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Associations between attainment of incentivized primary care indicators and incident sight-threatening diabetic retinopathy in England: A population-based historical cohort study

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Abstract

Aim: To examine the impact of attainment of primary care diabetes clinical indicators on progression to sight-threatening diabetic retinopathy (STDR) among those with mild non-proliferative diabetic retinopathy (NPDR).

Materials and Methods: An historical cohort study of 18,978 adults (43.63% female) diagnosed with type 2 diabetes before 1 April 2010 and mild NPDR before 1 April 2011 was conducted. The data were obtained from the UK Clinical Practice Research Datalink during 2010–2017, provided by 330 primary care practices in England. Exposures included attainment of the Quality and Outcomes Framework HbA1c (≤ 59 mmol/mol [$\leq 7.5\%$]), blood pressure ($\leq 140/80$ mmHg) and cholesterol (≤ 5 mmol/L) indicators in the financial year 2010–2011, as well as the number of National Diabetes Audit processes completed in 2010–2011. The outcome was time to incident STDR. Nearest neighbour propensity score matching was undertaken, and univariable and multivariable Cox proportional hazards models were then fitted using the matched samples. Concordance statistics were calculated for each model.

Results: A total of 1037 (5.5%) STDR diagnoses were observed over a mean follow-up of 3.6 (SD 2.0) years. HbA1c, blood pressure and cholesterol indicator attainment were associated with lower rates of STDR (adjusted hazard ratios [95% CI] 0.64 [0.55–0.74; $p < .001$], 0.83 [0.72–0.94; $p = .005$] and 0.80 [0.66–0.96; $p = .015$], respectively).

Conclusions: Our findings provide support for meeting appropriate indicators for the management of type 2 diabetes in primary care to bring a range of benefits, including improved health outcomes—such as a reduction in the risk of STDR—for people with type 2 diabetes.

KEYWORDS

general practice, National Diabetes Audit, Quality and Outcomes Framework, sight-threatening retinopathy, type 2 diabetes

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1 | INTRODUCTION

Sight-threatening diabetic retinopathy (STDR) is a common cause of preventable visual impairment in people with type 2 diabetes.¹ Although advances in the treatment of STDR have resulted in better outcomes over the last decade,²⁻⁵ preventing STDR remains the cornerstone for reducing visual morbidity.⁶⁻⁸ Optimal control of the three known modifiable risk factors, hyperglycaemia, hypertension and hyperlipidaemia, is key to preventing the development and progression of diabetic retinopathy (DR) to STDR.⁶⁻¹⁰ Clinical trials that have evaluated the role of lipid-lowering therapies in the progression to STDR have shown that fenofibrate alone, or in combination with statins, slows the progression to STDR, but the protective effect of statins alone is less convincing.⁹⁻¹¹

National screening programmes have been established in several countries worldwide to enable early identification and prompt treatment of STDR.^{12,13} As screening every person with diabetes annually is challenging and not cost-effective,¹⁴ various risk prediction models have been developed to predict the individual risk of STDR in order to plan risk-based screening.^{15,16} A strong predictor of STDR is the presence of DR.^{15,16} The severity of DR progresses from mild, moderate or severe non-proliferative DR (NPDR) to proliferative DR (PDR). Eyes with any severity of DR can also develop diabetic macular oedema (DMO). STDR is defined as any evidence of severe NPDR, PDR or DMO. Time to STDR differs with the severity level of DR. For example, the rate of progression to PDR in eyes with mild DR is 6.2%, while 54.8% of cases of severe NPDR progress to PDR in 1 year. Recent evidence suggests that the incidence and progression of STDR has reduced by approximately 2-3-fold over the last 3 decades.¹

Although the UK Prospective Diabetes Study (UKPDS) and the The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study were conducted approximately 15 years apart, both trials showed that controlling systemic risk factors after the development of DR could avert or delay the onset of STDR.^{6,8,17} However, the impact of control of individual risk factors and their combinations on the development of STDR in people with type 2 diabetes with DR, at the population level, has not been clearly elucidated recently. The Quality and Outcomes Framework (QOF) is a pay for performance scheme that was introduced in general practice in the UK in 2004, with the aim of improving clinical outcomes for a diverse group of conditions.¹⁸ The framework rewards maintenance of a register of adult patients with diabetes and achieving recommended targets for control of HbA1c (≤ 59 mmol/mol [$\leq 7.5\%$]), blood pressure (BP; $\leq 140/80$ mmHg) and total cholesterol (≤ 5 mmol/L).¹⁹ An additional national programme, the National Diabetes Audit (NDA), compares diabetes care in England with standards set by the National Institute of Health and Care Excellence (NICE) clinical guidelines and NICE quality standards. Among other things, it monitors provision of nine care processes recommended for all patients with diabetes annually. These consist of HbA1c, BP, serum cholesterol, serum creatinine, urine albumin-to-creatinine ratio (ACR), foot examination, retinal screening, body mass index (BMI) and smoking review.²⁰ Therefore, attainment of these QOF indicators and NDA standards is a proxy

measure of optimal control of the risk factors of STDR. This study aims to provide evidence of the impact of control of risk factors on the incidence of STDR among those with mild NPDR in England.

2 | MATERIALS AND METHODS

2.1 | Study design and data sources

The UK Clinical Practice Research Datalink (CPRD) GOLD database, which contains longitudinal patient data collected in routine general practice and dating back to 1987, was used to obtain this retrospective cohort. Consisting of more than 18 million patients (3 million of whom are currently registered), CPRD GOLD is representative of the UK primary care-registered population. Linked Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality data are available for most of the CPRD participants located in England. The database has been used to investigate diabetes care processes and outcomes.^{21,22} Only participants with linked HES and ONS data were eligible for inclusion. They entered the cohort on 1 April 2010 if they had an existing type 2 diabetes diagnosis, were aged 18 years or older, had been registered with their practice for at least 1 year, and were not censored prior to 1 April 2011. Only those with a mild NPDR diagnosis, as defined by the National Health Service Diabetes Eye Screening Programme (DESP) grade R1, before 1 April 2011, were included. The DESP R1 grade is equivalent to Early Treatment Diabetic Retinopathy Study (ETDRS) severity level 20-35 inclusive and includes background microaneurysms, retinal haemorrhages with or without hard exudates and venous loops.²³ Individuals with a type 1 diabetes or other specified non-type 2 diabetes diagnosis occurring at any time were excluded. Those prescribed insulin within 6 months of a diagnosis made at an age younger than 35 years, or within 3 months of a diabetes diagnosis at the age of 35 years or older, were also excluded. Cohort exit occurred at the earliest of transfer out of database, last CPRD data upload, death, or 31 December 2017 (end of study period). The code lists used in deriving the cohort are available in Table S1.

2.2 | Exposures

The exposures of interest included attainment of the QOF HbA1c (≤ 59 mmol/mol [$\leq 7.5\%$]), BP ($\leq 140/80$ mmHg) and total cholesterol (≤ 5 mmol/L) indicators within the 2010-2011 financial year. Attainment was classified according to the QOF Business Rules v38.0. Indicator status was determined using the most recent measurements in the year of interest. Where no measurement was made, the indicator was considered not to have been met. Another exposure variable describing implementation of NDA annual care processes during the 2010-2011 year was defined by categorizing the number of completed processes as 0-3, 4-6 or 7-8. NDA processes include eight measurements consisting of HbA1c, BP, cholesterol, serum creatinine, urine ACR, BMI, smoking history and foot examination. Retinal

screening was not included as an exposure because study participants already had DR at baseline. All exposures were statistically defined as of the end of the baseline period (31 March 2011).

2.3 | Outcome variable

The outcome was time to first CPRD or HES record of incident STDR (from 1 April 2011), as defined by the DESP classification.²³ STDR included severe NPDR graded as R2, PDR (active or stable) as R3 with or without retinal photocoagulation (P1) and the presence of any sign of diabetic maculopathy recorded as M1. The grade R2 equated to ETDRS severity level 43-57 and R3 included grades of 61 or higher.²³

2.4 | Covariates

The study covariates (measured at baseline before 1 April 2011) comprised sociodemographic factors (sex, age, ethnicity, 2010 patient-level index of multiple deprivation [IMD]), the individual's primary care practice geographical region and several disease-related variables (time from type 2 diabetes diagnosis, time from mild NPDR diagnosis, number of diabetes complications, number of glucose-lowering therapies [GLTs] prescribed and presence/absence of insulin prescription [the latter two variables measured within 6 months before baseline]). Co-morbidities (number of QOF registers that the individual appeared on in 2010-2011, number of hospital admissions in the same year, and the number of prescriptions in the 6 months before cohort entry) and lifestyle factors (BMI, smoking status and alcohol use) were also included. Full variable definitions are provided in Tables S2-S11.

2.5 | Statistical analysis

Cohort characteristics at baseline were summarized, as well as missing data. Missing IMD patient-level values were imputed using IMD practice-level data. Missing lifestyle and ethnicity information was imputed from the remaining variables by employing the *mice* package in RStudio 3.5.1²⁴ using five imputations. The *matchit* package was applied to conduct nearest neighbour propensity score matching using a 0.2 caliper for each exposure definition.²⁵ Matched samples for each exposure were used to fit univariate and multivariate Cox proportional hazards models with the corresponding exposure included as another covariate. Concordance statistics were obtained for each of the multivariate models. Sensitivity analyses were conducted to examine the effect of QOF indicator attainment among (a) participants meeting the other two indicators (i.e. those not being considered as the exposure); (b) those not meeting either of the other two indicators; (c) those attaining lower targets such as an Hb1Ac of less than 7.0% or of even less than 6.5%, BP of less than 130/80 mmHg and cholesterol of less than 4 mmol/L; and

TABLE 1 Baseline characteristics of those with a non-sight-threatening diabetic retinopathy diagnosis (N = 18,978)

| Variable | n or mean | % or SD |
|---|-----------|---------|
| Age, years | 69.49 | 11.97 |
| Sex: female | 8281 | 43.63% |
| Ethnicity | | |
| Asian | 1019 | 5.37% |
| Black | 349 | 1.84% |
| Mixed | 111 | 0.58% |
| Other | 216 | 1.14% |
| White | 16,260 | 85.68% |
| Missing | 1023 | 5.39% |
| IMD | | |
| Score | 10.29 | 5.56% |
| Missing | 9 | 0.05% |
| Region | | |
| North East | 524 | 2.76% |
| North West | 3292 | 17.35% |
| Yorkshire and the Humber | 753 | 3.97% |
| East Midlands | 413 | 2.18% |
| West Midlands | 2280 | 12.01% |
| East of England | 1965 | 10.35% |
| South West | 2586 | 13.63% |
| South Central | 2187 | 11.52% |
| London | 2553 | 13.45% |
| South East coast | 2425 | 12.78% |
| BMI | | |
| Underweight | 134 | 0.71% |
| Ideal weight | 2973 | 15.67% |
| Overweight | 6469 | 34.09% |
| Obese | 9249 | 48.74% |
| Missing | 153 | 0.81% |
| Never smoker | 9060 | 47.74% |
| Ex-smoker | 7449 | 39.25% |
| Current smoker | 2394 | 12.61% |
| Smoking: missing | 75 | 0.40% |
| Alcohol (units/week) | | |
| 0 | 3312 | 17.45% |
| 1-14 | 11,210 | 59.07% |
| 15-42 | 1817 | 9.57% |
| >42 | 368 | 1.94% |
| Missing | 2271 | 11.97% |
| Co-morbidities (count) | 2.51 | 1.70 |
| Prescriptions within preceding 6 months (count) | 9.17 | 9.00 |
| Hospitalizations during 2010-2011 (count) | 0.19 | 0.60 |
| Duration of diabetes (years) | 7.88 | 5.77 |
| Duration of retinopathy (years) | 4.21 | 3.78 |
| Number of diabetes complications (count) | 2.41 | 1.17 |

(Continues)

TABLE 1 (Continued)

| Variable | n or mean | % or SD |
|---|-----------|---------|
| GLT prescriptions within the preceding 6 months (count) | 1.48 | 0.99 |
| Insulin prescription within the preceding 6 months (yes/no) | 3803 | 20.04% |

Abbreviations: BMI, body mass index; GLT, glucose-lowering therapy; IMD, index of multiple deprivation; SD, standard deviation.

(d) those attaining combinations of any two of HbA1c, BP and cholesterol versus attaining fewer than two indicators.

3 | RESULTS

3.1 | Cohort characteristics

In total, 18,978 adults (43.63% female) with type 2 diabetes diagnosed before 1 April 2010 and mild NDPR prior to 1 April 2011 were identified as eligible for inclusion, across 330 practices (see Figure S1 for a flowchart). The baseline prevalence of any DR in our cohort was 28.8%, and mild (but not sight-threatening) retinopathy among the total who met all non-retinopathy-related cohort entry criteria (n = 84,441) was 22.5%. Baseline characteristics are described in Table 1. Mean (standard deviation) age was 69.5 (12.0) years, 85.7% were of White ethnic background and the average time since diabetes diagnosis was 7.9 (5.8) years. The average time since non-sight-threatening DR diagnosis was 4.2 (3.8) years. The majority were overweight or obese (82.8%), current or ex-smokers (51.9%) and/or consumed alcohol (70.6%). Participants had an average of 2.4 (1.2) diabetes complications and 2.5 (1.7) co-morbidities; and 9.2 (9.0) different prescriptions and 1.5 (1.0) different GLTs in the 6 months before study entry; also, 3803 participants (20.0%) had insulin prescriptions during that time.

Over a mean follow-up of 3.6 (2.0) years, 1037 (5.5%) STDR diagnoses were observed, corresponding to a diagnosis rate of 15.08 per 1000 person-years among individuals with DR. Furthermore, 829 (5.1%), 30 (8.6%), 95 (9.3%), 9 (8.1%), 14 (6.5%) and 60 (5.9%) STDR diagnoses were observed, corresponding to diagnosis rates of 14.28, 21.69, 23.51, 20.66, 15.69 and 15.16 per 1000 person-years for White, Black, Asian, mixed, other and missing ethnicities, respectively.

Table 2 presents the observed distribution of QOF indicator attainment and NDA process completion by the number of indicators/processes met. The HbA1c, BP and cholesterol QOF indicators were achieved by 12,010 (63.3%), 11,247 (59.3%) and 14,855 (78.3%), respectively; 6304 (33.2%) individuals met all three indicators. NDA process completion ranged from 15,288 (80.6%; urine ACR screening) to 18,397 (96.9%; BP screening). The majority (15,598, 82.2%) completed 7-8 NDA processes; 11,898 (62.7%) completed all eight, but only 2675 (14.1%) completed 4-6 processes. Those who did not have a measurement in 2010-2011 were classified as not meeting the corresponding indicator, which included 856 (4.5%), 581 (3.1%) and 1575 (8.3%) for HbA1c, BP and cholesterol, respectively.

Given the low counts observed for non-White ethnicities, wide confidence intervals were obtained and no consistent associations

TABLE 2 Number (%) of individuals who met each Quality and Outcomes Framework (QOF) indicator or completed each National Diabetes Audit (NDA) care process (columns), clustered by the number of QOF indicators or NDA care processes attained (rows)

| Number of indicators/ care processes met | QOF indicator met | | | | | | | | | | | |
|---|-------------------|-----------------|-----------------|-------------------|-----------------|-----------------|-------------------|------------------|-----------------|------------------|-----------------|-----------------|
| | TOTAL | HbA1c | BP | Total cholesterol | HbA1c | BP | Total cholesterol | Serum creatinine | Urine ACR | Foot examination | BMI | Smoking history |
| QOF indicators | 0 | 1105 (5.82%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 703 (63.62%) | 541 (48.96%) | 667 (60.36%) | 706 (63.89%) | 695 (62.9%) |
| | 1 | 3938 (20.75%) | 946 (24.02%) | 918 (23.31%) | 2074 (52.67%) | 3781 (96.01%) | 3276 (83.19%) | 3587 (91.09%) | 2881 (73.16%) | 3134 (79.58%) | 3437 (87.28%) | 3196 (81.16%) |
| | 2 | 7631 (40.21%) | 4760 (62.38%) | 4025 (52.75%) | 6477 (84.88%) | 7475 (97.96%) | 7274 (95.32%) | 7474 (97.94%) | 6335 (83.02%) | 6637 (86.97%) | 7105 (93.11%) | 6581 (86.24%) |
| | 3 | 6304 (33.22%) | 6304 (100%) | 6304 (100%) | 6304 (100%) | 6304 (100%) | 6304 (100%) | 6268 (99.43%) | 5531 (87.74%) | 5671 (89.96%) | 5988 (94.99%) | 5635 (89.39%) |
| NDA care | 0-3 | 705 (3.71%) | 121 (1.71%) | 214 (30.35%) | 62 (8.79%) | 390 (55.32%) | 87 (12.34%) | 186 (26.38%) | 40 (5.67%) | 96 (13.62%) | 141 (20%) | 149 (21.13%) |
| | 4-6 | 2675 (14.1%) | 1454 (54.36%) | 1459 (54.54%) | 1574 (58.84%) | 2484 (87.96%) | 1913 (71.51%) | 2284 (85.38%) | 1016 (37.98%) | 1192 (44.56%) | 1720 (64.3%) | 1353 (50.58%) |
| | 7-8 | 15,598 (82.19%) | 10,435 (66.9%) | 9574 (61.38%) | 13,219 (84.75%) | 15,563 (99.78%) | 15,403 (98.75%) | 15,562 (99.77%) | 14,232 (91.24%) | 14,821 (95.02%) | 15,375 (98.57%) | 14,605 (93.63%) |
| | 8 | 11,898 (62.69%) | 8104 (68.11%) | 7370 (61.94%) | 10,258 (86.22%) | 11,898 (100%) | 11,898 (100%) | 11,898 (100%) | 11,898 (100%) | 11,898 (100%) | 11,898 (100%) | 11,898 (100%) |
| TOTAL | | 18,978 (100%) | 12,010 (63.28%) | 11,247 (59.26%) | 14,855 (78.27%) | 18,122 (95.49%) | 18,397 (96.94%) | 17,403 (91.7%) | 15,288 (80.56%) | 16,109 (84.88%) | 17,236 (90.82%) | 16,107 (84.87%) |

Abbreviations: ACR, albumin creatinine ratio; BMI, body mass index; BP, blood pressure.

were observed between ethnicity and STDR across exposures. Asian ethnic background, the largest minority group recorded, was significantly associated with higher risks of STDR than White ethnic background upon accounting for three of the exposures, namely, HbA1c QOF indicator achievement, achievement of all three QOF indicators, and all QOF and NDA indicator achievement. The remaining ethnic minority groups showed no significant associations across exposures except that mixed ethnicity was significantly associated with a higher risk of STDR compared with White ethnicity upon accounting for meeting 4-6 versus 0-3 NDA processes.

3.2 | Associations between QOF indicator exposures and sight-threatening retinopathy

Table 3 provides the unadjusted and adjusted associations between exposure to attainment of each of the QOF indicators and incident STDR. HbA1c, BP and cholesterol indicator achievement were associated with lower rates of STDR in the unadjusted and adjusted analyses (adjusted hazard ratios [HRs] [95% CI] 0.64 [0.55-0.74; $p < .001$], 0.83 [0.72-0.94; $p = .005$] and 0.80 [0.66-0.96; $p = .015$], respectively). While a weak association was observed between achieving all QOF targets (vs. achieving fewer than three) and STDR in the univariate analysis, no significant association was found in the multivariate analysis (adjusted HR 0.85 [0.72-1.01; $p = .066$]), probably as a result of simply meeting any of the QOF indicators yielding a risk reduction in STDR. Complete model results (i.e. including unadjusted and adjusted HR estimates for all covariates) are provided in Tables S2, S4, S5, and S7-S11. Figure 1 presents Kaplan-Meier survival curve estimates across exposure definitions.

3.3 | Associations between NDA process completion exposures and sight-threatening retinopathy

Summaries of associations between NDA care process categories and incident STDR are shown in Table 4. No association was observed among the univariate or multivariate analyses ($p \geq .2179$) when comparing groups of the number of NDA processes met. However, the univariate analysis showed a risk reduction in STDR among those who met all

eight NDA processes (unadjusted HR 0.82 [0.72-0.95; $p = .006$]). However, this risk reduction was attenuated and became non-significant with the multivariate analysis (adjusted HR 0.87 [0.76-1.01; $p = .06$]). Full model results are available in Tables S3, S4, S6 and S7.

3.4 | Sensitivity analyses

Analyses of the QOF indicators restricted to those participants who met the other two QOF indicators showed a risk reduction in STDR only in the univariate analysis (unadjusted HR 0.78 [0.62-0.97]; $p = .023$) (Tables S8 and S9; Figure S2). Once confounders were accounted for in the multivariate model, this association was no longer statistically significant (adjusted HR 0.83 [0.66-1.04]; $p = .098$). A second sensitivity analysis assessed the effect of QOF indicator attainment on STDR risk among those who did not meet either of the other two indicators. Results were consistent with the primary analysis (adjusted HRs 0.45 [0.29-0.69; $p < .001$], 0.62 [0.45-0.85; $p = .003$] and 0.74 [0.56-0.98; $p = .036$] for HbA1c, BP and cholesterol, respectively [Tables S10 and S11; Figure S3]). A third sensitivity analysis using lower targets such as Hb1Ac of less than 7.0% or of even less than 6.5%, BP less than 130/80 mmHg and cholesterol less than 4 mmol/L, showed that the multivariate HRs were not overly sensitive to minor changes in exposure definitions, with all 95% CIs overlapping by exposure between the primary analyses and the corresponding sensitivity analyses. Table S12, which includes HRs and 95% CIs, summarizes these comparisons, with additional details included in Tables S13 and S14 and Figure S4. The results of the fourth sensitivity analysis showed that achieving any two QOF indicators was associated with significantly better outcomes than achieving fewer than two QOF indicators (adjusted HR 0.67; 95% CI 0.57-0.78; $p < .0001$) (Tables S15 and S16; Figure S5).

4 | DISCUSSION

4.1 | Summary of principal findings

Our study provides contemporary evidence of the incidence of STDR in England based on 18,978 individuals with type 2 diabetes who were previously diagnosed with DR and followed for a period of up to

TABLE 3 Unadjusted and adjusted hazard ratios (with corresponding 95% CIs and p -values) for sight-threatening diabetic retinopathy given QOF exposures after 1:1 propensity score matching

| Exposure (indicator met) | Unadjusted analyses | | | Adjusted analyses ^a | | |
|--------------------------|---------------------|-----------|--------|--------------------------------|-----------|--------|
| | HR | 95% CI | p | HR | 95% CI | p |
| HbA1c | 0.60 | 0.52-0.70 | <.0001 | 0.64 | 0.55-0.74 | <.0001 |
| Blood pressure | 0.82 | 0.72-0.94 | .0033 | 0.83 | 0.72-0.94 | .0054 |
| Cholesterol | 0.82 | 0.68-0.98 | .0319 | 0.80 | 0.66-0.96 | .0150 |
| All QOF indicators | 0.85 | 0.72-1.00 | .0483 | 0.85 | 0.72-1.01 | .0659 |

Abbreviations: CI, confidence interval; HR, hazard ratio; QOF, Quality and Outcomes Framework.

^aAdjusted for age, sex, ethnicity, index of multiple deprivation, practice region, body mass index, smoking status, alcohol consumption, number of other co-morbid conditions, hospitalizations, duration of diabetes, duration of non-sight-threatening retinopathy, diabetes complications, number of glucose-lowering therapies and insulin prescription status.

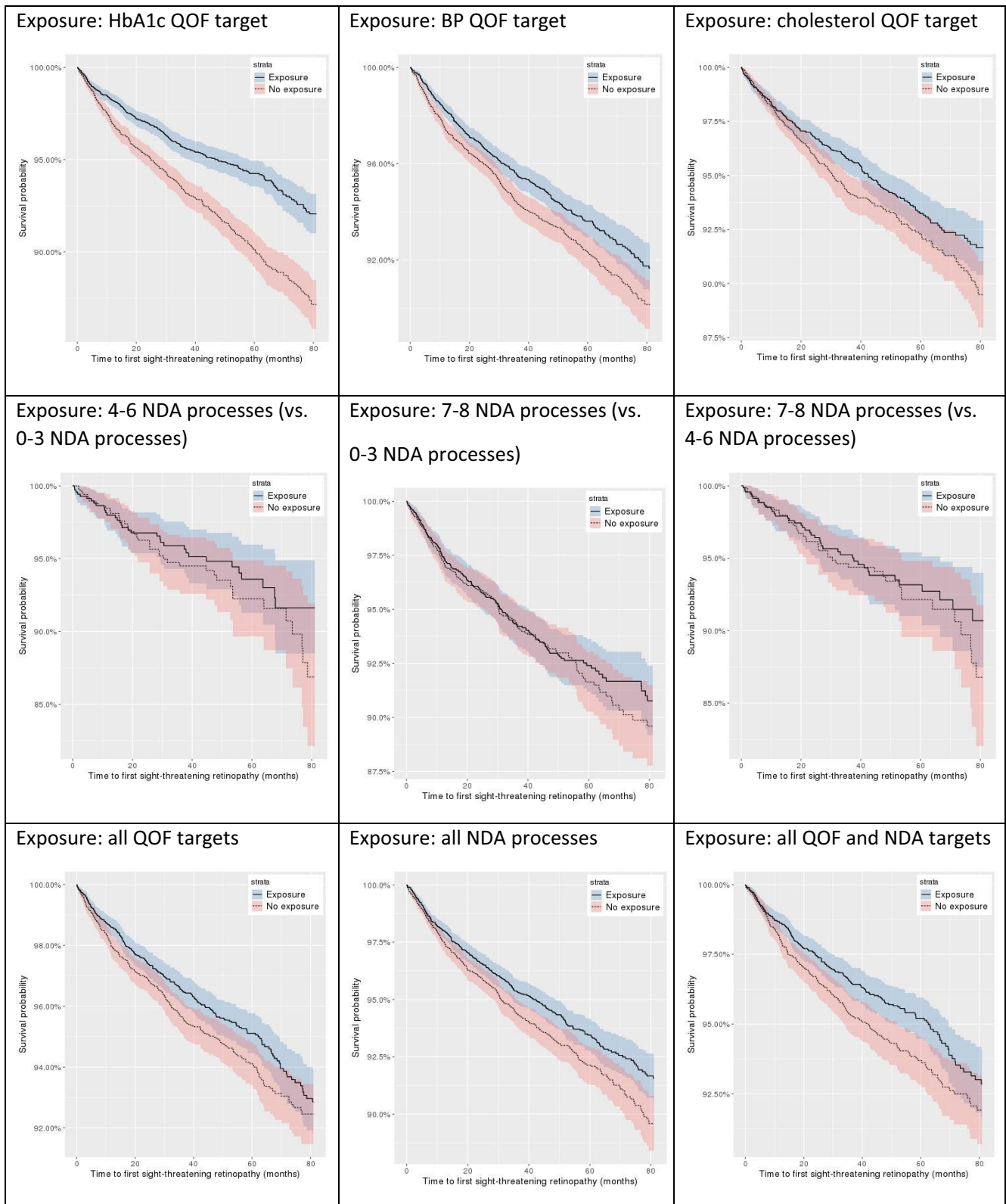


FIGURE 1 Kaplan-Meier survival curves (and corresponding 95% CIs) for risk of sight-threatening diabetic retinopathy after 1:1 propensity score matching across exposure definitions. BP, blood pressure; NDA, National Diabetes Audit; QOF, Quality and Outcomes Framework

6.75 years from 1 April 2011. Considering the cohort had a mean duration of diabetes of 7.9 (SD 5.8) years, 5.5% developed STDR over the study period, equivalent to 15.1 new cases per 1000 person-years

among those with mild NPDR. HbA1c, BP and cholesterol QOF indicator attainment was associated with significantly lower rates of STDR, with estimates ranging from 26% to 45%, 6% to 28% and 4%

TABLE 4 Unadjusted and adjusted hazard ratios (with corresponding 95% CIs and *p*-values) for sight-threatening diabetic retinopathy given National Diabetes Audit exposures after 1:1 propensity score matching

| Exposure (processes completed) | Unadjusted analyses | | | Adjusted analyses ^a | | |
|--------------------------------|---------------------|-----------|----------|--------------------------------|-----------|----------|
| | HR | 95% CI | <i>p</i> | HR | 95% CI | <i>p</i> |
| 4-6 (vs. 0-3) | 0.78 | 0.50-1.22 | .2772 | 0.75 | 0.47-1.19 | .2179 |
| 7-8 (vs. 0-3) | 0.94 | 0.76-1.17 | .5943 | 0.99 | 0.79-1.23 | .9212 |
| 7-8 (vs 4-6) | 0.85 | 0.55-1.30 | .4432 | 0.88 | 0.56-1.37 | .5649 |
| 8 (vs <8) | 0.82 | 0.72-0.95 | .0064 | 0.87 | 0.76-1.01 | .0594 |

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aAdjusted for age, sex, ethnicity, index of multiple deprivation, practice region, body mass index, smoking status, alcohol consumption, number of other co-morbid conditions, hospitalizations, duration of diabetes, duration of non-sight-threatening retinopathy, diabetes complications, number of glucose-lowering therapies and insulin prescription status.

to 34% lower, respectively. Our sensitivity analyses indicate that the primary analysis results are most relevant among those who do not meet the other two QOF indicators, and hence who may have worse baseline health (i.e. those for whom meeting the QOF exposure could imply a larger marginal impact on their risk of STDR). Thus, meeting any single QOF suffices to lower an individual's risk of STDR. However, we did not explore the roles of various interventions or any other measures in achieving these QOF indicators. Therefore, further research is required in these areas. This particularly applies to the role of statins and antihypertensives in preventing the progression to STDR, where current evidence is equivocal.

4.2 | Comparison with previous studies

The incidence of STDR observed in this study of 15.12 per 1000 person-years among individuals with DR concurs with the declining incidence of STDR observed in other reports, despite including severe NPDR and diabetic maculopathy as an STDR event.²⁶ Although the definition of progression of DR varied between studies, the ACCORD trial reported that only 12% of the study cohort had a two-step or higher increase in severity of DR in 4 years in 2014 compared with 30% in the Wisconsin epidemiological study of diabetic retinopathy reported in 1984.^{17,27} The ACCORD trial showed a stronger treatment effect of hyperglycaemia and hypercholesterolaemia in patients with mild DR than in those with no DR.¹⁷ The ACCORD trial and our study concur in that it is worthwhile persisting with control of hyperglycaemia and hypercholesterolaemia to reduce the rate of progression to STDR in people with DR. The ACCORD trial did not show a benefit with control of hypertension. Moreover, tight glycaemic control did not produce similar effects on DR progression in the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) trial or the Veterans Affairs Diabetes Trial (VADT).^{28,29} When we compare these study cohorts, the mean age of the patients in ACCORD, ADVANCE, VADT and our study was 62, 66, 60 and 69.5 years, and the duration of diabetes was 10, 8, 11.5 and 7.88 years, respectively.^{17,28,29} Another point we observed was that control of any one of the risk factors in people with poor control of all three risk factors is sufficient to reduce the rates of STDR. This may explain the differences observed between VADT and

ADVANCE with our study and the ACCORD trial. Although the VADT trial did not show an effect of tight glycaemic control on STDR, despite a baseline mean HbA1c of 79.2 mmol/mol (9.4%) and with 52% of the study population on insulin at baseline, the mean BP in this study population was already optimally controlled at 132/76 mmHg, and by 6 years the mean BP was 125/69 mmHg. However, our study highlights that having a BP target of 130/80 mmHg gives a 23% relative risk reduction compared with 17% for a BP target of 140/80 mmHg. Similarly, baseline HbA1c was 55.2 mmol/mol (7.2%) in the ADVANCE study compared with 65.0 mmol/mol (8.1%) and 79.2 mmol/mol (9.4%) in the ACCORD and VADT trials, respectively.^{17,28,29}

4.3 | Implications for policy and practice

While tight glycaemic control was defined as an HbA1c of less than 47.5 mmol/mol (6.5%) in the clinical trials, our study shows that even achieving an HbA1c of 59 mmol/mol (7.5%) is sufficient to lower the risk of progression to STDR among those with mild NPDR in whom all risk factors are suboptimally controlled. In clinical practice, it is challenging to ensure that a mean of less than 47.5 mmol/mol (6.5%) can be achieved at a population level. However, optimal control of all three risk factors is encouraged at an individual level to reduce the incidence of all complications of diabetes. Moreover, it is important that there is scope to enhance coverage of the achievement of QOF indicators, given their strong association with lower STDR incidence.

4.4 | Strengths and limitations

Our study included a large sample, which was reasonably representative of the English population. The prevalence of any DR in the CPRD cohort was 28.8%, in keeping with the UK prevalence of 30%. Baseline prevalence of STDR was 6.3%, providing reasonable validity that our study results are generalizable. The current study adjusted for important potential confounders, and the ascertainment of exposures (routine standardized recording) was strong, with low amounts of missing data.³⁰ However, certain limitations need to be

acknowledged. Not all patients with DR or STDR may be coded on their medical record, leading to some underascertainment of cases. While we accounted for major confounders in the analysis, there is still a possibility of residual confounding. While a large list of covariates were included within this study, they still comprise a closed set, and controlling for other covariates may provide further filtering of the exposure estimates. For some of the categories within covariates, there were low numbers of individuals who developed STDR, which resulted in wider confidence intervals, hence more uncertainty regarding the reliability of results for these covariates. STDR cases were comparatively few, which could have limited the statistical power for the sensitivity analysis. We did not consider the change in exposure attainment over time in the analysis, which may have potentially overestimated or underestimated the true effect estimates.

In conclusion, this study provides new information regarding the benefit of control of modifiable risk factors in reducing the incidence of STDR among those with mild NPDR at the population level. Our findings provide support for using appropriate indicators for the management of type 2 diabetes in primary care. Investing in such support for these management strategies could bring a range of benefits, including improved health outcomes—such as a reduction in the risk of STDR—for people with type 2 diabetes.

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CONFLICT OF INTEREST

The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

AUTHOR CONTRIBUTIONS

LHG, AJM, EPV, AM and SS contributed to the idea generation and protocol development. AJM and LHG prepared the data for analysis and LHG performed the statistical analyses. LHG, GM, AJM, EPV, AM and SS interpreted study results. AJM, LHG and GM had primary responsibility for writing the manuscript. MN, TS, EPV, AM and SS also contributed to manuscript writing. All authors critically reviewed the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14344>.

DATA AVAILABILITY STATEMENT

Permission for data usage was obtained from the CPRD Independent Scientific Advisory Committee (protocol number 17_217R). Linked pseudonymised data were provided by CPRD. Data were linked by National Health Service (NHS) Digital, the statutory trusted third party for linking data, using identifiable data held only by NHS Digital. Select general practices consent to this process at a practice level with individual patients having the right to opt-out.

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REFERENCES

- Liew G, Wong VW, Ho IV. Mini review: changes in the incidence of and progression to proliferative and sight-threatening diabetic retinopathy over the last 30 years. *Ophthalmic Epidemiol.* 2017;24(2):73-80.
- Sivaprasad S, Prevost AT, Vasconcelos JC, et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *Lancet.* 2017;389(10085):2193-2203.
- Chew EY, Ferris FL 3rd, Csaky KG, et al. The long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy: the early treatment diabetic retinopathy follow-up study. *Ophthalmology.* 2003;110(9):1683-1689.
- Elman MJ, Qin H, Aiello LP, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology.* 2012;119(11):2312-2318.
- Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology.* 2016;123(6):1351-1359.
- Matthews DR, Stratton IM, Aldington SJ, Holman RR, Kohner EM. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. *Arch Ophthalmol.* 2004;122(11):1631-1640.
- Stratton IM, Kohner EM, Aldington SJ, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. *Diabetologia.* 2001;44(2):156-163.
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352(9131):837-853.
- Keech AC, Mitchell P, Summanen PA, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet.* 2007;370(9600):1687-1697.
- Chew EY, Ambrosius WT, Davis MD, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med.* 2010;363(3):233-244.
- Shi R, Zhao L, Wang F, et al. Effects of lipid-lowering agents on diabetic retinopathy: a meta-analysis and systematic review. *Int J Ophthalmol.* 2018;11(2):287-295.
- Scanlon PH. Update on screening for sight-threatening diabetic retinopathy. *Ophthalmic Res.* 2019;62(4):218-224.
- Wong TY, Sabanayagam C. Strategies to tackle the global burden of diabetic retinopathy: from epidemiology to artificial intelligence. *Ophthalmologica.* 2020;243(1):9-20.

14. Scanlon PH, Aldington SJ, Leal J, et al. Development of a cost-effectiveness model for optimisation of the screening interval in diabetic retinopathy screening. *Health Technol Assess*. 2015;19(74):1-116.
15. Lund SH, Aspelund T, Kirby P, et al. Individualised risk assessment for diabetic retinopathy and optimisation of screening intervals: a scientific approach to reducing healthcare costs. *Br J Ophthalmol*. 2016;100(5):683-687.
16. Stratton IM, Aldington SJ, Taylor DJ, Adler AI, Scanlon PH. A simple risk stratification for time to development of sight-threatening diabetic retinopathy. *Diabetes Care*. 2013;36(3):580-585.
17. Chew EY, Davis MD, Danis RP, et al. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the action to control cardiovascular risk in diabetes (ACCORD) eye study. *Ophthalmology*. 2014;121(12):2443-2451.
18. Roland M. Linking physicians' pay to the quality of care—a major experiment in the United Kingdom. *N Engl J Med*. 2004;351(14):1448-1454.
19. Kontopantelis E, Springate DA, Reeves D, et al. Glucose, blood pressure and cholesterol levels and their relationships to clinical outcomes in type 2 diabetes: a retrospective cohort study. *Diabetologia*. 2015;58(3):505-518.
20. NHS Digital. National diabetes audit programme: aims and objectives of the NDA. <https://digital.nhs.uk/data-and-information/clinical-audits-and-registries/national-diabetes-audit#aims-and-objectives-of-the-nda>. Accessed March 2020.
21. Kontopantelis E, Reeves D, Valderas JM, Campbell S, Doran T. Recorded quality of primary care for patients with diabetes in England before and after the introduction of a financial incentive scheme: a longitudinal observational study. *BMJ Qual Saf*. 2013;22(1):53-64.
22. Iwagami M, Tomlinson LA, Mansfield KE, et al. Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared with national survey and registry data in the United Kingdom. *Nephrol Dial Transplant*. 2017;32(Suppl_2):ii142-ii150.
23. Scanlon PH. The English National Screening Programme for diabetic retinopathy 2003-2016. *Acta Diabetol*. 2017;54(6):515-525.
24. van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45(3):67.
25. Ho D, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. *J Stat Softw*. 2011;42(8):28.
26. Sabanayagam C, Banu R, Chee ML, et al. Incidence and progression of diabetic retinopathy: a systematic review. *Lancet Diabetes Endocrinol*. 2019;7(2):140-149.
27. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. X. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is 30 years or more. *Arch Ophthalmol*. 1989;107(2):244-249.
28. Beulens JW, Patel A, Vingerling JR, 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(10):2027-2036.
29. Duckworth W, Abaira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360(2):129-139.
30. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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