Supplementary Online Content

Widyaputri F, Rogers SL, Kandasamy R, Shub A, Symons RCA, Lim LL. Global estimates of diabetic retinopathy prevalence and progression in pregnant women with preexisting diabetes: a systematic review and meta-analysis. *JAMA Ophthalmol*. Published online March 24, 2022. doi:10.1001/jamaophthalmol.2022.0050

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Systematic Review Search Strategy

Databases		
Medline/OVID	1	diabetic retinopathy.ti,ab. or diabetic retinopathy/ti, ab or diabetic retinopathy/
	2	(pregnant or pregnancy).ti,ab. or pregnancy/
	3	1 AND 2
	4	limit 3 to (english language and humans)
	5	limit 4 to (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or journal article or multicenter study or observational study or pragmatic clinical trial or randomized controlled trial or twin study)
EMBASE/OVID	1	diabetic retinopathy.ti,ab. or diabetic retinopathy/ti, ab or diabetic retinopathy/
	2	(pregnant or pregnancy).ti,ab. or pregnancy/
	3	1 AND 2
	4	limit 3 to (human and english language and embase)
	5	limit 4 to (article and journal)
Scopus	1	TITLE-ABS-KEY ("diabetic retinopathy")
	2	TITLE-ABS-KEY (pregnant OR pregnancy)
	3	#1 AND #2
	4	#3 (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO(SRCTYPE,"j")) AND (LIMIT-TO (LANGUAGE, "English"))

eTable 2. Methodological and Reporting Quality Scoring

Item	Quality Criteria	Score
1	Appropriate method of **ascertaining diabetes prior to conception**. Appropriate inclusion of all persons with diabetes is important for accurate DR prevalence estimates. This may be defined based on a positive laboratory test (i.e., an oral glucose tolerance test or fasting blood glucose) and/or a self-reported history of physician's diagnosis and current diabetes treatment. A review of medical records or use of a national health registry to identify individuals with diabetes is also appropriate	**1 point** if method specifically described and prior to conception **0 points** if not described *(not included if not prior to conception, GDM excluded)*
2	Diabetes type is described and, if a mixture of types included in a study, the **data could be extracted separately for T1DM and T2DM**	2 points if type is described and DR grading data is published separately by DM type 1 point if type described and data can be extracted by type 0 if not described
3	Appropriate assessment of outcome. In this case, **retinal photography** must be **performed on all study participants** diagnosed with diabetes. *Retinal photography should not be limited to participants who have been diagnosed with DR from a clinical examination or where photographs served only as documentation of clinical findings*	2 points if all subjects 1 point if >=90% of subjects 0 if not performed for 90% of subjects or not at all
4	DR assessment: number **of eyes per person and retinal fields photographed**. *Studies that photographed only 1 randomly selected eye may miss detecting DR in the opposite eye. Studies that captured 1 field of 50 to 60-degree of retinal photos, they equal to more than 3 fields*[1]	**3 points** for 3 or more fields/eye and both eyes for all subjects with fundus photography; **2 points** for 3 or more fields/eye and both eyes for >=90% subjects with fundus photography; **2 points** of 2 fields/eye and both eyes for all subjects with fundus photography; **1 point** if only 1 field per eye, and both eyes for all subjects with fundus photography; **0 points** if no photos or only 1 eye per patient
5	Photos were graded more than once to reach **consensus**	1 point if graded by graders for consensus 0 point if not, or no photos.
6	DR grading was carried out by a dedicated, **trained grader or team of trained graders**	1 point if use of consistent, trained grader/team for all images 0 if many random graders 0 if not described
7	Grading of DR based on **standardized protocols** and definitions that can be comparable[a] to analysis categories 'none', 'NPDR', 'PDR', such as the ETDRS, modified Airlie House, WESDR, AAO or EURODIAB classification schemes.	2 points if a well-accepted, comparable[a], grading scheme was used 1 point if clearly describes their method but it is some other protocol 0 if not described

Item	Quality Criteria	Score
8	The **timing of baseline eye exam data/results** was specifically **described**	1 point if described 0 if not described
		Max total, prevalence: 13 points
Extra elements relevant to the progression outcomes		
9	Appropriate assessment of outcome. In the case of progression outcomes, retinal photography/exam must be **performed at the same frequency** on all study participants. *Retinal photography during follow-up should not be limited to participants who had diagnosed DR at baseline, or the frequency of follow-up photography should be the same in those with and without DR at baseline*	1 point if same frequency for all subjects 0 if frequency varied by initial clinical findings 0 if unclear or not described
10	**NPDR details**. DR grading scale has enough subtlety to detect the difference between mild and more severe grades of NPDR (thus the ability to detect progression/worsening *within* the NPDR grades)	2 points if follow-up data reported for differing severities of NPDR 0 if not reported or not described
11	DR grading was carried out **over follow-up time** by a dedicated, **trained grader or team of trained graders**	1 point if use of consistent, trained grader/team for all images 0 if many random graders 0 if not described
12	The **timing of follow-up** eye examination data/results was specifically described	2 points if described and baseline was 1st trimester (<14 weeks) and follow-up was in the 3rd trimester 1 point if timing described and baseline was mostly <22 weeks and follow-up was in the 3rd trimester or just after delivery (<12 weeks post-partum) 0 points if not described *(other timepoints were excluded)*
		Max total, progression: 19 points

Abbreviations: AAO, American Academy of Ophthalmology; DM, diabetes mellitus; DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; EURODIAB, Epidemiology and Prevention of Diabetes; GDM, gestational diabetes mellitus; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UK, United Kingdom; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

[a] National Screening Committee retinopathy standard (UK) specifically not listed as their 'maculopathy' category confuses the retinopathy status.

eTable 3. Determination of Score Thresholds for High-Quality Studies

Objective 1: Prevalence analysis	For objective 1, the scoring tool was applied to studies that were eligible for the prevalence analysis. The highest score that a study could receive was 13 points. The median score for studies eligible for objective 1 was 9.5 (IQR 6-10) for prevalence of any DR at Trimester 1, 10 (IQR 8-11) for prevalence of any DR at Trimester 3, 9 (IQR 6-11) for prevalence of PDR at Trimester 1, and 10 (IQR 7-12) for studies eligible for prevalence of PDR at Trimester 3. The threshold of ≥9/13 points was chosen as it covers the median score of each outcome of interest so can be considered to indicate studies that are average or better quality. This choice of threshold does not reject a large proportion of eligible studies from analyses (e.g., only rejects around 25% of eligible studies for Trimester 3 prevalence rates).
Objective 2: Progression analysis	For objective 2, the scoring tool was applied to studies that were eligible for the progression analysis. There was a total of 6 points relating to progression in addition to the earlier 13 points. Thus, the highest score a study could receive was 19 points. The median score for studies eligible for objective 2 was 13 (IQR 12-16) for progression from none to any DR, 12.5 (IQR 11-14) for worsened NPDR, 12.5 (IQR 11-16) for progression from NPDR to PDR, and 12 (IQR 11-14) for worsened PDR. The threshold of ≥12/19 was chosen as this covers the median score for outcomes of interest and rejects only between 20% and 33% of eligible studies depending on the specific progression outcome under assessment.

eTable 4. Quality Score of Included Studies

Study	qual 1	qual 2	qual 3	qual 4	qual 5	qual 6	qual 7	qual 8	qual 9	qual 10	qual 11	qual 12	Quality score[a]	
													1[b]	2[c]
T1DM only														
Arun, 2008[2]	1	2	2	1	0	1	2	0	0	2	1	1	**10**	**14**
Axer-Siegel, 1996[3]	1	2	2	3	1	1	1	1	1	2	1	0	**12**	**16**
Buchbinder, 2000[4]	1	2	2	1	0	0	2	1	1	0	0	1	**10**	**12**
Chew, 1995[5]	1	2	2	3	0	1	2	1	1	2	1	1	**12**	**17**
Dibble, 1982[6]	1	2	2	1	0	0	1	1	0	0	0	2	**10**	**12**
Klein, 1990[7]	1	2	2	3	0	1	2	1	1	2	1	1	**12**	**17**
Laatikainen, 1980[8]	1	2	2	1	0	1	1	1	1	0	1	2	**9**	**13**
Lapolla, 1998[9]	1	2	2	1	0	0	2	1	1	2	0	2	**11**	**16**
Lauszus, 2003[10]	1	2	2	3	1	1	2	1	1	2	1	2	**13**	**19**
Loukovaara, 2003[11]	1	2	2	3	0	1	2	1					**12**	NA
McElvy, 2001[12]	1	2	2	1	0	1	2	1	1	0	1	1	**10**	**13**
Moloney, 1982[13]	1	2	2	3	0	1	1	1					**11**	NA
Phelps, 1986[14]	1	2	2	2	0	1	2	1	1	0	1	1	**11**	**14**
Rahman, 2007[15]	1	2	0	0	0	1	2	1	0	2	1	2	7	**12**
Rosenn, 1992[16]	1	2	2	1	0	1	1	1	1	0	1	1	**9**	**12**
Vestgaard, 2010[17]	1	2	2	3	0	0	2	1	1	0	1	2	**10**	**14**
T2DM only														
Rasmussen, 2010[18]	1	2	2	3	0	1	2	1	1	2	1	2	**10**	**16**
Mixture of DM types														
Hampshire, 2013[19]	1	2	2	2	1	1	1	0	0	0	1	2	**10**	**13**

Abbreviations: NA, not applicable due to unavailable data; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

[a]Good quality score: ≥9 for prevalence analysis and ≥12 for progression analysis.
[b]Quality score with respect to a prevalence analysis (maximum possible score 13).
[c]Quality score with respect to a progression rate analysis (maximum possible score 19).

eTable 5. Characteristics of Pregnant Women in Each Study Population

Study	Subset characteristics	Maternal age (years) mean ± SD	Mean ± SD HbA1c level (%)		Eye exam timing	
			early pregnancy	around delivery	Early pregnancy	Late pregnancy
T1DM only						
Arun, 2008[2]		29 ± 5	7.2 ±1.3	6.7 ± 1.3	Trim 1 or 2	Trim 3
Axer-Siegel, 1996[3]		28.6 ± 4.6 range: 21 - 42	8.2 (95% CI 7.6 - 8.7)	7.1 (95% CI 6.6 - 7.4)	around conception	during pregnancy
Buchbinder, 2000[4]	Insulin lispro group	31.2 ± 6.3	NR	NR	Trim 1 or 2	early PP
	Regular insulin group	27.0 ± 5.4	NR	NR		
Chew, 1995[5]		27.8 ± 4.1	NR	NR	Trim 1	early PP
Dibble, 1982[6]		range: 18 - 32	NR	NR	Trim 1	Trim 3
Klein, 1990[7]		26.7 ± 4.8	NR	NR	Trim 1	Early PP
Laatikainen, 1980[8]		NR	NR	NR	Trim 1	Trim 3
Lapolla, 1998[9]		29 ± 4.7	7.2 ± 1.6	6.4 ± 0.8	Trim 1	Trim 3
Lauszus, 2003[10]		28 ± 5 range: 17 - 40	7.5 ± 1.1 range 5.3 - 10.2	7.5 ± 1.1 range: 5.5 - 11.8	Trim 1	Trim 3
Loukovaara, 2003[11]	Insulin lispro group	30.0 ± 4.4	7.2	6.5	Trim 1	Trim 3
	Regular insulin group	30.6 ± 4.7	7.5	7.2		
McElvy, 2001[12]		no progressed group = 26.2 ± 5.1 progressed group = 25.4 ± 4.5	no progressed group = 9.2 ± 1.7 progressed group = 9.9 ± 1.8	no progressed group = 7.5 ± 1.3 progressed group = 7.7 ± 1.0	Trim 1 or 2	Trim 3/early PP
Moloney, 1982[13]		28.0 ± 0.6	HMA present group = 9.4 ± 0.2[a] HMA absent group = 8.6 ± 0.2[a]	HMA present group = 8.4 ± 0.2[a] HMA absent group = 8.2 ± 0.2[a]	Trim 1	Trim 3
Phelps, 1986[14]		no DR group = 25.2 ± 1.3 background DR group = 28.9 ± 0.9 PDR group = 23.8 ± 1.7	NR	NR	Trim 1 or 2	Trim 3/early PP
Rahman, 2007[15]		23.5 ± 5.2 range: 18 - 34	6.9 ± 1.5	6.3 ± 1.2	Trim 1	Trim 3

Study	Subset characteristics	Maternal age (years) mean ± SD	Mean ± SD HbA1c level (%)		Eye exam timing	
			early pregnancy	around delivery	Early pregnancy	Late pregnancy
Rosenn, 1992[16]		no progressed group = 25.5 ± 4.6 progressed group = 25.6 ± 4.6	no progressed group = 9.3 ± 1.6 progressed group = 10.3 ± 2.0	no progressed group = 7.7 ± 1.2 progressed group = 7.7 ± 1.1	Trim 1 or 2	Trim 3/early PP
Vestgaard, 2010[17]		no progression group (-P) = median 31.5 (IQR: 28-34) mild-mod progression group (+P) = 29 (27-32) ST progression group (++P) = 29 (26-34)	-P = median 6.7 (IQR: 6.3-7.2) +P = 6.5 (6.1-6.7) ++P = 7.4 (6.9-8.7)	-P = median 5.9 (IQR: 5.7-6.3) +P = 5.9 (5.6-6.2) ++P = 5.7 (5.6-6.0)	Trim 1	Trim 3
T2DM only						
Rasmussen, 2010[18]		no progressed group = 32.5 ± 5.3 progressed group = 33.0 ± 5.8	no progressed group = 6.5 ± 1.1 progressed group = 7.2 ± 1.2	no progressed group = 5.7 ± 0.6 progressed group = 5.7 ± 0.6	Trim 1 or 2	Trim 3
Mixture of DM types						
Hampshire, 2013[19]		31	NR	NR	Trim 1	Trim 3

Abbreviations: CI, confidence interval; DR, diabetic retinopathy; HMA, haemorrhages; mod, moderate; NR, not reported; PDR, proliferative diabetic retinopathy; PP, postpartum; SD, standard deviation; ST, sight-threatening; T1DM, type 1 diabetes; T2DM, type 2 diabetes; Trim, trimester.

[a]Among 49 participants with DR.

eTable 6. Pooled Prevalence of Proliferative Diabetic Retinopathy Around Delivery

	N studies	Cases/Total	Prevalence per 100 (95% CI)	I^2 (%)	*P*-value
Study region					
Europe	4 subsets from 3 studies	6/183	2.30 (0.29 – 5.50)	0.0	.47
United States	3 studies	68/398	16.92 (13.33 – 20.83)	0.0	.95
Between-subgroup heterogeneity					*<.001*
Study era					
Pre-St. Vincent Declaration	3 studies	68/398	16.92 (13.33 – 20.83)	0.0	.95
Post-St. Vincent Declaration	4 subsets from 3 studies	6/183	2.30 (0.29 – 5.50)	0.0	.47
Between-subgroup heterogeneity					*<.001*
DR grading methods					
Modified Airlie House	3 studies	68/398	16.92 (13.33 – 20.83)	0.0	.95
ETDRS	3 subsets from 2 studies	2/80	1.28 (0.00 – 6.43)	12.3	.32
WESDR	1 study	4/103	3.88 (1.07 – 9.65)	NA	NA
Between-subgroup heterogeneity					*<.001*

Abbreviations: DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; NA, not applicable; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

[a] Type 1 diabetes studies only, by subgroups of interest, using studies with similar quality and diabetic retinopathy grading scheme.

eTable 7. Pooled Progression Rate of Nonproliferative Diabetic Retinopathy Worsening by at Least 1 Level

	N studies	Cases/Total	Progression rate per 100 (95% CI)	I^2 (%)	*P*-value
Type of diabetes					
T1DM	16 subsets from 15 studies	214/639	30.61 (22.38 – 39.45)	77.8	<.01
T2DM	2 studies	12/34	34.71 (19.09 – 52.01)	0.0	.
Between-subgroup heterogeneity					*.660*
Study region					
Europe	8 subsets from 7 studies[b]	63/233	26.43 (18.92 – 34.62)	36.4	.14
Middle East	2 studies	21/42	49.85 (34.45 – 65.26)	0.0	.
United States	8 subsets from 7 studies	142/398	31.42 (20.15 – 43.78)	80.1	<.01
Between-subgroup heterogeneity					*.031*
Study era					
Pre-St. Vincent Declaration	8 studies	170/425	42.77 (31.63 – 54.27)	79.9	<.01
Post-St. Vincent Declaration	10 subsets from 8 studies[b]	56/248	20.51 (13.79 – 28.01)	33.7	.14
Between-subgroup heterogeneity					*.002*
DR grading methods					
Modified Airlie House	6 subsets from 5 studies	111/311	31.62 (17.32 – 47.69)	83.8	<.01
WESDR/ modified WESDR	3 studies[b]	29/127	22.34 (15.13 – 30.43)	2.9	.357
ETDRS	2 studies	5/27	17.90 (4.48 – 35.99)	0.0	.
Eurodiab	1 study	2/15	13.33 (1.66 - 40.46)	NA	NA
UK NSCG	2 subsets from 1 study[b]	18/52	34.26 (21.64 - 48.01)	0.0	.
Other	4 studies	61/141	43.41 (23.20 - 64.76)	82.5	<.01
Between-group heterogeneity					*.175*

Abbreviations: DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; NA, not applicable; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UK NSCG, United Kingdom National Screening Committee guidelines; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

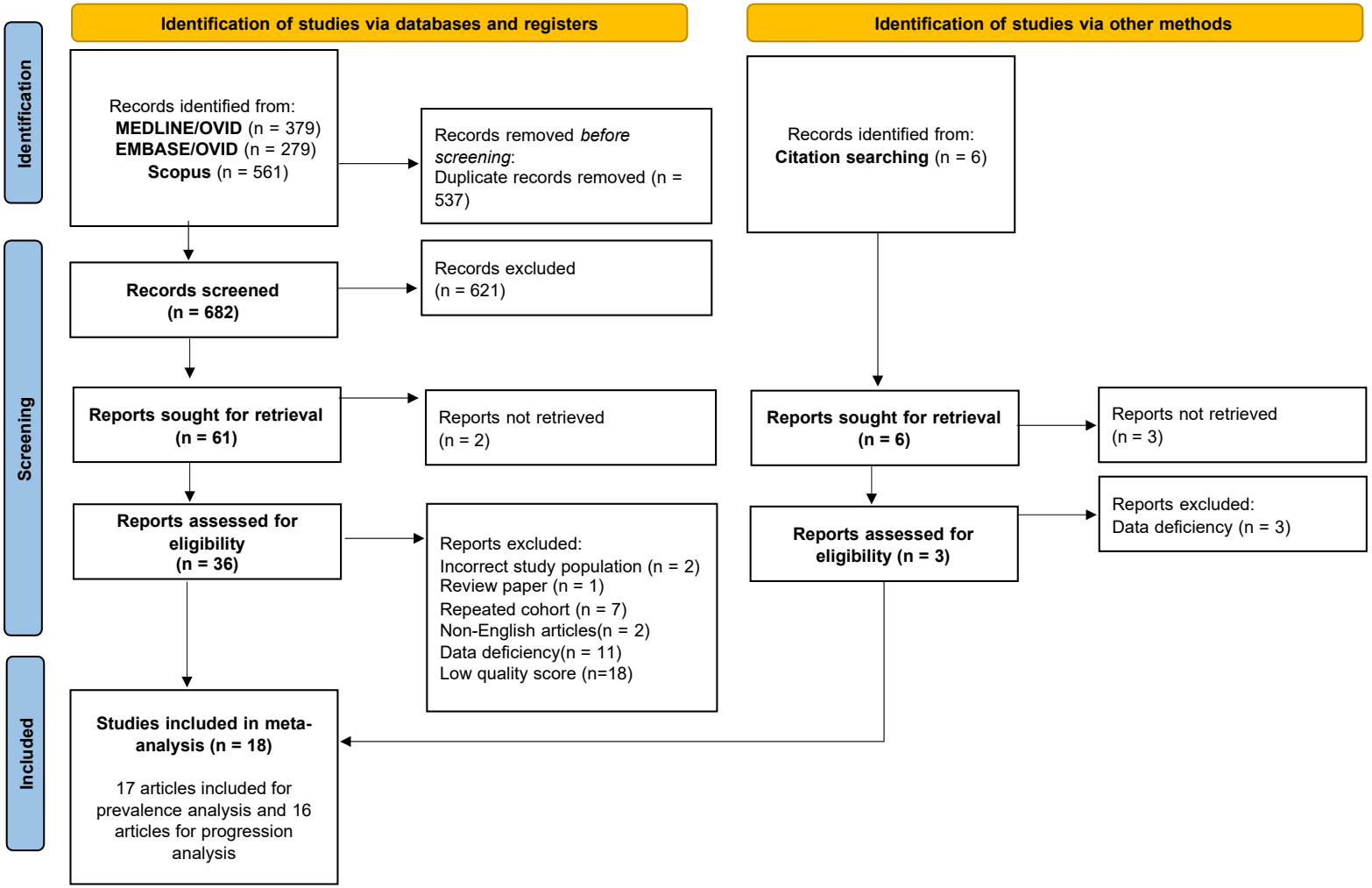
[a] In both diabetes type, by subgroups of interest, using studies with similar quality.
[b] Includes the T2DM study.

eTable 8. Comparison of Pooled Estimates Between Freeman-Tukey Double Arcsine Transformation and Random Intercept Mixed-Effects Logistic Regression Model

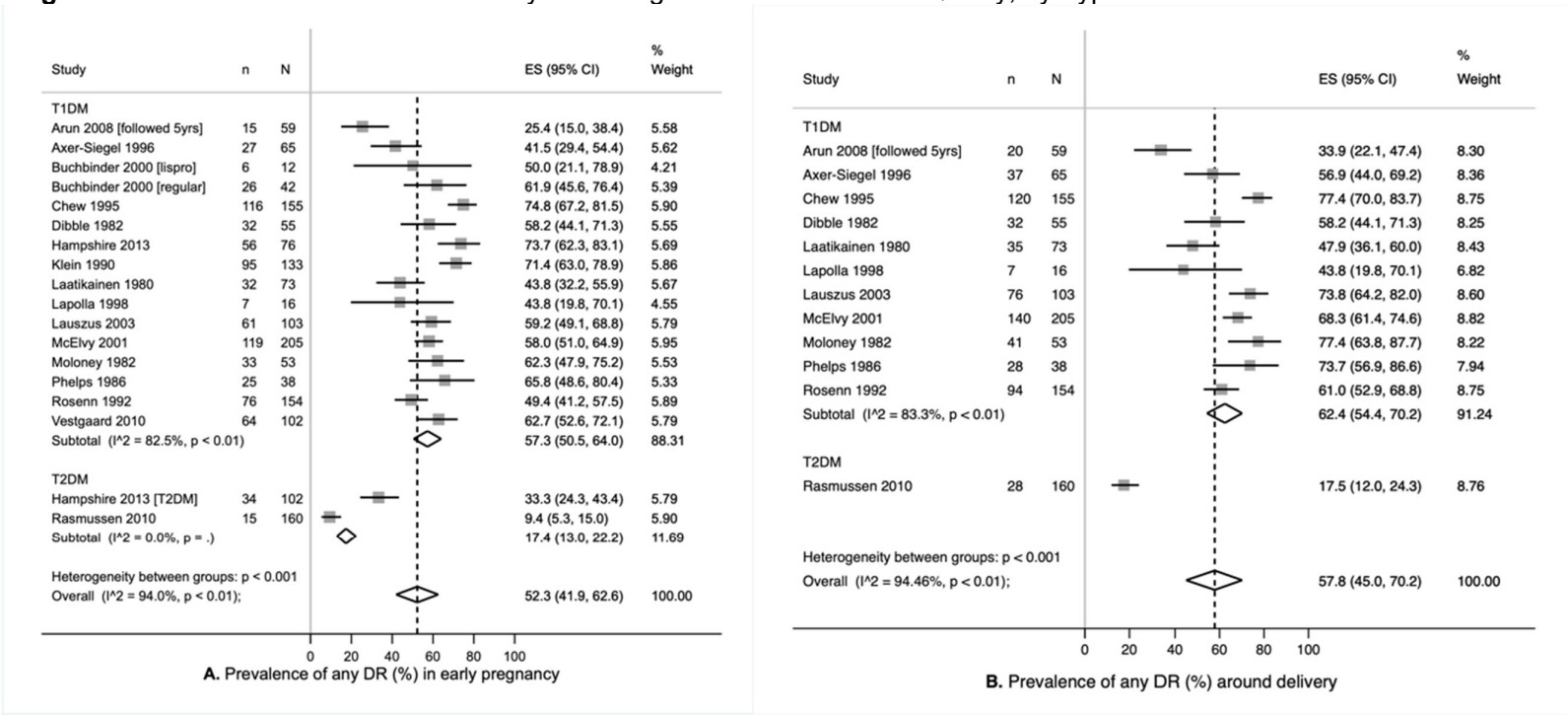
		Rate per 100 pregnancies (95%CI)	
		metaprop_one command with Freeman-Tukey double arcsine transformation option (FTT)	**metapreg** command for a random intercept mixed-effects logistic regression model[*]
Prevalence[a]			
Any DR	early pregnancy	55.5 (38.9 – 71.6)	55.2 (39.7 - 69.8)
	around delivery	59.5 (36.1 – 80.8)	59.7 (39.5 - 77.1)
PDR	early pregnancy	6.0 (2.2 - 11.2)	5.4 (2.2 - 12.7)
	around delivery	6.4 (1.7 - 13.4)	6.2 (2.6 - 14.3)
Progression[b]			
None to any DR		15.0 (9.9 - 20.8)	15.8 (11.3 - 21.6)
Worsened NPDR		30.9 (23.3 - 39.2)	30.3 (22.1 - 40.0)
NPDR to PDR		*6.3 (3.3 - 10.0)*	*8.2 (5.5 - 11.8)*
Worsened PDR		37.0 (21.2 - 54.0)	38.2 (24.4 - 54.3)

[*]random intercept logistic regression model described in Stijnen *et al.*[20]
[using Stata command metapreg, and confirmed using Stata command: meglm case || study: , family(binom denom) link(logit)]
[a] studies with similar quality and grading scheme.
[b] studies with similar quality

eFigure 1. Systematic Search and Selection of Eligible Literature

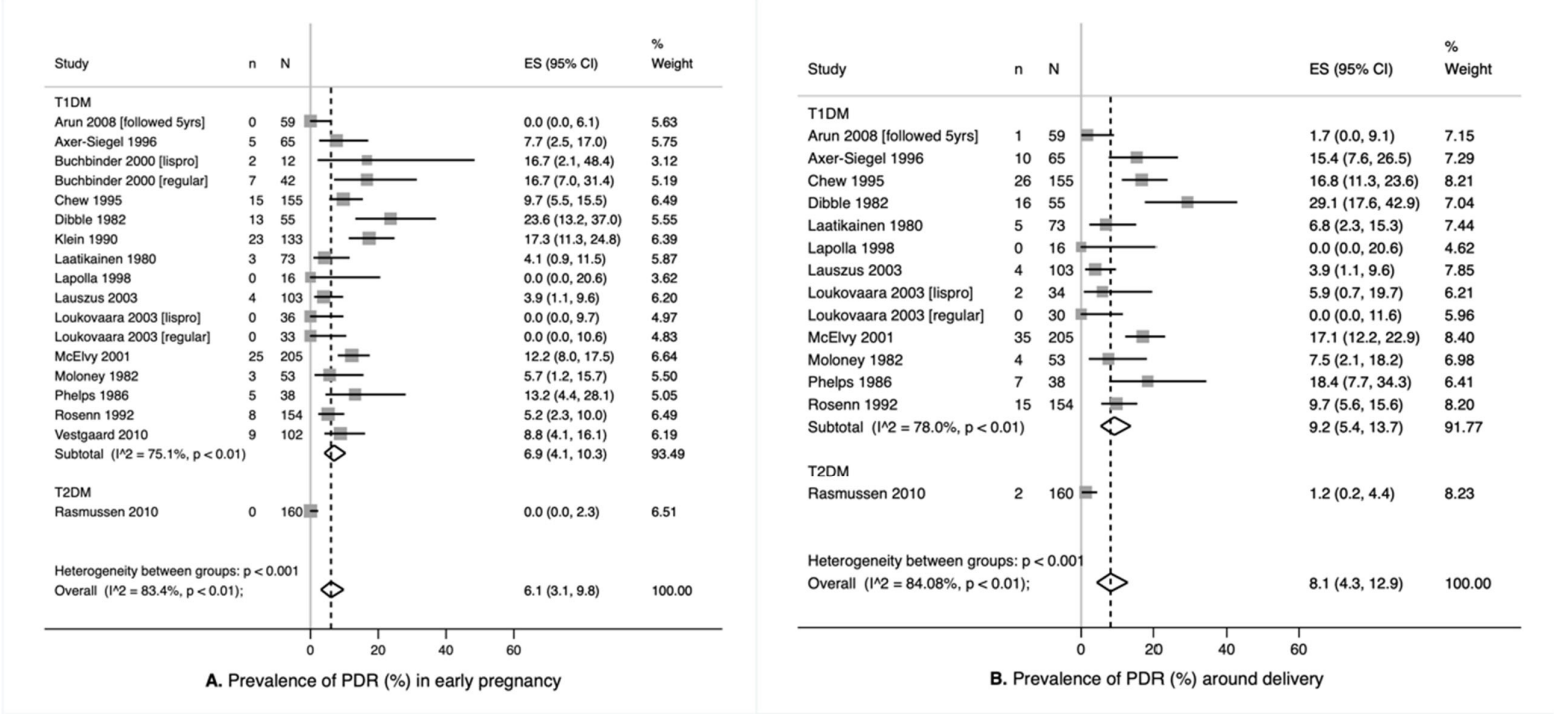


eFigure 2. Forest Plots of Prevalence of any DR Using Studies With Similar Quality, by Type of Diabetes



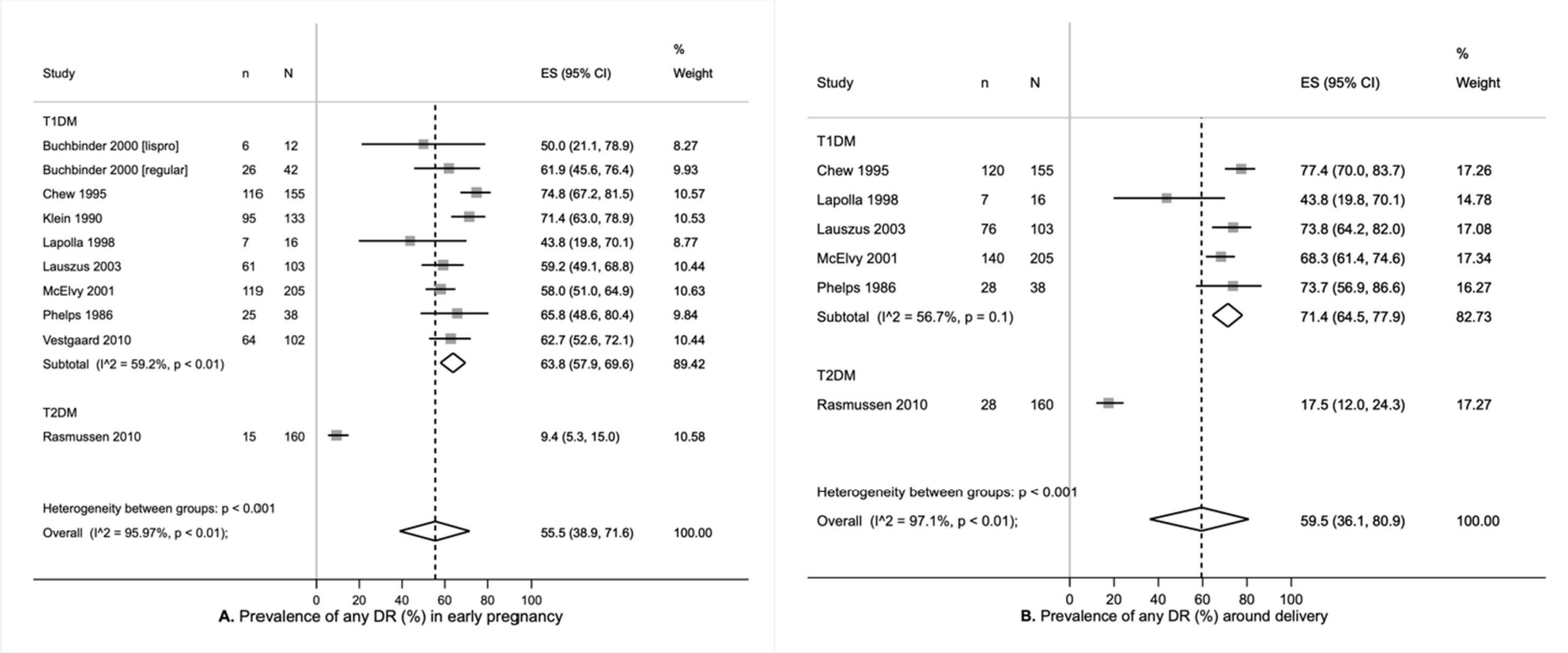
CI, confidence interval; DR, diabetic retinopathy; ES, effect size; T1DM, type 1 diabetes; T2DM, type 2 diabetes.
Weights are from random effects analysis.
[a] Quality score for prevalence ≥ 9

eFigure 3. Forest Plots of Prevalence of PDR Using Studies With Similar Quality, by Type of Diabetes



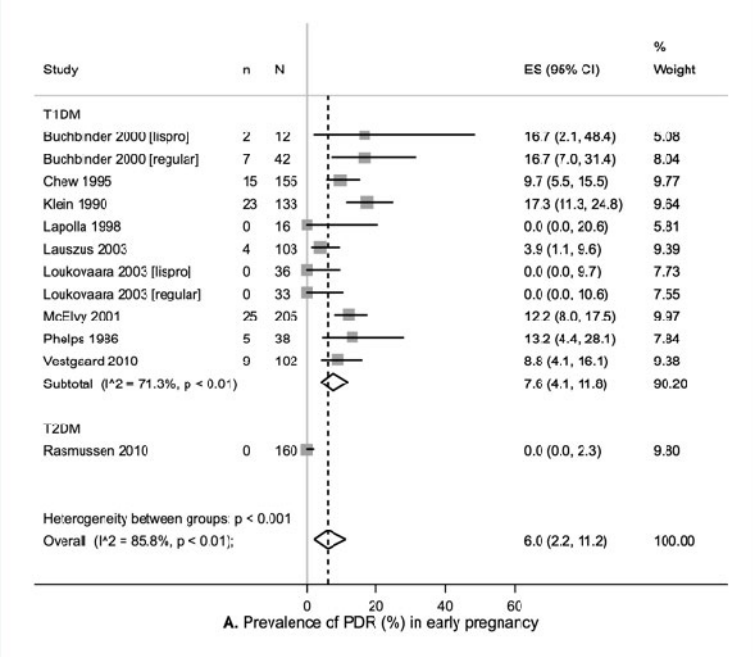
CI, confidence interval; ES, effect size; PDR, proliferative diabetic retinopathy; T1DM, type 1 diabetes; T2DM, type 2 diabetes.
Weights are from random effects analysis.
[a] Quality score for prevalence ≥ 9

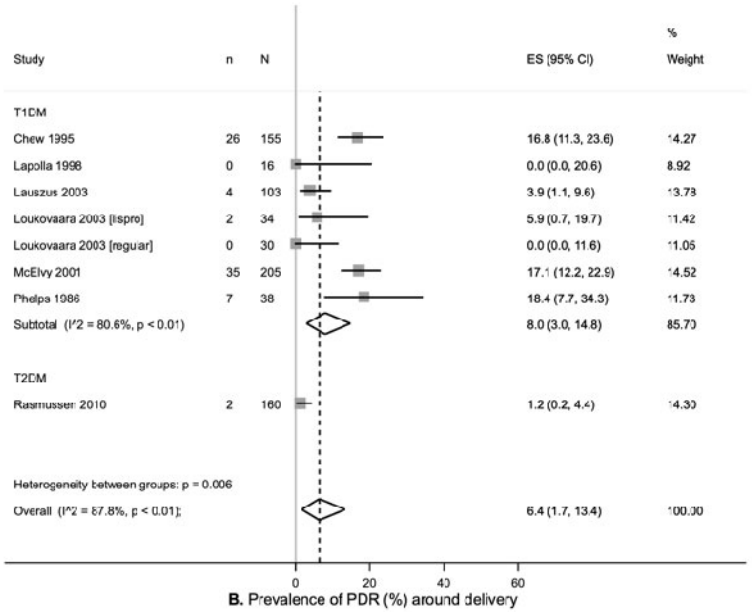
eFigure 4. Forest Plots of Prevalence of any DR Using Studies With Similar Quality and DR Grading Scheme, by Diabetes Type



CI, confidence interval; DR, diabetic retinopathy; ES, effect size; T1DM, type 1 diabetes; T2DM, type 2 diabetes.
Weights are from random effects analysis.
[a] Quality score for prevalence ≥ 9
[b] The ETDRS grading system or its modifications including modified Airlie House, WESDR, and modified WESDR methods

eFigure 5. Forest Plots of Prevalence of PDR Using Studies With Similar Quality and DR Grading Scheme, by Type of Diabetes





CI, confidence interval; ES, effect size; PDR, proliferative diabetic retinopathy; T1DM, type 1 diabetes; T2DM, type 2 diabetes.
Weights are from random effects analysis.
[a] Quality score for prevalence ≥ 9
[b] The ETDRS grading system or its modifications including modified Airlie House, WESDR, and modified WESDR methods

eReferences

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