
**An update systematic review with
meta-analysis of randomised trials on
topical ciclosporin A for dry eye
disease**

(Online Supplementary File)

Index of Online Supplementary Files

Online Supplementary File 1 Data source and search strategy

Online Supplementary File 2 Risk of bias

Online Supplementary File 3 Forest plot of TBUT at baseline

Online Supplementary File 4 Forest plot of Schirmer's test score at baseline

Online Supplementary File 5 Forest plot of Fluorescein staining score at baseline

Online Supplementary File 6 Forest plot of OSDI at baseline

Online Supplementary File 7 Subset analysis of TBUT by treatment duration

Online Supplementary File 8 Subset analysis of TBUT by regimen

Online Supplementary File 9 Meta-regression of TBUT by mean age

Online Supplementary File 10 Sensitivity analysis of TBUT

Online Supplementary File 11 Small study bias of TBUT

Online Supplementary File 12 Subset analysis of Schirmer's test score by treatment duration

Online Supplementary File 13 Subset analysis of Schirmer's test score by type of test

Online Supplementary File 14 Subset analysis of Schirmer's test score by regimen

Online Supplementary File 15 Meta-regression of Schirmer's test score by mean age

Online Supplementary File 16 Small study bias of Schirmer's test score

Online Supplementary File 1
Data source and search strategy

Online Supplementary File 1

Data source and search strategy (Cochrane database & Embase)

Database (n)	Search strategy
Cochrane (n = 12)	(conjunctivitis sicca OR keratoconjunctivitis sicca OR keratitis sicca OR Dry Eye Disease OR Dry eye syndrome OR Dry eye OR cornea xerosis OR corneal xerosis) and (ciclosporin A OR ciclosporine OR cyclosporine OR cyclosporin OR CsA) and (artificial tear OR artificial tears OR lubricant eye drop OR lubricant eye drops)
Embase (n = 420)	('dry eye'/exp OR 'conjunctivitis sicca' OR 'cornea xerosis' OR 'dry eye' OR 'dry eye syndrome' OR 'dry eye syndromes' OR 'xerosis conjunctivae' OR 'dry eye disease' OR 'keratoconjunctivitis sicca'/exp OR 'keratitis sicca' OR 'keratoconjunctivitis sicca' OR 'keratoconjunctivitis sicca' OR 'corneal xerosis') AND ('cyclosporin a'/exp OR 'adi 628' OR 'adi628' OR 'cicloral' OR 'ciclosporin' OR 'ciclosporin a' OR 'ciclosporine' OR 'consupren' OR 'cyclokat' OR 'cyclosporin a' OR 'cyclosporin neoral' OR 'cyclosporine a' OR 'equoral' OR 'gengraf' OR 'ikervis' OR 'iminoral' OR 'neoral' OR 'neoral-sandimmun' OR 'nova 22007' OR 'nova22007' OR 'ol 27400' OR 'ol27400' OR 'pulminiq' OR 'restasis' OR 'sandimmun' OR 'sandimmun neoral' OR 'sandimmune' OR 'sandimmune neoral' OR 'sandimun' OR 'sandimun neoral' OR 'sandimune' OR 'sang 35' OR 'sang35' OR 'sangcya' OR 'vekacia' OR ciclosporine OR ciclosporin OR cyclosporine OR 'cyclosporin'/exp OR 'cipol' OR 'cipol-n' OR 'cyclosporin' OR 'cyclosporine' OR 'deximune' OR 'implanta' OR 'imusporin' OR csa) AND ('artificial tear'/exp OR 'artificial tear' OR 'artificial tears' OR 'confort' OR 'contears' OR 'lubricant eye drops' OR 'lubricating eye drops' OR 'ocular lubricant' OR 'ocular lubricants' OR 'optive' OR 'refresh (drug)' OR 'refresh plus' OR 'tear, artificial' OR 'unisol')
PubMed (n = 104)	(conjunctivitis sicca OR keratoconjunctivitis sicca OR keratitis sicca OR Dry Eye Disease OR Dry eye syndrome OR Dry eye OR cornea xerosis OR corneal xerosis) AND (ciclosporin A OR ciclosporine OR cyclosporine OR cyclosporin OR CsA) AND (artificial tear OR artificial tears OR lubricant eye drop OR lubricant eye drops)
Scopus (n = 8)	(conjunctivitis sicca OR keratoconjunctivitis sicca OR keratitis sicca OR Dry Eye Disease OR Dry eye syndrome OR Dry eye OR cornea xerosis OR corneal xerosis) AND (ciclosporin A OR ciclosporine OR cyclosporine OR cyclosporin OR CsA) AND (artificial tear OR artificial tears OR lubricant eye drop OR lubricant eye drops)
Web of Science (n = 98)	TOPIC:((conjunctivitis sicca OR keratoconjunctivitis sicca OR keratitis sicca OR Dry Eye Disease OR Dry eye syndrome OR Dry eye OR cornea xerosis OR corneal xerosis)) AND TOPIC: ((ciclosporin A OR ciclosporine OR cyclosporine OR cyclosporin OR CsA)) AND TOPIC:((artificial tear OR artificial tears OR lubricant eye drop OR lubricant eye drops))

Online Supplementary File 2
Risk of bias

Online Supplementary File 3

Risk of bias

Trial	Bias 1	Bias 2	Bias 3	Bias 4	Bias 5	Bias 6	Bias 7
Altıparmak et al. 2009	Unclear	Unclear	Unclear	Low	Low	Low	Low
Demiryay et al. 2011	Unclear	Unclear	High	Low	Low	Unclear	Low
Kim et al. 2009	Low	Low	High	High	High	Low	Low
Perry et al. 2006	Low	Unclear	Low	Low	High	Low	Low
Prabhasawat et al. 2012	Low	Unclear	High	Low	Low	Low	Low
Rao et al. 2010	Low	Low	Low	Low	High	Low	Low
Salib et al. 2006	Low	Unclear	Low	Low	Low	Unclear	Low
Schechter et al. 2009	Low	Low	Low	Low	Low	Unclear	Low
Willen et al. 2008	Unclear	Low	Low	Low	Low	Low	Low
Wu et al. 2009	Unclear	High	High	High	Low	Unclear	Unclear
Yang et al. 2016	Unclear	Unclear	High	High	Low	Unclear	Unclear

Bias 1, sequence generation.

Bias 2, allocation concealment.

Bias 3, blinding of participants and personnel.

Bias 4, blinding of outcome assessment.

Bias 5, incomplete outcome data.

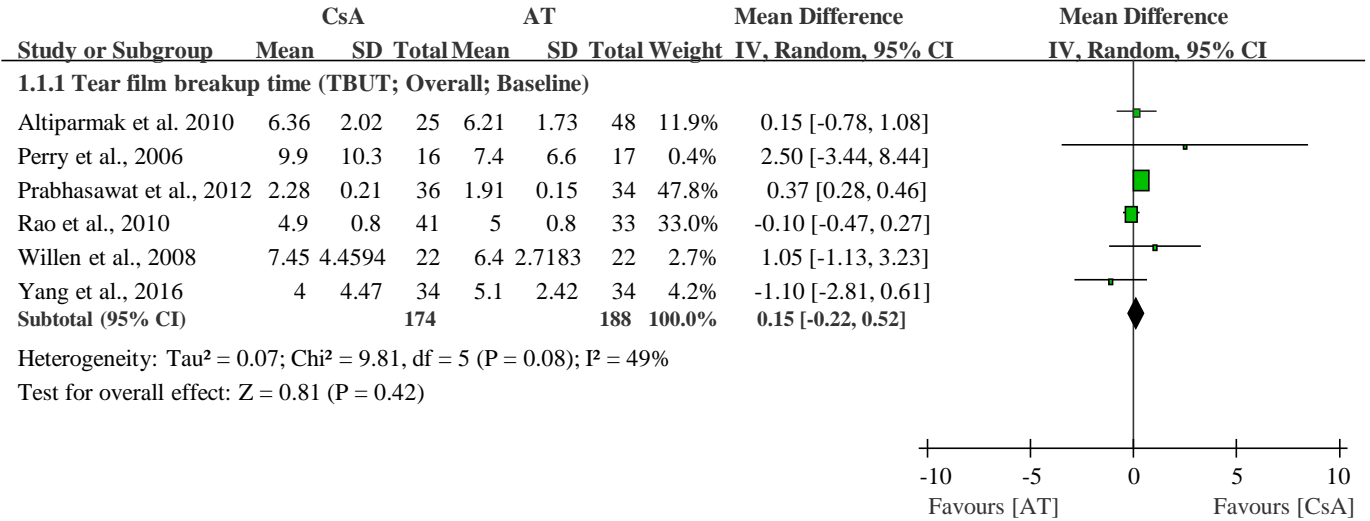
Bias 6, selective reporting.

Bias 7, other source of bias.

Online Supplementary File 3-6
Baseline

Online Supplementary File 3

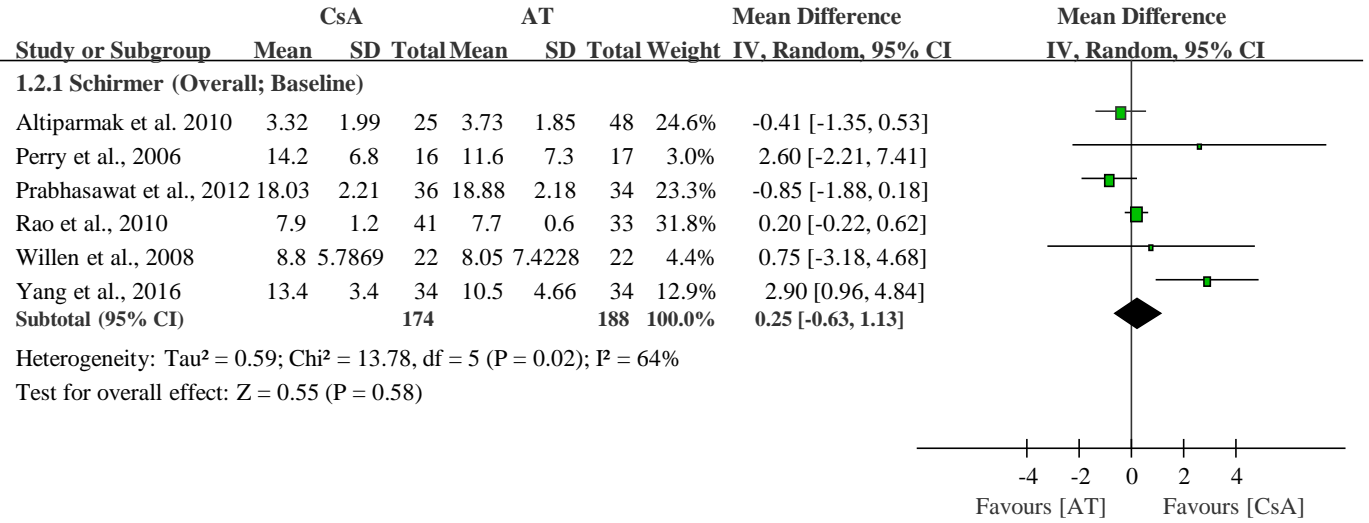
Forest plot of baseline TBUT



AT, artificial tears; CI, confidence interval; CsA, cyclosporine A; IV, inverse variance; SD, standard deviation.

Online Supplementary File 4

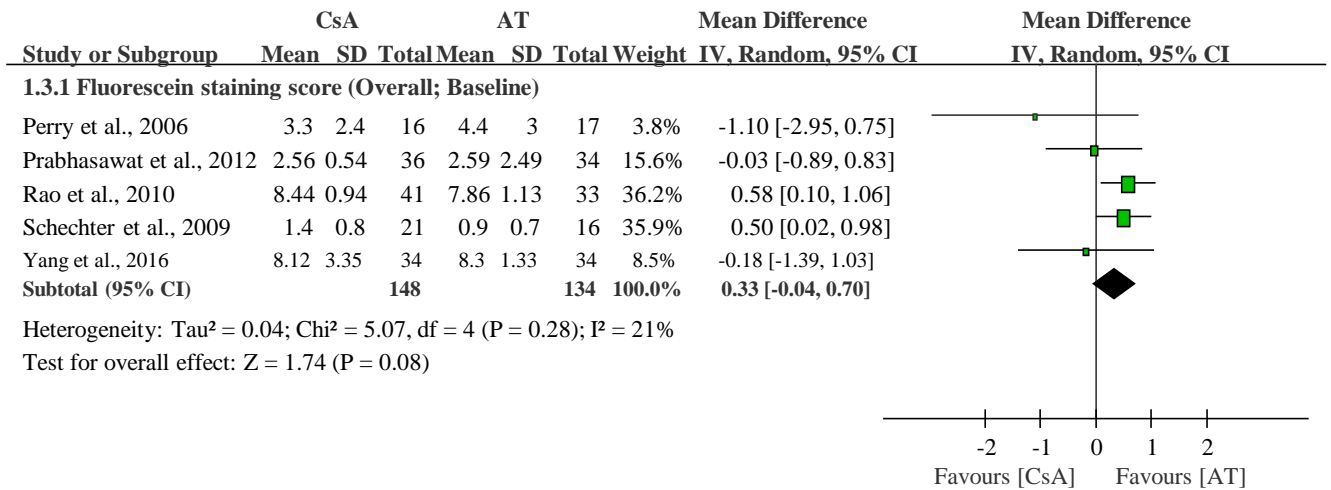
Forest plot of baseline Schirmer's test score



AT, artificial tears; CI, confidence interval; CsA, cyclosporine A; IV, inverse variance; SD, standard deviation.

Online Supplementary File 5

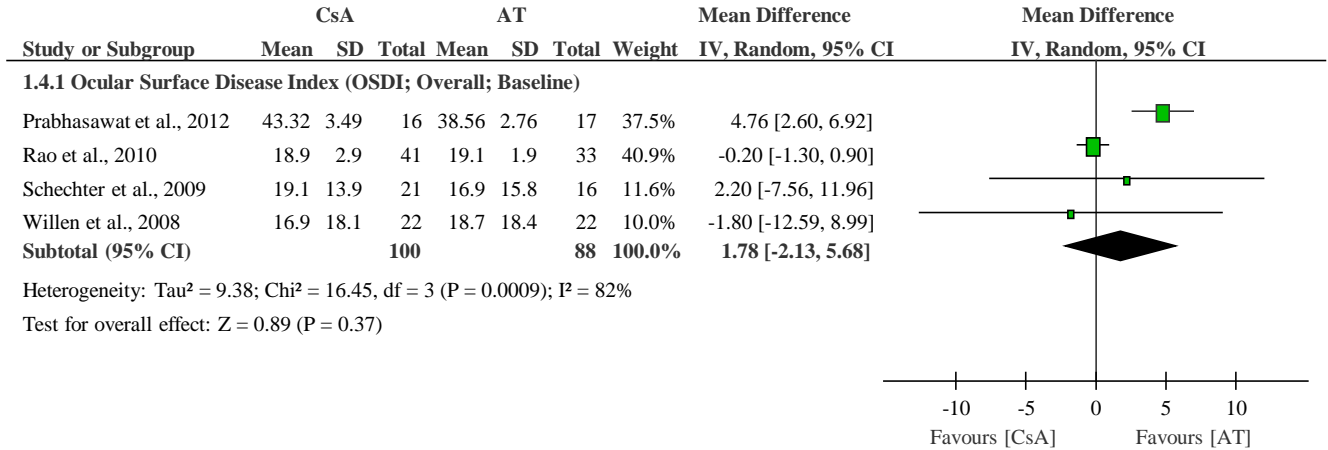
Forest plot of baseline Fluorescein staining score



AT, artificial tears; CI, confidence interval; CsA, cyclosporine A; IV, inverse variance; SD, standard deviation.

Online Supplementary File 6

Forest plot of baseline OSDI score

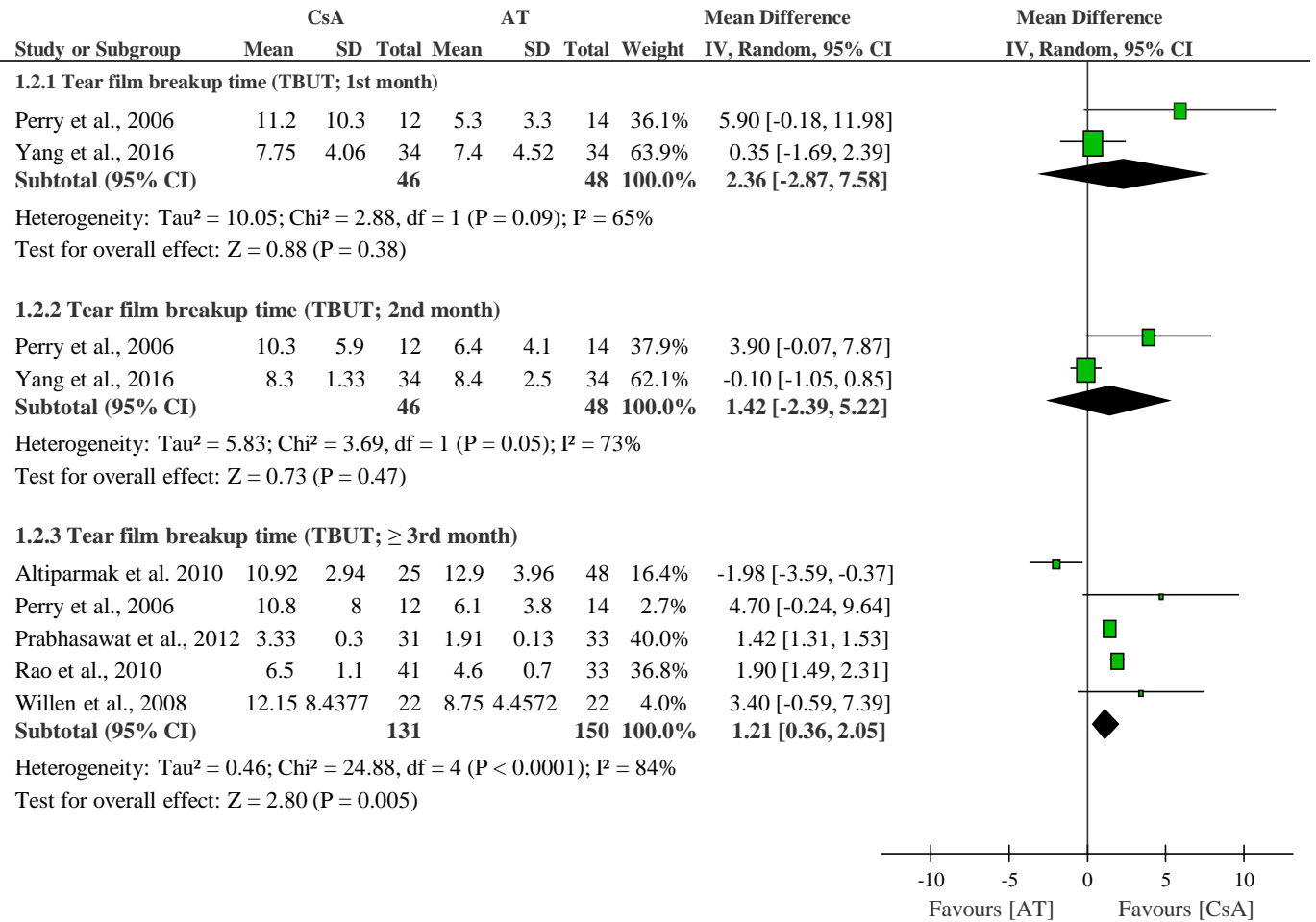


AT, artificial tears; CI, confidence interval; CsA, cyclosporine A; IV, inverse variance; SD, standard deviation.

Online Supplementary File 7-11
Further analysis of Tear breakup time (TBUT)

Online Supplementary File 7

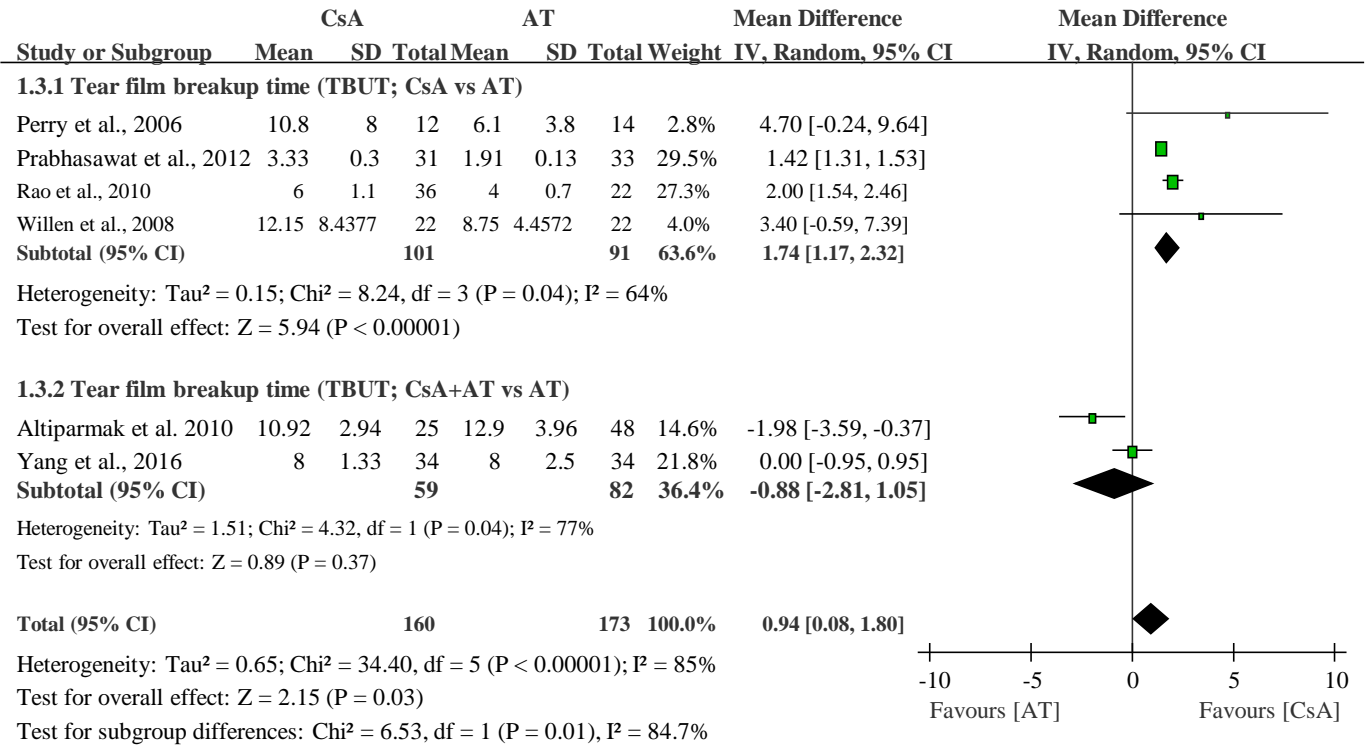
Subset analysis of TBUT by treatment duration



AT, artificial tears; CI, confidence interval; CsA, cyclosporine A; IV, inverse variance; SD, standard deviation.

Online Supplementary File 8

Subset analysis of TBUT by regimen

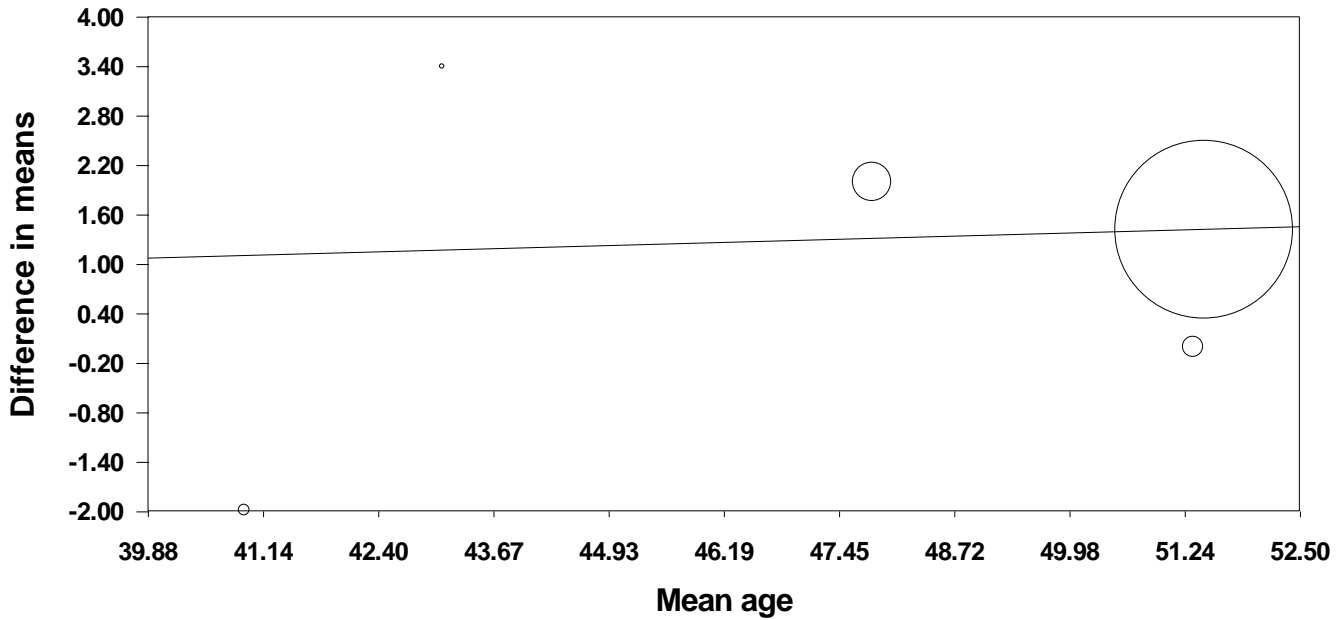


AT, artificial tears; CI, confidence interval; CsA, cyclosporine A; IV, inverse variance; SD, standard deviation.

Online Supplementary File 9

Meta-regression of TBUT by mean age

Regression of Mean age on Difference in means



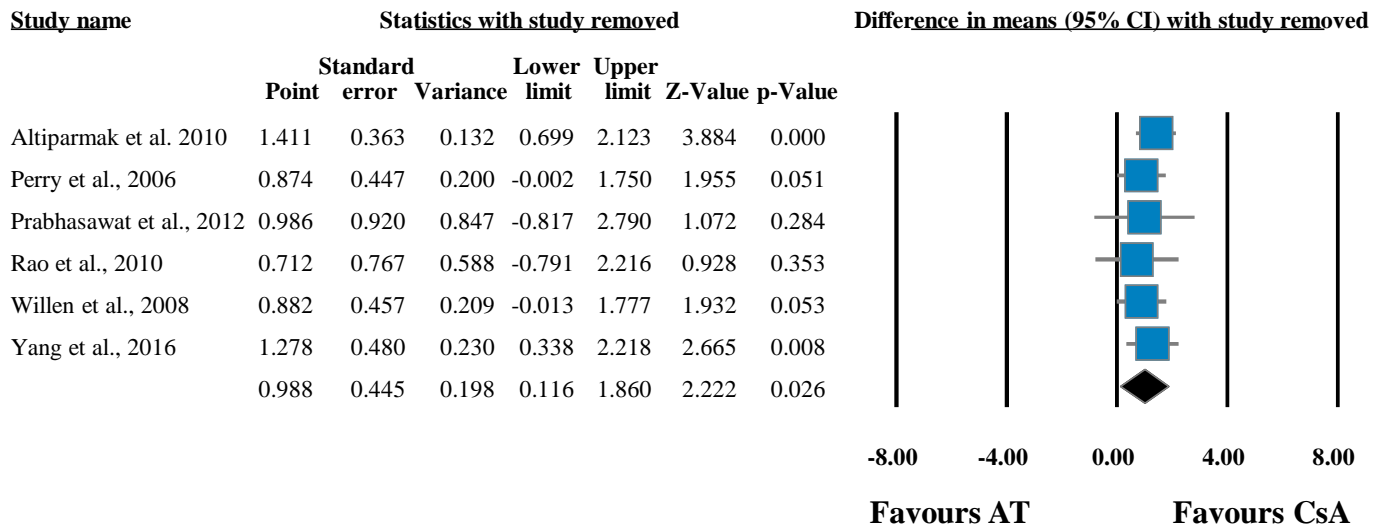
	Point estimate	Standard error	Lower limit	Upper limit	Z-value	p-Value
Slope	0.03015	0.05490	-0.07746	0.13776	0.54915	0.58290
Intercept	-0.12897	2.81383	-5.64398	5.38604	-0.04583	0.96344
Tau-squared	1.39847					

	Q	df	p-value
Model	0.30157	1.00000	0.58290
Residual	28.36159	3.00000	0.00000
Total	28.66316	4.00000	0.00001

Online Supplementary File 10

Sensitivity analysis of TBUT

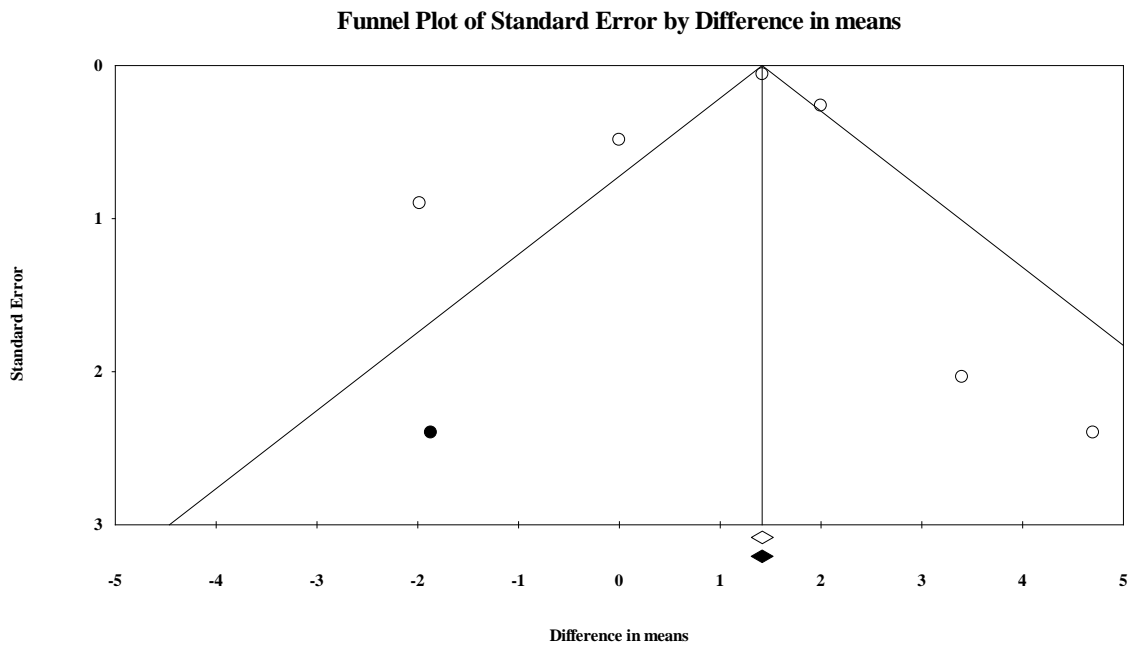
In random-effects model



AT, artificial tears; CI, confidence interval; CsA, cyclosporine A.

Online Supplementary File 11

Small study bias of TBUT



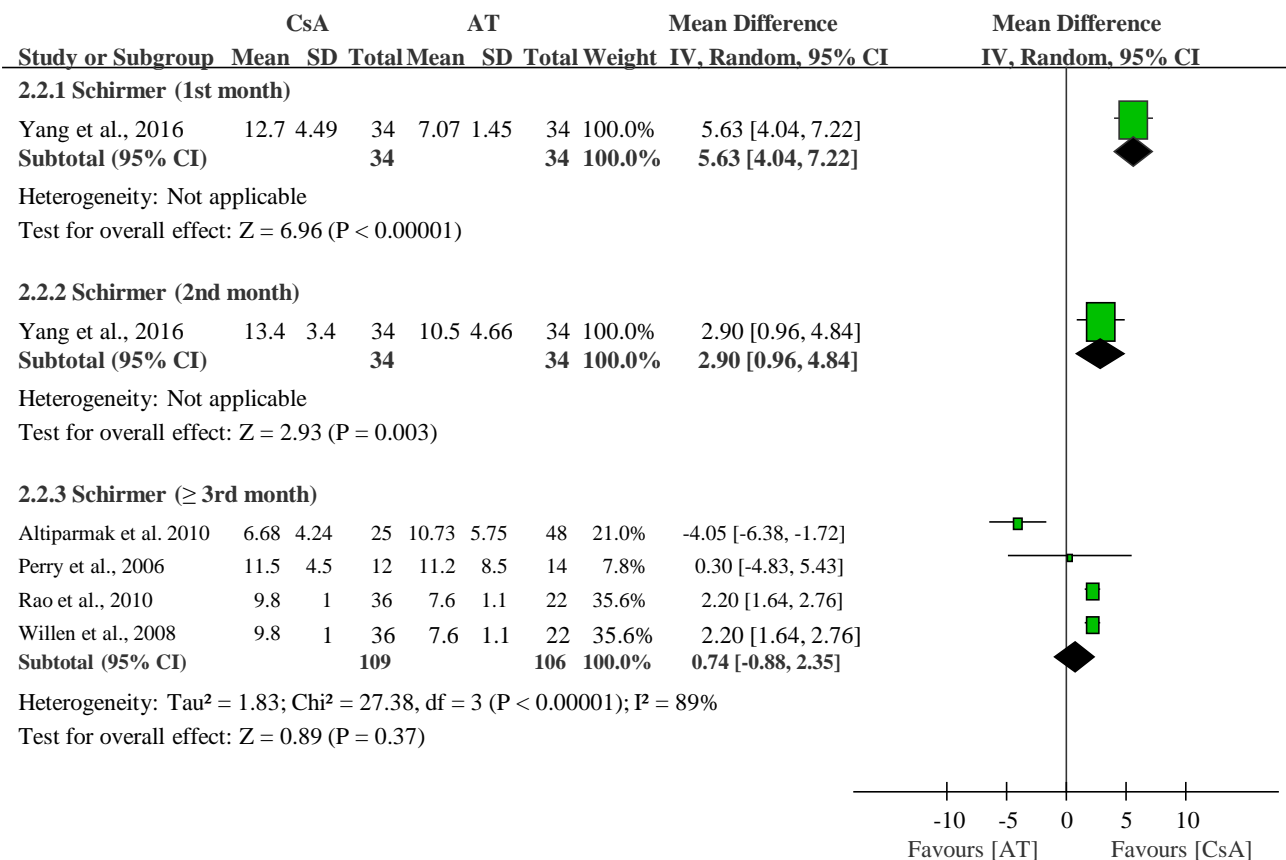
Egger's regression intercept

Intercept	-0.52007
Standard error	1.35233
95% lower limit (2-tailed)	-4.27472
95% upper limit (2-tailed)	3.23459
t-value	0.38457
df	4.00000
P-value (1-tailed)	0.36006
P-value (2-tailed)	0.72013

Online Supplementary File 12-16
Further analysis of Schirmer's test

Online Supplementary File 12

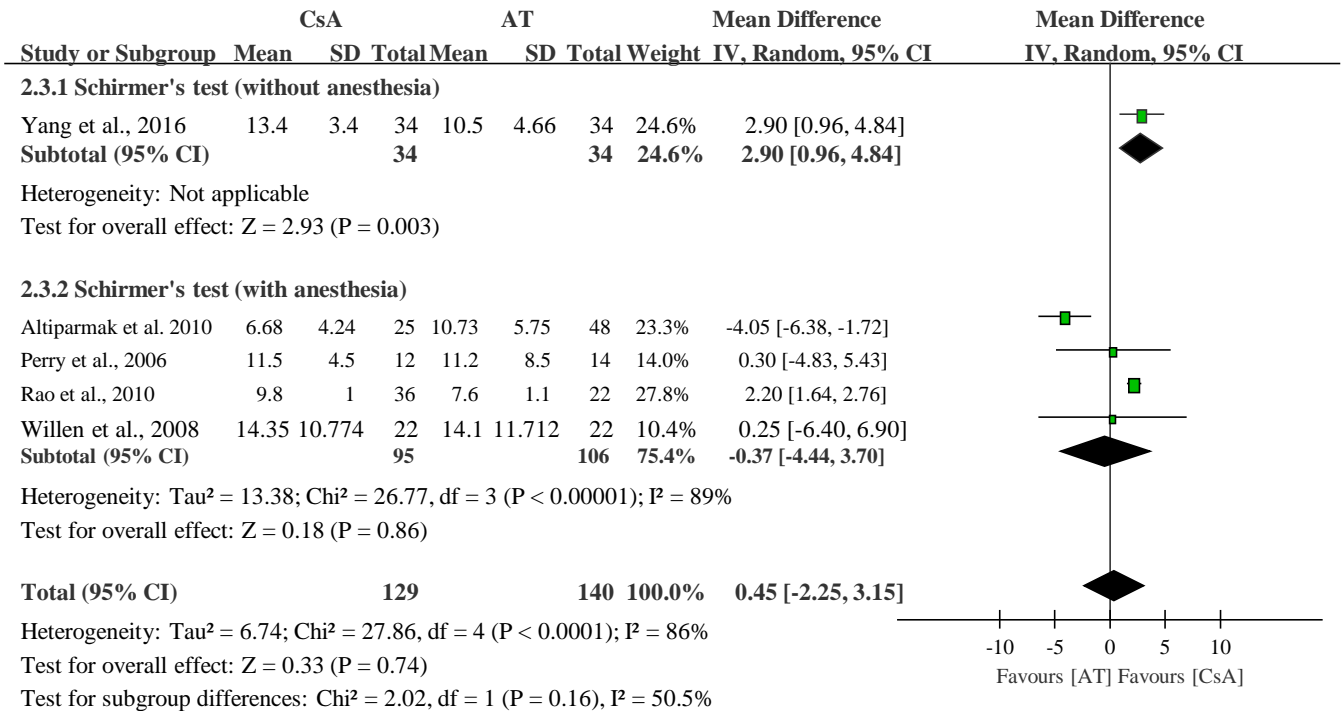
Subset analysis of Schirmer's test score by treatment duration



AT, artificial tears; CI, confidence interval; CsA, cyclosporine A; IV, inverse variance; SD, standard deviation.

Online Supplementary File 13

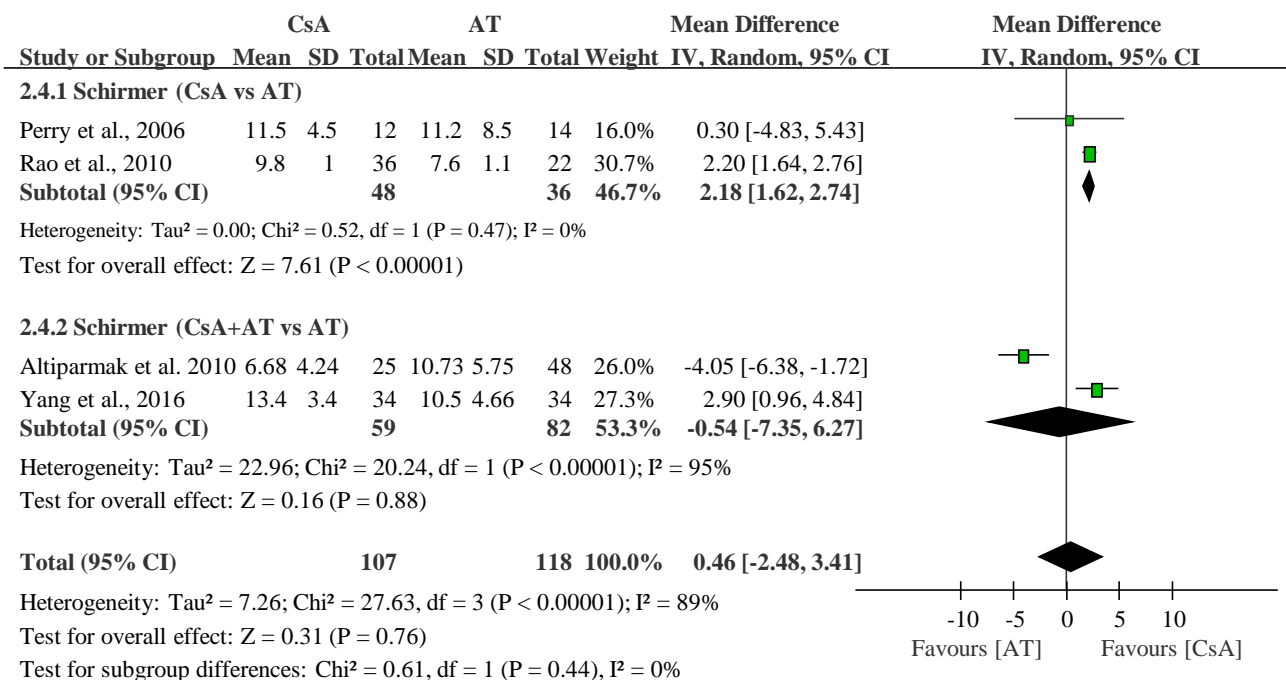
Subset analysis of Schirmer's test score by type of test



AT, artificial tears; CI, confidence interval; CsA, cyclosporine A; IV, inverse variance; SD, standard deviation.

Online Supplementary File 14

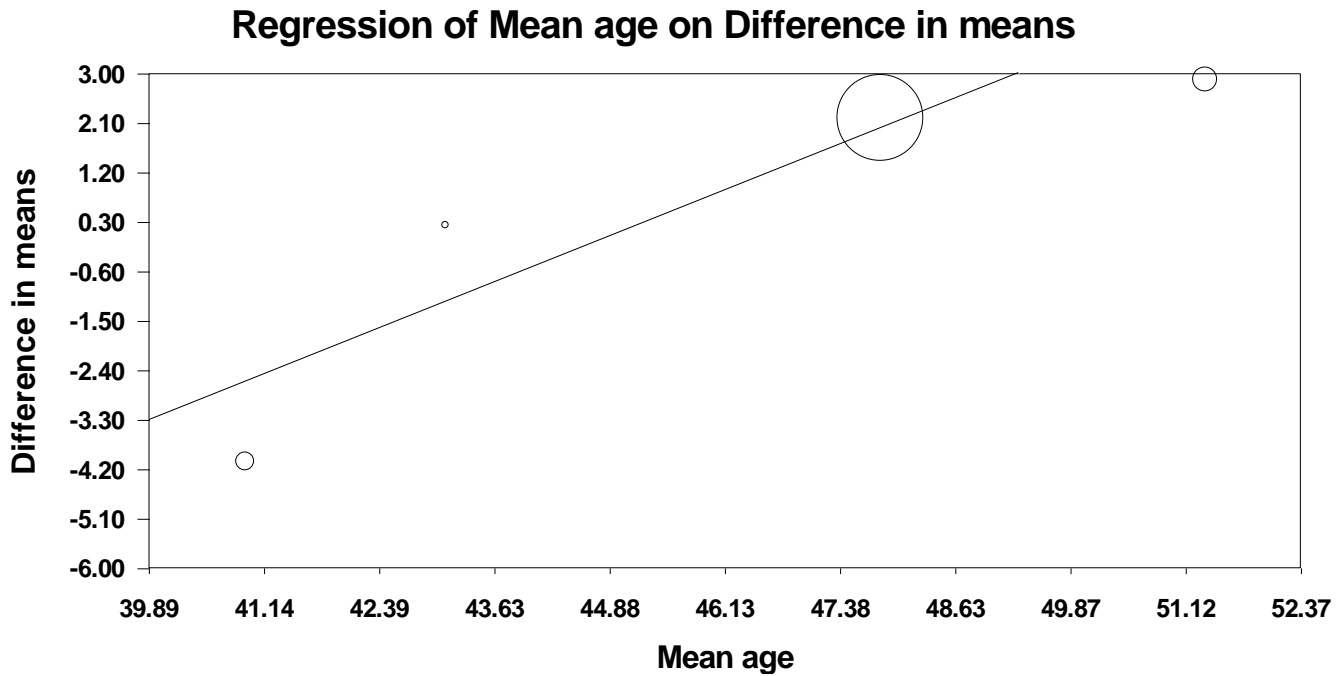
Subset analysis of Schirmer's test score by regimen



AT, artificial tears; CI, confidence interval; CsA, cyclosporine A; IV, inverse variance; SD, standard deviation.

Online Supplementary File 15

Meta-regression of Schirmer's test score by mean age

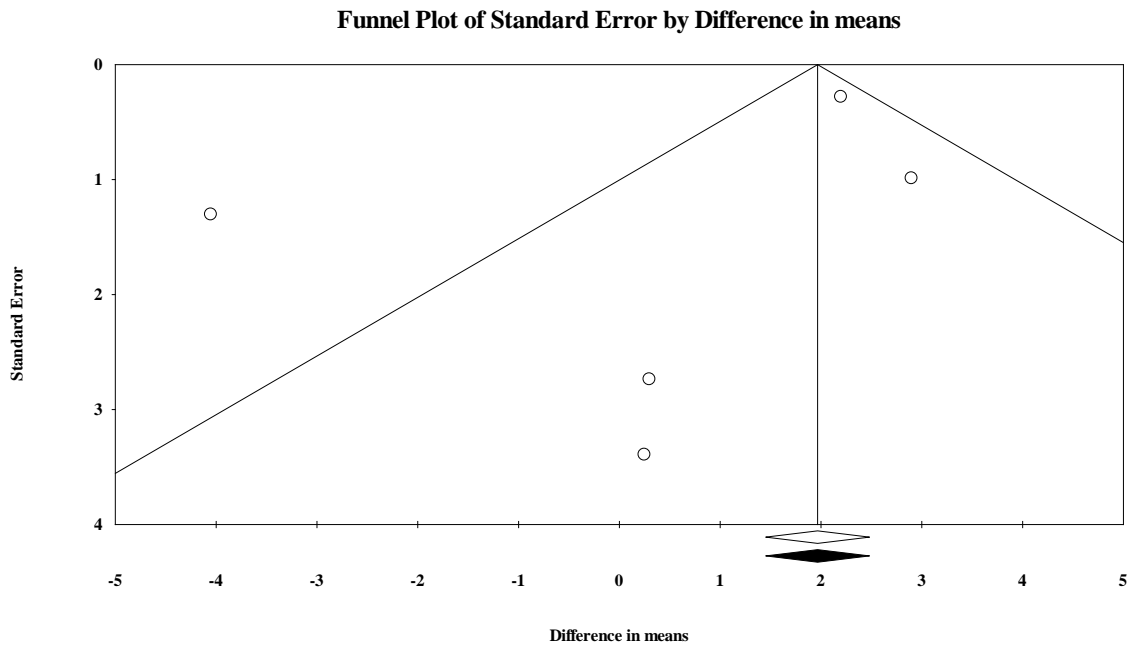


	Point estimate	Standard error	Lower limit	Upper limit	Z-value	p-Value
Slope	0.67066	0.15364	0.36953	0.97178	4.36520	0.00001
Intercept	-30.04324	7.34126	-44.43184	-15.65464	-4.09238	0.00004
Tau-squared	0.86348					

	Q	df	p-value
Model	19.05495	1.00000	0.00001
Residual	4.05734	2.00000	0.13151
Total	23.11229	3.00000	0.00004

Online Supplementary File 16

Small study bias of Schirmer's test score



Egger's regression intercept

Intercept	-1.56959
Standard error	1.51218
95% lower limit (2-tailed)	-6.38204
95% upper limit (2-tailed)	3.24285
t-value	1.03796
df	3.00000
P-value (1-tailed)	0.18780
P-value (2-tailed)	0.37560