

Long-term Cumulative Incidence of Clinically Diagnosed Retinopathy in the Finnish Diabetes Prevention Study

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Abstract

Context: Lifestyle intervention reduces the incidence of type 2 diabetes (T2D) in people with impaired glucose tolerance (IGT).

Objective: This work aimed to find out whether participation in an earlier lifestyle intervention had an effect on the occurrence of clinically diagnosed diabetic retinopathy (DR) during a median of 22 years of follow-up time.

Methods: The study included 505 individuals from the Finnish Diabetes Prevention Study (DPS) (mean age 55; range, 40–64 years at the onset of the study) with IGT who were originally randomly assigned to the intervention (weight loss, healthy diet, and physical activity) (N = 257) and usual care control groups (N = 248). The median follow-up was 22 years. Clinical retinopathy diagnoses were obtained from the Finnish national hospital Care Register for Health. Data on glycemic parameters, serum lipids, and blood pressure were available from both the intervention (median 4 years) and postintervention period (until year 7).

Results: No significant difference was found in the cumulative incidence of clinically diagnosed DR between the original intervention (N = 23, 8.9%) and control groups (N = 19, 7.7%) during the extended follow-up (odds ratio: 1.15; 95% CI, 0.61–2.21). A higher cumulative glycated hemoglobin A_{1c} (HbA_{1c}) was significantly associated with a higher risk of retinopathy (hazard ratio 1.4; 1.02–1.88, 95% posterior interval, adjusted for group, age, and sex). Furthermore, the incidence of retinopathy diagnosis was numerically more common among individuals who had developed diabetes during the follow-up (33/349) compared with those who had not (9/156); however, the comparison was not statistically significant (odds ratio: 1.86, 95% CI, 0.89–4.28, adjusted for group, age, and sex).

Conclusion: A higher cumulative HbA_{1c} was significantly associated with a higher risk of retinopathy. No evidence was found for a beneficial effect of a 4-year lifestyle intervention on the long-term occurrence of clinical DR during a median of 22-year follow-up.

Key Words: diabetes, glucose, HbA_{1c}, lifestyle intervention, prevention, retinopathy

Abbreviations: DPS, Finnish Diabetes Prevention Study; DR, diabetic retinopathy; HbA_{1c}, glycated hemoglobin A_{1c}; IGT, impaired glucose tolerance; MA, microaneurysm; T2D, type 2 diabetes.

Diabetic retinopathy (DR) is the most common diabetic microvascular complication (1). Currently, approximately 103 million individuals in the world suffer from DR which is the leading cause of vision loss in working-age individuals (1). DR is strongly associated with poor glycemic control, long duration of diabetes, hypertension, and dyslipidemia (2, 3). It is also associated with other late chronic complications of diabetes, such as diabetic kidney disease and cardiovascular disease (4). Microvascular complications of the retina constitute microaneurysms (MAs), hemorrhages, hard exudates and interretinal microvascular abnormalities, macular edema, and proliferative vessel growth (5). Such lesions result in progressive retinal disease and even permanent vision

loss if not treated properly (6). In people with diabetes, good glycemic control has a major effect on reducing the development and slowing the progression of DR (3, 6).

Several studies have demonstrated that lifestyle interventions aimed at permanent weight reduction, increased physical activity, and healthy diet can result in a more than 50% reduction in diabetes incidence in adults with impaired glucose tolerance (IGT) followed for 1 to 6 years (7, 8). Interestingly, DR signs such as MAs can be observed in individuals with prediabetes (9–12). Recent results from the Diabetes Prevention Program Outcome Study (20 years after random assignment into the Diabetes Prevention Program) showed no difference in DR between the original lifestyle intervention and control

groups but the prevalence of DR was higher in the people who had developed T2D (24%) than in those who remained without diabetes (14%) (13). In the Finnish Diabetes Prevention Study (DPS) (14), in individuals with IGT the lower risk of developing T2D was associated with a higher adherence to lifestyle changes and more marked improvement of insulin sensitivity and dyslipidemia (14–17). Furthermore, a lower prevalence of retinal microvascular abnormalities (MAs) was found in the intervention group (11). Besides glycemia, higher serum triglyceride level was associated with early DR abnormalities. Furthermore, n-3 long-chain unsaturated fatty acids, odd-chain fatty acid 15:0, and plasmalogen dm16:0 were associated with a lower risk of MAs (18). In the present study, we analyzed the prevalence of clinically diagnosed DR during the 22-year median follow-up in the former DPS study participants.

Materials and Methods

A total of 522 people with IGT were recruited into the multicenter-controlled DPS study in Finland during 1993 to 1998 (Fig. 1 and Table 1). The median intervention period lasted for 4 years and was then followed by a nonintervention follow-up lasting up to 11 years (16). The current results on the occurrence of clinically diagnosed retinopathy are based on the median total follow-up of 22 years. Originally, 265 people were randomly assigned to the intervention group, which received an intensive lifestyle intervention in terms of weight loss, healthy dietary choices, and increasing physical activity, whereas 257 people served as controls who received general instruction for a healthy lifestyle (14–16). In this follow-up study, we had data on 257 and 248 individuals from the original intervention and control groups, respectively, who gave consent for record linkage with national health registries.

We have previously reported early retinopathic changes based on fundus photographs in a subsample of the DPS study participants (11, 18). Detailed description of the methods, clinical characteristics, physiological, and biochemical measurements have been given in previous publications (14–16, 19). In brief, all participants had an annual oral glucose tolerance test, a medical history, and physical examination with measurements of height (without shoes), weight (in light indoor clothes), waist circumference (midway between the lowest rib and iliac crest), and blood pressure. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were determined from fasting samples using an enzymatic assay method. In the postintervention period until the last clinic visit, biannual examinations were carried out (16).

For the present postintervention study, the data on clinically diagnosed DR were collected through computerized register linkage to 2 nationwide health registers: the Care Register for Health and the Causes of Death Register, using the national personal identification number (ID). The DR cases were identified by searching the databases up until a predefined end-of-study date, December 31, 2018, for International Classification of Diseases, Tenth Revision (ICD-10) codes with the following prefixes: E10.3, E11.3, E12.3, E13.3, E14.3, H28.0, and H36.0; or CKC12/CKD05/CKD60/CKD65. New diabetes cases were diagnosed during the clinical study visits by a 2-hour oral glucose tolerance test, which was used as the primary source for DM diagnoses. After an

individual's last clinical visit, the search for DM diagnoses was continued through the Care Register for Health and the registers for Drug Reimbursements and Drug Purchases for ICD-10 codes starting with E11 or Anatomical Therapeutic Chemical (ATC) codes starting with A10A or A10B (excluding A10BX01). A diagnosis was then declared on the date of the first register entry indicating diabetes if an individual had either i) at least one (Drug Reimbursement code) or ii) 2 or more total register entries indicating DM. Data from these registers were also available for deceased individuals before death. In Finland, all residents have a personal ID. This number is used in all health registers covering all hospital admissions in the country. Using this ID number, we could identify all hospital admissions of the DPS participants. Deaths and clinically diagnosed retinopathy cases are based on a median of 22 years' follow-up time, which means there are no missing registry data for ID-coded individuals.

The study protocol was approved by the ethics committees of the National Public Health Institute in Helsinki, Finland (intervention phase), and of the North Ostrobothnia Hospital District (follow-up period). All study participants gave written informed consent at baseline and again at the beginning of the postintervention follow-up.

Statistical Analyses

Logistic regression models were used to assess whether the assignment to lifestyle intervention or getting a diabetes diagnosis during follow-up was associated with getting a retinopathy diagnosis during the entire follow-up, that is, the time from baseline to death or end-of-study date, defined here as December 31, 2018. Models assessing the possible contribution of the diabetes diagnosis were adjusted for the intervention group status, sex, age at baseline, and follow-up time. Two models were fitted separately: one using the diabetes diagnosis at any time during the follow-up as the predictor, and another one using the diagnosis of diabetes during the first 5 years of follow-up as the predictor. The model assessing the effect of the intervention assignment was adjusted for sex, age at baseline, and follow-up time. Individuals who died during the follow-up were also included in the analyses.

Associations between the cumulative risk factor histories (glycated hemoglobin A_{1c} [HbA_{1c}], fasting and 1-hour and 2-hour plasma glucose, serum total cholesterol, HDL cholesterol, triglycerides, systolic and diastolic blood pressure, and body mass index) and DR were assessed by joint modeling (20) of the respective longitudinal risk factor trajectory and the hazard for DR. The survival submodels were specified as proportional hazards models. For the longitudinal, linear mixed-effects models were used, and the possibly nonlinear shapes of the risk factor trajectories were accommodated by using natural cubic splines with 1 inner knot placed at a 5-year mark. Prior to the analyses, risk factors were centered to the means of their baseline distributions and scaled to units of their baseline SDs. To capture the cumulative effects the risk factors were assumed to have on the hazard of retinopathy, cumulative parameterization (21, 22) was used to link the 2 submodels, that is, incorporating the integral of risk factor trajectories into the linear predictor of the survival submodel. Both submodels were adjusted for intervention assignment, sex, and age at baseline.

In addition, we conducted sensitivity analysis, by which the individuals were censored after 7 years since their last clinical

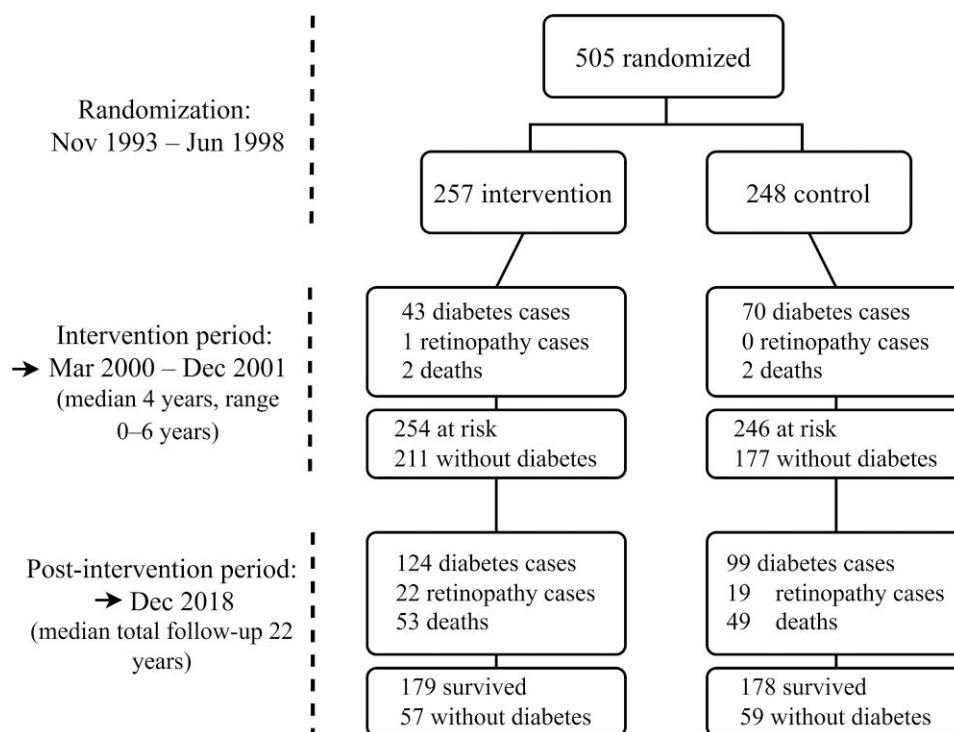


Figure 1. Flowchart of the Diabetes Prevention Study follow-up study.

Table 1. Baseline characteristics and follow-up data on antihypertensive and lipid and glucose-lowering drug treatment and self-reported physical activity at baseline and follow-up

	Intervention group	Control group
No. (men/women)	257 (88/169)	248 (78/170)
Follow-up time, median (interquartile range), y	22.3 (21.6-23.4)	22.2 (21.8-22.9)
Age, y	55 (7.3)	55 (6.9)
Body mass index	Men 30.1 (3.6) Women 32.1 (4.9)	Men 29.8 (3.6) Women 31.8 (4.7)
Fasting plasma glucose, mmol/L	6.1 (0.8)	6.2 (0.7)
2-h plasma glucose, mmol/L	8.9 (1.5)	8.9 (1.5)
HbA _{1c} , %	5.7 (0.6)	5.6 (0.6)
Serum total cholesterol, mmol/L	5.6 (1.0)	5.6 (0.9)
HDL cholesterol, mmol/L	Men 1.1 (0.3) Women 1.3 (0.3)	Men 1.1 (0.3) Women 1.3 (0.3)
Serum triglycerides, mmol/L	1.7 (0.8)	1.8 (0.8)
Systolic blood pressure, mm Hg	140 (18)	136 (17)
Diastolic blood pressure, mm Hg	86 (9.4)	86 (10)
Drug treatment for hypertension (%), baseline	71 (28%)	78 (31%)
Last visit during follow-up	155 (60%)	146 (59%)
Lipid-lowering drug treatment (%), baseline	11 (4%)	15 (6%)
Last visit during follow-up	113 (44%)	109 (44%)
Regular smokers, baseline (%)	14 (5%)	18 (7%)
Reported physical ^a activity, baseline (%)	162 (63%)	164 (66%)
Last visit during follow-up	167 (65%)	160 (65%)
Diabetes diagnosis during follow-up	167 (65%)	169 (68%)

Abbreviations: HbA_{1c}, glycated hemoglobin A_{1c}; HDL, high-density lipoprotein.

^aAt least 4 hours per week walking, bicycling, running, or other moderate intensity physical activity per week.

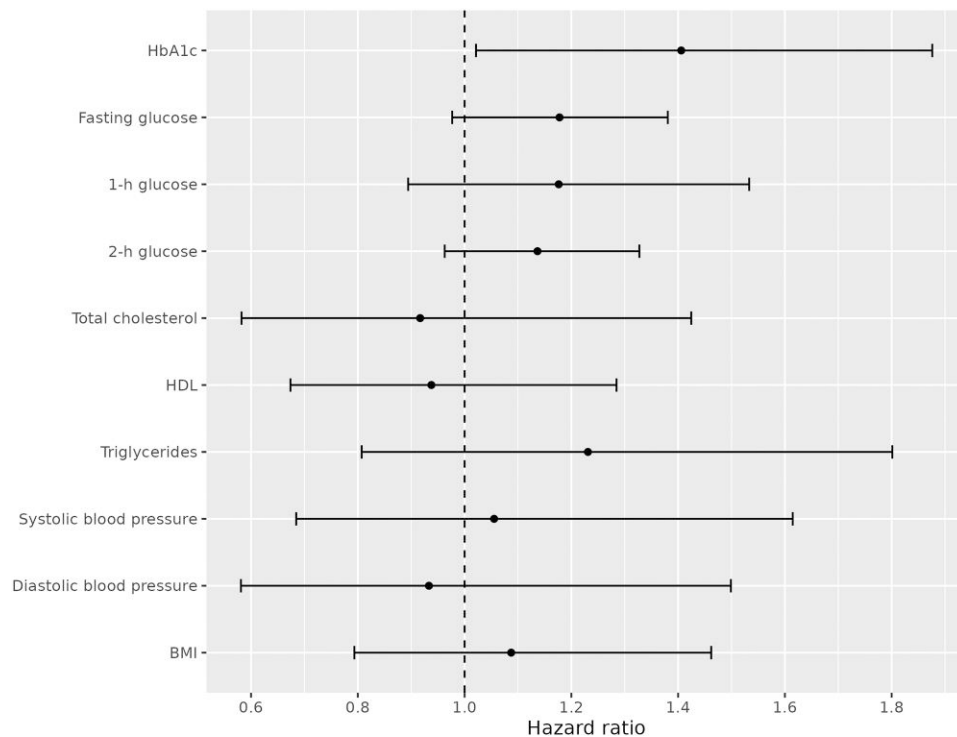


Figure 2. Estimated standardized hazard ratios and 95% posterior intervals associated with a 1-year increase in risk factor by 1 unit during the follow-up. The unit was calculated as 1 SD of the baseline value of the risk factor, and therefore the estimated hazard ratios among risk factors are directly comparable.

follow-up visit if not already censored for other reasons. The 7-year cutoff was chosen to limit the required extrapolation of estimated longitudinal trajectories while still retaining most of the clinical end points. The joint models were fitted using R software for statistical computing (version 4.3.0) and package JMbayes2 (version 0.4.5), using package-default priors. The results are presented as hazard ratios, interpretable as the effect associated with a 1-baseline-SD increase of the risk factor for 1 year. In addition, 95% posterior intervals for the estimates are reported, and considered statistically significant if the interval does not contain 1.

Results

Table 1 summarizes the baseline data of the study participants by group. Use of antihypertensive and lipid-lowering drugs increased markedly in both groups during the follow-up (see **Table 1**), but no differences between the groups were found in this regard.

Fig. 1 shows the flowchart of the formation of the present study population, cumulative incidence of diabetes and DR, and the number of deaths at the end of intervention period and after the extended follow-up of a median of 22 years. The outcome measures of the present study, that is, diabetes and DR, were based on the data documented in the Finnish health registers with computerized record linkage using the national personal ID resulting in a complete case-ascertainment during the follow-up. No significant difference was observed between the original intervention ($N=23$, 8.9%) and control groups ($N=19$, 7.7%) in the occurrence of DR (OR 1.15; 95% CI, 0.61-2.21). Next, we analyzed the effects of cumulative longitudinal trajectories of HbA_{1c}, fasting and 1-hour and 2-hour plasma glucose, serum lipids, blood pressure, and

body mass index on the hazard of DR in the entire study population (**Fig. 2**). HbA_{1c} was the only risk factor significantly associated with the hazard for DR (hazard ratio 1.4; 95% posterior interval, 1.02-1.88, adjusted for group, age, and sex). The estimates for other glycemic measures showed a similar but smaller association; however, they were not considered significant since the posterior intervals for hazard ratios overlap 1 (**Fig. 2**). The estimates remained similar in the sensitivity analysis.

Of the individuals who received a diabetes diagnosis at any time during the follow-up, almost 10% (33/349) also received a DR diagnosis, whereas this proportion among those who remained free of diabetes was 6% (9/156). The estimated odds ratio, adjusted for group, sex, age at baseline, and follow-up time, was 1.81 (95% CI, 0.86-4.19); however, the difference was not statistically significant.

Discussion

The main finding of the present study was that hyperglycemia revealed by a higher cumulative HbA_{1c} was significantly associated with an increased risk of DR. No evidence was found for an effect of lifestyle intervention on the occurrence of DR during the median of 22 years of follow-up. Furthermore, individuals who had developed diabetes during the follow-up were found to have a numerically higher risk of DR than those remaining free of diabetes (odds ratio 1.81; 95% CI, 0.86-4.19), although the result was not statistically significant. Nevertheless, this can also be taken as evidence for the effect of hyperglycemia.

Our previous report on the DPS follow-up suggested that an intensive lifestyle intervention for 4 years in overweight and obese individuals with IGT could prevent the appearance of

Table 2. Summary of previously published long-term follow-up of lifestyle intervention studies on diabetic retinopathy in high-risk people with diabetes or individuals with prediabetes

Study	Intervention	Effect on retinopathy	Comments
China Da Qing Diabetes Prevention Follow-up study (26)	Diet clinics, exercise clinics, diet and exercise clinics, and control clinics	40% reduction in any retinopathy in combined intervention clinics compared to original control clinics group	Randomization by clinics, mean follow-up time of 30 y after randomization
Diabetes Prevention Program Outcome Study (29)	Intensive lifestyle support, metformin, and control groups	No group differences in prevalence of any retinopathy	Fundus photographs examination data. Fewer microvascular complications in individuals who remained nondiabetic during follow-up (RR 0.72; $P < 0.001$).
Diabetes Prevention Program DPP Outcome study (13)	See previously mentioned original study groups	Prevalence of retinopathy smaller in individuals without diabetes (14%) than in those with incident diabetes (24%) after 16 y of follow-up period. No difference in any retinopathy between original study groups (lifestyle, metformin, placebo)	Main risk factor for retinopathy was glycemia/diabetes. OR for HbA _{1c} was 1.65 (1.48-1.83, $P < .0001$ per SD, 0.7%) after adjustments. Interestingly, less retinopathy in American Indian individuals
The Finnish Diabetes Prevention Follow-up Study (11)	Lifestyle (diet and exercise) intervention vs control group	Less early retinopathy in intervention than in control groups (24% vs 38%, adjusted OR 0.52; 0.28-0.97, 95% CI; $P = .039$).	Subgroup analysis based on retinal photographs
PREDIMET Study, Mediterranean Diet, Retinopathy, Nephropathy, and Microvascular Diabetes Complications: A Post Hoc Analysis of a Randomized Trial (28)	Mediterranean diet with EVOO (N = 1282) or with nuts (N = 1142) vs control group (N = 1190)	Multivariable-adjusted HRs for diabetic retinopathy were 0.56 (95% CI, 0.32-0.97) for MedDiet + EVOO and 0.63 (0.35-1.11) for MedDiet + Nuts compared to control diet group	Post hoc analysis in patients with diabetes. Incidence of retinopathy based on ophthalmological examination or photocoagulation therapy After 6 y of follow-up, incidence of any retinopathy was only 2% in whole study group

Abbreviations: EVOO, extra virgin olive oil; HbA_{1c}, glycated hemoglobin A_{1c}; HR, hazard ratio; OR, odds ratio; RR, relative risk.

retinal MAs (11). Nevertheless, in this long-term follow-up study with a median follow-up of 22 years, we did not find a significant difference in the occurrence of clinically diagnosed DR leading to hospital admission between the original intervention and control groups. Furthermore, we did not observe a significant association between DR and serum triglycerides that we observed in our earlier assessment on the occurrence of retinal MAs based on the fundus photography examination (11). Other lipid metabolites, including serum plasmalogens, were not associated with clinically diagnosed DR, either (18).

Several studies and meta-analyses have confirmed that T2D can be prevented or postponed in prediabetic individuals by lifestyle modification, pharmacological interventions, or a combined intervention (8, 23, 24). Only a few studies have examined whether lifestyle intervention in prediabetes could also prevent the development of DR (Table 2). Lifestyle intervention lasting 6 years in people with IGT in the Chinese Da Qing Diabetes Prevention Outcome Study delayed the onset of T2D and also reduced the incidence of cardiovascular events, microvascular complications, and cardiovascular and all-cause mortality, and increased life expectancy (25-27). Long-term results of this Chinese study showed a cumulative incidence of DR 13.5% in combined intervention groups and 30.7% in a control group over a 30-year interval (25). The reduced incidence of diabetes in the intervention group was suggested to be the main reason for the decreased DR in this Chinese study. In the Spanish PREDIMET study, the 6-year incidence of DR was only 2%, but it was 44% lower in the extra virgin olive oil group than in the control group (28). On the

other hand, the US Diabetes Prevention Program Outcome Study showed that lifestyle intervention as such did not decrease the risk of retinal complications, but the prevalence of DR was 14% in the nondiabetic group and 24% in the group with incident diabetes in that study, that is, those who developed diabetes had an increased prevalence of DR (13, 29; see Table 2). Our results on the prevalence of DR (8.9% in the intervention and 7.7% in the control group), are well in line with those of the Diabetes Prevention Program Outcome Study. The lower prevalence in the DPS study participants may be due to different methods applied to define the occurrence of DR. It is well known that DR may occur in adults with prediabetes and early T2D (11-13; see Table 2). Long-term hyperglycemia measured by elevated HbA_{1c} was a key risk factor for the development of DR across the entire glycemic range from prediabetes to diabetes in the Diabetes Prevention Program Outcome Study. Furthermore, weight and history of hypertension, dyslipidemia, and smoking were associated with DR in that study (13). Danish data revealed that HbA_{1c} was the most important factor in the progression of nonproliferative DR to proliferative DR (30). On the contrary, systolic and diastolic blood pressure or serum cholesterol did not show marked effects on DR progression (30), which is in line with our follow-up data. Furthermore, intensive treatment of hypertension and lipid disorders in the DPS participants may have modified the effect of elevated blood pressure and dyslipidemias on the risk of DR.

We can only speculate that the preventive effects of n-3 long-chain unsaturated fatty acids and plasmalogens may have a role in earlier phases of MA formation (11, 18) since

we did not find any association in the present study between these biomarkers and clinical DR diagnosed mostly in specialized hospital clinics.

Strengths of the study are the well-controlled DPS population with repeated follow-up assessments of conventional risk factors, glycemia, and a multitude of blood biomarkers. The national Care Register for Health data checked every year provided accurate diagnoses from health centers, hospitals, and other institutions with a complete case ascertainment. Our study does have weaknesses. The sample size was markedly lower than in the Diabetes Prevention Program Outcome Study (13) but was comparable to that in the Chinese Da Qing Follow-up study (25–27). We did not have baseline data on retinal changes, either. Formal power calculations concerning DR were not performed; however, as the number of DR events was relatively small, and the CIs relatively wide, null results should not be taken as evidence of absence of a clinically meaningful association.

In conclusion, based mostly on the Care Register for Health data, we confirm that in individuals with IGT a longitudinally good glycemic control and remaining free of diabetes for a long period of time are the key elements to prevent DR in prediabetic individuals. We did not observe that lifestyle intervention in the DPS study as such affected the risk of clinically diagnosed DR that was based on the Care Register for Health data.

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Author Contributions

M.V., S.K.K., J.T., J.L., and M.U. conceived the project, analyzed data, and wrote and edited the manuscript. K.K. interpreted results and wrote the manuscript. All authors approved the final version of the manuscript. M.U. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

The authors declare no disclosures for the manuscript.

Data Availability

Some or all data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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