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Diabetic Retinopathy and Quality of Life
A Systematic Review and Meta-Analysis

Mohammed G. Zayed, MSc; Waseem Karsan, MUDr; Tunde Peto, PhD; Ponnusamy Saravanan, PhD; Gianni Virgili, MD; David Preiss, PhD

IMPORTANCE The association between diabetic retinopathy (DR) and quality of life (QoL) has not been thoroughly investigated.

OBJECTIVE To investigate the association between DR and both vision-related QoL (VRQoL) and general health-related QoL (HRQoL).

DATA SOURCES MEDLINE, EBSCO, Embase, and Web of Science were searched from their inception to April 2022.

STUDY SELECTION Studies included adults with DR and a measure of QoL.

DATA EXTRACTION AND SYNTHESIS Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. Two assumption-free meta-analyses were conducted. Analysis 1 included studies with participants without DR as the referent group to which QoL scores of participants with DR, grouped according to DR severity, were compared. Analysis 2 included all studies with participants with DR and a measure of QoL. QoL scores were pooled within categories of DR severity, and comparisons were made between these categories.

MAIN OUTCOME AND MEASURES QoL measured using HRQoL and VRQoL scales.

RESULTS A total of 93 articles were included: 79 in the meta-analyses and 14 in the narrative results. VRQoL was recorded in 54 studies, HRQoL in 26, and both in 13 studies. The most commonly used scales were the National Eye Institute 25-item Visual Function Questionnaire (VFQ-25) (n = 49) for VRQoL and the Short Form (SF) Health Survey (n = 18) for HRQoL. Thirty-five studies reported VFQ-25 composite scores. Analysis 1 consisted of 8 studies including 1138 participants with DR and 347 participants without DR. Compared with participants without DR, the composite VFQ-25 score was 3.8 (95% CI, 1.0-6.7) points lower in those with non–vision-threatening DR (NVTDR), 12.5 (95% CI, 8.5-16.5) lower in those with any DR, and 25.1 (95% CI, 22.8-27.2) lower in VTDR ($P < .001$ for trend). Analysis 2 consisted of 35 studies including 6351 participants with DR. The pooled mean VFQ-25 composite score was 91.8 (95% CI, 91.0-92.7) for participants with NVTDR, 77.6 (95% CI, 76.9-78.3) for any DR, and 73.2 (95% CI, 72.6-73.7) for VTDR ($P < .001$ for trend). HRQoL scores had weak or no associations with NVTDR and strong associations with VTDR.

CONCLUSIONS AND RELEVANCE This study found that VRQoL declined with the presence and severity of DR. Interventions to reduce progression of DR at both early and more advanced stages could improve VRQoL.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Mohammed G. Zayed, MSc, Clinical Trials Service Unit, Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, United Kingdom (mohammed.zayed@ndph.ox.ac.uk); Ponnusamy Saravanan, PhD, University Hospitals Coventry & Warwickshire, Warwick Medical School, University of Warwick, Coventry CV4 7AL, United Kingdom (p.saravanan@warwick.ac.uk).

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Diabetic retinopathy (DR) is a progressive potentially sight-threatening microvascular complication of diabetes.[1] DR is the only major cause of visual loss worldwide that is still increasing.[2,3]

Clinical measures, including visual acuity (VA), do not necessarily reflect the overall impact of DR on daily activities. In fact, VA has been shown to be a poor indicator of overall visual function in certain DR populations, and patient-reported outcome measures were recommended to provide a comprehensive assessment of their functional deficits.[4]

Patient-reported outcome measures indicate functional status from the patients' perspectives.[5] Health-related quality-of-life (HRQoL) scales are 1 type of patient-reported outcome measure.[6] HRQoL scales can be general (relevant to a population with or without a chronic illness, eg, the EuroQoL 5-dimension questionnaire) or specific, assessing unique challenges in a particular population[7] (eg, vision-specific, hereafter vision-related QoL [VRQoL]).

Reviews of the literature studying the association between QoL and DR are limited. These reviews suggest that people with DR experience poor VRQoL and HRQoL[8] that is worse in advanced stages of DR[9,10] and diabetic macular edema.[11,12] However, some of these reviews did not follow rigorous systematic review methodology, and others were limited by lack of evidence at the time of publication. To our knowledge, no previous review has conducted a meta-analysis of evidence regarding the association between DR and QoL. We sought to provide an up-to-date systematic review and meta-analysis of evidence on the association between DR and both VRQoL and general HRQoL.

Key Points

Question What is the association between diabetic retinopathy and quality of life (QoL) from a systematic review and meta-analysis?

Findings Vision-related QoL declined with the presence of diabetic retinopathy and worsened further with its severity, a change that was not fully explained by the effect of diabetic retinopathy on visual acuity. Vision-specific QoL scales were more sensitive in identifying the functional deficit associated with diabetic retinopathy than general health-related QoL scales.

Meaning These results support the possibility that interventions to reduce progression of diabetic retinopathy, at both early and advanced stages, could improve vision-related QoL.

Methods

A protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[13] and registered in the international prospective register of systematic reviews (PROSPERO) in December 2021.[14] A search of the MEDLINE (via Ovid), EBSCO (CINAHL), Embase (via Ovid), and Web of Science (Science Citation Index) databases was conducted using a predefined search strategy (eTable 1 in Supplement 1) from their inception through April 2022.

Eligibility Criteria

Eligible studies included adults with DR (including all severities: nonproliferative DR, proliferative DR, and diabetic macular edema) and a reported measure of QoL using validated QoL scales. Studies that had a comparator group (individuals without DR) were included if QoL for groups with and without DR was reported separately. We excluded studies where the only outcome was utility values for health economics purposes. Interventional studies were included to extract relevant baseline data. Where studies included multiple assessment time points, baseline data were used. Abstract-only papers, protocols, and non–English-language articles were excluded.

Search Strategy and Data Extraction

Studies were screened based on titles and abstracts, and then full-text articles of potentially eligible studies were classified as eligible or ineligible by 2 independent reviewers. Reference lists of included studies and identified systematic reviews were reviewed for relevant articles. Discrepancies were resolved by discussion or by a third reviewer.

The following data were extracted: first author, year of publication, study methodology, participants' demographics, country where the study was conducted, type and duration of diabetes, measures of glycemic control, duration and severity of DR, DR grading scale, outcomes measured, and scales used.

Risk-of-Bias (Quality) Assessment

Two reviewers independently assessed the risk of bias using the 14-item standard quality assessment for evaluating primary research articles from a variety of fields.[15] Total scores range from 0 to 1, 0 indicating the lowest and 1 the highest quality. Studies scoring more than 0.75 were considered to represent high quality.[15] Disagreements were resolved by discussion or by a third reviewer.

Statistical Analysis

DR severity was classified as no DR, non-vision-threatening DR (NVTDR), any DR (studies combining scores for NVTDR and vision-threatening DR [VTDR]), and VTDR (severe nonproliferative DR, proliferative DR, and/or diabetic macular edema). Diabetic macular edema was also assessed separately and results reported in eTable 2 in Supplement 1. To avoid biases related to small-study effects, assumption-free (ie, fixed-effects) meta-analyses were performed.[16]

Two types of analyses were conducted. Analysis 1 included studies with a group of participants without DR. This group was selected as the referent to which we compared scores of participants with DR, grouped according to DR severity. Thus, differences in score between no DR and each DR severity type were calculated within studies. The mean difference in scores was calculated by meta-analysis for studies using the same QoL scale (for scales used in ≥3 studies). Standardized mean difference (SMD) was also calculated by meta-analysis for all studies using various VRQoL scales and separately for studies using HRQoL scales.

Analysis 2 included all eligible studies (whether or not studies included a referent group without DR). Where the same QoL

scale was used in 3 or more studies, scores were pooled within categories of DR severity and comparisons were made between these categories.

Meta-regression was conducted to investigate the effect of confounding variables, including age, sex, type and duration of diabetes, and VA. Two sensitivity analyses were performed, one using random-effects models and another only including studies with high-quality scores (>0.75). All analyses were conducted in Stata SE version 17.0 (StataCorp).

Results

First, 7767 articles were identified, of which 93 met our inclusion criteria (eFigure 1 in Supplement 1). These included 73 observational studies (50 cross-sectional, 12 cohort, 9 case-control studies, and 2 case series) and 20 interventional studies. Studies were conducted between 2001 and 2022 in 24 countries, most commonly the United States (n = 13) followed by India (n = 8) and China (n = 8).

Studies included data for 39 989 participants (29 467 with DR and 10 522 without DR). The number of participants in each study ranged from 8 to 7081 (median, 203). Thirty-seven studies included a referent group (without DR), and 56 studies were limited to participants with DR.

Fifty studies did not specify their DR grading method, while 1 used 2 different scales. The most commonly used scale was the Early Treatment of Diabetic Retinopathy Study severity scale (n = 22). A summary of all 93 studies' characteristics is available in eTable 3 in Supplement 1.

Outcomes

VRQoL was assessed in 54 studies, HRQoL in 26, and both in 13 studies. Five studies used 2 different scales to assess VRQoL, and 2 used 2 different measures for HRQoL. The most frequently used VRQoL scale was the National Eye Institute 25-item Visual Function Questionnaire (VFQ-25) (n = 49). The Short Form (SF) Health Survey with its different versions (36-item, 12-item, and RAND-36) was the most frequently used HRQoL scale (n = 18). The details of different scales (scoring system and subscales) are available in eTables 4 and 5 in Supplement 1.

Quality of Included Studies

The mean quality score was 0.79 (SD, 0.1; range, 0.55-0.96). A total of 36 studies were scored below the threshold for high quality (≤0.75). The most frequent reason for low-quality scores was the lack of or partial description of a sampling strategy (eFigure 2 in Supplement 1).

Association of DR and VRQoL

Analysis 1: Comparative Studies

For the VFQ-25, 10 studies were included in the analysis. Two studies reported subscale scores but no composite score. Composite score analysis of the remaining 8 studies included 1138 participants with DR (297 NVTDR, 187 any DR, and 654 VTDR) and 347 participants without DR. Compared with participants with no DR, the composite score was 3.8 (95% CI, 1.0-6.7) points lower in participants with NVTDR, 12.5 (95% CI, 8.5-16.5) lower in participants with any DR, and 25.1 (95% CI, 22.8-27.2) lower in participants with VTDR ($P < .001$ for trend) (**Figure 1**).[4,17-23]

There was progressive worsening in most VFQ-25 subscales at worse DR severity compared with no DR. Among the VTDR group results, the greatest effect was on mental health (mean difference, −22.5; 95% CI, −24.6 to −20.3) and near vision (mean difference, −22.1; 95% CI, −24.1 to −20.0), while the least effect was on ocular pain (mean difference, −6.5; 95% CI, −8.6 to −4.4). **Figure 2** summarizes the results for all the subscales.

For the Visual Function Index, 3 studies were included in the analysis, consisting of 95 participants with DR (41 NVTDR and 54 VTDR) and 1158 without DR. Compared with participants who had no DR, the Visual Function Index score was 6.5 (95% CI, 0.6-12.3) points lower in those with NVTDR and 34.6 (95% CI, 27.2-42.0) lower in those with VTDR ($P < .001$ for trend) (**Figure 3**).[24-26]

Analyses across studies using different VRQoL scales by SMD were possible for 15 studies, which reported VRQoL for 1573 participants with DR (512 NVTDR, 217 any DR, and 844 VTDR) and 2247 without DR. Compared with participants with no DR, the SMD was 0.23 (95% CI, 0.11-0.36) lower in those with NVTDR, 0.94 (95% CI, 0.71-1.17) lower in any DR, and 1.28 (95% CI, 1.15-1.41) lower in VTDR ($P < .001$ for trend) (eFigure 3 in Supplement 1).

Analysis 2: Noncomparative Studies

Thirty-five studies reported VFQ-25 composite scores, including 6351 participants with DR (482 NVTDR, 1702 any DR, and 4167 VTDR). The pooled mean VFQ-25 composite score was 91.8 (95% CI, 91.0-92.7) for participants with NVTDR, 77.6 (95% CI, 76.9-78.3) for those with any DR, and 73.2 (95% CI, 72.6-73.7) for those with VTDR ($P < .001$ for trend).

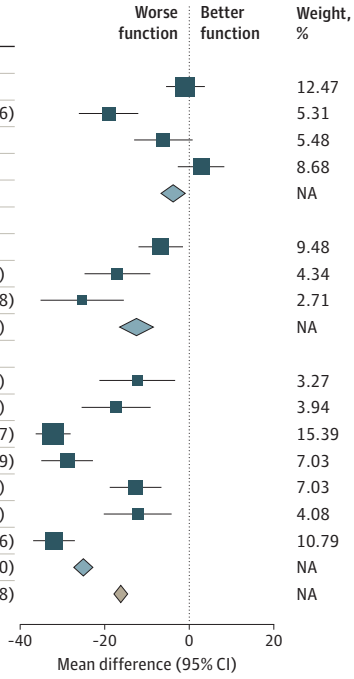
Meta-regression models were run to investigate such variables as age, sex, VA, and type and duration of diabetes against pooled VFQ-25 composite scores. Univariate meta-regression showed that reduced VA, older age, male sex, type 2 diabetes, and longer diabetes duration were associated with lower composite scores (eTable 6 in Supplement 1). eFigure 4 in Supplement 1 shows a bubble plot of the pooled VFQ-25 composite scores against various variables. The outcome of these variables was then investigated further using multivariable meta-regression to assess if they affect the association between DR and VRQoL. Only VA was found to be statistically significant considering all DR severity types (eTable 7 in Supplement 1). After adjusting for VA, VFQ-25 composite scores still declined among participants with VTDR as opposed to those with NVTDR (mean difference, −15.3; 95% CI, −18.5 to −12.1; $P < .001$) (eTable 8 in Supplement 1).

For the Visual Function Index analysis, 3 studies were included, consisting of 95 participants with DR (41 NVTDR and 54 VTDR). The pooled mean score was 85.3 (95% CI, 80.0-90.7) for participants with NVTDR and 56.9 (95% CI, 49.4-64.3) for those with VTDR ($P < .001$ for trend).

For the Retinopathy-Dependent Quality of Life questionnaire, 4 studies were included, representing 783 participants with DR (456 any DR and 327 VTDR). The pooled average weighted index of the score was −1.47 (95% CI, −1.63 to −1.31)

Figure 1. National Eye Institute 25-Item Visual Function Questionnaire Composite Score Meta-Analysis

Source	With DR		No DR		Mean difference (95% CI)	Weight, %
	No. of participants	Mean (SD) score	No. of participants	Mean (SD) score		
NVTDR						
Klein et al,[17] 2001	209	94.1 (8.3)	13	95.0 (6.1)	-0.90 (-5.49 to 3.69)	12.47
Akkaya et al,[18] 2016, stage 1	34	64.0 (22.1)	65	83.1 (13.6)	-19.09 (-26.12 to -12.06)	5.31
Akkaya et al,[18] 2016, stage 2	26	75.9 (18.8)	65	83.1 (13.6)	-6.12 (-13.04 to 0.80)	5.48
Akkaya et al,[18] 2016, stage 3	28	85.8 (9.1)	65	83.1 (13.6)	2.79 (-2.71 to 8.29)	8.68
					-3.82 (-6.69 to -0.95)	NA
Any DR						
Liao et al,[19] 2021	42	80.7 (16.3)	48	87.5 (8.5)	-6.75 (-12.02 to -1.48)	9.48
Lin and Chie,[20] 2010	48	63.7 (20.8)	34	80.7 (12.0)	-17.00 (-24.78 to -9.22)	4.34
Pereira et al,[21] 2017	97	73.9 (25.6)	26	99.3 (1.0)	-25.33 (-35.18 to -15.48)	2.71
					-12.49 (-16.48 to -8.50)	NA
VTDR						
Klein et al,[17] 2001, advanced DR	257	82.7 (16.4)	13	95.0 (6.1)	-12.30 (-21.26 to -3.34)	3.27
Chen et al,[4] 2019	30	78.2 (15.4)	15	95.5 (6.5)	-17.30 (-25.47 to -9.13)	3.94
Okamoto et al,[22] 2010, advanced DR	99	52.8 (19.0)	100	85.0 (9.1)	-32.20 (-36.33 to -28.07)	15.39
Okamoto et al,[23] 2008	51	56.3 (18.8)	46	85.2 (10.2)	-28.90 (-35.01 to -22.79)	7.03
Akkaya et al,[18] 2016	48	70.4 (19.6)	65	83.1 (13.6)	-12.70 (-18.81 to -6.59)	7.03
Klein et al,[17] 2001, DMO	131	82.8 (14.6)	13	95.0 (6.1)	-12.20 (-20.23 to -4.17)	4.08
Okamoto et al,[22] 2010, DMO	38	53.0 (20.5)	100	85.0 (9.1)	-32.00 (-36.94 to -27.06)	10.79
					-25.06 (-27.32 to -22.80)	NA
Overall					-16.20 (-17.82 to -14.58)	NA



Each diabetic retinopathy (DR) severity group was compared with the group who had no DR (reference) within studies. DR severity was classified as non–vision-threatening DR (NVTDR), any DR (studies combining scores for NVTDR and vision-threatening DR [VTDR]), and VTDR (severe nonproliferative DR, proliferative DR, and/or diabetic macular edema [DMO]). The analysis used a fixed-effects model. NA indicates not applicable.

for participants with any DR and −1.92 (95% CI, −2.14 to −1.7) for those with VTDR (P = .001 for trend).

Association of DR and HRQoL

Analysis 1: Comparative Studies

For the EuroQoL 5-dimension questionnaire, analysis consisted of 5 studies including 1016 participants with DR (32 NVTDR, 969 any DR, and 15 VTDR) and 1726 participants without DR. Compared with those who had no DR, the EuroQoL score was 0.03 (95% CI, −0.04 to 0.10) points higher in those with NVTDR, 0.02 (95% CI, 0.01 to 0.03) points lower in any DR, and 0.12 (95% CI, 0.02 to 0.21) lower in VTDR (P = .02 for trend) (**Figure 4**).[27-31]

For the SF Health Survey, analysis consisted of 4 studies including 337 participants with DR (186 NVTDR, 10 any DR, and 141 VTDR) and 3889 participants without DR. Compared with participants who had no DR, the mean SF physical component summary score was 3.9 (95% CI, 2.4 to 5.5) points lower in those with NVTDR, 9.3 (95% CI, 3.8 to 14.8) lower in those with any DR, and 8.8 (95% CI, 7.1 to 10.5) lower in VTDR (P < .001 for trend). The mean SF mental component summary score was 0.3 (95% CI, −1.4 to 1.9) points higher in NVTDR, 0.8 (95% CI, 4.3 to 5.9) lower in any DR, and 2.1 (95% CI, 0.4 to 3.9) lower in VTDR (P = .05 for trend). **Figure 5** shows forest plots for physical component summary and mental component summary scores.[25,32-34]

There was variation across SF subscales depending on DR severity. In the participants with VTDR, compared with no DR, the greatest effect was seen in general health (−8.2; 95% CI, −9.9 to −6.4), while no significant effect was seen in the mental health subscale (eFigure 5 in Supplement 1).

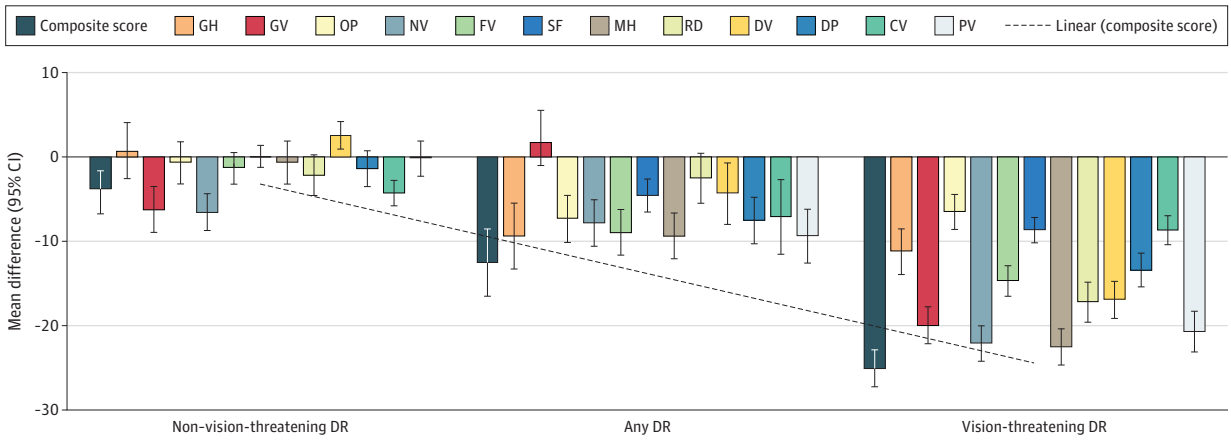
For HRQoL, analyses across studies using different scales by SMD was possible for 14 studies, which reported HRQoL for 1825 participants with DR (267 NVTDR, 1343 any DR, and 215 VTDR) and 6171 without DR. Compared with participants who had no DR, the SMD was 0.48 (95% CI, 0.34-0.62) lower in NVTDR, 0.32 (95% CI, 0.25-0.39) lower in those with any DR, and 0.94 (95% CI, 0.79-1.09) lower in those with VTDR (P < .001 for trend) (eFigure 6 in Supplement 1).

Analysis 2: Noncomparative Studies

For the EuroQoL 5-dimension questionnaire, analysis consisted of 12 studies including 3595 participants with DR (251 NVTDR, 2320 any DR, and 1024 VTDR). The pooled EuroQoL index score was 0.79 (95% CI, 0.76-0.82) for participants with NVTDR, 0.82 (95% CI, 0.82-0.83) for any DR, and 0.75 (95% CI, 0.74-0.76) for VTDR (P < .001 for trend).

For the SF Health Survey, analysis consisted of 8 studies including 975 participants with DR (186 NVTDR, 648 any DR, and 141 VTDR). The pooled physical component summary score was 45.6 (95% CI, 44.0-47.2) for participants with NVTDR, 44.7 (95% CI, 43.5-45.9) for those with any DR, and 40.0 (95% CI, 37.9-42.1) for VTDR (P < .001 for trend). Pooled mental component summary score was 52.7 (95% CI, 51.1-54.2) for NVTDR, 54.3 (95% CI, 53.1-55.5) for any DR, and 49.9 (95% CI, 48.1-51.7) for VTDR (P = .06 for trend).

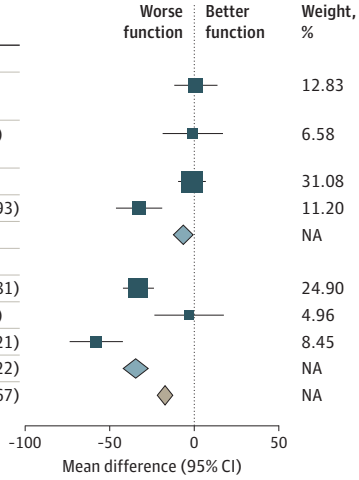
Figure 2. Summary of National Eye Institute 25-Item Visual Function Questionnaire Subscale Meta-Analysis



χ^2 Trend test is statistically significant: $P < .001$ for all subscales. CV indicates color vision; DP, dependency; DR, diabetic retinopathy; DV, driving; FV, far vision; GH, general health; GV, general vision; MH, mental health; NV, near vision; OP, ocular pain; PV, peripheral vision; RD, role difficulty; SF, social function.

Figure 3. Visual Function Index Meta-Analysis

Source	With DR: No. of participants	With DR: Mean (SD) score	No DR: No. of participants	No DR: Mean (SD) score	Mean difference (95% CI)	Weight, %
NVTDR						
Lundqvist and Mönestam,[24] 2012, mild	19	81.8 (25.6)	25	80.8 (17.7)	1.00 (-11.80 to 13.80)	12.83
Lundqvist and Mönestam,[24] 2012, moderate	7	80.0 (31.9)	25	80.8 (17.7)	-0.80 (-18.67 to 17.07)	6.58
Esteban et al,[25] 2008, mild	11	87.9 (10.8)	1096	89.23 (13.9)	-1.30 (-9.52 to 6.92)	31.08
Esteban et al,[25] 2008, moderate	4	56.6 (32.2)	1096	89.23 (13.9)	-32.63 (-46.33 to -18.93)	11.20
					-6.46 (-12.29 to -0.62)	NA
VTDR						
Kishimoto and Ohtsuki,[26] 2012	45	57.0 (27.0)	37	90.0 (10.0)	-33.00 (-42.19 to -23.81)	24.90
Lundqvist and Mönestam,[24] 2012	6	77.8 (39.9)	25	80.8 (17.7)	-3.00 (-23.57 to 17.57)	4.96
Esteban et al,[25] 2008	3	31.3 (29.5)	1096	89.2 (13.9)	-57.98 (-73.75 to -42.21)	8.45
					-34.62 (-42.03 to -27.22)	NA
Overall					-17.25 (-21.83 to -12.67)	NA



Each diabetic retinopathy (DR) severity group was compared with the group who had no DR (reference) within studies. DR severity was classified as non–vision-threatening DR (NVTDR), any DR (studies combining scores for NVTDR and vision-threatening DR [VTDR]), and VTDR (severe nonproliferative DR, proliferative DR, and/or diabetic macular edema). The analysis used a fixed-effects model. NA indicates not applicable.

Sensitivity Analyses

Analyses were repeated in studies with high-quality scores only (>0.75) and separately using a random-effects model. Estimates for the association of DR with VRQoL and HRQoL were largely supportive of those of the base case analysis. Details are available in eTables 9 and 10 in Supplement 1. Analyses were also conducted for diabetic macular edema separately, and results were similar to those for participants with VTDR (eTable 2 in Supplement 1).

Studies Not Included in the Meta-Analyses

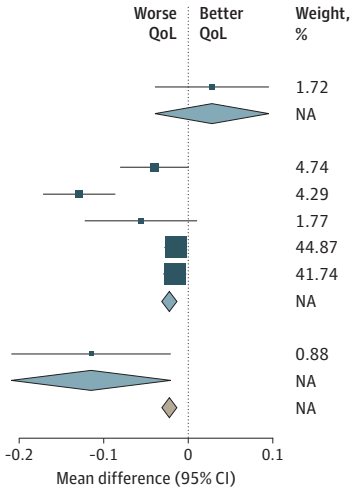
Fourteen studies were not included in the meta-analyses. The main reason was that the scale measuring QoL was only used in that study or the scores were not reported. In general, studies reported a decline in VRQoL and HRQoL with DR, which was worse at more severe DR (eTable 11 in Supplement 1).

Discussion

Results from this study show that DR is significantly associated with QoL. While worse VRQoL and HRQoL in people with VTDR are expected and have been previously demonstrated,[10,35,36] our study also demonstrates and quantifies the association of NVTDR with VRQoL. Results suggest that NVTDR is likely to have an important association with QoL at the population level given its high prevalence. In countries

Figure 4. EuroQoL 5-Dimensions Questionnaire Meta-Analysis

Source	With DR: No. of participants	With DR: Mean (SD) score	No DR: No. of participants	No DR: Mean (SD) score	Mean difference (95% CI)	Weight, %
NVTDR						
Ben et al,[27] 2021	32	0.8 (0.2)	157	0.8 (0.2)	0.03 (-0.04 to 0.10)	1.72
					0.03 (-0.04 to 0.10)	NA
Any DR						
Fenwick et al,[28] 2012	354	0.8 (0.3)	223	0.8 (0.2)	-0.04 (-0.08 to 0.00)	4.74
Morgan et al,[29] 2006	402	0.6 (0.3)	360	0.7 (0.3)	-0.13 (-0.17 to -0.09)	4.29
Kontodimopoulos et al,[30] 2012	55	0.7 (0.2)	264	0.7 (0.2)	-0.06 (-0.12 to 0.01)	1.77
Pan et al,[31] 2018, unilateral	56	1.0 (0.1)	722	1.0 (0.0)	-0.01 (-0.03 to -0.00)	44.87
Pan et al,[31] 2018, bilateral	102	1.0 (0.1)	722	1.0 (0.0)	-0.02 (-0.03 to -0.00)	41.74
					-0.02 (-0.03 to -0.01)	NA
VTDR						
Ben et al,[27] 2021	15	0.7 (0.3)	157	0.8 (0.2)	-0.12 (-0.21 to -0.02)	0.88
					-0.12 (-0.21 to -0.02)	NA
Overall					-0.02 (-0.03 to -0.01)	NA



Each diabetic retinopathy (DR) severity group was compared with the group who had no DR (reference) within studies. DR severity was classified as non–vision-threatening DR (NVTDR), any DR (studies combining scores for NVTDR and vision-threatening DR [VTDR]), and VTDR (severe nonproliferative DR, proliferative DR, and/or diabetic macular edema). The analysis used a fixed-effects model. NA indicates not applicable.

with a national retinal screening program, approximately 30% have NVTDR,[37] and this proportion is likely to be higher in regions where the treatment of diabetes is suboptimal and surveillance for complications is not available.

Our results also show that the effect at early DR stages is better captured using VRQoL scales, as opposed to general HRQoL scales, as previously reported.[9,10] However, as the DR severity progresses, a significant deterioration of QoL scores is seen using both VRQoL and HRQoL scales.

It is likely that therapies which are effective at reducing the development of NVTDR and its subsequent progression, such as glycemic control and lowering blood pressure, may provide important benefits, not simply because of reducing VTDR in the minority of people who might otherwise progress, but also because of the reduced effect of DR at earlier stages. This highlights the importance of conducting randomized trials of other strategies (such as ongoing trials of fenofibrate[38]) in people with NVTDR.

We explored the impact of potential confounders on the association between DR and VRQoL (specifically VFQ-25 composite score). In univariate analyses, older age, male sex, and worse VA were associated with worse VRQoL. However, when combined in a model, only VA had a significant impact. After controlling for VA, the deterioration in VRQoL associated with increasing severity of DR remained significant, suggesting that the association of DR with QoL is not fully explained by its effect on VA.

Health care organizations such as the National Institute for Health and Care Excellence in England place great emphasis on EuroQoL 5-dimension questionnaire results in randomized trials when making decisions about which therapies to fund. The current analyses suggest that, while that is reasonable for VTDR, such tools are insensitive to the subtle but important changes in VRQoL found in NVTDR.

Strengths and Limitations

The strengths of the study are its scale (93 studies involving 39 989 participants), inclusion of a broad range of participants (all types of DR severity, men and women, a wide range of age groups, type 1 and 2 diabetes), and pooling of data to quantify the association between DR and QoL. However, our study has important limitations. The cross-sectional nature of the data limited our ability to make causal inferences or to explore the association of DR with QoL over time. Some studies recruited particular groups of patients such that their results may not be generalizable. The lack of individual patient data introduced the possibility of bias and limited the number of potential confounders that we could explore, and we recognize that part of the association of DR with HRQoL and VRQoL may be mediated by other confounders, including comorbidities (which are more likely in people with complications of diabetes than in those without). We were only able to examine the impact of potential confounders on VFQ-25 (analysis 2) because data were limited for the reference group for analysis 1 and for other scales. We categorized study participants into different groups of DR severity based on the reported classification, but a large number of studies did not report their DR grading methods; therefore, there may be some inconsistency between studies. Heterogeneity of the results was high in some analyses, likely due to methodological and clinical variability between studies and differences in baseline characteristics and classification methods of DR.

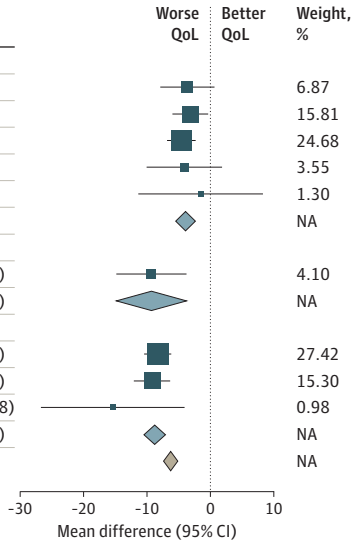
Recommendation for Future Studies

Future studies should consider using disease-specific scales to capture data on VRQoL, ideally sequentially over time. This will allow further refinement of the association

Figure 5. Meta-Analyses of Scores on the Short Form Health Survey Physical Component Summary (SF-PCS) and Mental Component Summary (SF-MCS)

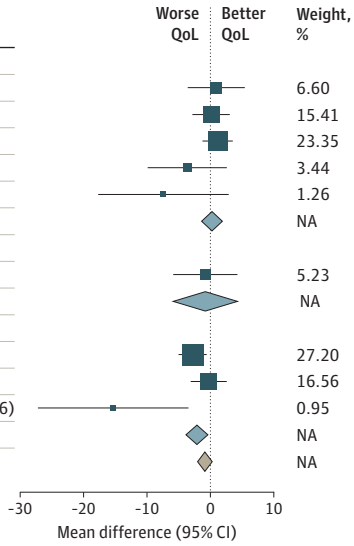
A SF-PCS meta-analysis

Source	With DR: No. of participants	With DR: Mean (SD) score	No DR: No. of participants	No DR: Mean (SD) score	Mean difference (95% CI)	Weight, %
NVTDR						
Venkataraman et al,[32] 2013, mild	17	46.6 (11.1)	2472	50.2 (9.0)	-3.63 (-7.91 to 0.65)	6.87
Venkataraman et al,[32] 2013, moderate	40	47.1 (12.8)	2472	50.2 (9.0)	-3.17 (-5.99 to -0.35)	15.81
Jiao et al,[33] 2017	114	45.8 (10.3)	220	50.3 (9.8)	-4.58 (-6.84 to -2.32)	24.68
Esteban et al,[25] 2008, mild	11	38.4 (11.9)	1066	42.6 (10.0)	-4.11 (-10.06 to 1.84)	3.55
Esteban et al,[25] 2008, moderate	4	41.0 (13.4)	1066	42.6 (10.0)	-1.54 (-11.37 to 8.29)	1.30
					-3.92 (-5.47 to -2.37)	NA
Any DR						
Pham et al,[34] 2020	10	37.3 (4.8)	131	46.6 (8.8)	-9.30 (-14.83 to -3.77)	4.10
					-9.30 (-14.83 to -3.77)	NA
VTDR						
Venkataraman et al,[32] 2013	72	41.9 (14.1)	2472	50.2 (9.1)	-8.31 (-10.45 to -6.17)	27.42
Jiao et al,[33] 2017	66	41.1 (12.2)	220	50.3 (9.8)	-9.21 (-12.08 to -6.34)	15.30
Esteban et al,[25] 2008	3	27.2 (5.7)	1066	42.6 (10.0)	-15.40 (-26.72 to -4.08)	0.98
					-8.78 (-10.48 to -7.09)	NA
Overall					-6.27 (-7.39 to -5.15)	NA



B SF-MCS meta-analysis

Source	With DR: No. of participants	With DR: Mean (SD) score	No DR: No. of participants	No DR: Mean (SD) score	Mean difference (95% CI)	Weight, %
NVTDR						
Venkataraman et al,[32] 2013, mild	17	51.9 (9.4)	2472	50.9 (9.5)	0.93 (-3.58 to 5.44)	6.60
Venkataraman et al,[32] 2013, moderate	40	51.1 (8.9)	2472	50.9 (9.5)	0.11 (-2.84 to 3.06)	15.41
Jiao et al,[33] 2017	114	53.9 (11.6)	220	52.8 (10.0)	1.14 (-1.26 to 3.54)	23.35
Esteban et al,[25] 2008, mild	11	52.5 (15.0)	1066	56.1 (10.5)	-3.65 (-9.89 to 2.59)	3.44
Esteban et al,[25] 2008, moderate	4	48.7 (17.2)	1066	56.1 (10.5)	-7.40 (-17.69 to 2.89)	1.26
					0.25 (-1.39 to 1.89)	NA
Any DR						
Pham et al,[34] 2020	10	57.8 (5.8)	131	58.6 (8.0)	-0.80 (-5.86 to 4.26)	5.23
					-0.80 (-5.86 to 4.26)	NA
VTDR						
Venkataraman et al,[32] 2013	72	48.1 (10.3)	2472	50.9 (9.5)	-2.80 (-5.02 to -0.58)	27.20
Jiao et al,[33] 2017	66	52.5 (11.4)	220	52.8 (10.0)	-0.26 (-3.10 to 2.58)	16.56
Esteban et al,[25] 2008	3	40.8 (17.4)	1066	56.1 (10.5)	-15.33 (-27.20 to -3.46)	0.95
					-2.13 (-3.86 to -0.39)	NA
Overall					-0.87 (-2.02 to 0.29)	NA



Each diabetic retinopathy (DR) severity group was compared with the group who had no DR (reference) within studies. DR severity was classified as non–vision-threatening DR (NVTDR), any DR (studies combining scores for NVTDR and vision-threatening DR [VTDR]), and VTDR (severe nonproliferative DR, proliferative DR, and/or diabetic macular edema). Both analyses used a fixed-effects model. NA indicates not applicable.

between DR and VRQoL. Newly developed scales that rely on item banking (a pool of questions measuring various domains of QoL, calibrated using computerized adaptive testing algorithms that customize the test for each test taker), such as RetCAT, may be of particular value in this regard.[39] The impact of low vision rehabilitation on QoL in patients with DR is also a topic of interest based on the current results.[40]

Conclusions

This analysis found that VRQoL declines with the presence and increasing severity of DR. This decline is not fully explained by the impact of DR on VA. Therapies that prevent the development or progression of DR, even before advanced stages, may improve VRQoL.

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Author Affiliations: Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom (Zayed, Karsan, Preiss); Populations, Evidence and Technologies, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, United Kingdom (Zayed, Saravanan); Centre for Public Health, Queen's University Belfast, Belfast, United Kingdom (Peto, Virgili); Department of Ophthalmology, Belfast Health and Social Care Trust, Belfast, United Kingdom (Peto, Virgili); Diabetes, Endocrinology and Metabolism, George Eliot Hospital NHS Trust, Nuneaton, United Kingdom (Saravanan).

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Concept and design: Zayed, Saravanan, Virgili, Preiss.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Zayed, Karsan.
Critical review of the manuscript for important intellectual content: Peto, Saravanan, Virgili, Preiss.
Statistical analysis: Zayed, Virgili.
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Supervision: Peto, Saravanan, Virgili, Preiss.

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