Ocular manifestations of Behçet's disease in children and adults: a systematic review and meta-analysis

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Competing interests: none declared.

ABSTRACT

Objective. Children and adults may develop Behçet's disease (BD), often with ocular involvement such as uveitis. This study aimed to determine the prevalence and type of ocular manifestations in childhood and adult BD.

Methods. Medline, Web of Science and Cochrane databases were searched from inception to October 5, 2018 to identify publications related to Behçet's disease comprising minimum twenty patients and providing the frequency of ocular manifestations (OC). Random effects models were used to combine the prevalence of OC in adults and children with BD. Heterogeneity was evaluated using I2.

Results. The search resulted in 3129 articles, of which 51 were included in meta-analysis. OCs were slightly more frequent in childhood onset BD with the mean [95% Confidence Interval] frequency of 45 [34-56%] compared to 36 [29-43%] in adults, however, this difference was not statistically significant (p=0.198). In both children and adults, posterior uveitis (children 27% vs. adults 25%, and retinal vasculitis in adults 16%) was the most common ocular manifestation, followed by anterior uveitis (children 18% vs. adults 23%). When comparing the distribution of OC in Behcet's in adults, there was geographic variation where OC were higher in Turkey and the Middle East 42%, followed by Europe and North America (36%), North Africa 26% and East Asia 25% but not significantly (p=0.27).

Conclusion. Ocular manifestations, predominantly uveitis; are common in BD. Ocular manifestations are not proportionately more frequent in adults with BD along the ancient Silk Road.

Introduction

Behçet's disease (BD) is a multisystem inflammatory disease which usually

starts around the age of 30 to 40. The hallmark of BD is the presence of mucocutaneous lesions in the mouth and/ or genital area. Oral ulcers are recurrent, quite painful, and mostly found on the mucous membranes of the soft palate, tongue, and lips (1). Genital ulcers occur less frequently than those in the mouth, but tend to be deeper and last longer (2). The aetiology of BD remains unknown. It has been hypothesised that herpes simplex virus-1 (HSV-1), streptococcal infections, and/or the presence of heat shock protein (HSP) antibodies are involved in the disease development (3-6). Genetic factors such as HLA-B51 and HLA-B5 increase BD 6-fold (7, 8). BD progression is often supported by the overexpression of inflammatory cytokines (9). Environmental factors such as diet and smoking habits can also impact disease activity (10).

Ocular involvement is common in BD and causes substantial functional limitations (5). However, data are contradictory with some studies showing the frequency of ocular conditions (OCs) as high as 67% (11), whereas others reporting it low, at 5% (12). Conclusive information regarding the types of OCs, their prevalence and manifestations in children compared to adults with BD is lacking (13-17). Patients with ocular involvement in BD are less likely to have genital ulceration or GI involvement (18). It is known that BD is more common along the ancient Silk Road and manifestations such as large vessel vasculitis seem to be more frequent in this geographical area, whereas oral and genital ulcers may be equally frequent in BD between different areas (19). The comparative frequency of eye involvement in different areas is not fully understood.

Therefore, we conducted a systematic review and meta-analysis to determine the prevalence and type of ocular manifestations in adults and children with BD and studied the frequency of eye involvement between geographical areas. While other studies have investigated the prevalence of OC in BD, this analysis examined differences in child *versus* adult-onset BD and frequency of OC between the Silk Road and other locations (20).

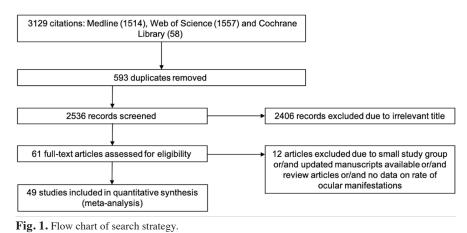
Methods

Study selection

The protocol of ocular manifestations in rheumatic conditions was registered at www.clinicaltrials.gov with the trial ID NCT03753893. A search of publications related to: conjunctivitis, keratoconjunctivitis sicca, xeropthalmia, uveitis, eye haemorrhage, optic neuritis, papilloedema, orbital disease, retinal artery/vein occlusion, macular oedema, retinitis, chorioretinitis, scleritis, iridocyclitis, choroid haemorrhage, blindness and amaurosis fugax in patients with BD was performed with the assistance of an information specialist. Medline, Cochrane and Web of Science were used, searching papers that spanned from their inception (1966, 1991 and 1990 respectively) to October 5, 2018. All studies that included a prevalence of ocular complications in the setting of juvenile and/or adult BD were included where data on adults or children with BD could be extracted such as types and frequency of ocular manifestations.

Inclusion criteria

Studies were included if they provided numerical data of the frequencies of ocular manifestations in BD. Studies were excluded if they were review articles, case reports where all patients experienced ocular manifestations, if different types of ocular manifestations were not reported separately (for subsets where frequencies of specific conditions such as anterior and posterior uveitis), and if the study included fewer than 20 patients with BD in order to increase certainty around the reported frequency which could be less accurate in smaller studies. Patients were considered as juvenile onset by each individual study criteria. The ocular involvement was also defined by the



authors of each paper (anterior/posterior/pan uveitis, iritis, retinitis, etc.). When the same study cohort was used in more than one analysis, the most recent or largest sample was included. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used to assess the quality of cohort, case-control, and cross-sectional studies where

studies are evaluated out of 22 points

for completeness and quality (21).

Data extraction

The following data were extracted for each study: first author, year of publication, location of study, study design, sample size, whether adults or children were included, and prevalence of each ocular complication. When studies included multiple ocular manifestations, data extraction and analysis were done overall and separately for each condition. Terms (uveitis, anterior uveitis, posterior uveitis, retinal vasculitis, etc.) were extracted as used by the authors in each paper. Complications from BD ocular involvement were also recorded such as glaucoma, cataracts, blindness, optic atrophy, etc. Some terms could have been related to BD related ocular activity or damage including macular oedema.

Statistical analysis

After extracting the frequency and type of ocular manifestations from the individual studies, Forest plots were constructed to create a 95% confidence interval (CI) using Wilson's score method. Variance and study weights were determined and a random effects

model was used to account for differences in study quality (22). I-squared and tau-squared tests were used to determine heterogeneity and variance across studies. Funnel plots were used to look for possible publication bias. Differences between prevalence were compared using single factor ANOVA. Due to differences in geography and prevalence of BD (23), a subset of analysis was done for countries with high BD (along the Silk Road) and the other countries to determine if the reported frequency of OC was different between adults and children with BD in areas with high versus low BD.

Results

The search process found 3129 articles, of which 49 were included (Fig. 1). There were 593 duplicate citations among the search terms/different databases; and an additional 2505 articles did not meet the inclusion criteria (Fig. 1). The studies ranged in size from 20 to 6500 patients with BD. The Supplementary table shows the included studies and ocular terms used within each paper. Overall STROBE score to assess quality ranged from 12 to 20.

The overall frequency of ocular involvement in juvenile BD was 45 [34-56%] and was similar to that of adult BD at 36 [29-43%] (p=0.198) (Fig. 2). In children, the most common ocular manifestation was posterior uveitis, affecting 27 [12-41%] of those with BD, followed by anterior uveitis (18 [6-31%]), cataracts 15% and optic atrophy (8 [3-13%]) (Fig. 3). In adults, the most common ocular manifestation was also posterior uveitis (25 [16A.

				Prevalence	Preva	lence
Study or Subgroup	Prevalence	SE	Weight	IV, Random, 95% CI	IV, Rando	m, 95% Cl
Atmaca 2011	0.30909091	0.04406129	13.8%	0.31 [0.22, 0.40]		
Citirik 2009	0.52941176	0.08560081	11.1%	0.53 [0.36, 0.70]		
Eldem 1998	0.8	0.08944272	10.9%	0.80 [0.62, 0.98]		
Fujikawa 1997	0.29032258	0.08152486	11.4%	0.29 [0.13, 0.45]		
Gallizzi 2017	0.43636364	0.04728544	13.6%	0.44 [0.34, 0.53]		
Kone-Paut 1998	0.61538461	0.06034343	12.8%	0.62 [0.50, 0.73]		
Sarica 1996	0.27368421	0.04574312	13.7%	0.27 [0.18, 0.36]		_ _
Sungur 2009	0.40322581	0.06229932	12.7%	0.40 [0.28, 0.53]		
Total (95% CI)			100.0%	0.45 [0.34, 0.56]		•
Heterogeneity: Tau ² = 0.02; Chi ² = 49.14, df = 7 (P < 0.00001); I ² = 86%						0 0.5 1
Test for overall effect: Z = 7.99 (P < 0.00001)						

B.

Study or Subgroup	Prevalence	SE	Weight	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
Ajili 2015		0.05286038	2.4%	0.39 [0.28, 0.49]	
Al-Aboosi 1996		0.10665365	2.0%	0.65 [0.44, 0.86]	
Al-Dalaan 1994		0.04380761	2.4%	0.65 [0.56, 0.73]	
Al-Dhibi 2011		0.02450603	2.5%	0.11 [0.06, 0.15]	-
Alli 2009	0.25821596		2.5%	0.26 [0.20, 0.32]	
Alpsoy 2002		0.06081018	2.3%	0.20 [0.20, 0.32]	
Alpsoy 2002	0.25	0.0559017	2.4%	0.25 [0.14, 0.36]	
Arida 2009		0.02653461	2.5%	0.57 [0.52, 0.62]	
Aydin 2003		0.08838835	2.2%	0.50 [0.33, 0.67]	
Azizlerli 2003		0.04154081	2.4%	0.28 [0.20, 0.36]	
		0.01146426	2.4%	•	-
Bang 2003 Bonitsis 2015		0.01140420		0.51 [0.49, 0.53]	_
Chamberlain 1977			2.5%	0.45 [0.42, 0.49]	
		0.07654655	2.2%	0.25 [0.10, 0.40]	
Chang 2002		0.04946912	2.4%	0.23 [0.14, 0.33]	
Cheng 2004		0.07848284	2.2%	0.35 [0.20, 0.51]	
Chung 1986		0.06505137	2.3%	0.66 [0.53, 0.79]	
Davari 2015		0.09330087	2.1%	0.65 [0.47, 0.84]	
Davatchi 2010		0.00614385	2.5%	0.57 [0.56, 0.58]	·
Demiroglu 1997		0.03263163	2.5%	0.39 [0.33, 0.46]	
El Fekih 2007	0.125	0.0584634	2.3%	0.13 [0.01, 0.24]	
Elgin 2004		0.03311454	2.5%	0.17 [0.11, 0.24]	
Frigui 2008		0.01101022	2.5%	0.05 [0.03, 0.07]	*
Hamdan 2006		0.05206306	2.4%	0.58 [0.48, 0.68]	
Hamzaoui 2006		0.02050589	2.5%	0.32 [0.28, 0.36]	-
Ideguchi 2011		0.02451686	2.5%	0.55 [0.50, 0.60]	-
Ilhan 2008	0.67741935	0.08395897	2.2%	0.68 [0.51, 0.84]	
Janati 2005	0.44247788	0.04672374	2.4%	0.44 [0.35, 0.53]	
Kacmaz 2008	0.10714286	0.02386261	2.5%	0.11 [0.06, 0.15]	-
Koç 1992	0.21518987	0.04623594	2.4%	0.22 [0.12, 0.31]	
Krause 2009	0.56428571	0.04190698	2.4%	0.56 [0.48, 0.65]	
Kural-Seyahi 2003	0.46962617	0.02412378	2.5%	0.47 [0.42, 0.52]	-
Lin 2018	0.18220339	0.02512724	2.5%	0.18 [0.13, 0.23]	
Mangelsdorf 1996	0.24	0.08541663	2.2%	0.24 [0.07, 0.41]	
Matsuo 2002	0.02631579	0.01298361	2.5%	0.03 [0.00, 0.05]	*
Mohammad 2013	0.25	0.06846532	2.3%	0.25 [0.12, 0.38]	
Mok 2002	0.27027027	0.07300949	2.3%	0.27 [0.13, 0.41]	
Shang 2009	0.46551724	0.0463133	2.4%	0.47 [0.37, 0.56]	
Sibley 2014	0.36986301	0.0326224	2.5%	0.37 [0.31, 0.43]	
Simsek 1991		0.06804138	2.3%	0.17 [0.03, 0.30]	
Sungur 2009		0.07493293	2.2%	0.62 [0.47, 0.77]	
Tunc 2002		0.02384293	2.5%	0.19 [0.14, 0.24]	-
Tursen 2003		0.00933751	2.5%	0.28 [0.26, 0.30]	-
Total (95% CI)			100.0%	0.36 [0.29, 0.43]	
Heterogeneity: Tau ² =	0.05. Chi2	614 42 46			
Test for overall effect			41 (P < 0	$(00001); 1^2 = 99\%$	-1 -0.5 0 0.5



35%]), followed by anterior uveitis (23 [11-36%]), and poster uveitis labelled as retinal vasculitis (16 [7-25%]) (Fig. 4). In adults with BD, ocular involve-

ment as the initial manifestation occurred in 12 [4-20%]. Tests for heterogeneity showed large variability between the studies analysed, therefore a random pooled effects model was used to generate forest plots and determine prevalence.

Due to regional differences in the preva-

	Provolonco	CE Wain	Prevalence	Prevalence
Study or Subgroup 1.4.1 A. Anterior U		SE Weig	ht IV, Random, 95% CI	IV, Random, 95% CI
Atmaca 2011		352729 7.4	4% 0.16 [0.09, 0.23]	
Citirik 2009	0.14705882 0.06			
Eldem 1998	0.14703882 0.00		• • • • • • • • • • • • • • • • • • • •	
Kone-Paut 1998	0.07692308 0.03			
Sungur 2009	0.5 0.06			
Subtotal (95% CI)	0.5 0.00	33.9		
Heterogeneity: Tau ²	= 0.02; Chi ² = 39.58	df = 4 (P < 0.	00001 ; $I^2 = 90\%$	
Test for overall effe	ct: $Z = 2.85 (P = 0.00)$	4)		
.4.2 B. Posterior U	veitis			
Atmaca 2011		393791 7.2	0.22 [0.14, 0.30]	
Citirik 2009	0.32352941 0.08			
Eldem 1998	0.52552541 0.00		0.55 [0.33, 0.77]	
Kone-Paut 1998	0.09230769 0.03			
Subtotal (95% CI)		23.7		
leterogeneity: Tau ²	= 0.02; Chi ² = 21.12	df = 3 (P < 0.	0001); $I^2 = 86\%$	
	ct: $Z = 3.58 (P = 0.00)$			
1.4.3 C. Optic Atro	ahv			
Atmaca 2011	0.05454545 0.02	165226 7.9	9% 0.05 [0.01, 0.10]	
Citirik 2009	0.05454545 0.02			
Eldem 1998	0.14703882 0.07			
Kone–Paut 1998	0.06153846 0.02		•	
Subtotal (95% CI)	0.00133040 0.02	25.3		
Heterogeneity: Tau ²	= 0.00; Chi ² = 4.99,	df = 3 (P = 0.1)		•
	ct: $Z = 2.98 (P = 0.00)$		<u></u>	
.4.4 D. Cataract				
tmaca 2011	0.00909091 0.00	904949 8.2	0.01 [-0.01, 0.03]	+
Citirik 2009	0.29411765 0.08		-	
Eldem 1998	0.2 0.10			
Subtotal (95% CI)		17.1	0.15 [-0.05, 0.36]	
Heterogeneity: Tau ²	= 0.03; Chi ² = 14.19	df = 2 (P = 0.	0008); $I^2 = 86\%$	
Test for overall effe	ct: $Z = 1.46 (P = 0.14)$			
Fotal (95% CI)		100.0	0% 0.17 [0.11, 0.23]	•
leterogeneity: Tau ²	= 0.01; Chi ² = 151.5	9, df = 15 (P <	0.00001); I ² = 90%	-1 -0.5 0 0.5
Test for overall effe	ct: Z = 5.74 (P < 0.00	001)		-1 -0.5 0 0.5
est for subgroup d	ifferences: $Chi^2 = 7.1$	1, df = 3 (P = 0)	$(0.07), 1^2 = 57.8\%$	

Fig. 3. The prevalence of ocular manifestations in juvenile BD. Anterior uveitis (A), posterior uveitis (B), optic atrophy (C), cataract (D).

lence of BD, frequencies of ocular manifestations were analysed comparing regions with high BD to those with low BD. OC in adult BD occurred most frequently in Turkey and the Middle East (40%) and nearly the same frequency was found in studies from North America and Europe (36%) and less common in North Africa (26%) and East Asia (25%). No gradient along the Silk Road vs. other regions such as North America and Europe was observed (p=0.27). In children, all but one of the studies found were from Turkish cohorts, therefore geographic analysis for paediatric BD was not performed. Figure 5 provides the frequency of BD by region. When comparing children to adults within studies from Turkey and the Middle East, the prevalence of OC in BD in

children was quite similar (5% difference). Supplementary figure S1 shows the prevalence of BD on the map.

Publication bias investigated was negligible as evidenced by funnel plots. When measuring overall heterogeneity, I2 = 86%, Z=7.74 (p<10-5) in children and I2=99%, Z=10.48 (p<10-5) in adults (Supplementary Fig. S1).

Discussion

The systematic review has shown that children with BD did not have higher prevalence of eye manifestations when compared to adults. Bilateral posterior uveitis was the most typical feature of OC in children which is known to result in significant decrease in visual activity (24). Approximately one-third of paediatric patients with ocular involvement showed decreased visual acuity over a mean of 5 years of follow up in one registry (25). Anterior uveitis and optic atrophy were also commonly seen in children with BD. Adult-onset BD was found to have OC in approximately 1/3 of patients especially with posterior uveitis and then anterior iritis.

The studies had some heterogeneity with considerable variation in the frequency of OC among studies. This might be related to the methodology of case ascertainment, the data sources, country, age and gender of patients, lack of standardisation of age of juvenile onset BD and ocular definitions, and the wide variation in follow-up. Indeed, ocular manifestations may vary according to sex, and age of onset; the occurrence and severity of uveitis is

tudy or Subgroup	Prevalence	SE	Weight	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
.3.1 A. Anterior Uvei		0.07948043	1.7%	0.28 (0.12, 0.44)	
ydin 2003 Thang 2002	0.28125		2.2%	0.28 [0.13, 0.44] 0.04 [-0.00, 0.09]	
theng 2004	0.13513513		1.9%	0.14 [0.02, 0.25]	
avatchi 2010	0.41230769		2.2%	0.41 [0.40, 0.42]	
l Fekih 2007	0.00892857		2.2%	0.01 [-0.00, 0.02]	
lamdan 2006		0.05270463	2.0%	0.50 [0.40, 0.60]	
lamzaoui 2006	0.03853565		2.2%	0.04 [0.02, 0.06]	•
anati 2005	0.08849558	0.02671782	2.2%	0.09 [0.04, 0.14]	-
acmaz 2008	0.10094637	0.02386261	2.2%	0.10 [0.05, 0.15]	~
habbazi 2018	0.56034483	0.04608449	2.0%	0.56 [0.47, 0.65]	
Iohammad 2013	0.175	0.06007807	1.9%	0.17 [0.06, 0.29]	
lok 2002	0.27027027	0.07300949	1.8%	0.27 [0.13, 0.41]	
ungur 2009	0.45238095	0.00933751	2.2%	0.45 [0.43, 0.47]	•
ubtotal (95% CI) leterogeneity: Tau ² =	0.05: Chi ² - 2	202 01 df -	26.9%	0.23 [0.11, 0.36]	•
est for overall effect:			12 (F < 0	.00001), 1 = 100%	
.3.2 B. Posterior Uve	itis				
hang 2002	0.04109589	0.02323407	2.2%	0.04 [-0.00, 0.09]	<u>∽</u>
heng 2004	0.05405405		2.1%	0.05 [-0.02, 0.13]	+
avatchi 2010	0.22446154		2.2%	0.22 [0.21, 0.24]	
amdan 2006	0.46666667		2.0%	0.47 [0.36, 0.57]	·
lamzaoui 2006	0.03853565		2.2%	0.04 [0.02, 0.06]	-
anati 2005	0.18584071	0.03659198	2.1%	0.19 [0.11, 0.26]	
acmaz 2008	0.42261905		2.1%	0.42 [0.35, 0.50]	
habbazi 2018	0.65517241	0.04413161	2.1%	0.66 [0.57, 0.74]	
Iohammad 2013		0.06846532	1.8%	0.25 [0.12, 0.38]	
ubtotal (95% CI)			18.9%	0.25 [0.16, 0.35]	
eterogeneity: Tau ² = est for overall effect:			(P < 0.0	0001); I ² = 99%	
.3.3 C. Retinal Vascu					
revalo 2015	0.11363636	0.02762343	2.2%	0.11 [0.06, 0.17]	
avatchi 2010	0.32107692		2.2%	0.32 [0.31, 0.33]	
lgin 2004	0.08527132		2.2%	0.09 [0.04, 0.13]	-
anati 2005	0.14159292		2.2%	0.14 [0.08, 0.21]	
acmaz 2008	0.14159292		2.1%	0.19 [0.14, 0.23]	-
habbazi 2008	0.36206897		2.2%		
rause 2009			2.0%	0.36 [0.27, 0.45]	
lohammad 2013	0.07857143		2.2%	0.08 [0.03, 0.12]	
lohammad 2013 lok 2002	0.1	0.04743417	2.0%	0.10 [0.01, 0.19]	
ubtotal (95% CI)	0.00100108	0.0440/428	19.3%	0.08 [-0.01, 0.17] 0.16 [0.07, 0.25]	•
leterogeneity: Tau ² =					
est for overall effect:		0.0004)			
.3.4 D. Macular Eder		0.03203133	3.36	0.00 (0.02, 0.12)	_
revalo 2015	0.07575758		2.2%	0.08 [0.03, 0.12]	
lamdan 2006 Jacmaz 2008	0.01111111		2.2% 2.2%	0.01 [-0.01, 0.03]	[-
ubtotal (95% CI)	0.12933754	0.01004/0/	6.6%	0.13 [0.09, 0.17] 0.07 [-0.01, 0.15]	
leterogeneity: Tau ² =	0.00 Chi ² = 3	df = 2			▼
est for overall effect:					
.3.5 E. Cataract					
avatchi 2010	0.19646154	0.00492817	2.2%	0.20 [0.19, 0.21]	· ·
lgin 2004	0.20930233		2.1%	0.21 [0.14, 0.28]	
lamdan 2006	0.04444444		2.2%	0.04 [0.00, 0.09]	~
acmaz 2008	0.08832808		2.2%	0.09 [0.06, 0.12]	~
habbazi 2018	0.32758621		2.1%	0.33 [0.24, 0.41]	
ubtotal (95% CI)	States and states and		10.8%	0.17 [0.09, 0.24]	◆
eterogeneity: Tau ² = est for overall effect:			P < 0.00	001); $I^2 = 96\%$	
.3.6 F. Glaucoma Igin 2004	0.19379845	0.03480182	2.1%	0.19 [0.13, 0.26]	-
acmaz 2008	0.00630915		2.1%	0.01 [-0.00, 0.02]	,
ubtotal (95% CI)	0.00030313	0.00444715	4.4%	0.10 [-0.09, 0.28]	
leterogeneity: Tau ² =					
est for overall effect:	Z = 1.03 (P =	0.30)			
.3.7 G. Blindness	0.05003015	0.00000000	2.241	0.0F (0.0. 0.00	
onitsis 2015	0.05087015		2.2%	0.05 [0.04, 0.07]	
amdan 2006	0.16666667		2.1%	0.17 [0.09, 0.24]	
amzaoui 2006	0.05973025		2.2%	0.06 [0.04, 0.08]	·
habbazi 2018 ubtotal (95% CI)	0.09482759	0.0272022	2.2% 8.7%	0.09 [0.04, 0.15] 0.07 [0.04, 0.10]	
eterogeneity: Tau ² =	0.00 Chi2 - 1	0.27 df - 2			•
est for overall effect:			. = 0.02)		
.3.8 H. Uveitis as Ini	tial Manifesta	tion			
avatchi 2010	0.08584615		2.3%	0.09 [0.08, 0.09]	
lgin 2004	0.17054264		2.1%	0.17 [0.11, 0.24]	
ubtotal (95% CI)			4.4%	0.12 [0.04, 0.20]	◆
leterogeneity: Tau ² =			= 0.01);		
est for overall effect:					
otal (95% CI)			100.0%	0.18 [0.14, 0.22]	•
		and the fillenger of the			
eterogeneity: Tau ² =	0.02; Chi ² = 7	123.07, df =	46 (P < 0	$(.00001); 1^2 = 99\%$	-1 -0.5 0 0.5

Fig. 4. The prevalence of ocular manifestations in adult BD. Anterior uveitis (A), posterior uveitis (B), retinal vasculitis (C), macular oedema (D), cataract (E), glaucoma (F), blindness (G), uveitis as initial manifestation (H).

				Prevalence	Prevalence			
Study or Subgroup	Prevalence	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
1.5.1 A. Turkey and the Middle East								
Al-Aboosi 1996		0.10665365	2.2%	0.65 [0.44, 0.86]				
Al-Dalaan 1994		0.04380761	2.6%	0.65 [0.56, 0.73]				
Al-Dhibi 2011	0.10691824	0.02451	2.7%	0.11 [0.06, 0.15]				
Alli 2009	0.25821596	0.02999	2.6%	0.26 [0.20, 0.32]				
Alpsoy 2002	0.20454545	0.06081	2.5%	0.20 [0.09, 0.32]				
Alpsoy 2003	0.25	0.0559	2.5%	0.25 [0.14, 0.36]				
Arida 2009 Aydin 2003	0.88752594	0.02653461 0.08839	2.7% 2.4%	0.89 [0.84, 0.94] 0.50 [0.33, 0.67]				
Azizlerli 2003		0.08839	2.4%	0.28 [0.19, 0.36]				
Davatchi 2010	0.56815385	0.00614	2.7%	0.57 [0.56, 0.58]				
Demiroglu 1997	0.39285714	0.03263	2.6%	0.39 [0.33, 0.46]				
Elgin 2004	0.17054264	0.03311	2.6%	0.17 [0.11, 0.24]				
Hamdan 2006	0.57777778	0.05206	2.6%	0.58 [0.48, 0.68]				
Ilhan 2008	0.67741935	0.08396	2.4%	0.68 [0.51, 0.84]				
Koç 1992	0.21518987	0.04623594	2.6%	0.22 [0.12, 0.31]				
Kural-Seyahi 2003	0.46962617	0.02412378	2.7%	0.47 [0.42, 0.52]	-			
Simsek 1991	0.16666667	0.06804	2.5%	0.17 [0.03, 0.30]				
Sungur 2009	0.61904762	0.07493	2.4%	0.62 [0.47, 0.77]				
Tunc 2002		0.02384293	2.7%	0.19 [0.14, 0.24]				
Tursen 2003	0.28015564	0.00934	2.7%	0.28 [0.26, 0.30]				
Subtotal (95% CI)			51.3%	0.40 [0.31, 0.50]				
Heterogeneity: Tau ² =			19 (P < 0.	.00001); $I^2 = 99\%$				
Test for overall effect	Z = 8.26 (P <	0.00001)						
1.5.2 B. Europe and M	North America	i i						
Bonitsis 2015		0.01820648	2.7%	0.45 [0.42, 0.49]	-			
Chamberlain 1977		0.07654655	2.4%	0.25 [0.10, 0.40]				
Davari 2015	0.65384615	0.0933	2.3%	0.65 [0.47, 0.84]				
Kacmaz 2008	0.10714286	0.02386	2.7%	0.11 [0.06, 0.15]				
Krause 2009	0.56428571	0.04191	2.6%	0.56 [0.48, 0.65]				
Mangelsdorf 1996	0.24	0.08541663	2.4%	0.24 [0.07, 0.41]				
Mohammad 2013	0.25	0.06847	2.5%	0.25 [0.12, 0.38]				
Sibley 2014	0.36986301	0.03262	2.6%	0.37 [0.31, 0.43]				
Subtotal (95% CI)			20.2%	0.36 [0.22, 0.49]	•			
Heterogeneity: Tau ² =			(P < 0.00	1001 ; $I^2 = 96\%$				
Test for overall effect	Z = 5.22 (P < 1)	0.00001)						
1.5.3 C. North Africa								
Ajili 2015	0.38823529	0.05286	2.6%	0.39 [0.28, 0.49]				
El Fekih 2007	0.125	0.05846	2.5%	0.13 [0.01, 0.24]				
Frigui 2008	0.04787234	0.01101	2.7%	0.05 [0.03, 0.07]				
Hamzaoui 2006	0.32177264	0.02051	2.7%	0.32 [0.28, 0.36]				
Janati 2005	0.44247788	0.04672	2.6%	0.44 [0.35, 0.53]				
Subtotal (95% CI)			13.1%	0.26 [0.09, 0.44]	◆			
Heterogeneity: Tau ² =			(P < 0.00)	10001 ; $I^2 = 98\%$				
Test for overall effect	: Z = 2.95 (P =	0.003)						
1.5.4 D. East Asia								
Chang 2002	0.23287671	0.04947	2.6%	0.23 [0.14, 0.33]				
Cheng 2002	0.35135135	0.07848	2.4%	0.35 [0.20, 0.51]				
Lin 2018	0.18220339	0.02513	2.7%	0.18 [0.13, 0.23]				
Matsuo 2002	0.02631579	0.01298	2.7%	0.03 [0.00, 0.05]				
Mok 2002	0.27027027	0.07301	2.5%	0.27 [0.13, 0.41]				
Shang 2009	0.46551724	0.0463133	2.6%	0.47 [0.37, 0.56]				
Subtotal (95% CI)			15.4%	0.25 [0.11, 0.39]				
Heterogeneity: Tau ² =			(P < 0.00	1001 ; $I^2 = 96\%$				
Test for overall effect	: Z = 3.48 (P =	0.0005)						
Total (95% CI)			100.0%	0.35 [0.28, 0.43]				
	= 0.06 [,] Chi ² –	3695 65 df -						
Heterogeneity: Tau ² = 0.06; Chi ² = 3695.65, df = 38 (P < 0.00001); l ² = 99% Test for overall effect: Z = 9.10 (P < 0.00001)								
Test for subgroup diff			(P = 0.26)), $I^2 = 24.9\%$				
J. Comp. Com		.,						

Fig. 5. The prevalence of ocular manifestations in adult BD by geographic location. Turkey and the Middle East (A), Europe and North America (B), North Africa (C), East Asia (D).

majority of publications were from Turkey where the prevalence is high and in fact, most patients with juvenile onset

associated with the male sex, gener-

ally after the age of ten years (26). The

BD were in Turkey. We were unable to adjust for gender without individual patient data.

As with any systematic review, there are limitations. Regional and ethnic

differences in BD were not accounted for in this analysis and there were geographic differences in adults with BD. BD is most common in Turkey and Middle East, which is often why it has

been referred to as 'Silk Road disease' (27). While BD is less common in regions beyond the Silk Road such as Europe (28), publications analysed from different locations were extracted similarly, even if they had varying rates of disease. A sub-analysis was performed studying countries along stretches of the ancient silk road compared with those further away. As expected, Turkey and the Middle East had a higher prevalence of ocular manifestations in BD compared with East Asia and North Africa. North America and Europe, however results were not significantly different. Perhaps this similarity can be attributed to an influx of immigration to Europe and North America from those regions.

Treatment was not considered in each study and could be confounding. For instance, there could be fewer ocular complications if effective early treatment was used and/or if the uveitis was less severe in studies compared to others. Advanced therapeutic interventions such as TNF (tumour necrosis factor) inhibitors may lessen the severity and/ or recurrence of OC. Adalimumab and infliximab have been studied in uveitis from BD (29-32). Conversely, some treatment options for BD have associated eye involvement as potential side effects such as topical and oral steroids contributing to cataracts and glaucoma (33-36) and uveitis can increase glaucoma. Some non-ocular features of BD are treated with oral steroids (37, 38). The ocular manifestations included disease activity from BD (such as anterior and posterior uveitis and retinal vasculitis); and complications such as optic atrophy, glaucoma, cataracts and blindness. Due to lack of standardisation of terms between studies, we extracted the data as labelled according to the author of each study. In addition, most of the studies analysed were cohort studies. As part of our analysis, we did not differentiate between sex and age (amongst adults), which could lead to bias.

Conclusions

The frequency of ocular involvement in children is not significantly different than adults with BD. The most common manifestation in the eyes is posterior uveitis and then anterior uveitis. Ocular involvement did not have significantly different regional involvement.

Take home messages

- BD is more common along the Silk Road and may be more severe there *versus* other geographic regions.
- However, the frequency of uveitis in adults with BD does not vary by geography.
- Ocular involvement in BD is slightly more frequent in children than in adult onset.

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