UNIVERSITY OF BIRMINGHAM

Literature search on the prevalence/incidence and progression of diabetic maculopathy and juvenile macular dystrophy and the progression of age-related macular degeneration

Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration

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For the Drivers Medical Group
DVLA
Swansea

ARIF

WMHTAC
West Midlands HTA Collaboration

About ARIF and the West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. The majority of staff are based in the Department of Public Health and Epidemiology at the University of Birmingham. Other collaborators are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility at the University of Birmingham, pharmacists and methodologists from the Department of Medicines Management at Keele University and clinicians from hospitals and general practices across the West Midlands and wider.

WMHTAC produces systematic reviews, technology assessment reports and economic evaluations for the UK National Health Service's Health Technology Assessment (HTA) programme, the National Institute for Health and Clinical Excellence (NICE). Regional customers include Strategic Health Authorities, Primary Care Trusts and regional specialist units. WMHTAC also undertakes methodological research on evidence synthesis and provides training in systematic reviewing and health technology assessment.

The two core teams within WMHTAC are the Aggressive Research Intelligence Facility (ARIF) and the Birmingham Technology Assessment Group (BTAG)

ARIF provides a rapid on-demand evidence identification and appraisal service primarily to commissioners of health care. Its mission is to advance the use of evidence on the effects of health care and so improve public health. The rapid response is achieved by primarily relying on existing systematic reviews of research, such as those produced by the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE), the NHS Centre for Reviews and Dissemination, and the NHS Health Technology Assessment (HTA) programme. In some instances, longer answers to questions are required in which case mini rapid reviews of existing systematic reviews and key primary studies are compiled, typically taking 1-2 months to complete.

Occasionally a full systematic review is required and then topics are referred to BTAG who coordinate the production of systematic reviews for several customers under a number of contracts. ARIF is intrinsically involved in the production of these systematic reviews.

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1 Aims

The aims of this report were to address the following questions submitted by the Driver Medical Group:

- What is the prevalence/incidence of diabetic maculopathy and juvenile macular dystrophy in adults?
- What is the long-term progression of diabetic maculopathy, juvenile macular dystrophy and age-related macular degeneration in adults, focussing on visual field and visual acuity outcomes? What is the effect of treatments on the rate of progression?

2 Background

Maculopathies are a broad group of conditions predominantly affecting central vision that lead to progressive deterioration in vision through reduced visual acuity and/or visual field loss. Advanced forms can be severe enough to result in a loss of driving privileges and legal blindness.

Different maculopathies are not given individual consideration for licensing purposes by the DVLA despite the fact that their aetiology and prognosis differ. If it were possible to target those drivers (and in particular Group 1 (non-vocational) licence holders) who have progressive disorders affecting visual acuity and/or field loss (along with other modalities of visual function) then appropriate review mechanisms can be put in place for these drivers.

As part of this process the Drivers Medical Group (DMG) commissioned this preliminary report to assess the evidence base on the incidence, prevalence and prognosis of some common maculopathies. These maculopathies are:

- Juvenile macular dystrophy – This encompasses a group of conditions, predominantly resulting from genetic defects that affect the macula in younger individuals. Some individuals will be mildly affected and able to obtain a driving licence. Examples of juvenile macular dystrophies include: Stargardt's disease, Best's disease, Doyne's honeycomb retinal dystrophy and Sorsby's disease. Stargardt's and Best's diseases were the primary focus of this category of dystrophy in this report.
- Diabetic maculopathy - Diabetes mellitus is a major medical problem and causes an array of long-term systemic complications, which have considerable impact on the patient. Ophthalmic complications include corneal abnormalities, glaucoma, iris neovascularisation, cataracts, and neuropathies. However, the most common and potentially most blinding of these complications is diabetic retinopathy and in particular that affecting central vision, diabetic maculopathy.
- Age related macular degeneration (ARMD) - This is the leading cause of irreversible visual loss in the industrialised world. It predominantly affects central vision and over the years has been classified in a number of ways. Currently, patients with minimal or moderate non-exudative age-related changes in the macula are classified as having age-related maculopathy (ARM). Advanced atrophy (advanced non-exudative changes) and/or the presence of proliferative vascular membranes are required for the diagnosis of ARMD.

Specifically this report concentrates on:

a) The prevalence and/or incidence of diabetic maculopathy and juvenile macular dystrophy in adults. Age related macular degeneration was not included as it has been previously addressed by ARIF/WMHTAC for the DMG (see *Prevalence of Visual Disorders by Age Group in Older People;* October 2006).
b) The (long-term) rate of progression of diabetic maculopathy, juvenile macular dystrophy and age-related macular degeneration in adults, focussing on visual acuity and visual field outcomes. In addition where data were available the effects of treatment on rates of progression were explored.

Finally it is worth mentioning that this report is primarily designed to give readers a starting point to consider the research evidence on this complex topic. Whilst utilising some systematic review methodologies and employing broad searches to identify the evidence, it is not a systematic review and it does not pretend to being totally comprehensive.

Given the complexity in this report, summary boxes have been used where appropriate to aid clarity. These boxes detail some of the relevant key findings but should be read in conjunction with the main text.

3 Methods

Outline methods were submitted to the Drivers Medical Group by email and acceptance subsequently confirmed by telephone (Appendix 1 – Outline methods).

Briefly these were:

- To undertake a search for studies looking at:
  a) The prevalence and/or incidence of diabetic maculopathy and juvenile macular dystrophy in adults.
  b) The long-term rate of progression of diabetic maculopathy, juvenile macular dystrophy and age-related macular degeneration in adults, focussing on visual field and visual acuity outcomes. In addition, where data were available, the effects of treatments on the rate of progression were to be explored.
- To initially search for existing systematic reviews, and if not available or sufficient to widen the searches to primary studies.
- To concentrate on systematic reviews, cohort and cross-sectional studies which report the relevant outcomes.
- In the first instance studies conducted in the UK were to be used, as the prevalence and progression may vary according to ethnicity for example. If no robust UK studies were identified, study criteria to be broadened to those conducted outside of the UK.
- Methodological quality of used studies was to be commented upon.
- Where appropriate and possible data on relevant outcomes were to be extracted and tabulated.

3.1 Searches

3.1.1 Existing Reviews.

Searches to identify existing systematic reviews on this topic were performed utilising the well-established ARIF search protocol (Appendix 2 – Search strategies).

3.1.2 Primary Studies

Searches were undertaken for primary studies in MEDLINE, EMBASE and the Cochrane Library. The search strategy employed MeSH headings and text terms for age related macular degeneration, diabetic maculopathy and juvenile macular dystrophy. Methodological 'filters' and search terms for disease progression and incidence and prevalence were also incorporated. The strategy was developed iteratively and modified accordingly.

The detailed search strategies can be found in Appendix 2 – Search strategies.

Searches were predominantly undertaken by an information specialist with additional searches by a research reviewer. Both interacted to ensure searches were conducted appropriately.

An information specialist and a research reviewer scanned the search results for relevance based on information in the title and abstract. Articles that adhered to the following broad criteria were obtained in full for further scrutiny:

Incidence and/or prevalence of juvenile macular dystrophy

Design:	Systematic reviews, cohort studies or cross-sectional studies
Population:	Includes people with juvenile macular dystrophy
Outcome:	Prevalence/incidence of juvenile macular dystrophy
Exclusion:	Studies with a sample size less than 50 participants
	Studies conducted on a population with a very different ethnic mix to the UK

Progression of juvenile macular dystrophy

Design:	Systematic reviews, cohort studies or cross-sectional studies
Population:	Includes adults with juvenile macular dystrophy
Outcome:	Progression of juvenile macular dystrophy (visual acuity, changes in visual field)
Exclusion:	Studies with a sample size less than 20 participants for Stargardt disease, unrestricted for rarer disorders
	Studies with a follow-up of less than a year

Incidence and/or prevalence of diabetic maculopathy

Design:	Systematic reviews, cohort studies or cross-sectional studies
Population:	Includes people with type 1 or type 2 diabetes mellitus
Outcome:	Prevalence/incidence of diabetic maculopathy
Exclusion:	Studies with a sample size less than 50 participants
	Studies conducted on a population with a very different ethnic mix to the UK

Progression of diabetic maculopathy

Design:	Systematic reviews, cohort studies or cross-sectional studies
Population:	Includes adults with type 1 or type 2 diabetes mellitus with diabetic maculopathy
Outcome:	Progression of diabetic maculopathy (visual acuity, changes in visual field)
Exclusion:	Studies with a sample size less than 50 participants
	Studies conducted on a population with a very different ethnic mix to the UK
	Studies with a follow-up of less than a year

Progression of age-related macular degeneration

Design:	Systematic reviews, cohort studies or cross-sectional studies

Population:	Includes adults with age-related macular degeneration
Outcome:	Progression of age-related macular degeneration (visual acuity, changes in visual field)
Exclusion:	Studies with a sample size less than 50 participants Studies conducted on a population with a very different ethnic mix to the UK Studies with a follow-up less than a year

Full copy articles were assessed for their match to the questions being addressed (external validity) and the most informative articles (closest match to population, longest follow-up) subjected to further scrutiny and reporting.

The reference lists of the most relevant articles were also checked in order to identify further relevant papers.

4 Results

The searches retrieved just under 2000 papers; 189 for the search on juvenile macular dystrophies, 1011 for the search on diabetic maculopathy, and 780 for the search on age related maculopathy. The titles and abstracts were scanned to select relevant studies.

For all conditions, progression data were mainly available for visual acuity rather than visual field data. Visual acuities were reported in various formats. Where possible, conversion to metric Snellen scores (at a distance of 6 m) is given. A conversion table is provided in Appendix 3 for reference.

Studies were excluded for reasons such as: unrepresentative study population with respect to the UK, participants mainly under 18 years at last follow-up, initial visual acuities of all patients too low for driving (for progression studies), small sample sizes (under 50 participants or as detailed above), follow-up periods less than one year (for progression studies), no relevant outcomes reported.

4.1 Juvenile macular dystrophies

For juvenile macular dystrophies, 22 papers were examined in full, including four extra papers identified though internet and bibliography searches. No large cohort studies were identified addressing all the factors of interest in the same population. Of the papers identified, two studies[1,2] were thought to offer the best evidence on prevalence (no studies on incidence were identified), and eight studies were thought to offer the best evidence on progression (five studies on Stargardt disease / fundus flavimaculatus[3-7] and three studies on Best's vitelliform macular dystrophy[8-10]).

4.1.1 Prevalence/incidence

The two identified studies only provided relevant information on the prevalence of juvenile macular dystrophies. Only one of the studies reported directly on the prevalence of specific juvenile macular dystrophies, the other reported the prevalence of hereditary retinal disorders as a broad category. None of the studies reported on incidence.

The most relevant study[2] was a cross-sectional study on the prevalence of hereditary retinal dystrophies in the North of France (Nord-Pas-de-Calais region). The study was retrospective (using data from the ophthalmologic service of the university hospital in Lille where all relevant cases were expected to have been referred) and covered 18 years (1972 to 1989) and a population of nearly 4 million inhabitants. Of a total of 1660 cases detected, there were 622 macular dystrophies (i.e. 37%), including 286 cases of Stargardt disease (estimated prevalence 1/8627), 93 cases of retinoschisis (1/28092), 33 cases of cone dystrophy (1/81937), 31 cases of late fundus flavimaculatus and X-linked dystrophies (1/83680), 106 cases of vitelliform dystrophies (1/22483), and 51 cases of pseudo-vitelliform dystrophies (1/46729). The authors also quote a study from the United States[11] which found a prevalence of 1/15000 for fundus flavimaculatus (all types and X-linked dystrophies).

The only UK study was a cross-sectional study of leading causes of certification for blindness and partial sight in England and Wales[1]. The study reported the registration of blindness or partially-sightedness from April 1999 to March 2000. Blindness was defined as visual acuity below 3/60 (corrected visual acuity), or worse than 6/60 with very contracted visual fields, or 6/60 or above with a very contracted visual field especially in the lower part of the field. Partial sight was defined as a visual acuity between 3/60 and 6/60 with a full visual field, or 6/24 or worse with moderate constriction of visual field or 6/18 or better with gross visual field defects. The main cause of visual loss was ascertained. The study included 13788 people who were certified as blind, and 19107 people certified as partially sighted. Of the people with a blindness certification, 2.8% had hereditary retinal disorders, but these were not defined any more closely and the proportion of juvenile macular dystrophies is uncertain. Of people with partial sight certification, 2% had hereditary retinal disorders. Again this was not defined more closely. Therefore, the study does not indicate the prevalence of juvenile macular dystrophies.

4.1.2 Progression

No studies were identified that reported on the rate of progression in juvenile macular dystrophies in general. Studies specifically on the progression of Stargardt disease (the most common form of juvenile-onset macular dystrophy, five studies[3-7]) and Best's vitelliform macular dystrophy (three studies[8-10]) were identified. Most studies reported visual acuity but not visual field data. A detailed summary data for all studies is shown in table 1. Studies were of modest quality and each contributed different aspects to the overall picture of progression.

All studies on Stargardt disease subdivided patients by stage of disease / phenotype based on fundus appearance, however the definitions of these stages / phenotypes differed slightly between studies (see table 1). Three studies[3-5] reported visual outcomes only for the respective subgroups, Oh et al. (2004)[6] reported data by five-year intervals of duration of follow-up, and Rotenstreich et al. (2003)[7] included in their main study of progression only patients with the best visual acuities although some data on other patients were also reported. The included studies were carried out in Northern Europe[3,10] or the USA[4-9]. All studies had a wide range of follow-up periods for individual patients. The majority of participants in all studies were adults, although most studies included children. Most of the studies only included limited information on methodology.

4.1.2.1 Stargardt disease

In a Belgian study, Gelisken and de Laey (1985)[3] studied a cohort of 49 patients with a clinical diagnosis of Stargardt disease, however only 22 of these patients were included in the follow-up study. Follow-up lasted between one and 13 years and visual acuity data were reported for initial exam and final exam for the three subgroups examined (group I: lesions confined to the macula, group II: macular lesion surrounded by perimacular flecks, group III: fundus flavimaculatus flecks). Mean follow-up times were two years for group I

(14 eyes), five years for group II (14 eyes), and six years for group III (14 eyes). In 16 of the eyes examined, visual acuity remained unchanged within the follow-up period, but mostly at a low level of 1/20 to 2/10. In 26 eyes a deterioration of visual acuity was seen. Where asymmetry was present at the first examination, it tended to disappear during the follow-up period. Patients in group I tended to maintain better visual function than patients in group II, who tended to maintain better vision than patients in group III. At the final examination, 56% of eyes from group I, 78% of eyes from group II and 100% of eyes from group III had visual acuities of 2/10 or less. However, definite conclusions cannot be drawn, as the patients in group I had a shorter follow-up period than patients in groups II and III. This was one of the two studies reporting visual field data, but data given were very limited. At baseline, a visual field examination was performed in 48 patients. Of these, six patients (12 eyes) had no defect peripherally or centrally, the remaining eyes only had a central scotoma of varying extension (5-15%) corresponding to the extent of the macular lesion. At follow-up the central field defects increased consistently with the progression of the macular lesion (in 16 of 21 patients followed up an obvious progression of retinal lesions, centrally and peripherally, was noted during fundus examinations and fluoroangiography).

Kim and Fishman (2006)[5] studied a cohort of 405 patients with Stargardt disease, follow-up data on visual acuity were available for 218 patients. Follow-up periods ranged from 0.5 to 31.5 years. Data were analysed by stage of disease (stage 1: parafoveal and perifoveal flecks, stage 2: flecks throughout posterior pole, anterior to vascular arcades and/or nasal to optic disk, stage 2-3: partially resorbed extensive flecks, stage 3: extensive flecks having resorbed almost entirely), patients in stage 1 had a mean follow-up period of 8.8 years, patients in stage 2 had a mean follow-up of 9.9 years and the other stages had progressively longer follow-up periods (no details given). The study excluded patients without clearly evident macular lesions. The cut-off point for visual acuity outcomes was very low, the authors only reported proportions of patients with visual acuities of “20/200 or better” (6/60), “20/225 to 20/400” (~6/68 to 3/60) and “worse than 20/400” (3/60). At baseline, 97.5% of stage 1 patients, 84.9% of stage 2 patients, 75.8% of stage 2-3 patients and 38.1% of stage 3 patients had visual acuities of 20/200 (6/60) or better in at least one eye. At their most recent follow-up visit, 93.4% of stage 1 patients, 75.5% of stage 2 patients, 61.1% of stage 2-3 patients and 26.7% of stage 3 patients had visual acuities of 20/200 (6/60) or better in at least one eye. The results suggest that patients with stage 1 disease were less likely to progress to visual acuities below 20/200 (6/60) than patients at more advanced stages (however, 33.9% of patients initially at stage 1 progressed to subsequent stages over the course of the study).

The cohort study by Itabashi et al. (1993)[4] reported on 73 patients (with follow-up data only being available for 35), but they provided more precise data for visual acuity and visual field measurements. Again, patients were subdivided into disease types (type 1: macular degeneration without flecks, type 2: macular degeneration with parafoveal flecks, type 3: macular degeneration with diffuse flecks (subdivided into 3E (early onset, <30 years) and 3L (late onset, $\geq$30 years)), type 4: diffuse flecks without macular degeneration). Mean follow-up time was 6.1 years. The mean visual acuities at baseline were 20/74 (~6/22) for type 1, 20/103 (~6/31) for type 2, 20/225 (~6/68) for type 3E, 20/47 for type 3L, and 20/20 (6/6) for type 4. Visual acuity declined by a mean of 0.25 octave/year during follow up (between -0.10 for type 1 and -1.03 for type 3L). The overall refractive error at follow-up was -0.59 D (no significant difference between types). Of the patients aged over 40 years (n=16), 25% became legally blind (visual acuity <20/200 (6/60) in the eye with

the better acuity). Patients with type 3L and type 4 disease had relatively good visual prognoses, whereas in patients with type 3E disease visual acuity declined to less than 20/200 (6/60) at a relatively early age. Peripheral visual field size at follow-up was between 60.7 (type 4) and 67.4 (type 3L) degree/radius (no significant change during the follow-up period). With respect to central visual field testing, a relative central scotoma was seen in 69.2% of type 1 patients, 71.4% of type 2 patients, 93.8% of type 3E patients and 93.3% of type 3L patients. Small ring scotoma was detected in one eye with type 4. Central scotoma size was between 2.97 for type 1 and 12.7 for type 3E, with a change of between +0.51 (type 3L) and +4.6 (type 3E) degree/radius/year.

Oh et al. (2004)[12] reported data on 214 patients with Stargardt disease, of which 131 were seen at multiple visits (historical cohort study). Patients were subdivided into three phenotypes (phenotype I: disease confined to macula, phenotype II: flecks outside the temporal arcades, phenotype III: retinal pigment epithelium atrophy, choroidal atrophy, or bone spicules extending outside the macula). Mean follow-up times were between 56 months for phenotype I and 148.5 months for phenotype III. As in the study by Kim et al., no detailed visual acuities were provided for visual acuities better than 20/200 (6/60). The authors report the likelihood of maintaining visual acuities of 20/200 (6/60) or better by age group and duration of follow-up. Overall, the likelihood of maintaining 20/200 (6/60) or better visual acuity dropped to below 50% by 40 to 49 years of age and a disease duration of more than 15 years. Visual outcomes were significantly better for patients with phenotype I, who had a 90% probability of maintaining VA of 20/200 (6/60) or better into the fifth decade of life and for 20 years follow-up, whereas the corresponding probabilities for phenotypes II and III (analysed separately) dropped below 50% by the third decade of life and 10 years follow-up.

The study by Rotenstreich et al. (2003)[7] assessed visual acuity loss in patients with Stargardt's disease. Of the 361 patients included in the cross-sectional part of the study, 23% had visual acuities of 20/40 (6/12) or better, 18% had visual acuities of 20/50 to 20/100 (6/15 to 6/30), 55% had visual acuities of 20/200 (6/60) to 20/400 (3/60), and 4% had visual acuities of worse than 20/400 (3/60). Seventy three patients with 20/40 or better visual acuity and 38 patients with 20/50 to 20/100 (6/15 to 6/30) visual acuity in the better eye at their initial visit who were followed for at least one year were included in a survival analysis. For analysis purposes these patients were categorised into four 20-year age groups according to their age at initial visit (20 years or less, 21-40 years, 41-60 years, and 61 years or older). In the patients with initial visual acuities of 20/40 (6/12) or better, the median time to develop visual acuities of 20/200 (6/60) or worse was 22 years. Those seen initially in the first two decades of life showed a median time of 7 years to reach a visual acuity of 20/200 (6/60) or worse, compared with 22 years and 29 years for those who were initially seen at ages 21 to 40 or 41 to 60, respectively. The differences between the age groups were significant (p=0.004). Respective times for reaching visual acuities of 20/50 to 20/100 (6/15 to 6/30) in this group were 16 years for all patients with initial visual acuities of 20/40 (6/12) or better taken together, and three years for the 0-20 year age group, and 20 and 15 years for those who were initially seen at ages 21 to 40 or 41 to 60, respectively. In the patients with initial visual acuities of 20/50 to 20/100 (6/15 to 6/30), the median time to develop 20/200 (6/60) vision or worse was six years, and this result was independent of age group at initial visit.

4.1.2.2 Best's vitelliform macular dystrophy

The largest cohort study on patients with Best's vitelliform macular dystrophy was the study by Mohler and Fine (1981)[9]. The study included 91 patients, of whom 54 were followed for five years or more, and 29 were followed for eight to ten years. At presentation, 45% of eyes had visual acuities of 20/20 (6/6) or better, while 20% had visual acuities of 20/50 to 2/100 (6/15 to 6/30) and 5% had visual acuities between 20/200 (6/60) and 20/400 (3/60). Respective values at the five year follow-up were 48%, 19% and 8%, indicating no significant change over this time period. Similarly, no evidence of worsening of visual acuity was seen with eight to ten years follow-up. When considering visual acuity by age group for all 91 patients, there was an increased number of eyes with moderate (20/50 to 20/100 ((6/15 to 6/30))) or severe (20/200 to 20/400 (6/60 to 3/60)) visual loss in patients in the 40-49 and 60-84 years age groups. Visual acuity was also worse for patients with atrophic maculas or fibrous scars (including the only patients who lost vision during a follow-up of eight to ten years (19% of 26)).

The study by Fishman et al. (1993)[8] was a cross-sectional study of 47 patients that analysed visual acuity data by age of the patient as an indicator of disease progression. A significant difference was noted in the visual acuities of the two eyes (two lines or greater in 64% of patients) and data were analysed separately for the eye with the best and the eye with the worst acuity. A significant correlation between visual acuity in each eye and patient age was found ($p<0.01$). There was also a significant correlation between stage of dystrophy and visual acuity in the eye with the worst acuity ($p<0.05$) but not in the eye with the best acuity, after correcting for age. The study uses the reference visual acuity value of 20/40 (6/12) (in the best eye), which in most US states is a requirement for obtaining an unrestricted driver's licence. In the eyes with the worst visual acuity, majority of patients aged 40 or younger had visual acuities below 20/40 (6/12) (64%). None of the patients older than 40 years had visual acuities better than 20/80 (6/24), and 73% had visual acuities of 20/200 (6/60) or worse. Seventy-four percent of patients older than 30 years and all of the patients aged 50 or older had a visual acuity of 20/100 (6/30) or worse in their worst eye. In the eyes with the best visual acuities, 76% of patients younger than 40 years had visual acuities of 20/40 (6/12) or better. However, of patients over 40 years, only 20% had a visual acuity of 20/40 (6/12) or better. Of patients older than 50 years, 43% had visual acuities of 20/70 (6/21) or better, but none had a visual acuity of 20/40 (6/12) or better.

The only European study[10] identified followed only nine patients between ten and 38 years. In three patients, visual acuity was unchanged over almost two decades (but only one patient had a good visual acuity of 20/20 (6/6) in both eyes, of the other two patients, one was down to finger counting at 2 m in both eyes, the other had visual acuities of 20/100 (6/30) (right eye) and 20/50 (6/15) (left eye)). Two patients experienced a reduction in visual acuity over 25 years (20/20 to 20/125 (6/6 to 6/38), and 20/25 to 20/63 (6/7.5 to 6/20)). A slight reduction in visual acuity was seen in three patients over approximately 10 years (no details given). One patients showed an improvement of visual acuity from 20/100 (6/15) at age 7 to 20/20 (6/6) at age 24. Of the whole group of 13 patients examined, 11 had a binocular visual acuity of 20/63 (6/20) or better (i.e. not fulfilling the Swedish criteria for visual handicap) at the final examination.

SUMMARY JUVENILE MACULAR DYSTROPHIES

- Data from the North of France suggest a prevalence of 1:3975 for hereditary (i.e. juvenile) macular dystrophies; with 46% of cases being due to Stargardt disease and 17% to vitelliform dystrophies (e.g. Best disease).
- All studies reported data for the “last follow-up” of individual patients who tended to have a large range of follow-up periods. Furthermore follow up was usually conducted on a subset rather than the whole study population. Therefore clear statements regarding progression over time are not possible.
- Different stages / phenotypes especially of Stargardt disease tend to show different progressions in terms of decline of visual acuity.
- For Stargardt disease one study reported that the likelihood of maintaining 6/60 or better visual acuity dropped to below 50% by 40 to 49 years of age and a disease duration of more than 15 years
- Another study on Stargardt disease found that in patients with initial visual acuities of 6/12 or better, the median time to develop visual acuities of 6/60 or worse was 22 years. Those seen initially in the first two decades of life showed a median time of seven years to reach a visual acuity of 6/60 or worse, compared with 22 years and 29 years for those who were initially seen at ages 21 to 40 or 41 to 60, respectively.
- For Stargardt disease, one study reported that peripheral visual field size at follow-up was between 60.7 and 67.4 degree/radius (depending on disease type, no significant change during the follow-up period). With respect to central visual field testing, a relative central scotoma was seen in between 69.2% and 93.8% of patients (depending on disease type). Central scotoma size was between 2.97 and 12.7, with a change of between +0.51 and +4.6 degree/radius/year.
- For Best’s vitelliform macular dystrophy, one study reported that none of the patients older than 40 years had visual acuities better than 6/24, and 73% had visual acuities of 6/60 or worse. Seventy-four percent of patients older than 30 years and all of the patients aged 50 or older had a visual acuity of 6/30 or worse in their worst eye. In the eyes with the best visual acuities, 76% of patients younger than 40 years had visual acuities 6/12 or better.
- None of the studies reported visual field data for Best’s vitelliform macular dystrophy.

Table 1 Data summary for studies on progression of juvenile macular dystrophies (Stargardt disease and Best's vitelliform macular dystrophy)

Study	Population	Results
STARGARDT DISEASE		
Gelisken 1985 Belgium *design:* cohort study *follow-up:* 1 to 13 years (for 22 of 49 patients)	Stargardt disease and/or fundus flavimaculatus n=49, FU only for n=22 (42 eyes) *three groups:* *group I*: lesions confined to the macula *group II*: macular lesion surrounded by perimacular flecks *group III*: fundus flavimaculatus flecks *gender:* 29 male, 20 female *age*: not stated *measurements:* (not described in detail) visual acuity measurements, visual fields, colour vision, dark adaptation, electroretinography, electro-oculography, ophthalmoscopy and fluoroangiography	**Visual acuity** for 42 eyes followed up 1 to 13 years (mean FU group I (14 eyes) 2 years, group II (14 eyes) 5 years, group III (14 eyes) 6 years) *baseline:* / *final exam:* *group I:* >6/10: 2 (14%) / 1 (7%) 5/10 to 3/10: 5 (36%) / 5 (36%) 2/10 to 1/20: 5 (36%) / 4 (28%) <1/20: 2 (14%) / 4 (28%) *group II:* >6/10: 7 (50%) / 2 (14%) 5/10 to 3/10: 0 / 1 (7%) 2/10 to 1/20: 6 (42%) / 5 (36%) <1/20: 1 (7%) / 6 (42%) *group III:* >6/10: 3 (22%) / 0 5/10 to 3/10: 0 / 0 2/10 to 1/20: 11 (78%) / 2 (14%) <1/20: 0 / 11 (86%) **Visual field** *baseline:* (measured in 48 patients) • Six patients (12 eyes): no defect peripherally or centrally • remaining eyes: only central scotoma of varying extension (5-15%) corresponding to extent of macular lesion *follow-up:* (limited details given) • central field defects increased consistently with the progression of the macular lesion
Kim 2006 USA *design:* cohort study *follow-up:* range 0.5 to 31.5 years, mean FU for patients in stages 1 and 2 8.8 and 9.9 years (longer for patients in stages 2-3 and 3)	Stargardt disease n=405 at baseline, n=218 at FU analysed by stage: *stage 1:* parafoveal and perifoveal flecks *stage 2:* flecks throughout posterior pole, anterior to vascular arcades and/or nasal to optic disk *stage 2-3:* partially resorbed extensive flecks *stage 3:* extensive flecks having resorbed almost entirely *gender:* not stated *age (mean (range)):* *stage 1:* 28.6 (6-75) *stage 2:* 30.1 (7-78) *stage 2-3:* 34.4 (9-69)	**Visual acuity** *baseline:* / *last visit:* *stage 1:* 20/200 or better: 194 (97.5%) / 71 (93.4%) 20/225 to 20/400: 3 (1.5%) / 5 (6.6%) worse than 20/400: 2 (1.0%) / 0 *stage 2:* 20/200 or better: 129 (84.9%) / 71 (75.5%) 20/225 to 20/400: 16 (10.5%) / 17 (18.1%) worse than 20/400: 7 (4.6%) / 6 (6.4%) *stage 2-3:* 20/200 or better: 25 (75.8%) / 11 (61.1%) 20/225 to 20/400: 4 (12.1%) / 5 (27.8%)

Study	Population	Results
	stage 3: 41.2 (27-57) *measurements:* best corrected visual acuity in the better eye reported (obtained from Snellen projection or Feinbloom low-vision charts); fluorescein angiography	worse than 20/400: 4 (12.1%) 2 (11.1%) *stage 3:* 20/200 or better: 8 (38.1%) 8 (26.7%) 20/225 to 20/400: 7 (33.3%) 15 (50.0%) worse than 20/400: 6 (28.6%) 7 (23.3%)
Itabashi 1993 USA *design:* cohort study *follow-up:* range 10 months to 19 years	Stargardt disease / fundus flavimaculatus n=73 at baseline, n=35 at FU analysed by stage: *type 1:* macular degeneration without flecks (n=18, FU 6.3±3.9 years) *type 2:* macular degeneration with parafoveal flecks (n=28, FU 8.3±5.6 years) *type 3:* macular degeneration with diffuse flecks (subdivided into 3E – early onset, <30 years (n=16, FU 4.1±4.0 years); and 3L – late onset, ≥30 years (n=10, FU 5.0±4.2 years)) *type 4:* diffuse flecks without macular degeneration (n=3, FU 2.2±0 years) *gender:* 39 male, 34 female *age:* mean age at initial symptoms 22.7±15.3 years; mean age at initial visit 27.4±15.7 years) *measurements:* • fundus photographs • best corrected VA (Snellen acuity chart at a distance of 20 ft), the degree of refraction needed to attain the best corrected Snellen acuity was expressed in spherical equivalence value (spherical + 0.5 cylindrical) in dioptres • the peripheral visual field was measured using a Goldmann perimeter, with V-4e isopter; four visual field measurements in the horizontal (right and left) and vertical meridians (upper and lower) carried out, the sum of these then was divided by 4, and the result (in degrees) was used as an index of the peripheral visual field size • the central visual field was examined with the Auto-Plot Tangent Screen, the data obtained with 1/1000 isopter (relative scotoma) were evaluated in the same manner as scotoma size	**Visual acuity** at follow-up *type 1:* mean VA: 20/74 (35 eyes) change of VA (octave/year): -0.10±0.2 (31 eyes) refractive error (dioptres) (spherical equivalence): -0.20±1.1 *type 2:* mean VA: 20/103 (55 eyes) change of VA (octave/year): -0.12±0.17 (17 eyes) refractive error (dioptres) (spherical equivalence): -1.03±1.5 *type 3E:* mean VA: 20/225 (32 eyes) change of VA (octave/year): -0.14±0.25 (10 eyes) refractive error (dioptres) (spherical equivalence): -0.16±0.8 *type 3L:* mean VA: 20/47 (19 eyes) change of VA (octave/year): -1.03±1.62 (10 eyes) refractive error (dioptres) (spherical equivalence): -0.59±1.4 *type 4:* mean VA: 20/20 (5 eyes) change of VA (octave/year): -0.37±0.32 (2 eyes) refractive error (dioptres) (spherical equivalence): -1.2±2.7 Four of 16 patients older than 40 years were legally blind (VA <20/200 in the eye with the better VA) **Visual field** at follow-up (peripheral visual field for 92 eyes, central visual field for 95 eyes) *type 1:* peripheral visual field size (degree/radius): 64.7±4.2 (26 eyes) relative central scotoma present: 69.2% central scotoma size (degree radius): 2.97±2.9 (26 eyes) change of scotoma size (degree/radius/year): 0.56±0.52 (7 eyes) *type 2:*

Study	Population	Results
		peripheral visual field size (degree/radius): 65.3±4.2 (34 eyes) relative central scotoma present: 71.4% central scotoma size (degree radius): 3.88±3.1 (35 eyes) change of scotoma size (degree/radius/year): 0.55±1.1 (7 eyes) *type 3E:* peripheral visual field size (degree/radius): 64.2±3.7 (20 eyes) relative central scotoma present: 93.8% central scotoma size (degree radius): 12.7±6.9 (16 eyes) change of scotoma size (degree/radius/year): 4.6±1.2 (2 eyes) *type 3L:* peripheral visual field size (degree/radius): 67.4±1.4 (9 eyes) relative central scotoma present: 93.3% central scotoma size (degree radius): 9.75±6.5 (15 eyes) change of scotoma size (degree/radius/year): 0.51±0.18 (4 eyes) *type 4:* peripheral visual field size (degree/radius): 60.7±7.8 (3 eyes) small ring scotoma present: 33.3% central scotoma size (degree radius): 3.25±5.6 (3 eyes) change of scotoma size (degree/radius/year): - no significant change in peripheral visual field size during FU (mean 6.1 years)
Oh 2004 USA *design:* historical cohort study *follow-up:* median FU for phenotype I 56 months, for phenotype II 60 months, for phenotype III 148.5 months	Stargardt disease n=214, n=131 seen at multiple visits subdivided by phenotype (at final visit): *phenotype I* (n=82): disease confined to macula *phenotype II* (n=62): flecks outside the temporal arcades *phenotype III* (n=70): retinal pigment epithelium atrophy, choroidal atrophy, or bone spicules extending outside the macula *gender:* not reported *age:* phenotype I 26 years, phenotype II 30 years, phenotype III 38 years (SDs not given) *measurements:* (not described in detail) fundus photographs, best corrected visual acuity	**Visual acuity** Likelihood of maintaining 20/200 or better visual acuity by age group (all phenotypes): 1-9 years: 100% 10-19 years: 95.7% 20-29 years: 82.1% 30-39 years: 68.8% 40-49 years: 47.7% 50-59 years: 33.8% 60-69 years: 11.2% 70+ years: 0.05% Likelihood of maintaining 20/200 or better visual acuity by years of FU (all phenotypes): <5 years: 84.1% 5-10 years: 72.6% 10-15 years: 54.5% 15-20 years: 36.3% 20-25 years: 26.6% 25-30 years: 11.8% 30-35 years: 0.08% 35+ years: 0

Study	Population	Results
		significant difference between phenotypes (p<0.0001), phenotype I: probability of maintaining VA of 20/200 or better into 5th decade of life and for 20 years FU 90%, probabilities for phenotypes II and III (analysed separately) dropped below 50% by 3rd decade of life and 10 years FU
Rotenstreich 2003 USA *design:* retrospective clinic-based cross-sectional study, retrospective cohort *follow-up:* at least 1 year	Stargardt disease n=361 included in survival analysis: n=73 with 20/40 or better vision at initial visit, n=38 with 20/50 to 20/100 vision in the better eye at initial visit; FU at least 1 year analysed by stage and age group (of initial visit): *stage 1:* flecks limited to vascular arcades *stage 2:* flecks anterior to vascular arcades and/or nasal to optic disk *stage 3:* most diffuse flecks resorbed, leaving diffuse retinal pigment epithelium (RPE) atrophy *stage 4:* diffusely resorbed fundus flecks, atrophy of RPE, diffuse choriocapillaris atrophy age groups (n=73): 20 years or less (21%), 21-40 years (49%), 41-60 years (25%), 61 years or older (5%) *gender:* 162 male, 199 female *age:* range 11 to 78 years, age group 1 16.3 SD3.0 years, age group 2 30.6 SD5.0 years, age group 3 49.9 SD4.3 years, age group 4 71.6 SD6.5 years) *measurements:* slit-lamp biomicroscopy and a detailed retinal examination; best corrected visual acuity (eye with better vision) using a projection Snellen or Feinbloom low vision chart	**Visual acuity** of 361 patients, 23% had VA 20/40 or better, 18% had VA 20/50 to 20/100, 55% had VA 20/200 to 20/400, 4% had VA worse than 20/400 *Patients with 20/40 or better visual activity* in patients with 20/40 or better visual activity at initial visit, median time (by survival analysis) to develop visual acuity of 20/200 or worse was 22 years (95% CI, 10 to 29 years) age group 0-20 years: median time to reach VA of 20/200 or less 7 years (95% CI, 5 to 8 years) age group 21-40 years: median time to reach VA of 20/200 or less 22 years (95% CI, 10 to 23 years) age group 41-60 years: median time to reach VA of 20/200 or less 29 years (95% CI, 12 to 29 years) age group 61+ years: no deterioration to VA 20/200 or worse significant difference between age groups (p=0.004) in patients with 20/40 or better visual activity at initial visit, median time to develop visual acuity of 20/50 to 20/100 was 16 years (95% CI, 6 to 26 years) age group 0-20 years: median time to reach VA of 20/50 to 20/100 3 years (95% CI, 1 to 5 years) age group 21-40 years: median time to reach VA of 20/50 to 20/100 20 years (95% CI, 3 to 25 years) age group 41-60 years: median time to reach VA of 20/50 to 20/100 15 years (95% CI, 5 to 25 years) *Patients with 20/50 to 20/100 VA* in patients with 20/50 to 20/100 VA at initial visit, median time to develop VA of 20/200 or worse was 6 years (95% CI, 3 to 8 years) age group 0-20 years: median time to reach VA of 20/200 or less 3 years (95% CI, 2 to 9 years) age group 21-40 years: median time to reach VA of 20/200 or less 6 years (95% CI, 4 to 9 years) age group 41-60 years: median time to reach VA of 20/200 or less 3 years (95% CI, 1 to 15 years) no significant difference between age groups

Study	Population	Results
BEST DISEASE		
Fishman 1993 USA *design:* cross-sectional study *follow-up:* none, but analysis by age-group	Best's vitelliform macular dystrophy n=47 *gender:* 28 male, 19 female *age:* mean 30.4 years *inclusion criteria:* only patients with a recognisable phenotype of Best vitelliform macular dystrophy; patients with absent foveal changes or with only minimal foveal pigment mottling and hypopigmentation in each eye were excluded *measurements:* (not described in detail) fundus photography, visual acuity	**Visual acuity** eye with worst acuity • 20/15 to 20/40 – 8/15 (53%) aged 1-15 years, 3/9 (33%) aged 16-30, 2/12 (17%) aged 31-40, none in older age groups • 20/50 to 20/70 – 4/15 (27%) aged 1-15 years, 4/9 (44%) aged 16-30, 3/12 (25%) aged 31-40, none in older age groups • 20/80 to 20/200 – none aged 1-30, 6/12 (50%) aged 31-40, 5/8 (63%) aged 51-75 • 20/400 or worse – none aged 1-30, 1/12 (8%) aged 31-40, none aged 41-50, 3/8 (38%) aged 51-75 eye with best acuity • 20/15 to 20/40 – 12/14 (86%) aged 1-15 years, 7/9 (78%) aged 16-30, 6/10 (60%) aged 31-40, 2/3 (67%) aged 41-50, none in oldest age group • 20/50 to 20/70 – 2/14 (14%) aged 1-15 years, 2/9 (22%) aged 16-30, 3/10 (30%) aged 31-40, 1/3 (33%) aged 41-50, 3/7 (43%) aged 51-75 • 20/80 to 20/200 – none aged 1-30, 1/10 (10%) aged 31-40, none aged 41-50, 3/7 (43%) aged 51-75 • 20/400 or worse – none aged 1-50, 1/7 (14%) aged 51-75 significant correlation between visual acuity and age for both eyes ($p<0.01$)
Mohler 1981 USA *design:* cohort study *follow-up:* at least 5 years for 54 patients, 8 to 10 years for 29 patients	Best's vitelliform macular dystrophy n=91 (but not all followed up), 107 eyes followed up for visual acuity *gender:* not stated *age:* (estimated from graph) 19% 1-9 years, 26% 10-19 years, 9% 20-29 years, 12% 30-39 years, 19% 40-49 years, 7% 50-59 years, 8% 60-84 years *measurements:* (not described in detail) annual fundus examinations, stereophotography, refracted visual acuity	**Visual acuity** *at presentation* *after 5 years* 20/20 or better: 48 eyes (45%) 51 eyes (48%) 20/25 to 20/40: 33 eyes (31%) 28 eyes (26%) 20/50 to 20/100: 21 eyes (20%) 20 eyes (19%) 20/200 to 20/400: 5 eyes (5%) 8 eyes (8%) • also no evidence of worsening of visual acuity in those eyes that were followed for 8-10 years • when considering visual acuity by age group for all 91 patients, there was an increased number of eyes with moderate (20/50 to 20/100) or severe (20/200 to 20/400) visual loss in patients in the 40-49 and 60-84 years age groups; for the 107 eyes followed for 5 years, no age group had a visual acuity profile reflecting worse vision after 5 years

Study	Population	Results
Ponjavic 1999 Sweden *design:* study of three families (13 patients) and retrospective follow-up of subgroup *follow-up:* between 10 and 38 years	Best's vitelliform macular dystrophy n=9 (people who were followed up retrospectively) *gender:* 3 male, 10 female (all 13 patients) *age:* mean 37.4 years (all 13 patients, including 2 children) *measurements:* slit-lamp inspection, ophthalmoscopy, fundus photography, corrected visual acuity	**Visual acuity** • Unchanged in three patients during almost two decades (1 patient finger counting 2m in both eyes, 1 patient 20/100 RE / 20/50 LE, 1 patient 20/20 both eyes) • reduction in visual acuity in 2 patients over 25 years – from 20/20 to 20/125, and from 20/25 to 20/63 • slight reduction in visual acuity in 3 patients over approximately 10 years (no details given) • improvement of visual acuity in 1 patient from 20/100 at age 7 to 20/20 at age 24

Abbreviations: CI=confidence interval, FU=follow-up, VA=visual acuity

4.2 Diabetic maculopathy

For diabetic maculopathy, 35 papers were thought to be relevant and were examined in full, including two extra papers identified though internet and bibliography searches. Of these papers, 12 studies were thought to offer the best evidence and these have formed the basis of the report. One of these was a systematic review[13] on the epidemiology of diabetic retinopathy and macular oedema, assessing mainly prevalence and incidence of macular oedema, rather than progression. Two studies provided information both on incidence / prevalence and progression: the Wisconsin Epidemiologic Study of Diabetic Retinopathy examined prevalence and incidence of diabetic macular oedema in type 1 and type 2 diabetes, as well as the incidence of doubling of the visual angle over 14 years' observation time in type 1 diabetes patients with macular oedema[13,14]. In addition, one Finish study examined prevalence and incidence of diabetic maculopathy in patients with type 2 diabetes, as well as changes in visual acuity (logMAR) over ten years[15]. Of the remaining nine studies, none examined all the factors of interest in the same population. With respect to prevalence / incidence of diabetic maculopathy, we included four relatively recent studies (published after 2000)[16-19] in addition to the systematic review (which had not included these studies). With respect to progression of diabetic maculopathy, we included one further observational study[20] that did not examine any particular interventions (in addition to the two mentioned above), and four intervention studies, all of which were randomised controlled trials[21-24]. Three of the trials had non-intervention control groups. All studies had follow-up times of at least two years.

4.2.1 Prevalence/incidence

Data in this section comes from one epidemiological systematic review and five additional primary observational studies. While the systematic review is considered to include the most complete set of relevant data, the supplementary primary studies add some newer data, some more information on the contribution of risk factors, and data relevant to the UK.

The systematic review[13] on the epidemiology of diabetic retinopathy and macular oedema included studies up to 2001. Summary data of the review are shown in table 2. The review used a thorough searching strategy and brief comments were made on study characteristics and methodology. UK studies were considered separately. The review included 359 articles in total. However, it has to be taken into account that particularly the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) accounted for a substantial number of articles, i.e. the number of studies included was lower but was not stated in detail. The authors of the review also caution that definition of clinically significant (i.e. threatening central vision) macular oedema, which was often reported by studies, was based on subjective criteria and it is possible that results between studies are not directly comparable because of different definitions / methodologies used. Similarly, studies differed in terms of the methodology used for retinal imaging (e.g. eight-field colour fundal photography versus two-field retinal imagery versus ophthalmoscopy versus slit-lamp examination), which could have led to further differences between studies.

The review included 153 references reporting prevalence data for diabetic retinopathy and reporting included prevalence of clinically significant macular oedema (threatening central visual function) by geographic region

and diabetes type (see table 2). Prevalence values for clinically significant macular oedema for UK data were 2.3 to 6.4% in type 1 diabetes, and 6.4 to 6.8% in mixed type1 / type 2 diabetes cohorts; prevalence values for clinically significant macular oedema from the USA were 6% for type 1 diabetes and 2 to 4% for type 2 diabetes; prevalence values in a European cohort were 5.4% for type 2 diabetes; prevalence values for Scandinavian data were 16% for type 1 diabetes, 0.6 to 26.1% for type 2 diabetes, and 8% for a mixed cohort.

Prevalence results were also listed for UK studies separately. The Liverpool Diabetic Eye Study[25] identified 357 patients who attended for slit-lamp biomicroscopy by a retinal specialist [data provided in the review supplemented here by data from the original study]. Of the 357 patients, 49 had type 1 diabetes, 40 had insulin-requiring (IR) type 2 diabetes, and 268 had non-insulin-requiring (NIR) type 2 diabetes. Maculopathy and macular oedema were subdivided as follows (only relevant categories listed): Maculopathy by exudate; level 1 – questionable, less than 50% certainty of presence of exudates, level 2 – exudate more than one disc diameter from fixation, level 3 – circinate ring of exudates within the macula more than one disc area in size but not within one disc diameter of fixation, level 4 - exudates within one disc diameter of fixation with or without presence of focal or grid photocoagulation scars, level 8 – non-diabetic macular exudate. Macular oedema; level 1 – questionable, less than 50% certainty of presence of oedema, level 2 – macular oedema but not clinically significant macular oedema, level 3 – circinate ring but not clinically significant macular oedema, level 4 – clinically significant macular oedema, level 8 – non-diabetic macular oedema. Values are given for the worse eye. Of all 357 patients, 0.6% had level 1 macular exudates (2.5% of type 2 IR and 0.4% of type 2 NIR), 2.0% had level 2 macular exudates (4.1% of type 1 and 1.9% of type 2 NIR), 0.6% had level 3 macular exudates (all type 2 NIR), 8.7% had level 4 macular exudates (4.1% of type 1, 17.5% of type 2 IR, 8.2% of type 2 NIR), and 0.3% had level 8 macular exudates (all type 2 NIR). As for macular oedema, of all patients (n=328), 1.5% had level 1 macular oedema (2.7% of type 2 IR and 1.6% of type 2 NIR), 1.5% had level 2 macular oedema (4.5% of type 1, 2.7% of type 2 IR, 0.8% of type 2 NIR), 0.9% had level 3 macular oedema (all type 2 NIR), 6.4% had level 4 macular oedema (2.3% of type 1, 16.2% of type 2 IR, 5.7% of type 2 NIR), and 0.6% had level 8 macular oedema (2.7% of type 2 IR and 0.4% of type 2 NIR). The systematic review lists two other UK studies[26,27], with one reporting a prevalence of 10% of maculopathy requiring treatment in 215 non-insulin treated type 2 diabetes patients, and the other reporting a prevalence of 6.8% of maculopathy in insulin-requiring diabetes mellitus. The latter study also reports an association of maculopathy prevalence with increasing age at diabetes onset and elevated systolic blood pressure.

Incidence estimates were not available for UK populations. Seventy studies were included reporting data on incidence of diabetic retinopathy of macular oedema. Incidence estimates for clinically significant macular oedema were 20.1% over 10 years for type 1 diabetes and 13.9% over 10 years for type 2 diabetes in cohorts from the USA; 7% per year in an Australian mixed cohort; and 3.4% over four years for type 1 diabetes in a Scandinavian cohort.

Table 2 Summary of data on macular oedema in the systematic review by Williams et al. 2004[13]

Population		Diabetes type	Pathology	Results
Prevalence of clinically significant macular oedema (CSMO)				
UK		type 1	CSMO	2.3-6.4%
		mixed cohort	CSMO	6.4-6.8%
USA		type 1	CSMO	6%
		type 2	CSMO	2-4%
African American		type 2	CSMO	8.6%
		mixed cohort	CSMO	8.6%
Australian		mixed cohort	CSMO	4.3-10%
European		type 2	CSMO	5.4%
Scandinavian		type 1	CSMO	16%
		type2	CSMO	0.6-26.1%
		mixed cohort	CSMO	8%
Incidence of clinically significant macular oedema (CSMO)				
USA		type 1	CSMO	20.1% over 10 years
		type 2	CSMO	13.9% over 10 years
Australia		mixed cohort	CSMO	7% per year
Scandinavian		type 1 diabetes	CSMO	3.4% over 4 years
UK studies cited – prevalence				
Broadbent et al. 1999[25]	Setting: population 357 patients from GP registers	all patients	CSMO	6.4%
		n=49 type 1	CSMO	2.3%
		n=40 type 2 insulin treated	CSMO	16.2%
		n=268 type 2 non-insulin treated	CSMO	5.7%
Sparrow et al. 1993[27]	Setting: population	n=215 non-insulin treated type 2	maculopathy requiring treatment	10%
McLeod et al. 1988[26]	Setting: population number of patients not stated	insulin-requiring diabetes mellitus	maculopathy	6.8% risk factors: increasing age at onset, elevated systolic BP
Relation to other factors – prevalence				
Wisconsin Epidemiologic Study of Diabetic Retinopathy[28]	Factor: diabetes duration	n=919 type 1	macular oedema	<5 years: 0% 20 years: 29%
		n=1121 type 2	macular oedema	<5 years: 3% 20 years: 28%
Wisconsin Epidemiologic Study of Diabetic Retinopathy[28,29]	Factor: insulin-treatment	n=902 type 1	macular oedema (after 15 years)	18%
		n=674 type 2 insulin-treated	macular oedema (after 15 years)	20%
		n=696 type 2 non-insulin-treated	macular oedema (after 15 years)	12%
Reuterving et al. 1999[30], Sweden	Factor: insulin-treatment n=1805 diabetes patients	type 1	macular oedema	16%
		type 2 insulin	macular oedema	26.1%
		type 2 oral antihyperglycaemic drugs	macular oedema	8.6%
		type 2 diet	macular oedema	0.6%
Relation to other factors – incidence				
Wisconsin Epidemiologic Study of Diabetic Retinopathy[31,32]	Factor: insulin-treatment	n=891 type 1	CSMO (4 year incidence)	4.3%
		n=987 type 2 insulin-treated	CSMO (4 year incidence)	5.1%
		non-insulin-treated	CSMO (4 year incidence)	1.3%
		n=996 type 1	CSMO (10 year incidence)	20.1%
		n=674 type 2	CSMO (10 year	25.4%

Population		Diabetes type	Pathology	Results
		insulin-treated	incidence)	
		n=696 type 2 non-insulin-treated	CSMO (10 year incidence)	13.9%
		n=634 type 1	CSMO (14 year incidence)	26%

Abbreviations: CSMO=clinically significant macular oedema

The systematic review also reported associations of prevalence and incidence of macular oedema with other factors. Both incidence and prevalence tended to increase with diabetes duration. For example, in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, prevalence of macular oedema with less than five years' diabetes duration was between 0 (type 1 diabetes) and 3% (type 2 diabetes), whereas after 20 years' diabetes duration, prevalence was 29 (type 1) and 28% (type 2). Similarly, four-year incidence of clinically significant macular oedema was between 1.3 and 5.1%, and ten-year incidence between 13.9 and 25.4% (see table 2). In the Wisconsin study, incidence of macular oedema with type 1 diabetes also increased with age (see figure 2). Macular oedema (both prevalence and incidence) was also different as a function of insulin-treatment and tended to be highest in insulin-treated type 2 diabetes patients. For example, macular oedema prevalence in the Wisconsin study was 18% in type 1 diabetes patients, 20% in insulin-treated type 2 diabetes patients and 12% in non-insulin treated type 2 diabetes patients; similarly, a Swedish study found a prevalence of macular oedema in 16% of type 1 patients, 26.1% insulin-treated type 2 patients, 8.6% type 2 patients treated with oral antihyperglycaemic drugs, and 0.6% diet-treated type 2 patients.

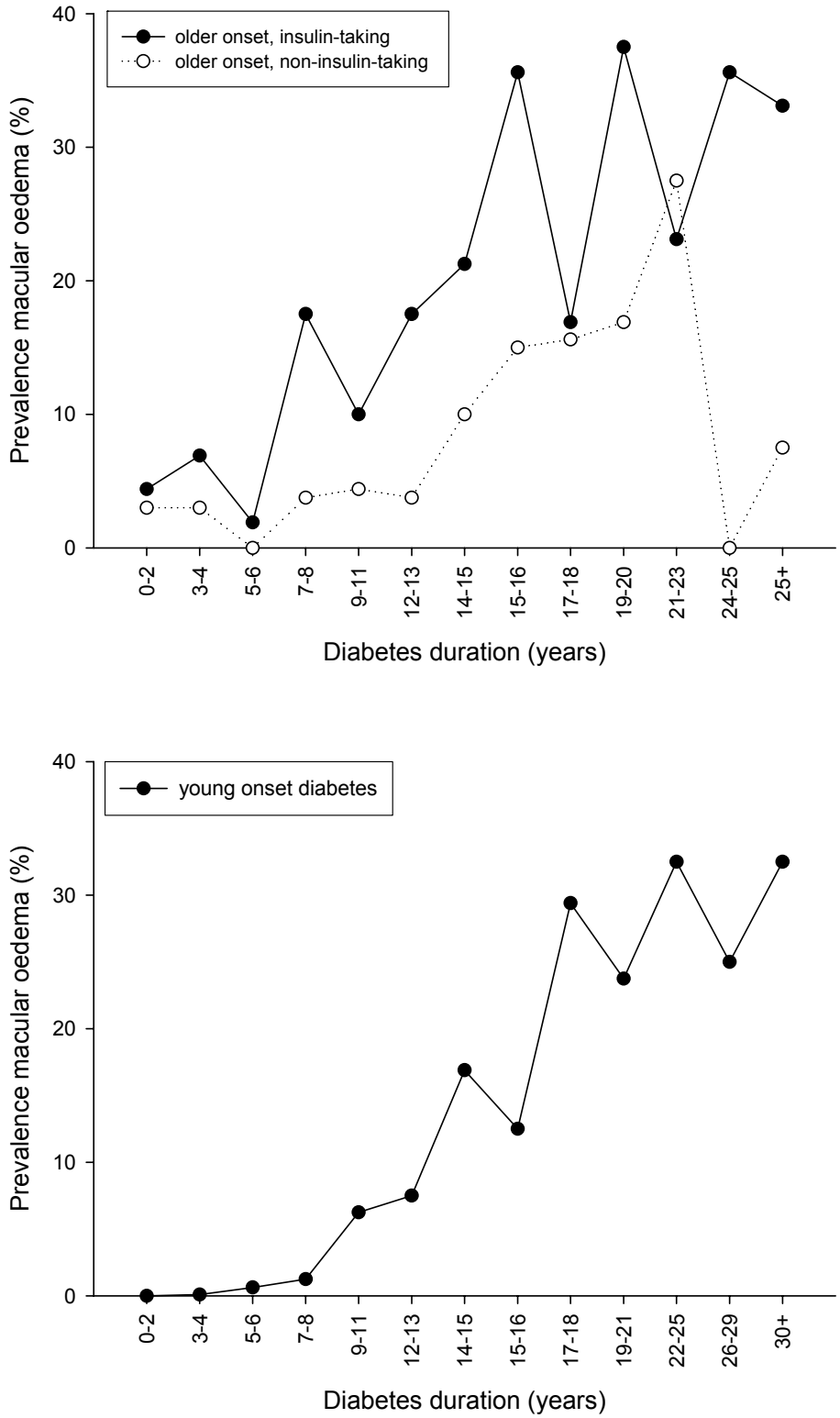

Figure 1 Prevalence of macular oedema by duration of diabetes in (upper graph) insulin- and non-insulin-treated type 2 diabetes patients and (lower graph) type 1 diabetes patients in the Wisconsin Epidemiologic Study of Diabetic Retinopathy[28] [numbers estimated from original graphs].

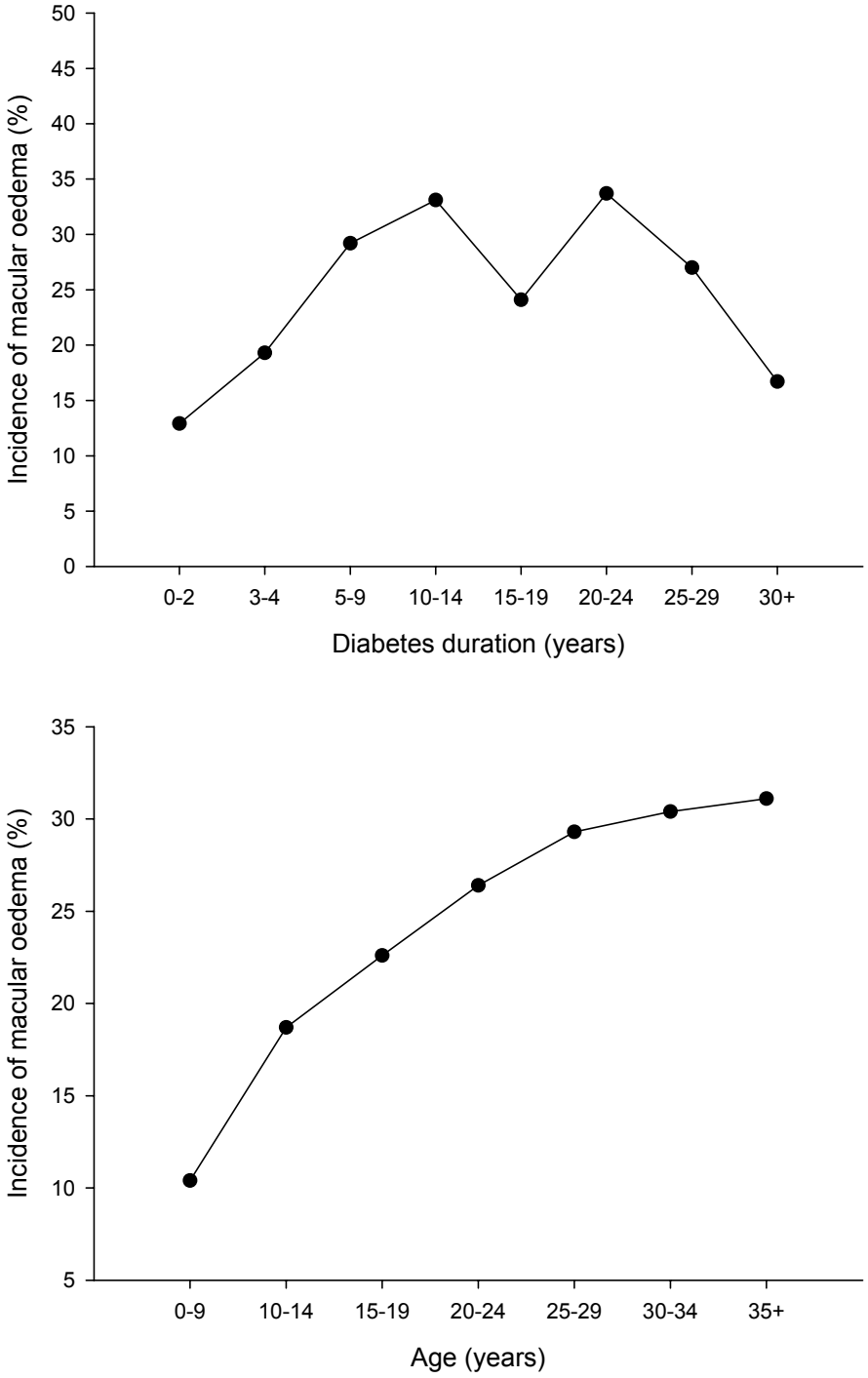

Figure 2 Incidence of macular oedema by diabetes duration (upper graph, p for trend 0.07) and age (lower graph, p for trend <0.005) in type 1 diabetes patients in the Wisconsin Epidemiologic Study of Diabetic Retinopathy[32].

Figure 1 shows the association between prevalence of macular oedema and diabetes duration by diabetes type and insulin treatment in the Wisconsin study. Figure 2 shows the association between incidence of macular oedema and both diabetes duration and age in patients with type 1 diabetes in the Wisconsin study. In both type 1 and type 2 diabetes patients in the Wisconsin study, an increased risk of macular oedema was also associated with higher levels of glycated haemoglobin and presence of proteinuria.

Table 3 summarises four additional European observational studies that were not included in the systematic review, including two large studies from the UK[16,17]. One study is also relevant to disease progression and has been summarised in table 4. The studies were included as they were rather recent, and most of them included quite a large number of patients and / or discussed some aspects, for example with respect to risk factors, that were not covered by the systematic review.

The study by Ling et al. (2002)[17] was a retrospective cohort study including 775 diabetes patients screened by the Exeter Diabetic Retinopathy Screening Programme between 1992 and 1998 (104 type 1, 517 non-insulin-requiring type 2, 154 insulin-requiring type 2). At baseline, the prevalence of clinically significant maculopathy (definition see table 3) was 11.5% for type 1 patients, 4.1% for non-insulin-requiring type 2 patients, and 9.1% for insulin-requiring type 2 patients. Prevalence for the whole population was 6.1%. After 1.8 years (round 2), total prevalence had risen to 7.1%, with an incidence of new clinically significant maculopathy of 4.79%. After 4.3 years, prevalence was at 8.6% and incidence at 5.18%.

Leese (2004)[16] studied risk factors for the incidence of diabetic maculopathy in a retrospective study using data from six hospital-based diabetes centres in Scotland that were part of the Royal College of Physicians of Edinburgh Diabetes Register. Their study included 1632 type 1 diabetes patients. The study only reported relative incidence values. Maculopathy incidence was significantly increased with increasing diabetes duration (see figure 3, relative incidence more than doubled by 10 to 15 years), increasing systolic blood pressure (adjusted relative incidence 2.91 (95% CI 1.38 to 6.12) for systolic blood pressure 140 mmHg or above), and increasing HbA1c values (adjusted relative incidence 2.48 (95% CI 1.28 to 4.82) for highest quartile of HbA1/A1c).

In a Spanish study, Romero et al. (2007)[18] studied 112 type 1 diabetes patients without retinopathy or nephropathy at baseline prospectively over a period of 15 years. Fifteen-year incidence of diabetic macular oedema was 20.5% (11.6% for the focal form, 8.9% for the diffuse form). The following factors were significantly associated with the development of diabetic macular oedema: high levels of LDL-cholesterol (p=0.013), high levels (>7.5%) of HbA1c (p=0.021), presence of macroangiopathy (p=0.022), severity of diabetic retinopathy (p=0.029), presence of arterial hypertension (p=0.037), presence of overt nephropathy (p=0.047). With respect to diabetes duration, the authors found peaks of macular oedema incidence at 15-20 years' and more than 35 years' duration.

A German cross-sectional study[19] examined 1796 type 1 and 1563 type 2 diabetes patients. Prevalence of diabetic maculopathy was 15% in type 1 diabetes patients and 23% in type 2 diabetes patients. Of the 28% of type 1 patients and the 38% of type 2 patients with background retinopathy, 42 and 53% respectively had diabetic maculopathy. In type 1 diabetes, presence of maculopathy was significantly associated with age at diabetes onset, and serum triglyceride and total cholesterol levels. In type 2 diabetes, presence of maculopathy was significantly associated with elevated creatinine levels and hypertension. For both types, maculopathy was associated with diabetes duration (see figure 4) and peripheral and/or autonomic neuropathy.

A Finish study[15] (summarised in table 4) examined diabetic maculopathy in 133 patients with newly diagnosed type 2 diabetes (compared to a non-diabetic control group) over a course of 10 years. At baseline, prevalence of diabetic maculopathy in the diabetes group was 3.4%. This rose to 21% by 10 years' follow-up. Ten-year incidence of diabetic maculopathy was 20%. Patients with poorer glycaemic control at the five year examination were of greater risk of diabetic maculopathy at 10 years (5-year HbA1c 8.1±1.9% in people without diabetic maculopathy at 10 years, 11.3±2.6% in people with maculopathy, $p<0.001$).

Table 3 Summary of additional prevalence / incidence studies for diabetic maculopathy published 2000 or later

Study	Population	Methodology	Results
Leese 2004 Royal College of Physicians of Edinburgh Diabetes Register Group UK *design:* retrospective cohort study (Royal College of Physicians of Edinburgh Diabetes Register, data from six hospital-based diabetes centres in Scotland) *follow-up:* median 4 years (2.5 to 5.5 years interquartile range)	type 1 diabetes (requiring insulin treatment, diagnosed before age 35) n=1632 *gender:* 54% male, 46% female *age:* not stated	• dilated direct ophthalmoscopy (diabetologist); if patients referred to ophthalmologist, results verified by slit-lamp examination • maculopathy defined as any haemorrhages, exudates or circinates within one disc diameter of the fovea, which required referral to an ophthalmologist for laser photocoagulation or ongoing clinic review • collection of data on HbA1c, cholesterol (one third of patients), blood pressure, urinary albumin, smoking status	only relative incidences reported with respect to reference value; incidence of maculopathy was significantly increased with: • increasing diabetes duration (longer than 10 years) ($p<0.05$ and less with increasing duration); relative incidences see figure 3 • systolic blood pressure ≥140 mmHg ($p<0.001$); adjusted relative incidence 2.91 (95% CI 1.38 to 6.12) • HbA1/A1c highest quartile ($p<0.01$); adjusted relative incidence 2.48 (95% CI 1.28 to 4.82)
Ling 2002 Exeter Diabetic Retinopathy Screening Programme UK *design:* retrospective cohort study (diabetes register of nine practices) *follow-up:* 4.3±0.32 years	type 1 and type 2 diabetes n=775 total n=104 type 1 diabetes n=517 type 2 non-insulin-requiring (NIR) n=154 type 2 insulin-requiring (IR) *gender:* 54.2% male, 45.8% female *age:* mean 72.1±14.5 years (range 15-99)	• dilated fundoscopy (screening technician), single 45° Polaroid photograph of each eye • Snellen visual acuity (but not reported for maculopathy separately) • clinically significant macular oedema defined as: more than five microaneurysms or haemorrhage within one disc diameter from the fovea, and ETDRS definition of clinically significant maculopathy	Clinically significant maculopathy *Round 1 (baseline):* prevalence type 1: 11.5% type 2 NIR: 4.1% type 2 IR: 9.1% total: 6.1% *Round 2 (1.8±0.24 years) (n=601):* prevalence: 7.1% incidence: 4.79% *Round 3 (4.3±0.32 years) (n=501):* prevalence: 8.6% incidence: 5.18%
Romero 2007 Spain *design:* prospective cohort study (Catalonian type 1 diabetes register) *follow-up:* 15 years	type 1 diabetes n=112 patients without retinopathy or nephropathy *gender:* 48.2% male, 51.8% female *age:* 39.94±10.53 years (range 24-61)	• stereoscopic viewing of the macula with a slit lamp and Goldman fundus contact lens; macular oedema present if: retinal thickening involving or within 500 µm of the centre of the macula; hard exudates at or within 500 µm of the centre of the macula, if associated with a thickening of the adjacent retina; zone(s) of retinal thickening one disc area (or larger) in size, any part of which being within one disc diameter of the centre of the macula • in all patients with macular oedema, fluorescein angiography performed to determine leakage (focal leakage, diffuse leakage, cystoid leakage) • since 2000 optical coherence tomography for all patients with macular oedema • collection of data on potential risk factors: gender, diabetes duration, HbA1c, arterial hypertension, macroangiopathy,	• incidence of diabetic macular oedema after 15 years: 20.5% (11.6% focal form, 8.9% diffuse form) • best corrected visual acuity correlated with central foveal thickness measured with optical coherence tomography significant factors in the development of diabetic macular oedema (logistic regression): • high levels of LDL-cholesterol ($p=0.013$) • high levels (>7.5%) of HbA1c ($p=0.021$) • presence of macroangiopathy

Study	Population	Methodology	Results
		triglyceride levels, cholesterol fractions (HDL, LDL), cigarette smoking	(p=0.022) • severity of diabetic retinopathy (p=0.029) • presence of arterial hypertension (p=0.037) • presence of overt nephropathy (p=0.047) • peaks of incidence of macular oedema at 15-20 years and >35 years diabetes duration
Zander 2000 Germany *design:* cross-sectional study (of total clinic population)	type 1 and type 2 diabetes n=1796 type 1 diabetes n=1563 type 2 diabetes *gender:* not stated *age:* type 1 diabetes: 44.3±0.6 years without maculopathy, 46.6±0.8 years with maculopathy; type 2 diabetes: 61.1±0.5 years without maculopathy, 62.1±0.4 years with maculopathy	• stereo slit lamp biomicroscopy (ophthalmologist), fundus photography, fluorescein angiography • clinically significant maculopathy defined by: retinal thickening at or within 500 µm of the centre of the macula; hard exudates at or within 500 µm of the centre of the macula, if associated with a thickening of the adjacent retina; zone(s) of retinal thickening one disc area (or larger) in size, any part of which being within one disc diameter of the centre of the macula • assessment of diabetic neuropathy, hypertension, nephropathy	type 1 diabetes: • prevalence of diabetic maculopathy: 15% • background retinopathy in 28%, 42% of whom had diabetic maculopathy • proliferative retinopathy in 10%, 35% of whom had diabetic maculopathy • significant risk factors for maculopathy in multiple logistic correlation analysis: age at manifestation, diabetes duration, triglycerides >2.2 mmol/L, cholesterol >6.5 mmol/L, peripheral and/or autonomic neuropathy type 2 diabetes: • prevalence of diabetic maculopathy:23% • background retinopathy in 38%, 53% of whom had diabetic maculopathy • proliferative retinopathy in 5%, 56% of whom had diabetic maculopathy • significant risk factors for maculopathy in multiple logistic correlation analysis: diabetes duration, elevated creatinine, hypertension, peripheral and/or autonomic neuropathy

Abbreviations: CI=confidence interval, EDTRS=Early Treatment Diabetic Retinopathy Study

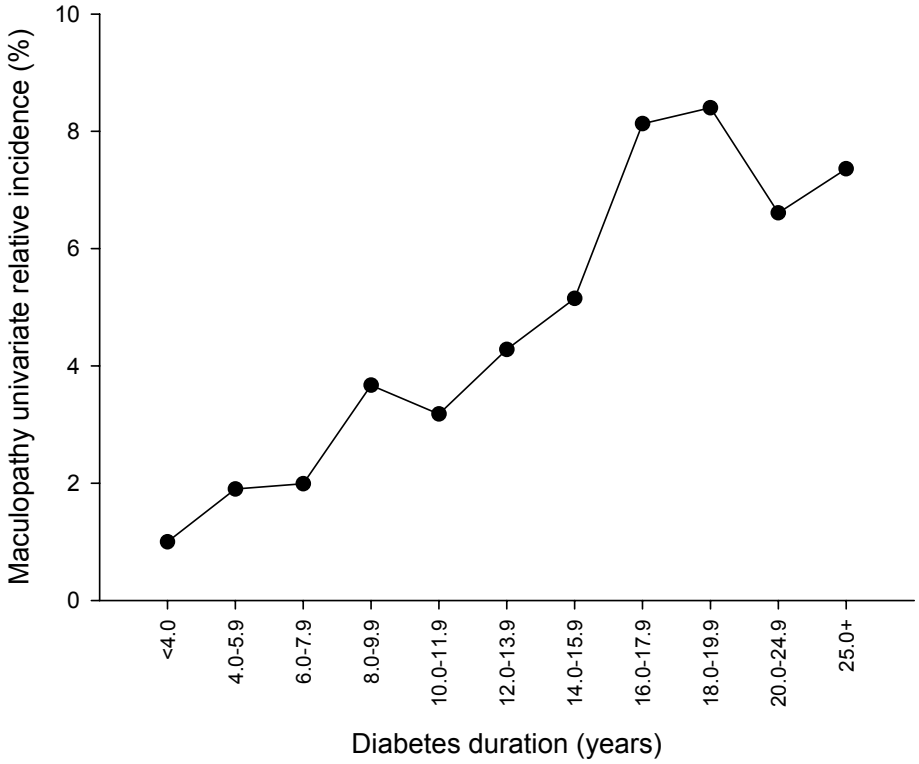

Figure 3 Univariate relative incidence of maculopathy by diabetes duration in type 1 diabetes patients (The Royal College of Physicians of Edinburgh Diabetes Register Group)[16].

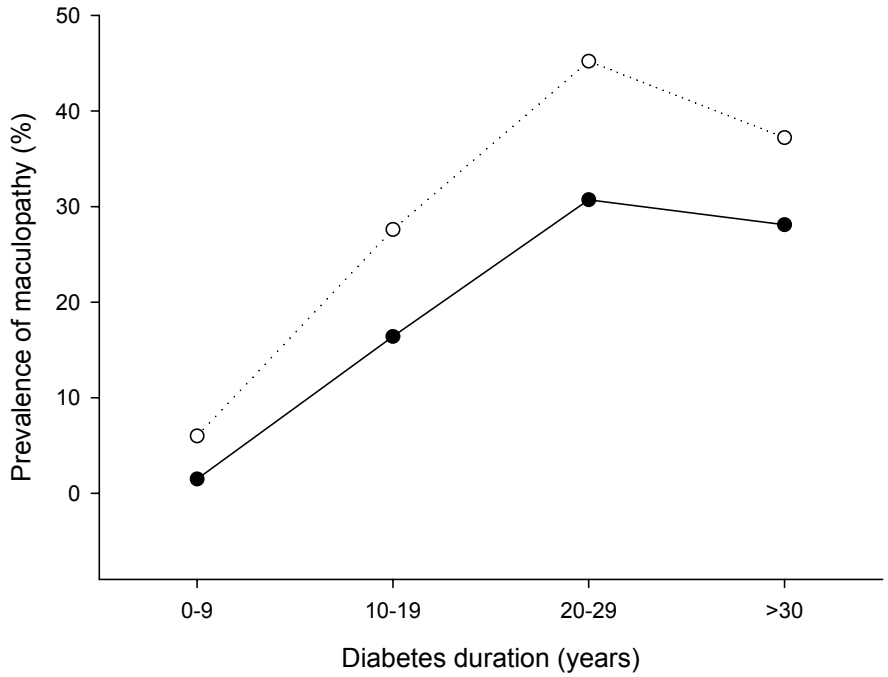

Figure 4 Prevalence of diabetic maculopathy by diabetes duration (Zander et al. 2000)[19] (solid line=type 1 diabetes, dotted line=type 2 diabetes).

4.2.2 Progression

4.2.2.1 Observational studies

Three observational studies gave some, albeit limited, information about progression of diabetic maculopathy over prolonged periods of time.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy[14] reported incidence of visual impairment (visual acuity 20/40 (6/12) or worse in the better eye), incidence of doubling of the visual angle and incidence of blindness (visual acuity 20/200 (6/60) or worse) over 14 years' observation time in 634 patients with type 1 diabetes. After 14 years, the incidences of visual impairment, doubling of visual angle, and blindness in patients with macular oedema were significantly greater than in patients without macular oedema (49.6% versus 15.9% for visual impairment ($p<0.0001$), 46.3% versus 16.4% for doubling of visual angle ($p<0.0001$), 19.4% versus 3.6% for blindness ($p<0.0001$)).

Coscas and Gaudric (1984)[20] carried out a rather small study with only a limited description of methodology of the progression of diabetic macular oedema in 38 patients. However, this study was the only one identified reporting visual acuity progression by type of macular oedema. The study showed that prognosis was best with non-cystoid macular oedema and became progressively worse for cystoid macular oedema without a central cyst in the foveal avascular zone, and for cystoid macular oedema with a large central cyst in the foveal avascular zone. At baseline, there were 30 eyes with non-cystoid macular oedema (of which 16 became cystoid over a mean follow-up period of five years). Visual acuity at baseline in these patients was 0.85 (~6/7) (range 1.0 to 0.4 (6/6 to 6/15)). This deteriorated to 0.6 (6/10) by five years' follow-up, and to 0.45 (~6/13) by six years. There were 27 eyes at baseline with a cystoid macular oedema without a central cyst in the foveal avascular zone (of which six developed a large central cyst in the foveal avascular zone, and six changed to non-cystoid oedema over a mean follow-up period of four years). In these patients, mean visual acuity at baseline was 0.65 (~6/9) (range 1.0 to 0.2 (6/6 to 6/30)). This deteriorated to 0.5 (6/12) by four years' follow-up. Finally, there were 18 eyes with cystoid macular oedema with a large central cyst in the foveal avascular zone at baseline (of which one became non-cystoid and the central cyst disappeared in another case over five years' follow-up). In these patients, mean visual acuity at baseline was 0.35 (~6/17) (range 1.0 to 0.1 (6/6 to 6/60)). This deteriorated to 0.1 (6/60) by five years' follow-up.

The Finish study of 133 patients with newly diagnosed type 2 diabetes mentioned in the previous section[15] also examined visual acuity changes. At baseline, visual acuities in the better eye were between 20/20 (6/6) and 20/21[33] (~6/6.3) and there were no significant differences in visual acuity between eyes that did or did not develop maculopathy later on. After 10 years' follow-up, mean visual acuity in right eyes with maculopathy was 20/27 (~6/8) and 20/23 (~6/7) in right eyes without maculopathy ($p=0.057$). The values for left eyes were 20/34 (~6/10) with maculopathy and 20/23 (~6/7) without ($p<0.001$).

Table 4 Progression of diabetic maculopathy – observational studies

Study	Population	Methodology	Results
Moss 1998 Wisconsin Epidemiologic Study of Diabetic Retinopathy USA *design:* population-based cohort study *follow-up:* 14 years	type 1 diabetes (insulin-taking, diagnosed before age 30) n=996 at baseline, 634 at 14 years *gender:* not stated *age:* not stated	• visual acuity measured by the Early Treatment Diabetic Retinopathy Study protocol • visual impairment defined as VA 20/40 or worse in the better eye; blindness defined as VA of 20/200 or worse • doubling of visual angle	• 14-year incidence of visual impairment in patients with macular oedema was 49.6% (versus 15.9% without, p<0.0001) • 14-year incidence of doubling of visual angle was 46.3% in patients with macular oedema (versus 16.4% without, p<0.0001) • 14-year incidence of blindness was 19.4% in patients with macular oedema (versus 3.6% without, p<0.0001)
Coscas 1984 France *design:* retrospective cohort study *follow-up:* 3-6 years (mean 5 years)	n=38 (60 eyes) with diabetic macular oedema n=42 panretinal photocoagulation before or during FU *gender:* not stated *age:* not stated *note:* numbers of patients / eyes do not quite add up	• limited description • fluorescein angiography	noncystoid macular oedema (n=30 eyes at baseline): • VA 0.85 at presentation (range 1.0 to 0.4), 0.6 at 5 years, 0.45 after 6 years • during mean FU of 5 years 16 of 30 eyes became cystoid cystoid macular oedema without a central cyst in the foveal avascular zone (n=27 eyes at baseline) • VA 0.65 at presentation (range 1.0 to 0.2), 0.5 at 4 years • during mean FU of 4 years 6 of 27 had a large central cyst in the foveal avascular zone, in 6 cases oedema became non-cystoid cystoid macular oedema with a large central cyst in the foveal avascular zone (n=18 eyes at baseline) • VA 0.35 at presentation (range 1.0 to 0.1), 0.3 at 3 years, 0.1 at 5 years • during mean FU of 4 years oedema became non-cystoid in 1 case, central cyst disappeared in 1 case
Voutilainen-Kaunisto 2001 Finland *design:* prospective cohort study *follow-up:* 10 years	n=133 patients with newly diagnosed type 2 diabetes (n=92 at 10 years) n=144 non-diabetic controls (n=128 at 10 years) *gender:* diabetes: 52.6% male, 47.4% female; control: 43.1% male, 56.9% female *age:* diabetes: 55.9±5.6 years; control: 53.7±5.4	• 45° fundus photographs • fluorescein angiograms • best corrected visual acuity measured in each eye after retinoscopy and subjective refraction • presence of maculopathy defined as focal or diffuse oedema with thickening of the adjacent retina with or without partial loss of transparency and/or as presence of hard exudates within one disc diameter from the centre of the macula	prevalence of maculopathy • diabetes patients: 3.4% at baseline, 0% at 5 years, 21% at 10 years • controls: 1.6% at baseline, 0.8% at 5 years, 0.9% at 10 years 10 year incidence of diabetic maculopathy (in diabetic patients) 20% risk factors • fasting plasma glucose, 1-h and 2-h glucose values and HbA1c at the 5 year examination were risk factors for maculopathy in diabetic patients at 10 years (5-year HbA1c 8.1±1.9% in people without diabetic maculopathy at 10 years, 11.3±2.6% in people with maculopathy, p<0.001) visual acuity in diabetic patients at 10 years • at baseline and 5 years people with maculopathy had nearly the same visual acuity in both eyes than those without • right eye with maculopathy: 20/27, logMAR +0.13

Study	Population	Methodology	Results
			right eye without maculopathy: 20/23, logMAR +0.06, p=0.057 • left eye with maculopathy: 20/34, logMAR +0.24 left eye without maculopathy: 20/23, logMAR +0.06, p<0.001

Abbreviations: FU=follow-up, VA=visual acuity

Table 5 Progression of diabetic maculopathy – treatment studies

Study	Population	Intervention / methodology
British Multicentre Study Group 1983 UK, Norway *design:* randomised controlled trial *follow-up:* at least 5 years (up to 7 years)	n=99 (n=60 at 5 years, n=23 had died, the rest dropped out for other reasons) type 1 and type 2 diabetes (but only 9 patients diagnosed at ages 0-29 years) *gender:* 50.5% male, 49.5% female *age:* 59.1 years (range 20-76) *diabetes duration:* 9.2 years (range 0-34) *inclusion criteria:* best corrected visual acuity 6/12 or worse with visual loss due to macular oedema in the presence of microvascular abnormalities with or without hard exudates; patients with visual acuities of 6/6 and 6/9 included if there was either documented visual loss or hard exudate rings were seen to encroach on the macula; patients included if two eyes affected similarly (difference within 2 lines of the Snellen chart), at least one eye 6/60 or better vision	Intervention: • each patient had one eye randomised to photocoagulation using the Xenon Arc, the other to no treatment • follow-up treatment of treated eye if there were new lesions between the superior and inferior temporal vessels outside the foveal area, or if new vessels developed in this area Methodology: • yearly assessment of visual acuity using standard back illuminated Snellen chart (examiner unaware of identity of treated eye)
Early Treatment Diabetic Retinopathy Study 1985-1991 USA *design:* randomised controlled trial *follow-up:* 4 to 5 years	n=5070 eyes (3711 patients) patient characteristics not reported *inclusion criteria:* (for the reported data) macular oedema and mild to moderate diabetic retinopathy in one or both eyes *exclusion criteria:* high risk proliferative retinopathy (moderate or severe optic nerve neovascularisation, any neovascularisation with haemorrhage), other significant ocular disease, visual acuity worse than 20/200 (6/60)	Intervention: • *macular oedema and less severe retinopathy* randomised to: early photocoagulation versus deferral (n=1429), early photocoagulation group randomised to immediate focal photocoagulation, with mild (n=365) or full (n=362) scatter photocoagulation added if severe nonproliferative or early proliferative retinopathy developed during follow-up, or immediate scatter photocoagulation (mild (n=365) or full (n=356)) with focal photocoagulation delayed for at least 4 months • *macular oedema and more severe retinopathy* randomised to: early photocoagulation versus deferral (n=1103), early photocoagulation group randomised to immediate focal and scatter photocoagulation (mild (n=276) or full (n=272)), or immediate scatter photocoagulation (mild (n=272) or full (n=270)) and focal photocoagulation delayed for at least 4 months Methodology: • visual loss measured, defined as severe (best corrected visual acuity

Study	Population	Intervention / methodology
		<5/200) at two consecutive follow-up visits (4 month intervals) or moderate (loss of 15 or more letters between baseline and follow-up visit, equivalent to doubling of visual angle) • visual field measurement: scores on Goldmann I/4e test object; percentage of eyes with paracentral scotoma
Olk 1986 USA *design:* randomised controlled trial *follow-up:* 2 years; follow-up for treated eyes of this trial and Olk 1990 for up to 5 years	n=92 (160 eyes, 68 patients bilateral involvement, 24 unilateral) (13 patients died during follow-up) 63% type 1, 37% type 2 diabetes *gender:* 34% male, 66% female *age:* 63 years (range 20-80) *diabetes duration:* 13 years (range 3 months to 29 years) *inclusion criteria:* diffuse macular oedema (two or more disc areas of retinal thickening and involving the centre of the macula); best corrected visual acuity had to be less than 20/32+2 and better than 20/200-3	Intervention: • modified grid argon (blue-green) laser photocoagulation versus observation (of 82 treated eyes, 29 were treated once, 38 twice, 15 three times) Methodology: • Goldmann visual field measurement • Best corrected visual acuity (improvement or worsening by two or more lines) • for 5 year follow-up, change of vision defined as three or more lines change on the EDTRS visual acuity chart (i.e. halving or doubling of visual angle) • assessment of risk factors: cystoid versus non-cystoid macular oedema, systemic vascular disease, hypertension
Olk 1990 USA *design:* randomised controlled trial *follow-up:* 2 years; follow-up for treated eyes of this trial and Olk 1986 for up to 5 years	n=132 (225 eyes, 186 eyes treated bilaterally) (14 patients died during follow-up) 69% type 1, 31% type 2 diabetes *gender:* 31% male, 69% female *age:* 60.9 years (range 20-81) *diabetes duration:* 16 years (range 1 month to 45 years) *inclusion criteria:* diffuse macular oedema (two or more disc areas of retinal thickening and involving the centre of the macula); best corrected visual acuity had to be better than 20/200-3	Intervention: • argon green (514 nm) versus krypton red (647 nm) modified grid laser photocoagulation • argon green: of 116 treated eyes, 44 were treated once, 52 twice, 16 three times, krypton red: of 109 treated eyes, 35 were treated once, 45 twice, 25 three times Methodology: • change of vision defined as three or more lines change on the EDTRS best corrected visual acuity chart (i.e. halving or doubling of visual angle) • Humphrey visual field measurement • assessment of risk factors: cystoid versus non-cystoid macular oedema, systemic vascular disease, hypertension

4.2.2.2 Treatment studies

Only randomised controlled trials were considered for assessing long-term results of treatments for diabetic maculopathy (compared to natural progression). There were four main randomised controlled trials, which all assessed laser photocoagulation. A summary of these trials is shown in table 5.

The British Multicentre Study[24] of photocoagulation for diabetic maculopathy included 99 patients at baseline, who had type 1 or type 2 diabetes and diabetic maculopathy. Patients were included if both eyes were affected similarly, and one eye was randomised to photocoagulation using the xenon arc, the other received no treatment. The treated eye could be treated more than once if deemed necessary. Patients were followed-up for at least five years (up to seven years). Of the 99 patients, 39 failed to complete the five-year follow-up (23 of them had died). On average, the mean visual acuity deteriorated by less than one line in the treated eyes over the five years of follow-up, whereas it deteriorated by more than two lines in the control group ($p<0.01$). The difference in deterioration was greatest in patients whole initial vision was 6/6 to 6/9 and was not significant in those whose initial visual acuity was 6/36 or worse (see figure 5). Thirteen eyes became blind in both eyes (visual acuity 6/60 or worse for two consecutive yearly assessments), whereas six became blind in the treated eye only and 26 in the control eye only ($p<0.01$). Again, the difference was greatest in those with an initial vision of 6/6 to 6/9, where one treated and 10 control eyes became blind ($p<0.01$). Hard exudates, microaneurysms, and haemorrhages improved more in the treated eyes than in the control eyes ($p<0.05$ to <0.001), and more control eyes developed new vessels during the follow-up period.

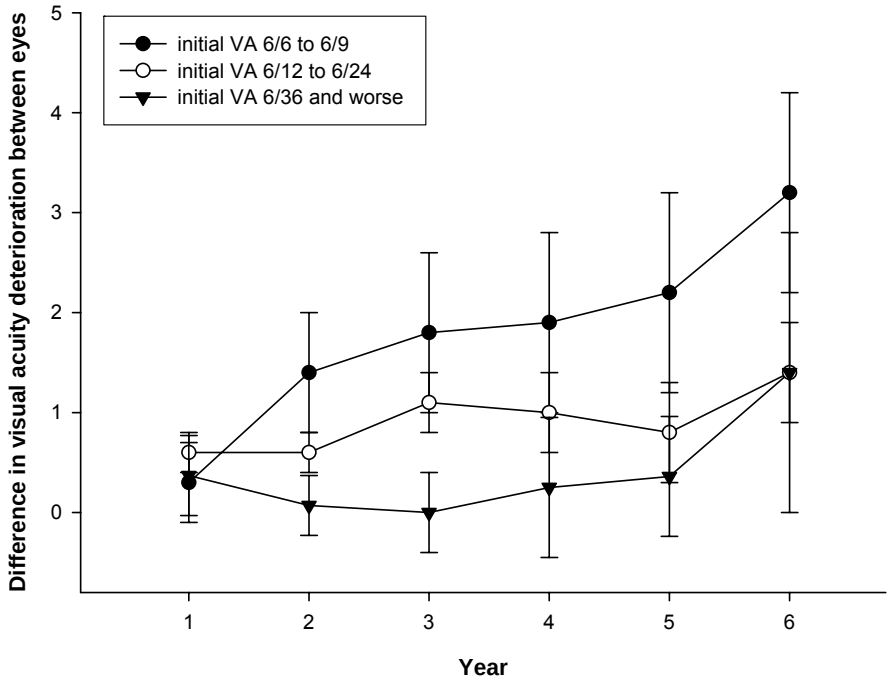

Figure 5 British Multicentre Study of photocoagulation for diabetic maculopathy, difference in visual acuity (lines) between treated and untreated eyes by initial visual acuity.

The largest study of photocoagulation (argon laser) for diabetic macular oedema was the Early Treatment Diabetic Retinopathy Study (ETDRS)[22,34,35]. The study included 5070 eyes with macular oedema and retinopathy. Eyes with macular oedema and less severe retinopathy were randomised to early photocoagulation versus deferral, the early photocoagulation group was further randomised into four groups: immediate focal photocoagulation, with mild or full scatter photocoagulation added if severe nonproliferative or early proliferative retinopathy developed during follow-up, or immediate scatter photocoagulation (mild or full) with focal photocoagulation delayed for at least four months. Eyes with macular oedema and more severe retinopathy were randomised to early photocoagulation versus deferral, the early photocoagulation group was also randomised into four groups: immediate focal and scatter photocoagulation (mild or full), or immediate scatter photocoagulation (mild or full) and focal photocoagulation delayed for at least four months. Follow-up data were published for up to five years and are shown in figure 6. Visual acuity results were reported for severe visual loss (best corrected visual acuity <5/200) at two consecutive follow-up visits (four month intervals)) and for moderate visual loss (loss of 15 or more letters between baseline and follow-up visit, equivalent to doubling of visual angle). For severe visual loss, analyses including the whole follow-up period revealed no statistically significant differences between and of the strategies of early photocoagulation and deferral within each disease category (macular oedema and less or more severe retinopathy). Relative risks for severe visual loss for all photocoagulation versus deferral were 0.59 (99% CI 0.32 to 1.09) for macular oedema and less severe retinopathy at baseline, and 0.70 (99% CI 0.44 to 1.11) for macular oedema and more severe retinopathy at baseline. There were some significant reductions in development of moderate visual loss in eyes treated with immediate focal photocoagulation, and these occurred earlier in eyes with macular oedema and less severe retinopathy (beginning in the first year of follow-up) and later for eyes with macular oedema and more severe retinopathy. For peripheral visual field measurements, scores for visual field worsened in all groups during follow-up. Scores for eyes assigned to immediate full scatter photocoagulation remained significantly worse than those for eyes assigned to referral ($p<0.001$). Similarly, there were more occurrences of reduced central visual field (paracentral scotoma) in patients assigned to immediate full scatter photocoagulation compared to referral ($p<0.001$). Some adverse effects of scatter photocoagulation on visual function were seen in the months immediately following photocoagulation. For macular oedema with less severe retinopathy, immediate focal coagulation with delayed scatter was the most effective strategy for reducing the risk of moderate visual loss. For macular oedema with more severe retinopathy, mild scatter combined with immediate focal coagulation was associated with the least visual loss (both moderate and severe).

Olk et al. conducted two similar randomised controlled trials, both in patients with diffuse diabetic macular oedema. One trial involving 92 patients (160 eyes) compared modified grid argon (blue-green) laser photocoagulation with observation[23], and the other involving 132 patients (225 eyes) compared argon green with krypton red photocoagulation[21]. Each trial reported outcome data for one and two years' follow-up, and outcome data for the laser treatments of the two trials taken together are reported for up to five years[36]. However, there were relatively large losses to follow-up; in the argon laser versus observation trial, only 49.4% of the initial eyes were left at the 24 month follow-up, in the argon versus krypton trial, 66% of eyes were left at 24 months. At five years, only 16% of the eyes examined at baseline were followed up.

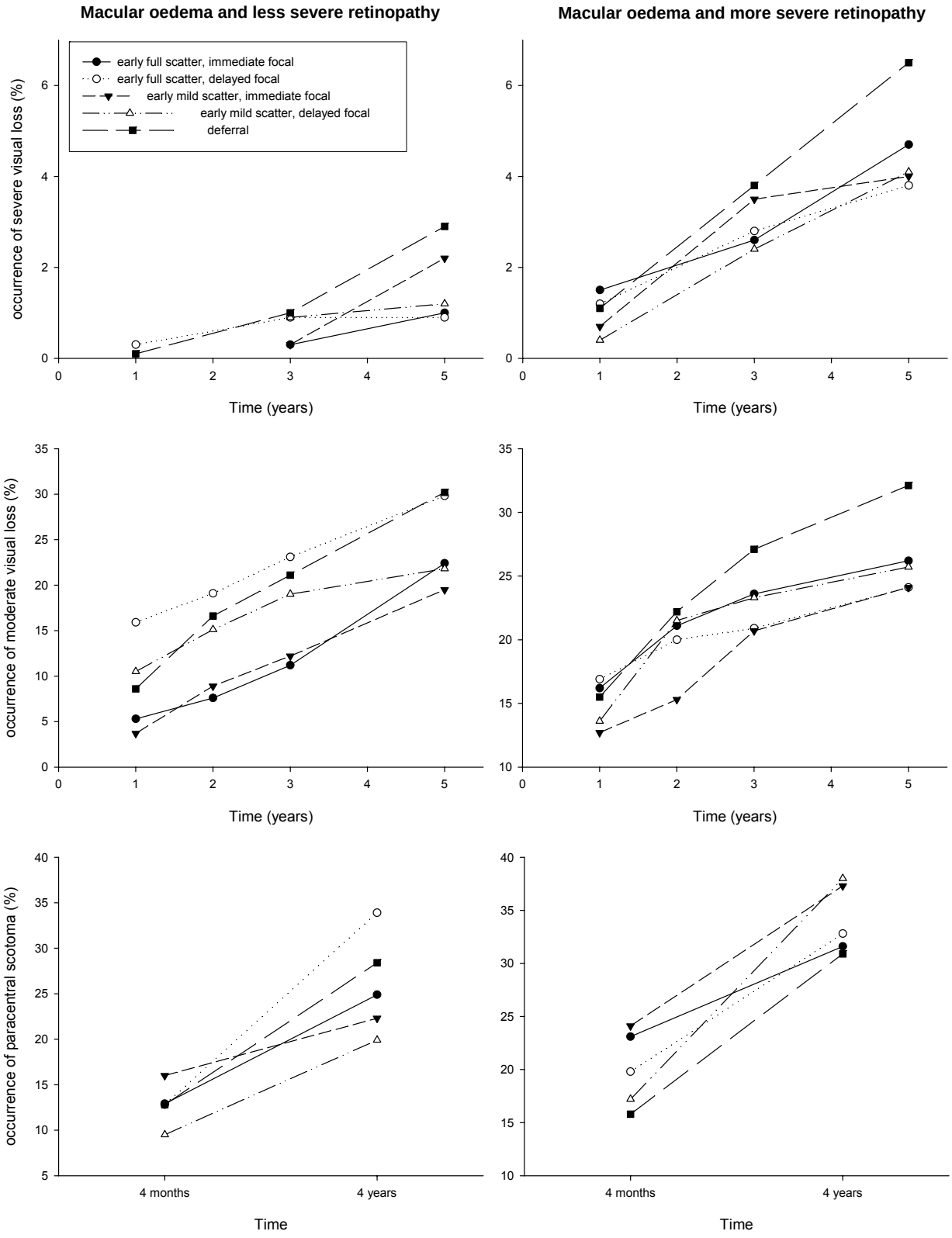

Figure 6 Early Treatment Diabetic Retinopathy Study (EDTRS), results for visual loss and central visual field.

Changes in visual acuity were only reported as changes “worsening”, “no change” or “improvement”, which for the argon versus observation trial was defined as change of two or more lines, and for the other two reports as change of three or more lines on the EDTRS chart. Results are shown in figure 7. At 24 months, of the eyes included in the argon versus observation trial, 45.2% had improved their visual acuity in the photocoagulation group compared with only 8.1% of eyes in the observation group (p=0.00031). Similarly, 43% of eyes in the observation group had worsened, compared to 10% in the treatment group (p=0.0007).

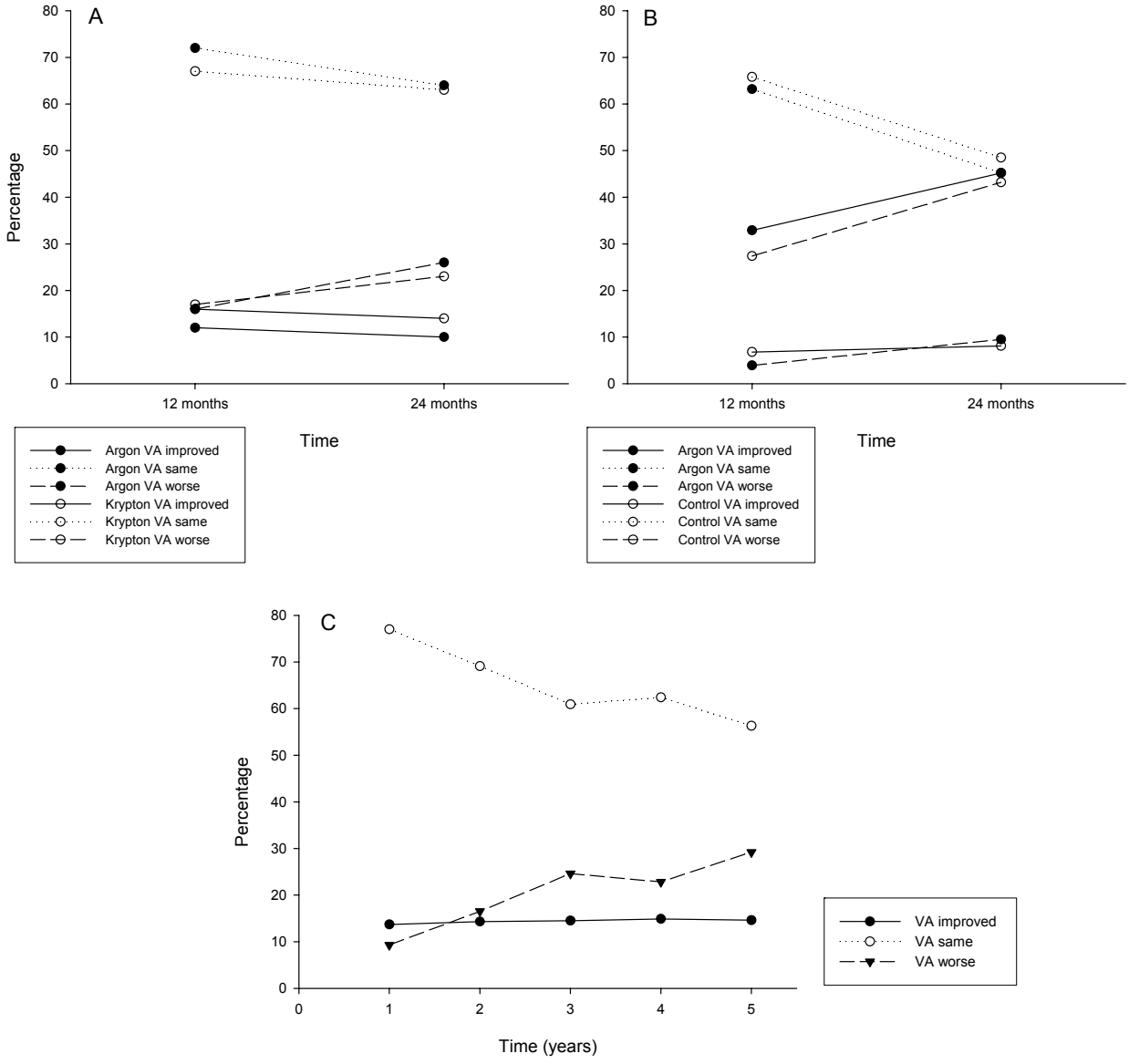

Figure 7 Trials by Olk et al. A: argon green versus krypton red modified grid laser photocoagulation, B: argon green versus observation, C: five-year follow-up data for all laser treatments taken together.

In the argon green versus krypton red trial, only 10 (argon) and 14% (krypton) of eyes had improved vision at 24 months, and 26 (argon) and 23% (krypton) had a worsened visual acuity (which could be due to a slightly different definition of visual change between the trials, see above). There was no significant difference

between the two laser treatments. Presence of hypertension, presence of systemic vascular disease, initial visual acuity, and presence of cystoid macular oedema had no significant effect on the results in both trials. As concerns side effects of the intervention, the majority of patients treated with either type of photocoagulation complained of either paracentral gridlike scotoma or a “haze or film” over the treated eye. This gradually diminished over time but was still evident at the 24 month visit. Over the five year follow-up, the proportion of eyes with improved vision remained relatively stable, whereas the proportion of eyes with worsened visual acuity increased progressively (to 29.2% at five years), and the proportion of eyes with unchanged visual acuity decreased progressively (to 56.3%).

SUMMARY DIABETIC MACULOPATHY

Incidence / prevalence of diabetic maculopathy

- A systematic review reported UK prevalence values of 2.3 to 6.4% of clinically significant (sight-threatening) macular oedema in type 1 diabetes patients and 6.4 to 6.8% in mixed type 1 / type 2 diabetes cohorts.
- One cohort study from the UK reported prevalence values of 11.5% for type 1 diabetes patients, 4.1% for non-insulin-requiring type 2 patients, and 9.1% for insulin-requiring type 2 patients. Prevalence for the whole population was 6.1%. After nearly two years, total prevalence had risen to 7.1%, with an incidence of new clinically significant maculopathy of 4.79%. After 4.3 years, prevalence was at 8.6% and incidence at 5.18%.
- Both prevalence and incidence increase with increasing diabetes duration and tends to be higher in insulin-treated type 2 diabetes patients than in non-insulin-treated type 2 diabetes patients. Other risk factors include poor blood glucose control (high levels of HbA1c) and hypertension.

Progression

- The Wisconsin Epidemiologic Study of Diabetic Retinopathy reported 14-year incidences of 49.6% for visual impairment, 46.3% for doubling of visual angle, and 19.4% for blindness in type 1 diabetes patients with macular oedema.
- Another observational study with baseline visual acuities of 6/6 to 6/6.3 in type 2 diabetes patients, reported 10-year visual acuities of 20/27 (~6/8) for right eyes with maculopathy and of 20/34 (~6/10) for left eyes with maculopathy.
- In the British Multicentre Study of photocoagulation for diabetic maculopathy, mean visual acuity deteriorated by less than one line in the treated eyes over the five years of follow-up, whereas it deteriorated by more than two lines in the control group ($p<0.01$). The treatment effect was greatest (both in terms of loss of visual acuity and development of blindness) in patients with initial visual acuities between 6/6 and 6/9.
- In the Early Treatment Diabetic Retinopathy Study (ETDRS), for macular oedema with less severe retinopathy, immediate focal coagulation with delayed scatter was the most effective strategy for reducing the risk of moderate visual loss; for macular oedema with more severe retinopathy, mild scatter combined with immediate focal coagulation was associated with the least visual loss (both moderate and severe).
- Laser photocoagulation tended to carry a risk of paracentral scotoma (reduced central visual field).

4.3 Age-related macular degeneration (progression)

For age-related macular degeneration, 31 papers were examined in full. These were mainly primary studies, and a supplementary search for systematic reviews identified relevant systematic reviews covering the subject areas of the primary studies. The systematic reviews were considered better evidence; therefore 12 systematic reviews were included. Four of these were dealing with the natural history of age-related macular degeneration[37-40], and the remaining eight were dealing with treatments[41-48]. For all reviews, follow-up data were reported for at least one year.

4.3.1 Natural history

We identified four systematic reviews reporting on the natural progression of age-related macular degeneration. All of them included a meta-analysis, i.e. a statistical summary of results from included studies. The reviews all had a slightly different emphasis, one dealing with visual loss in age-related macular degeneration in general with respect to the UK population, one dealing with neovascular age-related macular degeneration, one dealing with occult choroidal neovascularisation associated with age-related macular degeneration, and one dealing with subfoveal exudation associated with age-related macular degeneration. The reviews are summarised in table 6.

Owen et al. (2003)[37] included studies relevant to visual loss in patients with age-related macular degeneration of representative population based samples from predominantly white populations. All forms of age-related macular degeneration were included. For the analysis, data for relevant studies were requested so that incidence of partial sight and blindness could be estimated for different age groups. Data for six studies were obtained and these formed the basis of the analysis, including a total of 22206 participants. For the purpose of the study, in the absence of collection / presentation of visual field data for some of the studies, partial sight was defined as visual acuities in the better eye between 6/18 and better than 6/60, partial sight / blindness was defined as visual acuities between 6/60 and 3/60, and pure blindness as visual acuities below 3/60. All categories together are referred to as visual impairment. Results are shown in figure 8.

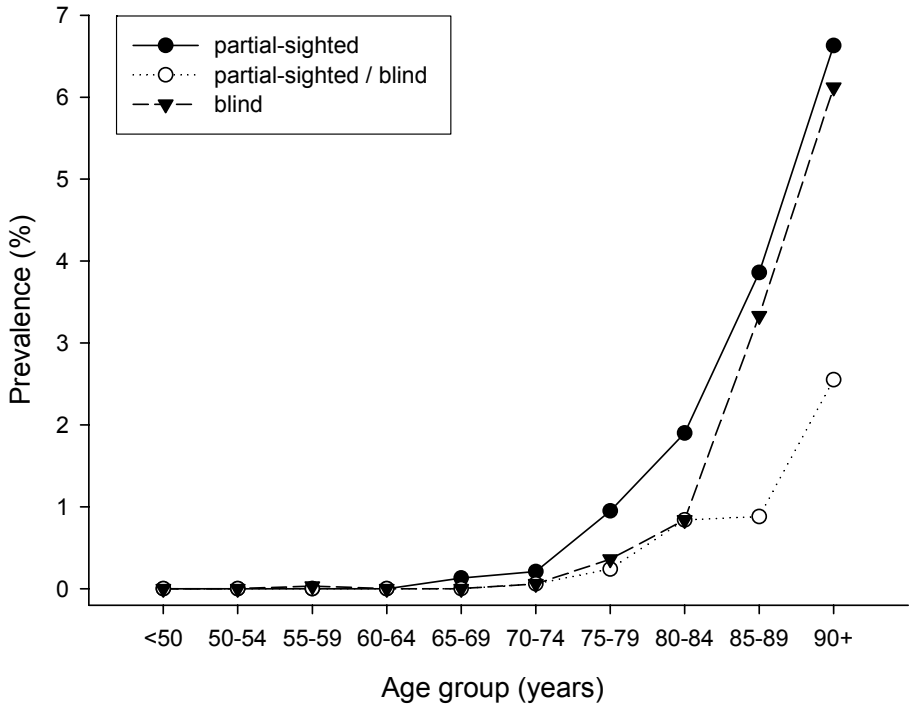

Figure 8 Owen et al. (2003): increase in prevalence of partial-sightedness, partial-sightedness / blindness, and blindness by age group in patients with age-related macular degeneration (population samples).

Prevalence of visual impairment due to age-related macular degeneration below age 70 was low, and increased exponentially from age 70 to age 85. In the 70 to 74 age band, prevalence for partial sight, partial sight / blindness and blindness were 0.21 (95% CI 0.09 to 0.44), 0.06 (95% CI 0.01 to 0.22) and 0.06% (95% CI 0.01 to 0.22) respectively, whereas in the 85 to 89 age group prevalence were 3.86 (95% CI 2.43 to 5.79), 0.88 (95% CI 0.29 to 2.04) and 3.33% (95% CI 2.02 to 5.16) respectively. Prevalence values for the different stages of visual impairment and for geographical and neovascular age related macular degeneration were applied to predictions of population growth for the UK population for the years 2001 and 2011. Visual impairment was predicted for 214,000 people in the UK with age-related macular degeneration in the year 2001 and 239,000 in the year 2011. In the year 2001, 109,000 of these were partial-sighted, 34,000 were partial-sighted/blind, and 71,000 were blind. For the year 2011, 121,000 were predicted to be partial-sighted, 38,000 partial-sighted/blind, and 80,000 blind.

Wong et al. (2007)[40] conducted a systematic review and meta-analysis on the natural history and prognosis of neovascular age-related macular degeneration. Standard systematic review methodology was used and results were summarised statistically in a meta-analysis. Fifty-three primary studies with a total of 4362 participants were included. Included studies were mostly of high quality. The studies included 28 randomised controlled trials, and 12 prospective and 13 retrospective observational studies. Data for untreated neovascular age-related macular degeneration were summarised. Mean patient age for all studies was 74 years (range 67 to 80) and 57.5% of patients were female. Where reported, 72.4% of patients had unilateral choroidal neovascularisation and 54.9% had concurrent hypertension. Results were reported for a follow-up time of up to three years. Some of the results are shown in figure 9. Mean baseline visual acuity was 0.64

logMAR (~6/26) (range 0.4 to 1.0 logMAR (6/15 to 6/60)). The mean change in visual acuity ranged from 0.1 logMAR (one line lost) at three months (11 studies with 770 patients) to 0.3 logMAR (three lines lost) at 12 months (12 studies with 944 patients) and 0.4 logMAR (four lines lost) at 24 months. There was no difference in results between randomised controlled trials and cohort studies. The percentage of patients with severe visual loss (more than six lines lost) increased from 19.8% at six months to 43.3% at three years. The proportion of patients losing fewer than three lines decreased from 65% to 43.6% over the same period (see figure 9). The proportion of patients whose visual acuity worsened increased from 45% at three months to 81.1% at two years. Visual acuity was worse than 20/200 (6/60) (legal blindness) in 19.7% of patients at baseline, this increased to 50.3% by three months and 77.6% by three years. Patients with occult choroidal neovascularisation appeared to have less of a visual loss than patients with classic choroidal neovascularisation (33.2 versus 43.7% loss of three to six lines of visual acuity by 12 months). However, this difference was not significant.

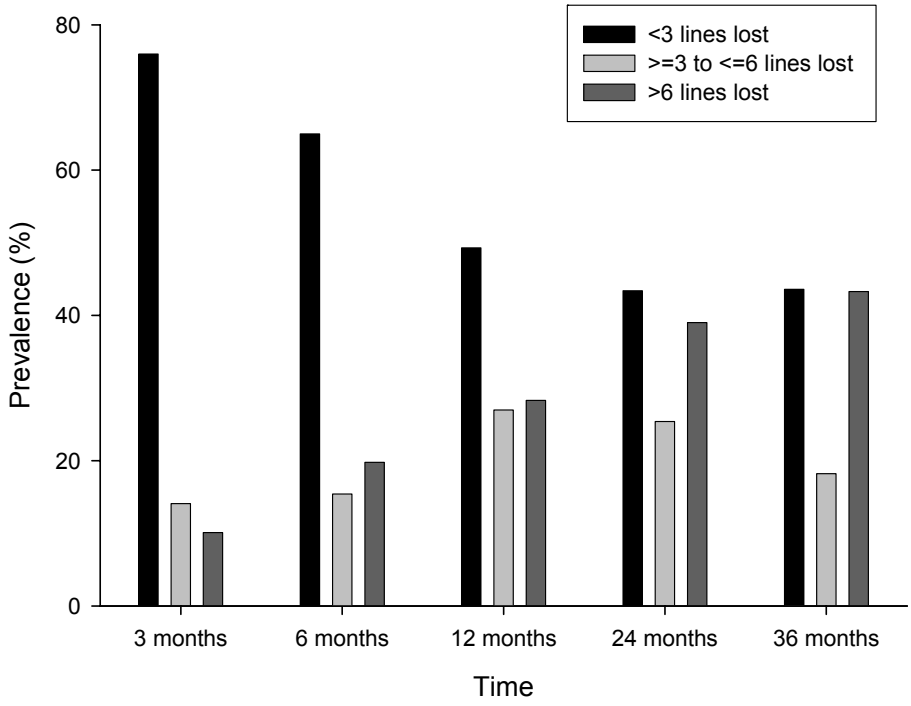

Figure 9 Wong et al. (2007): prevalence of visual loss over time with neovascular age-related macular degeneration.

Polito et al. (2006)[38] assessed the natural history of occult choroidal neovascularisation associated with age-related macular degeneration in a systematic review and meta-analysis. Standard systematic review methodology was used, although there was a limited description of study assessment. The review included eight studies; six of these were randomised controlled trials and two were observational case series. For the trials, data from eyes assigned to the control groups were used for the analysis. Results were reported as vision loss, which was either moderate (at least two or three or more lines lost, depending on the study) or severe (six lines or more lost). At least moderate vision loss was observed in 58.9% (95% CI, 53.4 to 64.5%) of patients at one year, and in 70.1% (95% CI, 64.0 to 76.3%) of patients at two to three years. Severe vision loss was observed in 33.7% (95% CI, 24.8 to 42.7%) of patients at one year, and in 47.2% (95% CI, 40.2 to

54.4%) of patients at two to three years. By one year of follow-up, 46.3% (95% CI, 39.0 to 53.6%) of patients had developed classic choroidal neovascularisation.

Shah et al. (2006)[39] performed a meta-analysis on the progression of visual loss in patients with subfoveal exudation in age-related macular degeneration. Control eye data from six randomised controlled trials in patients with exudative age-related macular degeneration were included. There was a broad variation in initial visual acuity when comparing these trials (ranging from 19 letters read to 52.6 letters read). Therefore, a horizontal translation factor was introduced to facilitate correlation analysis of a cumulative trend line. The cumulative visual acuity data for untreated control eyes fitted a straight line on a double reciprocal plot (r^2=0.95) (1/(letters lost) as a function of 1/(time)). The slope of the line predicts that patients would lose half of the maximum final vision lost within 10.88 months of the onset of exudation.

Table 6 Progression of age-related macular degeneration – natural history

Study	Study characteristics	Methodology	Results
Owen 2003 *design:* systematic review and meta-analysis *follow-up:* unclear, data analysed by age groups rather than follow-up	• *condition:* age-related macular degeneration • *number of patients included:* 22206 • *number of studies included:* 6 (all large observational population studies)	• studies of representative population-based samples included (predominantly white populations) • authors of relevant studies identified were contacted to provide data on visual impairment for different age bands • meta-analysis using random effects model • prevalence reported for partial-sighted (best VA 6/18 to >6/60), partial-sighted / blind (best VA 6/60 to 3/60), blind (best VA <3/60) by 5-year age bands 50-90 years; visual impairment (best VA 6/18 or less). Binocular VA. • prevalence figures applied to UK population predictions	• see figure 8 predictions for UK population for visual impairment due to age-related macular degeneration *visual impairment (total, n in thousands)* • 2001: 214 (95% CI 151 to 310) • 2011: 239 (95% CI 168 to 346) *partial-sighted (n in thousands)* • 2001: 109 (95% CI 65 to 187) • 2011: 121 (95% CI 72 to 208) *partial-sighted / blind (n in thousands)* • 2001: 34 (95% CI 13 to 92) • 2011: 38 (95% CI 15 to 103) *blind (n in thousands)* • 2001: 71 (95% CI 38 to 140) • 2011: 80 (95% CI 43 to 157)
Polito 2006 *design:* systematic review and meta-analysis *follow-up:* 1 to 3 years	• *condition:* occult choroidal neovascularisation associated with age-related macular degeneration • *number of patients included:* 372 eyes • *number of studies included:* 8 (6 RCTs reported in 8 papers and 2 observational case series)	• methodology of study identification and selection described, no description of study assessment • in the case of RCTs, data from eyes assigned to the observation group were used • vision loss reported; moderate vision loss defined as loss of at least 2 or 3 or more (depending on study) lines of visual acuity; severe vision loss defined as loss of 6 lines or more	at least moderate vision loss • 1 year: 58.9% (95% CI, 53.4 to 64.5%) • 2-3 years: 70.1% (95% CI, 64.0 to 76.3%) severe vision loss • 1 year: 33.7% (95% CI, 24.8 to 42.7%) • 2-3 years: 47.2% (95% CI, 40.2 to 54.4%) development of classic choroidal neovascularisation • 1 year: 46.3% (95% CI, 39.0 to 53.6%)
Shah 2004 *design:* meta-analysis *follow-up:* 12 to 48 months	• *condition:* age-related macular degeneration with subfoveal exudation • *number of patients included:* not reported • *number of studies included:* 6 (all RCTs)	• methodology of study identification, selection, and assessment not described • data for control eyes of trials used for meta-analysis • meta-analysis using Lineweaver-Burke plots (double reciprocal plots); horizontal translation factor introduced to standardise initial visual acuities; cumulative trend line calculated (r^2) • time to half the maximum visual acuity loss reported	• r^2=0.9521 for trend line • time to half maximum vision loss 10.88 months after exudation onset

Study	Study characteristics	Methodology	Results
Wong 2007 *design:* systematic review and meta-analysis *follow-up:* 3 months to 3 years	• *condition:* neovascular age-related macular degeneration • *number of patients included:* 4362 • *number of studies included:* 53 (28 RCTs, 12 prospective observational, 13 retrospective observational)	• study identification, study selection, assessment of study quality, data analysis described • meta-analysis using random effects model • data from untreated eyes used • visual acuities reported for groups: ≥20/50, <20/50 to ≥20/100, <20/100 to ≥20/200, <20/200 to ≥20/400, <20/400; vision loss reported: <3 lines lost, ≥3 to ≤6 lines lost, >6 lines lost	• see figure 9 change in visual acuity: • mean baseline VA 0.64 logMAR • 3 months: logMAR change 0.1 (1 line lost, 11 studies (770 patients)) • 12 months: logMAR change 0.3 (3 lines lost, 12 studies (944 patients)) • 24 months: logMAR change 0.4 (4 lines lost, 8 studies (720 patients)) • no significant difference in visual acuity results between RCTs and non-RCTs • Outcome was best corrected visual acuity in all included studies except two that were uncorrected.

4.3.2 Treatment

Eight systematic reviews assessed treatments for age-related macular degeneration (mostly for neovascular age-related macular degeneration). Treatments assessed included photocoagulation, photodynamic therapy (two studies), pegaptanib, ranibizumab, radiotherapy, surgery, and antioxidant and mineral supplements. Five of the reviews were Cochrane systematic reviews of randomized controlled trials, two were Health Technology Assessments carried out on behalf of the UK National Institute for Health and Clinical Excellence, and one was a systematic review on studies of various designs. The main visual results of the treatments are shown in table 7. Most reviews (and studies) reported outcomes related to loss of vision, rather than absolute visual acuities.

The effect of laser photocoagulation in neovascular age-related macular degeneration was explored in a Cochrane review by Virgili and Bini (2007)[47]. The review included 15 randomised controlled trials, 11 of which examined direct photocoagulation of the choroidal neovascularisation, one examined perifoveal photocoagulation, and three trials examined grid photocoagulation. The total number of patients in the included trials was 2064. Most of the included studies were of good quality. Twelve trials compared laser treatment to observation, one compared photocoagulation to submacular surgery, and two trials compared different lasers. For the studies of direct photocoagulation of extrafoveal, juxtafoveal and subfoveal choroidal neovascularisation, the treatment effect in comparison to observation at three months' follow-up was in the direction of harm, with the relative risk of losing six or more lines of vision being 1.41 (95% CI 1.08 to 1.82) of laser treatment versus control. After two years' of follow-up the effect in comparison to observation was in the direction of benefit for the same comparison, with a relative risk of losing six or mores lines of vision of 0.67 (95% CI 0.53 to 0.83). For perifoveal photocoagulation of subfoveal neovascularisation a statistically significant benefit was only seen at two years, whereas for grid photocoagulation of subfoveal neovascularisation no benefit for the laser treatment was found. Also, no differences in visual acuity outcomes were found for photocoagulation versus submacular surgery and for argon versus krypton lasers. The authors concluded that laser photocoagulation is an effective method for halting visual loss in patients with extra-foveal well-defined choroidal neovascularisation in age-related macular degeneration. However, the benefits on juxtafoveal or subfoveal lesions are limited or delayed. Laser treatment of subfoveal neovascularisation may also be associated with iatrogenic scotoma (i.e. a loss of central visual field due to the treatment).

Wormald et al. (2007)[48] performed a Cochrane review comparing photodynamic therapy with verteporfin compared to control (5% dextrose in water) for patients with neovascular age-related macular degeneration. Three randomised controlled trials were included in their analysis, studying a total of 1022 patients. All trials had a high quality rating. Participants received on average five treatments over two years. Visual loss was reported as the relative risk of losing three or more or six or more lines. After two years, the risk of losing three or six lines of vision was significantly reduced with verteporfin therapy (relative risk of losing three lines or more lines by two years 0.78 (95% CI, 0.7 to 0.87), relative risk of losing six or more lines 0.60 (95% CI, 0.49 to 0.73)). The mean number of lines lost was only reported for one trial and was 2.7 lines in the intervention group and 3.9 lines in the control group (a significant difference of 1.2 lines ($p<0.001$). Change in

central visual field function was reported for one trial. The mean area of the absolute scotoma increased significantly more in the placebo group than in the control group (2.5 mm^2 at baseline to 7.3 mm^2 at 24 months in the intervention group and 2.7 mm^2 to 31.5 mm^2 in the placebo group, $p<0.001$). The most serious adverse outcome of the treatment was acute (within seven days of treatment) severe visual decrease, which occurred in about one in 50 patients. The review authors concluded that photodynamic therapy was probably effective in reducing visual loss in patients with choroidal neovascularisation due to age-related macular degeneration but that further research was needed. A Health Technology Assessment[43] conducted on behalf of the UK National Institute of Clinical Excellence was completed earlier than the Cochrane review and only included two of the three trials, but the conclusions were essentially the same as those of the Cochrane review.

Sivagnanavel et al. (2004)[45] used Cochrane review methodology to summarise the evidence for the effects of radiotherapy versus control in neovascular age-related macular degeneration. Eleven trials including a total of 1078 participants were included. Trial quality was moderate. All trials used a similar method of delivering the radiotherapy treatment (external beam) and dosage ranged between 7.5 and 24 Gy. Control treatments were no treatment, sham irradiation or low dose irradiation (1 Gy). Outcomes were assessed for follow-up periods up to 24 months. There was considerable heterogeneity in outcomes at 12 months, and relative risks for losing three or more lines of vision ranged between 0.37 (95% CI, 0.15 to 0.90) and 1.22 (95% CI, 0.91 to 1.62). Relative risks for losing six or more lines of vision ranged between 0.21 (95% CI, 0.07 to 0.68) and 1.23 (95% CI, 0.56 to 2.68). There was less heterogeneity for results at 24 months, and the overall relative risk of losing six or more lines of vision was 0.76 (95% CI, 0.56 to 0.99, p=0.04). The pooled weighted mean difference in visual acuity as a continuous outcome was 0.02 logMAR (95% CI -0.06 to 0.11) at 12 months. The incidence of adverse events was low in all trials included. The review authors concluded that although radiotherapy may have a moderate treatment benefit, the results could not support a role for external beam radiotherapy in people with neovascular age-related macular degeneration.

In another Cochrane review, Evans (2006)[41] examined the effects of vitamin and mineral supplements compared to a control intervention for slowing the progression of age-related macular degeneration. Eight trials including a total of 5369 patients were included (this included a large US trial with 3640 participants (AREDS)). Various interventions were examined in the trials, including zinc, a broad spectrum antioxidant complex, vitamin E, and an antioxidant combination of vitamins C, E and beta-carotene with or without supplemental zinc. The studies seem to have been of good methodological quality. Overall, vitamin and mineral supplementation appeared to reduce visual loss in patients with age-related macular degeneration compared to placebo. The adjusted odds ratio for losing 15 or more letters over a follow-up period of up to seven years was 0.81 (95% CI 0.67 to 0.98, p=0.03). However, this result was only significant when using a fixed effects model and became non-significant when using a random effects model. Only the AREDS trial reported the effect of multivitamin supplements on loss of three or more lines (over a period of six years) and the visual acuity loss was significantly reduced in the multivitamin group (OR 0.77 (95% CI 0.62 to 0.96)). Similarly, zinc supplementation (two trials) significantly reduced visual acuity loss (follow-up two to six years) (OR for the loss of three or more lines 0.81 (95% CI 0.66 to 0.99)). The review authors conclude that antioxidant and mineral supplementation may slow the progression of age-related macular degeneration, but that the evidence is limited as it comes mainly from one large trial in a relatively well-nourished American

population and may not be generalisable to other populations. Long-term harmful effects of vitamin supplementation are unclear.

Reddy and Krzystolik (2006)[44] examined the effects of antiangiogenic therapy with interferon alfa-2a in neovascular age-related macular degeneration using Cochrane review methodology. Only one relevant randomised controlled trial was identified which included 481 patients from 45 centres worldwide and which compared interferon alfa-2a treatment (1.5, 3, and 6 MIU) with placebo over a period of 52 weeks. The trial was of good methodological quality. Visual loss was reported as loss of three or more lines of vision. The odds ratio for all three treatment groups versus placebo at 52 weeks was 1.60 (95% CI 1.01 to 2.53), indicating a 60% increase in the odds of losing three or more lines with interferon treatment and suggesting that the treatment has more harm than benefit.

Takeda et al. (2007)[46] carried out a Health Technology Assessment for the UK National Institute for Health and Clinical Excellence on the effects of pegaptanib and ranibizumab for neovascular age-related macular degeneration. Five good quality randomised controlled trials were included in the analysis, two on pegaptanib (the VISION study, comprising two concurrent trials) and three on ranibizumab. Only licensed doses of the drugs were considered by the review authors (0.3 mg for pegaptanib (injected every six weeks) and 0.5 mg for ranibizumab (injected monthly)). The VISION studies (n=601) compared pegaptanib with sham injection; and of the ranibizumab trials, the MARINA study (n=478) compared ranibizumab with sham injection, the ANCHOR study (n=283) compared ranibizumab plus sham photodynamic therapy with sham injection plus verteporfin photodynamic therapy, and the FOCUS study (n=162) compared ranibizumab plus photodynamic therapy with sham injection plus photodynamic therapy. The lesions considered by the studies were also different. The VISION studies included all lesions types of neovascularisation, the MARINA study included patients with occult or minimally classic neovascularisation, the ANCHOR study included patients with predominantly classic neovascularisation, and the FOCUS study included patients with both minimally and predominantly classic neovascularisation. Two year outcomes were only reported for the MARINA study. In the VISION studies during one year follow-up, 70% (95% CI 64.8 to 75.2%) of patients lost less than 15 letters with 0.3 mg pegaptanib compared to 55% (95% CI 49.8 to 61.0%, p<0.001) in the control group (RR 1.26 (95% CI 1.11 to 1.44)). Visual acuity changed by a mean of -7.5 letters in the intervention group compared to a mean of -14.5 letters in the control group (p<0.002). The proportion of patients with a visual acuity of 6/60 or worse at 12 months was 38% (95% CI 32.2 to 43.3%) in the intervention group and 56% (95% CI 50.1 to 61.4%, p<0.001) in the control group (RR 0.68 (95% CI 0.57 to 0.81)). In the MARINA study after two years of follow-up, 90.0% (95% CI 86.2 to 93.8%) of patients lost less than 15 letters with 0.5 mg ranibizumab compared to 52.9% (95% CI 46.6 to 59.3%, p<0.0001) in the control group (RR 1.70 (95% CI 1.50 to 1.93)). Visual acuity changed by a mean of +6.6 letters in the intervention group compared to a mean of -14.9 letters in the control group (p<0.0001). The proportion of patients with a visual acuity of 6/60 or worse at 24 months was 15% (95% CI 10.5 to 19.5%) in the intervention group and 47.9% (95% CI 41.6 to 54.3%, p<0.0001) in the control group (RR 0.31 (95% CI 0.23 to 0.44)). In the ANCHOR study after one year of follow-up, 96.4% (95% CI 93.3 to 99.5%) of patients lost less than 15 letters with 0.5 mg ranibizumab compared to 64.3% (95% CI 56.5 to 72.2%, p<0.001) with photodynamic therapy (RR 1.50 (95% CI 1.32 to 1.70)). Visual acuity changed by a mean of +11.3 letters in the intervention group compared to a mean of -9.5 letters in the control group (p<0.0001). The proportion of patients with a visual acuity of 6/60 or worse at

24 months was 16.4% (95% CI 10.4 to 22.7%) in the intervention group and 60.1% (95% CI 52.1 to 68.1%, p<0.0001) in the control group (RR 0.28 (95% CI 0.19 to 0.41)). In the FOCUS study after one year of follow-up, 90.5% (95% CI 84.9 to 96.1%) of patients lost less than 15 letters with 0.5 mg ranibizumab plus photodynamic therapy compared to 67.9% (95% CI 55.6 to 80.1%, p<0.001) with photodynamic therapy alone (RR 1.33 (95% CI 1.10 to 1.61)). Visual acuity changed by a mean of +4.9 letters in the intervention group compared to a mean of -8.2 letters in the control group (p<0.0001). The proportion of patients with a visual acuity of 6/60 or worse at 24 months was 29.5% (95% CI 20.8 to 38.2%) in the intervention group and 46.4% (95% CI 33.4 to 59.5%, p=0.006) in the control group (RR 0.64 (95% CI 0.42 to 0.96)). Adverse effects were common but were mostly mild to moderate transient events with serious ocular events being rare. The review authors concluded that both pegaptanib and ranibizumab appeared to be effective at slowing or stopping the progression of neovascular age-related macular degeneration. Ranibizumab was shown to be more effective than both control and photodynamic therapy and with various lesion types. Ranibizumab also appeared to be more effective than pegaptanib by indirect comparison.

Falkner et al. (2007)[42] conducted a systematic review and meta-analysis of surgical procedures for age-related macular degeneration, including removal of subfoveal choroidal neovascularisation, macular translocation, transplantation of pigment epithelium, and removal of subretinal haemorrhage, to compare the results to the results of the Submacular Surgery Trials, which did not show any benefits for surgery for subfoveal choroidal neovascularisation or surgery for haemorrhagic choroidal neovascularisation compared to control. Standard systematic review methodology was used, and 88 studies including a total of 1915 cases were included. Most of the studies were case series or poor quality cohort studies. The review included 765 cases after removal of subfoveal mostly classic choroidal neovascularisation with, 792 cases after macular transplantation, 94 cases with classic and occult choroidal neovascularisation after transplantation of pigment epithelium, and 264 cases with removal of subretinal haemorrhage. Follow-up periods ranged between six and 12 months. Visual acuity change was defined as a change by two or more lines. For removal of subfoveal neovascularisation, 28% of patients showed an improvement in vision and 25% showed a deterioration; for macular transplantation, 31% of patients showed an improvement and 27% showed a deterioration; for transplantation of pigment epithelium, 22% of patients showed an improvement and 21% showed a deterioration; and for removal of subretinal haemorrhage, 62% of patients showed an improvement and 13% showed a deterioration. Complication rates were 50% (range 12 to 100%) for removal of subfoveal neovascularisation, 71% (range 8 to 100%) for macular transplantation, 61% (range 29 to 100%) for transplantation of pigment epithelium, and 39% (range 0 to 100%) for removal of subretinal haemorrhage. The authors of the review suggest that there may still be indications for submacular surgery, such as patients with age-related macular degeneration with low preoperative visual acuity due to large haemorrhagic or fibrotic membranes or non-responders to photodynamic therapy.

Table 7 Effects of treatments on visual outcomes in age-related macular degeneration.

Treatment	Condition	Time of assessment	Main visual acuity outcome
Laser photocoagulation versus observation (n=2064)	neovascular age-related macular degeneration	3 months	*RR of losing 6+ lines* 1.41 (95% CI, 1.08 to 1.82)
		2 years	*RR of losing 6+ lines* 0.67 (95% CI, 0.53 to 0.83)
Photodynamic therapy (verteporfin) versus control (5% dextrose in water) (n=1022)	neovascular age-related macular degeneration	2 years	*RR of losing 3+ lines* 0.78 (95% CI, 0.7 to 0.87) *RR of losing 6+ lines* 0.60 (95% CI, 0.49 to 0.73)
Radiotherapy versus control (no treatment, sham irradiation or very low-dose irradiation)(n=1078)	neovascular age-related macular degeneration	12 months	*RR of losing 3+ lines* range 0.37 (95% CI, 0.15 to 0.90) to 1.22 (95% CI, 0.91 to 1.62) *RR of losing 6+ lines* range 0.21 (95% CI, 0.07 to 0.68) to 1.23 (95% CI, 0.56 to 2.68)
		2 years	*RR of losing 6+ lines* 0.76 (95% CI, 0.56 to 0.99, p=0.04)
Antioxidant vitamin and mineral supplements (n=5369)	age-related macular degeneration	1 to 7 years	*OR losing 3+ lines* multivitamins 0.77 (95% CI 0.62 to 0.96) *OR losing 3+ lines* zinc 0.81 (95% CI 0.66 to 0.99)
Interferon alfa 2a versus placebo (n=481)	neovascular age-related macular degeneration	12 months	*OR of losing 3+ lines* 1.60 (95% CI 1.01 to 2.53, p=0.04) (treatment harmful)
Pegaptanib (0.3 mg) versus sham (n=601)	neovascular age-related macular degeneration	12 months	*loss of <15 letters* RR 1.26 (95% CI 1.11 to 1.44) *mean change in VA (letters)* -7.5 versus -14.5, p<0.002 *VA 6/60 or worse* RR 0.68 (95% CI 0.57 to 0.81)
Ranibizumab (0.5 mg) versus sham (n=478)	occult / minimally classic neovascular age-related macular degeneration	24 months	*loss of <15 letters* RR 1.70 (95% CI 1.50 to 1.93) *mean change in VA (letters)* 6.6 versus -14.9, p<0.0001 *VA 6/60 or worse* RR 0.31 (95% CI 0.23 to 0.44)
Ranibizumab (0.5 mg) plus sham versus sham plus photodynamic therapy (n=283)	neovascular age-related macular degeneration	12 months	*loss of <15 letters* RR 1.50 (95% CI 1.32 to 1.70) *mean change in VA (letters)* 11.3 versus -9.5, p<0.0001 *VA 6/60 or worse* RR 0.28 (95% CI 0.19 to 0.41)

Treatment	Condition	Time of assessment	Main visual acuity outcome
Ranibizumab (0.5 mg) plus photodynamic therapy versus sham plus photodynamic therapy (n=162)	neovascular age-related macular degeneration	12 months	*loss of <15 letters* RR 1.33 (95% CI 1.10 to 1.61) *mean change in VA (letters)* 4.9 versus -8.2, p<0.0001 *VA 6/60 or worse* RR 0.64 (95% CI 0.42 to 0.96)
Submacular surgery • removal of choroidal neovascularisation (n=765)	neovascular age-related macular degeneration	6 to 12 months	*VA change ≥2 lines* 28% improvement, 25% deterioration
• macular translocation (n=792)	neovascular age-related macular degeneration	6 to 12 months	*VA change ≥2 lines* 31% improvement, 27% deterioration
• transplantation of pigment epithelium (n=94)	neovascular age-related macular degeneration	6 to 12 months	*VA change ≥2 lines* 22% improvement, 21% deterioration
• removal of subretinal haemorrhage (n=264)	neovascular age-related macular degeneration	at least 6 months	*VA change ≥2 lines* 62% improvement, 13% deterioration

SUMMARY AGE-RELATED MACULAR DEGENERATION

- In patients with age-related macular degeneration, prevalence of partial sight, partial sight / blindness and blindness were reported to be 0.21, 0.06 and 0.06% respectively in patients 70 to 74 years old, and 3.86, 0.88 and 3.33% respectively in patients in 85 to 89 years old.
- In patients with neovascular age-related macular degeneration and a mean baseline visual acuity of 0.64 logMAR (~6/26) (range 0.4 to 1.0 logMAR (6/15 to 6/60)), the mean change in visual acuity ranged from 0.1 logMAR (one line lost) at three months to 0.3 logMAR (three lines lost) at 12 months, and 0.4 logMAR (four lines lost) at 24 months of follow-up.
- Patients with subfoveal exudation in age-related macular degeneration were predicted to have lost half of their maximum final vision lost within 10.88 months of the onset of exudation.
- The following treatments were shown to preserve vision in patients with neovascular age-related macular degeneration: laser photocoagulation of extra-foveal well-defined choroidal neovascularisation, photodynamic therapy, pegaptanib, ranibizumab.
- The following treatments were of limited use in preserving vision in patients with neovascular age-related macular degeneration: laser photocoagulation of juxtafoveal or subfoveal choroidal neovascularisation, radiotherapy, vitamin and mineral (zinc) supplements, submacular surgery.
- The following treatments were not recommended for patients with neovascular age-related macular degeneration: interferon alfa-2a.

5 Conclusion

Evidence on the prevalence / incidence of juvenile macular dystrophies was limited, with only one study from Northern France providing relevant data for several hereditary macular dystrophies. More evidence (of limited quality) was available for the progression of selected juvenile macular dystrophies, in particular Stargardt disease and Best's vitelliform macular dystrophy. In both conditions, visual outcomes beyond age 40 were quite poor.

Good evidence was available regarding the prevalence / incidence and progression of diabetic maculopathy and / or diabetic macular oedema. This was provided by a comprehensive epidemiological systematic review and a number of recent observational studies, as well as by a number of randomized controlled trials on treatment by photocoagulation. Both prevalence and incidence increased with diabetes duration. Other risk factors such as high blood glucose levels, insulin treatment and hypertension also played a role. For progression of diabetic maculopathy observational studies were available that reported both absolute visual acuities after 10 years' observation time, and incidence of visual impairment / doubling of visual angle over 14 years. Several large studies assessing laser photocoagulation were available and the results suggested that laser photocoagulation helped to preserve vision in patients with maculopathy but carried a risk of central visual field loss.

For the progression of age-related macular degeneration, most of the evidence – especially with respect to treatment – was concerned with neovascular age-related macular degeneration, although natural history systematic reviews considered different types of age-related macular degeneration. Various high quality systematic reviews were available both assessing the natural progression (absolute visual acuities and visual loss) of several types of age-related macular degeneration and on treatments. However, data on dry age-related macular degeneration were limited. Prevalence of partial sight and blindness due to age-related macular degeneration increased sharply beyond age 75 and within two years, patients with neovascular age-related macular degeneration tended to lose four lines of vision. Treatments shown to preserve vision in patients with neovascular age-related macular degeneration included laser photocoagulation of extra-foveal well-defined choroidal neovascularisation, photodynamic therapy, pegaptanib, and ranibizumab.

Unit and Method of Analyses

There are fundamental differences in the way visual acuity and visual fields are generally measured in group 1 drivers and study participants. This can be as basic as the unit of analyses being the eye as oppose to the person. Many studies are interested with monocular testing in the better seeing and/or worse seeing eye; this is particularly the case for treatment studies. In addition the descriptions of some of the studies in this report were not clear about how assessments were undertaken. For driving, group 1 license holders must be able to succeed at the "number plate" reading test, which is a binocular test that is not only predominantly an assessment of visual acuity but also will be influenced to some extent by visual field and other visual functions (e.g. glare). Where drivers require a field test this is still a binocular rather than monocular assessment. Therefore, the generalisability of some of the study results above to the assessment of group 1 drivers should be undertaken with caution due to these differences in assessments and the lack of clarity

regarding assessment in some studies. Some of these issues also extend to the assessment of group 2 drivers.

5.1 Limitations of this report

This is not a systematic review but a rapid assessment for relevant literature. Although the search strategies were broad and comprehensive for both systematic reviews and primary studies, the searches for the latter were restricted to cross-sectional and cohort studies assessing the prevalence/incidence of diabetic maculopathy and juvenile macular dystrophy or progression of juvenile macular dystrophy, diabetic maculopathy and age-related macular degeneration. To aid comprehensiveness the reference lists of relevant articles were scanned for further studies and further relevant studies were identified by this method. When selecting studies, systematic reviews of observational studies or randomised controlled trials were preferred, as these were expected to provide a more complete picture than single primary studies. In the absence of systematic reviews – and to cover relevant aspects not included in the systematic reviews – the next best evidence were considered to be large high quality cohort or cross-sectional studies to assess prevalence, large high quality cohort studies to assess incidence, large high quality cohort studies with a follow-up time of several years to assess progression, and large randomised controlled trials with follow-up times of several years to assess treatments in comparison to natural progression.

Most studies reported data relevant to visual acuity and visual loss, and only very limited information was available on visual field outcomes. Treatment studies in particular tended not to report absolute visual acuities and therefore only data relevant to prevention of visual loss could be reported. Some studies reported visual outcomes in visual acuity ranges already starting at relatively low levels of visual acuity, whereas for assessing ability to drive it would have been more relevant for data to be reported for visual acuity ranges relevant for driving. Furthermore, as mentioned above there is an issue with regard to the measurement of visual acuity and fields in studies and the relevance of these to driving standards.

Good quality evidence – particularly good quality systematic reviews – was available for the questions relating to diabetic maculopathy and age-related macular degeneration. For diabetic maculopathy, most studies assessed diabetic macular oedema, although some also included broader definitions of diabetic maculopathy. In the case of age-related macular degeneration, most studies were concerned with neovascular age-related macular degeneration.

The included studies may have been susceptible to various sources of bias. For example, some of the larger population studies and randomised controlled trials both for diabetic maculopathy and age-related macular degeneration were already published in the 1980s or early 1990s and due to changes over time, for example of standard treatments used, outcomes reported at the time might differ from those that would occur today. Also, natural history data obtained from cohort studies may differ from results obtained from control groups of randomised controlled trials, as the trials may have more restricted inclusion criteria for patients and patients in trials may therefore be less representative of the relevant patient population as a whole. In one meta-analysis[40] on the progression of age-related macular degeneration, this issue specifically was addressed in a subgroup analysis and no significant difference was found in visual outcomes between cohorts from trials

and cohorts from observational studies, but the situation could have been different for other studies. In the case of juvenile macular dystrophies, only lower quality studies could be identified and it was not always clear if they were true cohort studies or just case series. In all studies on Stargardt disease or Best's vitelliform macular dystrophy following patients up for prolonged periods of time, follow-up periods for individual patients varied greatly so that it is unclear to what extent "final outcomes" at a certain mean follow-up time really reflected the average progression that a cohort of patients followed up over a similar period of time would experience. One cross-sectional study listed outcome by age group which for a hereditary disease and in the absence of comparable follow-up data might present a way of estimating progression over time; but here again biases such as different factors regarding treatment, life experiences etc. in different age groups could influence the results and might yield less reliable results than if individual participants were followed over time. Studies of juvenile macular dystrophies mostly included children as well as adults, and it was not always clear what proportion of patients were children. Progression data could not be separated into data for adults and data for children.

While some of the studies reported here included UK populations, studies of populations expected to be similar to the UK (North America, Western Europe) were also included to complete the picture.

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7 Appendices

7.1 Appendix 1 – Outline methods

- The report will focus on
  a) The prevalence and/or incidence of diabetic maculopathy and juvenile macular dystrophy in adults. Age-related macular degeneration will not be included as it has been previously addressed in ARIF request 11 (prevalence of visual disorders by age group in older people).
  b) The long-term rate of progression of diabetic maculopathy, juvenile macular dystrophy and age-related macular degeneration in adults, focussing on visual field and visual acuity outcomes. In addition, where data are available, the effects of treatments on the rate of progression will be explored.
- MEDLINE (1966-2007), EMBASE (1980-2007) and the Cochrane Library (2007) will be searched using a comprehensive search strategy.
- The identified studies will be screened by an analyst for relevance.
- Cohort and cross-sectional studies which report the relevant outcomes will be selected and the most robust commented upon.
- In the first instance studies conducted in the UK will be searched for, as the prevalence and progression may vary according to ethnicity. If no robust UK studies are identified, searches will be broadened to outside of the UK.
- Methodological quality of these studies will be discussed.
- Data on relevant outcomes will be extracted and reported and where possible.

7.2 Appendix 2 – Search strategies

7.2.1 ARIF Reviews Protocol

SEARCH PROTOCOL FOR ARIF ENQUIRIES

(October 2007)

In the first instance the focus of ARIF's response to requests is to identify systematic reviews of research. The following will generally be searched, with the addition of any specialist sources as appropriate to the request.

1. Cochrane Library

- Cochrane Reviews
- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

2. ARIF Database

An in-house database of reviews compiled by scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

3. NHS CRD

- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4. Health Technology Assessments

- NICE guidance (all programmes)
- West Midlands Health Technology Assessment Collaboration
- Evidence Based Commissioning Collaboration (Trent R & D Support Unit). Links to Trent Purchasing Consortia reports and Wessex DEC reports (both no longer published)
- SBU – Swedish Council on Technology Assessment in Health Care
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Agency for Drugs and Technologies in Health
- New Zealand Health Technology Assessment
- Agency for Healthcare Research and Quality (AHRQ)
- Alberta Heritage Foundation
- McGill Medicine Technology Assessment Unit of MUHC (McGill University Health Centre)
- Monash reports – Centre for Clinical Effectiveness, Monash University
- US Department of Veterans Affairs
- NHS QIS (Quality Improvement Scotland)
- SIGN (Scottish Intercollegiate Guidelines Network)

5. Clinical Evidence

6. Bandolier

7. National Horizon Scanning Centre

8. TRIP Database

9. Bibliographic Databases

- Medline – systematic reviews
- Embase – systematic reviews
- Other specialist databases

10. Contacts

- Cochrane Collaboration (via Cochrane Library)
- Regional experts, especially Pharmacy Prescribing Unit, Keele University (& MTRAC) and West Midlands Drug Information Service for any enquiry involving drug products.

7.3.2. Primary Studies - Bibliographic database search strategies

Juvenile Macular Dystrophy: incidence and prevalence

Cochrane Library (See disease progression strategy below)

MEDLINE (Ovid) 1950-August 2007

1 juvenile macular dystrophy.mp.
2 macular dystrophy.mp.
3 Macular Degeneration/
4 adolescent/ or exp child/ or infant/
5 or/2-3
6 4 and 5
7 1 or 6
8 survey$.mp.
9 prevalence.mp.
10 incidence.mp.
11 cohort$.mp.
12 cohort studies/
13 or/8-12
14 7 and 13

EMBASE (Ovid)1980 - 2007
1 juvenile macular dystrophy.mp.
2 macular dystrophy.mp.
3 retina macula degeneration/
4 adolescent/ or child/ or infant/
5 or/2-3
6 4 and 5
7 1 or 6
8 survey$.mp.
9 prevalence.mp.
10 incidence.mp.
11 cohort$.mp.
12 or/8-11
13 7 and 12

Juvenile macular dystrophy: disease progression

Cochrane Library 2007 Issue 3

#1 juvenile next macular next dystrophy
#2 macular next dystrophy
#3 MeSH descriptor Macular Degeneration explode all trees
#4 (#2 OR #3)
#5 adolescent or child* or infant*
#6 (#4 AND #5)
#7 (#1 OR #6)

MEDLINE 1950 – Aug 2007

1 juvenile macular dystrophy.mp.
2 macular dystrophy.mp.
3 Macular Degeneration/
4 adolescent/ or exp child/ or infant/
5 or/2-3
6 4 and 5
7 1 or 6

8 limit 7 to "prognosis (optimized)"

EMBASE (Ovid) 1980 - 2007

1 juvenile macular dystrophy.mp.
2 macular dystrophy.mp.
3 retina macula degeneration/
4 adolescent/ or child/ or infant/
5 or/2-3
6 4 and 5
7 1 or 6
8 limit 7 to "prognosis (optimized)"

Diabetic maculopathy: incidence and prevalence

Cochrane Library 2007 Issue 3

#1 diabetic next maculopathy
#2 macular next edema
#3 macular next oedema
#4 csme
#5 maculopathy
#6 diabetes
#7 MeSH descriptor Diabetes Mellitus explode all trees
#8 (#2 OR #3 OR #4 OR #5)
#9 (#6 OR #7)
#10 (#8 AND #9)
#11 (#1 OR #10)
#12 survey*
#13 prevalence
#14 incidence
#15 cohort*
#16 MeSH descriptor Cohort Studies explode all trees
#17 (#12 OR #13 OR #14 OR #15 OR #16)
#18 (#11 AND #17)

MEDLINE (Ovid) 1950 to Aug 2007

1 diabetic maculopathy.mp.
2 macular edema, cystoid/
3 macular edema.mp.
4 macular oedema.mp.
5 csme.mp.
6 maculopathy.mp.
7 exp Diabetes Mellitus/
8 or/2-6
9 7 and 8
10 1 or 9
11 survey$.mp.
12 prevalence.mp.
13 incidence.mp.
14 cohort$.mp.
15 cohort studies/
16 or/11-15
17 10 and 16
18 limit 17 to "reviews (optimized)"

EMBASE (Ovid) 1980 – Aug 2007

1 exp retina maculopathy/
2 macular edema.mp.
3 macular oedema.mp.
4 csme.mp.

5 maculopathy.mp.
6 or/1-5
7 exp diabetes mellitus/
8 6 and 7
9 diabetic maculopathy.mp.
10 8 or 9
11 survey$.mp.
12 prevalence.mp.
13 incidence.mp.
14 cohort$.mp.
15 or/11-14
16 10 and 15
17 limit 16 to "reviews (2 or more terms min difference)"

Diabetic maculopathy: disease progression

Cochrane Library 2007 Issue 3

#1 diabetic next maculopathy
#2 macular next edema
#3 macular next oedema
#4 csme
#5 MeSH descriptor Macular Edema, Cystoid explode all trees
#6 maculopathy
#7 MeSH descriptor Diabetes Mellitus explode all trees
#8 (#2 OR #3 OR #4 OR #5 OR #6)
#9 diabetes
#10 (#7 OR #9)
#11 (#8 AND #10)
#12 (#1 OR #11)
#13 prognos* or predict* or course* or cohort*
#14 (#12 AND #13)

MEDLINE (Ovid) 1950 – Aug 2007

1 diabetic maculopathy.mp.
2 macular edema, cystoid/
3 macular edema.mp.
4 macular oedema.mp.
5 csme.mp.
6 maculopathy.mp.
7 exp diabetes mellitus/
8 or/2-6
9 7 and 8
10 1 or 9
11 limit 10 to "prognosis (optimized)"
12 limit 11 to "reviews (optimized)"

EMBASE (Ovid) 1980 – Aug 2007

1 exp retina maculopathy/
2 macular edema.mp.
3 macular oedema.mp.
4 csme.mp.
5 maculopathy.mp.
6 or/1-5
7 exp diabetes mellitus/
8 6 and 7
9 diabetic maculopathy.mp.
10 8 or 9
11 limit 10 to "prognosis (specificity)"
12 limit 11 to "reviews (2 or more terms min difference)"

Age Related Macular Degeneration: disease progression

Cochrane Library 2007 Issue 3

#1 age next related next macular next degeneration
#2 amd
#3 MeSH descriptor Macular Degeneration, this term only
#4 MeSH descriptor Retinal Degeneration, this term only
#5 (#1 OR #2 OR #3 OR #4)
#6 prognos* OR predict* OR course* OR cohort*
#7 (#5 AND #6)

MEDLINE (Ovid) 1950 - Aug 2007

1 macular degeneration/
2 retinal degeneration/
3 amd.mp.
4 age related macular degeneration.mp.
5 or/1-4
6 limit 5 to "prognosis (specificity)"
7 limit 6 to "reviews (optimized)"

EMBASE (Ovid) 1980 - Aug 2007

1 retina macula degeneration/
2 amd.mp.
3 age related macular degeneration.mp.
4 or/1-3
5 limit 4 to "prognosis (specificity)"
6 limit 5 to "reviews (2 or more terms min difference)"

7.3 Appendix 3 – Visual acuity conversion table

Table 8 Visual acuity conversion table[43]

4 m	6 m	20 ft	visual angle (minutes)	line of chart	distance tested (m)	decimal fraction	LogMAR unit	no. of letters read
		20/800		1	1	0.025	+1.6	5
		20/640	32	2	1	0.031	+1.5	10
		20/500		3	1	0.04	+1.4	15
	3/60	20/400		1	2	0.05	+1.3	20
		20/320	16	2	2	0.063	+1.2	25
		20/250		3	2	0.08	+1.1	30
4/40	6/60	20/200		4	2	0.1	+1.0	35
4/32	6/48	20/160	8	5	2	0.125	+0.9	40
4/25	6/38	20/125		6	2	0.16	+0.8	45
4/20	6/30	20/100		7	2	0.2	+0.7	50
4/16	6/24	20/80	4	8	2	0.25	+0.6	55
4/12	6/20	20/63		9	2	0.32	+0.5	60
4/10	6/15	20/50		10	2	0.4	+0.4	65
4/8	6/12	20/40	2	11	2	0.5	+0.3	70
4/6.3	6/10	20/32		12	2	0.63	+0.2	75
4/5	6/7.5	20/25		13	2	0.8	+0.1	80
4/4	6/6	20/20	1	14	2	1.00	0.0	85
4/3.2	6/5	20/16		12	4	1.25	-0.1	90
4/2.5	6/3.7	20/12.5		13	4	1.6	-0.2	95
4/2	6/3	20/10		14	4	2.00	-0.3	100