
Review Article

Cataract surgery and age-related macular degeneration. An evidence-based update

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ABSTRACT.

Purpose: Age-related macular degeneration (AMD) and cataract often coexist in patients and concerns that cataract surgery is associated with an increased risk of incidence or progression of existing AMD has been raised. This systematic review and meta-analysis is focused on presenting the evidence concerning progression of AMD in patients undergoing cataract surgery.

Methods: We performed a systematic literature search in the PubMed, Medline, Cochrane Library and CINAHL databases. Two randomized trials and two case-control trials were identified. Quality of the studies was assessed using the Cochrane risk of bias tool, data were extracted, and meta-analyses were performed. Quality of the available evidence was evaluated using the GRADE system.

Results: We found that visual acuity at 6–12 months follow-up was significantly better (6.5–7.5 letters) in eyes that had undergone cataract surgery than in unoperated eyes, but the included number of subjects was small, and hence, the quality of evidence was downgraded to moderate. We did not find an increased risk of progression to exudative AMD 6–12 months after cataract surgery [RR 3.21 (0.14–75.68)], but the included number of subjects was small, and thus, the quality of the evidence was moderate.

Conclusion: Cataract surgery increases visual acuity without an increased risk of progression to exudative AMD, but further research with longer follow-up is encouraged.

Key words: age-related macular degeneration – cataract surgery – exudative age-related macular degeneration – outcome – visual acuity

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Introduction

Cataract and age-related macular degeneration (AMD) are both common

causes of impaired visual acuity and blindness in the elderly population in westernized countries. Globally, cataract is the most common cause of

blindness (Resnikoff et al. 2004). In westernized countries where there is relative easy access to cataract surgery, blindness from cataract is very rare, but it remains the leading cause of impaired visual acuity in the elderly population with AMD ranking second (Klaver et al. 1998). In Denmark, cataract and AMD together account for 74% of the number of visually impaired in the age group >65 years and 57% of the number of blinded individuals >65 years (Buch et al. 2004). Cataract can be treated effectively by removing the opaque lens, and exudative AMD can be treated by intravitreal injection of anti-VEGF, but we still do not have a treatment for the dry form of AMD.

Concern has been raised that cataract surgery may increase the risk of incident AMD or progression of pre-existing AMD. Early histological examinations (van der Schaft et al. 1994) and case studies reported an occurrence of wet AMD after cataract surgery (Blair & Ferguson 1979; Pollack et al. 1997, 1998). In theory, two likely mechanisms could lead to a progression in AMD after cataract surgery. One theory is based on blue light toxicity (Algvere et al. 2006; Glazer-Hockstein & Dunaief 2006). Intense, acute exposures to short-wavelength irradiation are toxic to the retina (Ham Jr. et al. 1976). The aged human lens effectively absorbs short wavelengths (Kessel et al. 2010)

thereby providing protection against short-wavelength irradiation. During cataract surgery, the natural lens is removed and replaced with an artificial intraocular lens (IOL) that provides less protection against short wavelengths (Mainster 2006). The relationship between short wavelengths and AMD has, however, so far not been proven. The second theoretical link between AMD progression and cataract surgery is related to the immune system and inflammatory response induced by cataract surgery. Increasing evidence points towards imbalance in inflammatory regulation as a hallmark in the pathogenesis of AMD (Buschini et al. 2011) as well as in the progression to neovascular AMD (Singh et al. 2012). Manipulation of the immune system could form the basis of a potential future therapy for the dry form of AMD (Chen & Smith 2012). At least in theory, cataract surgery could upset the immunological balance and thereby increase the risk of progression of AMD although no evidence supports this theory yet.

Cataract and AMD often coexist in patients. The presence of AMD may adversely affect the visual outcome after cataract surgery. However, deferring surgery for visually significant cataract in patients with AMD will also negatively influence the visual function of patients. At the same time, case reports and cohort studies have raised concern that cataract surgery may increase the risk of progression of AMD. So, how do we advise the patient with visually significant cataract and AMD?

The effect of cataract surgery on progression of AMD was previously evaluated by a Cochrane review (Casparis et al. 2012). That review only included data from published randomized controlled trials, resulting in a recommendation based on one included study. Thus, the authors of this study found it reasonable to review the literature to include data from prospective, non-randomized trials in addition to randomized, clinical trials. Furthermore, the evidence from epidemiologic studies will be summarized. The present work was undertaken after an initiative by the Danish National Health and Medicines Authorities to formulate evidence-based national guidelines on surgery for age-related cataract.

Methods

The aim of the present meta-analysis was to examine whether cataract surgery increases the risk of progression of dry AMD using an evidence-based approach. The systematic review and subsequent meta-analysis were performed based on the principles described in the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Guyatt et al. 2011f). The first step in the working process was to define the topic of the systematic review using the PICO approach (Guyatt et al. 2011a). In short, PICO stands for: Patient, Intervention, Comparison and Outcome.

For this specific meta-analysis, we chose to examine the risk of progression of AMD in patients with AMD and age-related cataract (P) after cataract surgery by comparing eyes with AMD and cataract that underwent cataract surgery (I) to eyes with AMD and cataract where cataract surgery was not performed or where surgery was postponed for 6–12 months to allow for a sufficient long observational period (C). As specific outcome measures, we chose best corrected distance visual acuity (BCDVA) as well as fundoscopic (photographs, fluorescein angiograms, fundus autofluorescence or OCT) signs of AMD progression as defined by the studies at least three months after surgery (O).

A systematic literature search was conducted in August 2014 in the Embase, Medline, Cochrane Library and CINAHL databases using a combination of the search terms (((disease progression) OR age-related macular degeneration) OR macular degeneration) AND ((cataract extraction) OR cataract surgery). The search was limited to references published from 1996 and onwards in the English or Scandinavian languages. The search yielded a total of 1765 hits. Of those hits, 52 references were of potential interest, and full-text papers were obtained. Whenever there could be any doubt as to the relevance of a reference, the abstract was read, and if there was still any doubt, the reference was read in full-text. In addition, four papers that were not identified by the systematic literature search were identified by other means, for example the literature list of search-hit references.

The quality of each included study was assessed using the Cochrane risk of bias tool (Higgins & Green 2011). In short, the Cochrane risk of bias tool assesses risk of bias associated with the selection of patients (randomization or patient allocation and concealment of allocation), study performance (blinding of patients and personnel), detection of outcomes (blinding of outcome assessment), attrition of data (such as missing patients or dropouts), reporting of study findings (selective outcome reporting) or other types of bias. This part of the systematic review was carried out using the Review Manager Software (Review Manager (RevMan) 2014).

The quality of the evidence for each prespecified outcome was evaluated across the included studies using the GRADE system. Each outcome was analysed for study limitations that could affect the outcome (risk of bias, e.g. lack of allocation concealment or lack of blinding of patients or outcome assessors, incomplete accounting of patients and outcome, selective outcome reporting or other limitations) (Guyatt et al. 2011g), inconsistency (different results between studies) (Guyatt et al. 2011d), indirectness (e.g. use of surrogate measures) (Guyatt et al. 2011c), imprecision (large confidence intervals or the lack of statistical strength by included studies to answer the posed question) (Guyatt et al. 2011b) and risk of publication bias (e.g. lack of reporting of negative findings) (Guyatt et al. 2011e). The quality of the evidence for each of the prespecified outcomes could be up- or downgraded based on the assessment of each of the limitations mentioned above. This part of the review including preparation of summary of finding tables was prepared using the Grade Profiler Software (GRADE profiler 2011).

For each prespecified outcome, data were extracted from the included studies independently by two reviewers (LK and DE). Cases of disagreement in data extraction were solved by consensus.

Dichotomous outcome data were analysed by calculating risk ratios. Continuous outcome data were analysed using the mean differences approach. The Review Manager 5 Software (Review Manager (RevMan) 2014) was used for estimation of overall treatment effects. Random-effects

models were used to calculate pooled estimates of effects.

Results

After a systematic literature search, we identified two randomized, controlled trials that evaluated the progression of AMD after cataract surgery (Lamoureaux et al. 2007; Hooper et al. 2009; Brunner et al. 2013). One of the studies was published in two separate publications (Lamoureaux et al. 2007; Hooper et al. 2009). Only the most recent publication was included in the analyses below (Hooper et al. 2009). Furthermore, we identified three case-control studies evaluating the outcome in patients with AMD after cataract surgery (Armbrecht et al. 2000, 2003; Baatz et al. 2008; Wang et al. 2012). Again, one of the studies was published in two separate publications (Armbrecht et al. 2000, 2003), and only the most recent publication was included in the analyses below (Armbrecht et al. 2003). One of the non-randomized studies was excluded because the control group included patients that could have had cataract surgery within the last 12 months of the 36 months follow-up period, but the number of eyes that did have cataract surgery in the control group was not reported (Wang et al. 2012). The last case-control study reported visual function and progression to wet AMD in a group of patients with AMD who underwent cataract surgery and compared with a group of patients who were diagnosed with dry AMD in the same time period (Baatz et al. 2008). Thus, two random-

ized, controlled trials and two case-control studies were available for the analyses below. Randomized and non-randomized studies were analysed separately. The characteristics of included and excluded studies are provided in Table S1 and Table S2, respectively.

Visual acuity 6–12 months after cataract surgery

Visual acuity after cataract surgery was reported in all four included studies. One of the randomized studies used a design where surgery was performed immediately in one group and deferred 6 months in another group, but visual acuity was not reported before 12 months after the first surgery, that is at a time-point when both groups had had surgery (Brunner et al. 2013). Hence, the study result could not be included in the analysis below. The two case-control studies reported visual acuity after 1 year of follow-up (Armbrecht et al. 2003; Baatz et al. 2008). Visual acuity was significantly better in patients with AMD who underwent cataract surgery, and the mean difference (95% CI) was -0.15 (-0.28 to -0.02) logMAR for the RCT and -0.13 (-0.17 to -0.09) for the case-control studies corresponding to 7.5 and 6.5 letters on the 20 feet ETDRS chart for the RCT and case-control studies, respectively. The differences were highly statistically significant (see Fig. 1).

The quality of evidence concerning visual outcome after cataract surgery was graded as moderate for the randomized trials and very low for the

case-control studies. According to the GRADE guidelines, non-RCTs start as low-quality evidence (Balsheim et al. 2011). The quality of evidence was downgraded because of the low number of patients included (RCTs) and the imbalance in AMD characteristics between the surgery and non-surgery groups (case-control studies). The quality of the evidence and summary of findings are presented in Table 1.

Progression to exudative AMD

All four included studies reported the number of eyes progressing to wet AMD within the observational period. One of the RCTs used a study design where only patients with a high risk of progression were included (Hooper et al. 2009) whereas this was not part of the study design in the other RCT (Brunner et al. 2013). One of the case-control studies had an unequal distribution of wet AMD at baseline with 5% of eyes in the surgery group and the 25.6% of eyes the control group (Armbrecht et al. 2003). Furthermore, control subjects were younger (75 years versus 80 years), potentially suggesting a more aggressive course in the control group than in the surgery group. The second case-control study did not report the duration of AMD in patients in the surgery group at baseline (Baatz et al. 2008). By comparison, early AMD had been diagnosed 1 year before follow-up in the control group. In other words, there is a risk that AMD severity was not balanced in the surgery and control groups in the case-control studies. In total, 30 eyes of 1242

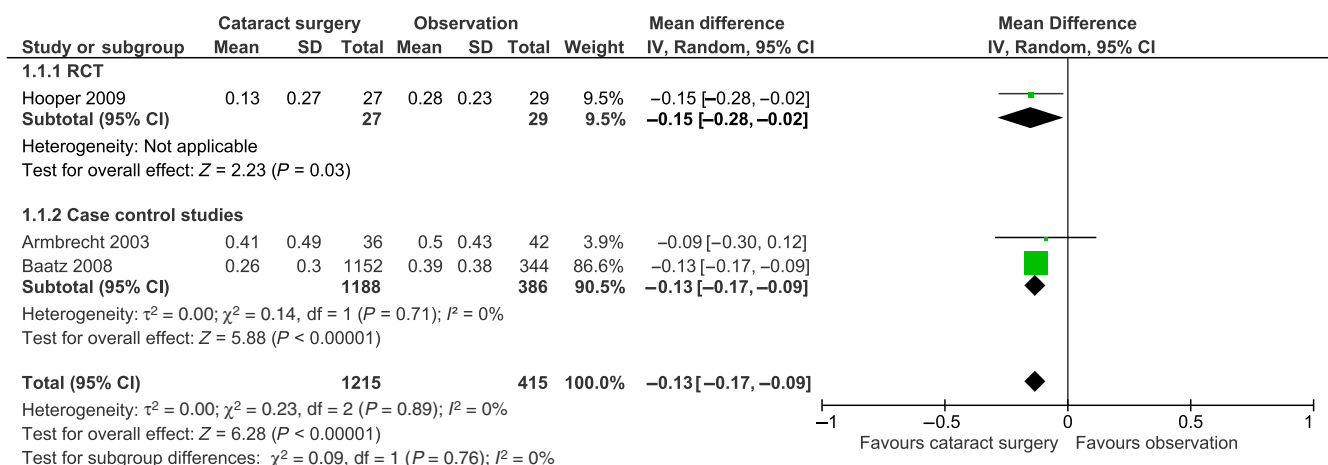


Fig. 1. Forest plot comparing visual acuity (logMAR) at 6 months (Hooper et al. 2009) or 12 months (Armbrecht et al. 2003 and Baatz et al. 2008) after cataract surgery or observation. SD = standard deviation, IV = inverse variance, CI = confidence interval.

Table 1. Quality of evidence and summary of findings.

Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk without surgery	Risk difference with cataract surgery (95% CI)
Visual acuity (RCT)	56 (1 study)	⊕⊕⊕⊖ MODERATE* due to imprecision			The mean visual acuity in the surgery group was 0.15 logMAR lower (0.28–0.02 lower)
Visual acuity (case control)	1574 (2 studies)	⊕⊖⊖⊖ VERY LOW† due to risk of bias			The mean visual acuity in the surgery group was 0.13 logMAR lower (0.17–0.09 lower)
Progression to exudative AMD (RCT)	105 (2 studies)	⊕⊕⊕⊖ MODERATE* due to imprecision	RR 3.21 (0.14–75.68)	0 per 1000	Could not be estimated due to low event rate
Progression to exudative AMD (case control)	1574 (2 studies)	⊕⊖⊖⊖ VERY LOW† due to risk of bias	RR 1.25 (0.55–2.85)	21 per 1000	5 more per 1000 (from 9 fewer to 38 more)

CI = confidence interval, RR = risk ratio, RCT = randomized controlled trial.

GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

* Very few subjects were included.

† AMD characteristics were not balanced between surgery and control groups in the case-control studies.

in the surgery group (2.4%) and 8 of the 437 control eyes (1.8%) progressed to exudative AMD. The difference was not statistically significant. Risk ratios (95% CI) were 3.21 (0.14–75.68) for the RCTs and 1.25 (0.55–2.85) for the case-control studies, see Fig. 2.

The quality of evidence concerning progression of AMD to wet AMD after cataract surgery was graded as moderate for the randomized trials and very low for the case-control studies. The quality of evidence was downgraded due to low number of included subjects (RCTs) and due to the imbalance in AMD characteristics between the operated and non-operated eyes in the case-control studies. The quality of evidence and summary of findings are presented in Table 1.

Overview of findings on cataract, cataract surgery and AMD risk from epidemiologic studies

A number of large cross-sectional or prospective epidemiologic studies have reported on the association between cataract, cataract surgery and AMD risk. These findings are tabulated in Table 2. The odds ratio (95% CI) for any AMD was significantly increased in participants who had cataract at baseline examination [1.7 (1.5–2.0)]

and for participants who had cataract surgery before baseline examination [1.5 (1.1–2.1)] but not for incident AMD <5 years after cataract surgery [1.1 (0.8–1.7)]. The odds ratio for early AMD was non-significant except for an increased OR for early AMD in participants with cataract at baseline examination [1.9 (1.0–3.6), p = 0.05]. The odds ratio (95% CI) of late AMD was 1.1 (0.7–1.7) for participants with cataract at baseline examination, 1.7 (1.3–2.3) for participants who had had cataract surgery at baseline, 1.4 (1.0–2.1) for incident late AMD <5 years after cataract surgery, 2.2 (1.4–3.5) for incident late AMD >5 years after cataract surgery and 1.6 (0.7–3.9) for incident late AMD >10 years after cataract surgery. The odds ratios for neovascular or geographic AMD were not significant.

Discussion

Cataract and AMD often coexist, especially in elderly patients. Concerns have been raised that cataract surgery may increase the risk of progression of AMD. The many large epidemiologic studies do not provide a clear indication of whether cataract surgery is associated with an increased risk of AMD progression or not. The general picture,

based on the overview of findings in Table 2, is that the risk of AMD is not greater in patients undergoing cataract surgery than in patients with unoperated cataracts. The presence of cataract may preclude the diagnosis of AMD or correct staging of AMD (Dong et al. 2009). Late stage AMD can be assessed reliably before cataract surgery, whereas retinal pigment epithelium abnormalities may be harder to diagnose correctly prior to cataract surgery (Pham et al. 2005). This may be an important confounder in studies evaluating the association between cataract surgery and AMD progression. Much of the data from the epidemiologic studies dates back to the mid- or late 1990s and the type of cataract surgery (phacoemulsification versus extracapsular or intracapsular cataract extraction), and hence, the degree of surgical trauma was not reported in any of the epidemiologic studies and is likely to have changed over the years. For these reasons, we chose to restrict our analyses to studies using phacoemulsification. Considering the high relevance of the topic and the high prevalence of coexisting cataract and AMD, it is surprising that only two randomized (Lamoureux et al. 2007; Hooper et al. 2009; Brunner et al. 2013) and two case-control studies (Armbrecht et al.

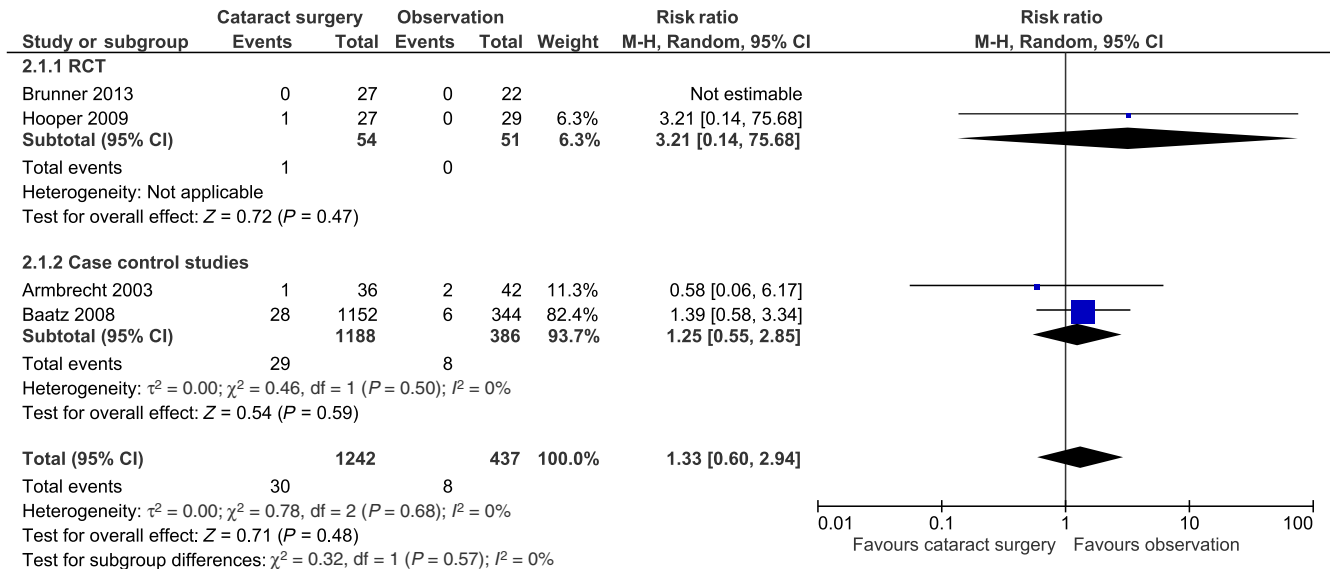


Fig. 2. Forest plot showing progression to exudative AMD during a 6 (Hooper et al. 2009) to 12 months follow-up period (Armbrecht et al. 2003; Baatz et al. 2008 and Brunner et al. 2013) in eyes with AMD undergoing cataract surgery or being observed without surgery. M-H = Mantel-Haenszel, CI = confidence interval.

2003; Baatz et al. 2008) were identified and could be included in the meta-analysis. A great number of other studies were identified by the literature search but could not be included as these studies did not compare the clinical course in patients with AMD undergoing versus not undergoing cataract surgery.

The aim of our review was to provide evidence-based recommendation on the care of patients with coexisting AMD and cataract. Evidence-based medicine has been criticized for not being suited for patients with complex disease patterns as most patients in the primary studies are patients with a single disease and also because some guidelines have focused more on statistical significant p-values than clinical relevance (Greenhalgh et al. 2014). Our review was performed based on the principles described by the GRADE working group (Grades of Recommendation, Assessment, Development and Evaluation) (Guyatt et al. 2011f). The GRADE system was developed to counteract the criticism of the evidence-based medicine movement (Tovey et al. 2014). Thus, we find that the chosen methodology was the currently, best available for performing and formulating evidence-based guidelines.

Our meta-analysis showed that visual function (measured by high contrast visual acuity charts) was better in patients who underwent cataract surgery and that the risk of progression

to wet AMD was not higher in patients undergoing cataract surgery than in those who did not have surgery. However, the number of included patients was low in the randomized trials, and the quality of the evidence was graded as moderate. For the case-control studies, surgery patients and controls were not matched for AMD characteristics, and hence, the quality of the evidence was graded as very low. We found that cataract surgery increased the visual acuity corresponding to 6.5–7.5 letters on the ETDRS 20 feet chart. This is less than the 10 letter improvement found in ANCHOR and MARINA participants undergoing cataract surgery (Rosenfeld et al. 2011), but it is still a visual improvement that is noticeable to patients.

Cataract surgery most often results in favourable visual outcome even in patients with AMD (Shuttleworth et al. 1998). As expected, the degree of visual gain is directly related to the severity of AMD at the time of surgery (Forooghian et al. 2009; Huynh et al. 2014). Visual acuity may decline in the years following cataract surgery, and the rate of decline is faster in patients with AMD than in eyes without comorbidity (Monestam & Lundqvist 2012). Although the self-assessed visual outcome of cataract surgery is poorer for patients with AMD with 24.5% of patients with AMD reporting questionable or no benefit from surgery versus 11.1% in non-AMD patients, the great

majority of AMD patients (75.6%) still report that they had very good, good or moderate benefit of cataract surgery (Lundstrom et al. 2002). Cataract surgery increases the quality of life in AMD patients (Armbrecht et al. 2000). The benefit (in terms of visual gain and subjective visual function) of cataract surgery in patients with AMD is sustained at least for 2–3 years postoperatively (Pham et al. 2007). Furthermore, cataract surgery offers the opportunity of implanting special optics IOLs to increase magnification or displace the image to healthy retina (Orzalesi et al. 2007; Potgieter & Claoue 2014) although these techniques are still experimental. Although the long-term results of cataract surgery in AMD patients, both visually and with respect to potential worsening of AMD, are still unknown, it does seem reasonable to offer the patient the visual benefit of cataract surgery and not limit access to surgery based on long-term theoretical risks, especially when the age group of AMD and cataract patients is taken into consideration.

With the introduction of anti-VEGF treatment, a large number of patients with exudative AMD retain fair visual function for many years (Bloch et al. 2012). However, patients with exudative AMD are older patients, and they often have or develop cataract to an extent that is considered to interfere with visual function. We did not find

Table 2. Overview of AMD risk and cataract or cataract surgery in epidemiologic studies.

Study	Any AMD	Early AMD	Late AMD (neovascular + geographic)	Neovascular AMD	Geographic AMD	Number of participants in study
Baseline cataract (without surgery) and AMD risk						
Baltimore Eye Study (Freeman et al. 2003)			2.1 (0.3–17.8)			7364
Copenhagen Eye Study (Buch et al. 2005)		1.9 (1.0–3.6)	1.3 (0.6–2.2)			311
France-DMLA Study (Chaine et al. 1998)	1.7 (1.5–2.0)					1844
Los Angeles Latino Eye Study (Fraser-Bell et al. 2010)			0.5 (0.2–1.1)	0.7 (0.2–1.7)	0.8 (0.2–3.5)	5875
Proyecto (Freeman et al. 2003)			1.3 (0–5–2.9)			9477
Salisbury Eye Evaluation (Freeman et al. 2003)			1.3 (0.6–2.8)			4627
<i>Pooled Odds Ratio (95% CI)</i>	<i>1.7 (1.5–2.0)</i>	<i>1.9 (1.0–3.6)</i>	<i>1.1 (0.7–1.7)</i>	<i>0.7 (0.2–1.7)</i>	<i>0.8 (0.2–3.5)</i>	
Baseline cataract surgery and AMD risk						
Baltimore Eye Survey (Freeman et al. 2003)			2.6 (0.9–7.5)			7364
Blue Mountains Eye Study (Wang et al. 1999)		0.7 (0.4–1.2)	1.3 (0.6–2.6)			3654
Copenhagen Eye Study (Buch et al. 2005)		1.3 (0.7–2.4)	1.6 (0.8–3.2)			311
France-DMLA Study (Chaine et al. 1998)	1.5 (1.1–2.1)					1844
Los Angeles Latino Eye Study (Fraser-Bell et al. 2010)			2.2 (1.1–4.4)	2.8 (0.8–9.6)	2.6 (0.4–14.7)	5875
Proyecto (Freeman et al. 2003)			1.9 (0.9–4.1)			9477
Salisbury Eye Evaluation (Freeman et al. 2003)			1.3 (0.7–2.4)			4627
<i>Pooled Odds Ratio (95% CI)</i>	<i>1.5 (1.1–2.1)</i>	<i>0.9 (0.5–1.7)</i>	<i>1.7 (1.3–2.3)</i>	<i>2.8 (0.8–9.6)</i>	<i>2.6 (0.4–14.7)</i>	
Incident AMD <5 years after cataract surgery						
Baltimore Eye Survey (Freeman et al. 2003)			1.8 (0.4–7.5)			7363
Beaver Dam Eye Study (Klein et al. 2012)		0.9 (0.7–1.3)	1.8 (1.0–2.9)			4926
CSAMD (Wang et al. 2012)		1.1 (0.7–1.7)	0.7 (0.3–1.8)			1244
Rotterdam Eye Study (Ho et al. 2008)	1.1 (0.8–1.7)	1.2 (0.8–1.7)		1.0 (0.4–2.3)		12 002
Salisbury Eye Evaluation (Freeman et al. 2003)			1.4 (0.7–2.9)			4504
<i>Pooled Odds Ratio (95% CI)</i>	<i>1.1 (0.8–1.7)</i>	<i>1.1 (0.8–1.3)</i>	<i>1.4 (1.0–2.1)</i>	<i>1.0 (0.4–2.3)</i>		
Incident AMD >5 years after cataract surgery						
AREDS (Chew et al. 2009)				0.8 (0.4–1.3)	0.6 (0.3–1.0)	2335
Beaver Dam Eye Study (Klein et al. 2012)		1.3 (0.9–1.9)	2.2 (1.3–3.7)			3722
Salisbury Eye Evaluation (Freeman et al. 2003)			1.9 (0.7–4.9)			4504
Baltimore Eye Survey (Freeman et al. 2003)			3.5 (0.8–15.0)			7363
<i>Pooled Odds Ratio (95% CI)</i>		<i>1.3 (0.9–1.9)</i>	<i>2.2 (1.4–3.5)</i>	<i>0.8 (0.4–1.3)</i>	<i>0.6 (0.3–1.0)</i>	
Incident AMD >10 years after cataract surgery						
Blue Mountains Eye Study (Cugati et al. 2006)		1.3 (0.7–2.3)	1.6 (0.7–3.9)	2.1 (0.8–5.8)	1.0 (0.3–3.8)	1952
<i>Pooled Odds Ratio (95% CI)</i>		<i>1.3 (0.7–2.3)</i>	<i>1.6 (0.7–3.9)</i>	<i>2.1 (0.8–5.8)</i>	<i>1.0 (0.3–3.8)</i>	

The table shows odds ratios [OR, with confidence intervals (CI)] for risk of AMD in association to cataract and cataract surgery as reported in the referenced studies. If available, sex- and age-adjusted odds ratios were used. When more than one study reported OR for a given outcome, a pooled OR (95% CI) was calculated using the Review Manager Software (Review Manager (RevMan) 2014). Incident AMD was defined as AMD not present at the baseline examination but present on follow-up examination.

any prospective studies evaluating the course of exudative AMD in patients receiving or not receiving cataract surgery. Case series have shown favourable outcome at one month postoperatively in patients with wet AMD receiving combined cataract surgery and intravitreal bevacizumab (Furino et al. 2009). Combined intravitreal bevacizumab and cataract surgery was found to prevent reactivation of chorioidal neovascularizations (CNV) in patients previously treated for CNV (Ruiz-Moreno et al. 2010). Two case series did not find that the need for anti-VEGF injections was increased after cataract surgery (Muzyka-Wozniak 2011; Grixti et al. 2014). A small, retrospective study found that cataract

surgery should be performed after a sufficiently long exudative-free period to prevent recurrence of exudation (Lee et al. 2014).

Conclusions and Recommendations

In conclusion, we found that cataract surgery increases visual function in patients with AMD and that the 6- to 12-month risk of exudative AMD was not increased after cataract surgery. However, further studies with longer follow-up are encouraged. We recommend that patients with AMD and cataract are offered cataract surgery if the cataract is thought that affect vision significantly. We cannot provide evi-

dence-based recommendations concerning cataract surgery in patients with exudative AMD receiving anti-VEGF treatment, but we suggest that cataract surgery can be performed when the exudative AMD is in a quiet phase, and combination of cataract surgery with intravitreal anti-VEGF injection seems to be advisable.

References

Algvere PV, Marshall J & Seregard S (2006): Age-related maculopathy and the impact of blue light hazard. *Acta Ophthalmol Scand* **84**: 4–15.
 Armbrrecht AM, Findlay C, Kaushal S, Aspinall P, Hill AR & Dhillon B (2000): Is cataract surgery justified in patients with age related

- macular degeneration? A visual function and quality of life assessment *Br J Ophthalmol* **84**: 1343–1348.
- Armbrecht AM, Findlay C, Aspinall PA, Hill AR & Dhillon B (2003): Cataract surgery in patients with age-related macular degeneration: one-year outcomes. *J Cataract Refract Surg* **29**: 686–693.
- Baatz H, Darawsha R, Ackermann H, Schari-oth GB, de Ortueta D, Pavlidis M & Hattenbach LO (2008): Phacoemulsification does not induce neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci* **49**: 1079–1083.
- Balshem H, Helfand M, Schunemann HJ et al. (2011): GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* **64**: 401–406.
- Blair CJ, Ferguson J Jr (1979): Exacerbation of senile macular degeneration following cataract extraction. *Am J Ophthalmol* **87**: 77–83.
- Bloch SB, Larsen M & Munch IC (2012): Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000 to 2010. *Am J Ophthalmol* **153**: 209–213.
- Brunner S, Mora A, Fonseca J, Weber T, Falkner-Radler CI, Oeser R & Binder S (2013): Monitoring of drusen and geographic atrophy area size after cataract surgery using the MD3RI tool for computer-aided contour drawing. *Ophthalmologica* **229**: 86–93.
- Buch H, Vinding T, La Cour M, Appleyard M, Jensen GB & Nielsen NV (2004): Prevalence and causes of visual impairment and blindness among 9980 Scandinavian adults: the Copenhagen City Eye Study. *Ophthalmology* **111**: 53–61.
- Buch H, Vinding T, la Cour M, Jensen GB, Prause JU & Nielsen NV (2005): Risk factors for age-related maculopathy in a 14-year follow-up study: the Copenhagen City Eye Study. *Acta Ophthalmol Scand* **83**: 409–418.
- Buschini E, Piras A, Nuzzi R & Vercelli A (2011): Age related macular degeneration and drusen: neuroinflammation in the retina. *Prog Neurobiol* **95**: 14–25.
- Casparis H, Lindsley K, Kuo IC, Sikder S & Bressler NB (2012): Surgery for cataracts in people with age-related macular degeneration. *Cochrane Database Syst Rev* **6**: CD006757.
- Chaine G, Hullo A, Sahel J et al. (1998): Case-control study of the risk factors for age related macular degeneration. France-DMLA Study Group. *Br J Ophthalmol* **82**: 996–1002.
- Chen J & Smith LE (2012): Protective inflammatory activation in AMD. *Nat Med* **18**: 658–660.
- Chew EY, Sperduto RD, Milton RC et al. (2009): Risk of advanced age-related macular degeneration after cataract surgery in the Age-Related Eye Disease Study: AREDS report 25. *Ophthalmology* **116**: 297–303.
- Cugati S, Mitchell P, Rochtchina E, Tan AG, Smith W & Wang JJ (2006): Cataract surgery and the 10-year incidence of age-related maculopathy: the Blue Mountains Eye Study. *Ophthalmology* **113**: 2020–2025.
- Cugati S, de Loryn LT, Pham T, Arnold J, Mitchell P & Wang JJ (2007): Australian prospective study of cataract surgery and age-related macular degeneration: rationale and methodology. *Ophthalmic Epidemiol* **14**: 408–414.
- Demirel S, Bilici S, Batioglu F & Ozmert E (2014): The effect of age and cataract surgery on macular pigment optic density: a cross-sectional, comparative study. *Graefes Arch Clin Exp Ophthalmol* **252**: 213–218.
- Dong LM, Stark WJ, Jefferys JL, Al-Hazzaa S, Bressler SB, Solomon SD & Bressler NM (2009): Progression of age-related macular degeneration after cataract surgery. *Arch Ophthalmol* **127**: 1412–1419.
- Fong CS, Mitchell P, Rochtchina E, de Loryn LT, Hong T & Wang JJ (2011): Sustainability of visual acuity in the first 2 years after cataract surgery. *Br J Ophthalmol* **95**: 1652–1655.
- Forooghian F, Agron E, Clemons TE, Ferris FL III & Chew EY (2009): Visual acuity outcomes after cataract surgery in patients with age-related macular degeneration: age-related eye disease study report no. 27. *Ophthalmology* **116**: 2093–2100.
- Fraser-Bell S, Choudhury F, Klein R, Azen S & Varma R (2010): Ocular risk factors for age-related macular degeneration: the Los Angeles Latino Eye Study. *Am J Ophthalmol* **149**: 735–740.
- Freeman EE, Munoz B, West SK, Tielsch JM & Schein OD (2003): Is there an association between cataract surgery and age-related macular degeneration? Data from three population-based studies *Am J Ophthalmol* **135**: 849–856.
- Furino C, Ferrara A, Cardascia N, Besozzi G, Alessio G, Sborgia L & Boscia F (2009): Combined cataract extraction and intravitreal bevacizumab in eyes with choroidal neovascularization resulting from age-related macular degeneration. *J Cataract Refract Surg* **35**: 1518–1522.
- Glazer-Hockstein C & Dunaief JL (2006): Could blue light-blocking lenses decrease the risk of age-related macular degeneration? *Retina* **26**: 1–4.
- GRADE profiler (2011): Grade working group 2004-2007. www.gradeworkinggroup.org
- Greenhalgh T, Howick J & Maskrey N (2014): Evidence based medicine: a movement in crisis? *BMJ* **348**: g3725.
- Grixti A, Papavasileiou E, Cortis D, Kumar BV & Prasad S (2014): Phacoemulsification surgery in eyes with neovascular age-related macular degeneration. *ISRN Ophthalmol* **2014**: 417603.
- Guyatt GH, Oxman AD, Vist G et al. (2011a): GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol* **64**: 407–415.
- Guyatt GH, Oxman AD, Kunz R et al. (2011b): GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol* **64**: 395–400.
- Guyatt GH, Oxman AD, Kunz R et al. (2011c): GRADE guidelines 6. Rating the quality of evidence—imprecision. *J Clin Epidemiol* **64**: 1283–1293.
- Guyatt GH, Oxman AD, Kunz R et al. (2011d): GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol* **64**: 1303–1310.
- Guyatt GH, Oxman AD, Kunz R et al. (2011e): GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol* **64**: 1294–1302.
- Guyatt GH, Oxman AD, Montori V et al. (2011f): GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol* **64**: 1277–1282.
- Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P & Knottnerus A (2011g): GRADE guidelines: a new series of articles in the *Journal of Clinical Epidemiology*. *J Clin Epidemiol* **64**: 380–382.
- Ham WT Jr, Mueller HA, Sliney DH (1976): Retinal sensitivity to damage from short wavelength light. *Nature* **260**: 153–155.
- Higgins JPT & Green S. (2011): *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration, www.cochrane-handbook.org.
- Ho L, Boekhoorn SS, Liana et al. (2008): Cataract surgery and the risk of aging macula disorder: the rotterdam study. *Invest Ophthalmol Vis Sci* **49**: 4795–4800.
- Hooper CY, Lamoureux EL, Lim L, Fraser-Bell S, Yeoh J, Harper CA, Keeffe JE & Guymer RH (2009): Cataract surgery in high-risk age-related macular degeneration: a randomized controlled trial. *Clin Experiment Ophthalmol* **37**: 570–576.
- Howard KP, Klein BE & Klein R (2013): Examining absolute risk of AMD in relation to cataract surgery. *Ophthalmology* **120**: 1509–1510.
- Huynh N, Nicholson BP, Agron E, Clemons TE, Bressler SB, Rosenfeld PJ & Chew EY (2014): Visual acuity after cataract surgery in patients with age-related macular degeneration: age-related eye disease study 2 report number 5. *Ophthalmology* **121**: 1229–1236.
- Iwami H, Kohno T, Yamamoto M, Kaida M, Miki N, Ataka S & Shiraki K (2011): Progression of cataracts following photodynamic therapy combined with intravitreal triamcinolone injection in cases of age-related macular degeneration. *Osaka City Med J* **57**: 49–57.
- Kaiserman I, Kaiserman N, Elhayany A & Vinker S (2007): Cataract surgery is associated with a higher rate of photodynamic therapy for age-related macular degeneration. *Ophthalmology* **114**: 278–282.
- Kessel L, Lundeman JH, Herbst K, Andersen TV & Larsen M (2010): Age-related changes in the transmission properties of the human lens and their relevance to circadian entrainment. *J Cataract Refract Surg* **36**: 308–312.
- Klaver CC, Wolfs RC, Vingerling JR, Hofman A & de Jong PT (1998): Age-specific prevalence and causes of blindness and visual impairment in an older population: the Rotterdam Study. *Arch Ophthalmol* **116**: 653–658.
- Klein R, Klein BE, Wang Q & Moss SE (1994): Is age-related maculopathy associated with cataracts? *Arch Ophthalmol* **112**: 191–196.
- Klein R, Klein BE, Jensen SC & Cruickshanks K J (1998): The relationship of ocular factors to the incidence and progression of age-related maculopathy. *Arch Ophthalmol* **116**: 506–513.

- Klein R, Klein BE, Wong TY, Tomany SC & Cruickshanks KJ (2002): The association of cataract and cataract surgery with the long-term incidence of age-related maculopathy: the Beaver Dam eye study. *Arch Ophthalmol* **120**: 1551–1558.
- Klein BE, Howard KP, Lee KE, Iyengar SK, Sivakumaran TA & Klein R (2012): The relationship of cataract and cataract extraction to age-related macular degeneration: the Beaver Dam Eye Study. *Ophthalmology* **119**: 1628–1633.
- Kovacevic D, Misljenovic T, Njiric S, Mikulicic M & Vojnikovic B (2008): Appearance of age related maculopathy after cataract surgery. *Coll Antropol* **32**(Suppl 2): 9–10.
- Kovacevic D, Vuceric TM & Caljkusic-Mance T (2010): Progression of age related maculopathy in phakic versus pseudophakic eyes. *Coll Antropol* **34**(Suppl 2): 21–23.
- Lamoureaux EL, Hooper CY, Lim L, Pallant JF, Hunt N, Keeffe JE & Guymer RH (2007): Impact of cataract surgery on quality of life in patients with early age-related macular degeneration. *Optom Vis Sci* **84**: 683–688.
- Lee TG, Kim JH, Chang YS, Kim CG & Kim JW (2014): Factors influencing the exudation recurrence after cataract surgery in patients previously treated with anti-vascular endothelial growth factor for exudative age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* **252**: 1573–1579.
- Lundstrom M, Brege KG, Floren I, Lundh B, Stenevi U & Thorburn W (2002): Cataract surgery and quality of life in patients with age related macular degeneration. *Br J Ophthalmol* **86**: 1330–1335.
- Mainster MA (2006): Violet and blue light blocking intraocular lenses: photoprotection versus photoreception. *Br J Ophthalmol* **90**: 784–792.
- Mitchell P, Wang JJ, Foran S & Smith W (2002): Five-year incidence of age-related maculopathy lesions: the Blue Mountains Eye Study. *Ophthalmology* **109**: 1092–1097.
- Monestam E & Lundqvist B (2012): Long-term visual outcome after cataract surgery: comparison of healthy eyes and eyes with age-related macular degeneration. *J Cataract Refract Surg* **38**: 409–414.
- Muzyka-Wozniak M (2011): Phacoemulsification in eyes with neovascular AMD treated with anti-VEGF injections. *Eur J Ophthalmol* **21**: 766–770.
- Nolan JM, O'Reilly P, Loughman J, Stack J, Loane E, Connolly E & Beatty S (2009): Augmentation of macular pigment following implantation of blue light-filtering intraocular lenses at the time of cataract surgery. *Invest Ophthalmol Vis Sci* **50**: 4777–4785.
- Orzalesi N, Pierrotet CO, Zenoni S & Savaresi C (2007): The IOL-Vip System: a double intraocular lens implant for visual rehabilitation of patients with macular disease. *Ophthalmology* **114**: 860–865.
- Pham TQ, Wang JJ, Maloof A & Mitchell P (2005): Cataract surgery in patients with age-related maculopathy: preoperative diagnosis and postoperative visual acuity. *Clin Experiment Ophthalmol* **33**: 360–363.
- Pham TQ, Cugati S, Rochtchina E, Mitchell P, Maloof A & Wang JJ (2007): Age-related maculopathy and cataract surgery outcomes: visual acuity and health-related quality of life. *Eye (Lond)* **21**: 324–330.
- Pollack A, Marcovich A, Bukelman A & Oliver M (1996): Age-related macular degeneration after extracapsular cataract extraction with intraocular lens implantation. *Ophthalmology* **103**: 1546–1554.
- Pollack A, Marcovich A, Bukelman A, Zalish M & Oliver M (1997): Development of exudative age-related macular degeneration after cataract surgery. *Eye (Lond)* **11**(Pt 4): 523–530.
- Pollack A, Bukelman A, Zalish M, Leiba H & Oliver M (1998): The course of age-related macular degeneration following bilateral cataract surgery. *Ophthalmic Surg Lasers* **29**: 286–294.
- Potgieter FJ & Claoue CM (2014): Safety and efficacy of an intraocular Fresnel prism intraocular lens in patients with advanced macular disease: initial clinical experience. *J Cataract Refract Surg* **40**: 1085–1091.
- Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP & Mariotti SP (2004): Global data on visual impairment in the year 2002. *Bull World Health Organ* **82**: 844–851.
- Review Manager (RevMan) [Computer program] (2014). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration.
- Rohart C, Fajnkuchen F, Nghiem-Buffet S, Abitbol O, Badelon I & Chainé G (2008): [Cataract surgery and age-related maculopathy: benefits in terms of visual acuity and quality of life—a prospective study]. *J Fr Ophthalmol* **31**: 571–577.
- Rosenfeld PJ, Shapiro H, Ehrlich JS & Wong P (2011): Cataract surgery in ranibizumab-treated patients with neovascular age-related macular degeneration from the phase 3 ANCHOR and MARINA trials. *Am J Ophthalmol* **152**: 793–798.
- Ruiz-Moreno JM, Montero JA, Amat-Peral P & Lugo LF (2010): Intravitreal bevacizumab and cataract surgery after wet age-related macular degeneration. *Int J Ophthalmol* **10**: 1245–1247.
- van der Schaft TL, Mooy CM, de Bruijn WC, Mulder PG, Pameyer JH & de Jong PT (1994): Increased prevalence of disciform macular degeneration after cataract extraction with implantation of an intraocular lens. *Br J Ophthalmol* **78**: 441–445.
- Shuttleworth GN, Luhishi EA & Harrad RA (1998): Do patients with age related maculopathy and cataract benefit from cataract surgery? *Br J Ophthalmol* **82**: 611–616.
- Singh A, Faber C, Falk M, Nissen MH, Hviid TV & Sorensen TL (2012): Altered expression of CD46 and CD59 on leukocytes in neovascular age-related macular degeneration. *Am J Ophthalmol* **154**: 193–199.
- Stolba U, Binder S & Velikay M (1989): [Does cataract surgery with lens implantation influence the course of age-related macular degeneration?]. *J Fr Ophthalmol* **12**: 897–901.
- Sutter FK, Menghini M, Barthelmes D, Fleischhauer JC, Kurz-Levin MM, Bosch MM & Helbig H (2007): Is pseudophakia a risk factor for neovascular age-related macular degeneration? *Invest Ophthalmol Vis Sci* **48**: 1472–1475.
- Tabandeh H, Chaudhry NA, Boyer DS, Kon-Jara VA & Flynn HW Jr (2012): Outcomes of cataract surgery in patients with neovascular age-related macular degeneration in the era of anti-vascular endothelial growth factor therapy. *J Cataract Refract Surg* **38**: 677–682.
- Tovey D, Churchill R & Bero L (2014): Evidence based medicine: looking forward and building on what we have learnt. *BMJ* **349**: g4508.
- Wang JJ, Mitchell PG, Cumming RG & Lim R (1999): Cataract and age-related maculopathy: the Blue Mountains Eye Study. *Ophthalmic Epidemiol* **6**: 317–326.
- Wang JJ, Klein R, Smith W, Klein BE, Tomany S & Mitchell P (2003): Cataract surgery and the 5-year incidence of late-stage age-related maculopathy: pooled findings from the Beaver Dam and Blue Mountains eye studies. *Ophthalmology* **110**: 1960–1967.
- Wang JJ, Fong CS, Rochtchina E et al. (2012): Risk of age-related macular degeneration 3 years after cataract surgery: paired eye comparisons. *Ophthalmology* **119**: 2298–2303.
- Xu L, You QS, Cui T & Jonas JB (2011): Association between asymmetry in cataract and asymmetry in age-related macular degeneration. The Beijing Eye Study. *Graefes Arch Clin Exp Ophthalmol* **249**: 981–985.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Characteristics of included studies

Table S2 Characteristics of excluded studies