

Supplementary Online Content

Subhi Y, Schmidt DC, Al-Bakri M, Bach-Holm D, Kessel L. Diagnostic test accuracy of the red reflex test for ocular pathology in infants: a meta-analysis. *JAMA Ophthalmol*. Published online November 12, 2020. doi:10.1001/jamaophthalmol.2020.4854

eMethods 1. Literature Search in Different Databases

eMethods 2. Details of Data Analysis

eTable 1. Methods for Index and Reference Test in Included Studies

eTable 2. Risk of Bias Within Individual Studies

eTable 3. Sensitivity Analyses of the Bivariate Meta-analysis of the Diagnostic Test Accuracy of the Red Reflex on Detecting Any Ocular Pathology

eTable 4. Sensitivity Analyses of the Bivariate Meta-analysis of the Diagnostic Test Accuracy of the Red Reflex on Detecting Any Medical or Surgical Intervention–Demanding Ocular Pathology

eFigure 1. Calculated Summary Prevalence Estimate of Any Ocular Pathology, Risk of Bias Across Studies, and Sensitivity Analyses

eFigure 2. Calculated Summary Prevalence Estimate of Medical or Surgical Intervention–Demanding Ocular Pathology, Risk of Bias Across Studies, and Sensitivity Analyses

eFigure 3. Hierarchical Summary Receiver Operating Characteristics Model (HSROC) Curve for Evaluating the Association Between Sensitivity and Specificity for the Red Reflex in Identifying Ocular Pathology

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Literature Search in Different Databases.

PubMed:

History

[Download history](#)[Clear history](#)

Search	Add to builder	Query	Items found	Time
#1	Add	Search ("red reflex" OR "Brückner test" OR "Bruckner test")	236	09:54:23

Cochrane Central:

21 **Trials matching** "red reflex" OR "Brückner test" OR "Bruckner test" in Title Abstract Keyword - (Word variations have been searched)

[Cochrane Central Register of Controlled Trials](#)

Issue 4 of 12, April 2020

EMBASE:

Search history sorted by search number ascending						
# ▲	Searches	Results	Type	Actions	Annotations	
1	("red reflex" or "Brückner test" or "Bruckner test").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	306	Advanced	Display Results More		

ClinicalTrials.gov:

9 Studies found for: "red reflex" OR "Brückner test" OR "Bruckner test"

ClinicalTrials.gov Search Results 04/19/2020

Title	Status	Study Results	Conditions	Interventions	Locations
1 Anterior Chamber Illumination in Cataract Surgery for Eyes With Poor Red Reflex	Completed	No Results Available	•Cataract Senile	•Procedure: Anterior chamber illumination in cataract surgery	•Alexandria university, Alexandria, Egypt
2 Pediatric Red Reflex Study	Recruiting	No Results Available	•Abnormal Vitreous Humor Morphology •Abnormal Choroid Morphology •Optic Nerve Diseases •Retinal Disease •Retinal Hemorrhage	•Diagnostic Test: Direct ophthalmoscope	•Children's National Medical Center, Washington, District of Columbia, United States
3 Determination of the Sensitivity and Specificity of a Smartphone Application to Detect Retinoblastoma	Active, not recruiting	No Results Available	•Retinoblastoma •Cataracts Infantile •Glaucoma, Congenital •Leucocoria	•Other: CRADLE •Other: Red reflex testing	•St. Jude Children's Research Hospital, Memphis, Tennessee, United States
4 Comparative Validation of "Blinq" and "ZWIN" Vision Screeners	Completed	No Results Available	•Strabismic Amblyopia •Refractive Amblyopia •Strabismus	•Diagnostic Test: objective pediatric vision screen, "blinq,"	•Alaska Children's EYE & Strabismus, Anchorage, Alaska, United States
5 Reduced Infant Response to a Routine Care Procedure After Glucose 25% Analgesia in Comparison to Materna RTF Stage 1	Unknown status	No Results Available	•Infant, Newborn, Diseases	•Drug: Glucose 25% •Dietary Supplement: Materna RTF Stage 1 •Other: Water for Injection	•NICU Department, The Baruch Padeh medical Center - Poriya, Tiberias, Israel
6 Lofeprednol vs Prednisolone for the Treatment of Intraocular Inflammation Following Cataract Surgery in Children	Completed	Has Results	•Cataract	•Drug: Lofeprednol etabonate •Drug: Prednisolones acetate	•Bausch & Lomb Inc, Rochester, New York, United States
7 Reduced Infant Response To A Routine Care Procedure After Glucose 25% Analgesia	Terminated	No Results Available	•Infant •Newborn Diseases	•Drug: Glucose 25%	
8 Cataract Surgery With Intracameral Triamcinolone in Infants	Completed	No Results Available	•Cataract	•Drug: Triamcinolone acetonide •Drug: Prednisolone syrup	•Alino Ventura Foundation, Recife, Pernambuco, Brazil
9 Screening Aid to Identify Corneas That May Have Pathologies or Other Conditions	Completed	No Results Available	•Corneal Diseases		•Shiley Eye Center-University of California San Diego, La Jolla, California, United States •Carmel Mountain Vision Care Center, San Diego, California, United States •Dishier Laser Institute, Greenwood Village, Colorado, United States •Pacific University, Forest Grove, Oregon, United States

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

CINAHL:

Sunday, April 19, 2020 10:16:28 AM

#	Query	Limiters/Expanders	Last Run Via	Results
S1	TX "red reflex" OR "Brückner test" OR "Bruckner test"	Expanders - Apply equivalent subjects Search modes - Proximity within five words	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	272

Combined search into following databases: Web of Science (WOS), BIOSIS Previews (BIOSIS), Current Contents Connect (CCC), Data Citation Index (DRCI), Derwent Innovations Index (DIIDW), KCI-Korean Journal Database (KJD), Russian Science Citation Index (RSCI), SciELO Citation Index (SCIELO):

Results: 371

(from All Databases)

You searched for: TOPIC: ("red reflex" OR "Brückner test" OR "Bruckner test")

Timespan: All years. **Databases:** WOS, BIOSIS, CCC, DRCI, DIIDW, KJD, RSCI, SCIELO.

Search language=Auto

eMethods 2. Details of Data Analysis

We presented 2x2 data with 95% confidence intervals (95% CI) for sensitivity and specificity. To account for the correlation between sensitivity and specificity, we analyzed results based on an approach to fit random effects using the hierarchical summary receiver operating characteristics model (SROC). The hierarchical SROC model accounts for the across study variability and estimates summary accuracy measures of sensitivity and specificity. For this analysis, we used MetaDTA version 1.45.⁹ We conducted sensitivity analyses for all analyses by excluding each study in turn and re-calculating summary estimates to evaluate the overall robustness of the findings. Using the hierarchical SROC model, we interpreted the summary sensitivity and specificity point to reflect the average observed accuracy.¹⁰ We made a separate subgroup analysis to evaluate the diagnostic test accuracy of intervention demanding ocular pathology among the cases reported as defined by a senior pediatric ophthalmologist (L.K.). Unit of assessment was per person investigated. This strategy was chosen since the evaluation of the red reflex on one eye to some extent may depend on the red reflex on the other eye. For studies where data per person was not possible to extract, we extracted data per eye.

To provide context into diagnostic test accuracy estimates, we also evaluated the prevalence of any ocular pathologies and intervention demanding ocular pathologies. We conducted prevalence meta-analyses using MetaXL 5.3 (EpiGear International, Sunrise Beach, QLD, Australia) for Microsoft Excel 2013. A random-effects model was employed to account for potential heterogeneity between studies. To avoid variance instability, which can be an issue in prevalence meta-analyses, we transformed all prevalence numbers using the double arcsine method for analysis and then back-transformed for interpretation.¹¹ Heterogeneity was evaluated using Cochran's Q and I². Risk of bias across studies was evaluated with Funnel and Doi plots.^{12,13} Sensitivity analyses were made to evaluate the robustness of the prevalence estimates. These prevalence estimates were used to evaluate the positive predictive value (PPV) and the negative predictive value (NPV) given the calculated diagnostic test accuracy measures. To further understand the PPV and the NPV in different scenarios, we evaluated the consequences of increasing and decreasing the disease prevalence on the PPV and the NPV.

eTable 1. Methods for Index and Reference Test in Included Studies

Reference	Index test method	Index test with pupillary dilation?	Reference test method	Reference test with pupillary dilation?
Ludwig et al., 2018	Pediatrician performed the RRT, and the study extracted results from patient journals.	No	Digital images were taken of the externa, the iris, and the fundus. Eyes were dilated. Images were interpreted by ophthalmologists.	Yes
Ma et al. 2018	Pediatrician performed the RRT using a direct ophthalmoscope.	No	Digital images were taken of the anterior and the posterior segment. Eyes were dilated. Images were interpreted by ophthalmologists.	Yes
Mussavi et al. 2014	Pediatrician performed the RRT with an indirect ophthalmoscope without dilation. Redness was scored in 0–10 (0=milky white/asymmetry; 10=bold red). Only 10 was considered normal.	No	Eyes were dilated and examined by an ophthalmologist in a dark room.	Yes
Sun et al. 2016	Pediatric ophthalmologists performed the RRT using a direct ophthalmoscope.	No	Eyes were examined using a hand-held slit lamp. Images were taken of the anterior and the posterior segment. Images were examined onsite by ophthalmologist.	Yes
Viquez & Wu, 2020	An ophthalmologist performed the Brückner test.	No	Eyes were examined by an ophthalmologist.	Yes

Abbreviations: RRT = red reflex test.

eTable 2. Risk of Bias Within Individual Studies

Reference	Patient Selection: Risk of Bias	Patient Selection: Applicability	Index Test: Risk of Bias	Index Test: Applicability	Reference Standard: Risk of Bias	Reference Standard: Applicability	Flow and Timing: Risk of Bias
Ludwig et al., 2018	U	L	L	L	L	U	L
Ma et al. 2018	U	L	L	L	L	U	H
Mussavi et al. 2014	L	L	L	U	L	L	H
Sun et al. 2016	H	U	L	L	L	L	L
Viquez & Wu, 2020	L	U	L	L	H	L	L

Signs for evaluating risk of bias: L: low; U: unclear. H: high.

eTable 3. Sensitivity Analyses of the Bivariate Meta-analysis of the Diagnostic Test Accuracy of the Red Reflex on Detecting Any Ocular Pathology

Excluded study	Sensitivity (95% CI)	Specificity (95% CI)
Ludwig et al., 2018	18 % (2–69 %)	93 % (60–99 %)
Ma et al. 2018	14 % (14–14 %)	95 % (95–95 %)
Mussavi et al. 2014	4 % (1–23 %)	100 % (83–100 %)
Sun et al. 2016	6 % (0.1–70 %)	98 % (57–100 %)
Viquez & Wu, 2020	5 % (0.1–63 %)	99 % (66–100 %)

eTable 4. Sensitivity Analyses of the Bivariate Meta-analysis of the Diagnostic Test Accuracy of the Red Reflex on Detecting Any Medical or Surgical Intervention–Demanding Ocular Pathology

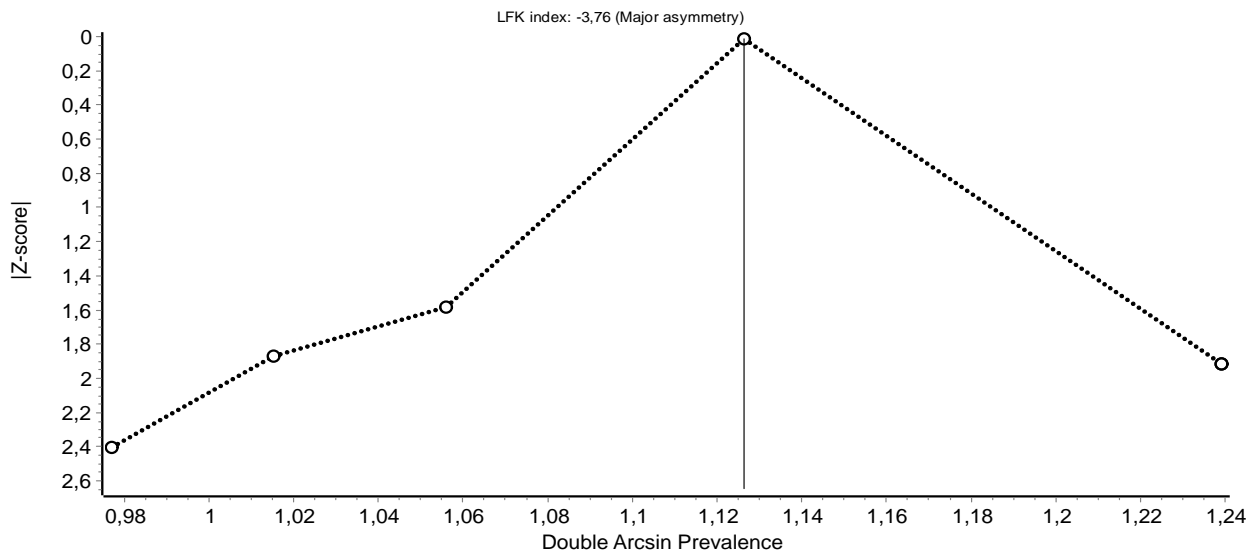
Excluded study	Sensitivity (95% CI)	Specificity (95% CI)
Ma et al. 2018	62 % (0.2–100 %)	95 % (83–98 %)
Sun et al. 2016	56 % (0.7–100 %)	98 % (73–100 %)
Viquez & Wu, 2020	6 % (2–17 %)	99 % (95–100 %)

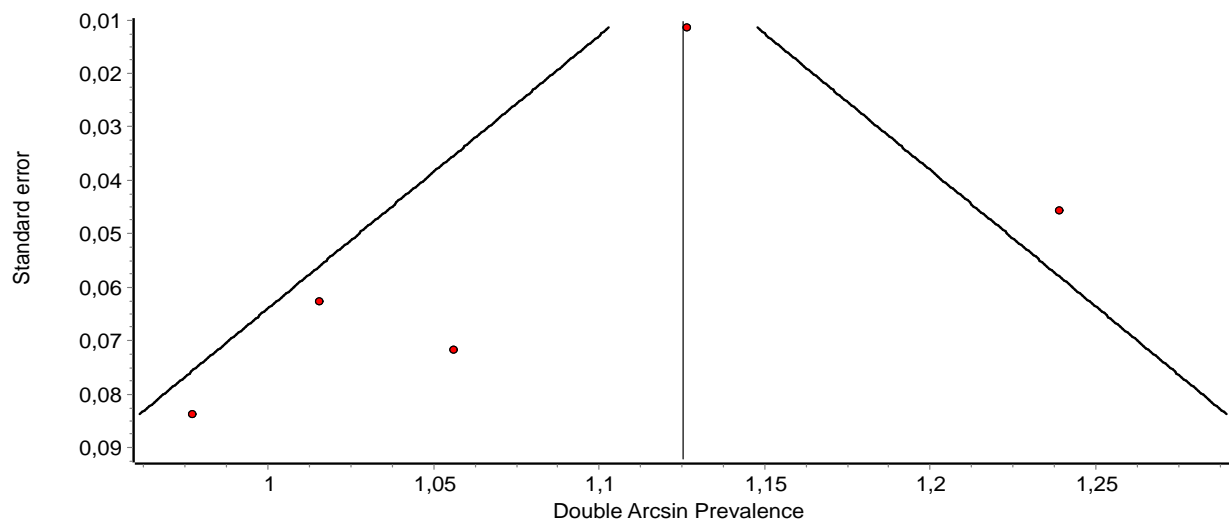
Figure 1. Calculated Summary Prevalence Estimate of Any Ocular Pathology, Risk of Bias Across Studies, and Sensitivity Analyses

Prevalence estimate:

Study	Prevalence	LCI 95%	HCI 95%	weight (%)
Ludwig et al. 2018	25%	19%	32%	15%
Ma et al. 2018	34%	30%	38%	22%
Mussavi et al. 2014	24%	19%	29%	18%
Sun et al. 2016	29%	27%	30%	31%
Viquez & Wu, 2020	22%	15%	29%	13%
Pooled	27%	24%	31%	100%
Statistics				
I-squared	70.13	23.82	88.29	
Cochran's Q	13.39			
Chi2, p	0.01			
tau2	0.00			

Risk of bias across studies:





Sensitivity analysis:

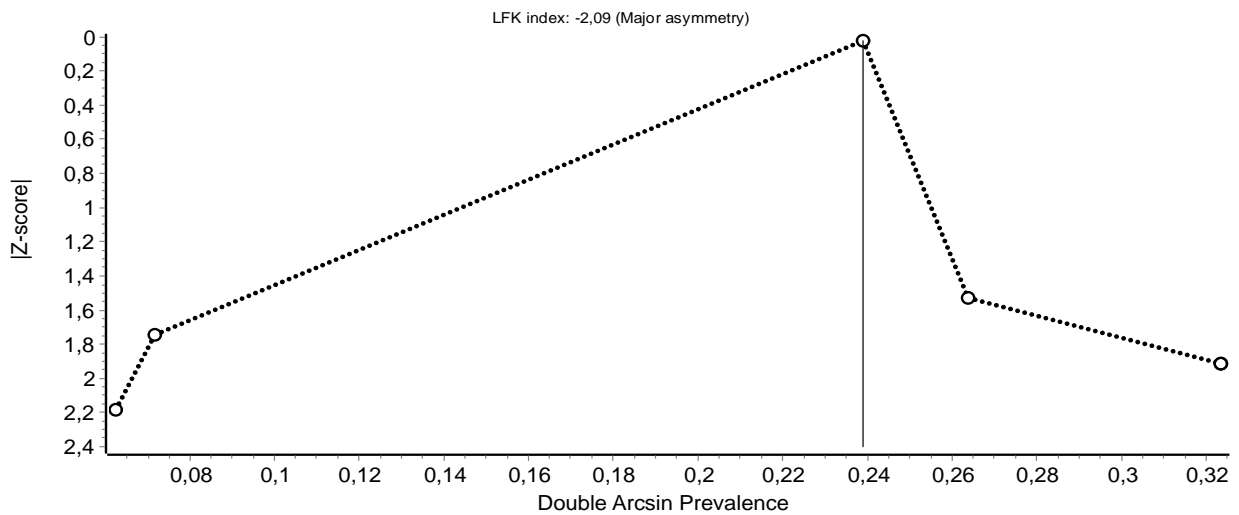
Excluded study	Pooled Prevalence	LCI 95%	HCI 95%	Cochran Q	p	I ²	I ² LCI 95%	I ² HCI 95%
Ludwig et al. 2018	28%	24%	32%	12.43	0.01	75.87	33.55	91.24
Ma et al. 2018	26%	22%	29%	6.81	0.08	55.96	0.00	85.41
Mussavi et al. 2014	28%	24%	32%	10.20	0.02	70.59	15.82	89.73
Sun et al. 2016	26%	21%	32%	13.32	0.00	77.48	38.87	91.71
Viquez & Wu, 2020	28%	25%	32%	10.20	0.02	70.60	15.84	89.73

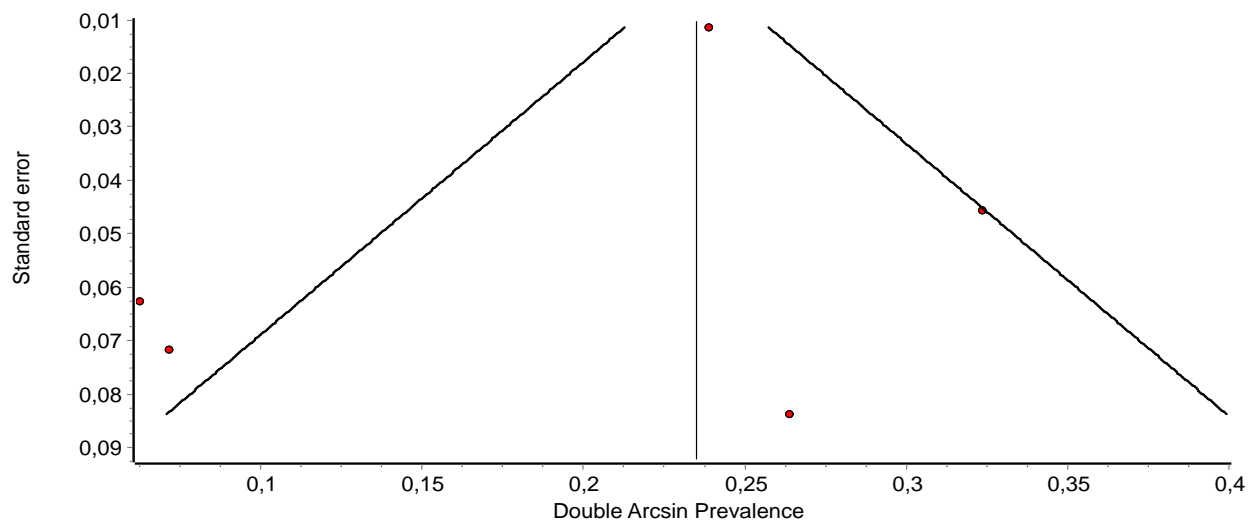
eFigure 2. Calculated Summary Prevalence Estimate of Medical or Surgical Intervention–Demanding Ocular Pathology, Risk of Bias Across Studies, and Sensitivity Analyses

Prevalence estimate:

Study	Prevalence	LCI 95%	HCI 95%	weight (%)
Ludwig et al. 2018	0.0%	0.0%	0.9%	16%
Ma et al. 2018	2.5%	1.3%	4.1%	22%
Mussavi et al. 2014	0.0%	0.0%	0.7%	18%
Sun et al. 2016	1.4%	1.2%	1.7%	29%
Viquez & Wu, 2019	1.4%	0.0%	4.2%	14%
Pooled	0.9%	0.2%	2.0%	100%
Statistics				
I-squared	76.17	41.81	90.24	
Cochran's Q	16.79			
Chi2, p	0.00			
tau2	0.01			

Risk of bias across studies:





Sensitivity analysis:

Excluded study	Pooled Prevalence	LCI 95%	HCI 95%	Cochran Q	p	I ²	I ² LCI 95%	I ² HCI 95%
Ludwig et al. 2018	1.2%	0.4%	2.4%	11.48	0.01	73.86	26.82	90.66
Ma et al. 2018	0.5%	0.0%	1.7%	12.81	0.01	76.57	35.87	91.44
Mussavi et al. 2014	1.3%	0.5%	2.4%	8.95	0.03	66.49	1.92	88.55
Sun et al. 2016	0.8%	0.0%	2.4%	15.88	0.00	81.11	50.63	92.77
Viquez & Wu, 2019	0.8%	0.1%	1.9%	16.67	0.00	82.00	53.45	93.04

eFigure 3. Hierarchical Summary Receiver Operating Characteristics Model (HSROC) Curve for Evaluating the Association Between Sensitivity and Specificity for the Red Reflex in Identifying Ocular Pathology

any ocular pathology (left) and any medical or surgical intervention demanding ocular pathology (right)

