The psychological, social, and everyday visual impact of diabetic macular oedema and diabetic retinopathy: a systematic review

Running title: The impact of diabetic eye disease: a systematic review

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Conflicts of Interest

The authors have no conflicts of interest.

Research Statement

What is already known?

- Diabetic eye disease is a leading cause of preventable vision loss.
- Diabetic eye disease is negatively associated with health-related quality of life.

What are the new findings?

- There is considerable impact to visual functioning which is more impaired in people with greater disease severity.
- Diabetic eye disease limits activities including working, driving, walking and reading.
- Vision loss in diabetic retinopathy has the potential to negatively impact psychological well-being.

How might this impact on clinical practice in the foreseeable future?

- The review shows the importance in clinical practice to measure and consider the everyday impacts of diabetic retinopathy and diabetic macular oedema, which include psychological well-being, functional status, quality of life, and impacts on work.

Abstract

Aims

To synthesise evidence on the impact of diabetic retinopathy and diabetic macular oedema from the patient perspective.

Methods

A systematic literature review was conducted using MEDLINE Complete, PsycINFO, EMBASE, and AMED. We included articles investigating the impact of the condition on quality of life, symptoms, visual functioning, activities of daily living, well-being, social, and financial. Studies were observational; cross-sectional, prospective cohort and retrospective cohort study designs. Outcome data were extracted and synthesised. The review is registered on PROSPERO (CRD42018088254).

Results

Searches yielded 5114 publications. After screening, 85 studies were included, measuring the following outcomes: visual functioning (n=41), quality of life (n=23), well-being (n=16), functional status (n=14), work (n=2), and visual task performance (n=2). Diabetic retinopathy has a considerable impact on visual functioning, which is greater in people with greater disease severity. Diabetic retinopathy significantly limits activities including working, driving, walking and reading and has the potential to negatively impact psychological well-being.

Conclusions

Diabetic retinopathy is associated with poor self-reported visual functioning, well-being, and health-related quality of life. Ability to perform basic everyday tasks appears to diminish with disease

severity. Some studies suggest impaired mobility and problems with work but there are gaps in this evidence.

Keywords

Diabetes

Diabetic macular oedema

Diabetic retinopathy

Functional status

Patient reported outcomes

Psychological well-being

Quality of life

Visual acuity

Visual functioning

Work

Introduction

Diabetic eye disease is a leading cause of preventable vision loss in working age people [1], affecting approximately one third of individuals with diabetes worldwide [2]. It is responsible for 6.4% and 5.3% of sight impairment and severe sight impairment registrations respectively, in England and Wales [3]. Diabetic eye disease can be broadly classified into non-proliferative diabetic retinopathy, characterised by microaneurysms, intraretinal haemorrhages, venous beading or intra retinal microvascular abnormalities, and proliferative diabetic retinopathy, characterised by retinal neovascularisation. Diabetic maculopathy occurs when the macula is affected; this most commonly manifests as diabetic macular oedema (DME), where central vision loss results from thickening of the macula [4]. Proliferative diabetic retinopathy indicates greater severity of diabetic retinopathy in comparison to non-proliferative diabetic retinopathy, and proliferative diabetic retinopathy and DME are both considered sight-threatening forms of diabetic retinopathy.

As the number of people with DME and diabetic retinopathy increases [5-8], driven in part by increased longevity, it is important to understand the impact that these conditions have on the individual. This includes their everyday visual and functional abilities (i.e. ability to perform activities of daily living), psychological well-being, social functioning and quality of life. Reviews of the literature suggest that people with diabetic retinopathy experience poor health-related quality of life [9], particularly in the vision-threatening stage of the condition [10]. Reviews specific to DME are limited, but also suggest reduced vision and health-related quality of life [11]. These reviews have however, focused only on health or vision-related quality of life rather than explore the full spectrum of possible impact, lacked rigorous systematic review methodology and are limited by the lack of empirical evidence at the time of their publication. We hypothesise that there are other real-world impacts of importance in diabetic retinopathy and DME that previous reviews have not reported.

The aim of this systematic review is to therefore synthesise current evidence on the psychological, social, and everyday visual impact of DME and diabetic retinopathy from the patient

perspective. We aim to provide insight into the everyday lives of people with diabetic retinopathy and DME, by synthesising the impact of these conditions on psychological well-being, functional status, performance in everyday tasks, quality of life, work and visual functioning. This is the first review to integrate existing literature from all of these domains.

Participants and Methods

A systematic literature review was conducted in in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12] and the Guidance on the Conduct of Narrative Synthesis in Systematic Reviews [13]. The study is registered on the PROSPERO database, registration number CRD42018088254.

Participants

Adults (aged 18 years or older) with any form of diabetic eye disease, including all severities of non-proliferative retinopathy, maculopathy, and proliferative retinopathy.

Interventions or Comparators

This systematic review did not evaluate the effectiveness or efficacy of interventions or treatments for diabetic eye disease. Interventional studies were included in the review, but only to extract baseline data for the relevant outcomes. The included studies could be a single group design or include a comparison group, for example those with vision loss from another condition, the general population or those with diabetes but without diabetic eye disease.

Outcome

The systematic review aimed to assess the impact of diabetic eye disease from the patient perspective in relation to the following outcomes:

- Quality of life, including generic and health-related quality of life
- Symptoms, such as pain
- Self-reported visual disturbance
- Activities of daily living, such as loss of driving licence and physical functioning
- Psychological well-being, such as depression and anxiety
- Social impact on family relationships, and participation in social activities
- Economic impact; financial costs to patient, loss of earnings, absence or inability to work, work productivity, employment

These outcomes could be measured using validated or unvalidated scales, using either patient-reported, observer-reported or performance-based tools. The review excluded studies in which the only outcomes were utility values for health economic modelling purposes.

Study Type

Included studies were observational, which included cross-sectional, prospective cohort and retrospective cohort study designs. When observational studies included multiple assessment time points, all points were considered. Randomised controlled trials and quasi-experimental studies were included to extract the relevant data at baseline. Qualitative and case studies were excluded. All articles had to be published in peer-reviewed scientific journals and in English.

Search Strategy

The literature search was conducted in MEDLINE Complete, and PsycINFO (via EBSCOhost), and EMBASE, and AMED (via OVID) from inception to 31st January 2018. Medical subject heading (MeSH) terms were used to identify the most relevant articles (example shown of MEDLINE MeSH terms in appendix). Reference lists of included studies and any identified systematic reviews were also reviewed for relevant articles.

Studies were screened for inclusion using Covidence, a computerised literature review extraction software. Search results were imported directly into Covidence, where duplicates were removed. The title and abstract for each article were screened by two authors independently, followed by the full text articles of those deemed to be relevant. Any disagreements at either stage were discussed until consensus was reached, with a third reviewer acting as an adjudicator if needed.

Data analysis

The following information was extracted from the journal articles independently by the two reviewers; citation, study country, study type, study institution/sponsor, study objectives, study inclusion/exclusion criteria, sample size, study duration, participant characteristics (gender, age, disease type, treatment history, disease duration, disease severity, diabetes type, duration of diabetes), outcomes measured, results for each outcome, and overall conclusions. Study quality was assessed independently by two authors, using the 14-item standard quality assessment for evaluating primary research papers from a variety of fields [14]. Total scores range from 0 to 1 with 0 indicating the lowest and 1 the highest possible quality. Scores exceeding 0.55 or 0.75 may be considered acceptable, depending on whether a 'liberal' or 'conservative' viewpoint is taken [14]. Any item level disagreements were discussed until consensus was reached, with a third reviewer acting as an adjudicator if needed.

Results

The search yielded a total of 5114 publications. After duplicates were removed and studies were screened at abstract and full text level, 85 studies were deemed eligible for inclusion in the review (Figure 1). Details of each study included, including a summary of data extracted and quality appraisal scores can be found in Table 1. Mean quality appraisal score was 0.84 (standard deviation ±0.13, range 0.32 to 1.00). Depending on the threshold used, either 2 studies (using liberal threshold) or 15 studies (using conservative threshold) fell outside acceptable limits for quality scores. Most frequent sources of bias were related to failing to control for confounding (22% of studies) and failing to report some estimate of variance for main results (9% of studies). Studies were conducted across 21 countries, the most frequent of these were: USA (n=27); Australia (n=11); UK (n=6); Japan (n=5); Sweden (n=5); Singapore (n=4); Spain (n=4); Turkey (n=4). The majority of studies were of a cross-sectional design (n=49). Other designs included clinical trials and interventional studies (n=17), case control (n=5), cohort (n=12), and case series (n=4). In the 78 studies that reported their sample size the number of people with diabetic retinopathy ranged from 8-1097. The samples were either exclusively people with diabetic retinopathy or DME (n=55); other samples consisted of people with diabetes (n=16), and people with other conditions which included diabetic retinopathy (n=14).

Participant Characteristics

The proportion of male participants ranged from 18-75% in the 73 studies that reported this characteristic. Of the 70 articles in the review that reported age, mean age ranged from 29-77 years. Fewer than half of the studies reported diabetes duration (n=39). Durations were reported as time since diagnosis using median, mean, and percentage above, in or below certain age ranges. Mean disease duration ranged from 3 years to 39 years.

Outcomes

Results are organised according to the following outcomes: self-reported visual functioning (n=41), quality of life (n=23), psychological well-being (n=16), functional status (n=14), work (n=4), and visual task performance (n=3), using 51 different outcome measures. These six categories were based on groupings previously put forth by Mitchell and Bradley [15]. Forty-eight of these were patient reported outcome measures and 3 performance based or objective measures. Details of study characteristics by outcome are shown in Table 2.

Studies were categorised in the review into psychological well-being if they included measures of mood, depression, and/or anxiety. Functional status studies were those that investigated a person's ability to carry out tasks of daily living, not specific to vision. Articles were grouped into visual task performance if they included objective outcomes that measured performance of vision-related tasks. Quality of life studies were those that measured components relevant to quality of life. Work studies included those that measured the impact on work, education and/or employment. Studies were grouped into self-reported visual functioning if they measured self-reported ability to perform vision-related tasks including reading, writing, recognising faces, watching television or driving.

Psychological Well-Being

Summary

Seventeen studies explored the psychological well-being of individuals with diabetic retinopathy using 19 different measures (Rees et al., 2017, Sahni et al., 2017, Rees et al., 2016, Karlson and Agardh, 1997, Sinzato et al., 1985, Rees et al., 2012, Xu et al., 2015, Jacobson et al., 1985, Wulsin et al., 1993, Wulsin et al., 1991, Bernbaum et al., 1988, Williams and Ponchillia, 1998, Hirai et al., 2012, Le Floch et al., 2014, Upton et al., 1998, Saglam et al., 2010). All were patient reported outcome measures, 17 were generic measures (Rees et al., 2017, Sahni et al., 2017, Rees et al., 2016, Karlson and Agardh, 1997, Sinzato et al., 1985, Rees et al., 2012, Xu et al., 2015, Jacobson et al., 1985, Wulsin et al., 1993, Wulsin et al., 1991, Bernbaum et al., 1988, Williams and Ponchillia, 1998, Hirai et al., 2012, Le Floch et al., 2014, Upton et al., 1998, Saglam et al., 2010), and two were specific to diabetes (Rees et al., 2017, Bernbaum et al., 1988). Seventeen of the measures had shown previous validity and 4 of the measures showed negligible to no validity in any population. Study quality ranged from 0.55 to 1.00.

Impact of presence of diabetic retinopathy

After controlling for potential confounders, people with diabetic retinopathy were at greater risk of experiencing symptoms of anxiety and depression (Rees et al., 2012, Le Floch et al., 2014) and were more poorly adjusted to living with their condition (Wulsin et al., 1993, Bernbaum et al., 1988) than people with diabetes, but without diabetic retinopathy.

Impact of diabetic retinopathy severity

Findings about diabetic retinopathy severity and its relationship with depression and anxiety were mixed. Two correlational studies found that greater diabetic retinopathy severity was associated with increased symptoms of depression (Rees et al., 2016) and trait as opposed to state anxiety (Sinzato et al., 1985). Other studies however, failed to replicate these findings for depression (Hirai et al., 2012, Karlson and Agardh, 1997, Xu et al., 2015).

Increased depressive symptoms were associated with worse diabetic retinopathy severity in terms of worse visual acuity (Williams and Ponchillia, 1998, Xu et al., 2015). Worse visual acuity resulting from diabetic retinopathy was also associated with poor adjustment and negative psychological symptoms (Wulsin et al., 1993, Wulsin et al., 1991) in individuals with stable vision, but not in those with recent vision loss (Wulsin et al., 1993).

Functional Status

Five studies reported on functional status in diabetic retinopathy (Gupta et al., 2017, Agrawal et al., 2010, Le Floch et al., 2014, Upton et al., 1998, Ivers et al., 1998), with four generic patient reported outcome measures used. Study quality ranged from 0.55 to 0.91.

The activities of daily living scale showed no significant associations in impairments of activities of daily living between individuals with diabetes without diabetic retinopathy, non-proliferative diabetic retinopathy, and proliferative diabetic retinopathy. However, significant differences were seen for instrumental activities of daily living between these groups, with the greatest impairment seen in proliferative diabetic retinopathy (Le Floch et al., 2014). Another study showed people with diabetic retinopathy had significantly more problems in instrumental activities of daily living in comparison to non-diabetic people with other types of vision loss (Upton et al., 1998).

Results regarding falls were mixed. Two studies reported no association between diabetic retinopathy and risk of falling (Agrawal et al., 2010, Ivers et al., 1998). In contrast, another study reported that individuals with mild or moderate diabetic retinopathy had significantly elevated odds of falling in comparison to people with diabetes but without diabetic retinopathy (Gupta et al., 2017).

Visual Task Performance

Three studies objectively investigated performance of everyday tasks in people with diabetic retinopathy (Warrian et al., 2010, Warrian et al., 2015, Szlyk et al., 2004). Study quality ranged from 0.55 to 0.95. People with diabetic retinopathy made significantly more errors and took longer to complete a mobility course in comparison to healthy volunteers. Another study found no association between driving performance on an interactive simulator and diabetic retinopathy severity. However, focal laser scars were significantly associated with poorer performance on the driving simulator in this sample (Szlyk et al., 2004).

Quality of Life

Summary

The review identified 23 studies assessing quality of life using 11 different outcome measures (Ahola et al., 2010, Alcubierre et al., 2014, Brose and Bradley, 2010, Bujang et al., 2017, Daher et al., 2015, Davidov et al., 2009, Esteban et al., 2008, Fenwick et al., 2017, Granado-Casas et al., 2017, Granstrom et al., 2015, Hannula et al., 2014, Hirai et al., 2013, Hui et al., 2017, Jiao et al.,

2017, Leksell et al., 2005, Wang et al., 2012, Mazhar et al., 2011, Ramu et al., 2017, Scanlon et al., 2015, Sepulveda et al., 2015, Venkataraman et al., 2013, Wu et al., 2016, Xu et al., 2015). Seven of the patient reported outcome measures used were generic, two specific to diabetes, and two diabetic retinopathy specific. Study quality ranged from 0.82 to 1.00. Although the majority of quality of life studies were cross-sectional or cohort in design, two studies were interventional using quality of life as endpoints to measure efficacy of treatment (Ramu et al., 2017, Wu et al., 2016).

Impact of presence of diabetic retinopathy

Poorer overall quality of life was seen in individuals with diabetic retinopathy along with significantly poorer physical functioning, general health, and vitality compared with people with diabetes but without diabetic retinopathy (Alcubierre et al., 2014, Daher et al., 2015, Granado-Casas et al., 2017). Conversely, three studies showed that diabetic retinopathy was not associated with poorer quality of life in comparison to people with diabetes but without diabetic retinopathy (Ahola et al., 2010, Bujang et al., 2017, Sepulveda et al., 2015). In comparison to the general population and samples without any diabetes, diabetic retinopathy was associated with poorer quality of life in some studies (Esteban et al., 2008, Hui et al., 2017, Jiao et al., 2017), but not others (Lin and Yu, 2012).

Impact of diabetic retinopathy severity

The impact of disease severity on quality of life was mixed. Whilst one study found no differences between proliferative and non-proliferative diabetic retinopathy in generic quality of life, diabetes-specific quality of life was significantly worse in the proliferative diabetic retinopathy group (Brose and Bradley, 2010). Similarly, significantly worse general quality of life was found amongst individuals with proliferative diabetic retinopathy in comparison to those with less severe diabetic retinopathy or no diabetic retinopathy (Hannula et al., 2014) and greater severe disease severity was associated with poorer physical health quality of life, but not mental health quality of life (Mazhar et al., 2011, Venkataraman et al., 2013). Other studies however, showed no significant associations between diabetic retinopathy severity or visual impairment and quality of life (Granstrom et al., 2015, Hirai et al., 2013).

Poorer visual acuity was associated with significantly poorer quality of life in people with diabetic retinopathy (Davidov et al., 2009, Leksell et al., 2005, Scanlon et al., 2015, Xu et al., 2015).

Work

Four studies explored the impact of diabetic retinopathy on work (Abraldes et al., 2016, Davidov et al., 2009, Beaulieu et al., 2016, Brook et al., 2015). Study quality ranged from 0.83 to 0.95. People with diabetic retinopathy reported impaired work over the previous 7 days due to their vision 20-23% of the time (Beaulieu et al., 2016). Using an unvalidated questionnaire (Abraldes et al., 2016) 4.3% of respondents with DME had reduced their working hours, 1.2% had to switch jobs/careers, 1.5% had lost their job, 6.7% decreased their economic income, 5.1% had to quit their job, and 6.3% had been granted or requested a disability pension in the past 3 months due to their condition. One study reported 17.4% of their sample had a reduction in earning capacity due to diabetic retinopathy (Davidov et al., 2009). Another study used figures taken from the Human Capital Management Services Group Research Reference Database completed by businesses (Brook et al., 2015); workers with diabetic retinopathy were absent from work for significantly more days in comparison to controls without diabetes; there were no differences between people with DME and people with diabetic retinopathy.

Self-Reported Visual Functioning

Summary

Visual functioning in diabetic retinopathy was reported by 46 studies using 11 different outcome measures (Ahmadian and Massof, 2008, Aroney et al., 2016, Bailey and Sparrow, 2001, Beaulieu et al., 2016, Bertelmann et al., 2016, Bressler et al., 2016, Bressler et al., 2014, Broman et al., 2002, Cetin et al., 2012, Gabrielian et al., 2010, Gillies et al., 2014, Granstrom et al., 2015, Hariprasad et al., 2008, Henricsson and Heijl, 1994, Hui et al., 2017, Jannuzzi et al., 2014, Kamel et al., 2000, Kishimoto and Ohtsuki, 2012, Klein et al., 2001, Lamoureux et al., 2010, Lamoureux et al., 2004, Lin and Chie, 2010, Lin and Yu, 2012, Lloyd et al., 2013, Loftus et al., 2011, Man et al., 2016, Matza et al., 2008, Mazhar et al., 2011, Mitchell et al., 2013, Nilsson, 1986, Okamoto et al., 2008, Okamoto et al., 2010, Okamoto et al., 2014, Pereira et al., 2017, Ramu et al., 2017, Ratanasukon et al., 2016, Scanlon et al., 2015, Toprak et al., 2005, Trento et al., 2017, Trento et al., 2013, Tsilimbaris et al., 2013, Turkoglu et al., 2015, Vijayan et al., 2017, Warrian et al., 2010, Willis et al., 2017, Hirai et al., 2011). Study quality ranged from 0.32 to 0.95. All used patient reported outcome measures, eight of which had been validated, with three having negligible or no evidence of validity.

Impact of presence of diabetic retinopathy

Diabetic retinopathy was associated with worse visual functioning in comparison to individuals with diabetes but not diabetic retinopathy (Pereira et al., 2017, Lamoureux et al., 2010, Aroney et al., 2016, Gillies et al., 2014), those with diabetes and good vision (Ratanasukon et al., 2016) and those with other conditions including age-related macular degeneration, glaucoma, and cataract (Hariprasad et al., 2008) even when visual acuity was controlled for (Lin and Yu, 2012, Broman et al., 2002). One study however, reported uveitis to have a more debilitating impact on visual functioning than diabetic retinopathy (Hui et al., 2017), even after controlling for visual acuity. Greatest restrictions on visual functioning due to diabetic retinopathy included reading print, mobility, work, leisure activities (Lamoureux et al., 2004) driving a car (Bertelmann et al., 2016, Bressler et al., 2016), seeing faces, watching television and reading newspapers (Henricsson and Heijl, 1994, Nilsson, 1986). However, one study found no significant differences in visual functioning between a DME sample and a non-diabetic retinopathy sample or between people with diabetic retinopathy and individuals with low vision from other causes with equivalent visual acuity (Ahmadian and Massof, 2008). Two studies reported visual functioning as worse in bilateral (but not unilateral) diabetic retinopathy in comparison to diabetes without any diabetic retinopathy (Man et al., 2016, Mazhar et al., 2011).

Impact of diabetic retinopathy severity

People with proliferative diabetic retinopathy had significantly worse visual functioning compared to non-proliferative diabetic retinopathy (Gabrielian et al., 2010, Lamoureux et al., 2010). One study reported progression or improvement of severity in diabetic retinopathy was not associated with visual functioning when analysed independently of visual acuity changes (Hirai et al., 2011). Another study showed that people with severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy reported more difficulties with reading and noticing objects to the side than people with mild or moderate non-proliferative diabetic retinopathy and no diabetic retinopathy even after controlling for visual acuity and DME (Willis et al., 2017). However, no differences in difficulty with close-up work, finding objects on a crowded shelf, walking down steps, stairs, or curbs, and driving were found. After controlling for potential confounders, these differences only remained significant when comparing severe non-proliferative diabetic retinopathy

and proliferative diabetic retinopathy to individuals with no diabetic retinopathy. One of the studies also showed visual functioning to be worse for people with DME when compared with people with diabetic retinopathy, but no DME (Man et al., 2016).

Several studies reported significant associations between visual functioning and visual acuity; as visual acuity in people with diabetic retinopathy and those with DME became poorer, problems with visual functioning increased (Cetin et al., 2012, Granstrom et al., 2015, Mazhar et al., 2011, Okamoto et al., 2008, Okamoto et al., 2010, Trento et al., 2013, Scanlon et al., 2015). Visual acuity in the better eye was reported to be significantly correlated with better visual functioning, with no association with the worse eye (Warrian et al., 2010). Trento et al. (2017) investigated visual functioning in mild diabetic retinopathy compared to people with diabetes but without diabetic retinopathy. Whilst, no significant differences were found for the majority of the visual functioning domains, vision specific mental health was significantly better in the diabetic retinopathy group in comparison to the non-diabetic retinopathy diabetes group. Vision specific role difficulties was significantly worse in the mild diabetic retinopathy group in comparison to the non-diabetic retinopathy diabetes group.

Descriptive results

Some included studies purely described NEI VFQ-25 scores in a sample of individuals with diabetic retinopathy, without a comparison group, or any further analysis. In comparison to scores of individuals with diabetes but no diabetic retinopathy reported in other studies (Klein et al., 2001, Pereira et al., 2017) people with diabetic retinopathy reported worse overall visual functioning (Beaulieu et al., 2016, Bressler et al., 2014, Lloyd et al., 2013, Loftus et al., 2011, Matza et al., 2008, Mitchell et al., 2013, Okamoto et al., 2014, Ramu et al., 2017, Toprak et al., 2005, Tsilimbaris et al., 2013, Turkoglu et al., 2015, Vijayan et al., 2017). One descriptive study reported that people with DME or proliferative diabetic retinopathy had difficulties with seeing the television screen, reading normal print, seeing at night, and recognizing faces (Bailey and Sparrow, 2001).

Discussion

Presence of diabetic retinopathy was associated with reported difficulties with instrumental activities of daily living (i.e. activities essential for independent living such as managing one's own finances, housework and shopping); this worsened with disease severity. Some individuals with diabetic retinopathy also reported ceasing or reducing working. Limited evidence from objective performance based measures suggested that diabetic retinopathy may be associated with impaired mobility when considering walking, yet driving and falls risk may remain unaffected. There was clearer consensus however, for the association between diabetic retinopathy severity and physical quality of life, and this supports results of a previous review [10]. As the majority of included quality of life measures were generic, these may not be sensitive to the specific impact of diabetic retinopathy on the individual; future studies would benefit from utilising diabetic retinopathy-specific measures such as the DME/DR item banks [16] and the RetDQoL [17].

The quality of life and well-being articles in this review had a strong focus on how the clinical characteristics of DME and diabetic retinopathy, particularly diagnosis and severity, are associated with these outcomes. Recent literature has however suggested that clinical characteristics are not the best predictors of quality of life or well-being in ophthalmic conditions. Beliefs and feelings about a condition, its treatment and social support are better predictors of anxiety, depression, and quality of life [18-20]. This suggests that psychosocial well-being and quality of life are amenable to change through psychosocial interventions, alongside traditional low vision services. Further

research is therefore needed in DME and diabetic retinopathy to establish whether these same relationships are present and if so to develop interventions that help support patients and improve their well-being. A recent systematic review and meta-analysis [21] has highlighted a lack of evidence on the effectiveness of psychosocial interventions in low vision and called for high-quality trials in the field. Trials in recent years [22, 23] have shown problem-solving treatment to be a potentially useful intervention for depressive symptoms in low vision.

Over half of included studies investigated visual functioning in diabetic retinopathy, with the vast majority utilising the NEI-VFQ-25. People with mild diabetic retinopathy reported little to no impact on visual functioning; whilst visual functioning impairment increased with diabetic retinopathy severity and worsening visual acuity. Diabetic retinopathy was associated with poorer visual functioning compared to other eye conditions, even after controlling for visual acuity. This suggests the impact of diabetic retinopathy on visual functioning is not due to its diminishing impact on visual acuity alone, but due to specific symptoms and complications related to diabetic retinopathy. The results indicate the potential need in clinical practice to measure and consider the everyday impacts of diabetic retinopathy and DME, which include psychological well-being, functional status, quality of life, and impacts to work. Indeed, there is a growing body of literature on the value of PROMs in everyday clinical practice [24-26], with the caveat that questionnaire use ought to be coupled with good patient-practitioner communication.

The inconsistency within our results might arise from heterogeneous sample sizes, different cultural backgrounds and disease severity definitions between studies making reliable comparisons problematic. Furthermore, some studies did not control for or were unable to adjust for confounding variables in analyses, potentially biasing results. Very few articles compared the impact of DME to non-DME diabetic retinopathy samples [27-30], making it difficult to know of any potential differences between these two conditions. Further research is therefore needed.

Our results are consistent with those of previous reviews. One non-systematic review [9] published over ten years ago also reports reduced quality of life as a result of diabetic retinopathy. In a systematic review from Fenwick et al [10] quality of life was reported to be worst affected in the vision-threatening stages of diabetic retinopathy; this was seen in our systematic review with proliferative diabetic retinopathy associated with worst quality of life. Chen et al [11] reviewed the humanistic burden of DME in the USA and selected European countries and included two articles reviewed in this systematic review [31, 32]. Their findings suggested that DME may be associated with increased economical and societal costs. However, conclusions were limited by scarcity of evidence at the time. Whilst our results benefit from a greater wealth of evidence overall, studies focussing specifically on DME remain scarce. Finally, the most recent review by Fenwick et al [33] concluded that diabetic retinopathy may have a considerable impact on psychological well-being. The authors called for more large scale studies to be conducted, with increased consistency in methodology. More than half of the studies included in our review were however published since this, and whilst several included large sample sizes, there remains little consistency across study methodology.

It is important to consider these findings in light of the limitations of this review. Firstly, only articles published in peer-reviewed journals were included, which may have influenced the results due to submission and/or publication bias. Due to lack of translation resources, papers that were not published in English were excluded. The quality of any systematic review is in part based on the quality of the included studies, which in the case of this review was mixed. One of the limitations of this is review is that we did not discriminate between articles of lower quality and those of higher quality. Also, the review did not include studies with qualitative methodologies (e.g. studies from

Devenney et al. [34], Fenwick et al. [35], and Coyne et al. [36]), such studies have the potential to provide rich insights into the impact of having DR/DME and ought to be the subject of a future review. A further limitation relates to the multiple categories under which results are arranged. In reality, all of these categories fall under the broader holistic construct of quality of life. Furthermore, there is some overlap between the categories used in this review. For example, some of the results in the visual functioning section relate to psychological well-being, and some items within the IVI and NEI VFQ-25 relate to health-related quality of life. However, we have attempted to organise results according to their main outcome, based on the categories presented in existing research literature [15]. Finally, it is likely that individuals taking part in research studies and clinical trials may be in better health than a random sample of the population. This could be remedied by only including studies using routinely collected data from medical records. Given that data on QoL etc. is not currently routinely collected in clinics this is not possible at this time. It is therefore possible that our results underestimate the scale of the issues described here.

This systematic review supplements existing literature by providing an extensive investigation of the impact of DR/DME. Diabetic retinopathy was found to have a considerable impact on visual functioning, which is more impaired in individuals with greater disease severity. The research indicates that diabetic retinopathy has the potential to limit activities including working, driving, walking and reading, and thus limiting autonomy in life. Vision loss in diabetic retinopathy was associated with greater frequency of depressive symptoms and poorer quality of life. Although this review has its limitations it is the first to synthesise the literature across a range of patient-centred outcomes in diabetic retinopathy, and as such has allowed previously unanswered questions to be addressed as well as identifying important gaps in the literature.

Our results hint at several further implications for future research. A wide range of tools were used for each domain, making cross-comparisons between studies in this review difficult. Moreover, a number of studies used unvalidated questionnaires. The issue of inconsistency in PROMs has been cited as a substantial challenge to overcome in maximising the impact of PROMs (37). We suggest that future research takes steps to address this, by providing evidence for the most appropriate tool for use in DR, including involvement of individuals with diabetic eye disease from the start of and throughout the PROM design process [38], and educating clinicians and researchers in the importance of appropriate PROM selection when designing studies and clinical trials. This might require an overhaul of traditional PROM delivery, for example use of computerised adaptive testing and item banking [16], or complementing PROMs with objective performance based measures of visual performance. Only two studies included in this review objectively measured performance of everyday tasks in diabetic retinopathy. It is well evidenced that this type of outcome complements patient-reported outcomes and provides additional information on the impact of eye disease, as well as being less susceptible to cultural and literacy barriers [39-42]. Future research in this field ought to substantiate this review's findings relating to everyday visual functioning in DR using performance based measures.

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Authorship

DT and OC completed screening, analysis, article quality review, data analysis, and drafting of the manuscript. DC and HB were the principal investigators of the study. All authors provided critical feedback and helped shape the research, analysis and manuscript. All authors approved the final version of the manuscript to be published.

Data Availability

Further details of articles included and excluded, quality review and tables of results are available at request from the author.

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