Associations between diabetic retinopathy and modifiable risk factors: an umbrella review of meta-analyses

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Abstract (250/250)

Aims: Several modifiable risk factors have been meta-analysed for diabetic retinopathy (DR), such as physical activity and vitamin D status. To date, these factors have not been systematically aggregated and the credibility of evidence assessed. Therefore, the aim of this umbrella review was to aggregate all modifiable risks of DR and assess the credibility of evidence.

Methods: An umbrella review of meta-analyses was undertaken. For each meta-analytic association, random-effects effect size, 95% confidence intervals (CIs), heterogeneity, small-study effects, excess-significance-bias and 95% prediction intervals were calculated. The credibility of significant evidence ($p<0.05$) was graded from I to IV, using pre-defined criteria.

Results: After initial searches, 13 studies were included covering 34 independent outcomes (total participants=824,372). Positive associations were found between insulin usage and diabetic macular oedema (RR=4.5; 95%CI 3.1-6.6), and DR risk (RR=2.3; 95%CI 1.4-3.9) in people with type 2 diabetes. Vitamin D deficiency was associated with DR risk (OR=2.8 95%CI 1.1-7.1), as was obesity (RR=1.34; 95% CI 1.06-1.68) and sedentary behaviour (RR=1.22; 95%CI 1.03-1.44). Intensive blood pressure targets (RR=0.8 95%CI 0.8-1.0), and moderate physical activity (RR=0.69 95%CI 0.53-0.91) yielded significant protective associations with DR.

Conclusions: People with type 2 diabetes on insulin have high risk of macular oedema and DR. Vitamin D deficiency yielded almost 3 times greater odds of DR, while intensive blood pressure control reduces DR risk by 20% and moderate physical activity by 31%. Healthcare professionals should use this evidence to identify those people most at risk to ensure that proper treatment and healthy lifestyles are recommended.

Introduction

Diabetes mellitus can cause several long-term macrovascular changes, leading to accelerated cardiovascular and cerebrovascular diseases. Furthermore, diabetes mellitus can also cause microvascular complications including nephropathy, neuropathy, and retinopathy[1]. Diabetic retinopathy (DR) has been reported as the leading cause of blindness among diabetic adults[2], and is characterised by microvascular changes in different parts of the eye, including the retina, causing visual impairment and eventually blindness if left untreated[1]. It has been reported that almost all people with diabetes are likely to suffer with some form of DR over a 20-year period, however not all cases lead to visual impairment[1]. Indeed, DR can be broadly categorised as non-sight-threatening, sight-threatening, and clinically significant macular oedema (DME). It has recently been estimated that the global prevalence on DR in people with diabetes is 22.3%[3]. Furthermore, 6.2% and 4.1% of people with diabetes have been reported as having sight-threatening DR and DME, respectively, with projections indicating that the global burden of DR will significantly increase by 2045[3].

Several conditions have been associated with DR and DME, of which several can be classified as modifiable risk factors (defined as 'a determinant that can be modified by intervention'[4]), including serum vitamin D status, smoking status, and sedentary behaviour[5–7]. To date, meta-analytic data regarding these modifiable risk factors have not been aggregated according to the strength and credibility of the evidence.

In order to address the breadth of the literature of complex conditions and multiple outcomes, an increasing number of studies have used an 'umbrella review' approach: a novel method of synthesising existing meta-analyses to capture the breadth and credibility of outcomes associated with a given exposure[8–11].

Therefore, the aim of the present study was to assess the strength and credibility of the evidence on the associations between DR and any type of modifiable risk factor, derived from published meta-analyses of existing studies using an umbrella review approach. We aimed to answer the following questions:

1. What modifiable risk factors are associated with any type of DR and DME?
2. What is the epidemiological credibility of the reported relationships?

3. Which modifiable risk factors yield the highest effect size regarding DR and/or DME risk?

Because these meta-analytic associations have not been systematically graded according to the credibility of evidence, this study contributes a novel addition to the literature that has the potential to yield several benefits. For example, results of this study have the potential to inform practitioners, people with diabetes, and public health policy makers on what evidence exists in order to create targeted interventions, inform patients on modifiable risks of DR, and to inform further research.

Methods

We performed a systematic review adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations[12] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[13], according to a pre-published protocol in the International prospective register of systematic reviews (PROSPERO registration number CRD42021245155). There were no changes to the pre-registered protocol.

Search strategy and selection criteria

We searched Embase, Pubmed, and CINAHL databases (from inception to 26/3/2021) to identify systematic reviews with meta-analyses pooling any type of studies examining associations between DR and/or DME and any modifiable risk factor. The following search key was used: "(risk OR risk factor) AND (diabetic retinopathy OR diabetic macular edema OR diabetic macular oedema OR proliferative diabetic retinopathy OR proliferative retinopathy OR sight threatening retinopathy OR retinopathy) AND (meta anal* or meta-anal* or systematic review). Two independent reviewers (MT, RD) searched titles/abstracts for eligibility, and then evaluated the full text of the articles remaining after the title/abstract phase. A third, senior reviewer (SP) resolved any potential conflict where a consensus was not reached. When more than one meta-analysis assessed the same risk factor and outcome, we only included the one with the larger number of studies[14–16].

Exclusion criteria were: 1) studies published in languages other than English, 2) meta-analyses reporting only one study for an independent outcome, since no meta-analysis was possible.

Data extraction

Two reviewers (MT, RD) independently extracted data in a bespoke, pre-defined excel spreadsheet. For each meta-analysis, the following were extracted: PMID/DOI; first author; publication year; population included in the study; study design; number of included studies; the total sample size and number of cases (i.e., people having the outcome of interest); type/grade of diabetic retinopathy; type of diabetes; individual study effect sizes (ES) and 95% confidence intervals (CIs); and any adjustments made. The

methodological quality and risk of bias of each included meta-analysis was assessed with the Joanna Briggs Institute (JBI) critical appraisal for systematic reviews[17] by two independent investigators (MT, RD).

Data analysis

For each meta-analysis, the meta-analysis was re-performed, calculating the pooled ES with 95% CIs using a random-effects model, stratified by study design (case-control or cross-sectional; cohort; and randomised controlled trail (RCT) designs)[18]. If individual meta-analyses stratified their results according to type of DR (for example, sight-threatening and non-sight threatening), we also reported these stratified results. Heterogeneity was assessed with the I^2 statistic, with <50% being considered low, 50-75% moderate, and >75% as high heterogeneity[19]. Additionally, 95% prediction intervals (PIs) were calculated for the summary effect sizes[20]. The presence of small-study effect bias[14,21–23] was also tested, which was deemed to be present in case of (a) the pooled estimate being larger than the effect size of the largest study (defined as having the smallest standard error), or (b) the presence of publication bias (Egger's regression asymmetry test $p<0.10$). Furthermore, the excess significance bias test was conducted by evaluating whether the observed number of studies with statistically significant results was different from the expected number of studies with statistically significant results[23,24].

Assessment of the credibility of the evidence

The credibility of meta-analyses was assessed according to stringent criteria established on previously published umbrella reviews[16,21,22,25–27]. In brief, associations that presented nominally significant random-effects summary ESs ($p<0.05$) were ranked as Grade I, II, III, or IV based on the number of events, strength of the association, and the presence of several biases (see **Table 1** for full criteria).

RESULTS

Search

The flow diagram of search, selection and inclusion process is fully reported in **Figure 1**. The initial search yielded 1,565 hits, of which (after automatic duplicate removal) 926 studies were assessed at title/abstract level against the inclusion and exclusion criteria by two independent reviewers (MT, RD). Of these, 66 articles were selected for full-text examination and assessed independently by the same two reviewers (MT, RD). After full text review – 13 systematic reviews with meta-analyses were included[5–7,28–36] with a total of 34 independent outcomes, and a total of 824,372 participants. The median participants per outcome was 6,989, and the median studies per outcome was 6. The majority (10/13) of studies pooled people with both type 1 and 2 diabetes, and three studies exclusively included people with type 2 diabetes. Table 2 shows full descriptive statistics of included studies and Supplementary Table 1 shows a list of full text studies that were excluded, with justifications.

Meta-analysis

Overall, 14 outcomes yielded statistically nominal results (p=<0.05), one of which was graded Grade II, four Grade III, and the remaining nine significant outcomes were graded as Grade IV (see Table 3 and Figures 2-4). Of the significant outcomes, three yielded low heterogeneity (I^2<50%; moderate physical activity; vitamin D deficiency; intensive versus conventional blood pressure targets), three outcomes yielded moderate heterogeneity (I^2=50-75%; obesity; sedentary behaviour; intensive versus conventional glycaemic control), with the remaining significant outcomes yielding high heterogeneity (I^2=>75%). Five significant outcomes yielded a PI that excluded the null hypothesis, 12 had evidence of small-study effects, while four had evidence of excess significance bias (see Table 3 for full details).

Risk of bias

All included meta-analyses were judged to be of sufficient methodological quality (see Supplementary Table 2), however most studies (9/13) did not have more than one independent reviewer critically appraising the quality of included studies. Furthermore,

the majority (7/13) of studies did not measure and/or discuss publication bias in their respective analyses.

Modifiable risk factors:

Glycaemic control in type 2 diabetes

Four outcomes assessed glycaemic control and DME or DR risk in type 2 diabetes, three of which examined insulin use and one assessed intensive glycaemic control (versus conventional glycaemic control). Intensive glycaemic control yielded a significantly lower risk of DR versus conventional glycaemic control (RR=0.79 95%CI 0.67-0.94), and the use of insulin in type 2 diabetes was positively associated with DR risk and DME risk in cohort studies (RR=2.30 95%CI 1.35-3.93; RR=4.51 95% 3.10-6.56, respectively). In case control/cross-sectional studies, there was a non-significant association between insulin use in type 2 diabetes and DME risk (RR=1.45 95% CI 0.52-4.07).

Alcohol intake

Two outcomes examined risk of DR and alcohol intake were included, both of which were found not to be significant (case control/cross-sectional OR=0.90 95% CI 0.77-1.07; cohort OR 0.95 95% CI 0.66-1.36).

Blood pressure

Five outcomes examined associations between blood pressure and DR, four of which were RCTs, with the other outcome including case control/cross-sectional studies. Intensive blood pressure targets (versus conventional blood pressure targets) yielded a significant negative association (RR=0.83 95% CI 0.72-0.96), however intensive versus conventional blood pressure targets yielded non-significant results regarding DR progression (RR=0.93 95%CI 0.79-1.10) and proliferative DR incidence (RR=0.97 95%CI 0.72-1.30). Blood pressure levels as part of metabolic syndrome yielded non-significant results (OR=1.39 95% CI 0.96-1.95), and non-significant results were found regarding the effect of blood pressure lowering medication and DR risk (RR=0.83 95%CI 0.68-1.02).

BMI

Four outcomes assessed DR risk and BMI related outcomes (obesity versus no obesity in cohort studies; overweight versus normal weight; BMI as a continuous variable in case-control/cross-sectional and cohort studies). Analysis showed that obesity (versus no obesity) was positively associated with DR risk (RR=1.34 95% CI 1.06-1.68). All other

outcomes yielded non-significant associations (overweight vs normal weight OR=0.87 95% CI 0.69-1.09; BMI as a continuous variable in case-control/cross-sectional studies OR=0.99 95% CI 0.96-1.01; BMI as a continuous variable in cohort studies OR=1.04 95% CI 0.93-1.17).

Dyslipidaemia

Two outcomes assessed DR risk and dyslipidaemia: specifically high-density lipoprotein (HDL), and triglyceride (TG) levels, with all outcomes being non-significant (HDL OR=0.97 95% CI 0.94-1.01; TG OR=0.85 95% CI 0.63-1.15).

Four outcomes assessed dyslipidaemia and DME risk: specifically total cholesterol, HDL levels, low-density lipoprotein (LDL) levels, and TG levels, three of which were significant. The meta-analysis yielded significantly higher total cholesterol levels in participants with DME (versus no DME; SMD=30.05mg/dL 95% 21.14-38.95mg/dL), significantly higher LDL levels in participants with DME (versus no DME; SMD=18.63mg/dL 95% CI 5.72-31.54mg/dL), and significantly higher TG levels in participants with DME (versus no DME; SMD=24.8mg/dL 95% CI9.24-40.35mg/dL). HDL levels yielded no significant differences (SMD=2.23mg/dL 95% -0.19-4.66mg/dL).

Physical activity/sedentary behaviour

Eight outcomes examined associations between physical activity/sedentary behaviour and DR risk, seven of which assessed physical activity, and one assessing sedentary behaviour.

Total physical activity

Two outcomes measured total physical activity and DR risk. Only the case control/cross-sectional studies were found to be significant (RR=0.95 95% CI 0.91-0.99), with cohort studies showing no significant risk (RR=0.98 95% CI 0.68-1.42). Two outcomes measured overall physical activity and sight-threatening DR specifically, both which were non-significant (case control/cross-sectional RR 0.91 95%CI 0.81-1.02; cohort RR=0.75 95%CI 0.54-1.05).

Stratified physical activity

Three outcomes measured physical activity that was stratified by intensity (low, moderate, or vigorous –the original authors did not specify the parameters of stratification) and overall DR risk, of which only moderate physical activity yielded significant negative significant associations (a protective effect) (RR=0.69 95%CI 0.53-0.91). Low intensity (RR=1.05 95%CI 0.51-2.16) and vigorous intensity (RR=0.93 95%CI 0.66-1.31) physical activity both yielded non-significant associations.

Sedentary behaviour

One outcome examined sedentary behaviour and DR risk, yielding a significant positive association between time spent in sedentary behaviour and DR risk (RR=1.22 95%CI 1.03-1.44).

Smoking

Two outcomes examined associations between smoking and DR, both of which were non-significant (case control/cross-sectional OR=1.01 95%CI 0.93-1.10; cohort OR=1.03 95% CI 0.95-1.12).

Vitamin D status

Vitamin D deficiency

Two outcomes examined associations between vitamin D deficiency and DR, with both outcomes yielding significant associations (cohort studies OR=1.28 95% CI 1.06-1.56; case control/cross sectional studies OR=2.79 95%CI 1.09-7.14).

Serum 25-hydroxy-vitamin D (25(OH)D) levels

One outcome examined 25(OH)D levels (as a continuous variable) and DR risk, with people with DR having significantly lower 25(OH)D levels than people with no DR (SMD=-0.12ng/mL 95% CI -0.19;-0.04ng/mL).

Discussion

The present umbrella review, including 13 meta-analyses with 34 independent modifiable risk factors, provides a broad overview of the existing evidence. Furthermore, this review provides a systematic evaluation of the methodological quality of available meta-analyses. According to the stringent grading criteria, one outcome yielded Grade II evidence, four outcomes yielded Grade III evidence, and nine outcomes yielded Grade IV evidence. Moreover, this umbrella review reports on the magnitude of meta-analytic risks for each outcome. The modifiable risk factors that yielded the highest magnitude of meta-analytic risks were positive associations between insulin use and DME risk, insulin use and DR risk, and vitamin D deficiency.

Glycaemic control and DR/DME in people with type II diabetes

Strong associations were found between insulin use in people with type 2 diabetes and DME/DR risk. Although the precise mechanisms of insulin usage and DME/DR risk are unknown, it is likely that the duration of diabetes, which has been independently shown as a risk factor for both DR and DME[37], has a role to play. Indeed, in one of the included meta-analyses, when including only studies that adjusted for diabetes duration, insulin usage was not associated with DR[38]. Another possible mechanism could be the result of increased vascular leakage: mice-based studies have shown that insulin treatment resulted in increased vascular leakage, signalled by the epidermal growth factor receptor[39]. Further research to ascertain whether insulin use is a risk factor independent of duration of diabetes is warranted. Furthermore, future research should focus on the effect of other types of anti-hyperglycaemic agents, including Piogglitazone, GLP1Ra, and SGLT2i on DR and DME risk.

Vitamin D

All three outcomes measuring vitamin D status yielded significant associations, with vitamin D deficiency (serum 25(OH)D levels <20 ng/mL versus >20ng/mL) being significantly linked with a higher risk of DR, and total serum 25(OH)D levels being negatively associated with DR risk. One possible mechanism leading to the protective effect is the anti-inflammatory effects of vitamin D. Indeed, vitamin D has been reported

to inhibit vascular smooth cell growth[40] inhibiting the expression of transforming growth factor β1[41], and is a key regulator of several genes also associated with DR[16].

Physical activity

Total physical activity was shown to be a significant protective factor against DR (in case control/cross-sectional studies only), however when stratified according to DR type, total physical activity did not correlate with sight-threatening DR, meaning that it is not possible to conclude that physical activity is protective against sight threatening DR. This result, however, was based on fewer studies, so it is possible that this result could have been due to a lack of statistical power. Indeed, large cohort studies have found physical activity to be an independent factor in reducing the progression of DR[42]. Further study is warranted to confirm or refute this finding.

When stratified according to type of physical activity, only moderate intensity physical activity was significantly correlated with DR risk. Moreover, sedentary behaviour was found to be significantly associated with DR risk. It has well-reported that physical activity is important for control of diabetes, with uncontrolled diabetes leading to a high risk of complications of diabetes including DR[43]. Of the different intensities of physical activity, moderate intensity physical yielded significant protective benefits, however this should not lead to practitioners and researchers concluding that low intensity physical activity has no protective effect, as this review has also showed that the reduction of sedentary activity has a significant beneficial effect. Indeed, the meta-analysis which reported the stratified physical activity data had not defined the terms low, moderate, and vigorous physical activity, therefore these stratified results should be treated with caution. It is worth noting that vigorous physical activity is contra-indicated in people with sight-threatening DR, and could risk to vitreous haemorrhaging or retinal detachment[43,44] due to potential dramatic changes in blood pressure, and should not be recommended[7].

Blood pressure

Surprisingly, blood pressure (as a symptom of metabolic syndrome) was not found to be associated with DR in this review. One possible reason for this is because the meta-analysis in which the data was collected did not stratify between systolic or diastolic blood

pressure but reported blood pressure as a component of metabolic syndrome. It has been reported in several large cohort studies that elevated systolic blood pressure is a much stronger indicator of DR risk than diastolic blood pressure[45–48], therefore it is possible that this pooling of diastolic and systolic blood pressures may not have yielded a significant risk.

The use of intensive blood pressure targets versus conventional targets, however, was found to be a significant protective component against DR, however this protective effect size was small, and the certainty of evidence was low. The authors of the review do not oppose that hypertension is an independent risk factor of DR and should be treated/managed accordingly.

BMI

Of the outcomes that examined BMI related outcomes and DR risk, the presence (versus absence) of obesity was significantly associated with increased risk of DR. Whilst it is known that obesity is major risk factor for diabetes, the exact mechanisms surrounding BMI and DR risk are sparse[30] and more research is warranted.

Dyslipidaemia

Of the outcomes that examined dyslipidaemia and DR/DME risks, LDL cholesterol, TG, and total cholesterol were significantly higher in people with DME compared to people with no DME. LDL cholesterol has been reported to be toxic to endothelial cells (as opposed to HDL, which has been reported as having a potential vaso-protective role)[29], which could lead to microvascular changes in the retina of people with diabetes. It is not surprising that participants with DME had higher total cholesterol and triglyceride levels as several studies have found associations between total cholesterol levels, triglyceride levels, and the presence of hard exudates linked to DME (and DR)[49–51]. It is possible that these associations with dyslipidaemia were only observed in DME rather than DR because a paucity of data precluded stratification by disease stage. Indeed, one of the included meta-analyses reported no significant associations between serum lipid levels in participants with non-proliferative DR, whereas with proliferative DR yielded significant associations[28]. These data, however, was not included in the current umbrella review

because individual study data for the stratified types of DR were not given. Although HDL is considered 'good' cholesterol, all outcomes that examined HDL cholesterol yielded non-significant results which suggests that it may be the disruptive effect of LDL rather than protective effect of HDL which influences DR. This warrants more research.

Umbrella reviews provide top-tier evidence and insights, and this is the first review to systematically pool meta-analyses of DR/DME risk and modifiable risk factors and rate the evidence's credibility. The results of this study, however, should be considered within its limitations. Although we measured for heterogeneity, many of the meta-analyses included in this review pooled different types of diabetes and stages of DR – further meta-analyses should aim to stratify between type of DR (e.g. sight-threatening versus non-sight threatening), and also type of diabetes wherever possible. Furthermore, meta-analyses have inherent limitations in that the findings are dependent on estimates that are selected from each primary study, and dependent on how they are applied in the meta-analysis[52]. For example, some of the included ESs are based on unadjusted univariate models, while others are based on adjusted multivariate models. Finally, several of the included meta-analyses had small numbers of included studies and participants. Future research is warranted to strengthen or refute the findings of this review.

Conclusion

The results of this umbrella review show that insulin usage in type 2 diabetes has the strongest association with DR and DME risk, with vitamin D deficiency also yielding strong associations. Other significant modifiable risk factors include obesity, and sedentary behaviour. Furthermore, total physical activity levels, moderate physical activity levels, intensive (versus conventional) blood pressure and intensive (versus conventional) glycaemic control appear to have a protective effect against DR. Clinicians should take note of these and consider these associations in the management of diabetes to reduce the risk of diabetic related blindness. Furthermore, public health policies should reflect and address these associations in healthcare policies, practices, and guidelines.

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Table 1: Credibility assessment criteria and grading

Grading of evidence	Criteria (must hit all criteria)
Grade I	1. Statistical significance of $p<1*10^{-6}$, including more than 1, 000 cases (or more than 20, 000 participants for continuous outcomes) 2. Have the largest component study reporting a significant result ($p<0.05$), have a 95% prediction interval that excluded the null 3. Did not have large heterogeneity (I^2 <50%) 4. Showed no evidence of small study effects ($p>0.10$) and excess significance bias ($p>0.10$)
Grade II	1. Significance of $p<0.001$, including more than 1,000 cases (or more than 20, 000 participants for continuous outcomes) 2. Have the largest component study reporting a statistically significant result ($p<0.05$)
Grade III	1. Significance of $p<0.01$ with more than 1,000 cases (or more than 20, 000 participants for continuous outcomes)
Grade IV	1. Remaining significant associations with $p<0.05$

Table 2: Descriptive Characteristics of included studies and outcomes

Author	Type of modifiable risk factor	Type of outcome	Study type(s)	Type of diabetes	Total included studies	Total participants	Total cases/controls	Age range
Chen et al[31]	Alcohol intake	Alcohol intake and DR risk	Case control/cross-sectional	Mixed	10	30,125	11,310/18,815	15-65
			Cohort	Mixed	5	7,165	1,401/5,764	20-81
Zhou et al[30]	BMI	BMI (as a continuous variable) and DR risk	Case control/cross-sectional	Mixed	18	25,230	NR	NR
			Cohort	Mixed	5	5,358	NR	
		BMI ≥25 vs <25 and DR risk	Case control/cross-sectional	Mixed	5	22,853	NR	
Zhu et al[32]		Obese versus non-obese and risk of DR	Cohort	Mixed	13	14,587	NR	NR
Das et al[29]	Dyslipidaemia (DME)	Total cholesterol and DME risk	Case control/cross-sectional	NR	7	1,151	391/760	NR
		LDL levels and DME risk		NR	7	1,151	391/760	
		HDL levels and DME risk		NR	7	1,151	391/760	
		Triglyceride levels and DME risk		NR	7	1,151	391/760	
Zhou et al.[33]	Blood pressure	Intensive vs conventional blood pressure targets DR incidence	RCT	NR	6	6989	NR	55-66

		Intensive vs conventional blood pressure targets DR progression		NR	5	6989	NR	
		Intensive vs conventional blood pressure targets PDR incidence		NR	5	6989	NR	
Emdin et al.[34]		Bloody pressure lowering medication and DR risk	RCT	Mixed	7	19,347	9,781/9,566	NR
Zhou et al[28]		Blood pressure levels as a symptom of metabolic syndrome and DR risk	Case control/cross-sectional	Mixed	4	2,256	NR	NR
	Dyslipidaemia (DR)	HDL levels and DR risk		Mixed	3	2,086	NR	
		Triglyceride levels and DR risk		Mixed	3	2,086	NR	
		Metabolic syndrome and DR risk		Mixed	8	3,607	NR	
			Cohort	Mixed	3	1,892	NR	
Ren et al[7]	Physical Activity	Overall physical activity and DR risk	Case control/cross-sectional	Mixed	14	56,752	NR	8-81
			Cohort	Mixed	6	7,142	NR	13-64

		Overall physical activity and sight-threatening DR risk	Case control/cross-sectional	Mixed	3	2,855	NR	NR
			Cohort	Mixed	2	NR	NR	8-81
		Low intensity physical activity and DR risk	Case control/cross-sectional	Mixed	2	2,462	NR	10-81
		Moderate intensity physical activity and DR risk		Mixed	4	2,863	NR	18-60
		Vigorous intensity physical activity and DR risk		Mixed	4	2,510	NR	18-60
	Sedentary behaviour	Sedentary behaviour and risk of DR		Mixed	7	23,601	NR	10-81
Cai et al[6]	Smoking	Smoking status and risk of DR	Case control/cross-sectional	Mixed	44	212,837	64,273/148,564	20-74
			Cohort	Mixed	33	43,648	16,898/26,750	NR
Luo et al[5]	Vitamin D levels	Vitamin D deficiency and risk of DR	Case control/cross-sectional	NR	5	2,261	1,299/962	
			Cohort	NR	3	11,174	5,683/5,491	
		25(OH)D levels and risk of DR	Case control/cross-sectional	NR	10	5,540	2,043/3,497	
Hemmingsen et al. [35]	Glycaemic control	Intensive versus conventional	RCT	Type II	7	19,795	11,458/8,337	49-62

		glycaemic control and DR risk						
Zhang et al.[36]		Insulin use and DME risk	Case control/cross-sectional	Type II	3	51.656	NR	NR
			Cohort	Type II	11	254,617	NR	NR
Zhao et al.[38]		Insulin use and DR risk	RCT	Type II	7	19,107	NR	NR

Table 3: Meta-analysis results

Type of modifiable risk factor	Type of outcome	Study type(s)	Total included studies	Total participants	Effect size type	Effect size (95% CI)	p	I2	Small study effect	Excess significance bias	PI	Level of evidence
Alcohol intake	Alcohol intake and DR risk	Case control/cross-sectional	10	30,125	OR	0.90 (0.77-1.07)	0.233	68.07	Yes	NS	0.56-1.45	NS
		Cohort	5	7,165	OR	0.95 (0.66-1.36)	0.761	54.93	No	NS	0.31-2.88	NS
BMI	BMI (as a continuous variable) and DR risk	Case control/cross-sectional	18	25,230	OR	0.99 (0.96-1.01)	0.236	71.70	Yes	NS	0.91-1.07	NS
		Cohort	5	5,358	OR	1.04 (0.93-1.01)	0.450	88.90	No	NS	0.26-4.23	NS
	BMI ≥25 vs <25 and DR risk	Case control/cross-sectional	5	22,853	OR	0.87 (0.69-1.09)	0.214	71.45	No	NS	0.42-1.80	NS
Dyslipidaemia	Total cholesterol and DME risk	Case control/cross-sectional	7	1,151	SMD	30.05 (21.14-38.95)	$<1^{-6}$	99.75	Yes	No	0.18-59.99	Grade IV
	LDL levels and DME risk		7	1,151	SMD	18.63 (5.72-31.54)	0.005	99.94	Yes	No	-27.26-64.52	Grade IV
	HDL levels and DME risk		7	1,151	SMD	2.23 (-0.19-4.66)	0.071	99.88	Yes	NS	-5.64-10.10	NS
	Triglyceride levels and DME risk		7	1,151	SMD	24.80 (9.24-40.35)	0.002	99.84	Yes	No	-23.18-72.77	Grade IV

	HDL levels and DR risk		5	2,086	OR	0.97 (0.94-1.01)	0.200	0.00	No	NS	0.94-1.01	NS
	Triglyceride levels and DR risk		5	2,086	OR	0.85 (0.63-1.15)	0.299	76.36	No	NS	0.30-2.41	NS
Obesity	Obese versus non-obese and risk of DR	Cohort	13	14,587	RR	1.34 (1.06-1.68)	0.014	72.44	Yes	No	0.67-2.67	Grade IV
Physical Activity	Overall physical activity and DR risk	Case control/cross-sectional	15	56,752	RR	0.95 (0.91-0.99)	0.008	81.31	Yes	No	0.91-0.99	Grade III
		Cohort	6	7,142	RR	0.98 (0.68-1.42)	0.916	82.18	No	NS	0.26-3.65	NS
	Overall physical activity and sight-threatening DR risk	Case control/cross-sectional	3	2,855	RR	0.91 (0.81-1.02)	0.091	0.00	No	NS	0.81-1.02	NS
		Cohort	2	NR	RR	0.75 (0.54-1.05)	0.092	0.00	No	NS	0.54-1.05	NS
	Low intensity physical activity and DR risk	Case control/cross-sectional	2	2,462	RR	1.05 (0.51-2.16)	0.899	88.63	Yes	NS	NA	NS
	Moderate intensity physical activity and DR risk		4	2,863	RR	0.69 (0.53-0.91)	0.008	0.00	Yes	No	0.53-0.91	Grade IV
	Vigorous		4	2,510	RR	0.93	0.670	0.00	No	NS	0.66-1.31	NS

	intensity physical activity and DR risk					(0.66-1.31)						
Sedentary behaviour	Sedentary behaviour and risk of DR		7	23,601	RR	1.22 (1.03-1.44)	0.019	74.98	Yes	Yes	0.73-2.03	Grade IV
Smoking	Smoking status and risk of DR	Case control/cross-sectional	44	212,837	OR	1.01 (0.93-1.10)	0.815	58.65	No	NS	0.72-1.41	NS
		Cohort	33	43,648	OR	1.03 (0.95-1.12)	0.476	35.08	No	NS	0.80-1.33	NS
Vitamin D levels	Vitamin D deficiency and risk of DR	Case control/cross-sectional	5	2,261	OR	2.79 (1.09-7.14)	0.032	93.71	Yes	No	0.08-100.49	Grade IV
		Cohort	3	11,420	OR	1.28 (1.06-1.56)	0.011	37.99	No	Yes	0.2-8.23	Grade IV
	25(OH)D levels and risk of DR	Case control/cross-sectional	10	5,786	SMD	-1.70 (-2.75; -0.66)	0.001	80.42	Yes	No	-0.37-0.13	Grade III
Blood pressure	Blood pressure levels and DR risk (as part of metabolic syndrome)	Case control/cross-sectional	6	2,256	OR	1.39 (0.96-1.95)	0.084	45.52	No	NS	0.53-3.52	NS
	Intensive vs conventional blood	RCT	6	6989	RR	0.83 (0.72-0.96)	0.012	0.00	Yes	Yes	0.72-0.96	Grade IV

	pressure targets DR incidence											
	Intensive vs conventional blood pressure targets DR progression	RCT	5	6989	RR	0.93 (0.79-1.10)	0.398	11.97	No	NS	0.65-1.32	NS
	Intensive vs conventional blood pressure targets PDR	RCT	5	6989	RR	0.97 (0.72-1.30)	0.828	55.02	No	NS	0.40-2.36	NS
	Bloody pressure lowering medication and DR risk	RCT	7	19,347	RR	0.83 (0.68-1.02)	0.071	51.08	Yes	NS	0.48-1.42	NS
Glycaemic control	Intensive versus conventional glycaemic control and DR risk	RCT	7	19,795	RR	0.79 (0.67-0.94)	0.008	59.97	No	Yes	0.48-1.29	Grade III
	Insulin use and DME risk	Case control/cross-sectional	3	51.656	RR	1.45 (0.52-4.07)	0.475	95.88	No	NS	0.00-635542.7	NS
		Cohort	11	254,617	RR	4.51	$<1^{-6}$	76.95	Yes	No	1.38-14.72	Grade II

						(3.10-6.56)						
	Insulin use and DR risk	RCT	7	19,107	RR	2.30 (1.35-3.93)	0.002	89.20	Yes	No	0.36-14.62	Grade III

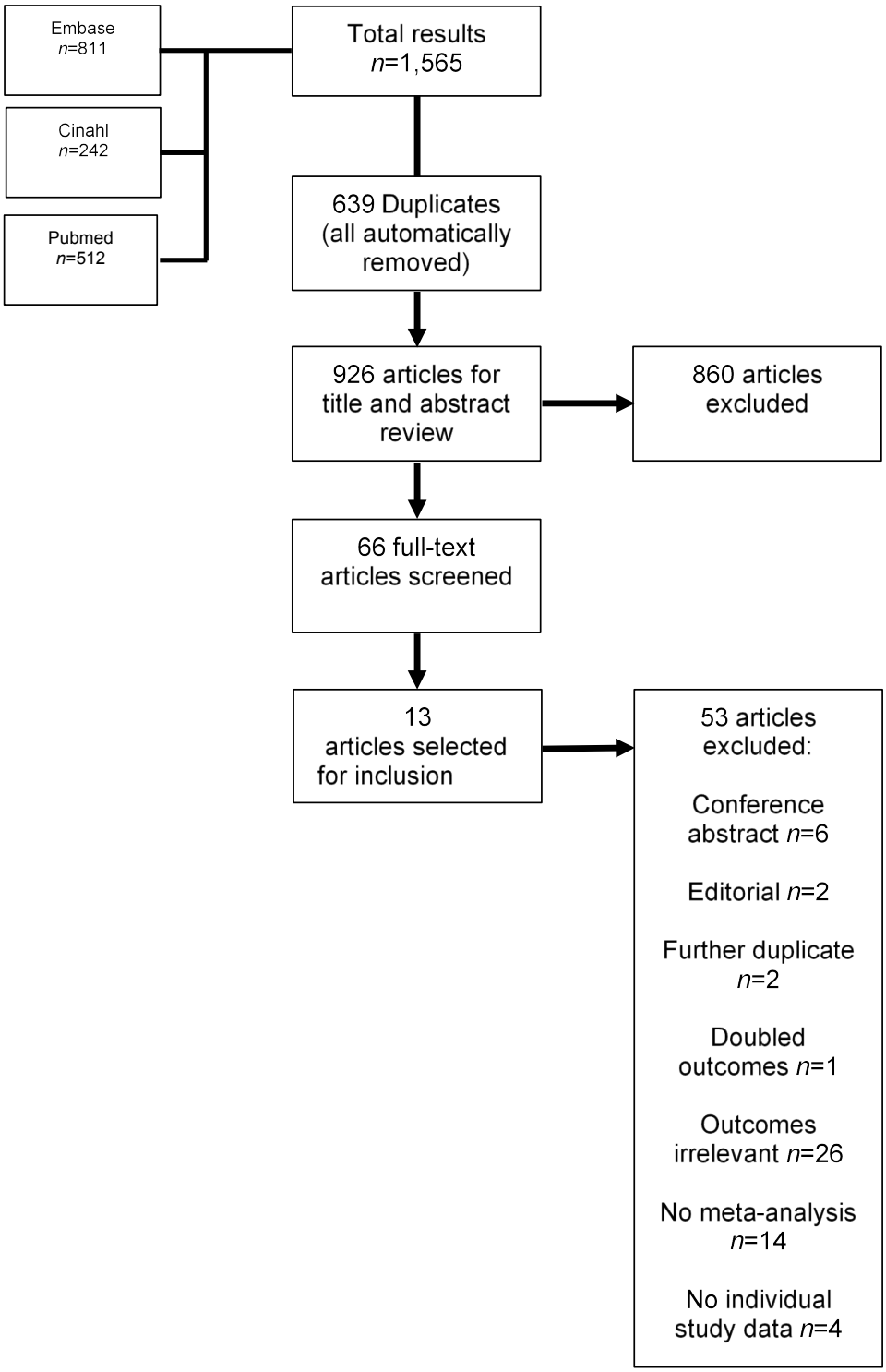

Figure 1: PRIMSA Flowchart of included studies and outcome

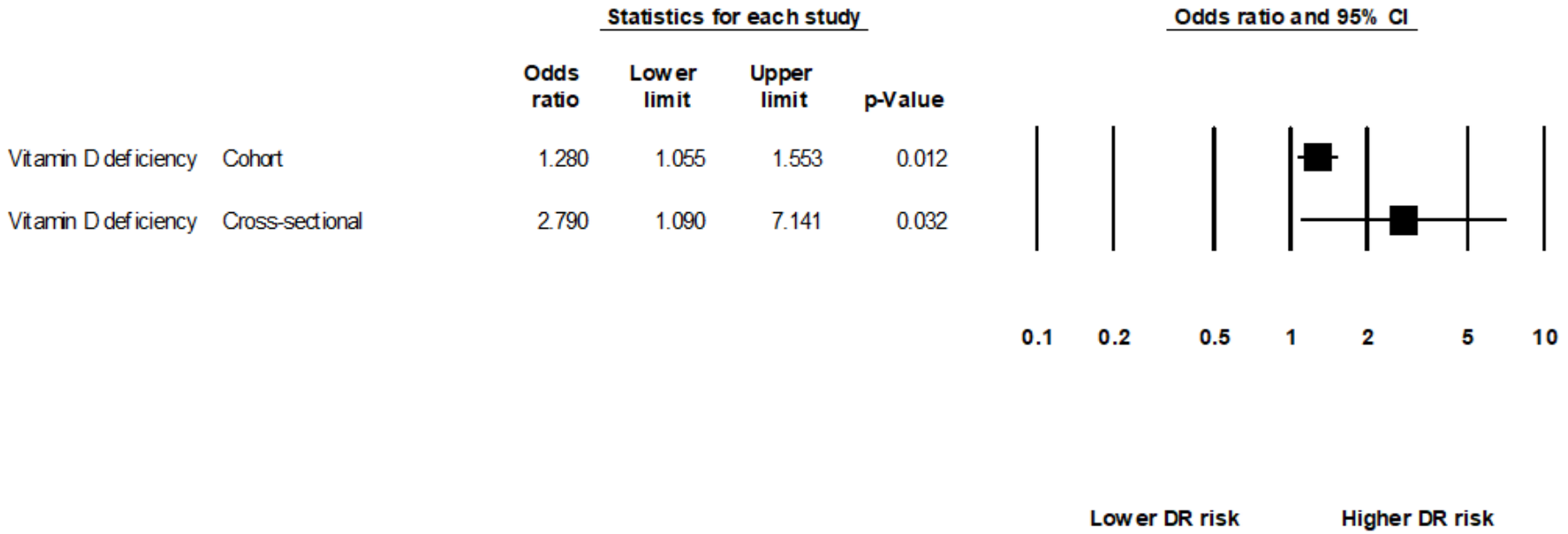

Figure 2: Forest plot showing significant associations as odds ratios between modifiable risk factors and diabetic retinopathy.

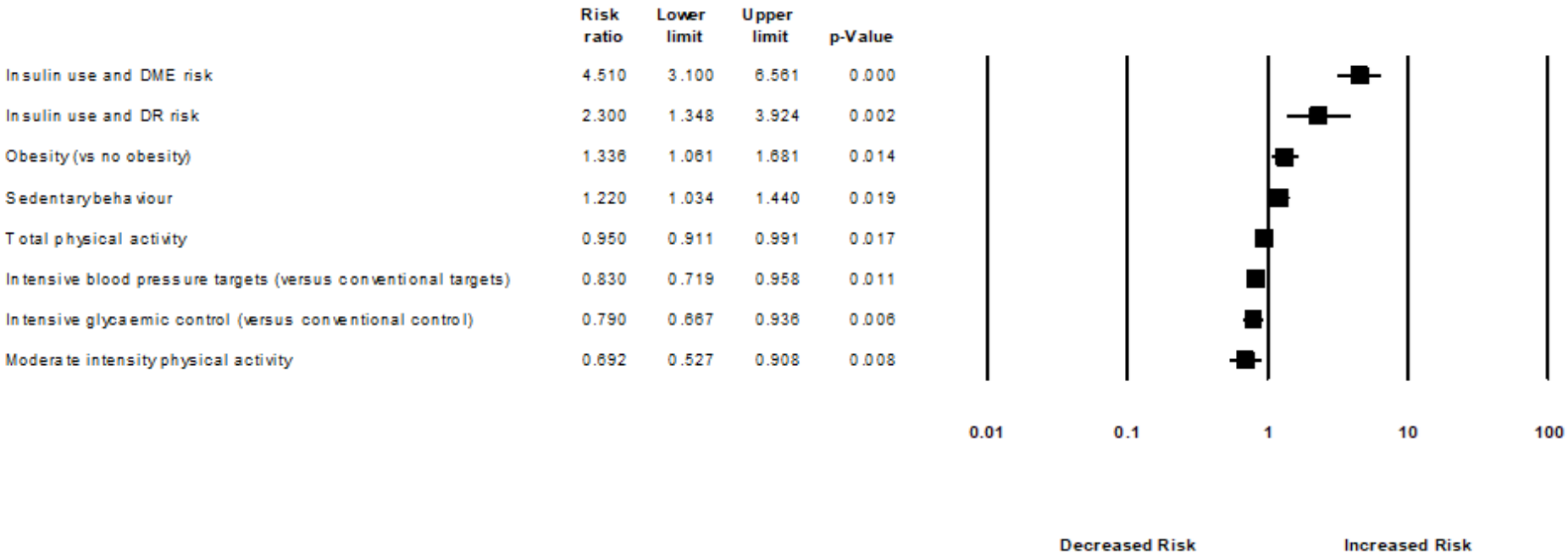

Figure 3: Forest plot showing significant associations as risk ratios between modifiable risk factors and diabetic retinopathy.

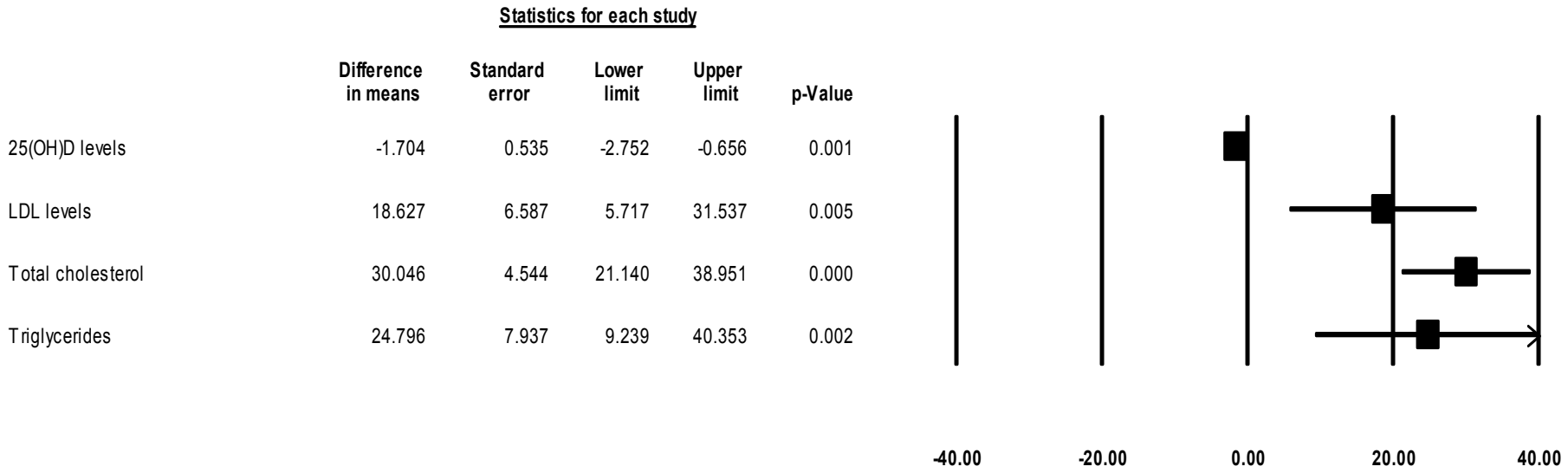

Figure 4: Forest plot showing significant associations as standard mean differences between modifiable risk factors, diabetic retinopathy (for 25(OH)D only), and diabetic macular edema.