Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

How to perform better intervention to prevent and control diabetic retinopathy among patients with type 2 diabetes: A meta-analysis of randomized controlled trials

Mayinuer Yusufu [a], *Xuxi Zhang* [b,c], *Xinying Sun* [b], *Hein Raat* [c], *Ningli Wang* [a,*]

[a] *Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China*
[b] *Public Heath School, Health Science Center, Peking University, Beijing, China*
[c] *Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands*

ARTICLE INFO

Article history:
Received 15 March 2019
Received in revised form
5 August 2019
Accepted 29 August 2019
Available online 21 September 2019

Keywords:
Diabetic retinopathy
Type 2 diabetes
Prevention
Multifactorial intervention
Meta-analysis

ABSTRACT

This meta-analysis of randomized controlled trials (RCTs) aims to investigate how to perform better interventions targeting modifiable risk factors of diabetic retinopathy (DR) to prevent and control DR in patients with type 2 diabetes by comparing different intervention types and follow-up intervals. Literature published before June 1st, 2019 were searched on Pubmed, Embase and ScienceDirect. RCTs targeting modifiable risk factors of DR (including blood glucose, blood pressure, lipid, dietary, physical activity and smoking) were selected by two reviewers and double checked for accuracy. Random effects models were estimated to calculate pooled Odds Ratios (OR). Twenty-two RCTs (n = 22,511) were included. In general, interventions targeting modifiable risk factor of DR reduced the risk of developing DR (I^2 = 26.7%; OR = 0.60; 95% CI 0.45 to 0.79) and DR worsening (I^2 = 0.0%; OR = 0.62; 95% CI 0.47 to 0.80; P < 0.001). Multifactorial interventions had better effect on reducing the risk of development and progression of DR in comparison with other interventions, while only blood-pressure-control interventions showed significant effect on slowing down DR worsening. Additionally, interventions with follow-up >5 years had better effect on reduction of DR development, and interventions with follow-up >2 years had better effect on reducing the risk of DR worsening.

Contents

* Corresponding author at: No. 1, Dongjiaominxiang Street, Dongcheng District, Beijing, China.
E-mail address: wningli@vip.163.com (N. Wang).

https://doi.org/10.1016/j.diabres.2019.107834
0168-8227/

1. Introduction

Diabetic retinopathy (DR), a microvascular complication of diabetes, is the leading cause of preventable blindness in working age population [1,2]. It is reported that after 20 years, nearly all patients with type 1 diabetes and more than 60% of those with type 2 diabetes will develop DR [3].

Studies have identified risk factors of DR development and progression, such as duration of diabetes, hyperglycemia/glycated hemoglobin value (HbA1c), hypertension, hyperlipidemia, pregnancy, nephropathy/renal disease, obesity, smoking, moderate alcohol consumption and physical activity [1,3].

Several intervention studies aiming at identifying the effect of intervention targeting modifiable risk factors of DR among patients with type 2 diabetes have been conducted. However, the results of these trials are not consistent in terms of the effect of interventions on reducing the risk of developing DR and/or its worsening. For instance, with regard to the interventions on hyperglycemia, the Veterans Affairs Diabetes Trial (VADT) found intensive glucose control had no significant effect on preventing DR development but had significant effect on slowing down its worsening [4,5], while the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial found that intensive glucose control had no effect on delaying DR progression (development or worsening) [6]. In the meantime, another study conducted in Japan found that intensive glucose control had significant effect on reducing the risk of both development and worsening of DR [7]. With respect to interventions on hypertension, the Appropriate Blood Pressure Control in Diabetes (ABCD) trail [8] found intensive blood pressure control had no effect on preventing DR development, but UK Prospective Diabetes Study (UKPDS) [9,10] found it to be significantly effective. In addition, some trails have also proven that interventions on multi-factors like blood glucose, blood pressure, dietary, physical activity and smoking were effective [11–13]. To date, no study has gathered all the evidence on different kinds of interventions targeting modifiable risk factors of DR and compared their effects to find out how to better perform interventions to prevent and control DR among patients with type 2 diabetes.

This study aims to answer the following three questions by carrying out a meta-analysis of randomized control trials (RCTs).

First, could interventions targeting modifiable risk factors of DR (blood glucose, blood pressure, lipid, dietary, physical activity and smoking) reduce the risk of developing DR and/or its worsening among patient with type 2 diabetes?

Second, among these interventions, what type of intervention is most effective in reducing the risk of developing DR and/or its worsening?

Third, how long should follow-up interval of interventions be to better reduce the risk of developing DR and/or its worsening?

2. Materials and methods

2.1. *Data sources and searches*

Pubmed, Embase and ScienceDirect were searched with terms related to our study aim, including “prevention”, “intervention”, “glycemic control”, “HbA1c”, “blood pressure control”, “lipids”, “diet”, “physical activity”, “smoking”, “diabetic retinopathy”, “DR”, “type 2 diabetes”, “T2DM” and other synonyms to identify articles related to our study from January 1st, 1980 to June 1st, 2019. PubMed was searched with MeSH terms and other synonyms in title/abstract/keywords and 503 articles were identified. Embase was searched with Emtree terms and other synonyms in title/abstract/keywords and 1008 articles were identified. ScienceDirect was searched with keywords in title/abstract/keywords of research articles and 885 articles were identified. After excluding duplicates, a total of 1991 articles were identified, and details of the search syntax can be found in the Supplementary Data.

2.2. Study selection

Eligible studies were screened from the 1991 articles based on the inclusion and exclusion criteria below.

Inclusion criteria:

1. Studies with a randomized-controlled design presenting original research
2. Study participants: patients with type 2 diabetes (If the type of diabetes was unclear, the study was included if the mean age of patients was over 30 because most of these patients were likely to have type 2 diabetes.)
3. Studies that aimed to study the effect of interventions targeting modifiable risk factors of DR (including blood glucose, blood pressure, lipid, dietary, physical activity and smoking) on the prevention and control of DR
4. Studies that provided data that could be used to calculate Odds Ratio (OR) in order to evaluate the effect of interventions targeting modifiable risk factors of DR on the prevention and control of DR (e.g. The number of patients who developed or did not develop DR in both intervention group (IG) and control group (CG); the number of DR patients whose condition worsened or did not worsen in both groups; or other related data from which the useful data could be derived)

Exclusion criteria:

1. Study participants: Patients under 18 years old
2. The intervention is medical treatment of DR rather than just targeting modifiable risk factors of DR (e.g. drugs, medical examinations, and surgeries)
3. Non-English publications

Of the 1991 articles, on the basis of the study titles and abstracts, two reviewers (Yusufu and Zhang) excluded 1903 articles that: were not RCTs, were not original research (e.g. reviews, secondhand-data analysis, and design studies), studied type 1 diabetes, gestational diabetes or other specific types of diabetes, studied patients under 18 years old, did not study the effect of interventions targeting modifiable risk factors of DR on the prevention and/or control of DR, adopted medical treatment of DR as interventions (e.g. drugs or medicines, medical examinations, or surgeries), or were not published in English. Two reviewers (Yusufu and Zhang) independently examined the full-text of the remaining 88 articles. Among those, 72 were excluded mainly due to lack of basic data that would be needed to evaluate the effect of intervention on the prevention and control of DR (Fig. 1). In case of disagreement, the reviewers discussed with a third researcher (Sun) to reach an agreement and all disagreements were resolved by consensus. Finally, 16 articles [5–8,10–21] on 22 studies were included in this meta-analysis.

2.3. Data extraction and quality assessment

Data from the 22 studies were extracted by two reviewers (Yusufu and Zhang) with a standardized data extraction form. The extraction form included: the name of the study (most studies had an official name; if not, the study was named after the first author), the year of publication, number of participants, follow-up interval, the characteristics of participants (including data of IG and CG respectively, e.g. types of patients, gender ratio, mean age, duration of diabetes, glycated hemoglobin, blood pressure, total cholesterol, body mass index and percentage of patients without DR at baseline), study design and location, intervention methods, the number of participants who developed or did not develop DR in both IG and CG, and/or the number of DR patients whose condition worsened or did not worsen in both groups, and/or the number of participants with DR progression (For studies failing to provide distinctive data on new onset and worsening DR, the term "progression" was adopted to cover both new onset and worsening DR). The details of each study can be found in Supplementary Tables S1 and S2.

In all 22 studies, ophthalmologists diagnosed and/or evaluated DR based on on-site ophthalmoscopy or report from the primary care physicians. Most studies adopted the protocol of the Early Treatment Diabetic Retinopathy Study (ETDRS) to define the grade of DR and make diagnosis of DR [5–8,10,14,18,19,21]. Some studies adopted the Wisconsin Epidemiologic Study of Diabetic Retinopathy [15,17], the EURODIAB six-level grading [11,12,16], and other grading scales [13,20] to define the grade of DR and make diagnosis of DR. DR worsening was defined as a change of at least two steps from baseline measurement in any eye [5,7,8,10,14]. One study defined DR worsening based on an increase of at least one level in any eye [11]. DR progression was defined as a change of at least two or three steps from baseline measurement in any eye [6,18,19,21]. Two studies defined DR progression as an increase of at least one level in any eye [12,16]. The detailed criteria used for the diagnosis, worsening and progression of DR in each study can be found in Supplementary Table S3.

Some studies did not provide the needed data, in which case, the data needed for the evaluation of the effect of interventions were obtained through calculation. One study only provided the percentage of patients who developed DR at follow-up in the IG and CG respectively [8]. We calculated the number of patients with newly developed DR based on the percentage and the number of patients. One study provided the number of patients without DR at baseline and follow-up respectively in both IG and CG [15]. We subtracted the number of patients without DR at follow-up from the number of patients without DR at baseline to obtain the number of patients with newly developed DR. One study provided the number of patients with DR at baseline and follow-up in both IG and CG [13]. We subtracted the number of patients with DR at baseline from the number of patients with DR at follow-up to get the number of patients with newly developed DR.

The interventions were classified into five categories based on modifiable risk factors: (1) Blood-pressure-control intervention, (2) Glycemic-control intervention, (3) Lipid-control intervention, (4) Dietary-control intervention, and (5) Multifactorial intervention (interventions targeting more than one risk factors).

We applied the Cochrane Collaboration's tool to assess the risk of bias in our study. This tool consists of six domains:

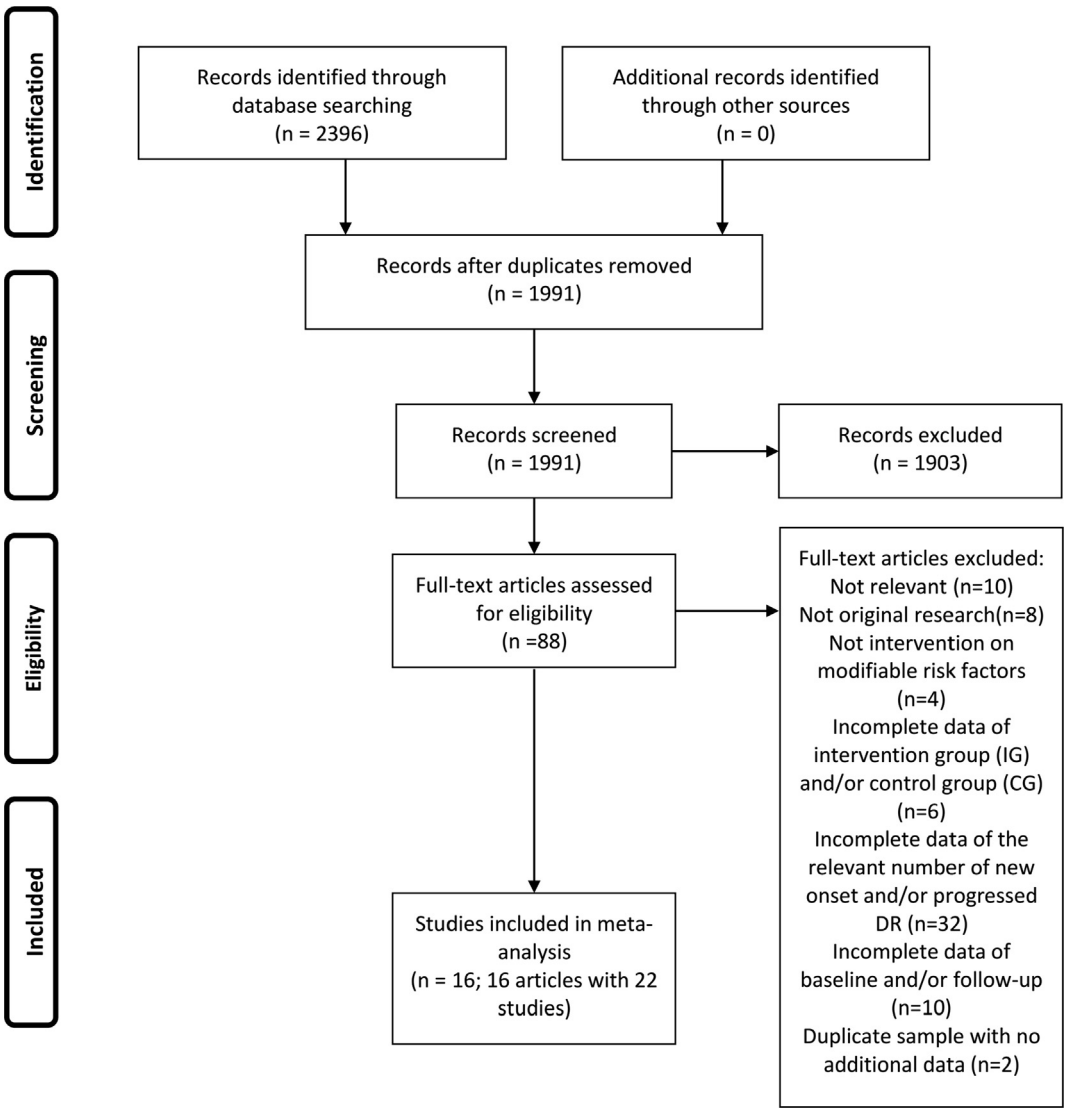

Fig. 1 – Flowchart of study selection.

selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. For each domain, the study was graded as having a low risk, high risk, or unclear risk of bias [22]. Grades of Recommendations Assessment, Development and Evaluation (GRADE) was used to evaluate the level of evidence in the meta-analysis with GRADEpro3.2. Two reviewers (Yusufu and Zhang) assessed each study independently. Disagreements between the reviewers were discussed with a third researcher (Sun) in order to reach an agreement.

2.4. *Data synthesis and analysis*

The heterogeneity between the studies was evaluated with the I^2 test. Random effects models were estimated to calculate pooled Odds Ratios (OR) of DR development, worsening and progression. For these analyses we considered a value of $P < 0.05$ to be significant. A sensitivity analysis was performed to test the stability of the studies by excluding one study at a time. Possible publication bias was assessed by estimating funnel plots with Begg and Egger tests, and a value of $P < 0.1$ was considered to be significant [23,24]. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist to report our meta-analysis study [25]. All statistical analyses were performed using Stata 11.0.

3. Results

3.1. *Study selection and study characteristics*

The 22 studies included in this meta-analysis studied a total of 22,511 participants. The number of participants in each study ranged from 35 [15] to 11,140 [6]. In most studies, the number of males and females was similar [6–8,10–13,15–21], but in two studies [5,14], over 90% of participants were male. The follow-up interval of the interventions ranged from 1 year [15] to 8 years [21]. Blood-pressure-control intervention was evaluated in 4 studies [8,9,19,21], glycemic-control intervention was evaluated in 9 studies [5–7,14,15,18,19,21]. Lipid-control intervention was evaluated in 2 studies [19,21].

Dietary-control intervention was evaluated in 2 studies [20]. Multifactorial intervention was evaluated in 5 studies [11–13,16,17]. More details of the included studies can be found in Supplementary Table S1.

3.2. Risk of bias

None of the RCTs included in this review were double-blinded. In all studies, no high risk of bias was found in the domains of selection bias, detection bias, attrition bias, reporting bias, and other bias. More details of the risk of bias could be found in Supplementary Table S4.

Quality of the evidence for most results on new onset DR and DR worsening was moderate to high, except the results of glycemic-control intervention (new onset DR), glycemic-control intervention (DR Worsening), follow-up <2 years (DR Worsening) and follow-up >5 years (DR Worsening) (The details are presented in Supplementary Tables S5 and S6). Quality of the evidence for most results on DR progression was moderate to low (The details are presented in Supplementary Table S7), which was mainly caused by the substantial heterogeneity in this subgroup.

3.3. Results of intervention effects on DR prevention

A total of 11 studies from 10 articles provided data on the number of patients with newly developed DR [5,7,8,10,11,13–15,17,20]. In one article [20], there were two intervention groups (Mediterranean diet supplemented with extra virgin olive oil group and Mediterranean diet supplemented with mixed nuts group) and one control group. Therefore, we divided this study into two studies by matching the control group with two intervention groups separately. Out of the 11 studies, 7 studies from 6 articles [7,10,11,13,17,20] revealed a significant reduction in the number of newly developed DR in intervention group compared with control group, and 4 studies from 4 articles [5,8,14,15] showed no effect.

Results on the effectiveness of all interventions targeting modifiable risk factors of DR in reducing the risk of developing DR among patients with type 2 diabetes are presented in Fig. 2. Heterogeneity between studies was small (I^2 = 26.7%). The pooled results indicated that interventions targeting modifiable risk factor of DR reduced the risk of developing DR among patients with type 2 diabetes significantly (OR = 0.60; 95% CI 0.45 to 0.79; P < 0.001). The sensitivity of the 11 studies was low, and the Begg and Egger tests did not reveal publication bias. More details on the sensitivity analysis and publication bias assessment can be found in Supplementary Figs. S1 and S2.

Results of subgroup analyses on the effectiveness of different types of interventions are presented in Fig. 2, Part A. There was moderate heterogeneity among blood-pressure-control intervention studies (I^2 = 41.9%). Blood-pressure-control intervention had no significant effect on reducing the risk of developing DR (OR = 0.68; 95% CI 0.41 to 1.14; P = 0.143). There was moderate heterogeneity among glycemic-control intervention studies (I^2 = 38.2%). Glycemic-control intervention had no significant effect on reducing the risk of developing DR (OR = 0.70; 95% CI 0.31 to 1.57; P = 0.387). There was no heterogeneity between dietary-control intervention studies (I^2 = 0%). Dietary-control intervention reduced the risk of developing DR significantly (OR = 0.64; 95% CI 0.43 to 0.95; P = 0.025). There was no heterogeneity among multifactorial intervention studies (I^2 = 0%). Multifactorial intervention reduced the risk of developing DR significantly (OR = 0.27; 95% CI 0.14 to 0.53; P = <0.001).

Results of subgroup analyses on the effectiveness of different follow-up intervals are presented in Fig. 2, Part B. There was substantial heterogeneity among interventions with follow-up < 2 years (I^2 = 53.8%). Interventions with follow-up < 2 years had no significant effect on reducing the risk of developing DR (OR = 0.59; 95% CI 0.15 to 2.34; P = 0.452). There was substantial heterogeneity among interventions with follow-up of 2–5 years (I^2 = 53.1%). Interventions with follow-up of 2–5 years had no significant effect on reducing the risk of developing DR (OR = 0.59; 95% CI 0.34 to 1.02; P = 0.060). There was no heterogeneity among interventions with follow-up over 5 years (I^2 = 0%). Interventions with follow-up of over 5 years reduced the risk of developing DR significantly (OR = 0.57; 95% CI 0.42 to 0.78; P < 0.001).

3.4. Results of intervention effects on DR control

3.4.1. Effects on DR worsening

A total of 7 studies from 7 articles [5,7,8,10,11,14,15] provided data on the number of patients suffering from worsening DR. Out of the 7 studies, 4 studies from 4 articles [5,7,10,11] found a significant effect on slowing the worsening of DR in intervention group compared with control group, while the remaining 3 studies from 3 articles [8,14,15] showed no effect.

Results on the effectiveness of all interventions targeting modifiable risk factors of DR in reducing the risk of DR worsening among patients with type 2 diabetes are presented in Fig. 3. The pooled results showed that interventions targeting modifiable risk factor of DR reduced the risk of DR worsening in patients with type 2 diabetes significantly (OR = 0.62; 95% CI 0.47 to 0.80; P < 0.001). No heterogeneity between studies (I^2 = 0.0%) was found. The sensitivity of the 7 studies was low, and the Begg and Egger tests did not reveal publication bias. More details of sensitivity analysis and publication bias assessment can be found in Supplementary Figs. S3 and S4.

Results of subgroup analyses on the effectiveness of different types of interventions are presented in Fig. 3, Part A. Blood-pressure-control intervention had significant effect on slowing down the worsening of DR (OR = 0.52; 95% CI 0.34 to 0.78; P = 0.002) and no heterogeneity among blood-pressure-control intervention studies was found (I^2 = 0.0%). Glycemic-control intervention reduced the risk of DR worsening, but not significantly (OR = 0.71; 95% CI 0.50 to 1.00; P = 0.053), and no heterogeneity among glycemic-control intervention studies was found (I^2 = 0.0%). There is no pooled results of multifactorial intervention because there was only one study in this subgroup.

Results of subgroup analyses on different follow-up intervals are presented in Fig. 3, Part B. Interventions with follow-up <2 years had no significant effect on reducing the risk of DR worsening (OR = 0.91; 95% CI 0.40 to 2.09; P = 0.826), and there was no heterogeneity (I^2 = 0%). Interventions with follow-up of 2–5 years reduced the risk of DR worsening significantly (OR = 0.68; 95% CI 0.49 to 0.94; P = 0.020), and there

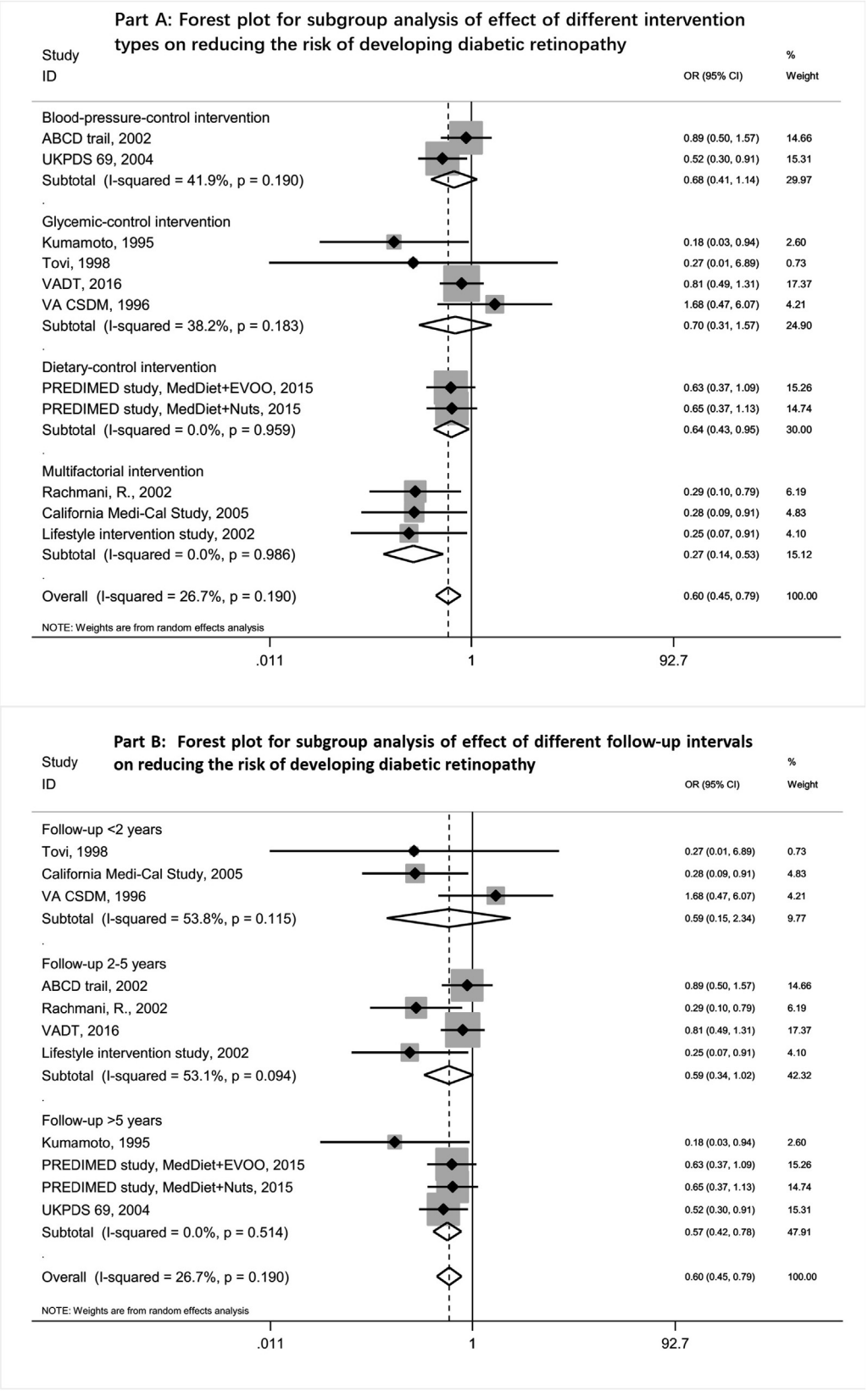

Fig. 2 – Forest plots for subgroup analysis on reducing the risk of developing diabetic retinopathy.

was no heterogeneity ($I^2 = 0\%$). Interventions with follow-up of over 5 years had significant effect on reducing the risk of DR worsening (OR = 0.41; 95% CI 0.24 to 0.69; $P = 0.001$) and there was no heterogeneity ($I^2 = 0\%$).

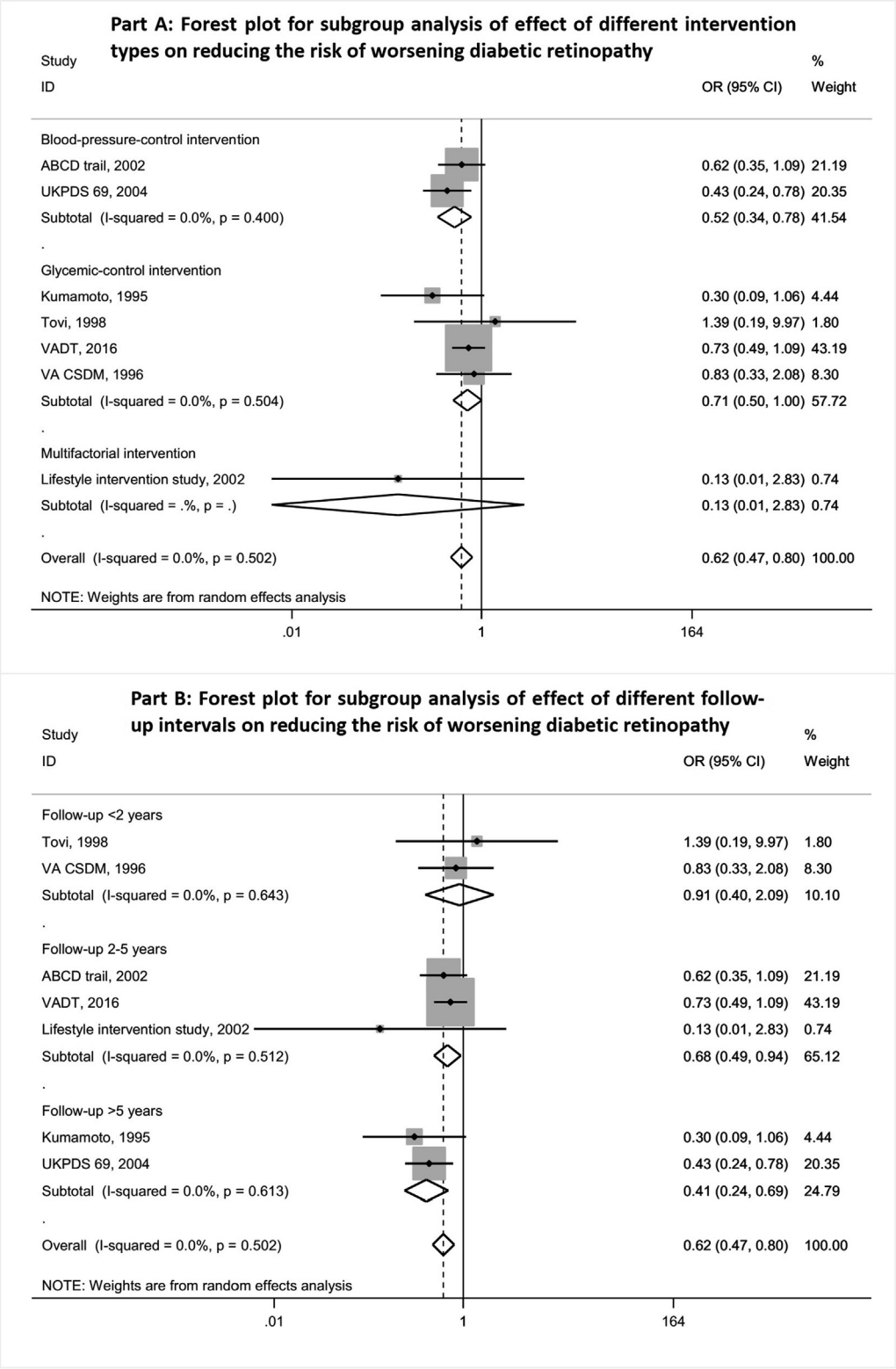

Fig. 3 – Forest plot for subgroup analysis on reducing the risk of worsening diabetic retinopathy.

3.4.2. *Effects on DR progression*

A total of 10 studies from 6 articles [6,12,16,18,19,21] provided data on the number of patients with DR progression. There are two articles [19,21] each reporting the results on three studies. Out of the 10 studies, 5 studies from 4 articles [12,16,19,21] found a significant reduction in the progression of DR in intervention group compared with control group, and 5 studies from 4 articles [6,18,19,21] showed no effect.

Results on the effectiveness of all interventions targeting modifiable risk factors of DR in reducing the risk of DR pro-

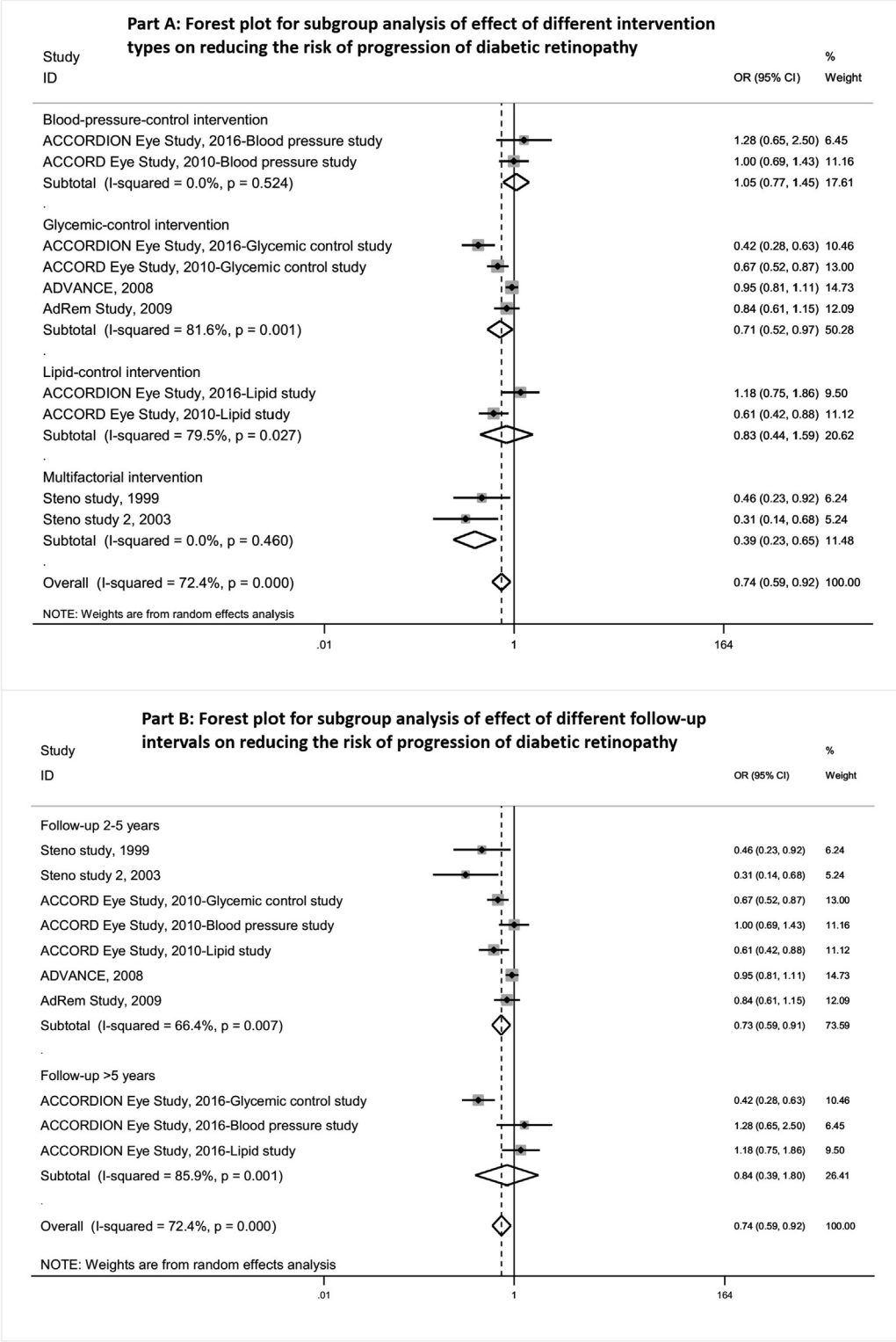

Fig. 4 – Forest plot for subgroup analysis on reducing the risk of progression of diabetic retinopathy.

gression among patients with type 2 diabetes are presented in Fig. 4. The pooled results revealed that interventions targeting modifiable risk factor of DR reduced the risk of DR progression among patients with type 2 diabetes significantly (OR = 0.74; 95% CI 0.59 to 0.92; $P = 0.007$). The overall heterogeneity among studies was substantial ($I^2 = 72.4\%$). The sensitivity of the 10 studies was low, and the Begg and Egger tests did not reveal publication bias. More details of sensitivity analysis and publication bias assessment can be found in Supplementary Figs. S5 and S6.

Results of subgroup analyses on the effectiveness of different types of interventions are presented in Fig. 4, Part A.

Blood-pressure-control intervention had no effect on reducing the risk of DR progression (OR = 1.05; 95% CI 0.77 to 1.45; $P = 0.749$), and there was no heterogeneity ($I^2 = 0.0\%$). Glycemic-control intervention reduced the risk of DR progression significantly (OR = 0.71; 95% CI 0.52 to 0.97; $P = 0.032$), and the heterogeneity was substantial ($I^2 = 81.6\%$). Lipid-control intervention had no significant effect on reducing the risk of DR progression (OR = 0.83; 95% CI 0.44 to 1.59; $P = 0.581$), and the heterogeneity was substantial ($I^2 = 79.5\%$). Multifactorial intervention reduced the risk of DR progression significantly (OR = 0.39; 95% CI 0.23 to 0.65; $P < 0.001$), and there was no heterogeneity among multifactorial intervention studies ($I^2 = 0.0\%$).

Results of subgroup analyses on different follow-up intervals are presented in Fig. 4, Part B. There was substantial heterogeneity among interventions with follow-up of 2–5 years ($I^2 = 66.4\%$). Interventions with follow-up of 2–5 years reduced the risk of DR progression significantly (OR = 0.73; 95% CI 0.59 to 0.91; $P = 0.006$). There was substantial heterogeneity among interventions with follow-up of over 5 years ($I^2 = 85.9\%$). Interventions with follow-up of over 5 years had no significant effect on reducing the risk of DR progression (OR = 0.84; 95% CI 0.39 to 1.80; $P = 0.648$).

4. Discussion

Our study found multifactorial intervention with individualized target and communication between health professionals and patients was more effective than other interventions in the prevention and control of DR. Interventions with follow-up of over 5 years had better effect on reduction of DR development, and interventions with follow-up of 2–5 years and over 5 years had better effect on reducing the risk of DR worsening.

Our study showed that the effect of multifactorial intervention on reducing the risk of DR development was superior to that of blood-pressure-control intervention, glycemic-control intervention or dietary-control intervention. A previous study on multifactorial intervention among patients with type 2 diabetes also found that "intensive intervention with multiple drug combinations and behavior modification had sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from cardiovascular causes" [26]. Apart from controlling multiple factors, we also found that the similarities of the multifactorial interventions on prevention of DR in the subgroup analysis were individualization and communication. Interventions and support for patients with type 2 diabetes were provided based on patients' situation [11,13,17]. For example, patients could get recommendations on individualized goals to reach and could attend age and gender-adjusted fitness programs [13]. Moreover, health professionals would communicate with patients through education sessions, phones and emails [11,13,17].

Additionally, we found dietary-control intervention (Mediterranean diet supplemented with olive oil or nuts) are effective in preventing DR. A systematic review on dietary intake and diabetic retinopathy also found that Mediterranean diet, dietary fiber, fruits and vegetables, and oily-fish have protective effect on DR [27]. However, both studies in our subgroup analysis of dietary-control intervention are from the same article. The number of intervention studies exploring the effect of dietary intake on DR is very limited [20,27], thus more longitudinal studies in this field are needed. According to our pooled results, controlling blood pressure or blood glucose alone had no significant effect on preventing DR among patients with type 2 diabetes. The finding on blood glucose control is consistent with results from a previous meta-analysis on the effects of intensive glycemic control in ocular complications in patients with type 2 diabetes, which found no significant difference in the incidence of retinopathy [1]. However, our finding on blood pressure is different from the result of a review of 15 RCTs on blood pressure stating that "the available evidence supports a beneficial effect of intervention to reduce blood pressure with respect to preventing diabetic retinopathy for up to 4 to 5 years" [28]. The possible reason of the differences might be that in our study blood pressure control alone would be regarded as blood-pressure-control intervention, while in that review article, blood pressure control alone and blood pressure control in combination with other interventions were all classified as blood-pressure-control intervention. In addition, we only included studies on patients with type 2 diabetes but the review included patients with both type 1 and type 2 diabetes. Regarding to the follow-up intervals, our results showed that compared with interventions with follow-up of 5 years or less, interventions with follow-up of over 5 years had better effect on preventing DR. A previous meta-analysis also had similar result that "more intensive glucose control over 5 years reduced both kidney and eye events" among patients with type 2 diabetes [29].

Moreover, we explored the effect of interventions targeting modifiable risk factors of DR on its worsening specifically, which was rarely studied by previous meta-analysis studies. We found blood-pressure-control intervention was effective in slowing down DR worsening. However, controlling blood glucose alone had no significant effect on the control of DR worsening. A systematic review on DR also suggested that there is no evidence that rapid improvement of blood glucose control will reduce the risk of DR worsening [30]. As for follow-up intervals, our results showed that compared with interventions with follow-up of less than 2 years, interventions with follow-up of 2–5 years and over 5 years had better effect on reducing the risk of DR worsening. According to the analysis on the follow-up intervals, the effect of interventions on preventing DR can be observed after over 5 years, while the effect on slowing down DR worsening can be observed after 2 years, indicating that effect of interventions on delaying DR worsening could be observed earlier than that on preventing DR development.

Regarding DR progression (new onset or worsening), our results indicated that multifactorial intervention also had better effect on reduction of DR progression compared with the blood-pressure-control intervention, glycemic-control intervention and lipid-control intervention. Individualized methods were adopted in the multifactorial intervention to control the progression of DR [11,12,16]. For example, if patients could not reach the blood pressure goal and/or blood glucose goal set at the beginning after three months, stepwise

approaches were adopted based on patients' situation [12,16]. Additionally, we found glycemic-control intervention could reduce the risk of DR progression, which is consistent with previous meta-analysis [1,29]. The control of blood pressure or lipid level alone had no significant effect on reduction of DR progression among type 2 diabetes according to our pooled results. A recent subgroup meta-analysis of 4 RCTs found a borderline significant reduction in DR progression with more intensive blood pressure lowering, which is different from our finding [31]. However, they did not focus on diabetic patients and also reported substantial heterogeneity of subgroup analysis. More studies on the effect of blood pressure control on DR would be needed. As for follow-up intervals, our results showed that compared with interventions with follow-up of over 5 years, interventions with follow-up of 2–5 years had better effect on reduction of DR progression. However, the heterogeneity among interventions with follow-up of over 5 years on DR progression was substantial. More studies are still needed to verify this finding.

4.1. *Strengths and limitations*

This meta-analysis is the first to report variation among different intervention types targeting modifiable risk factors of DR, and among different follow-up intervals of interventions in patients with type 2 diabetes. However, the study still has several limitations. First, no RCT included in our meta-analysis was double-blinded study. Second, in subgroup analyses, the number of studies in some subgroups (blood-pressure-control intervention, dietary-control intervention and lipid-control intervention) was small and there was a high level of heterogeneity in some subgroups (the groups of glycemic-control intervention and follow-up of over 5 years for the analysis on effect on DR progression). One possible reason of heterogeneity might be studies included in the analyses of DR progression did not provide distinctive data for new onset and worsening DR, and the variation between studies might be large. Third, subgroup analyses on the influence of other factors (e.g. duration of diabetes, duration of DR, intervention duration and frequency) could not be conducted due to the limited number of studies. Fourth, our meta-analysis has not been registered online.

4.2. *Implications for practice and future researches*

We found that multifactorial interventions can significantly reduce the risk of developing DR and its progression among patients with type 2 diabetes. More importantly, we found all these multifactorial interventions contained individualization of targets and communication between health professionals and patients, suggesting ophthalmologists and diabetes health professionals should work together with patients to set more individualized targets while taking into account multiple factors so as to achieve optimal effect in DR prevention and control. Training on interventions on DR prevention and control should be carried out for general practitioners in primary level health facilities so that they can educate the patients with type 2 diabetes in this regard. In the future, guidelines on how to perform better and more effective DR prevention and control should be developed for general practitioners. In addition, more studies on the effectiveness of interventions targeting various modifiable risk factors of DR in prevention and control of DR are needed.

Acknowledgement

The authors thank Dr. Carmen Betsy Franse from Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands for language revision of the manuscript.

Author contributions

MY was responsible for the conception, design, study searching, study selection, data extraction, quality assessment, data analysis, interpretation of data and manuscript writing. XZ was engaged in the conception, design, study searching, study selection, data extraction, quality assessment, interpretation of data and critical revision of manuscript. NW, HR and XS were engaged in the critical revision of manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

XZ is supported by a China Scholarship Council (CSC) PhD Fellowship for her PhD study in Erasmus MC, Rotterdam, the Netherlands. The scholarship file number is 201706010358, CSC URL: [http://www.csc.edu.cn/].

Declaration of Competing Interest

None.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107834.

REFERENCES

[1] Zhang X, Zhao J, Zhao T, Liu H. Effects of intensive glycemic control in ocular complications in patients with type 2 diabetes: a meta-analysis of randomized clinical trials. Endocrine 2014;49:78–89.

[2] Crossland L, Askew D, Ware R, Cranstoun P, Mitchell P, Bryett A, et al. Diabetic retinopathy screening and monitoring of early stage disease in australian general practice: tackling

preventable blindness within a chronic care model. J Diabetes Res 2016;2016:1–7.
[3] Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. JAMA, J Am Med Assoc 2007;298:902–16.
[4] Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–30.
[5] Azad N, Bahn GD, Emanuele NV, Agrawal L, Ge L, Reda D, et al. Association of blood glucose control and lipids with diabetic retinopathy in the veterans affairs diabetes trial (VADT). Diabetes Care 2016;39:816–22.
[6] Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. New Engl J Med 2008;358:2560–72.
[7] Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103–17.
[8] Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086–97.
[9] Group UPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. In: BMJ. p. 703–13.
[10] Matthews DR, Stratton IM, Aldington SJ, Holman RR, Kohner EM, Group UKPDS. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. Arch Ophthalmol (Chicago, Ill: 1960) 2004;122:1631–40.
[11] Trento M, Passera P, Bajardi M, Tomalino M, Grassi G, Borgo E, et al. Lifestyle intervention by group care prevents deterioration of Type II diabetes: a 4-year randomized controlled clinical trial. Diabetologia 2002;45:1231–9.
[12] Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. New Engl J Med 2003;348:383–93.
[13] Rachmani R, Levi Z, Slavachevski I, Avin M, Ravid M. Teaching patients to monitor their risk factors retards the progression of vascular complications in high-risk patients with Type 2 diabetes mellitus–a randomized prospective study. Diabet Med J Br Diabetic Assoc 2002;19:385–92.
[14] Emanuele N, Klein R, Abraira C, Colwell J, Comstock J, Henderson WG, et al. Evaluations of retinopathy in the VA cooperative study on glycemic control and complications in type II diabetes (VA CSDM). A feasibility study. Diabetes Care 1996;19:1375–81.
[15] Tovi J, Ingemansson SO, Engfeldt P. Insulin treatment of elderly type 2 diabetic patients: effects on retinopathy. Diabetes Metab 1998;24:442–7.
[16] Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet (London, England) 1999;353:617–22.
[17] Pettitt DJ, Okada Wollitzer A, Jovanovic L, He G, Ipp E. Decreasing the risk of diabetic retinopathy in a study of case management: the California Medi-Cal Type 2 Diabetes Study. Diabetes Care 2005;28:2819–22.
[18] Beulens JW, Patel A, Vingerling JR, Cruickshank JK, Hughes AD, Stanton A, et al. Effects of blood pressure lowering and intensive glucose control on the incidence and progression of retinopathy in patients with type 2 diabetes mellitus: a randomised controlled trial. Diabetologia 2009;52:2027–36.
[19] Chew EY, Ambrosius WT, Davis MD, Danis RP, Gangaputra S, Greven CM, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. New Engl J Med 2010;363:233–44.
[20] Diaz-Lopez A, Babio N, Martinez-Gonzalez MA, Corella D, Amor AJ, Fito M, et al. Mediterranean diet, retinopathy, nephropathy, and microvascular diabetes complications: a post hoc analysis of a randomized trial. Diabetes Care 2015;38:2134–41.
[21] Action to Control Cardiovascular Risk in Diabetes Follow-On Eye Study G, the Action to Control Cardiovascular Risk in Diabetes Follow-On Study G. Persistent Effects of Intensive Glycemic Control on Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study. Diabetes care. 2016;39:1089–100.
[22] Cochrane Handbook for Systematic Reviews of Interventions 5.1.0. 2011.
[23] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[24] Schnee S, Enoch M, Noriega-Crespo A, Sayers J, Terebey S, Caselli P, et al. Bias in meta-analysis detected by a simple, graphical test. In: BMJ. p. 629–34.
[25] Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336–41.
[26] Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. New Engl J Med 2008;358:580–91.
[27] Wong MYZ, Man REK, Fenwick EK, Gupta P, Li LJ, van Dam RM, et al. Dietary intake and diabetic retinopathy: a systematic review. PLoS ONE 2018;13 e0186582.
[28] Do DV, Wang X, Vedula SS, Marrone M, Sleilati G, Hawkins BS, et al. Blood pressure control for diabetic retinopathy. Cochr Database Syst Rev 2015;1. CD006127-CD.
[29] Zoungas S, Arima H, Gerstein HC, Holman RR, Woodward M, Reaven P, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:431–7.
[30] Feldman-Billard S, Larger E, Massin P. Standards for screeningand surveillance of ocular complications in people with diabetes SFDsg. Early worsening of diabetic retinopathy after rapid improvement of blood glucose control in patients with diabetes. Diabetes Metab 2018;44:4–14.
[31] Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet 2016;387:435–43.