APPENDIX

Table I. Systematic Review of the Yield of Temporal Artery Biopsy in Patients with Suspected Giant Cell Arteritis, January 1998 to December 2017 (n=113)

Study (Year, Author)	n	Yield	Age	% Female	Country	ACR >=3	Length	% Bilat	Vision Symp	Claudication	GC < 2 wks
2017, Aranda-Valera (1)	451	0.43	81.0	0.88	Spain	0.56					
2017, Bharadwaj (2)	409	0.18	71.3	0.69	UK		13.2				
2017, Bowling (3)	129	0.13	75.0	0.75	UK	0.83	9.8	0.00			0.79
2017, Gajree (4)	715	0.35	71.0	0.69	UK			0.00	0.31	0.18	
2017, Grossman (5)	240	0.26	72.2	0.62	Israel		10.7	0.00	0.24	0.11	
2017, Ing (6)	688	0.26	73.5	0.68	Canada	0.45	19.0	0.23	0.22		1.00
2017, Papadakis (7)	116	0.55	76.1	0.58	Germany		9.4	0.00			
2017, Ponte (a) (8)	363	0.29			Portugal						
2017, Rheaume (9)	171	0.18	71.0	0.74	Canada	0.80	4.3	0.00	0.50	0.28	0.50
2017, Roncato (10)	42	0.55	75.8	0.69	France				0.19		1.00
2017, Tanveer (a) (11)	148	0.25			UK		11.8	0.03			
2016, Calamia (a) (12)	2539	0.27	74.0	0.64	US			0.50			
2016, Cristaudo (13)	50	0.04	70.0	0.65	Australia	0.76		0.04			0.95
2016, Frost (14)	696	0.17	70.4	0.71	US			0.05			
2016, Hussain (15)	96	0.16	72.0	0.69	UK	0.53	30.0		0.34		0.52
2016, Jones (a) (16)	422	0.23	72.4	0.69	UK		13.9				
2016, Lariviere (17)	24	0.25	74.0	0.67	France	0.63			0.30	0.21	1.00
2016, Luqmani (18)	381	0.39	71.1	0.72	UK		10.0		0.35	0.43	1.00
2016, Neale (a) (19)	71	0.25	75.0	0.73	UK	1.00		0.00			
2016, Oh (20)	538	0.23		0.68	Australia		17.5	0.00			
2016, Taylor (a) (21)	157	0.17			UK	0.33					
2016, Yousif (a) (22)	17	0.24	74.0	0.70	UK	0.70					

2015, Au (23)	96	0.21	72.0	0.60	Australia		16.0	0.00			
2015, Bateman (a) (24)	31	0.35			UK						0.22
2015, De Lott (25)	404	0.22	73.8	0.67	US						
2015, El-Dairi (26)	204	0.24	71.6	0.71	US			0.06	0.26	0.17	
2015, Fritzlen (a) (27)	231	0.39	77.0		US				0.03	0.11	
2015, Germano (28)	105	0.33	73.4	0.70	Italy	0.66			0.09	0.24	
2015, Han (a) (29)	257	0.35			Canada			0.33			
2015, Lally (30)	188	0.12		0.81	UK						
2015, Le (31)	237	0.15	71.0	0.70	US	0.56	24.1	0.72		0.32	
2015, McKay (32)	32	0.13	68.0	0.66	UK	0.81	8.3		0.34	0.16	
2015, McMurran (33)	56	0.13			UK		14.0				
2015, Mohammad (34)	4216	0.20	75.9	0.68	Sweden						
2015, Sharma (35)	13	0.38	67.0		India					0.53	
2015, Siemonsen (36)	11	0.82	75.3	0.72	Germany				0.55		1.00
2015, Sloane (a) (37)	471	0.26	72.0		UK		15.6				
2015, Somogyi (a) (38)	143	0.10			US						
2015, Stacy (39)	58	0.36	74.0	0.55	US		14.0	0.00	0.67	0.22	
2015, Sutton (a) (40)	57	0.28		0.70	UK	0.70					
2014, Cavazza (41)	871	0.41		0.26	Italy			0.02	0.07		
2014, Croft (a) (42)	24	0.71			UK	0.41					
2014, Kaptanis (43)	144	0.14	68.9	0.74	UK	0.62	6.4	0.01			
2014, Klink (44)	98	0.63	71.7	0.68	Germany	1.00					1.00
2013, Al-Mossawi (a) (45)	35	0.34	67.0		UK						
2013, Gonzalez-Lopez (46)	335	0.24		0.66	Spain		7.3	0.54	0.20	0.16	1.00
2013, Ibbett (a) (47)	73	0.21	72.0	0.60	Australia			0.66	0.43	0.28	
2013, Kisza (48)	744	0.29		0.74	US						
2013, Pieri (49)	50	0.06	70.0	0.76	UK		9.0	0.00			
2013, Suelves (50)	38	0.68	74.0	0.68	Spain				0.37		
2013, Yates (a) (51)	325	0.37	75.6	0.71	UK					0.08	
2012, Avitabile (52)	16	0.44	70.1		Italy						
2012, Bury D (53)	111	0.21	70.0	0.68	UK			0.01			0.41

2012, Hassouna (a) (54)	98	0.16		0.71	UK						
2012, Pfenninger (55)	85	0.45		0.61	Switzerland			0.00			
2012, Quinn (56)	185	0.31	71.0	0.72	Ireland	0.43		0.01	0.14	0.18	1.00
2012, Saedon (57)	153	0.21	70.8	0.60	UK		9.6				
2012, Thomassen (58)	143	0.24	71.0	0.62	Netherlands		9.8		0.21	0.17	
2011, Abdul-Rahman (59)	363	0.19	73.0	0.71	New Zealand				0.11	0.09	
2011, Bartlett (60)	244	0.12						0.68			
2011, Brunso (a) (61)	342	0.21	74.9	0.54	Spain		12.6				
2011, Goslin (62)	47	0.38	70.7	0.72	US	0.55	14.2	0.13			
2011, Lugo (63)	138	0.24	74.0	0.76	US				0.26		
2011, Patel (a) (64)	79	0.32			UK		11.4	0.08			
2011, Tornabene (p) (65)	105	0.04	72.0	0.71	US	0.68			0.28	0.15	0.93
2011, Verner-Cole (a) (66)	95	0.29	81.0		US						
2011, Walvick (67)	3001	0.15			US						
2011, Ypsilantis (68)	966	0.21	74.0	0.68	UK		10.0	0.00			
2010, Cowey (a) (69)	60	0.35		0.65	UK						
2010, Famorca (a) (70)	258	0.13		0.79	Canada						
2010, Maldini (71)	284	0.16	72.2	0.64	France	0.25		0.03			
2010, Manjuka (72)	54	0.26			Australia						
2009, Breuer (73)	132	0.39			Israel			1.00			1.00
2009, Mader (74)	20	0.15			US				0.05		
2009, Mari (75)	278	0.28	74.0	0.65	Spain	0.68	10.0		0.09	0.26	0.95
2009, Zhou (76)	107	0.25	72.0	0.70	US			0.10			0.42
2008, Bley (77)	41	0.51	71.0	0.53	Germany	0.76					
2008, Cetinkaya (78)	108	0.14	72.4	0.72	US		20.0	0.00	0.60	0.27	1.00
2008, Moutray (79)	110	0.19		0.78	UK				0.43	0.18	
2008, Sintler (80)	66	0.08	70.8	0.65	UK				0.24	0.08	
2007, Chaudhry (81)	102	0.07		0.45	Saudi Arabia			0.04	0.81	0.09	
2007, Ramstead (82)	141	0.26			Canada						
2007, Rodriguez-Pla (83)	125	0.37	73.8	0.67	Spain	0.57		0.00	0.30	0.18	
2007, Sharma (84)	157	0.20	76.0	0.69	Australia		11.8	0.01			

2007, Zaragoza Garcia (85)	23	0.26			Spain						
2006, Davies (86)	111	0.18	71.0	0.66	UK	0.68		0.03	0.00		1.00
2006, Karahaliou (87)	49	0.37		0.55	Greece	0.40		0.00	0.13	0.05	
2006, Lenton (88)	44	0.16	74.0		UK						1.00
2006, Mahr (89)	1520	0.15	73.1	0.67	France		13.3	0.05			
2006, Su (90)	40	0.18			US		21.7				
2005, Chong (91)	70	0.14			Australia		16.0	0.05			
2005, Taylor-Gjevre (92)	136	0.27	75.2	0.72	Canada		17.6	0.00			
2005, Vianna (93)	26	0.31			Canada						1.00
2004, Reinhard (94)	48	0.69	68.0		Germany			0.00			0.95
2004, Romera-Villegas (95)	68	0.32	77.0	0.71	Spain	1.00		0.00		0.06	
2004, Varma (96)	53	0.25	69.0		UK	0.68		0.00			
2004, Younge (97)	1113	0.34	71.2	0.64	US	0.15	28.3	0.59	0.10	0.17	0.89
2003, Hall, JK (98)	201	0.16			US					0.18	
2003, Murgatroyd (99)	12	0.58			UK			0.00			
2002, Dalbeth (100)	111	0.27			New Zealand		10.0	0.05		0.14	
2002, LeSar (101)	32	0.22	73.1	0.66	US			0.75	0.25		
2002, Mohamed (102)	51	0.33	69.5	0.71	UK		10.0		0.16	0.12	0.95
2002, Nesher (103)	32	0.28			Israel			0.94			
2002, Ray-Chaudhuri (104)	11	0.82	75.0	0.73	UK	1.00	12.0		0.27		0.18
2002, Schmidt (105)	127	0.17	70.0		Germany	0.20				0.50	1.00
2001, Liu (106)	121	0.17	70.0	0.71	US						
2000, Chakrabarty (107)	172	0.14	70.0	0.75	UK		10.0				1.00
2000, Danesh-Meyer (108)	91	0.43			US		33.0	1.00			
2000, Pless (109)	60	0.33	79.0		US			1.00			
2000, Poller (110)	102	0.34			UK		6.0	0.00			
1999, Albertini (111)	35	0.20			US		22.0	0.26			
1999, Boyev (112)	182	0.18			US		16.5	1.00			
1999, Morales-Angulo (113)	33	0.18	76.0	0.66	Spain			0.03	0.24	0.15	

Legend for Table I

n: number of temporal artery biopsies performed in each study

Yield: proportion of positive temporal artery biopsies in each study

Age: average age of patients in the study

% Female: proportion of females in the study

Country: country in which the study was performed

NZ: New Zealand

ACR >=3: proportion of patients with American College of Rheumatology score >=3

Length: average length of temporal artery biopsy specimens in millimeters

% Bilat: proportion of bilateral temporal artery biopsies performed in the study

Vision Symp: proportion of patients with vision symptoms in each study

Claudication: proportion of patients with jaw claudication

GC < 2 wks: proportion of patients who underwent temporal artery biopsy within 2 weeks of glucocorticoid initiation

Table II. Comments on Selected Article Inclusions and Exclusions Used in the Systematic Review

Main Article in systematic Review	Also retained in systematic review	Related articles that were excluded	Comment
Ing (2017)		Durling (2014) (114) Toren (2016) (115), Weis (2017) (116) Knecht (2015) (117)	Data from the excluded series are incoporated in the Ing paper. The Ottawa studies of Toren, Weis and Durling involved the same series of 259 patients.
Aranda-Valera (2017)		Garcia Carazo (2013) (118)	Both are Doppler ultrasound articles are from Hospital La Paz Madrid, Spain and Garcia Carazo is the 2nd author in the Aranda-Valera study. Although the actualy study dates are not specified, the 2017 article presents 451 consecutive patients. The 2013 paper is a meeting abstract discussing 267 patients.
Rheaume (2017) Patients from 2002-2008	Famorca (2010) Patients from 2007-2014		Both series from Hamilton with only one year of potential overlap between them.
Oh (2016)		Oh (2017)*	The original Oh article contained more patient details than the 2017 article on the same series of patients
Luqmani (2016)		Singh (2014) (119)	In these TABUL studies , Singh's 2014 article, was entitled a preliminary report, with Luqmani as a co-author, and significant overlap could not be excluded.
Kisza (2013) Patients from 1994-2011	Danesh-Meyer (2000) Patients from 1988-1998	Murchison (2012) (120)Patients from 2001-2006	In these Wills Eye Neuro-ophthalmology reports, the Murchison study time frame overlapped Kisza completely, but Danesh Meyer had six potential years of non overlapping patients.
Bley (2008)		Bley (2005) (121)	Apparent overlap of study patients

Ramstead (2007) Patients from 1998-2003	Taylor-Gjevre (2005) Patients from 1996-2002		Both series from Sasakatoon, SK with marked overlap in study periods. As such Ramstead's patients from the eye clinic were excluded from the city-wide calculations of Taylor-Gjevre.
Younge (2004) Patients from 1988-1997	Calamia Patients from 1994-2004 Fritzlen (2015) Patients from 2004-2010	Kermani (2012) (122)Patients from 2000-2008 Chandran (2015) (123) (2000-2009) Udayakamar (2013) (124)Patients from 2005-2009 Rieck (2011) (125) Patients from 2002-2006	In these Mayo Clinic articles. Younge reported all Rochester cases from 1988 to 1997. Fritzlen reported Mayo Rochester patients from 2004-2010. Calamia reported Mayo patients from Rochester, Jacksonville and Scottsdale from 1994-2004. Chandran reported Mayo Rochester patients from 2000-2009, specifically Olmsted County. Kermani reported Mayo Rochester patients from 2000-2008. Udayakumar reported Mayo Rochester patients from 2005-2009. Rieck reported his single surgeon series from 2002-2006 at Mayo Rochester.

* Oh, L. J., Wong, E., Andrici, J., McCluskey, P., Smith, J. E.H. and Gill, A. J. (), The full blood count as an ancillary test to support the diagnosis of giant cell arteritis. Intern Med J. Accepted Author Manuscript. doi:10.1111/imj.13713 (epub ahead of print)

CLARIFICATION OF HEALED ARTERITIS

The inclusion of healed arteritis in our group of positive biopsy results requires a caveat.

There are no absolute histopathological features that distinguish healed arteritis from changes due to atherosclerosis, arteriosclerosis or trauma (often referred to as "healed arterial injury"). (126) (127) (128) Indeed, in a study of the interobserver variability in the histopathologic diagnosis of giant cell arteritis, the category of healed arteritis had the greatest interobserver variability (up to 50%).(1) The interpretation of this result as representing healed arteritis is a clinic-pathologic decision made in conjunction with the clinical and serological features of each individual patient. Most studies do not specify the diagnostic criteria used to qualify a case as healed arteritis, but as this diagnosis results in treatment, this was included as a positive biopsy.

SUM number of cases and biopsies (Stata Code)

```
egen sumn = sum(n)

egen sumcases = sum(cases)
```

HISTOGRAM COMMAND (Stata Code)

```
histogram _ES, bin(14) frequency ytitle(Number of studies) xtitle(Proportion of Positive Biopsies)
xlabel(#20) title(Yield of Temporal Artery Biopsy from 113 Studies)
```

RISK OF BIAS SUMMARY GRAPH (Stata Code)

```
. tab selectionbias

  Selection |
```

bias	Freq.	Percent	Cum.
+	84	74.34	74.34
-	21	18.58	92.92
?	8	7.08	100.00
Total	113	100.00	

. tab performancebias

Performance bias	Freq.	Percent	Cum.
+	107	94.69	94.69
-	4	3.54	98.23
?	2	1.77	100.00
Total	113	100.00	

. tab attritionbias

Attrition bias	Freq.	Percent	Cum.
+	48	42.48	42.48
-	50	44.25	86.73
?	15	13.27	100.00
Total	113	100.00	

. tab reportingbias

Reporting bias	Freq.	Percent	Cum.
+	102	90.27	90.27
-	8	7.08	97.35
?	3	2.65	100.00
Total	113	100.00	

. tab otherbias

Other bias	Freq.	Percent	Cum.
+	99	87.61	87.61
-	11	9.73	97.35
?	3	2.65	100.00
Total	113	100.00	

var1	**low**	**high**	**unclear**
Selection_bias	.7434	.1858	.0708
Performance_bias	.9483	.0354	.0177
Detection_bias	.1034	0	.8966
Attrition_bias	.4248	.4425	.1327
Reporting_bias	.9027	.0708	.0265
Other_bias	.8761	.0973	.0265

```
generate total = low + high + unclear
generate order = 1 if var1=="Selection_bias"
replace order = 2 if var1=="Performance_bias"
replace order = 3 if var1=="Detection_bias"
replace order = 4 if var1=="Attrition_bias"
replace order = 5 if var1=="Reporting_bias"
replace order = 6 if var1=="Other_bias"

graph hbar (asis) low high unclear, over (var1, sort(order) ) stack title ("Risk of Bias Summary")
bar(1,color(gs14)) bar(2,color(black)) bar (3,color(gs8))
```

MEAN & MEDIAN CALCULATIONS

sum _ES, detail

```
                             ES
-------------------------------------------------------------
      Percentiles      Smallest
 1%          .04       .0380952
 5%     .1048951            .04
10%     .1317829            .06       Obs                 113
25%     .1656051       .0686275       Sum of Wgt.         113

50%          .25                      Mean           .2768651
                        Largest       Std. Dev.      .1523542
75%     .3431373          .6875
90%        .4375       .7083333       Variance       .0232118
```

```
95%     .6326531        .8181818        Skewness        1.444497
99%     .8181818        .8181818        Kurtosis        5.457795
```

95% confidence interval of the median   (n=113)

http://www.ucl.ac.uk/ich/short-courses-events/about-stats-courses/stats-rm/Chapter_8_Content/confidence_interval_single_median

The lower 95% confidence limit is given by the:

$$\frac{n}{2} - \frac{1.96\sqrt{n}}{2} \text{ }^{\text{th}} \text{ ranked value}$$

The upper 95% confidence limit is given by the:

$$1 + \frac{n}{2} + \frac{1.96\sqrt{n}}{2} \text{ }^{\text{th}} \text{ ranked value}$$

Lower confidence limit

$$\frac{113}{2} - 1.96 \times \frac{\sqrt{113}}{2}$$

$= 46.08246\ldots$

Which is approximately the 46^{th} ranked value =0.2143

Upper confidence limit

$$1 + \frac{113}{2} + 1.96 \times \frac{\sqrt{113}}{2}$$

$= 67.91754\ldots$

Which is approximately the 68th ranked value = 0.2703

Rank Yield

40	.2038217
41	.2054795
42	.2072072
43	.2076023
44	.2083333
45	.2091503
46	.2142857
47	.21875
48	.2227723
49	.2251185
50	.2342007
51	.2352941
52	.2377622
53	.2391304
54	.2401961
55	.241791
56	.245283
57	.25
58	.25
59	.2523364
60	.2535211
61	.2569002
62	.2583333
63	.2592593
64	.2601744
65	.2608696
66	.2624114
67	.2682158
68	.2702703
69	.2720588
70	.2807018

Random Effects Meta-Analysis (Stata 14.2)

On meta-analysis of proportions using random effects analysis with Freeman-Tukey double arcsine transformation and exact confidence intervals, the pooled estimate was

0.25 (95% confidence interval 0.23, 0.27)

I^2 (variation in effect size attributeable to heterogeneity) = 92.08%

```
metaprop cases n, random ftt cimethod(exact)
```

Study	ES	[95% Conf.	Interval]	% Weight
1	0.04	0.01	0.09	0.92
2	0.04	0.00	0.14	0.77
3	0.06	0.01	0.17	0.77
4	0.07	0.03	0.14	0.92
5	0.08	0.03	0.17	0.84
6	0.10	0.06	0.17	0.97
7	0.12	0.08	0.17	1.03
8	0.12	0.08	0.18	1.00
9	0.13	0.04	0.29	0.66
10	0.13	0.05	0.24	0.80
11	0.13	0.09	0.18	1.03
12	0.13	0.08	0.20	0.95
13	0.14	0.09	0.21	0.97
14	0.14	0.08	0.22	0.93
15	0.14	0.09	0.20	0.99
16	0.14	0.07	0.25	0.85
17	0.15	0.13	0.17	1.10
18	0.15	0.03	0.38	0.53
19	0.15	0.11	0.20	1.02
20	0.15	0.14	0.17	1.11
21	0.16	0.09	0.24	0.91
22	0.16	0.12	0.21	1.04
23	0.16	0.07	0.30	0.74
24	0.16	0.11	0.22	1.01
25	0.16	0.10	0.25	0.91
26	0.17	0.14	0.19	1.09

27	|	0.17	0.10	0.24	0.94
28	|	0.17	0.11	0.24	0.95
29	|	0.17	0.11	0.23	0.98
30	|	0.17	0.07	0.33	0.72
31	|	0.18	0.14	0.22	1.06
32	|	0.18	0.11	0.26	0.93
33	|	0.18	0.13	0.25	0.99
34	|	0.18	0.13	0.25	1.00
35	|	0.18	0.07	0.35	0.67
36	|	0.19	0.12	0.28	0.93
37	|	0.19	0.15	0.24	1.05
38	|	0.20	0.19	0.21	1.11
39	|	0.20	0.08	0.37	0.68
40	|	0.20	0.14	0.28	0.98
41	|	0.21	0.12	0.32	0.86
42	|	0.21	0.14	0.29	0.93
43	|	0.21	0.17	0.25	1.05
44	|	0.21	0.13	0.30	0.91
45	|	0.21	0.15	0.28	0.98
46	|	0.21	0.19	0.24	1.09
47	|	0.22	0.09	0.40	0.66
48	|	0.22	0.18	0.27	1.06
49	|	0.23	0.19	0.27	1.06
50	|	0.23	0.20	0.27	1.08
51	|	0.24	0.07	0.50	0.49
52	|	0.24	0.17	0.32	0.97
53	|	0.24	0.17	0.32	0.96
54	|	0.24	0.18	0.30	1.01
55	|	0.24	0.20	0.29	1.05
56	|	0.25	0.14	0.38	0.79
57	|	0.25	0.18	0.33	0.97
58	|	0.25	0.10	0.47	0.58
59	|	0.25	0.17	0.35	0.93
60	|	0.25	0.16	0.37	0.85
61	|	0.26	0.22	0.30	1.07
62	|	0.26	0.20	0.32	1.02
63	|	0.26	0.15	0.40	0.79
64	|	0.26	0.23	0.29	1.08
65	|	0.26	0.10	0.48	0.57
66	|	0.26	0.19	0.34	0.97
67	|	0.27	0.25	0.29	1.11
68	|	0.27	0.19	0.36	0.93
69	|	0.27	0.20	0.35	0.96
70	|	0.28	0.17	0.42	0.80
71	|	0.28	0.14	0.47	0.66

72	0.28	0.23	0.34	1.04
73	0.29	0.24	0.34	1.05
74	0.29	0.26	0.32	1.09
75	0.29	0.21	0.40	0.91
76	0.31	0.14	0.52	0.60
77	0.31	0.25	0.39	1.00
78	0.32	0.22	0.43	0.87
79	0.32	0.22	0.45	0.84
80	0.33	0.22	0.47	0.82
81	0.33	0.24	0.43	0.92
82	0.33	0.21	0.48	0.78
83	0.34	0.31	0.36	1.10
84	0.34	0.19	0.52	0.68
85	0.34	0.25	0.44	0.92
86	0.35	0.31	0.39	1.09
87	0.35	0.23	0.48	0.82
88	0.35	0.30	0.42	1.03
89	0.35	0.19	0.55	0.65
90	0.36	0.24	0.50	0.81
91	0.37	0.31	0.42	1.05
92	0.37	0.23	0.52	0.77
93	0.37	0.28	0.46	0.95
94	0.38	0.25	0.54	0.76
95	0.38	0.14	0.68	0.42
96	0.39	0.32	0.45	1.02
97	0.39	0.30	0.48	0.96
98	0.39	0.34	0.44	1.06
99	0.41	0.37	0.44	1.09
100	0.43	0.38	0.48	1.07
101	0.43	0.33	0.54	0.90
102	0.44	0.20	0.70	0.47
103	0.45	0.34	0.56	0.89
104	0.51	0.35	0.67	0.72
105	0.55	0.39	0.70	0.73
106	0.55	0.46	0.64	0.94
107	0.58	0.28	0.85	0.40
108	0.63	0.53	0.73	0.91
109	0.68	0.51	0.82	0.71
110	0.69	0.54	0.81	0.76
111	0.71	0.49	0.87	0.58
112	0.82	0.48	0.98	0.38
113	0.82	0.48	0.98	0.38
Random pooled ES	0.25	0.23	0.27	100.00

```
Heterogeneity chi^2 =    1414.23 (d.f. = 112) p =       0.00
I^2 (variation in ES attributable to heterogeneity) =     92.08%
Estimate of between-study variance Tau^2 =       0.04

Test of ES=0 : z=      42.35 p =       0.00
```

IV Het analysis (MetaXL)

`=MAInputTable("Fixed effects, heterogeneity","Prev","IVhet",Ax:Cy)`

where x and y are the row designation in Excel

Figure I: Forest Plot   Pooled estimate =0.23 (95% CI 0.20, 0.27)   n=113, I^2 =92%

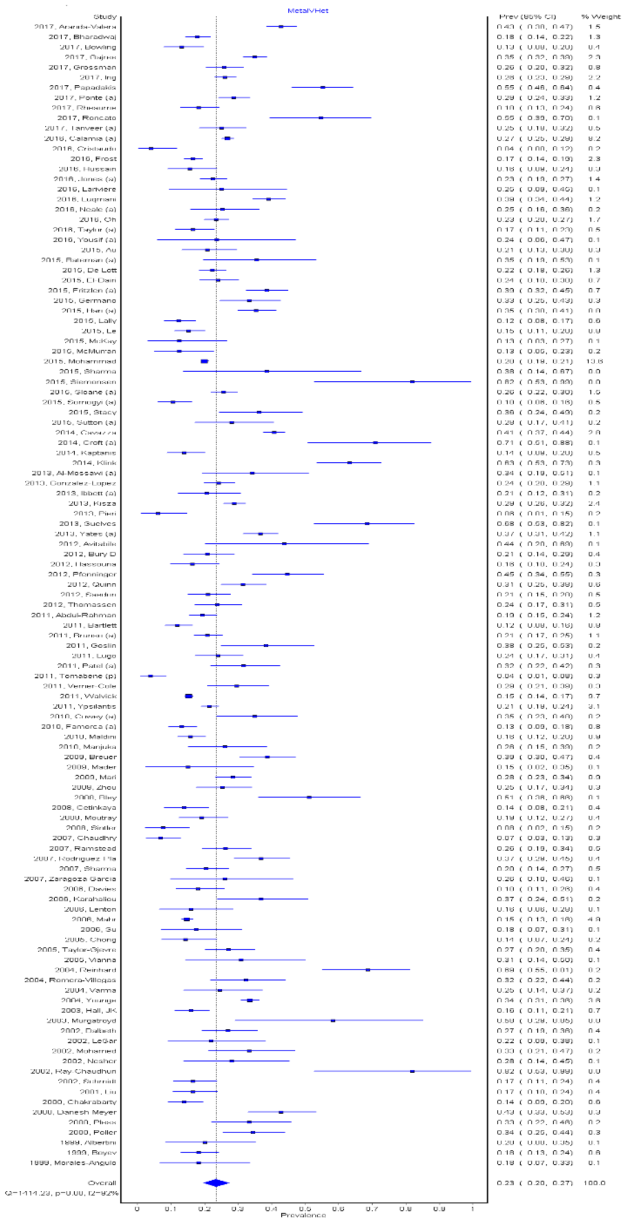
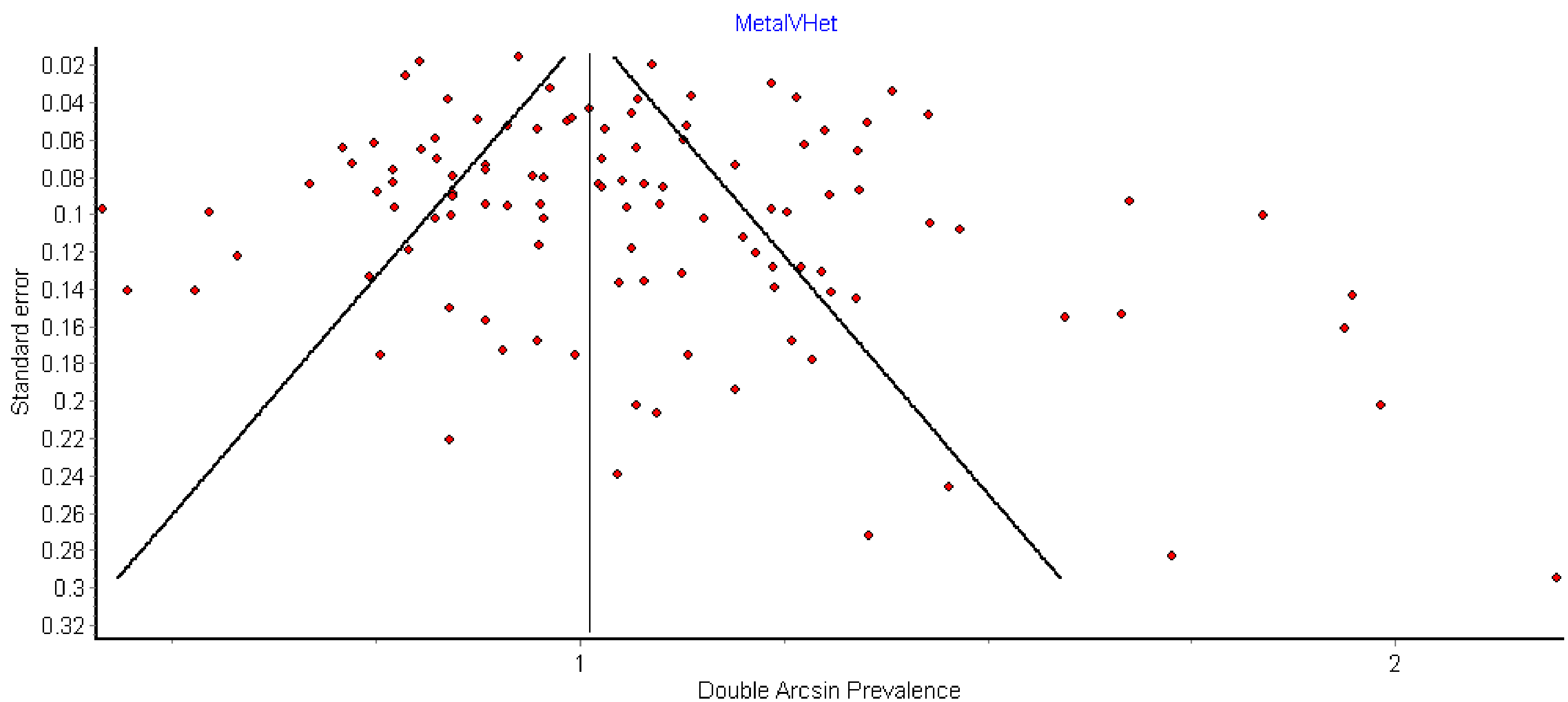

MetaIVHet
Study
Prev (95% CI)
% Weight
2017, Aranda-Valera 0.43 (0.38, 0.47) 1.5
2017, Bharadwaj 0.18 (0.14, 0.22) 1.3
2017, Bowling 0.13 (0.08, 0.20) 0.4
2017, Gajree 0.35 (0.32, 0.39) 2.3
2017, Grossman 0.26 (0.20, 0.32) 0.8
2017, Ing 0.26 (0.23, 0.29) 2.2
2017, Papadakis 0.55 (0.46, 0.64) 0.4
2017, Ponte (a) 0.29 (0.24, 0.33) 1.2
2017, Rhesurrie 0.18 (0.13, 0.24) 0.6
2017, Roncato 0.55 (0.39, 0.70) 0.1
2017, Tanveer (a) 0.25 (0.18, 0.32) 0.5
2016, Calamia (a) 0.27 (0.25, 0.29) 8.2
2016, Cristaudo 0.04 (0.00, 0.12) 0.2
2016, Frost 0.17 (0.14, 0.19) 2.3
2016, Hussain 0.16 (0.09, 0.24) 0.3
2016, Jones (a) 0.23 (0.19, 0.27) 1.4
2016, LaMere 0.25 (0.09, 0.46) 0.1
2016, Luqmani 0.39 (0.34, 0.44) 1.2
2016, Neale (a) 0.25 (0.16, 0.36) 0.2
2016, Oh 0.23 (0.20, 0.27) 1.7
2016, Taylor (a) 0.17 (0.11, 0.23) 0.5
2016, Yousif (a) 0.24 (0.06, 0.47) 0.1
2015, Au 0.21 (0.13, 0.30) 0.3
2015, Bateman (a) 0.35 (0.19, 0.53) 0.1
2015, De Lott 0.22 (0.18, 0.26) 1.3
2015, El-Dairi 0.24 (0.18, 0.30) 0.7
2015, Fritzlen (a) 0.39 (0.32, 0.45) 0.7
2015, Germano 0.33 (0.25, 0.43) 0.3
2015, Han (a) 0.35 (0.30, 0.41) 0.8
2015, Lally 0.12 (0.08, 0.17) 0.6
2015, Le 0.15 (0.11, 0.20) 0.8
2015, McKay 0.13 (0.03, 0.27) 0.1
2015, McMurran 0.13 (0.05, 0.23) 0.2
2015, Mohammad 0.20 (0.18, 0.21) 13.8
2015, Sharma 0.38 (0.14, 0.67) 0.0
2015, Siemonsen 0.82 (0.53, 0.99) 0.0
2015, Sloane (a) 0.26 (0.22, 0.30) 1.6
2015, Somogyi (a) 0.10 (0.06, 0.16) 0.5
2015, Stacy 0.36 (0.24, 0.49) 0.2
2015, Sutton (a) 0.29 (0.17, 0.41) 0.2
2014, Cavazza 0.41 (0.37, 0.44) 2.0
2014, Croft (a) 0.71 (0.51, 0.88) 0.1
2014, Kaptanis 0.14 (0.09, 0.20) 0.5
2014, Klink 0.63 (0.53, 0.73) 0.3
2013, Al-Mossawi (a) 0.34 (0.19, 0.51) 0.1
2013, Gonzalez-Lopez 0.24 (0.20, 0.29) 1.1
2013, Ibbott (a) 0.21 (0.12, 0.31) 0.2
2013, Kisza 0.29 (0.26, 0.32) 2.4
2013, Pieri 0.08 (0.01, 0.15) 0.2
2013, Suelves 0.68 (0.53, 0.82) 0.1
2013, Yates (a) 0.37 (0.31, 0.42) 1.1
2012, Avitabile 0.44 (0.20, 0.69) 0.1
2012, Bury D 0.21 (0.14, 0.29) 0.4
2012, Hassouna 0.16 (0.10, 0.24) 0.3
2012, Pfenninger 0.45 (0.34, 0.55) 0.3
2012, Quinn 0.31 (0.25, 0.38) 0.6
2012, Saedon 0.21 (0.15, 0.29) 0.5
2012, Thomassen 0.24 (0.17, 0.31) 0.5
2011, Abdul-Rahman 0.19 (0.15, 0.24) 1.2
2011, Bartlett 0.12 (0.08, 0.16) 0.9
2011, Bruneo (a) 0.21 (0.17, 0.25) 1.1
2011, Goslin 0.38 (0.25, 0.53) 0.2
2011, Lugo 0.24 (0.17, 0.31) 0.4
2011, Patel (a) 0.32 (0.22, 0.42) 0.3
2011, Tomabene (p) 0.04 (0.01, 0.08) 0.3
2011, Verner-Cole 0.29 (0.21, 0.39) 0.3
2011, Walvick 0.15 (0.14, 0.17) 9.7
2011, Ypsilantis 0.21 (0.19, 0.24) 3.1
2010, Cravey (a) 0.35 (0.23, 0.48) 0.2
2010, Famorca (a) 0.13 (0.09, 0.18) 0.8
2010, Maldini 0.16 (0.12, 0.20) 0.9
2010, Manjuka 0.26 (0.15, 0.39) 0.2
2009, Breuer 0.39 (0.30, 0.47) 0.4
2009, Mader 0.15 (0.02, 0.35) 0.1
2009, Mari 0.28 (0.23, 0.34) 0.9
2009, Zhou 0.25 (0.17, 0.34) 0.3
2008, Riley 0.51 (0.36, 0.66) 0.1
2008, Cetinkaya 0.14 (0.08, 0.21) 0.4
2008, Moutray 0.19 (0.12, 0.27) 0.4
2008, Sintler 0.08 (0.02, 0.15) 0.2
2007, Chaudhry 0.07 (0.03, 0.13) 0.3
2007, Ramstead 0.26 (0.19, 0.34) 0.5
2007, Rodriguez Pla 0.37 (0.29, 0.45) 0.4
2007, Sharma 0.20 (0.14, 0.27) 0.5
2007, Zaragoza Garcia 0.26 (0.10, 0.46) 0.1
2006, Davies 0.18 (0.11, 0.26) 0.4
2006, Karahaliou 0.37 (0.24, 0.51) 0.2
2006, Lenton 0.16 (0.06, 0.29) 0.1
2006, Mahr 0.15 (0.13, 0.18) 4.9
2006, Su 0.18 (0.07, 0.31) 0.1
2005, Chong 0.14 (0.07, 0.24) 0.2
2005, Taylor-Gjevre 0.27 (0.20, 0.35) 0.4
2005, Vianna 0.31 (0.14, 0.50) 0.1
2004, Reinhard 0.69 (0.55, 0.81) 0.2
2004, Romera-Villegas 0.32 (0.22, 0.44) 0.2
2004, Varma 0.25 (0.14, 0.37) 0.2
2004, Younge 0.34 (0.31, 0.38) 3.6
2003, Hall, JK 0.16 (0.11, 0.21) 0.7
2003, Murgatroyd 0.58 (0.29, 0.85) 0.0
2002, Dalbeth 0.27 (0.19, 0.36) 0.4
2002, LeSar 0.22 (0.09, 0.38) 0.1
2002, Mohamed 0.33 (0.21, 0.47) 0.2
2002, Nesher 0.28 (0.14, 0.45) 0.1
2002, Ray-Chaudhuri 0.82 (0.63, 0.99) 0.0
2002, Schmidt 0.17 (0.11, 0.24) 0.4
2001, Liu 0.17 (0.10, 0.24) 0.4
2000, Chakrabarty 0.14 (0.09, 0.20) 0.6
2000, Danesh Meyer 0.43 (0.33, 0.53) 0.3
2000, Pless 0.33 (0.22, 0.46) 0.2
2000, Poller 0.34 (0.25, 0.44) 0.3
1999, Albertini 0.20 (0.08, 0.35) 0.1
1999, Boyev 0.18 (0.13, 0.24) 0.6
1999, Morales-Angulo 0.18 (0.07, 0.33) 0.1
Overall 0.23 (0.20, 0.27) 100.0
Q=1414.23, p=0.00, I2=92%
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Prevalence

Figure II: Funnel plot of 113 studies used in Systematic Review



The funnel plot was asymmetric, with minor asymmetry (1.79) on LFK index from doi plot (126).

Metaregression commands (Stata)

```
metareg _ES   variable, wsse (_seES)

metareg _ES  Age, wsse (_seES) graph
```

Subgroup Analysis

Subgroup analysis is more appropriate for categorical variables rather than continuous variables. However to further explore causes of heterogeneity, subgroup analysis of the predictors were dichotomized at their aggregate mean cut points. Using the IVHet model did *not* show a statistically significant difference in the TAB yield from articles with older versus younger patients, shorter versus longer biopsy lengths, articles published in the first versus second decade of the systematic review, smaller versus larger studies, or studies with a higher versus lower proportion of: jaw claudication, vision symptoms, bilateral TAB, or non-histologic ACRscore >3. Imaging studies, a lower proportion of women than men, and a higher proportion of patients biopsied within 2 weeks of glucocorticoid initiation were associated with a higher TAB yield, at p values <.05. However, the two latter subgroup t-tests would not be statistically significant with Bonferroni correction at p=.005.

Table III: Sub Group Analysis using Inverse Variance Heterogeneity Model

	n	Mean	Yield of TAB Pooled Estimate	95% confidence interval	Q (p=0.00 for all)	I^2	LFK index (asymmetry)	t-test, equal variance p value
Overall	113	N/A	0.23	0.20, 0.27	1414.23	92%	1.79 (minor)	N/A
Age < 72.7 years	40	70.6	0.24	0.20, 0.29	458.89	92%	1.59 (minor)	0.999
Age >=72.7 years	33	75.2	0.24	0.17, 0.31	439.61	93%		
%Female < 0.68	31	0.61	0.26	0.19, 0.33	483.95	94%	1.00 (no)	0.034
%Female >=0.68	44	0.72	0.23	0.18, 0.28	521.70	92%		
Avg. Length < 14 mm	25	10.0	0.23	0.17, 0.28	337.35	92%	0.38 (no)	0.080
Avg. Length >= 14 mm	17	20.0	0.26	0.21, 0.31	103.9	85%		
Bilat. TAB < 20%	40	0.02	0.24	0.18, 0.29	523.21	93%	0.06 (no)	0.092
Bilat. TAB >=20%	15	0.68	0.27	0.21, 0.34	119.04	88%		
ACR>=3 in < 62%	13	0.44	0.29	0.21, 0.37	175.56	93%	-0.17 (no)	0.057
ACR>=3 in > =62%	18	0.81	0.23	0.15, 0.32	187.88	91%		
Jaw Claud. < 20%	21	0.13	0.28	0.22, 0.34	215.04	90%	-1.75 (minor)	0.393
Jaw Claud. >=20%	12	0.32	0.26	0.19, 0.33	77.78	86%		
Vision Symp < 27%	21	0.16	0.30	0.25, 0.35	150.61	87%	-1.34 (minor)	0.508
Vision Symp >=27%	16	0.43	0.28	0.16, 0.41	222.99	93%		
Steroids <2wks <85%	7	0.43	0.20	0.13, 0.28	29.87	80%	0.38 (no)	0.020
Steroids <2 wks >=85%	21	0.98	0.29	0.20, 0.38	285.45	93%		
Study Size < 273	88	96	0.24	0.21, 0.27	719.54	88%	1.79 (minor)	0.195
Study Size >=273	25	897	0.23	0.19, 0.28	694.10	97%		
Non-imaging Study	96	N/A	0.23	0.19, 0.27	1255.17	92%	1.79 (minor)	0.001
Imaging Study	17	N/A	0.34	0.23, 0.45	95.80	84%		
Studies: 1988-2007	33	N/A	0.23	0.15, 0.31	303.74	89%	1.79 (minor)	0.401
Studies: 2008-2017	80	N/A	0.24	0.19, 0.28	1109.23	93%		

n = # of studies

%Female = proportion of females in study

Bilat. TAB = bilateral temporal artery biopsy

ACR>=3 = American College of Rheumatology Score of 3 or greater

Jaw Claud = jaw claudication

Vision Symp = Vision symptoms

Steroids < 2 weeks: proportion of patients who were biopsied within the 2-week corticosteroid treatment window

N/A = not applicable

Multivariable Meta-regression of 15 studies: (Age, %female, Vision Symptoms, Steroid duration prior to biopsy)

When the statistically significant predictors from univariate metaregression (age, imaging study) and subgroup analysis (sex, steroid duration, imaging) were combined in a multivariable metaregression, 15 studies could be analyzed, but none of the predictors was statistically significant.

```
metareg _ES  avg_age fetomaratio imagestudy steroids252 , wsse (_seES)

Meta-regression                                       Number of obs  =       21
REML estimate of between-study variance               tau2           =  .01495
% residual variation due to heterogeneity             I-squared_res  =  64.39%
Proportion of between-study variance explained        Adj R-squared  = -32.95%
Joint test for all covariates                         Model F(4,16)  =    0.60
With Knapp-Hartung modification                       Prob > F       =  0.6714
------------------------------------------------------------------------------
         _ES |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     avg_age |   .0207356   .0239508     0.87   0.399    -.0300377     .071509
 fetomaratio |  -.8894943    1.12986    -0.79   0.443    -3.284691    1.505703
  imagestudy |   .0864345   .1233424     0.70   0.494    -.1750397    .3479087
 steroids252 |   .0671905   .1752626     0.38   0.706    -.3043497    .4387306
       _cons |  -.6743519   1.903786    -0.35   0.728    -4.710199    3.361495
```

There are WIDE fluctuations in the meta-regression coefficients depending on the chosen model

```
metareg _ES  imagestudy n era avg_age fetomaratio visionsympt steroids252 , wsse (_seES )

Meta-regression                                       Number of obs  =       15
REML estimate of between-study variance               tau2           =  .01573
```

```
% residual variation due to heterogeneity           I-squared_res  =  69.38%
Proportion of between-study variance explained      Adj R-squared  = -204.95%
Joint test for all covariates                       Model F(7,7)   =     0.97
With Knapp-Hartung modification                     Prob > F       =   0.5149
------------------------------------------------------------------------------
         _ES |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  imagestudy |   .0688246   .1319523     0.52   0.618    -.2431929    .3808422
           n |   .0001984   .0001714     1.16   0.285    -.0002068    .0006036
         era |  -.2360274   .1473591    -1.60   0.153    -.5844762    .1124214
     avg_age |   .0824388   .0382439     2.16   0.068    -.0079935    .1728712
 fetomaratio |   4.626139   2.685168     1.72   0.129    -1.723274    10.97555
 visionsympt |  -.3557774   .4184898    -0.85   0.423    -1.345349    .6337938
 steroids252 |   .0586908    .244369     0.24   0.817      -.51915    .6365316
       _cons |  -8.729352   3.992941    -2.19   0.065    -18.17116    .7124539
```

```
metareg _ES  imagestudy n era , wsse (_seES)

Meta-regression                                     Number of obs  =      113
REML estimate of between-study variance             tau2           =   .00468
% residual variation due to heterogeneity           I-squared_res  =   52.02%
Proportion of between-study variance explained      Adj R-squared  =   11.75%
Joint test for all covariates                       Model F(3,109) =     4.97
With Knapp-Hartung modification                     Prob > F       =   0.0028
------------------------------------------------------------------------------
         _ES |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  imagestudy |   .1315084    .036263     3.63   0.000     .0596363    .2033804
           n |  -.0000108   .0000131    -0.83   0.409    -.0000368    .0000151
         era |   .0110774   .0251072     0.44   0.660    -.0386843     .060839
       _cons |   .2382717   .0226986    10.50   0.000     .1932838    .2832596
------------------------------------------------------------------------------
```

```
. metareg _ES  imagestudy n era avg_age , wsse (_seES)

Meta-regression                                     Number of obs  =       73
REML estimate of between-study variance             tau2           =  .004515
% residual variation due to heterogeneity           I-squared_res  =   52.97%
Proportion of between-study variance explained      Adj R-squared  =   19.03%
Joint test for all covariates                       Model F(4,68)  =     3.28
With Knapp-Hartung modification                     Prob > F       =   0.0162
------------------------------------------------------------------------------
         _ES |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  imagestudy |   .1115744   .0484321     2.30   0.024     .0149296    .2082191
```

```
           n |  -.0000163    .000016    -1.02   0.311    -.0000483    .0000156
         era |   .0048111   .0324969     0.15   0.883    -.0600355    .0696577
     avg_age |   .0100658    .005383     1.87   0.066    -.0006758    .0208074
       _cons |  -.4816891   .3886093    -1.24   0.219    -1.257147    .2937687
------------------------------------------------------------------------------

. metareg _ES  imagestudy n era avg_age fetomaratio , wsse (_seES)

Meta-regression                                       Number of obs  =      62
REML estimate of between-study variance               tau2           = .005038
% residual variation due to heterogeneity             I-squared_res  =  56.85%
Proportion of between-study variance explained        Adj R-squared  =  10.08%
Joint test for all covariates                         Model F(5,56)  =    2.49
With Knapp-Hartung modification                       Prob > F       =  0.0420
------------------------------------------------------------------------------
         _ES |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  imagestudy |   .0793995   .0567131     1.40   0.167    -.0342106    .1930095
           n |  -.0000214   .0000174    -1.23   0.222    -.0000562    .0000134
         era |   .0095294   .0363508     0.26   0.794    -.0632899    .0823487
     avg_age |   .0169112   .0070417     2.40   0.020     .0028051    .0310174
 fetomaratio |  -.3010814   .2648558    -1.14   0.260    -.8316513    .2294885
       _cons |  -.7775278   .5150593    -1.51   0.137    -1.809316    .2542599
------------------------------------------------------------------------------

. metareg _ES  imagestudy n era avg_age fetomaratio avglengthmm , wsse (_seES)

Meta-regression                                       Number of obs  =      29
REML estimate of between-study variance               tau2           = .005458
% residual variation due to heterogeneity             I-squared_res  =  56.19%
Proportion of between-study variance explained        Adj R-squared  = -42.90%
Joint test for all covariates                         Model F(6,22)  =    0.66
With Knapp-Hartung modification                       Prob > F       =  0.6847
------------------------------------------------------------------------------
         _ES |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  imagestudy |  -.0039082   .1161649    -0.03   0.973    -.2448194     .237003
           n |  -.0000365   .0000545    -0.67   0.510    -.0001496    .0000766
         era |  -.0279562   .0533419    -0.52   0.605    -.1385806    .0826682
     avg_age |   .0085066   .0112448     0.76   0.457    -.0148136    .0318268
 fetomaratio |  -.5488729   .3956106    -1.39   0.179    -1.369319    .2715732
 avglengthmm |   .0004405   .0035341     0.12   0.902    -.0068889    .0077699
       _cons |    .017964   .9470775     0.02   0.985    -1.946154    1.982082
------------------------------------------------------------------------------

. metareg _ES  imagestudy n era avg_age fetomaratio avglengthmm visionsympt , wsse (_seES
> )

Meta-regression                                       Number of obs  =      13
REML estimate of between-study variance               tau2           = .000043
% residual variation due to heterogeneity             I-squared_res  =  11.12%
```

```
Proportion of between-study variance explained       Adj R-squared  =  97.69%
Joint test for all covariates                        Model F(7,5)   =    1.57
With Knapp-Hartung modification                      Prob > F       =  0.3199
------------------------------------------------------------------------------
         _ES |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  imagestudy |  -.2404681   .1113514    -2.16   0.083     -.526706    .0457697
           n |   .0001374   .0001107     1.24   0.269     -.000147    .0004219
         era |  -.2002113    .102732    -1.95   0.109    -.4642925    .0638698
     avg_age |   .0178085   .0212713     0.84   0.441    -.0368711    .0724882
 fetomaratio |   .4271131   .6017581     0.71   0.510    -1.119755    1.973982
 avglengthmm |  -.0120055   .0049521    -2.42   0.060    -.0247353    .0007242
 visionsympt |   .2243924   .2167431     1.04   0.348    -.3327634    .7815482
       _cons |  -1.041231    1.59407    -0.65   0.542    -5.138917    3.056455
------------------------------------------------------------------------------
```

```
metareg _ES  imagestudy n era avg_age fetomaratio avglengthmm visionsympt jaw_claudicat
> ion , wsse (_seES)

Meta-regression                                      Number of obs  =      11
REML estimate of between-study variance              tau2           =       0
% residual variation due to heterogeneity            I-squared_res  =   0.00%
Proportion of between-study variance explained       Adj R-squared  = 100.00%
Joint test for all covariates                        Model F(8,2)   =    1.61
With Knapp-Hartung modification                      Prob > F       =  0.4388
----------------------------------------------------------------------------------
             _ES |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-----------------+----------------------------------------------------------------
      imagestudy |  -.3196802   .1494194    -2.14   0.166    -.9625799    .3232195
               n |   .0004399   .0002035     2.16   0.163    -.0004357    .0013155
             era |  -.2349203   .1625687    -1.45   0.285     -.934397    .4645564
         avg_age |   .0257228   .0256818     1.00   0.422    -.0847772    .1362228
     fetomaratio |  -.0653678   .6342706    -0.10   0.927    -2.794414    2.663678
     avglengthmm |  -.0263791   .0132786    -1.99   0.185    -.0835121    .0307539
     visionsympt |   .4616056   .3160286     1.46   0.282    -.8981557    1.821367
jaw_claudication |   .0803299   .2399634     0.33   0.770    -.9521494    1.112809
           _cons |  -1.257362    1.84918    -0.68   0.567    -9.213743    6.699019
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