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Risk factors for diabetic macular oedema in type 2 diabetes: A case-control study in a United Kingdom primary care setting

E. Martín-Merino[a,*,1], J. Fortuny[b], E. Rivero-Ferrer[b], M. Lind[c,d], L.A. Garcia-Rodriguez[a]

[a] Centro Español de Investigación Farmacoepidemiológica, Madrid, Spain
[b] DS&E—Global Clinical Epidemiology, Novartis Farmaceutica S.A., Barcelona, Spain
[c] Institute of Medicine, University of Gothenburg, Gothenburg, Sweden
[d] Department of Medicine, NU-Hospital Organization, Uddevalla, Sweden

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ABSTRACT

Aim: To identify risk factors associated with the development of DMO among patients diagnosed with type 2 diabetes managed in a primary care setting in the UK.

Methods: A case-control study nested in a cohort of incident Type 2 diabetes identified in The Health Improvement Network database from 2000–2007. Cases were people with DMO (N = 211) and controls were a DMO-free sample (N = 2194). No age restrictions were applied. Adjusted odds ratios and 95%CIs were estimated (OR; 95%CI).

Results: DMO increased with high alcohol use (2.88; 1.49–5.55), cataracts (4.10; 2.73–6.15), HbA1c ≥7% (1.58; 1.08–2.32), systolic blood pressure ≥160 mm Hg (2.03; 1.17–3.53), total cholesterol ≥5 mmol/L (1.66; 1.15–2.39), LDL ≥3 mmol/L (1.73; 1.14–2.61), and microalbuminuria (1.78; 1.16–2.73). Diuretic drugs were associated with a reduced risk of DMO (0.68; 0.47–0.99), as did smoking (0.47; 0.28–0.77), overweight (0.53; 0.30–0.96) or obesity (0.52; 0.30–0.91) at diabetes diagnosis, and high triglyceride levels (0.51; 0.35–0.74). Patients treated with anti-diabetic drugs showed higher risk of DMO than non-treated patients, particularly those with sulphonylureas (3.40; 2.42–4.78), insulin (3.21; 1.92–5.36) or glitazones (1.88; 1.17–3.04).

Conclusion: In patients with type 2 diabetes managed in primary care, multiple factors associated with DMO were identified, such as cataracts, microalbuminuria and high levels of HbA1c, systolic BP, total cholesterol, and LDL. Diuretic drugs were associated with a reduced risk of DMO. Treated diabetes, particularly with sulphonylureas, insulin or glitazones showed highest risk of DMO. The inverse association between smoking, obesity, and triglycerides and DMO deserves further research.

* *Corresponding author at*: c/Almirante 28, 2°; 28005 Madrid, Spain. Fax: +34 915 312 871.
E-mail address: elisaceife@gmail.com (E. Martín-Merino).
[1] Present address: División de Farmacoepidemiología y Farmacovigilancia, Subdirección General de Medicamentos de Uso Humano, Agencia Española de Medicamentos y Productos Santiarios- AEMPS, Calle Campezo 1 Edificio 8 28022, Madrid, Spain.

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1. Introduction

Diabetic retinopathy (DR) is a leading cause of blindness in the working-age population in the United Kingdom (UK) [1]. Visual loss in the population with diabetes may be caused by diabetic macular oedema (DMO), macular ischaemia, or retinal or optic neovascularization [2]. Particularly, retinal thickening results from fluid leakage due to breakdown of the blood-retina barrier [3]. Although the risk for impaired vision increases at advanced stages of DR [4], DMO can appear at early stages of retinopathy and cause loss of vision [5].

It has been estimated that 1% of patients with type 2 diabetes will develop sight-threatening maculopathy after 9-years with diabetes [6], and 5% in a 6-year period from the first retina screening [7,8]. In a UK primary care setting, the estimated incidence rate of newly diagnosed DMO was 1.80 per 1000 p-y [9]. However, the diagnosis of DMO is challenging and the data about its incidence is inconsistent [10].

In contrast to other eye complications of diabetes, DMO is such a complicated condition in clinical practice that retinal damage persists after standard treatment with photocoagulation in a large proportion of patients [2,11]. However, there are few studies assessing DMO predictors. Epidemiological research aim at identifying and quantifying risk factors of DMO for potentially improving DMO prevention strategies. Hyperglycemia and longer diabetes duration as well as hypertension, dyslipidemia, micro- and macroalbuminuria have been associated with increased risk of DMO in persons with type 2 diabetes, whereas obesity has shown an inverse relationship [10,12,13].

The aim of this study was to identify risk factors associated with the development of DMO among patients with type 2 diabetes managed in a primary care setting in the UK.

2. Material and methods

2.1. Data source

The Health Improvement Network (THIN) is a longitudinal primary care medical records database containing anonymised data on over 3 million patients registered with participating UK primary care practices at the moment the studied was performed [14]. These patients are representative of the entire UK population with respect to age, sex, and geographic region [15]. The THIN database contains individual patient demographic and clinical information recorded by primary care practitioners (PCPs) as part of their routine care, including information such as PCP consultations, referrals, hospitalizations, laboratory test results, and prescriptions issued by PCPs. Letters from specialist visits and hospital admissions (i.e. discharge letters) are also available. Diagnoses and test procedures are recorded using Read codes [16,17]. Prescriptions written by PCPs are generated and recorded automatically in the database using a coded drug dictionary (MultiLex) [18].

2.2. Study cohort and case ascertainment

A case-control analysis nested in a cohort of patients newly diagnosed with type 2 diabetes was performed. Detailed information on the diabetic study cohort has been published elsewhere [19,20]. In summary, the study cohort comprised all patients newly diagnosed with type 2 diabetes (N = 63,226) between January 2000 and December 2007. Diabetes onset was defined as the date of the first recorded diabetes diagnosis or the first recorded anti-diabetic prescription.

The study cohort was followed from diabetes onset until the first record of diabetic maculopathy, including DMO, in the period 2000–2008 [20]. Among all identified maculopathies, potential DMO cases were ascertained through specific codes. Diagnoses of DMO were validated in a two-step procedure comprised of a manual review of computerized patient profiles including PCPs' free-text comments and responses to questionnaires sent to PCPs. DMO diagnosis was confirmed in 90% of all cases initially identified [19].

Controls were selected from the pool of patients with type 2 diabetes that were not affected by diabetic maculopathy or DMO. A group of 2194 controls was selected using density sampling by generating a random date within the study period for each potential control. If the random date for a patient was included in his/her eligible person-time (follow-up period), that person was marked as an eligible control. The index date to compare cases with controls was the first recorded date of DMO diagnosis for cases and the random date for controls.

2.3. Risk factors assessment

The following information on potential risk factors was derived from the THIN database:

1. Demographic and lifestyle factors: age, sex, body mass index (BMI, kg/m^2), smoking status and alcohol consumption (units per week; 1 unit of alcohol is equal to 10 mL (~8 g) ethanol), using the most recent status before the diabetes onset.
2. Healthcare service use: number of PCP visits and referrals and hospitalizations, from one year before to 15 days before the index date.
3. Relevant laboratory test results between the onset of diabetes and the index date: glycated haemoglobin (HbA1c, (%), the first value after diabetes diagnosis and the mean value of all available measurements), systolic and diastolic blood pressure (BP, mmHg, the last value before the index date and the mean value of all available measurements), microalbuminuria (defined as having a recorded value of urine albumin of 30–300 mg/L or 3–30 mg/mmol of creatinine), proteinuria (defined as having a recorded value of urine albumin of 300–30,000 mg/L or >30 mg/mmol of creatinine), and lipid levels (including total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL] and triglycerides, all in mmol/L, using the last values recorded before the index date).
4. Prior history of other diseases, including ocular and cardiovascular diseases, was collected at any time before index date.
5. Exposure to hypoglycaemic agents and drugs used for cardiovascular diseases was ascertained prior to the index date and classified into 3 mutually exclusive time windows: (1) current use, when the most recent prescription lasted until the index date or ended in the 30 days prior to

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the index date; (2) recent use, when use ended between 31 and 365 days prior to the index date; and (3) non-use, when there was no recorded use during the year before the index date. Combination therapies (i.e. metformin and sulphonylureas or oral hypoglycaemic drugs and insulin) were also evaluated for current users. Concomitant use of sulphonylureas, metformin and/or insulin was defined as the use of 2 drugs, with the most recent prescriptions lasting until the index date or ending in the 30 days prior to the index date.

For those variables with missing data an extra category was created including patients with unknown value.

2.4. Statistical analysis

A nested case-control analysis was performed to estimate the odds ratios (OR) and 95% confidence intervals (CI) for the demographic and lifestyle factors, the relevant medical conditions, and the drug exposures associated with DR. After univariate analyses, two models of multivariate unconditional logistic regression were created. The first model included sex, age at the index date, time since the onset of diabetes, and PCP visits. The fully adjusted model also included other risk factors that remained statistically significant in the univariate analyses (Tables' footnotes). The OR for anti-diabetic drugs were not adjusted by HbA1c, which was assumed as an intermediate factor. No participant was excluded from regression models due to missing data; instead a category for unknown values was created when needed. All statistical analyses were performed using Stata/IC version 11.1.

3. Results

A total of 211 DMO cases and a sample of 2194 controls were identified in the cohort of people with incident Type 2 diabetes who were used in the nested case-control analysis.

Baseline characteristics for cases and controls are shown in Table 1. Over one-half of DMO cases occurred in men (59%), mean age at DMO diagnosis was 64 years (SD 11.6), with around 60% (N = 126) receiving the DMO diagnosis during the first 3 years of diabetes (mean 2.86 years (SD 1.88)). Twenty-eight percent of cases (N = 59) had a record of DR within 1 month of DMO. Of these, 44.1% had background DR, 16.7% had proliferative DR, and 39.0% did not have a specified retinopathy grading. Among controls, there were 10 (0.5%) with a code of DR within 1 month of the index date (four background DR, one proliferative DR, and five with no specified retinopathy grading). Forty-one DMO cases had prior recorded maculopathy, while none of the controls had maculopathy. For controls, mean time from diabetes onset was 2.65 years (SD 1.94).

3.1. Life-style characteristics

Current smoking showed a negative association with risk of developing DMO (full adjusted OR: 0.47; 95% CI: 0.28–0.77) as did former smoking (Table 1). Overweight patients had an OR of 0.53 (95% CI: 0.30–0.96), and the OR was 0.52 (95% CI: 0.30–0.91) among obese patients. High alcohol consumption increased the risk of DMO (OR: 2.88; 95% CI: 1.49–5.55).

3.2. Healthcare service use

Referrals to specialist care (OR: 1.59; 95% CI: 0.95–2.66) and previous hospitalizations (OR: 2.07; 95%CI: 1.42–3.02) were associated with DMO while no association was found with the number of PCP visits.

3.3. History of ocular disease

History of cataracts was associated with a four-fold increased risk of DMO (OR: 4.10; 95% CI: 2.73–6.15) while no significant association was found with glaucoma (Table 1).

3.4. Urine characteristics

Microalbuminuria was associated with an OR of 1.78 (95% CI: 1.16–2.73), while proteinuria did not show a significant association (Table 1).

3.5. Diabetic control

The majority of DMO patients (79%) had poor HbA1c control (≥7%) at first diabetes diagnosis compared to 46% of the controls, conferring an aggregated OR of 2.53 (95% CI: 1.67–3.82) compared with patients with well-controlled diabetes (<7% HbA1c, data not shown). In addition, the mean HbA1c level between onset of diabetes and index date was associated with DMO (OR HbA1c ≥7%: 1.58; 95% CI: 1.08–2.32), translating into a gradient of risk that increased from a non-significant 15% in patients with 7–8% HbA1c to around a 2.7-fold risk in those with HbA1c ≥10%.

3.6. Blood pressure and cardiovascular disease

High systolic BP (≥160 mmHg) doubled the risk of DMO, both at first diabetes diagnosis (OR: 2.22; 95% CI: 1.39–3.54, data not shown) and as the mean of systolic BP values between diabetes onset and index date (OR: 2.03; 95% CI: 1.17–3.53) (Table 2). Diastolic BP was not associated with DMO. Neither diagnosed hypertension (OR: 1.14; 95% CI: 0.81–1.60, Table 2) nor other cardiovascular diseases (cerebrovascular disease, heart failure, or ischaemic heart disease) showed an association with DMO (data not shown).

3.7. Blood lipids

There was an increased risk of DMO with total cholesterol ≥5 mmol/L (OR: 1.66; 95% CI: 1.15–2.39) and LDL ≥3 mmol/L (OR: 1.73; 95% CI: 1.14–2.61). There was no statistically significant association between HDL and DMO. Borderline to high triglyceride levels showed a significant decrease in the risk of DMO (OR: 0.51; 95% CI: 0.35–0.74) (Table 2).

3.8. Medications

Patients with diabetes treated with diuretic drugs had a reduced risk of DMO (OR: 0.68; 95% CI: 0.47–0.99), while users of angiotensin converting enzyme inhibitors or alpha-1 antagonists showed borderline increased risk versus non-users (OR: 1.43; 95% CI: 0.99–2.05 and OR: 1.73; 95% CI: 1.05–2.86, respec-

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Table 1 – Frequency distribution of demographic factors, diabetes duration, and health services use among DMO cases and controls, and its association with DMO occurrence.

	Controls N = 2194		DMO cases N = 211		OR[a]	95% CI	OR[b]	95% CI
	n	%	n	%				
Men	1174	53.5	124	58.8	1.26	0.94–1.69	1.19	0.85–1.67
Age at diabetes diagnosis, year								
<40	122	5.6	4	1.9	0.26	0.09–0.76	0.29	0.10–0.88
40–49	299	13.6	38	18.0	1	–	1	–
50–59	550	25.1	46	21.8	0.67	0.42–1.05	0.78	0.48–1.29
60–69	665	30.3	73	34.6	0.85	0.56–1.29	1.00	0.63–1.61
70–85	558	25.4	50	23.7	0.70	0.45–1.10	0.58	0.33–1.00
Age at index date, year								
<40	84	3.8	3	1.4	0.29	0.09–0.98	0.37	0.10–1.33
40–49	236	10.8	31	14.7	1	–	1	–
50–69	1125	51.3	105	49.8	0.70	0.46–1.08	0.87	0.54–1.40
70–85	749	34.1	72	34.1	0.70	0.45–1.10	0.66	0.38–1.13
Interval from diabetes diagnosis to index date, year								
<1	535	24.4	37	17.5	1	–	1	-
1–3	817	37.2	89	42.2	1.62	1.09–2.42	1.01	0.64–1.61
3–4	540	24.6	50	23.7	1.36	0.88–2.13	0.72	0.43–1.21
5–9	302	13.8	35	16.6	1.67	1.03–2.72	0.70	0.39–1.23
Smoking status at diabetes diagnosis								
Non-smoker	968	44.1	98	46.4	1	–	1	–
Smoker	443	20.2	23	10.9	0.49	0.31–0.79	0.47	0.28–0.77
Former	541	24.7	31	14.7	0.53	0.35–0.81	0.52	0.33–0.82
Unknown	242	11.0	59	28.0	2.50	1.74–3.58	1.21	0.68–2.16
Alcohol consumption at diabetes diagnosis, units per week								
0–1	1051	47.9	70	33.2	1	–	1	–
2–21	622	28.4	47	22.3	1.10	0.74–1.62	1.29	0.85–1.96
≥22	103	4.7	17	8.1	2.37	1.31–4.28	2.88	1.49–5.55
Unknown	418	19.1	77	36.5	2.85	2.01–4.05	1.28	0.72–2.28
BMI at diabetes diagnosis, kg/m^2								
13–19	10	0.5	1	0.5	0.77	0.09–6.32	0.80	0.08–7.84
20–24	197	9.0	24	11.4	1	–	1	–
25–29	635	28.9	39	18.5	0.47	0.27–0.80	0.53	0.30–0.96
≥30	955	43.5	63	29.9	0.51	0.31–0.85	0.52	0.30–0.91
Unknown	397	18.1	84	39.8	1.75	1.07–2.86	1.22	0.65–2.32
Cataracts	199	9.1	58	27.5	4.36	3.02–6.29	4.10	2.73–6.15
Glaucoma	86	3.9	13	6.2	1.58	0.86–2.91	1.71	0.87–3.37
Urine protein maximum value								
Normal	799	36.4	63	29.9	1	–	1	–
Microalbuminuria	291	13.3	52	24.6	2.18	1.47–3.23	1.78	1.16–2.73
Proteinuria	158	7.2	20	9.5	1.54	0.90–2.63	1.35	0.76–2.39
No measure or wrong units	946	43.1	76	36.0	1.14	0.79–1.64	1.10	0.74–1.64
General practitioner visits								
0–5	122	5.6	7	3.3	0.53	0.24–1.16	0.75	0.31–1.78
6–12	697	31.8	56	26.5	0.72	0.52–0.99	0.86	0.60–1.23
≥13	1375	62.7	148	70.1	1	–	1	–
Referred vs. non-referred	1807	82.4	191	90.5	1.82	1.12–2.96	1.59	0.95–2.66
Hospitalized vs. non-hospitalized	287	13.1	55	26.1	2.29	1.63–3.22	2.07	1.42–3.02

BMI, body mass index; CI, confidence interval; DMO, diabetic macular oedema; OR, odds ratio.

[a] OR adjusted by sex, age at index date, primary care practitioner visits, and time to event.

[b] OR adjusted by sex; age at index date; smoking before diabetes; alcohol consumption before diabetes; body mass index before diabetes; diabetes duration; referrals and hospitalizations; systolic blood pressure; glycated haemoglobin; urine protein; cataracts; and hypoglycaemic drugs, including insulin and oral anti-diabetic drugs.

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Table 2 – Frequency distribution of glycated haemoglobin, blood pressure, lipid pattern, and cardiovascular drug use among DMO cases and controls and its association with DMO occurrence.

	Controls N = 2194		DMO cases N = 211		OR[a]	95% CI	OR[b]	95% CI
	n	%	n	%				
HbA1c, %, mean								
4–5.9	241	11.0	9	4.3	0.55	0.26–1.15	0.59	0.27–1.27
6–6.9	682	31.1	45	21.3	1	–	1	–
7–7.9	581	26.5	62	29.4	1.60	1.07–2.39	1.15	0.74–1.81
8–8.9	238	10.8	44	20.9	2.88	1.84–4.50	1.72	1.04–2.84
9–9.9	111	5.1	19	9.0	2.66	1.48–4.76	1.37	0.72–2.64
10–11	84	3.8	28	13.3	5.67	3.29–9.79	2.73	1.45–5.11
No measure/null values	257	11.7	4	1.9	0.29	0.10–0.85	0.26	0.08–0.81
Systolic BP, mean								
<130 mmHg	497	22.7	45	21.3	1	–	1	–
130–159 mmHg	1403	63.9	132	62.6	1.08	0.75–1.55	1.08	0.73–1.60
≥160 mmHg	187	8.5	31	14.7	2.11	1.27–3.52	2.03	1.17–3.53
No measure/null values	107	4.9	3	1.4	0.48	0.14–1.62	1.05	0.28–3.93
Diastolic BP, mean								
<85 mmHg	1535	70.0	136	64.5	1	–	1	–
≥85 mmHg	552	25.2	72	34.1	1.52	1.11–2.07	1.16	0.81–1.67
No measure/null values	107	4.9	3	1.4	0.47	0.14–1.56	0.47	0.02–9.04
Lipid pattern in mmol/L, last measure before index date:								
Total cholesterol								
Desirable <5	1360	62.0	133	63.0	1	–	1	–
≥5	505	23.0	67	31.8	1.64	1.18–2.27	1.66	1.15–2.39
No measure/null values	329	15.0	11	5.2	0.53	0.26–1.08	0.96	0.44–2.09
LDL								
Desirable <3.0	1020	46.5	101	47.9	1	–	1	–
High ≥3.0	321	14.6	52	24.6	1.89	1.31–2.73	1.73	1.14–2.61
No measure/null values	853	38.9	58	27.5	1.08	0.66–1.75	1.02	0.60–1.71
HDL								
Healthiest/Desirable (men ≥1.0 & women ≥1.3)	1031	47.0	121	57.4	1	–	1	–
Low (men <1.0 & women <1.3)	607	27.7	57	27.0	0.97	0.68–1.38	1.14	0.77–1.68
No measure/null values	556	25.3	33	15.6	0.97	0.53–1.77	1.27	0.67–2.39
Triglycerides								
Desirable <1.7	853	38.9	120	56.9	1	–	1	–
Borderline–high ≥1.7	802	36.6	63	29.9	0.54	0.39–0.76	0.51	0.35–0.74
No measure/null values	539	24.6	28	13.3	0.46	0.25–0.84	0.44	0.23–0.84
Diagnosed hyperlipidaemia before index date								
No	1530	69.7	164	77.7	1	–	1	–
Yes	664	30.3	47	22.3	0.62	0.44–0.87	0.71	0.49–1.03
Hypertension								
No	800	36.5	77	36.5	1	–	1	–
Yes	1394	63.5	134	63.5	0.96	0.70–1.30	1.14	0.81–1.60
Current cardiovascular drugs vs. non-use in previous 1 year[c]								
Statins	1350	61.5	139	65.9	0.98	0.70–1.36	0.94	0.66–1.35
ASA low-dose	819	37.3	92	43.6	1.10	0.81–1.50	1.28	0.92–1.78
Antihypertensive drugs:								
Alpha-1 antagonists	175	8.0	27	12.8	1.68	1.07–2.64	1.73	1.05–2.86
ACE inhibitors	874	39.8	107	50.7	1.61	1.16–2.22	1.43	0.99–2.05
Angiotensin II receptor antagonists	281	12.8	28	13.3	1.29	0.81–2.05	1.19	0.71–1.98
Calcium-channel blockers	505	23.0	50	23.7	0.99	0.70–1.42	0.92	0.62–1.36
Beta-blockers	519	23.7	39	18.5	0.68	0.46–0.99	0.77	0.51–1.16
Diuretics	724	33.0	60	28.4	0.69	0.49–0.98	0.68	0.47–0.99

HbA1c, glycated haemoglobin; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ASA, acetylsalicylic acid; ACE, angiotensin converting enzyme; CI, confidence interval; DMO, diabetic macular oedema; OR, odds ratio.

[a] OR adjusted by sex, age at index date, primary care practitioner visits, and time to event.

[b] OR adjusted by sex; age at index date; smoking; alcohol consumption; body mass index; diabetes duration; referrals and hospitalizations; systolic BP; HbA1c; urine protein; cataracts; and hypoglycaemic drugs, including insulin and oral anti-diabetic drugs. For lipids, OR was adjusted by pattern of lipids (HDL + LDL + triglycerides).

[c] Antihypertensive drugs were not adjusted by systolic BP.

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Table 3 – Frequency distribution of hypoglycaemic drugs at index date among DMO cases and controls and its association with DMO occurrence.

	Controls N = 2194		DMO cases N = 211		OR[a]	95% CI	OR[b]	95% CI
	n	%	n	%				
Diabetes therapy								
No treatment in previous 1 year	859	39.2	28	13.3	1	–	1	–
Any treatment in previous 1 year	1335	60.9	183	86.7	4.09	2.69–6.22	3.70	2.39–5.74
Diabetes therapy								
No treatment in previous 1 year	859	39.2	28	13.3	1	–	1	–
Insulin & Oral in previous 30 days	53	2.4	13	6.2	7.54	3.61–15.75	6.17	2.80–13.60
Insulin alone in previous 30 days	63	2.9	18	8.5	8.87	4.59–17.12	5.32	2.61–10.84
Oral alone in previous 30 days	1152	52.5	147	69.7	3.83	2.50–5.85	3.54	2.27–5.52
Remainder	67	3.1	5	2.4	2.32	0.86–6.25	2.53	0.90–7.13
Metformin								
Non-use in previous 1 year	1107	50.5	77	36.5	1	–	1	–
Current use in previous 0–30 days	987	45.0	122	57.8	1.50	1.07–2.09	1.47	1.03–2.11
Recent use in previous 31–365 days	100	4.6	12	5.7	1.22	0.61–2.42	1.07	0.51–2–25
Sulphonylureas								
Non-use in previous 1 year	1686	76.8	100	47.4	1	–	1	–
Current use in previous 0–30 days	451	20.6	99	46.9	3.49	2.54–4.80	3.40	2.42–4.78
Recent use in previous 31–365 days	57	2.6	12	5.7	2.24	1.10–4.54	2.63	1.21–5.71
Metformin & Sulphonylureas patterns								
Non-use of either in previous 1 year	930	42.4	45	21.3	1	–	1	–
Only metformin, current use in previous 0–30 days	731	33.3	57	27.0	1.64	1.07–2.50	1.56	0.99–2.47
Only sulphonylureas, current use in previous 0–30 days	195	8.9	34	16.1	3.64	2.22–5.95	3.26	1.93–5.49
Both, current use in previous 0–30 days	256	11.7	65	30.8	5.58	3.56–8.74	5.42	3.37–8.72
Remainder	82	3.7	10	4.7	2.33	1.09–4.94	2.60	1.15–5.90
Glitazones								
Non-use in previous 1 year	1996	91.0	174	82.5	1	–	1	–
Current use in previous 0–30 days	173	7.9	33	15.6	2.19	1.40–3.42	1.88	1.17–3.04
Recent use in previous 31–365 days	25	1.1	4	1.9	0.82	0.25–2.73	0.64	0.18–2.34
Insulin								
Non-use in previous 1 year	2073	94.5	176	83.4	1	–	1	–
Current use in previous 0–30 days	116	5.3	31	14.7	4.11	2.55–6.61	3.21	1.92–5.36
Recent use in previous 31–365 days	5	0.2	4	1.9	7.87	1.91–32.49	4.90	1.14–21.09

CI, confidence interval; DMO, diabetic macular oedema; OR, odds ratio.
[a] OR adjusted by sex, age at index date, primary care practitioner visits, and time to event.
[b] OR adjusted by sex; age at index date, smoking alcohol consumption, body mass index; diabetes duration; referrals and hospitalizations; systolic BP; urine protein; cataracts; and hypoglycaemic drugs, including insulin and oral antidiabetic drugs.

tively). Use of statins (OR: 0.94; 95% CI: 0.66–1.35) and low-dose acetylsalicylic acid (ASA) use (OR: 1.28; 95% CI: 0.92–1.78, Table 3) were not associated with DMO.

Approximately 76% of cases and 55% of controls were current users of oral anti-diabetic drugs (mainly metformin and sulphonylureas) at the index date (Table 3). Further, 15% and 5% of cases and controls, respectively, used insulin. Overall, patients treated with oral anti-diabetic drugs had a significantly increased occurrence of DMO versus non-treated patients. Those treated with glitazones had an OR of 1.88 (95% CI: 1.17–3.04), and those treated with sulphonylureas or insulin had a greater than three-fold increased risk.

4. Discussion

In this population of patients with type 2 diabetes managed in primary care, multiple factors associated with DMO were identified, such as cataracts, high HbA1c, high systolic BP, high total cholesterol, high LDL, and microalbuminuria. Diuretic drugs were associated with a reduced risk of DMO. Patients with diabetes treated with anti-diabetic drugs showed a higher risk of DMO than non-treated patients, particularly those with sulphonylureas or insulin.

Our results show that, apart from high alcohol consumption that increased DMO risk, certain modifiable factors that are markers of cardiovascular risk, such as smoking, overweight, hyperlipidaemia, and triglyceride levels, carry a reduced DMO risk. We do not currently have a clear explanation for these findings. It might be that patients with those factors were missing diabetic eye screening appointments more often than healthier patients and so were less frequently diagnosed with DMO (potential detection bias). Guilt about poor control causing retinopathy or fear is one of the reasons that deterred patients from attending eye screening in previous studies [21] which might happen more often among patients with more cardiovascular risk factors. Also, it might

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happen that certain selection bias, by which survival or treatment only in specialist setting may lead to more severe cases being unidentified, may play a role in these findings. Furthermore, the BMI results may be due to better glycaemic control among overweight patients, which first option is commonly metformin that appears to decrease the risk of diabetes-related endpoints in these patients compared to insulin and sulphonylureas [22]. In contrast, sulphonylureas are usually considered for normal weight patients [23], and we found that users of sulphonylureas were associated with an increased risk of DMO.

The reduction of DMO risk among smokers is consistent with the decrease in retinopathy progression found in the UK Prospective Diabetes Study [24], whereas no association was found in multivariate analysis in other studies [13,25].

Some well-known risk factors for DMO and DR progression were confirmed in the present study, including HbA1c [20,22–24], high systolic BP [20] and hypoglycaemic treatment [29,30]. In contrast with previous studies, we did not find an association between diastolic BP and DMO [31]. The increased risk of DMO among patients referred to a specialist or hospitalized before diabetes onset could indicate poor health status and more concerned about health caring, and/or a higher probability to be diagnosed, or a combination of both.

Microalbuminuria was found to increase the risk of DMO, consistent with other studies of retinopathy progression [32]. However, there was no association with proteinuria, which is similar to another study reporting no relation between proteinuria and DMO during the first 10 years of diabetes [33], although a marginal association was shown after 25 years [20]. Anatomical retinal changes are observed earlier than renal functional abnormalities and may be markers of preclinical nephropathy [34]. As mentioned before, selection bias of healthier cases related to survival may be a potential explanation.

Lipids may play a role in the development of DMO [28] and potentially in its clinically significant form [35–37], although this association is not clear [38,39]. While lipid-lowering drugs have been shown to positively affect DMO treatment [40], our results show that use of statins was not related to DMO, and use of non-statin lipid-lowering drugs was limited. Further research is needed to confirm the link between DMO and both lipids and lipid-lowering drugs.

We detected an increase in DMO risk among patients with cataracts. Cataracts in patients with type 2 diabetes may merely be a marker of diabetic control rather than sharing a common pathologic mechanism, since cataract development may be accelerated in severe uncontrolled diabetes due to changes in fluid electrolyte balance [41].

A number of DMO cases were detected during the first years after initial recorded diabetes diagnosis, indicating a lack of certainty in determining the onset date of diabetes, as reported in our previous publication [20]; accordingly, no association between diabetes duration (within the duration of the study) and DMO risk was observed in the current analysis. The mean duration of diabetes in patients with DMO participating in previous studies was between 10 to 18 years [31,35,36] much longer than the one observed in this study. Although diabetes duration has been observed as a significant factor in the progression of DMO [38], others have shown that difficulty in dating the onset of diabetes and decreased survival may explain the lack of an association between diabetes duration and DMO incidence [33,42].

In the present population, a high number of patients with type 2 diabetes were under antihypertensive therapy, and a reduced risk of DMO was observed among diuretics users; this may indicate abnormal fluid flow in the blood-retinal barrier in DMO. Low-dose ASA therapy did not show any effect on DMO occurrence, in line with the Early Treatment Diabetic Retinopathy Study that found no effect of ASA on retinopathy progression [43].

The increased risk of DMO among glitazone users is consistent with previous case reports [44–46]. Fluid retention driven by glitazones may be responsible for this effect, although its mechanism is not fully understood [44]. It is possible that these drugs could increase vascular endothelial growth factor levels [47], which are high in DMO. Patients treated with sulphonylureas or insulin were also shown to have a high risk of DMO. This is in contrast with previous studies that concluded that intensive blood glucose control with either sulphonylureas or insulin substantially decreased the risk of microvascular complications in patients with type 2 diabetes [48,49]. However, mitogenic, atherogenic, and thrombogenic effects of insulin, particularly insulin lispro or glargine, on vascular permeability have been proposed [50–52]. On the other hand, the link between anti-diabetic drugs and the increased risk may be because anti-diabetic drug use merely indicates the severity of diabetes and, thereby, greater historical hyperglycaemic exposure.

4.1. *Limitations*

Several limitations of the present study include the validity of the exact timing of type 2 diabetes onset, which is frequently diagnosed later than the actual occurrence. The lack of precision in this date complicates assessment of the actual implication of early glycaemia control [53], hypoglycaemic drugs [54], and metabolic memory [23] in the development of DMO in these patients with delayed diabetes diagnosis. That the severity of diabetes is an indication for hypoglycaemic treatment also confounds the potential implications of these drugs. Furthermore, the eye affected or retinopathy grading was often missing; this may have affected the evaluation of the association between retinopathy level and DMO. Finally, for certain variables, there were missing data and/or information not systematically recorded in a small number of patients and this should be taken into account when interpreting the results.

5. Conclusion

In patients with type 2 diabetes managed in primary care, multiple factors were associated with development of DMO. To minimize the occurrence of DMO, good control of alcohol consumption, HbA1c, systolic BP, total cholesterol, and LDL is needed. Cataracts and microalbuminuria are important markers of the presence of DMO. Diuretic drugs were associated with reduced risk of DMO. Patients with type 2 diabetes on glitazones, sulphonylureas, or insulin, were at high risk of DMO.

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Concerns about the effect of insulin analogues on retinopathy progression as well as the inverse association between smoking, obesity, and triglycerides deserve further research.

Conflict of interest statement

Elisa Martín-Merino was an employee of Centro Español de Investigación Farmacoepidemiológica (CEIFE) at the time of the study, which has received research funding from Novartis Farmacéutica S.A.; Luis Alberto García-Rodríguez is employed by CEIFE. Joan Fortuny and Elena Rivero Ferrer were employees of Novartis Farmacéutica S.A., Barcelona, Spain, at the time of the study; currently, they are employees of RTI Health Solutions; JF and ERF have no other financial or non-financial competing interests to declare that present a potential conflict of interest. Marcus Lind has received research grants from Astra Zeneca, DexCom, Novonordisk, been consultant or received honoraria from Abbot Scandinavia, Astra Zeneca, Eli Lilly, Medtronic and Novonordisk and participated in advisory boards for Novonordisk.

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Ethics committee approval

The study research protocol was approved by the UK Research Ethics Committee (09/H0305/64).

Authors' contributions

J.F., E.R., and L.A.G.-R. conceived the study. E.M.-M., J.F., E.R., and L.A.G.-R. designed the study. E.M.-M. performed the statistical analysis. E.M.-M., J.F., E.R., L.A.G.-R. and M.L. were involved in analyzing and interpreting data and writing of the manuscript. All authors had full access to all of the data in the study. L.A.G.-R. is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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