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Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy (Review)

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[Diagnostic Test Accuracy Review]

Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy

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ABSTRACT

Background

Diabetic macular oedema (DMO) is a thickening of the central retina, or the macula, and is associated with long-term visual loss in people with diabetic retinopathy (DR). Clinically significant macular oedema (CSMO) is the most severe form of DMO. Almost 30 years ago, the Early Treatment Diabetic Retinopathy Study (ETDRS) found that CSMO, diagnosed by means of stereoscopic fundus photography, leads to moderate visual loss in one of four people within three years. It also showed that grid or focal laser photocoagulation to the macula halves this risk. Recently, intravitreal injection of antiangiogenic drugs has also been used to try to improve vision in people with macular oedema due to DR.

Optical coherence tomography (OCT) is based on optical reflectivity and is able to image retinal thickness and structure producing cross-sectional and three-dimensional images of the central retina. It is widely used because it provides objective and quantitative assessment of macular oedema, unlike the subjectivity of fundus biomicroscopic assessment which is routinely used by ophthalmologists instead of photography. Optical coherence tomography is also used for quantitative follow-up of the effects of treatment of CSMO.

Objectives

To determine the diagnostic accuracy of OCT for detecting DMO and CSMO, defined according to ETDRS in 1985, in patients referred to ophthalmologists after DR is detected. In the update of this review we also aimed to assess whether OCT might be considered the new reference standard for detecting DMO.

Search methods

We searched the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database (HTA) and the NHS Economic Evaluation Database (NHSEED) (*The Cochrane Library* 2013, Issue 5), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to June 2013), EMBASE (January 1950 to June 2013), Web of Science Conference Proceedings Citation Index - Science (CPCI-S) (January 1990 to June 2013), BIOSIS Previews (January 1969 to June 2013), MEDION and the Aggressive Research Intelligence Facility database (ARIF). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 25 June 2013. We checked bibliographies of relevant studies for additional references.

Selection criteria

We selected studies that assessed the diagnostic accuracy of any OCT model for detecting DMO or CSMO in patients with DR who were referred to eye clinics. Diabetic macular oedema and CSMO were diagnosed by means of fundus biomicroscopy by ophthalmologists or stereophotography by ophthalmologists or other trained personnel.

Data collection and analysis

Three authors independently extracted data on study characteristics and measures of accuracy. We assessed data using random-effects hierarchical sROC meta-analysis models.

Main results

We included 10 studies (830 participants, 1387 eyes), published between 1998 and 2012. Prevalence of CSMO was 19% to 65% (median 50%) in nine studies with CSMO as the target condition. Study quality was often unclear or at high risk of bias for QUADAS 2 items, specifically regarding study population selection and the exclusion of participants with poor quality images. Applicablity was unclear in all studies since professionals referring patients and results of prior testing were not reported. There was a specific 'unit of analysis' issue because both eyes of the majority of participants were included in the analyses as if they were independent.

In nine studies providing data on CSMO (759 participants, 1303 eyes), pooled sensitivity was 0.78 (95% confidence interval (CI) 0.72 to 0.83) and specificity was 0.86 (95% CI 0.76 to 0.93). The median central retinal thickness cut-off we selected for data extraction was 250 µm (range 230 µm to 300 µm). Central CSMO was the target condition in all but two studies and thus our results cannot be applied to non-central CSMO.

Data from three studies reporting accuracy for detection of DMO (180 participants, 343 eyes) were not pooled. Sensitivities and specificities were about 0.80 in two studies and were both 1.00 in the third study.

Since this review was conceived, the role of OCT has changed and has become a key ingredient of decision-making at all levels of ophthalmic care in this field. Moreover, disagreements between OCT and fundus examination are informative, especially false positives which are referred to as subclinical DMO and are at higher risk of developing clinical CSMO.

Authors' conclusions

Using retinal thickness thresholds lower than 300 µm and ophthalmologist's fundus assessment as reference standard, central retinal thickness measured with OCT was not sufficiently accurate to diagnose the central type of CSMO in patients with DR referred to retina clinics. However, at least OCT false positives are generally cases of subclinical DMO that cannot be detected clinically but still suffer from increased risk of disease progression. Therefore, the increasing availability of OCT devices, together with their precision and the ability to inform on retinal layer structure, now make OCT widely recognised as the new reference standard for assessment of DMO, even in some screening settings. Thus, this review will not be updated further.

PLAIN LANGUAGE SUMMARY

Optical coherence tomography measurement of central retinal thickness to diagnose diabetic macular oedema

Background
Diabetic macular oedema (DMO) is a thickening of the central part of the retina, the macula, that may affect people with diabetic retinopathy (DR). Diabetic retinopathy is a complication of diabetes in which the retina (a layer of tissue at the back of the eye) becomes progressively damaged. Diabetic macular oedema is detected by means of visual examination by an ophthalmologist. The most severe form of DMO - clinically significant macular oedema (CSMO) - is associated with sight loss in the long-term. This condition is treatable. Laser photocoagulation (where a laser is used to burn off blood vessels) has been used for many years to reduce the risk of visual loss. More recently, antiangiogenic therapy (which prevents fluid leakage from retinal vessels) has been approved to try to improve vision.

Review question
Optical coherence tomography (OCT) is based on how light is reflected. It can be used to measure retinal thickness. We originally aimed to assess the accuracy of OCT for diagnosing diabetic macular oedema (DMO), as well as to investigate differences in diagnostic performance. However, the role of OCT is expanding so in the update of this review we also aimed to assess whether OCT might be considered the new standard for diagnosing DMO.

Search date
This review is updated as of June 2013.

Study characteristics
Our review included 10 studies (830 participants, 1387 eyes) published between 1998 and 2012. Nine of these studies investigated the ability of OCT to diagnose CSMO.

Study funding sources

There were no overt declarations of potential conflicts of interest in terms of the manufacturer of the OCT device being involved in funding the research.

Key results

We found that OCT retinal thickness measurement is not sufficiently accurate to detect CSMO, involving the centre of the macula, using clinical fundus examination as the reference standard. Of 10 patients with diabetic retinopathy, 5 of whom have CSMO, 1 of 5 with no CSMO would be wrongly diagnosed as having CSMO, and about 1 of 5 with CSMO would be missed.

However, researchers have found that disagreements between OCT and clinical examination occur because OCT can detect early, subclinical retinal thickening in people without CSMO and more advanced retinopathy. They suggested that such cases of subclinical macular oedema are followed more closely, since they are at increased risk of progression to CSMO. Furthermore, OCT is an essential tool to manage antiangiogenic therapy in patients with DMO and is believed by many to be a new reference standard for its diagnosis.

Quality of the evidence

Study quality was often unclear because of incomplete reporting or because it was at risk of bias. Specifically, this concerned how patients were selected in the study, who referred them and how, and exclusion of those for whom poor quality images were obtained. Furthermore, many studies included both patient's eyes, which is a problem in data analyses.

SUMMARY OF FINDINGS

Summary of findings 1. Optical coherence tomography (OCT) for diagnosing clinically significant diabetic macular oedema

Optical coherence tomography for detection of macular oedema in patients with diabetic retinopathy The presentation of the following results assumes that fundus photography or biomicroscopy are valid reference standards for diagnosing diabetic macular oedema (DMO). Readers should be aware of the fact that additional information offered by OCT regarding retinal thickness with respect to the reference standard is useful, specifically for false positives or subclinical DMO, a condition that was found to increase the risk of developing clinically significant macular oedema (CSMO).		
Patients or population: patients affected by diabetic retinopathy. Setting: referral eye clinics IndexTest: optical coherence tomography.[1] Reference Test: stereoscopic fundus photography or contact lens or non-contact lens biomicroscopy of the fundus. Threshold: proven or probable CSMO based on ETDRS definition		
Test result	**Number of results per 1000 patients tested** (95% CI)	**Quality of the evidence (GRADE)**
Median prevalence 500 per 1000, which is typically seen in patients with diabetes of 15 to 20 years duration since diagnosis, older patients, and patients with additional risk factors.		
	All studies (697 participants, 1242 eyes, 9 studies)	
Sensitivity (95% CI)	**0.81 (0.74 to 0.87)**	
True positives	**403 per 1000** (371 to 428 per 1000)	Low[2, 3]
False negatives	**98 per 1000** (72 to 129 per 1000)	
Specificity (95% CI)	**0.85 (0.75 to 0.91)**	
True negatives	**424 per 1000** (374 to 456 per 1000)	
False positives	**77 per 1000** (44 to 126 per 1000)	
Footnotes: [1] **Note:** Index Test was OCT 2000 in 2 studies, Stratus in 5 studies, and Cirrus OCT in 2 studies using cut-off retinal thickness 230 µm to 300 µm. [2] **Risk of bias (-1):** patient selection and missing data were of concern in most studies. [3] **Imprecision (-1)**: unit of analysis issues (eyes v. individuals) may bias precision.		
Low prevalence 100 per 1000, which is typically seen in patients with diabetes of 5 to 10 years duration since diagnosis and no other risk factors.		
	Estimates at prevalence less than 50% (19% to 40%: 4 studies)	
Sensitivity (95% CI)	**0.74 (0.68 to 0.86)**	
True positives	**74 per 1000**	Very low[2, 3, 4]
False negatives	**26 per 1000**	
Specificity (95% CI)	**0.92 (0.87 to 0.97)**	

True negatives	**828 per 1000**
False positives	**72 per 1000**
CI: Confidence interval, **OCT**: Optical coherence tomography, **ETDRS**: Early Treatment Diabetic Retinopathy Study	

[1] **Note:** Index Test was OCT 2000 in 2 studies, Stratus in 5 studies, and Cirrus OCT in 2 studies using cut-off retinal thickness 230 µm to 300 µm.
[2] **Risk of bias (-1):** patient selection and missing data were of concern in most studies.
[3] **Indirectness (-1)**: low-prevalence subgroup estimate is far from values expected in primary care.
[4] **Imprecision (-1)**: unit of analysis issues (eyes v. individuals) may bias precision.

BACKGROUND

Target condition being diagnosed

Diabetes mellitus results in considerable morbidity and mortality, affecting about 180 million people worldwide (WHO 2002). The total number of people with diabetes is expected to rise to an estimated 300 million cases by the year 2025, with the most significant increases in developing countries. The increase is thought to be the result of population growth, ageing, obesity and sedentary lifestyle (King 1998).

Approximately 25% of people with diabetes have at least some form of diabetic retinopathy (DR) and the incidence increases with the duration of the diabetes. At 10 years the prevalence of retinopathy in diabetic patients is 7%, after 25 years it is more than 90% (Aiello 1998). In developed countries, NIH 1995 found that diabetic eye disease represents the leading cause of blindness in adults under 75 years of age.

There are two main complications of DR causing visual loss (Aiello 2003; Kiire 2013). These are proliferative retinopathy and diabetic macular oedema (DMO). Proliferative DR is the occurrence of retinal neovascularisation caused by retinal ischaemia and may lead to severe visual loss due to intraocular haemorrhage and retinal detachment. Diabetic macular oedema is a thickening of the central portion of the retina, called the macula. It is often associated with deposits of lipoproteins or hard exudates and may lead to gradual loss of central vision due to deterioration of the retinal cells. Clinically significant macular oedema (CSMO) is the most severe form of DMO. Diabetic macular oedema increases with the duration of diabetes and its prevalence is 5% within the first five years after diagnosis and 15% at 15 years (Aiello 1998). A review of studies found a prevalence of CSMO in people with diabetes ranging from 2% to almost 10% (Williams 2004).

According to the Diabetic Retinopathy Study (DRS) Group, the risk of severe visual loss at two years was 3.2% for eyes with non-proliferative DR (DRS 1987). The presence of CSMO increases the risk of moderate visual loss to approximately 30% to 50% depending on the level of baseline visual acuity. It is an indication for grid or focal laser treatment (Javitt 1989).

Stereoscopic fundus photography was used to diagnose macular oedema in the Early Treatment Diabetic Retinopathy Study (ETDRS 1985) and has been used as a standard method in research. In clinical practice, ophthalmologists routinely use contact or non-contact stereoscopic fundus biomicroscopy to diagnose macular oedema. In primary care, other healthcare professionals may use direct ophthalmoscopy or non-stereoscopic fundus photography to detect DR, but these methods do not allow the examiner to perceive retinal thickening as a primary sign of macular oedema. Only hard exudates or indirect signs, such as haemorrhages or microaneurysms in the macula, can be identified. Telemedicine is increasingly used for photographic screening and monitoring DR in diabetic patients (Aiello 2003).

People with DR are referred to ophthalmologists for confirmatory diagnosis and treatment of visually impairing complications such as proliferative retinopathy or CSMO. Nearly three decades ago, the ETDRS study showed that grid or focal laser photocoagulation reduces the risk of moderate visual loss by 50% in patients with CSMO (ETDRS 1985).

Recent studies found that intravitreal steroids (Grover 2008) or, in particular, antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEFG) properties, also injected intravitreally, may improve vision in patients affected by macular oedema due to DR (Cunningham 2005; DRCR Network 2007a; DRCR Network 2010; RESOLVE 2010; Virgili 2014).

Index test(s)

Optical coherence tomography (OCT) produces cross-sectional images of optical reflectivity in the retina, analogous to an ultrasound B-scan but with higher resolution (Hee 1998). Measurements of retinal thickness may be obtained directly from the tomograms either by manually measuring the distance between the inner and outer retinal boundaries or by using computer image processing techniques. Optical coherence tomography is increasingly used for detecting macular oedema in people with DR because OCT is an objective and reliable tool (DRCR Network 2007b). Furthermore, OCT allows a quantitative follow-up of the effects of treatment and has become a tool for routine management of macular oedema by ophthalmologists (Schimel 2011).

Other macular changes are of interest to researchers and clinicians using OCT, such as macular hyporeflective cavities or cysts due to fluid accumulation, subretinal fluid, or a thickened adherent hyaloid suggestive of vitreous traction (Chan 2005). Newer spectral domain OCT devices have higher resolution than previously and may show further abnormalities of the retinal layers, including those of the photoreceptor layer (Alasil 2010). However, because the construct underlying DMO is that of thickening, we will only consider thickness-related measures in this review.

This review is a diagnostic test accuracy review aimed at investigating the performance of OCT for detecting an anatomic target condition (DMO and particularly its severe form, CSMO). The target condition was shown several years ago to be relevant to affected people in terms of prognosis and an indication for treatment (ETDRS 1985). However, the increasing availability of OCT devices, coupled with their precision and the ability to inform on retinal layer structure, make OCT increasingly recognised as the new reference standard for assessment of DMO, even in screening settings (Olson 2013; Ontario HTA 2009). Thus, this review will not be updated further.

Clinical pathway

In the updated version of this review, we acknowledge that the clinical pathway of patients with DMO is unclear and probably dependent on the country and setting. Thus, the applicability of the results of the review will depend on patient selection in included studies, such as inclusion criteria and results of prior testing. Different levels of care may include DR screening programmes of diabetic patients (Hautala 2013; Peto 2012), DR detection by optometrists and other non-medical eye care professionals in public or private eye care settings, and diagnosis and treatment in secondary or tertiary care by ophthalmologists or retinal specialists.

Diabetic retinopathy screening by means of non-mydriatic fundus photography and telemedicine is now established in many countries (Andonegui 2012; Mansberger 2013; Peng 2011; Peto 2012; Vaziri 2013). The increasing availability and decreasing cost of OCT devices is making OCT attractive as a means of improving DMO detection within photographic telemedicine programmes, especially for reducing false positive referrals compared to fundus imaging alone (Adhi 2013; Mackenzie 2011; Olson 2013).

In many European and North-American countries, optometrists or other professionals may screen referred or self-referred patients for some ocular diseases, such as diabetic retinopathy or glaucoma, and then refer some patients to ophthalmologists based on tests such as fundus examination or photography and ocular pressure measurement. Other countries, such as Italy, rely on ophthalmologists for primary care needs. There is an interest in using OCT devices at this level of care (Shelton 2013).

Patients referred from primary care to ophthalmologists for suspect DR are first assessed by means of fundus biomicroscopy. Therefore, OCT and fluorescein angiography are used if DMO or proliferative retinopathy are found. In countries such as the UK, the choice between antiangiogenic therapy and laser also depends on OCT thickness, following the decision of the National Institute for Clinical Excellence (NICE 2011) of reimbursing ranibizumab only if central retinal thickness is 400 µm or more, based on a subgroup analysis of the RESTORE 2011 study.

The classification of DMO to decide on treatment options is not standardised and may ultimately depend on the ophthalmologist's assessment of several clinical components. These may include visual acuity and the chronicity of the condition, the existence of a thickened and adherent hyaloid, an epiretinal membrane and vitreous traction to the retina, the degree of ischaemia and the presumed "vasogenic" origin which was believed to benefit more with laser photocoagulation compared to the diffuse type (Bandello 2010). Optical coherence tomography is able to display some of these features, particularly the vitreous-retina interface, as well as any subretinal fluid, the integrity of the photoreceptor layers, and patterns of uncertain interpretation such as hyperreflective foci (Framme 2012; Yohannan 2013). The attempt to classify DMO in focal or diffuse patterns in clinical trials, based on the amount of leakage from microaneurysms, failed to show an impact on prognosis and the response to angiogenic therapy (RESTORE 2011). In addition, such classification was found to have been used inconsistently (Browning 2008c). Diagnostic questions related to these features are complex and cannot be investigated in the diagnostic accuracy framework, according to our judgement.

Prior test(s)

In the accuracy framework in which OCT is used in primary care to detect DMO and then verified by an ophthalmologist with fundus biomicroscopic examination, prior testing should be fundus examination or photography interpreted by optometrists, trained nurses, general practitioners, or automated software.

Role of index test(s)

Given the ill-defined nature and the complexity of clinical pathways, plus the increasing importance of OCT, this updated review differs from the original version. It reinforces the statement that DMO detection primarily by means of OCT, followed by referral to an ophthalmologist using fundus biomicroscopy as verification, is an accuracy question that can be relevant only in specific settings in which this pathway is followed; perhaps in some primary eye-care settings (Shelton 2013).

When ophthalmologists have to decide on treatment and prognosis of DMO, OCT has a dominant role, and in this revised review we agree that fundus examination cannot be used as a reference standard in clinical contexts (Ontario HTA 2009). At this step of care, research has focused on the patterns of agreement between OCT and fundus examination (Davis 2008), and particularly on the clinical characteristics of subclinical DMO, which is detected by OCT as a retinal thickness in the 225 µm to 300 µm range in the absence of biomicroscopic detection of CSMO (Bhavsar 2011; Browning 2008a; Browning 2008b; DRCR Network 2012; Pires 2013). In fact, landmark ETDRS 1985 and ETDRS 1995 studies on photocoagulation showed that DMO less than CSMO may have a good prognosis and less benefit, compared to those with CSMO, with photocoagulation compared to observation. Recently, OCT has offered additional clues on the relationship between central retinal thickness and treatment response. RESTORE 2011 showed that the gain in vision with ranibizumab treatment compared to photocoagulation is about the same as photocoagulation when OCT retinal thickness is less than 300 µm. In 2011, the UK National Institute for Clinical Excellence (NICE) decided to reimburse ranibizumab treatment only in cases where OCT thickness is less than 400 µm (NICE 2011). Apparently contradicting this finding, based on further subgroup analyses based on RESTORE 2011 data, Mitchell 2013 has shown that quality of life gain, measured with the National Eye Institute Visual Functioning Questionnaire, is greater with ranibizumab than laser when thickness is lower than 400 µm and vision is better than about 68 letter, or about 20/50. These results are difficult to interpret since the subgroups are small and because vision-related quality of life is conventionally presumed to be dependent on the eye with better vision, although visual loss in diabetic patients is not only more symmetric but also milder than in age-related macular degeneration.

Alternative test(s)

Despite the fact that retinal thickness measurements with OCT have been compared to those obtained using the Retinal Thickness Analyzer in at least one study, such a comparison is no longer of interest given the dominant use of OCT devices (Goebel 2006). Therefore, OCT is the only index test evaluated in this review.

Rationale

When this review was first published, it was important because OCT was increasingly used at all levels of care to confirm the presence or absence of DMO and to monitor treatment outcomes. As stated before, at present the results of this review may be applicable to inform decisions only in specific contexts.

OBJECTIVES

To determine the diagnostic accuracy of OCT for detecting DMO and CSMO, defined according to ETDRS 1985, in patients referred to ophthalmologists after DR is detected. In the update of this review we also aimed to assess whether OCT might be considered the new reference standard for detecting DMO.

Secondary objectives

1) Heterogeneity investigation

To determine which retinal thickness cut-off or which OCT algorithm yields the best diagnostic performance. In fact, clinicians may use different thresholds of retinal thickness to define DMO and CSMO. Furthermore, thickness can be calculated using different algorithms (such as, previously, central point thickness or, currently, central subfield thickness, which were found to be highly correlated in DRCR Network 2008) or other algorithms that try to detect paracentral retinal thickening (Sadda 2006).

Based on a previous systematic review on this topic, conducted by some of the authors (Virgili 2007), we initially planned to investigate the following sources of clinical heterogeneity.

A. Heterogeneity related to retinal thickness cut-off

We originally planned to explore which cut-off value of central retinal thickness represents the best trade-off of sensitivity and specificity for clinical use. We selected only two pre-planned cut-offs because data driven cut-off selection has been found to lead to optimistic estimates of sensitivity and specificity, especially in small studies (Leeflang 2008). Based on the Virgili 2007 review, we expected to report on a sensitive and a specific threshold, corresponding to values of 250 µm and 300 µm (± 25 µm for both cut-offs). However, only one study reported both thresholds and we used the available information as explained later in the review. Furthermore, the calibration of different OCT devices was found to vary, making the effect of using a specific threshold inconsistent (Wolf-Schnurrbusch 2009).

B. Heterogeneity related to index test

1. Which OCT definition of CSMO should be preferred, such as using the central thickness subfield or complex diagnostic algorithms?
2. What is the difference between OCT models of different generations which were found to yield different measurements (Forooghian 2008; Kiernan 2009; Wolf-Schnurrbusch 2009)?

C. Heterogeneity related to reference standard

1. What is the impact of the type of reference standard used, i.e. stereophotography, contact or non-contact lens biomicroscopy?

D. Heterogeneity related to characteristics of the study population

1. What is the performance of OCT in higher versus lower prevalence studies? (Taking into account that we planned to include clinic-based series, a level of prevalence around 30% was considered a priori.)

E. Heterogeneity related to methodological study quality items

See Appendix 1 of the QUADAS 2 checklist (Whiting 2011) which replaced QUADAS (Whiting 2003) in the update of this review. We dichotomised QUADAS 2 items using yes versus other categories and planned to use a Risk of Bias or Applicability as covariate if the smaller subgroup included at least three studies.

2) To assess whether OCT might be considered the new reference standard

The updated version of this review included an introductory section on the clinical pathways and the role of the index test, which is now a mandatory item in RevMan 2012. The diagnostic accuracy framework is valid if the clinical reference standard is the best available method for establishing the presence or absence of the target (Bossuyt 2008) and implies that, in patients with discordant results, the reference standard is true and the index test is wrong. Diagnostic studies can take the "agreement" rather than the "accuracy" perspective to compare OCT and fundus examination, implying that neither test was believed to be more valid than the other. Browning 2008b; Ockrim 2010; Olson 2013 and Ontario HTA 2009 believed that OCT is more sensitive than clinical examination or stereoscopic fundus photography for the detection of retinal thickening. Lord 2006 and Lord 2009 advised that whenever clinicians use a new diagnostic test because it is more sensitive than an old test, they need to be clear about the assumptions linking this evidence to improved patient outcomes, such as evidence that the new test detects the same spectrum of disease as the old test, or that similar treatment efficacy exists across the spectrum of disease. Although this issue is not an aim of our review, and we did not try to systematically investigate it, it is clearly key in interpreting and using our results and will be discussed based on articles assessed during the preparation of this review, as well as their relevant references.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include all prospective and retrospective consecutive series of patients and case-control studies that evaluated the accuracy of OCT for diagnosing DMO. As discussed above, we acknowledge that the clinical pathway is unclear and may vary across settings and countries. Therefore, we accepted studies in which a two-by-two table was presented which crossed the results of OCT retinal thickness, dichotomised at the approximate thresholds of interest, with ophthalmologists' detection of DMO or CSMO by means of fundus biomicroscopy or photography as defined later. We recorded the settings in which patients were recruited and examined in each study.

Participants

Included participants were people referred to ophthalmologists because they had been found to have some level of DR, expectedly by primary care professionals, such as optometrists, diabetologists and general practitioners, or by other ophthalmologists.

Prevalence is often an indicator of severity of disease spectrum in a study. If patients with any level of DR were examined, the prevalence of DMO would be expected to be lower than 10% (Williams 2004; Yau 2012). However, a relatively high prevalence of DMO was expected, as found in studies included in a previous systematic review (Virgili 2007) and conducted in retina practices, suggesting that a diagnosis of more severe DR, or even any DMO, had already been carried out in the study population.

Index tests

The index test was OCT, regardless of the generation of development of the instrument (low or high resolution, three-dimensional or spectral-domain OCTs).

Despite the fact that retinal thickness measurements with OCT have been compared to those obtained with the Retinal Thickness Analyzer in at least one study (Goebel 2006), based on our knowledge we believe that such a comparison is no longer of interest given the dominant use of OCT devices. We are not aware of any other instruments that can be compared to OCT.

Target conditions

Our review considered the target conditions as both the general definition of DMO and its most severe type, CSMO. In fact, finding the milder form of DMO still has implications regarding the need for closer follow-up as well as on visual prognosis (ETDRS 1985). The ETDRS definitions of DMO and CSMO were adopted in the original version of this review because these definitions have proven prognostic value and CSMO has represented for years the main indication for focal or grid laser photocoagulation (ETDRS 1985); although this treatment technique is less used with the advent of antiangiogenic therapy (Virgili 2014). The most common type of CSMO is the central type, defined as retinal thickening within 500 µm of the centre of the macula or, alternatively, hard exudates within 500 µm of the centre of the macula and with thickening of the adjacent retina. The non-central type of CSMO is less common and is defined as a zone of retinal thickening, one disc area or larger, any portion of which is located within one disc diameter from the centre of the macula.

Anatomic lesions different from retinal thickening such as the presence of intraretinal cysts, retinal layer abnormalities (Alasil 2010; Yohannan 2013), or a thickened posterior vitreous surface adhering to the macula, which is better seen using OCT, have been suggested to be relevant features of DMO in OCT (Chan 2005). However, there is currently no widely accepted standard to define and report these clinical and OCT aspects and to relate them to the ETDRS definitions of DMO and CSMO, which rely on retinal thickening. Finally, we did not take into account the role of other biomicroscopic findings, including a thickened hyaloid, and their influence on the diagnostic performance of OCT in DMO patients.

Reference standards

In the ETDRS study DMO was defined on the basis of stereoscopic fundus photography (ETDRS 1985). This technique is complicated and difficult to use in a clinical setting. It was replaced by contact fundus biomicroscopy, which was found to be in close agreement with stereophotography, particularly for CSMO (Kinyoun 1989). Non-contact fundus biomicroscopy is more commonly used, since sophisticated fundus lenses have been proposed for binocular fundus observation during the past two decades, yet it has been shown to be slightly less sensitive than contact fundus biomicroscopy in the study conducted by Browning et al (Browning 2004).

When this review was conceived, we considered that valid reference tests were stereoscopic fundus photography and contact lens or non-contact lens biomicroscopy of the fundus. As reported above, in the update of this review, we acknowledge that OCT is increasingly thought of as a new reference standard for DMO (Olson 2013; Ontario HTA 2009) and will not update the review further. Although the American Academy of Ophthalmology’s Preferred Practice Patterns (AAO PPP 2012) still considers clinical examination as the current recommendation for routine diagnosis of DMO, Schneider 2013 found that the use of OCT has greatly increased for patients with neovascular age-related macular degeneration or DMO in recent years, while that of fluorescein angiography or fundus photography has decreased.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database (HTA) and the NHS Economic Evaluation Database (NHSEED) (*The Cochrane Library* 2013, Issue 5), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to June 2013), EMBASE (January 1950 to June 2013), Web of Science Conference Proceedings Citation Index - Science (CPCI-S) (January 1990 to June 2013), BIOSIS Previews (January 1969 to June 2013), MEDION and the Aggressive Research Intelligence Facility database (ARIF). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 25 June 2013.

See: Appendices for details of search strategies for *The Cochrane Library* (Appendix 2), MEDLINE (Appendix 3), EMBASE (Appendix 4), CPCI-S (Appendix 5), BIOSIS Previews (Appendix 6), MEDION (Appendix 7) and ARIF (Appendix 8).

Searching other resources

We handsearched the following journals from 2000 to 2009: American Journal of Ophthalmology; Archives of Ophthalmology; British Journal of Ophthalmology; Investigative Ophthalmology and Visual Science; Ophthalmology and Retina.

We also handsearched the references of the articles obtained in full-text.

Data collection and analysis

Selection of studies

The assessment of the titles and abstracts for eligibility was conducted independently by two review authors. We planned to sort abstracts into 'definitely exclude' and 'possibly include' categories, recognising that sometimes it is not possible to judge from the abstract whether a reference fulfils the criteria or not. All abstracts selected by at least one review author were placed in the 'possibly include' category and we retrieved the corresponding full-text reports and further independently assessed their eligibility as 'include' or 'exclude'. This was done by two review authors. Disagreements at each step were resolved by discussion between the two review authors and a third senior author.

Data extraction and management

We extracted data on the number of:

- true positives (TP), i.e. patients categorised as diseased by both the reference and index test;
- false negatives (FN), i.e. patients categorised as diseased by the reference test, but as non-diseased by the index test;
- true negatives (TN), i.e. patients categorised as non-diseased by both the reference and index tests;
- false positives (FP), i.e. patients categorised as non-diseased by the reference test, but as diseased by the index test;
- patients with uninterpretable index test results;
- patients with both eyes included in the analyses;

- missing data, i.e. patients included in the study but not in the analyses, by causes of exclusion.

Uninterpretable OCT results are found when thickness is difficult to obtain because of low quality examinations, such as when ocular media are opaque or the pupil has very poor dilation, or both. For each study, we recorded how these patients were treated in the analyses.

The data were extracted independently by two review authors to ensure consistency and entered in to Review Manager (RevMan 2012).

Assessment of methodological quality

In the updated of this review, the review authors moved to QUADAS 2 (Whiting 2011) tool to assess the susceptibility to bias of the included studies, based on guidance presented in Appendix 1. Additional quality items were on study sponsorship and the unit of analysis issue which is specific to ophthalmology, such as when analyses included both eyes of some individuals. The methodologic quality of the included studies was assessed independently by two review authors and disagreement on study quality was resolved by a third senior author.

Statistical analysis and data synthesis

We conducted two separate analyses, one for each definition of the target condition; that is DMO and its more severe form CSMO.

We had planned to use the *METADAS* macro (Takwoingi 2008) to fit hierarchical summary ROC curve (HSROC) models in SAS for the primary analysis in this review, as well as to explore the effect of covariates on accuracy and threshold. Harbord 2007 has shown that the bivariate (Reitsma 2005) and the HSROC models are mathematically equivalent and, as a result, *METADAS* derives pooled sensitivity and specificity and the effect of covariates on them. In the original version of this review we used the bivariate model approach to assess the effect of covariates on sensitivity and specificity, since a selection at specified thresholds was planned, and then a meta-analysis of a few studies including a restricted range of thresholds was possible. As in the original version, when updating this review, we found convergence problems of the bivariate model with some covariates, and decided to fit the HSROC model in SAS but still present the effect of covariates on sensitivity and specificity, as allowed by *METADAS*.

Since DMO is often bilateral, there may be unit of analysis issues in diagnostic studies on this diabetic complication. We originally planned to consider studies as high quality if only one eye of each individual was included or less than 10% of individuals had both eyes included in the study. Studies including patients with both eyes affected but only one randomly selected were also considered as high quality. We planned to conduct subgroup analyses of high versus low quality studies regarding this criterion to investigate heterogeneity.

We had planned to refer to Dukic 2003 for conducting statistical analyses that included several thresholds extracted from the same study. However, this was not possible even in this update.

Investigations of heterogeneity

The investigations were primarily concerned with exploring heterogeneity in sensitivity and specificity as these are the quantities we intended to estimate. Therefore, we used:

- forest plots to look for evidence of heterogeneity within sensitivity and within specificity;
- ROC plots to look for evidence of a threshold effect and heterogeneity due to differences in accuracy;
- effects of covariates, corresponding to the sources of potential heterogeneity listed in the 'Investigation of sources of heterogeneity' section, on sensitivity or specificity, or both, in the model.

Sensitivity analyses

We planned to restrict analyses by excluding case-control studies if they were found when updating this review. We also conducted a sensitivity analysis restricted to newer OCT models (Stratus or spectral-domain OCTs).

Assessment of reporting bias

We had planned to assess publication bias using funnel plots displaying lnDOR on the x-axis and $1/ESS^{1/2}$ (where ESS is the effective sample size) on the y-axis, as recommended by Deeks 2005, provided that 10 or more studies were included. However, only nine studies were included in the largest meta-analysis.

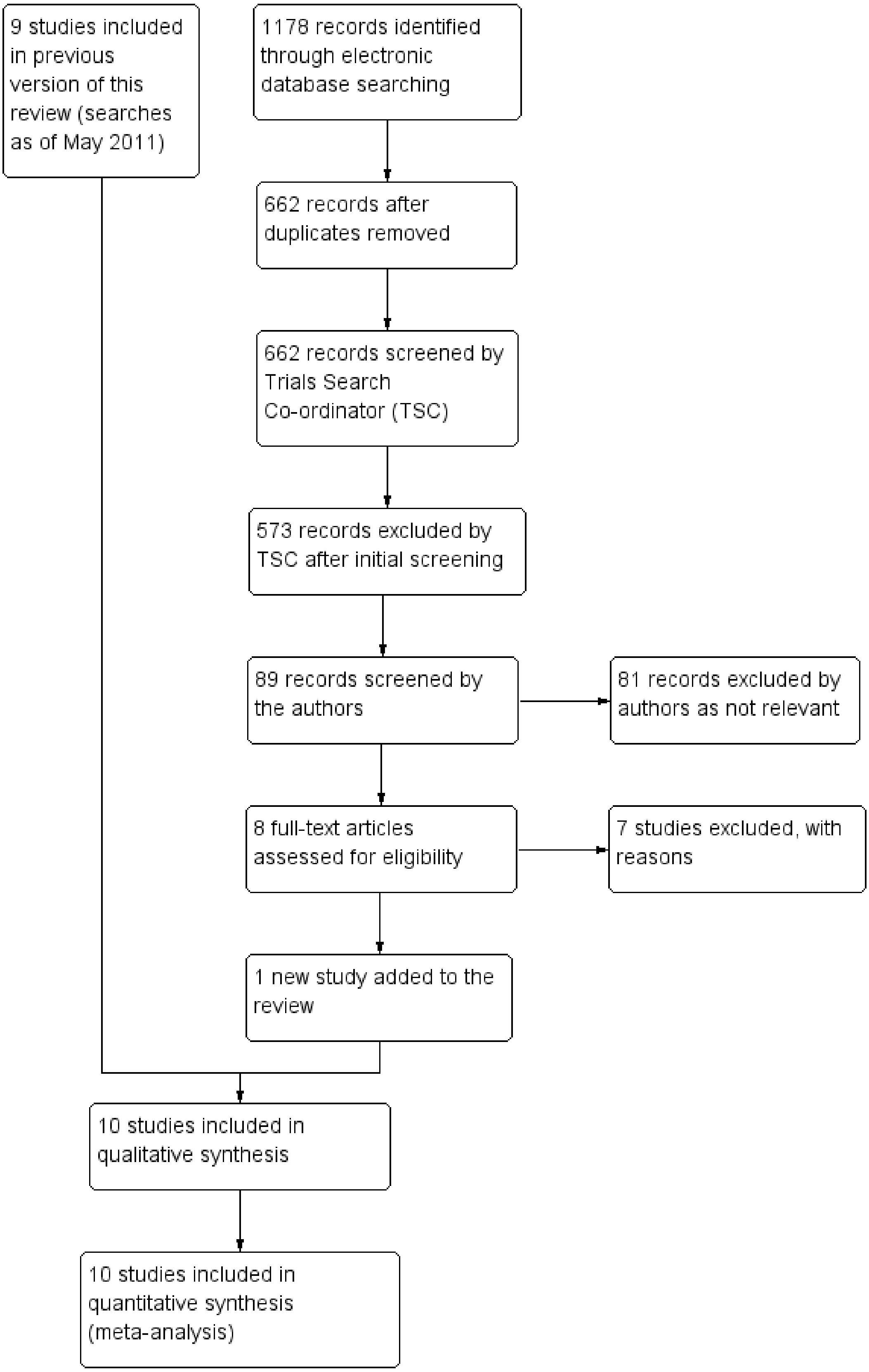
RESULTS

Results of the search

The original electronic searches yielded a total of 3777 records. After deduplication we screened 1672 titles and abstracts for potential inclusion in the review; we rejected 1652 reports as they were not relevant. Of the two authors who screened the results, one author selected 20 reports for potential inclusion and one author selected 17. After disagreements were discussed with a third review author, we obtained the full-text copies of 20 studies. Of these, 11 were excluded for reasons presented in the 'Characteristics of excluded studies' table and nine met the inclusion criteria for our review since they used an appropriate index and reference test in patients having or not having DMO or CSMO as defined by the ETDRS study.

An update search run in June 2013 yielded a further 1178 records (Figure 1). After deduplication the Trials Search Co-ordinator scanned 662 records and removed 573 records which were not relevant to the scope of the review. We reviewed 89 records and rejected 81 abstracts as not eligible for inclusion in the review. We obtained full-text copies of eight reports for further examination. We included one new study (Medina 2012) and excluded seven other studies, see Characteristics of excluded studies table for reasons for exclusion.

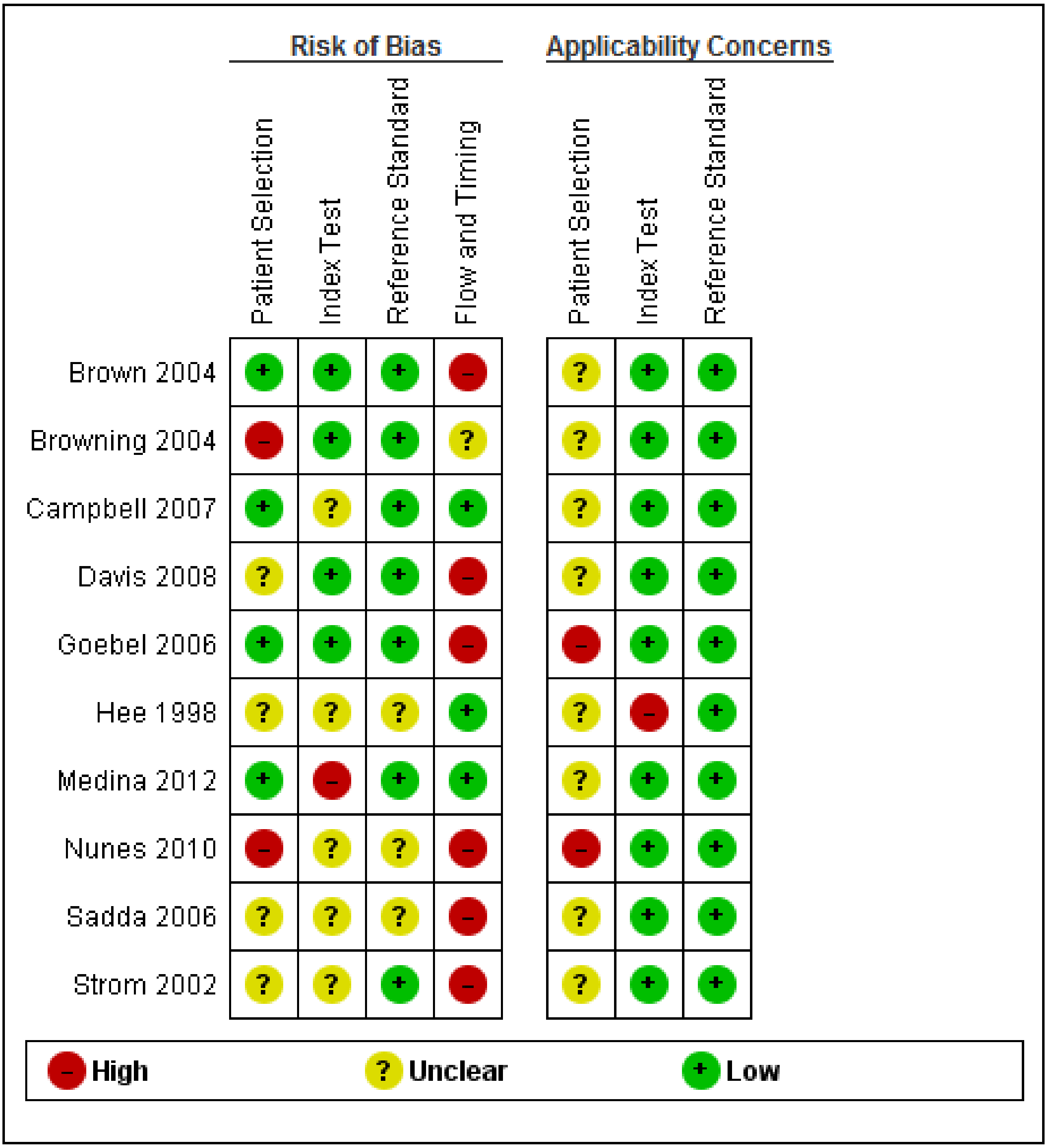
Figure 1. Results from searching for studies for inclusion in the review.



Methodological quality of included studies

Methodological quality is presented in Figure 2, and details are given in the 'Characteristics of included studies' table.

Figure 2. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study



Participant selection

Participant selection was of unclear risk of bias since in four studies it was unclear whether patients were consecutive and only three studies were prospective. Moreover, Goebel 2006 included 13 healthy patients (13 eyes) out of 82 participants (137 eyes) and in Nunes 2010 all eyes had either central or non-central CSMO and were drawn from Reading Centre records. The latter is potentially too narrow as a disease spectrum but we believed it was consistent with other studies, which limited the CSMO definition to the central type in all but one study (Goebel 2006). CSMO prevalence varied between 19% and 58% (median 50%) in eight studies and in a ninth study (Nunes 2010) all eyes had either central (N = 40) or non-central (N = 22) CSMO. Data were extracted for detecting the central type (as 65% prevalence), since all but one of the other studies considered only central CSMO as the target disease.

The professional who referred patients was unclear in all studies, although Medina 2012 reported referral by primary care. Previous testing and the setting from which patients had been referred was unclear in all studies. Thus, we scored applicability as unclear in all studies.

Index test

Five out of 10 studies either did not report masking (blinding) of index test result interpretation (N = 4) or mentioned a lack of masking (N = 1). All but two studies stated the retinal thickness cut off was pre-specified. Applicability was judged to be good overall regarding index test execution and characteristics.

Reference standard

Masking of reference standard results interpretation from index test results was unclear for three studies. The type of reference standard and its execution was appropriate in all studies.

Flow and timing

Three out of 10 studies neither reported on uninterpretable results nor explained withdrawals. An additional study (Nunes 2010) gave an unclear explanation of missing data, described as statistical outliers in a primary analysis correlating visual acuity with retinal thickness. The overall proportion of missing data for any cause, that is the differences between eyes included in the study and those analysed, was 0% to 9% in five studies reporting on them (thus, below the 10% threshold which we planned to use for subgroup analyses) and was 11% in a sixth study (Nunes 2010).

Additional quality items

Unit of analysis was an issue, which was recorded as poor quality for all studies but Medina 2012, since the proportion of patients with both eyes in the analysis was 68% to 95%. Medina 2012 included only one eye of 62 patients. Failure to take into account the correlation between eyes of the same patient can lead to too narrow estimates of the standard error of sensitivity and specificity in the studies. Thus, 95% CIs of summary sensitivity and specificity in our review should be wider. Although Campbell 2007 provided sensitivity and specificity estimates adjusting for within subject correlation, using the design effect correction factor we extrapolated data using the total number of eyes, rather than participants, to be able to include this study in this review.

There were no overt declarations of potential conflicts of interest in terms of the manufacturer of the OCT device being involved in funding the research.

Findings

Ten studies included a total of 830 participants and 1436 eyes, of which 1387 eyes contributed to the analyses (49 eyes were missing or excluded). All studies used OCT to measure central retinal thickness. In addition, Campbell 2007 also used retinal volume as an outcome measure - stating that it was slightly superior to thickness - but without a formal statistical comparison. For this reason we reported only on the use of central retinal thickness as the OCT outcome measure (Summary of findings 1).

Five studies adopted the diagnostic accuracy paradigm in their analysis (Campbell 2007; Goebel 2006; Hee 1998; Medina 2012; Sadda 2006) and five analysed data in terms of agreement, thus assuming that neither test was preferable (Brown 2004; Browning 2004; Davis 2008; Nunes 2010; Strom 2002).

Although all patients were seen at specialised retina clinics, only Medina 2012 mentioned referral by primary care practitioners, but how the referral decision was made and what test was used were unclear.

Diagnosis of CSMO

Nine studies provided data on 1303 eyes for the analysis on CSMO (Figure 3; Figure 4; Summary of findings 1), which is the most severe form of DMO requiring treatment. The meta-analytic summary estimates corresponded to a sensitivity of 0.81 (95% CI 0.74 to 0.86) and a specificity of 0.85 (95% CI 0.75 to 0.91). The positive likelihood ratio was 5.3 (3.2 to 8.7), the negative likelihood ratio was 0.23 (0.18 to 0.30) and the diagnostic odds ratio (DOR) was 23 (13 to 40). Using OCT in a sample of 1000 people, of which 500 have CSMO, will lead to missing 98 patients (false negatives) and will over-diagnose 77 patients (false positives).

Figure 3. Forest plot of OCT for detection of CSMO.

Study	TP	FP	FN	TN	CSMO prevalence	OCT generation	Reference standard	OCT cut-off	Sensitivity (95% CI)	Specificity (95% CI)
Brown 2004	22	6	11	133	0.19	Stratus	Biomicroscopy	300.0	0.67 [0.48, 0.82]	0.96 [0.91, 0.98]
Browning 2004	42	17	8	76	0.35	Stratus	Both	265.0	0.84 [0.71, 0.93]	0.82 [0.72, 0.89]
Hee 1998	56	10	22	105	0.4	2000	Biomicroscopy	250.0	0.72 [0.60, 0.81]	0.91 [0.85, 0.96]
Campbell 2007	21	1	8	35	0.45	Stratus	Stereophotography	240.0	0.72 [0.53, 0.87]	0.97 [0.85, 1.00]
Medina 2012	29	6	2	25	0.5	Cirrus	Biomicroscopy	276.0	0.94 [0.79, 0.99]	0.81 [0.63, 0.93]
Sadda 2006	31	4	4	24	0.56	Stratus	Both	300.0	0.89 [0.73, 0.97]	0.86 [0.67, 0.96]
Davis 2008	205	73	42	112	0.57	Stratus	Stereophotography	250.0	0.83 [0.78, 0.87]	0.61 [0.53, 0.68]
Goebel 2006	53	11	11	36	0.58	2000	Stereophotography	230.0	0.83 [0.71, 0.91]	0.77 [0.62, 0.88]
Nunes 2010	37	6	3	16	0.65	Cirrus	Stereophotography	262.0	0.93 [0.80, 0.98]	0.73 [0.50, 0.89]

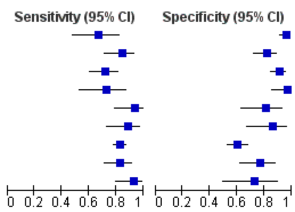
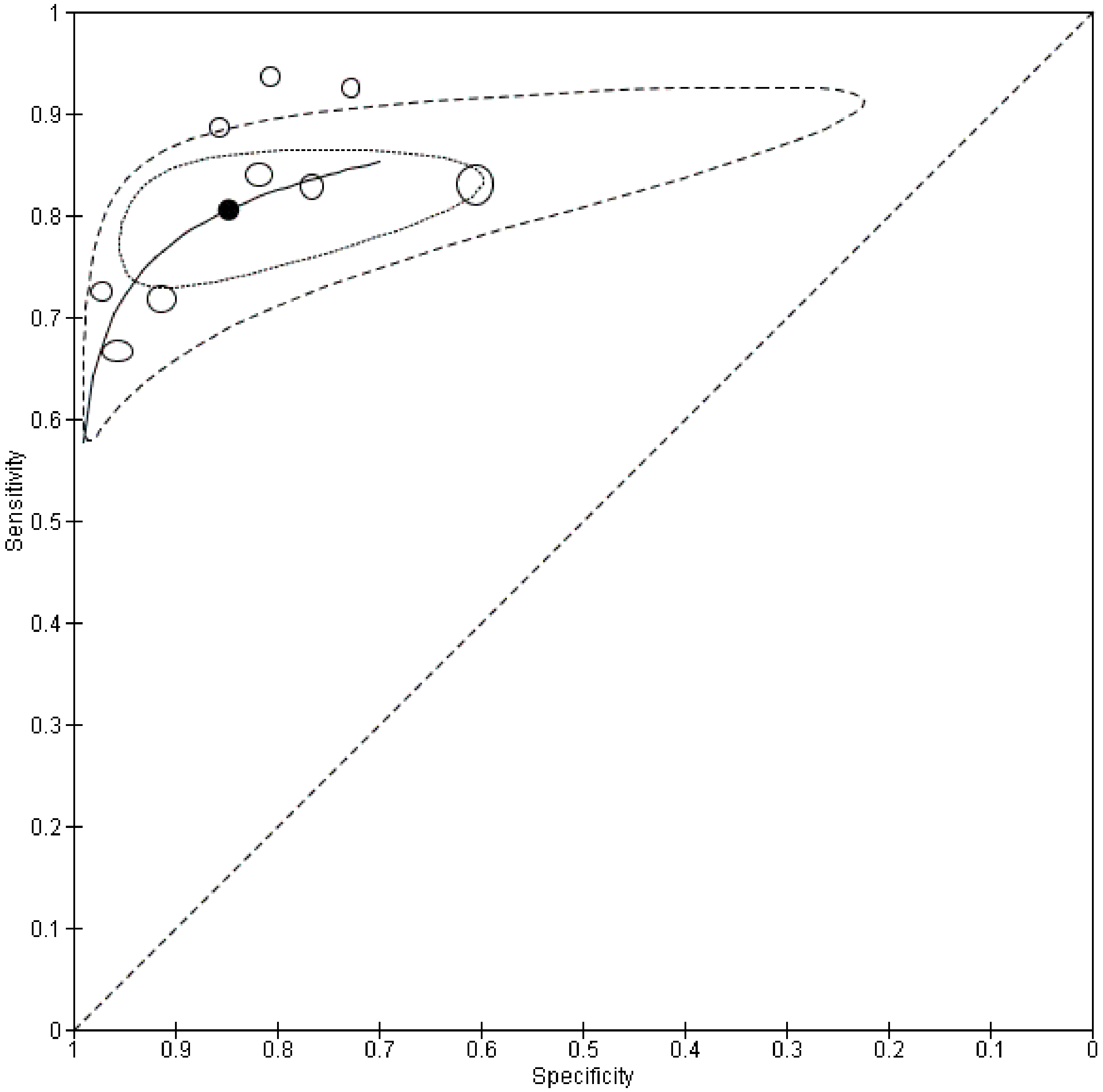


Figure 4. Summary ROC Plot of OCT for detection of CSMO.



Subgroup and sensitivity analyses for diagnosis of CSMO

Among relevant pre-planned covariates, no overall effect of low risk of bias (vs unclear and high risk of bias) could be demonstrated for any QUADAS 2 domain, with P values larger than 0.6 in all analyses.

We present subgroup analyses for other covariates in Table 1. Only prevalence had a statistically significant effect on the overall model parameters, but including the study at median prevalence (Medina 2012; 50% patients with CSMO) in the high prevalence (P = 0.011) or low prevalence (P = 0.109) group caused the overall covariate effect to cross the nominal statistical significance threshold.

The exclusion of two studies (Goebel 2006; Hee 1998) using an obsolete OCT model (OCT 2000) did not change the pooled estimate (sensitivity: 0.83, 95% CI 0.75 to 0.88; specificity: 0.85; 95% CI 0.72 to 0.93).

Additional information on completeness of reporting

Retinal thickness cut-off

We describe in more detail how studies reported and analysed accuracy at different retinal thickness thresholds since this is a key issue for applicability. In fact, macular thickness cut-off with OCT was variably reported. Brown 2004 presented a figure with cut-offs at 200 µm, 300 µm and 400 µm. Browning 2004 used the upper limit of the normal range for each subfield (265 µm for the central subfield). Campbell 2007 reported on cut-offs from 190 µm to 240 µm, and we used the thickest value because it was the closest to those pre-specified in this review. Davis 2008 used a cut-off of 246 µm and quoted an unpublished study on 260 individuals, conducted by the OCT producer, which found that this was the upper limit for normality (mean + 2 standard deviations (SDs); we rounded this up to 250 µm for descriptive purposes). Goebel 2006 used a cut-off of 230 µm for the central subfield. Hee 1998 presented a figure with the crude number of eyes with and without CSMO at 25 µm from 100 µm to 800 µm, and we extracted data at a cut-off of 250 µm because it was the most commonly used in studies included in this review. Sadda 2006 used the MG5 algorithm to detect both central and non-central CSMO and provided data separately for both types; they used a cut-off of 300 µm for central CSMO and we used this value for the whole sample in subgroup analyses by retinal thickness cut-off because sensitivity and specificity were nearly identical for the two types of CSMO. Nunes 2010 used a cut-off of 262 µm computed as two standard deviations above mean thickness of an age-matched control population of 29 eyes of healthy volunteers. Medina 2012 compared three different spectral domain OCT models as well as measurements in mydriasis and myosis and reported the best cut-off in the central and eight paracentral fields.

No definite sensitivity and specificity pattern was apparent for the two subgroups of studies using cut-offs above or below 250 µm (Table 1), which is not surprising given the narrow range of thickness cut-offs (230 µm to 300 µm), which are clinically similar. In fact, retinal thickness values in people with CSMO often range between 300 µm and 600 µm, or even more.

Missing data

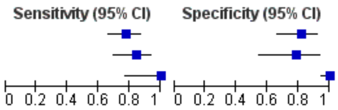
Information on missing data, that is participants included in the study but not analysed, was available for Brown 2004 (3%), Davis 2008 (6%), Goebel 2006 (9%), and Nunes 2010 (11%) at the eye level. There were no missing data for Campbell 2007 and Strom 2002. Such information was not fully available for Browning 2004, Hee 1998 and Sadda 2006. Owing to incomplete reporting of the various types of missing data and the small amount when reported, we did not undertake subgroup analyses for this item as planned in the protocol. We observed that the overall proportion of missing data was small, when reported, although this may impact sensitivity and specificity estimates since few counts are often recorded at their numerator.

Diagnosis of DMO

Three studies provided data on 258 eyes included in this analysis on DMO (Figure 5). Sensitivities were 0.78 (95% CI 0.66 to 0.87), 0.84 (95% CI 0.70 to 0.93) and 1.00 (95% CI 0.77 to 1.00), and specificities were 0.82 (95% CI 0.66 to 0.92), 0.79 (95% CI 0.54 to 0.94), and 1.00 (95% CI 0.95 to 1.00), respectively, in Goebel 2006; Sadda 2006, and Strom 2002; the latter reported perfect sensitivity and specificity. We did not compute pooled estimates of sensitivity and specificity of OCT to detect DMO because only three studies provided data for this analysis; one of which yielded a perfect performance.

Figure 5. Forest plot of OCT for detection of DMO.

Study	TP	FP	FN	TN	OCT generation	Reference standard	OCT cut-off	Sensitivity (95% CI)	Specificity (95% CI)
Goebel 2006	56	7	16	32	2000	Stereophotography	230.0	0.78 [0.66, 0.87]	0.82 [0.66, 0.92]
Sadda 2006	37	4	7	15	Stratus	Both	300.0	0.84 [0.70, 0.93]	0.79 [0.54, 0.94]
Strom 2002	14	0	0	70	2000	Stereophotography		1.00 [0.77, 1.00]	1.00 [0.95, 1.00]



Disagreements between OCT and fundus biomicroscopy

As reported before, the diagnostic accuracy framework is valid if the clinical reference standard is the best available method for establishing the presence or absence of the target (Bossuyt 2008) and implies that, in patients with discordant results, the reference standard is true and the index test is wrong. The included study Medina 2012 is a recent example of a study in which such a diagnostic accuracy question has been made again on OCT testing for DMO. In these cases, it is important to investigate whether additional information is offered by the newer, or index, test in case of disagreements.

We did not find studies which used both OCT and fundus photography or biomicroscopy to detect CSMO and simultaneously tried to resolve all disagreements using a fair 'umpire' test, such as concurrent testing, prognosis or treatment response, a methodology which has been advised to accept a new diagnostic test as a better reference standard (Glasziou 2008). DRCR Network 2007c compared the correlation of OCT and photography with visual acuity, both cross-sectionally and longitudinally, but did not use the standard CSMO definition and did not specifically address disagreements. Hereafter we report on some useful studies on spectrum of disease and prognosis in cases of disagreement between our index and reference tests (Bhavsar 2011; Browning 2008a; Browning 2008b; DRCR Network 2012; Pires 2013), which are useful to examine the characteristics of OCT false positives which disagree with fundus biomicroscopy or photography on the existence of CSMO.

Browning 2008b reported on retinal thickening in 100 healthy people and 283 diabetic patients without clinically detected macular oedema. They found OCT central retinal thickness exceeding the normal range in 6% of patients with DR, nearly all of whom had thickness values below 300 µm according to presented data. Such thickness values are within the range of cut-offs used in studies included in this review, and in the low range of OCT retinal thickening recorded in patients with macular oedema, which may reach values as high as 600 µm to 1000 µm. Browning 2008b also suggested that more cases of OCT thickening are found in people with severe non-proliferative retinopathy. This means that disagreements are more common in patients who were not included in ETDRS 1985, who had mild to moderate retinopathy. On the other hand, this is a retrospective, single physician study and retinopathy subgroups were relatively small.

More interestingly, Browning 2008a reported on the follow-up of 153 patients with subclinical DMO, i.e. eyes with OCT thickening of the macula but not meeting the CSMO definition, who had good visual acuity and baseline central thickness of 238 µm (SD 39 µm). They did not report on visual acuity in detail but found that about a third of these patients progressed to CSMO within 35 months (median follow-up 14 months), then received laser treatment. The authors commented that "subclinical DMO does not inexorably progress, and when it progresses, tends to do so slowly". These patients may resemble those with questionable CSMO or minimal non-central macular thickening in ETDRS 1985, who were both at less risk of visual loss and had less or no benefit from photocoagulation laser compared to those with definite oedema (ETDRS 1995).

Further research has confirmed these findings. DRCR Network 2012 screened 891 eyes among 582 study participants and found that 43 eyes (4.8%) of 39 participants had OCT central retinal thickness between 225 µm and 299 µm. Nine of 43 eyes (21%) required treatment for DMO by 2 years, whereas 27% and 38% were estimated to either have been treated or have met an OCT worsening criterion (i.e. thickness increased by 50 µm or becoming 300 µm or more) at the one or two year visit. Nonetheless, average visual acuity was unchanged at the time of progression in these patients.

In 348 eyes with type 2 diabetes and non-proliferative diabetic retinopathy, Pires 2013 found that 6 out of 32 eyes/patients presenting subclinical DMO at baseline developed CSMO (18.7%), while 20 out of 316 eyes without subclinical DMO developed CSMO (6.3%) within two years.

Bhavsar 2011 followed for an average of 19 months a total 124 eyes of 73 diabetic patients of whom 52 eyes of 37 diabetic patients with subclinical CSMO in one or both eyes, whereas a control group included 72 eyes of 36 patients without macular oedema. Sixteen eyes of 13 subjects (35%) progressed to CSMO in the study group, compared with six eyes of four subjects (11%) in the control group. They found a 15% increase in odds of progression with each 10 µm increase in central macular thickness. Thus, we agree with Browning 2008a that such extra cases should be monitored more closely.

DISCUSSION

Summary of main results

The results of this review must be interpreted in relation to the role of OCT and clinical fundus examination in the diagnostic pathway, a role that has evolved over time. The first two of the following paragraphs, and also the Summary of findings 1, adopt the diagnostic accuracy perspective with clinical fundus examination as reference standard, i.e. the true result in case of disagreement with the index test. The third of the following paragraphs summarises the literature on the additional information offered by measuring OCT central thickness with respect to clinical examination, in support of its use as a new reference standard for diagnosing DMO.

OCT for detecting CSMO

Our systematic review of 10 studies found that central retinal thickness measured with OCT is not sensitive enough (0.81) nor specific enough (0.85) to detect the central type of CSMO defined using fundus examination or photography according to the conventional ETDRS definition, which has guided for decades the use of laser photocoagulation, until antiangiogenic therapy became available. Of 1000 people, 500 of whom have CSMO, a substantial proportion would be missed (N = 98), and there would be some over-referrals (N = 77) (Summary of findings 1). The thickness cut-off extracted from studies included in this review ranged between 230 µm and 300 µm, and was a median of 250 µm.

The precision of summary sensitivity and specificity estimates in this review are likely to be inflated by the fact that both eyes of most patients were included in the studies without accounting for within patient correlation.

In the original version of this review, prevalence was found to have an effect on threshold so that OCT tended to be more specific and less sensitive in studies with lower CSMO prevalence (< 50%). Among mechanisms that may be responsible for sensitivity and specificity varying with prevalence (Leeflang 2009), patient spectrum and reference standard misclassification may apply to this review. However, in this update we found such analysis to be sensitive to the inclusion of a new study (Medina 2012), in which CSMO prevalence was at the median value among nine studies, in the high or low prevalence subgroups.

OCT for detecting DMO

There were only three studies reporting on accuracy of OCT to detect DMO. Two studies found moderate sensitivity and specificity (about 80%) and a third study found perfect sensitivity and specificity (both equal to 1). Since estimates were heterogeneous across studies, a meta-analysis was not performed.

Role of OCT as a new reference standard for detecting DMO

While the original version of this review assumed that deciding upon laser photocoagulation was an appropriate decision making context for using OCT, since the biomicroscopic ETDRS definition of CSMO has been used for more than three decades for this purpose (ETDRS 1985; ETDRS 1995), in this update of the review we re-examined the use of OCT based on studies suggesting that central retinal thickness measures with OCT can be considered a new, objective reference standard for diagnosing DMO (Olson 2013; Ontario HTA 2009). Specifically, several studies have shown that extra cases of DMO detected by OCT, but not by fundus examination, i.e. the so called subclinical DMO, are to be followed up closely due to the increased risk of developing CSMO. Furthermore, RCTs demonstrating the superiority of antiangiogenic therapy over laser photocoagulation (Virgili 2014) have established the primary role of OCT testing for monitoring treatment response, and, thus, in clinical practice. Finally, since OCT is acknowledged by many to be the new reference standard for diagnosing DMO, this review will no longer be updated.

Strengths and weaknesses of the review

Strengths

Merits of this review are a comprehensive literature search, the quality assessment of studies and a meta-analytic summary estimate of diagnostic accuracy based on recommended methodology.

Weaknesses

The main weakness of this review is related to the fact that no clinical pathway could be pre-specified, nor was it reported in any included study, and that the role of OCT has changed over the last decade, gaining importance in the diagnostics of chorioretinal disease.

The number of studies in this review is small and only two studies adopted the latest generation OCTs, which also record slightly higher values of retinal thickness compared with the Stratus OCT

(Forooghian 2008; Kiernan 2009; Wolf-Schnurrbusch 2009), and two studies used an obsolete OCT model (OCT 2000), although their exclusion did not change the pooled estimate in a sensitivity analysis. Liu 2014 investigated decision-making on monitoring antiangiogenic therapy for DMO and found that newer spectral domain OCTs rarely lead to different treatment decisions compared to the Stratus OCT.

More importantly, we could not investigate the effect at pre-specified retinal thickness cut-offs on sensitivity and specificity because data were not available in the included studies.

Another limitation of this review is that we could not obtain data for individuals as the unit of analysis, as nine studies included both eyes of the majority of patients and treated them as if they were independent of each other. Therefore, summary estimates of sensitivity and specificity will have too narrow CIs because the correlation between eyes of the same individual was not taken into account. Apart from this item, at least one QUADAS 2 domain was at unclear or high risk of bias in all studies.

Completeness of the evidence on the use of OCT central retinal thickness as reference standard

We did not search systematically the literature on disagreements between OCT and clinical fundus examination. However, we found several studies showing that evidence is accumulating on prognosis and treatment of subclinical DMO cases detected with OCT, i.e. false positives in our review.

We found no studies on clinical and OCT findings of OCT false negatives, i.e. cases in which ophthalmologist's fundus examination but not OCT identifies DMO or CSMO. This problem is particularly important for its use in the primary care setting, since these could be missed referrals exposed to consequences of lack of treatment until they are detected. Moreover, we found no observational studies on the consequences of withholding treatment in these patients, that is those with CSMO who did not have central thickening on OCT (nearly 8% at an average CSMO prevalence of 50% in our review). A potential cause of false negative OCT results may be the fact that, with the exception of Sadda 2006, the included studies assessed only the central type of CSMO. Although this was made explicit, it is unclear how in reality clinicians applying the reference standard were able to handle overlapping with the non-central type of CSMO, which is less common and is also influenced by detection of hard exudates, which are not included in the definition of OCT thickness-based positivity but would be identified by concurrent fundus imaging.

Applicability of findings to the review question

Readers who wish to use and interpret the results of this review should consider the setting and clinical pathway to which they could be applied. The studies included in this review were carried out in tertiary care settings and patients had a high prevalence of CSMO, around 50%. Furthermore, we found that OCT sensitivity decreased and its specificity increased at lower prevalence, usually associated with milder disease profile, but this subgroup analysis may not be reliable as it was based on few studies.

Newer spectral-domain OCT devices have higher resolution than previous devices and may show further abnormalities of the retinal layers, including those of the photoreceptor layer (Alasil 2010; Yohannan 2013). However, because the construct underlying DMO and CSMO is that of thickening, we only considered thickness-related measures in this review.

Some recent RCTs on anti-VEGF treatment for macular oedema due to DR have included patients in whom our index test and reference standard were both positive, that is affected by clinically detected CSMO and central retinal thickening on OCT (DRCR Network 2010; RESOLVE 2010). Also, changes in OCT retinal thickness were used to decide on the need for ranibizumab re-treatment in DRCR Network 2010 and RESOLVE 2010. This has made OCT an essential tool to manage antiangiogenic treatment of macular oedema in diabetic patients.

AUTHORS' CONCLUSIONS

Implications for practice

There is substantial disagreement between OCT central retinal thickness, used at cut-offs between 230 µm and 300 µm, and fundus biomicroscopy carried out by an ophthalmologist to diagnose CSMO. According to some studies, the characteristics of cases of disagreement may be different and often correspond to milder macular oedema in false positive cases. The identification if such subclinical DMO cases is still useful, as found by Browning 2008b and others, suggesting that these patients should be followed more carefully by means of clinical examination. The clinical profile of OCT false negatives is unclear, given the studies we used and the literature we searched while preparing and updating this review.

Although fundus biomicroscopy is still the current recommendation for routine diagnosis of DMO (AAO PPP 2012), OCT is increasingly used (Schneider 2013) and many find it the new reference standard (Olson 2013; Ontario HTA 2009). Thus, no further update of this review will be performed.

Implications for research

Diagnostic accuracy no longer seems to be a useful framework to investigate the use of OCT for diagnosing DMO, given its dominant role in modern practice (Olson 2013; Ontario HTA 2009). The clinical characteristics and outcome of disagreements between OCT and clinical assessment of the macula to detect CSMO would be usefully reported, especially documenting false negative cases.

Our review also shows that the unit of analysis issue is a common analytic issue in diagnostic research on macular oedema in patients with DR.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Brown 2004

Study characteristics	
Patient sampling	Cohort of consecutive diabetic patients with varying levels of retinopathy, examined during a 6-week period; 59/95 severe non-proliferative or proliferative diabetic retinopathy. Both eyes selected for 80% of subjects enrolled.
Patient characteristics and setting	172 eyes of 95 participants, 66% Caucasian; mean age 62 years, diabetes duration 19 years, visual acuity 0.33 logMAR (slightly less than 6/12), treated with focal laser an average of 1.5 times. Subjects were examined at the Retinal Vascular Center at the Wilmer Eye Institute, Baltimore, USA. Exclusion criteria included the presence of any retinal or choroidal disease, other than diabetes, that could affect retinal thickness or preclude identification of edema involving the centre of the macula. Professional referring patients and prior testing were unclear.
Index tests	Stratus OCT (OCT3; Zeiss-Humphrey Systems, Dublin, CA, USA). OCT exams were carried out by a trained OCT technician, masked to the physician's assessment of foveal edema, using six 6 mm radial scans. Each scan was interpreted by a second masked observer, who assessed the quality of the OCT image and recorded the retinal thickness at the centre of the macula. Positive test defined as central point thickness 300 µm or more based on 6 spokelike scans. No sponsorship by OCT producers declared.
Target condition and reference standard(s)	CSMO diagnosed with fundus biomicroscopy by retina specialists. Clinical assessment of macular oedema performed before OCT. CSMO prevalence 19%.
Flow and timing	Consecutive series of patients and there is no mention of a selection for stereophotography based on OCT status. Only one reference standard. Out of 97 participants who accepted entrance in to the study, only "2 patients were excluded after enrolment because one was unable to complete OCT testing during the clinic visit as a result of time constraints and another left before OCT testing without offering an explanation". The OCT scans were of sufficient quality for interpretation in 170 (99%) of 172 cases.
Comparative	
Notes	Research supported in part by the Wilmer Eye Institute (Johns Hopkins) Macular Research Fund, Baltimore, MD

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Brown 2004 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Did all patients receive a reference standard	Yes		
		High	

Browning 2004

Study characteristics

Browning 2004 *(Continued)*

Patient sampling	Prospective case series. Patients with central or non-central CSMO in one or both eyes seen in a private retina practice were examined for the presence of central thickening. "The study protocol attempted to enrol consecutive patients during the period of the study, but consecutivity was not, in fact, achieved". Professional referring patients and prior testing were unclear.		
Patient characteristics and setting	143 eyes of 80 patients seen at Charlotte Eye, Ear, Nose, and Throat Associates, Charlotte, North Carolina. Demographic participants' characteristics not reported. Patients with media opacities, poor pupillary dilation, high refractive error, or otherwise technically unsatisfactory studies with poor foveal thickness reproducibility were excluded. Professional referring patients and prior testing were unclear.		
Index tests	Stratus OCT (OCT3; Zeiss-Humphrey Systems, Dublin, CA, USA). Thickness of 250 µm used as cut-off for positive result. OCT conducted by certified ophthalmic photographers experienced in performing OCT and masked to the results of the clinical examination. Central subfield value from standard software retinal map used to measure thickness. No sponsorship by OCT producers declared.		
Target condition and reference standard(s)	CSMO (central type) diagnosed with stereoscopic slit-lamp biomicroscopy using a non-contact 78 dioptre fundus lens, by retina specialists. The clinical examination was masked from the results of the OCT because all OCTs were performed after the clinical examination. CSMO prevalence 35%.		
Flow and timing	Some patients were excluded due to media opacities, poor pupillary dilation, high refractive error, or otherwise technically unsatisfactory studies with poor foveal thickness reproducibility, but number not provided. Study report mentioned that "eligible patients did not participate because of their unwillingness" but numbers not given.		
Comparative			
Notes	None		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Browning 2004 *(Continued)*

		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
Did all patients receive a reference standard	Yes		
		Unclear	

Campbell 2007

Study characteristics	
Patient sampling	Patients with diabetic retinopathy ("the degree of diabetic retinopathy in the sample was representative of the spectrum of this disease") referred to the retina and comprehensive ophthalmology services were prospectively enrolled. Professional referring patients and prior testing were unclear.
Patient characteristics and setting	34 participants (65 eyes) with type 1 or type 2 diabetes mellitus visited at university-based clinic in Ontario, Canada. Demographic characteristics not reported. Patients were excluded if they exhibited clinical evidence of any retinal disease other than diabetic retinopathy.
Index tests	Stratus OCT (OCT3; Zeiss-Humphrey Systems, Dublin, CA, USA). Central subfield thickness (retinalmap) 240 µm or more used as positive test result. The study also used a novel retinal volume sector analysis to detect central and non-central CSMO. This analysis examined the 5 central sectors in the most magnified OCT output mode and was defined as the number of sectors with a volume greater than the 95th percentile among diabetic eyes without CSMO. Hence, individual scores for this variable ranged from 0 to 5. All participants underwent OCT and stereo fundus photography on the same day, but no other detail given about masking. No sponsorship by OCT producers disclosed.

Campbell 2007 *(Continued)*

Target condition and reference standard(s)	CSMO diagnosed with fundus biomicroscopy and stereophoto assessment by experienced retina specialists, in a masked fashion. Eyes were then classified as either CSMO present or CSMO absent according to ETDRS definitions. CSMO prevalence 45%.		
Flow and timing	All OCT results were classified as positive or negative and no uninterpretable results or withdrawals were reported.		
Comparative			
Notes	Supported in part by a grant from the University of Ottawa Medical Research Fund.		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			

Campbell 2007 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
	Low

Davis 2008

Study characteristics	
Patient sampling	Prospective, consecutive case series study. Study comprised subjects with diabetic retinopathy selected among those enrolled in a randomised trial on treatment of DMO at retina clinics. Participants had to be gradable for both OCT and fundus photography. Therefore, there was a selection of patients in the study but this depended both on the index test and the reference standard. Both eyes were enrolled for some patients.
Patient characteristics and setting	257 patients (462 eyes) with diabetic retinopathy and CSMO in at least one eye enrolled in a multicentre clinical trial (USA). Some eyes had no evidence of DMO at all. Mean age 59 years; 40% women, 65% white, 18% African American, 9% Hispanic, and 8% other races. Type 2 diabetes in 93% of the participants, mean duration of diabetes 14 years. Mean visual acuity 20/32. Retinopathy severity was non-proliferative in 90% of eyes (32% mild to moderate, 46% moderately severe, and 11% severe). Professional referring the patients and clinical pathway were unclear.
Index tests	Stratus OCT (OCT 3 or OCT 2; Zeiss-Humphrey Systems, Dublin, CA, USA). Fast macular map central subfield thickness 250 µm or more used to define positive result. Fundus photography and OCT were evaluated independently of each other and independently of visits preceding or after the visit being graded. Retinal thickness in µm at the centre point, mean thickness in each of the 9 subfields, and retinal volume within the grid as a whole, were considered. No sponsorship by OCT producers disclosed.
Target condition and reference standard(s)	CSMO diagnosed by stereophotography at photograph reading centre. CSMO prevalence 57%. “Grading methods for DME were the same as those used in the ETDRS, except that areas of retinal thickening and hard exudates were estimated as continuous variables rather than on ordinal scales”. Fundus photography and OCT were evaluated independently of each other and independently of visits preceding or after the visit being graded.
Flow and timing	“Of the 462 eyes that were candidates for analysis, 27 (6%) were excluded because of missing or ungradable images (OCT 10 eyes, FP 15 eyes, both 2 eyes) leaving a total of 435 eyes (309 study eyes and 126 non-study eyes) of 257 participants. These 435 eyes were eligible for all baseline analyses comparing OCT measurements and FP gradings.” There were no withdrawals since these were people voluntarily participating in a randomised controlled trial.

Davis 2008 *(Continued)*

Comparative			
Notes	Supported by a cooperative agreement from the National Eye Institute, Grants EY14231, EY14269, and EY14229.		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Davis 2008 *(Continued)*

Were all patients included in the analysis?	No		
Did all patients receive a reference standard	Yes		
		High	

Goebel 2006

Study characteristics			
Patient sampling	Patients with diabetic retinopathy of any level seen at a university-based clinic in Germany. Not mentioned if study was prospective or retrospective and study setting. Thirteen eyes of 13 subjects without diabetes mellitus or other vascular diseases and normal central retina shown by stereo biomicroscopy served as controls. These were also enrolled in order to calculate the mean retinal thickness cut-off value. Only one eye per subject was selected.		
Patient characteristics and setting	124 eyes of 69 consecutive patients with diabetic retinopathy of any stage and 13 eyes of 13 healthy patients; diabetic patients mean ± SD (range) age 61.1 ± 14.0 (18 to 83) years; controls 62.0 ± 16.2 (35 to 81) years. Professional referring patients and prior testing were unclear.		
Index tests	OCT 2000 Scanner (Zeiss-Humphrey, San Leandro, CA, USA), Software Revision A6.1. Standard macular map central subfield thickness 230 µm or more used to define positive result. Index and reference tests obtained independently. No sponsorship by OCT producers disclosed.		
Target condition and reference standard(s)	CSMO or DMO diagnosed with digital stereoscopic fundus photography. CSMO prevalence 58%, DMO 79%. “Assessment of SFP was done without knowing the results of OCT and RTA measurements”.		
Flow and timing	13 eyes with ungradable fundus photograph and 6 with ungradable OCT (3 eyes excluded because scans could not be obtained and 3 eyes were excluded due to < 50% valid measurement data). No withdrawals reported.		
Comparative			
Notes	None		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Goebel 2006 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
		Low	**High**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Did all patients receive a reference standard	Yes		
		High	

Hee 1998

Study characteristics	
Patient sampling	Patients with diabetic retinopathy seen at the New England Eye Center of Tufts University. Unclear if patients were consecutively collected.
Patient characteristics and setting	182 eyes from 107 participants with diabetic retinopathy (mean age 60 years; range 25 to 81 years), including 98 eyes from 55 men and 84 eyes from 52 women. On slit-lamp examination, 148 eyes were diagnosed with non-proliferative, or background, diabetic retinopathy and 34 eyes had proliferative diabetic retinopathy. Professional referring patients and prior testing were unclear.
Index tests	Early, non-commercial OCT model and software (presumably prototype OCT 2000, Zeiss-Humphrey, San Leandro, CA, USA). Macular map central subfield thickness 250

Hee 1998 *(Continued)*

	µm or more used to define positive result (more than one cut-off could be extracted from Figure 2). No sponsorship by OCT producers disclosed.		
Target condition and reference standard(s)	CSMO or DMO diagnosed with fundus biomicroscopy by retina specialists. CSMO prevalence 40%.		
Flow and timing	The number of patients included in the study matches patients included in the analysis. No uninterpretable results or withdrawals were reported.		
Comparative			
Notes	Supported in part by N1H Grant 9-RO-I-EY11289-10, Bethesda, Maryland; MFEL Grant N00014-94-1-0717, Arlington, Virginia; an unrestricted departmental grant from Research to Prevent Blindness, Inc., New York, New York; and the Massachusetts Lions Eye Research Fund, Inc, Boston, Massachusetts		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Low**

Hee 1998 *(Continued)*

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Did all patients receive a reference standard	Yes	
		Low

Medina 2012

Study characteristics	
Patient sampling	Quote: “A total of 62 consecutive patients with diabetes without recent loss of vision (in the 6 months before enrollment) referred by their primary care physicians to the ophthalmology services of the participating hospitals in compliance with the standard protocol for the care of patients with diabetes were recruited over a 9-month period. Patients were considered to be diabetic if they were taking any glucose-lowering medication.” “Early nonproliferative diabetic retinopathy was found in 23 patients, moderate nonproliferative diabetic retinopathy was found in 13 patients, severe nonproliferative diabetic retinopathy was found in 15 patients, and proliferative diabetic retinopathy was found in 11 patients. CSME was diagnosed in 31 (50%) eyes by noncontact lens biomicroscopy. The mean corrected visual acuity (Snellen) was 0.69 logMAR.”
Patient characteristics and setting	Quote: “Consecutive patients with diabetes without recent loss of vision (in the 6 months before enrolment) referred by their primary care physicians to the ophthalmology services of the participating hospitals. Patients were considered to be diabetic if they were taking any glucose-lowering medication. Exclusion criteria were patients with significant corneal opacities that could result in a poor OCT signal, patients with any ocular disease other than diabetes, and patients who had undergone any intraocular surgery, including cataract surgery. One eye per patient was studied and the study was limited to phakic eyes.” Comment: although referring professional is reported, prior testing is unclear.
Index tests	Quote: "Three commercially available SD OCT devices were used: a Topcon 3D-1000 (Topcon, Tokyo, Japan), a Cirrus HD (Carl Zeiss Meditec, Inc, Dublin, California, USA), and a Spectralis OCT (Heidelberg Engineering, Dossenheim, Germany)." "Different systems cannot be used interchangeably for the measurement of macular thickness. Thus, although we considered edema detected by means of OCT to be present when foveal thickness was greater than a given cutoff point, we were unable to establish a common cutoff point of retinal thickness to diagnose macular edema when we used 3 different SD OCT instruments. OCT was performed by clinicians unaware of the patients diagnosis." Comment: choice of threshold does not seem pre-specified since, in the results, the authors state they used the best cut-off, thus potentially inflating accuracy.
Target condition and reference standard(s)	Quote: “Noncontact lens biomicroscopy of the fundus was considered the gold standard. Clinically significant macular edema was defined according to the Early Treatment Diabetic Retinopathy Study criteria. The diagnosis of clinically significant macular edema (CSME) was made by an independent ophthalmologist who was blinded to the results of the OCT measurements.”

Medina 2012 *(Continued)*

Flow and timing	Interval between OCT and reference standard not specified but we assumed this would be short for all studies if unclear. Quote: “One eye of each patient was selected at random.”		
Comparative			
Notes	None		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		High	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index	Yes		

Medina 2012 *(Continued)*

test and reference standard?	
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Did all patients receive a reference standard	Yes
	Low

Nunes 2010

Study characteristics			
Patient sampling	A series of patients with type 2 diabetes classified on stereocolour fundus photography at an independent reading centre, as having clinically significant macular oedema using the ETDRS classification, but no other detail given.		
Patient characteristics and setting	37 participants (70 eyes) affected by CSMO. 62 eyes of 32 participants included in the analysis. Age mean ± SD (range) years: 64.1 ± 8.7 (44 to 79); sex (male/female): 22/14; duration of diabetes mean ± SD (range) years: 10.8 ± 6.8 (1 to 30). Eyes with photocoagulation treatment within the 3 months before inclusion in the study and eyes with cataract or any other eye disease that may interfere with fundus examination were excluded from the study. Professional referring patients and prior testing were unclear.		
Index tests	Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, California, USA). Cirrus HD-OCT fundus references were coregistered to the respective colour fundus photographs and the average RT for the 500 µm diameter circle, centred at the identified foveal location, was computed resorting to thin plate spline interpolation. Central subfield thickness 262 µm or more used to define positive result, computed as 2 SDs above mean thickness of an age-matched control population of 29 eyes from healthy volunteers. No sponsorship by OCT producers disclosed.		
Target condition and reference standard(s)	Central (type 1) CSMO diagnosed with stereocolour fundus photography.		
Flow and timing	8 eyes excluded. 4 eyes excluded for segmentation errors on OCT but 4 were excluded due to being considered outliers on the statistical analysis.		
Comparative			
Notes	None		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Nunes 2010 *(Continued)*

Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	**High**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Did all patients receive a reference standard	Yes		
		High	

Sadda 2006

Study characteristics	
Patient sampling	Retrospectively review of patients referred to the Doheny Ocular Imaging Unit with a diagnosis of DMO who underwent OCT imaging using both the MG5 algorithm.

Sadda 2006 *(Continued)*

Patient characteristics and setting	71 eyes of 40 participants with a diagnosis of diabetic macular oedema. No other clinical characteristics of sample population were reported. Professional referring patients and prior testing were unclear.
Index tests	Stratus OCT machine (Carl Zeiss Meditec, Inc., Dublin, CA, USA) using both the standard Fast Macular Thickness Map (FMTM) pattern and a concentric grid pattern, Macular Grid 5 (MG5). The MG5 algorithm was used to detect central CSMO as well as the non-central type of CSMO. For central CSMO a cut-off retinal thickness of 300 µm was used to define positive test result. No sponsorship by OCT producers disclosed.
Target condition and reference standard(s)	CSMO or DMO diagnosed with fundus photography by retina specialists. CSMO prevalence 56%, DMO 83%.
Flow and timing	The clinical and imaging records of 71 eyes were retrospectively reviewed. 63 cases had both scanning protocol with correct boundary detection, and were used for the analysis. In cases in which the clinical record did not clearly categorise the CSMO, stereoscopic colour photographs obtained for the patient were reviewed by a trained member of the Doheny Image Reading Center in an attempt to classify the oedema. This fact was not believed to represent differential verification, provided that trained observers were used.
Comparative	
Notes	Supported in part by National Institutes of Health, Bethesda, Maryland (grant nos.: R01 EY013516, R01-EY013178-5, P30-EY008098); Eye and Ear Foundation, Pittsburgh, Pennsylvania; National Eye Institute and National Center on Minority Health and Health Disparities (grant nos.: EY11753, EY 03040); and an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York.

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**

Sadda 2006 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Did all patients receive a reference standard	Yes		
		High	

Strom 2002

Study characteristics	
Patient sampling	A series of patients diagnosed as having diabetic macular oedema less severe than CSME or as having untreatable CSME in one or both eyes by slit lamp biomicroscopy (before data collection) in 2 clinics in Denmark. Unclear if prospective or retrospective and if patients were referred to the clinic.
Patient characteristics and setting	96 eyes of 48 patients with diabetes were studied. Mean age 53 years; female to male ratio, 11:36; type I to type II diabetes mellitus ratio 7:40; mean duration of diabetes: type I, 13.8 years (range 2 to 26.7), type II, 23.5 years (range 16 to 32.2). Control group of 33 eyes in 25 healthy control participants, mean age 48.2 years, served to determine the cut-off used to define a positive OCT result (mean + 2 SDs of normal participants). Professional referring patients and prior testing were unclear.
Index tests	OCT 2000 (Zeiss-Humphrey Inc., Dublin, CA, USA, with software application version A4.1). In each eye, six radiating cross-sectional B scans of 6 mm, were obtained by a well trained technician, with the centre of each scan being the centre of the fovea. The OCT maps and subjective evaluation of stereo fundus photographs were assessed by the same person with a minimum of 7 days between the two assessments. No sponsorship by OCT producers was disclosed. "The algorithm used for interpolation of the OCT scans in this study compared the retinal thickness of the study eyes to a mean value ± 2 SD of healthy control eyes."

Strom 2002 *(Continued)*

Target condition and reference standard(s)	CSMO or DMO diagnosed with fundus photography by retina specialists. CSMO prevalence 17%. The subjective assessment of retinal thickening on the fundus photographs took place before assessment of the OCT topographic maps.		
Flow and timing	12 eyes were excluded for the following reasons: epiretinal fibrosis (1), missing OCT scan (3), poor photograph quality (no stereo effect) in Early Treatment Diabetic Retinopathy Study (ETDRS) standard field 2 (4), poor photograph clarity due to lens opacification (4), and poor quality of the OCT scans due to cataract (1). Thus, a total of 84 eyes (43 right and 41 left eyes) in 47 patients underwent analysis.		
Comparative			
Notes	None		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			

Strom 2002 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Did all patients receive a reference standard	Yes	
		High

CSMO: clinical significant macular oedema
DMO: diabetic macular oedema
FP: false positives
logMAR: logarithm of the Minimum Angle of Resolution
OCT: optical coherence tomography
SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alkuraya 2006	Mean and standard deviation but no sensitivity and specificity data available.
Bolz 2009	Diseased patients only.
Deak 2010	Only CSMO cases.
Gaucher 2005	Study primary objective was investigating the association of DMO and vitreous detachment. Cases were eyes with DMO on biomicroscopy; control eyes included eyes of diabetic patients without DMO on biomicroscopy and OCT. Thus, both OCT and biomicroscopy were used to define disease status, which is invalid to determine diagnostic accuracy.
Giovannini 1999	No CSMO or DMO definition, mainly a follow-up study.
Goebel 2002	Mean and standard deviation but no sensitivity and specificity data available.
Hannouche 2012	No sensitivity and specificity data available.
Lattanzio 2002	No sensitivity and specificity data available.
Maheshwary 2010	No sensitivity and specificity data available.
Murakami 2012a	No sensitivity and specificity data available.
Murakami 2012b	No sensitivity and specificity data available.
Otani 1999	CSMO definition not used for reporting data.
Otani 2010	No sensitivity and specificity data available.

Study	Reason for exclusion
Sànchez-Tocino 2002	Mean and standard deviation but no sensitivity and specificity data available.
Uji 2012	No sensitivity and specificity data available.
Vujosevic 2006	No sensitivity and specificity data available.
Yang 2001	CSMO definition not used for reporting data; only 2 CSMO eyes.
Özdek 2005	No sensitivity and specificity data available.

CSMO: clinically significant macular oedema
DMO: diabetic macular oedema
OCT: optical coherence tomography

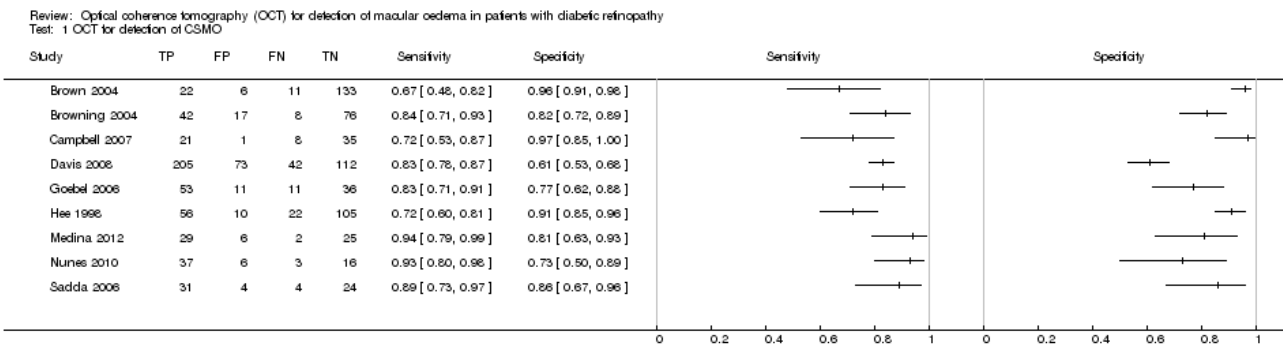
DATA

Presented below are all the data for all of the tests entered into the review.

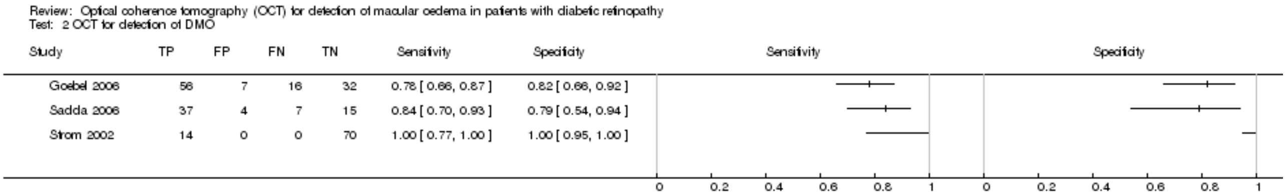
Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 OCT for detection of CSMO	9	1303
2 OCT for detection of DMO	3	258

Test 1. OCT for detection of CSMO.



Test 2. OCT for detection of DMO.



ADDITIONAL TABLES

Table 1. Subgroup analyses

Covariate	Subgroup	N studies	Sensitivity	Specificity	Overall P values vs no subgroups
Retinal thickness	≤ 250 µm	5	0.86 (0.76 to 0.92)	0.85 (0.75 to 0.92)	
	> 250 µm	4	0.77 (0.69 to 0.84)	0.85 (0.64 to 0.95)	
	P value		0.103	0.971	0.034
Prevalence	≥ 50% (50% to 65%)	5	0.86 (0.81 to 0.90)	0.74 (0.64 to 9.82)	
(Medina 2012 in high prevalence group)	< 50% (19% to 45%)	4	0.74 (0.68 to 0.80)	0.92 (0.84 to 0.97)	
	P value		0.004	0.002	0.011
Prevalence	> 50% (56% to 65%)	4	0.86 (0.81 to 0.90)	0.72 (0.57 to 0.83)	
(Medina 2012 in low prevalence group)	≤ 50% (19% to 50%)	5	0.74 (0.69 to 0.84)	0.91 (0.84 to 0.95)	
	P value		0.148	0.018	0.109
Reference standard	Biomicroscopy	4	0.78 (0.69 to 0.86)	0.89 (0.79 to 0.95)	
	Photography or both	5	0.82 (0.74 to 0.88)	0.79 (0.64 to 0.89)	
	P value		0.474	0.193	0.653

APPENDICES

Appendix 1. Methodological quality assessment guidance for QUADAS 2

DOMAIN	yes (high)	no	unclear

(Continued)

PATIENT SELECTION	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):		
Was a consecutive or random sample of patients enrolled?	Consecutive sampling or random sampling of patients with DR referred to an ophthalmologist because they are suspected of having DMO based on prior testing, i.e. fundus examination or photography by primary eye care professionals	Non-random sampling or retrospective recruitment of patients or selection of patients among people already followed-up by ophthalmologists in diabetic retinopathy services or eye care hospital-based services	Unclear whether consecutive or random sampling used
Was a case-control design avoided?	No selective recruitment of DR patients with or without DMO, or nested case-control designs (systematically and randomly selected from a defined population cohort)	Selection of either cases or control in a predetermined, non-random fashion; or enrichment of the cases from a selected population	Unclear selection mechanism
Did the study avoid inappropriate exclusions?	Exclusions are detailed and felt to be appropriate, including OCT ungradable because of poor quality	Inappropriate exclusions are reported, e.g. patients with questionable DMO on biomicroscopy	Exclusions are not detailed (pending contact with study authors)
Risk of bias: Could the selection of patients have introduced bias?	Overall judgement at reviewer's discretion, with reasons		
Concerns regarding applicability: Are there concerns that the included patients do not match the review question?	Inclusion of patients with a significant degree of diabetic retinopathy that may be associated with diabetic macular oedema (DMO) or are suspected of having DMO; clinical pathway in which clinical verification of OCT findings is meaningful for decision-making, with setting and prior testing reported	Inclusion of healthy controls or diabetic patients with no retinopathy, such as in case-control studies	Unclear inclusion criteria, setting and prior testing
INDEX TEST	Describe the index test and how it was conducted and interpreted:		
Were the index test results interpreted without knowledge of the results of the reference standard?	Test performed “masked” or “independently and without knowledge of” reference standard results is sufficient and full details of the masking procedure are not required; or clear temporal pattern to the order of testing that precludes the need for formal masking	Reference standard results available to those who conducted or interpreted the index tests	Unclear whether results are interpreted independently
If a threshold was used, was it pre-specified?	Central retinal thickness cut-off used to dichotomise data is declared to be pre-specified or data at several cut-offs are presented that enable extraction in the range of interest (250 µm to 350 µm)	A study is classified at higher risk of bias if the authors define the optimal retinal thickness cut-off post hoc based on their own study data	No information on pre-selection of index test cut-off values
Risk of bias: Could the conduct or interpretation of the index test have introduced bias?	Overall judgement at reviewer's discretion, with reasons		
Concerns regarding applicability: Are there concerns that	OCT model, OCT execution, and OCT diagnostic criteria clearly described and judged to be adequate	Older OCT models, such as OCT 2000, used or methods to max-	Insufficient details to assess this item

(Continued)

the index test, its conduct, or interpretation differ from the review question?		imise the quality of results not adopted	
REFERENCE STANDARD	Describe the reference standard and how it was conducted and interpreted:		
Is the reference standard likely to correctly classify the target condition?	Fundus stereoscopic photography or fundus biomicroscopy with a contact and non-contact lens and Early Treatment Diabetic Retinopathy Study (ETDRS) definition of DMO and clinically significant macular oedema (CSMO) used by an ophthalmologist or a trained technician in a photograph reading centre (in case photography is used)	Definition of DMO and CSMO different from ETDRS although photography or biomicroscopy are used	Insufficient details to assess this item
Were the reference standard results interpreted without knowledge of the results of the index test?	Reference standard performed "masked" or "independently and without knowledge of" index test results are sufficient and full details of the masking procedure are not required; or clear temporal pattern to the order of testing that precludes the need for formal masking	Index test results available to those who conducted the reference standard	Unclear whether results are interpreted independently
Risk of bias: Could the reference standard, its conduct, or its interpretation have introduced bias?	Overall judgement at reviewer's discretion, with reasons		
Concerns regarding applicability: Are there concerns that the target condition as defined by the reference standard does not match the review question?	Signalling question 1 high quality criteria fulfilled	Signalling question 1 high quality criteria not fulfilled	Insufficient details to assess this item
FLOW AND TIMING	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2 x 2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard		
Was there an appropriate interval between index test(s) and reference standard?	'Yes' for all studies because the index test is commonly collected with the reference standard although this is not specified	Not applicable	Not applicable
Did all patients receive a reference standard?	No discrepancies between the number of patients recruited into the study and the number of patients in the 2 x 2 table; or there are discrepancies but they are motivated and are not related to severity of diabetic retinopathy or presence of DMO or CSMO	There are discrepancies or they are motivated but related to severity of diabetic retinopathy or presence of DMO or CSMO	Insufficient details to assess this item.
Did all patients receive the same reference standard?	The same reference standard was used for all patients; different reference standards were used, such as fundus photography for some patients and fundus biomicroscopy for others, but it is clearly explained that there was no predetermined criterion	Different reference standards were used, such as fundus photography for some patients and fundus biomicroscopy for others, and it is not clearly ex-	Insufficient details to assess this item

(Continued)

	that might relate the type of reference standard to severity of diabetic retinopathy or presence of DMO or CSMO	plained whether there was a predetermined criterion that might relate the type of reference standard to severity of diabetic retinopathy or presence of DMO or CSMO	
Were all patients included in the analysis?	The number of patients included in the study matches the number in analyses or patients with undefined or borderline test results are excluded	The number of patients included in the study does not match the number in analyses and patients with undefined or borderline test results are excluded from the analyses	The number of patients analysed, but not that included in the study, are reported, or unclear if there were inappropriate exclusions
Risk of bias: Could the patient flow have introduced bias?	Overall judgement at reviewer's discretion, with reasons		

Appendix 2. *The Cochrane Library* search strategy

#1 MeSH descriptor Tomography
#2 MeSH descriptor Tomography, Optical Coherence
#3 MeSH descriptor Ophthalmoscopy
#4 optical* near/2 coherence* near/2 tomograph*
#5 OCT
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Macular Edema
#8 macula* near/3 oedema
#9 macula* near/3 edema
#10 maculopath*
#11 CME or CSME or CMO or CSMO
#12 DMO or DME
#13 (#7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14 MeSH descriptor Diabetes Mellitus
#15 MeSH descriptor Diabetic Retinopathy
#16 MeSH descriptor Diabetes Complications
#17 diabet*
#18 retinopath*
#19 (#14 OR #15 OR #16 OR #17 OR #18)
#20 (#6 AND #13 AND #19)

Appendix 3. MEDLINE (OvidSP) search strategy

1. tomography/
2. tomography, optical coherence/
3. ophthalmoscopy/
4. (optical$ adj2 coherence$ adj2 tomograph$).tw.
5. OCT.tw.
6. or/1-5
7. exp macular edema/
8. (macula$ adj3 oedema).tw.
9. (macula$ adj3 edema).tw.
10. maculopath$.tw.
11. (CME or CSME or CMO or CSMO).tw.
12. (DMO or DME).tw.

13. or/7-12
14. exp diabetes mellitus/
15. diabetic retinopathy/
16. diabetes complications/
17. diabet$.tw.
18. retinopath$.tw.
19. or/14-18
20. 6 and 13 and 19

Appendix 4. EMBASE (OvidSP) search strategy

1. tomography/
2. tomography, optical coherence/
3. (optical$ adj2 coherence$ adj2 tomograph$).tw.
4. OCT.tw.
5. or/1-4
6. exp retina macula edema/
7. (macula$ adj3 oedema).tw.
8. (macula$ adj3 edema).tw.
9. maculopath$.tw.
10. (CME or CSME or CMO or CSMO).tw.
11. (DMO or DME).tw.
12. or/6-11
13. exp diabetes mellitus/
14. diabetic retinopathy/
15. diabet$.tw.
16. retinopath$.tw.
17. or/13-16
18. 5 and 12 and 17

Appendix 5. ISI Web of Science search strategy

14 #4 AND #10 AND #13
13 #11 OR #12
12 TS=retinopath*
11 TS=diabet*
10 #5 OR #6 OR #7 OR #8 OR #9
9 TS=(DMO OR DME)
8 TS=(CME or CSME or CMO or CSMO)
7 TS=maculopath*
6 TS=macula* oedema
5 TS=macula* edema
4 #1 OR #2 OR #3
3 TS=OCT
2 TS=tomograph*
1 TS=optical* coherence* tomograph*

Appendix 6. BIOSIS Previews search strategy

14 #4 AND #10 AND #13
13 #11 OR #12
12 TS=retinopath*
11 TS=diabet*
10 #5 OR #6 OR #7 OR #8 OR #9
9 TS=(DMO OR DME)
8 TS=(CME or CSME or CMO or CSMO)
7 TS=maculopath*
6 TS=macula* oedema
5 TS=macula* edema
4 #1 OR #2 OR #3
3 TS=OCT
2 TS=tomograph*
1 TS=optical* coherence* tomograph*

Appendix 7. MEDION search strategy

Database was searched on ICPC code field. Using code "f" for ophthalmology.

Appendix 8. ARIF search strategy

optical coherence tomography AND diabet* AND *edema

WHAT'S NEW

Date	Event	Description
13 April 2015	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2009
Review first published: Issue 7, 2011

Date	Event	Description
25 June 2013	New citation required but conclusions have not changed	QUADAS 2 adopted. The included study does not change conclusions; subgroup analysis on median prevalence shown to be sensitive to new study allocation to either group (low versus high prevalence). The discussion on disagreements between OCT and the reference standard (clinical or photographic examination) has been updated and a secondary objective has been added regarding whether OCT can now be considered a new reference standard for diagnosing DMO.
25 April 2013	New search has been performed	Updated electronic searches yielded one new study (Medina 2012).

CONTRIBUTIONS OF AUTHORS

Conceiving the review: GV
Designing the review: GV, FM, VM, EP, FR, GC
Co-ordinating the review: GV
Data collection for the review:
- designing electronic search strategies: Cochrane Eyes and Vision Group editorial base
- undertaking manual searches: EP, FR
- screening search results: VM, FM
- organising retrieval of papers: VM, FM
- screening retrieved papers against inclusion criteria: VM, FM
- appraising quality of papers: VM, FM, GV
- extracting data from papers: FM, VM, EP, FR, GV
- writing to authors of papers for additional information: GV
- providing additional data about papers: GV
- obtaining and screening data on unpublished studies: GV
Data management for the review:
- entering data into RevMan 2012: EP, FR, GV
Analysis of data: GV, GC
Interpretation of data:
- providing a methodological perspective: GV,

- providing a clinical perspective: FM, VM, GV
- providing a policy perspective: GV
Writing the review: GV, EP, FR, VM, GC
Providing general advice on the review: GC
Securing funding for the review: GV
Performing previous work that was the foundation of the current study: GV, FM

DECLARATIONS OF INTEREST

None known.

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Internal sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We originally planned to conduct statistical analyses based on the users' written macro *gllamm* in Stata Software. For the primary analysis we used the *METADAS* macro to fit hierarchical sROC models in SAS for all analyses. In fact, we tried to fit the bivariate model first but it did not give convergence. Then, we accepted the fact that the two models usually provide very close results and decided to use the HSROC model. This is also justified by the fact that study specific thickness cut-offs were very close from a clinical point of view (230 µm to 300 µm), and with only eight studies in the analysis, the effect of such similar thickness cut-offs could not be assessed reliably.

In the 2014 update of this review, we moved from QUADAS (Whiting 2003) to QUADAS 2 (Whiting 2011) to assess the susceptibility to bias of included studies. We included an additional study (Medina 2012) but summary estimates of sensitivity and specificity did not change. Because of the expanding role of OCT for diagnosing DMO, we have considered a literature review of the potential role of OCT as a new reference standard. In particular, we have summarised the studies on the characteristics of false positives (so called subclinical DMO) and briefly reported on the role of OCT in assessing treatment indication and response to antiangiogenic therapy.

INDEX TERMS

Medical Subject Headings (MeSH)

Diabetic Retinopathy [*complications]; Diagnostic Errors; Macular Edema [*diagnosis] [etiology] [pathology]; Randomized Controlled Trials as Topic; Retina [pathology]; Selection Bias; Sensitivity and Specificity; Tomography, Optical Coherence [*methods]

MeSH check words

Humans