

Relative Importance and Contribution of Risk Factors for Diabetic Retinopathy and Macular Edema

Xie J¹, Fenwick EK¹, Taouk Y¹, Nicolaou TE¹, Wang JJ^{1,2}, Wong TY^{1,3,4} and Lamoureux EL^{1,3,4*}

¹Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, University of Melbourne, Australia

²Centre for Vision Research, Department of Ophthalmology, Westmead Hospital, Australia

³Singapore Eye Research Institute, National University of Singapore, Singapore

⁴Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore

Abstract

Purpose: This study determined the relative importance of risk factors for Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME) and assessed their independent and joint contributions.

Methods: A prospective study of patients with type 2 diabetes was conducted in a tertiary eye hospital in Melbourne, Australia. Patients underwent a comprehensive eye examination and completed standardized administered questionnaires. Blood samples were assessed for glycosylated haemoglobin (HbA1c); fasting blood glucose; and serum lipids. Dilated fundus photographs were obtained and graded for DR and DME. The relative importance of the risk factors was determined by the independent and common variance explained in DR and DME using Commonality analysis.

Results: A total of 497 patients with type 2 diabetes were included in this analysis. The key risk factors accounted for 44.6% and 19.5% of total variances in DR and DME, respectively. The most important risk factor for any DR was duration of diabetes (16.5% of total explained variance), followed by insulin use (13.1%), HbA1c (8.5%), age (3.7%) and gender (2.8%). The most important risk factor for any DME was HbA1c (9.45%); followed by age (5.75%); duration of diabetes (3.92%) and systolic blood pressure (SBP) (0.36%). Sixty-one percent of the total explained variance in DR was due to common variance among these risk factors, compared to only 31% of the in DME.

Conclusion: The total, independent and joint contributions of the key risk factors for DR and DME differ in patients with type 2 diabetes, which suggest that may require specific prevention and intervention strategies for these two diabetic complications.

Keywords: Diabetic retinopathy; Diabetic macular edema; Haemoglobin A1c; Duration of diabetes; Commonality analysis

Introduction

Diabetic retinopathy (DR) and diabetic macular edema (DME) are common complications of diabetes and the leading causes of blindness in the working-age population worldwide [1-3]. DME can occur at any stage of DR and affects central visual acuity [4]. It is well recognized that the duration of diabetes, glycosylated haemoglobin (HbA1c), hypertension, dyslipidemia, and the onset of diabetes are the key risk factors for the prevalence, incidence and progression of DR and DME. Most previous studies assessing the association between these major risk factors and DR/DME use traditional regression methods (e.g., logistic regression models), which do not fully explain the amount of variation in DR/DME, partly due to the non-inclusion of shared or common variations among the risk factors [5-10]. Other methods, such as hierarchical regression analysis, have been used to determine the amount of variance in the dependent variable that is explained by the independent variable(s). However, the results obtained from hierarchical regression analysis can be influenced by the order of variables entered into the equation.

Furthermore, current estimates of the key risk factors for DR and DME are mostly reported as odds ratios (ORs) or hazard ratios (HRs) and their relative importance are easily misinterpreted by the absolute values of ORs [11,12]. In fact, of relevance to clinicians are which variables are more important to focus on and the relative magnitude of their unique and joint contributions to the risk of DR. To date, however, the relative importance and contribution of these risk factors for DR remains unclear [1,5,13-15]. Understanding the

relative importance allows prioritization of strategies for DR and DME screening and management.

Commonality analysis (CA) is designed to identify the proportions of variance in the dependent variables to which each of the independent variables uniquely, and also the proportions of variance attributed by various combinations of independent variables [16-19]. CA has been successfully used in the social and behavioural sciences [16-18,20-22], but not in medical diseases. In this study, we assessed the independent and joint contributions of the key risk factors of DR and DME, and determined the relative importance of these risk factors using CA.

Method

Study Population

The Diabetes Management Project (DMP) is a longitudinal study of adults with diabetes residing in Victoria, Australia. The methodology

***Corresponding author:** Ecosse Lamoureux, Centre for Eye Research Australia, 32 Gisborne Street, East Melbourne 3002, Victoria, Australia, Tel: +61 3 9929 8371; Fax: +61 3 9662-3859; E-mail: ecosse@unimelb.edu.au

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has been described previously [23]. In brief, English-speaking adults aged 18 years or older with type 1 or type 2 diabetes, free of significant hearing and cognitive impairment, and living independently in the community were invited. Patients were primarily recruited from the Royal Victorian Eye and Ear Hospital (RVEEH). This paper reports on the cross-sectional data for patients with type 2 diabetes. All study procedures adhered to the tenets of the Declaration of Helsinki and all privacy requirements were met. Ethical approval for the DMP was provided by the RVEEH Human Research and Ethics Committee (08/815H). Each individual signed a consent form that outlined the aims and methodology of the DMP.

DMP testing protocol

All examinations were conducted at the Centre for Eye Research Australia (CERA) Melbourne Australia, located at the RVEEH.

Fundus photography

Two-field 45° digital non-stereo colour fundus photographs of both eyes were taken from each individual using a non-mydratic retinal camera (Canon CR6 – 45NM), Canon Inc, Japan, with all images being stored electronically using Digital Healthcare software. DR and DME were assessed using dilated fundus photography. Missing data (fundus images) were encountered in 13 cases (2.5%). DR severity was classified according to the International Clinical Diabetic Retinopathy Severity Scale into: 1) non-proliferative DR (NPDR) and 2) proliferative DR (PDR). NPDR was further grouped into three progressive stages - mild, moderate and severe - with each stage having defined retinal pathologic signs.

DME severity was classified using the American Academy of Ophthalmology classification as no DME; mild DME; moderate DME; and severe DME (clinical significant macular edema). The presence and severity of DME was also confirmed with OCT images (Stratus) and an ophthalmologist (Co-author TYW).

OCT

Fast macular scans (right and left eye) with retinal map analysis (fast macular thickness map, retinal thickness/volume tabular), as well as retinal nerve fibre layer scans (retinal nerve fibre layer 3.4 mm/average retinal nerve fibre layer thickness), were obtained using the OCT Stratus Model 3000 machine (Carl Zeiss Meditec Inc., Dublin, CA, USA).

Questionnaires

Information associated with lifestyle and psychosocial risk factors were collected using validated questionnaires. We report on data collected only from the general questionnaire on self-reported medical and ocular history; diabetes status and duration; demographics and medication use.

Blood Pressure (BP) measurements

Each participant underwent a blood pressure (BP) assessment using an automated BP machine, model 5200-103Z (Welch Allyn, NZ). The average of two separate measurements was recorded for both systolic (SBP) and diastolic (DBP) measurements.

Blood collection

Fasting blood (≥ 8 hours) was obtained to assess HbA1c levels, fasting glucose and lipids (total cholesterol [TC], triglyceride [TG],

and high-density lipoprotein cholesterol [HDL-C]). Low-density lipoprotein cholesterol [LDL-C] was measured using the Friedewald formula. All biochemical parameters were analysed at Melbourne Pathology, Melbourne, Australia. Fasting plasma glucose and serum lipids were assessed using the Hitachi MODULAR P analyser from Roche Diagnostics (Mannheim, Germany).

Statistical analyses

Continuous variables are presented as median (interquartile range [IQR]) for data with skewed distribution and mean (standard deviation [SD]) for normally distributed data, whereas categorical variables are presented as absolute (n) and relative frequencies (%) and 95% confidence interval (95% CI). Differences in continuous variables between participants with and without DR were evaluated by the Mann-Whitney-Wilcoxon test for skewed data, and the t-test for normally distributed data. The proportions between participants with and without DR were compared using the Chi-square test.

The relationships between DR, DME and HbA1c and other risk factors were examined separately using a stepwise logistic regression model and all significant factors therefore were included in the CA. CA was used to decompose the total variation of the model into unique and common variance. Unique variance reflects how much variance a risk factor independently contributes to DR or DME that is not shared with other risk factors. In contrast, common variance can provide detailed information that identifies and quantifies the variances explained by a group of risk factors. The relative importance of the risk factors was determined by considering the percentages of the sum of unique and common variance explained. CA was performed in R. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Sociodemographic and clinical characteristics of patients with and without DR

Patients with any DR (n=297) were younger, had higher use of insulin, and longer duration of diabetes compared to those without (n=200; Table 1, $p < 0.001$ for all). One hundred and thirty four (27.0%) had proliferative diabetic retinopathy (PDR). Patients with any DR also had higher fasting plasma glucose, HbA1c, and lower HDL cholesterol than those without ($p < 0.05$ for all). However, there was no difference between the two groups in educational attainment, income, DBP, body mass index (BMI), LDL-C, and triglycerides.

Patients with any DME (n=158) were younger, more likely to use insulin and have more comorbidities, longer duration of diabetes, higher fasting plasma glucose, HbA1c and LDL cholesterol level compared to those without any DME (Table S1, $p < 0.001$ for all).

Risk factors for DR and DME

Stepwise logistic regression analysis was used to determine the independent risk factors for DR and DME, separately (Table 2). In the stepwise logistic model, younger age (odds ratio [OR]=0.95, 95% CI: 0.92-0.97, $p = 0.021$), gender (OR=0.53, 95% CI: 0.33-0.87; $p = 0.011$), higher HbA1c level (OR = 1.34, 95% CI: 1.13-1.60, $p = 0.001$), longer duration of diabetes (OR = 1.10, 95% CI: 1.07-1.14, $p < 0.001$), and insulin use (OR=2.64, 95% CI: 1.50-4.64, $p = 0.001$) were independently associated with having any DR (Table 2). These five risk factors were therefore included in the CA for DR.

Only four factors were significantly associated with DME: younger

Characteristic	Diabetic Retinopathy (n=497)				p
	Absent (n=200)		Present (n=297)		
Categorical variable	N ^a	%	N ^a	%	
Gender (male)	110	55.0	212	71.4	<0.001
Income					
<\$30,000	134	74.9	190	69.3	0.20
≥\$30,000	45	25.1	84	30.7	
Education					
Primary school or below	32	16.4	42	14.6	0.62
Secondary school	105	53.9	168	58.3	
14 years or above	58	29.7	78	27.1	
Current/past smoker	113	57.4	156	53.1	0.35
Insulin use	29	14.7	148	50.0	<0.001
Comorbidities* (yes)	178	89.0	248	83.5	0.09
Diabetic complication (yes) ^Δ	44	22.0	116	39.1	<0.001
Continuous variable	Mean/ median	SD/IQR	Mean/ median	SD/IQR	p
Age (years) [§]	69.0	14.5	64.0	14.0	<0.001
Systolic blood pressure, mmHg	138.5	19.0	141.8	19.2	0.057
Diastolic blood pressure, mmHg	77.0	8.2	75.9	9.1	0.17
Duration of diabetes (years) [§]	8.0	9.0	16.3	13.0	<0.001
BMI (kg/m ²)	30.6	6.7	31.4	6.2	0.25
Fasting plasma glucose, mg/dL [§]	7.0	2.4	8.4	7.8	<0.001
HbA1c (%) [§]	7.0	1.4	7.8	1.9	<0.001
Total cholesterol, mmol/L [§]	4.6	1.5	4.3	1.5	0.18
HDL cholesterol, mmol/L	1.44	0.48	1.29	0.38	<0.001
Triglycerides, mmol/L [§]	1.5	0.9	1.6	1.2	0.49
LDL cholesterol, mmol/L [§]	2.2	1.2	2.2	1.2	0.86

Data shown as medians (IQR) [§] for skewed data and mean (SD) for normally distributed data

*Includes hypertension, angina, irregular heartbeat, stroke, high cholesterol, asthma, anaemia, migraine, arthritis, and osteoporosis

Δ: nephropathy, peripheral vascular disease, neuropathy

[§]Varies because of missing data. Bolded values indicate significant results

BMI: Body Mass Index; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; SD: Standard Deviation; IQR: Interquartile Range. HbA1c: Haemoglobin A1c

Table 1: Patients' characteristics (n=497) of those with and without diabetic retinopathy.

Risk factor	DR ^a		DME ^a	
	OR (95% CI)	p	OR (95% CI)	p
Gender (female)	0.53 (0.33-0.87)	0.011		
Insulin use	2.64 (1.50-4.64)	0.001		
At least one comorbidity				
Diabetic complication				
Age (years)	0.95 (0.92-0.97)	<0.001	0.95 (0.93, 0.97)	<0.001
SBP, mmHg			1.01 (1.00, 1.02)	0.092
Duration of diabetes (years)	1.10 (1.07-1.14)	<0.001	1.04 (1.02, 1.07)	<0.001
HbA1c (%)	1.34 (1.13-1.60)	0.001	1.41 (1.20, 1.67)	<0.001

DR: Diabetic Retinopathy; DME: Diabetic Macular Edema; HbA1c: Haemoglobin A1c; SBP: Systolic Blood Pressure

^aThe independent variables include age, sex, body mass index (BMI), diabetes duration, smoking history, HbA1c, systolic blood pressure, total cholesterol, HDL-cholesterol, insulin use, other diabetic complication, fasting plasma glucose, and comorbidities

Table 2: Associations between risk factors for DR and DME in patients with type 2 diabetes from multiple logistic regression models.

age (OR=0.95, 95% CI: 0.92-0.97, p=0.021), higher HbA1c level (OR = 1.34, 95% CI: 1.13-1.60, p=0.001), longer duration of diabetes (OR = 1.10, 95% CI: 1.07-1.14, p<0.001), and insulin use (OR=2.64, 95% CI: 1.50-4.64, p=0.001) were independently associated with having any DME (Table 2). These four factors were therefore included in the CA for DME.

Relative importance of key identified risk factors

The commonality coefficients, which represent the proportion of variance in DR and DME explained by each risk factor uniquely and in combination, are shown in Tables 3 and 4, respectively. Overall, the commonality models indicate that these variables in total accounted for minimal to moderate proportions of variance in DME (19.48%) and

DR (44.6%), respectively. However, these values were still higher when compared to results obtained from multivariable logistic regression models (DME: R²=12.77%; and DR: R²=26.14%; Table 5).

There were also some important differences in the CA results between DR and DME. Of the five risk factors, duration of diabetes (8.7% of common variance and 7.9% of unique variance) was the largest contributor to the explained variance for DR. The unique and common contributions of HbA1c to DR were 2.1% and 6.4%, respectively (Figure 1). However, HbA1c was the largest contributor (9.45% in total: 5.41% of common variance and 4.04% of unique variance) to the explained variance of DME, followed by age, duration of DM and SBP (Figure 1).

Negative commonality coefficients indicate that two or more risk

Risk factor	commonality coefficient	% Total
Unique to age	3.20	10.62
Unique to gender	1.51	5.01
Unique to HbA1c	2.12	7.03
Unique to insulin use	2.79	9.25
Unique to duration of diabetes	7.85	26.05
Common to age, and gender	0.50	1.67
Common to age, and HbA1c	2.29	7.61
Common to gender, and HbA1c	-0.15	-0.51
Common to age, and insulin use	0.73	2.41
Common to gender, and insulin use	-0.26	-0.87
Common to HbA1c, and insulin use	0.38	1.27
Common to age, and duration of diabetes	-1.85	-6.15
Common to gender and duration of diabetes	0.85	2.83
Common to HbA1c, and duration of diabetes	1.46	4.86
Common to insulin use and duration of diabetes	7.10	23.54
Common to age, gender, and HbA1c	-0.03	-0.09
Common to age, gender, and insulin use	-0.01	-0.03
Common to age, HbA1c, and insulin use	0.52	1.74
Common to gender, HbA1c, and insulin use	0.04	0.14
Common to age, gender, and duration of diabetes	-0.21	-0.70
Common to age, HbA1c, and duration of diabetes	-0.64	-2.14
Common to gender, HbA1c, and duration of diabetes	0.11	0.37
Common to age, insulin use, and duration of diabetes	-0.8	-2.65
Common to gender, insulin use, and duration of diabetes	0.25	0.82
Common to HbA1c, insulin, and duration of diabetes	2.29	7.59
Common to age, gender, HbA1c, and insulin use	0.00	0.01
Common to age, gender, HbA1c, and duration of diabetes	0.07	0.23
Common to age, gender, insulin use, and duration of diabetes	0.01	0.04
Common to age, HbA1c, insulin use, and duration of diabetes	-0.12	-0.41
Common to gender, HbA1c, insulin use, and duration of diabetes	0.10	0.33
Common to age, gender, HbA1c, insulin use, and duration of diabetes	0.04	0.14
Total (%)	30.14	100

Note: Commonality coefficient identifying suppression underlined. HbA1c: Hemoglobin (hemoglobinA1c). $\sum \text{Commonality coefficient} = \text{multiple } R^2$ (% Total= (Commonality coefficient)/(multiple R^2))

Table 3: Commonality matrix of risk factors for diabetic retinopathy (DR) in patients with type 2 diabetes.

Risk factor	commonality coefficient	% Total
Unique to age	0.0386	23.92
Unique to SBP	0.0046	2.84
Unique to HbA1c	0.0404	25.07
Unique to duration of diabetes	0.0358	22.23
Common to age and SBP	-0.0018	-1.14
Common to age and HbA1c	0.0398	24.68
Common to SBP and HbA1c	0.0016	1.00
Common to age and duration of diabetes	-0.01	-6.18
Common to SBP and duration of diabetes	0.00	0.00
Common to HbA1c and duration of diabetes	0.0216	13.43
Common to age, SBP and HbA1c	-0.0011	-0.7
Common to age, SBP, and duration of diabetes	-0.0004	-0.28
Common to age, HbA1c, and duration of diabetes	-0.0087	-5.38
Common to SBP, HbA1c, and duration of diabetes	-0.0003	-0.21
Common to age, SBP, HbA1c, and duration of diabetes	0.0012	0.73
Total (%)	0.1612	100

Note: Commonality coefficient identifying suppression underlined.
DME: Diabetic Macular Edema; HbA1c: Haemoglobin A1c; SBP: Systolic Blood Pressure
 $\sum \text{Commonality coefficient} = \text{multiple } R^2$
% Total= (Commonality coefficient)/(multiple R^2)
Unique variance=x's unique variance; Common=common variance; Total=Unique+Common;

Table 4: Commonality matrix of risk factors for diabetic macular edema (DME) in patients with type 2 diabetes.

factors affected in opposition directions (Tables 3,4). For example, the most negative regression effect was confounded by the combinations of duration of diabetes and age (-1.85%, Table 3), indicating that age was a protective factor and duration of diabetes was a risk factor for DR.

Overall, more than half (27.1/44.6=60.8%) of the total explained variation of DR was shared among the five risk factors (Table 5). The largest common variance on DR is due to insulin use (10.3%), representing the jointly effect with other factors. However, only 38.71% of the total explained variation of DME was shared variation among the four risk factors (Table 5).

Subgroup analysis showed the commonality models accounted for large amount of variation in VTDR (61.8%) and PDR (63.50%) (Table

S5). The variance of HbA1c was higher in patients with VTDR (unique variance: 3.5%; common variance: 11.2%) and PDR (unique variance: 3.4%; common variance: 8.5%), compared to that in patients with no DR.

Discussion

This study investigated the relative importance of major risk factors for DR and DME in a clinical cohort of adults with type 2 diabetes. The total variation; and independent and joint contributions of the key risk factors of DR and DME are markedly different. Our findings confirm that the etiology and pathogenesis of these two conditions are different and require prevention and intervention strategies. For example, based on our data, strategies for screening DR should prioritize knowing the

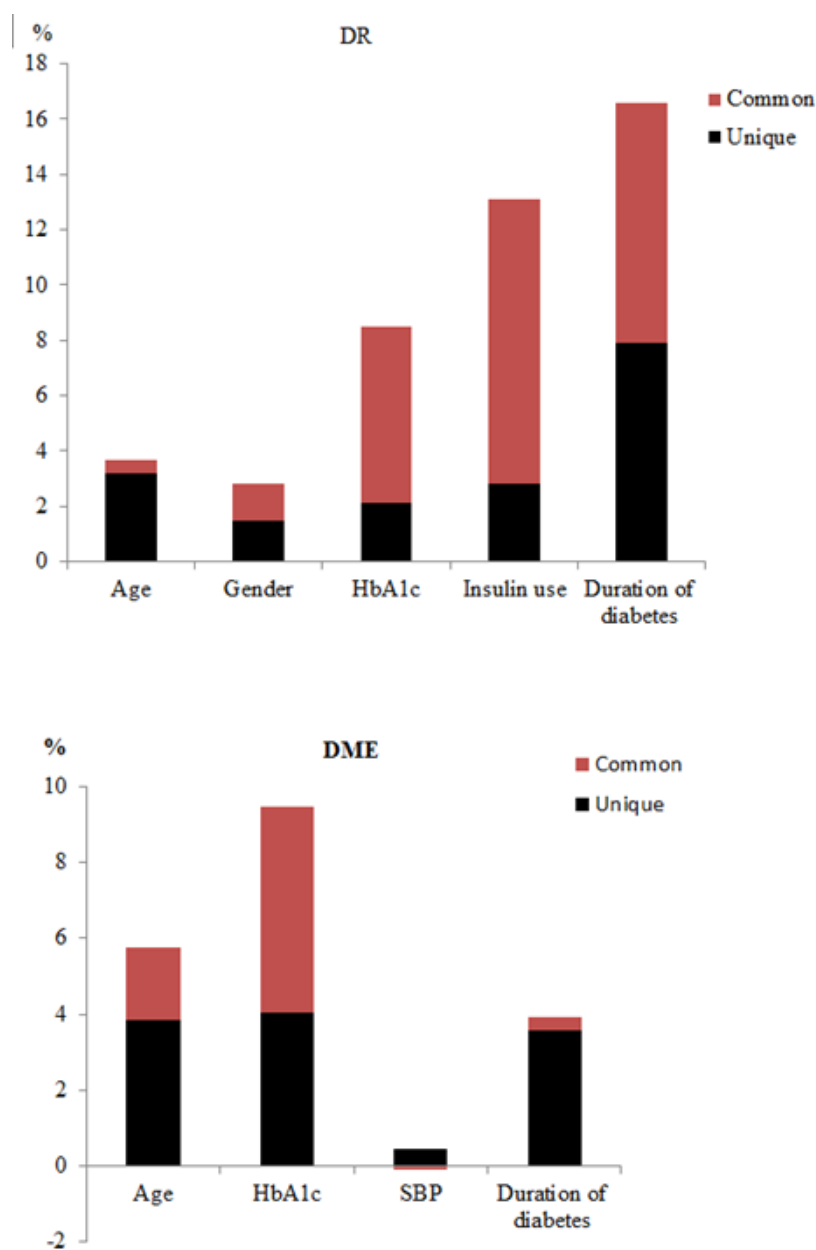


Figure 1: The unique and common variance (given as the percentage of the total explained variance) of the risk factors for Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME) in patients with type 2 diabetes.

Outcome: DR						
Risk factor (x)	Logistic regression			Commonality analysis		
	OR	p	Adjusted R ² (%)	Unique (%)	Common (%)	Total (%)
Age	0.95	<0.001		3.2	0.5	3.7
Gender	0.53	0.005		1.5	1.3	2.8
HbA1c	1.34	0.001		2.1	6.4	8.5
Insulin use	2.64	<0.001		2.8	10.3	13.1
Duration of diabetes	1.10	<0.001		7.9	8.7	16.5
Total			26.14	17.5	27.1	44.6
Outcome: DME						
Risk factor (x)	Logistic regression			Commonality analysis		
	OR	p	Adjusted R ² (%)	Unique (%)	Common (%)	Total (%)
Age	0.95	<0.001		3.86	1.89	5.75
HbA1c	0.66	<0.083		4.04	5.41	9.45
SBP	1.41	<0.001		0.46	-0.1	0.36
Duration of diabetes	1.05	<0.001		3.58	0.34	3.92
Total	0.95	<0.001		11.94	7.54	19.48

Table 5: The results of the multiple logistic regression analysis and the commonality analysis for diabetic retinopathy (DR) and diabetic macular edema (DME).

duration of diabetes and the level of HbA1c. For DME, strategies for screening should prioritize the level of HbA1c, the duration of diabetes and SBP.

While the results of this study are consistent with previous findings exploring individually the major risk factors for DR using logistic regression models [3,15,24], the CA model provides additional information about the components of their regression effects. Because the pathogenesis of DR and DME is multi-factorial, identification of the relative importance of the major risk factors using traditional regression methods is difficult due to the collinearity present among explanatory variables, which may bias the importance of each individual risk factor. Furthermore, results tend to rely heavily on regression coefficients, which are not comparable directly due to different measurement scales.

The relative importance of the risk factors for DR and DME was evaluated by examining the proportion of unique and common variance using CA. Our study showed that the most important risk factors of DR are duration of diabetes, followed by insulin use, HbA1c, age, and gender. While it has been assumed that chronic hyperglycemia is critical to the development of DR, our study showed that HbA1c alone only contributed 2.1% of the total variance explained for DR. One previous study also reported that HbA1c and duration of diabetes explained only about 11% of the variation in risk of DR for the entire study population using traditional regression models, but this study did not include the common variance between these risk factors [10]. Blood pressure and HDL cholesterol were significantly associated with DR in the univariate analysis, but these associations disappeared in the adjusted model. Commonality analysis including SBP and HDL showed that those two factors explained a very small amount of variation in DR (online supplementary Table S2).

Our results from CA firstly showed that more than half of the total explained variation of DR was related to the joint variation between the five risk factors, which highlighted that multifactorial risk management approach to prevent DR is needed. On the other hand, we found that all those four risk factors in total explained a relative small proportion of total variance in DME by both logistic regression (12.77%) and CA (19.48%). SBP was significant associated with DME and contributed 0.4% of total explained variance. Importantly, our study showed that HbA1c is the primary risk factor for DME, which has strong clinical and public-health importance. On the other hand, the four independent risk

factors for DME explains around 20% of the variance, which suggesting that further research beyond the inclusion of traditional risk factors, is needed to understand the etiology and pathogenesis of DME.

The strengths of our study include the use of a novel statistical technique to demonstrate the relative importance of the main risk factors for DR and DME in a large clinical sample of patients with type 2 diabetes. The value of CA resides in the fact that the procedure yields unique and common variance explained from each of the risk factors. Our targeted study sample, patients of specialised eye clinics, may mean that our results are not generalizable to a wider population of patients with diabetes and DR/DME. Finally, we lacked sufficient power to explore the relative importance of risk factors for the severity of DR/DME and the relative importance of risk factors for DR in patients with Type 1 diabetes, and further work is required to investigate this.

In conclusion, we demonstrated that the total variation; and independent and joint contributions of the key risk factors of DR and DME are markedly different in patients with type 2 diabetes. Our findings confirm that the etiology and pathogenesis of these two conditions are different and require prevention and intervention strategies.

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Contributors

All authors contributed to the paper. JX undertook the analysis and prepared the manuscript. EF, JJW and TYW edited the paper. JX is guarantor of the data analysis. EL is the Principal Investigator and is overall guarantor for the whole study.

Ethical Approval

Ethical approval for the DMP was provided by the RVEEH Human Research and Ethics Committee (08/815H).

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