predispose to venous thrombosis [4]. Since that seminal observation several studies have addressed VWT and this systematic review and meta-analysis attempts to assess consistency throughout the studies and to identify clinical and/or laboratory variables that may relate to venous thickening.

2 MATERIAL AND METHODS

2.1 Research hypothesis and outcome measures

To evaluate the consistency of venous wall thickening (VWT) in BD we calculated the standardized mean VWT [or intima media thickness (IMT)] differences between BD patients and healthy controls and between BD subgroups without or with certain clinical features, and these represented our outcome measures. For this meta-analysis we averaged the mean of the right and left VWT and used such average in all our analysis.

2.2 Search strategy

The Medline and Embase databases were screened from inception to October 2023 using the Medical Subject Headings ("Behcet's disease" [All fields] AND ("venous thickening") [All fields]. The final search was done on the 10th of October 2023. To reduce the effect of possible publication bias, the same search terms in natural language were used to screen the Grey Literature via the DANS EASY Data Archive, the OAlster Date base as well as Google. We also reviewed the reference list of the articles included in the systematic review to evaluate whether we had missed any relevant articles.

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

2.4 Exclusion criteria: 1) VWT 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 FB, checked independently the resulting citations for relevancy and removed duplicates (via EndNote); MM and JDA 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. JDA and MM also screened the reference list of retrieved papers for papers that could have been missed. Eventual articles not written in English were translated.

2.5 Data extraction/protocol

MM and PRJA independently extracted data from the articles that considered: year of publication, study design, sample size, demographic data, disease duration, disease activity, smoking status, clinical features of BD, inflammatory markers, outcomes (mean or median) and dispersion measures (standard deviation or confidence intervals). In addition, and where study allowed, we calculated and charted the male/female ratio, the smoker/non-smoker ratio, the ratio of users/non-users of anti-inflammatory and immune suppressive medication 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). Because our data derive from case-control and observational studies with no therapeutic intervention, we did not subscribe the systematic review to a registry with; the electronic sheets with collected data will be available on request.

2.6 Evaluation of the quality of the studies

The quality of the studies included in the meta-analysis was determined by the Newcastle Ottawa Quality Assessment Scale for observational case-control studies and for cohort studies [6]; two investigators, MM and FG, scored the studies independently and PRJA resolved any discrepancies. The inter-rater agreement (Cohen kappa) between the two assessors was 0.597 (95% CI 0.325, 0.788).

2.7 Statistical analysis

The Comprehensive Meta-analysis (Version 3, Englewood, NJ 2013, USA) software was employed for the statistical analysis; because our estimates derived from cross-sectional observational studies and not from clinical trials, we performed random effect meta-analysis for continuous outcomes [7]. The I^2 statistics assessed study heterogeneity: a value of 0% indicated no heterogeneity; values less than 25% indicated low, between 25% and 50% moderate and over 50% high heterogeneity [8]. We did not assess publication bias because a funnel plot with fewer than 10 studies does not distinguish chance from real asymmetry (9). Sensitivity analyses were performed by meta-regression and by subgroup according to results, clinical plausibility and judgement.

3 RESULTS

3.1 Number and type of studies in quantitative assessment

The database search up to October 2023 yielded 54 records; following the screening and exclusion processes indicated in Figure 1 we included 9 cross-sectional case-control and 1 cohort study that examined the relationship between BD and VWT [10-19] (Table 1). One study reported patients with complete and incomplete BD: we included only the patients with complete BD in the meta-analysis [16]. Only one study provided prospective follow-up data [12].

3.2 Reporting of disease activity

The studies varied in their disease activity scoring systems: two studies adopted the Behçet`s Disease Current Activity Form [15, 17] two studies adopted the Behcet's Syndrome Activity Score [10, 13], one study used both scoring systems [14] whereas the remaining did not report disease activity.

3.3 Varied characteristics of the studies

Three studies reported IMT (17–19), two of which reported also VWT (17, 19), the remaining studies reported VWT alone.

3.4 Conversion of median and range/interquartile range into mean and standard deviation

Data reported as median and range CRP (12, 13) or as median and interquartile range VWT (14, 16, 17, 18) were converted into mean and standard deviation according to a published method (20).

3.5 Thickness of common femoral vein in Behcet's disease and in controls

The effect size of pooled data from 8 adult and 1 paediatric case-control studies comprising 650 BD patients and 396 controls favoured BD ($p<0.0001$) with wide heterogeneity (I^2=94.1%, $p<0.0001$) (Figure 2A). Neither effect size nor heterogeneity changed after removal of the paediatric study (16) ($p<0.0001$, I^2=94.8%, $p<0.0001$). A sensitivity analysis by meta-regression evaluated mean age of BD participants, male to female ratio, disease duration and activity, and ratio of users/non-users of colchicine, azathioprine and anti-tumour necrosis factor as moderator variables: part of the heterogeneity variance was positively explained by age, disease duration, smoking, azathioprine and anti-tumour necrosis factor use and to a much lesser extent by male gender (Table 2A). A sensitivity analysis by subgroups assessing disease activity and smoking status revealed that smoking affected the heterogeneity variance (Table 2B). Pooled data from two studies comprising 117 BD patients and 92 controls evaluated the IMT of the CFV (17,19): the effect size was neutral with wide heterogeneity (I^2=96.3%, $p<0.0001$) (not shown).

3.6 Thickness of greater saphenous vein in Behcet's disease and in controls

The effect size derived from pooled data on 3 adult case-control studies comprising 215 BD patients BD and 139 controls favoured BD ($p<0.0001$) with wide heterogeneity (I^2=80.5%, $p=0.006$) (Figure 2B).

3.7 Thickness of common femoral vein by vascular involvement

Five studies explored the relation between vascular involvement and the full thickness of the CFV: these comprised 189 BD patients with and 140 patients without vascular involvement; the effect size favoured vascular involvement (p=0.0001) with no heterogeneity (Figure 3A). We did not include in this analysis a sixth study that compared CFV thickness according to major organ involvement but not vascular involvement (13). Two studies explored the relation between vascular involvement and the IMT of the CFV (17.18): these comprised 35 BD patients with and 60 patients without vascular involvement; the effect size was neutral with high heterogeneity (I^2=52.6%, p=0.14) (not shown).

3.8 Thickness of greater saphenous vein by vascular involvement

Three studies explored the relation between vascular involvement and thickness of GSV: these comprised 104 BD patients with vascular involvement and 97 patients without such involvement; the effect size favoured vascular involvement (p<0.0001) with no heterogeneity (Figure 3B).

4 DISCUSSION

The effect size of our meta-analysis indicates that the CFV and GSV thickness may be considered a vascular feature of BD, with several factors that explained the heterogeneity variance: indeed, age and disease duration of BD participants related to CFV thickness, implying that the latter may increase over time, in keeping with the age-dependent increase in the wall thickness of the GSV of health people (21); measured in four studies only (12, 13, 15, 19), CRP explained part of the heterogeneity variance hinting that inflammation is involved in the VWT alongside male gender, more prone to vascular disease than female gender [22].

Smoking slightly explained the heterogeneity variance: smoking is not a risk factor for BD development (23, 24) but favours inflammasome activation in macrophages (25) and endothelial cells (26), particularly in patients with the glutathione S transferase polymorphism (27), contributing eventually to an increased risk of vascular involvement in established BD patients. Indeed, venous, as well as arterial endothelial cells, lose their antiadhesive and antithrombotic properties and become lined with fibrin in the thrombo-inflammation process mediated by hyperactive neutrophils (2); moreover, veins are equipped with a denser meshwork of vasa vasorum than arteries (28) and the vasa vasorum undergo the same inflammatory fate as the major veins they supply eventually contributing to VWT.

The latter was consistently greater in the CFV and GSV of BD patients with a history of venous thromboembolism (VTE), even if the occlusions did not directly affect either CFV or GSV. VTE is followed by a localized sterile immune response mediated by the Toll receptor 9 (29), a pathway involved in the inflammasome activation in BD (30) that may add to the background inflammation and promote further vein thickening: this post-thrombotic thickening was described outside the vasculitis setting but limited to the veins affected by the previous occlusion (31), indirectly highlighting that VTE in BD has systemic effects beyond the occluded site; indeed, VTE was associated with greater IMT in BD (3)

Finally, clots not only occlude the internal vasa vasorum preventing the supply of oxygen and nutrients from the venous lumen into the vein layers, but also create a resistance to flow in the external vasa vasorum, from the adventitia into the vein wall, with eventual trapping of mononuclear cells that enhance local inflammation and thickening (32). From the drug perspective, azathioprine and anti-tumour necrosis factor explained the heterogeneity variance, indicating that at the time of VWT measurements patients either had a high disease activity or major organ involvement necessitating best available treatment (15)

Several factors affect the current meta-analysis: 1) the limited number of articles included as only 10 articles have been published on the topic; 2) the cross-sectional nature of the studies, bar one with a prospective arm (12); 3) the different disease activity systems

prevented a proper understanding of their relation with VWT; 4) the paucity of the studies that measured CRP, preventing an adequate understanding of the relation between inflammation and VWT; 5) the explanatory effect of the immune suppressive or biologic agents on VWT should be interpreted with caution because: a) only few studies reported the drugs used, b) we inserted in the meta-regression the ratio of users/non-users of a given drug rather than drug doses that were not available, c) patients might have been on multiple drugs.

4.1 Conclusions

Despite these shortcomings our meta-analysis indicates that: 1) VWT represents a vascular feature of BD the significance of which needs expanding, also in relation to the vasa vasorum; 2) VWT is certainly explained by age, male gender, disease duration and possibly by smoking, inflammation and by the immune-suppressive and anti-inflammatory use; 3) prospective studies are required to investigate whether the latter drugs modify VWT and to explain whether VWT might represent either a general disease activity marker or a more specific "vascular" disease activity marker.

Declaration of competing interests

None of the authors declares any financial or non-financial competing interest

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Table 1. Demographics, clinical and therapeutic variables of control and Behcet's disease participants

Ref No	Study type Author Year	CTR No	M/F	Age years $\bar{x} \pm \sigma$	CFV mm $\bar{x} \pm \sigma$	BD No	M/F	Age years $\bar{x} \pm \sigma$	CFV mm $\bar{x} \pm \sigma$	DD years $\bar{x} \pm \sigma$	S/NS ratio	A/NA ratio	C/NC ratio	aT/NaT ratio
	Case control													
	Alibaz-Oner 2019	37	37/0	30±5	0.4±0.2	61	61/0	32.6±5.9	0.8±03	9.6±6				
	Seyahi 2019	50	43/7	36 ± 6.8	0.56±0.05	100	86/14	37±48.5	0.8[illegible]34	10.5±6.2	1.85	0.88	0.78	0.07
	Alibaz-Oner 2021a	51	40/11	30±6	0.346±0.1	152	110/42	[illegible]	0.775±0.2	8.8±7	0.52			
	Alibaz-Oner 2021b	38	21/17	37.1±7	0.34±0.1	69	33/36	37.9±8	0.78±0.2	10±8	0.38			
	Kaymaz 2021	30	14/16	40 21-60	0.52±1.45	63	41/22	38 20-71	0.81±0.275		0.46	0.5	0.96	0.18
	Tezcan 2022	52	32/20	36±12	0.44±0.105	54	32/22	38±10	0.83±0.25	7.3±6		2.17	0.46	
	Atalay 2023	27	16/11	19±38	0.545±0.118	13		19.4±2.4	0.72±0.151	5.3±4.8		0.44	12	0.71
	Eturk 2023	70	41/29	34±10	0.565±0.09	84	50/34	37±9	0.68±0.115	4.7	0.21		5	
	Sevik 2023	41	22/19	36.8 ± 8.3	0.195±0.04	53	32/21	39±10.3	0.745±0.165	7±7.4	0.51	1.3	1.2	0.10
	Cohort													
	del Peral-Fanjul 2023					42	23/19	48±12.8	0.545±0.141	13±9.4				

Abbreviations. Ref: reference; No: number; CTR: control; M/F male/female; CFV: common femoral vein; BD: Behcet's disease; DD: disease duration; S/NS smokers/non-smokers; A/NA: azathioprine/non-azathioprine; C/NC: colchicine/non-colchicine; aT/NaT: anti-tumor necrosis factor/ non-anti-tumour necrosis factor; mm: millimetre; $\bar{x} \pm \sigma$: mean ± standard deviation

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

A) Sensitivity analysis by meta-regression				
	Studies No	**CC**	**95% CI**	**p-value**
Mean age of BD	9	0.051	0.033, 0.071	<0.0001
Minus paediatric study	8	0.054	0.033, 0.070	<0.0001
Male/female ratio	7	0.469	-0.036, 0.902	0.03
Disease duration	9	0.211	0.129, 0.293	<0.0001
Minus paediatric study	8	0.209	0.123, 0.295	<0.0001
Smoking	6	1.498	-0.136, 3.134	0.06
C-reactive protein	4	0.155	0.099, 0.211	<0.0001
Azathioprine	5	1.492	0.761, 2.224	<0.0001
Colchicine	5	0.186	-0.053, 0.260	0.12
Anti-TNFα	4	3.014	2.081, 3.940	<0.0001
B) Sensitivity analysis by subgroups				
	Studies	**Heterogeneity**		**Effect size**
By disease activity				
BSAS	3	95.1	<0.0001	0.02
BDCAF	3	93.2	<0.0001	<0.0001
Not reported	3	96.1	<0.0001	0.01
By smoking status				
Reported	6	96.2	<0.0001	<0.0001
Not reported/excluded	3	41.4	0.181	<0.0001

Abbreviations. C: correlation coefficient; CI: confidence interval; BD: Behcet's disease; NOQAS: Newcastle Ottawa Quality Assessment Score; anti-TNFα: anti-tumour necrosis factor; BSAS: Behcet's Syndrome Activity Score; BDCAF: Behçet's Disease Current Activity Form

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 A) common femoral wall thickness and B) greater saphenous wall thickness in in Behcet's disease and controls.

Figure 3: forest plot of studies comparing A) common femoral wall thickness and B) greater saphenous wall thickness in BD patients with and without vascular involvement

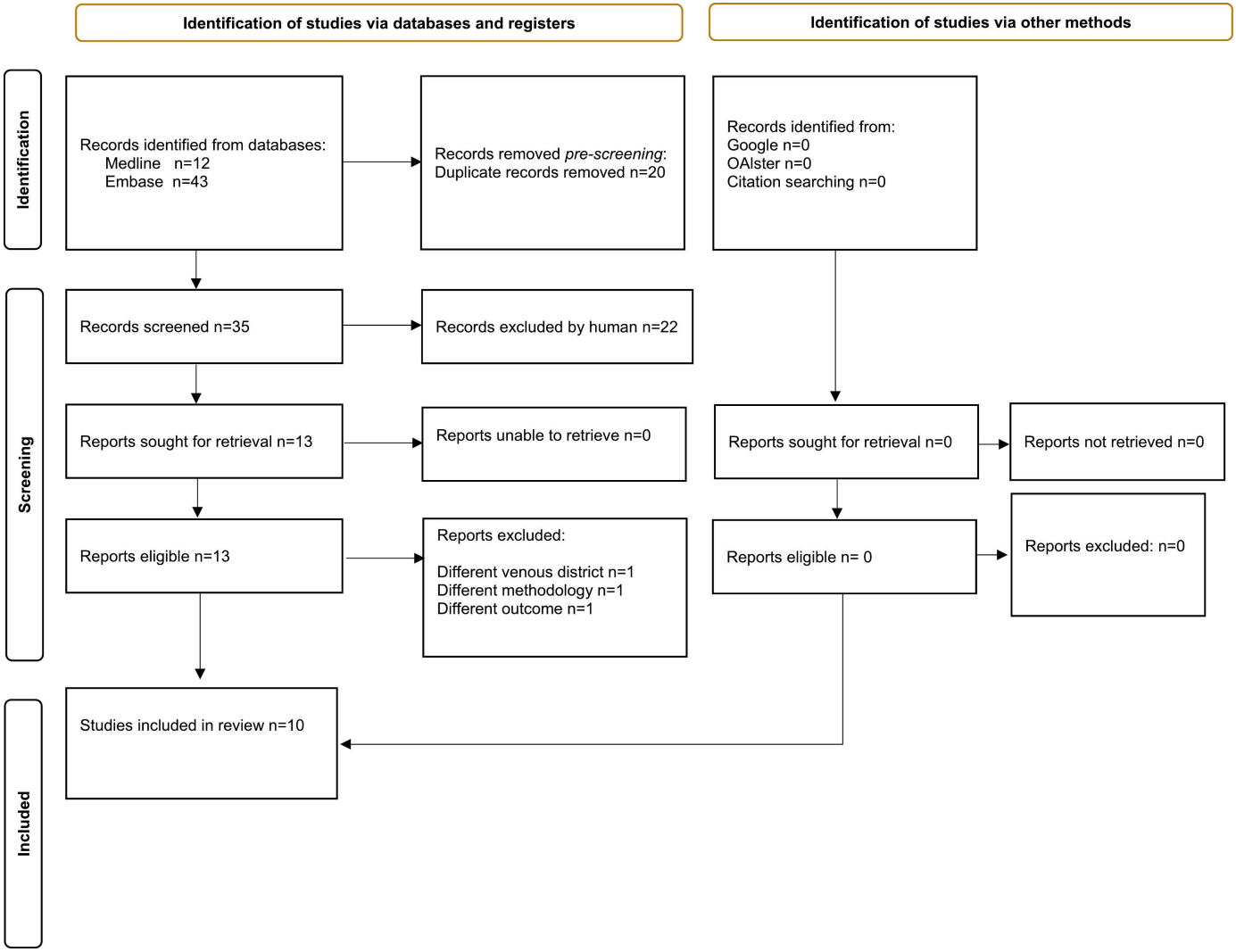
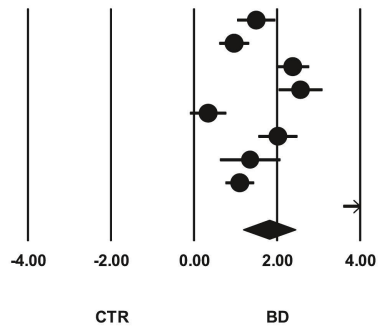

Identification of studies via databases and registers
Identification of studies via other methods
Identification
Records identified from databases:
Medline n=12
Embase n=43
Records removed *pre-screening*:
Duplicate records removed n=20
Records identified from:
Google n=0
OAlster n=0
Citation searching n=0
Screening
Records screened n=35
Records excluded by human n=22
Reports sought for retrieval n=13
Reports unable to retrieve n=0
Reports sought for retrieval n=0
Reports not retrieved n=0
Reports eligible n=13
Reports excluded:
Different venous district n=1
Different methodology n=1
Different outcome n=1
Reports eligible n= 0
Reports excluded: n=0
Included
Studies included in review n=10

Figure 1

Common femoral vein thickness in Behcet's disease

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Alibaz-Oner 2019	1.499	0.234	0.055	1.039	1.958	6.397	0.000
Seyahi 2019	0.966	0.182	0.033	0.609	1.322	5.308	0.000
Alibaz-Oner 2021a	2.378	0.200	0.040	1.986	2.771	11.874	0.000
Alibaz-Oner 2021b	2.565	0.267	0.072	2.041	3.089	9.589	0.000
Kaymaz 2021	0.341	0.223	0.050	-0.096	0.779	1.529	0.126
Tezcan 2022	2.020	0.239	0.057	1.553	2.488	8.462	0.000
Atalay 2023	1.353	0.370	0.137	0.628	2.078	3.658	0.000
Eturk 2023	1.102	0.174	0.030	0.761	1.442	6.346	0.000
Sevik 2023	4.337	0.379	0.143	3.595	5.079	11.456	0.000
	1.814	0.321	0.103	1.185	2.442	5.658	0.000

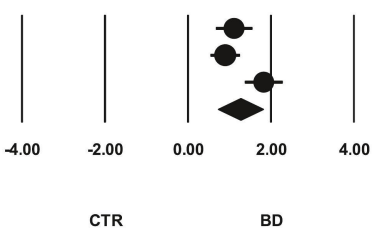


Overall I square 94.1%

A

Greater saphenous vein thickness in Bechets's disease

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Alibaz-Oner 2019	1.112	0.223	0.050	0.675	1.549	4.987	0.000
Seyahi 2019	0.898	0.181	0.033	0.544	1.252	4.967	0.000
Tezcan 2022	1.827	0.231	0.053	1.373	2.280	7.898	0.000
	1.266	0.276	0.076	0.725	1.808	4.586	0.000



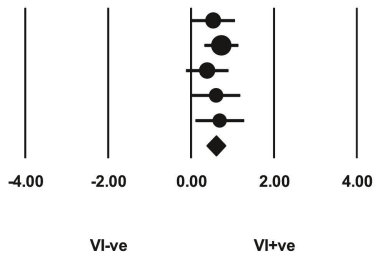
Overall I square 80.53%

B

Figure 2

Common femoral vein thickness by vascular involvement

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Alibaz-Oner 2019	0.533	0.265	0.070	0.014	1.053	2.013	0.044
Seyahi 2019	0.731	0.207	0.043	0.326	1.136	3.538	0.000
Kaymaz 2021	0.388	0.260	0.068	-0.121	0.897	1.492	0.136
Tezcan 2022	0.602	0.294	0.087	0.025	1.179	2.045	0.041
Sevik 2023	0.692	0.298	0.089	0.109	1.276	2.325	0.020
	0.601	0.115	0.013	0.375	0.826	5.211	0.000

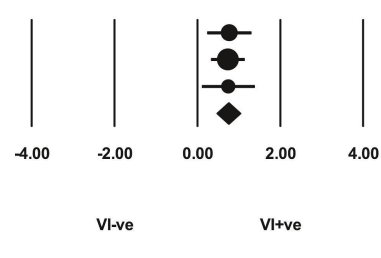


Overall I square 0%

A

Greater saphenous vein thickness by vascular involvement

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Alibaz-Oner 2019	0.770	0.270	0.073	0.241	1.299	2.852	0.004
Seyahi 2019	0.735	0.207	0.043	0.330	1.140	3.558	0.000
del Peral-Fanjul 2023	0.747	0.325	0.105	0.110	1.383	2.299	0.022
	0.748	0.146	0.021	0.461	1.035	5.106	0.000



Overall I square 0%

B

Figure 3