CRANFIELD UNIVERSITY

BHASKAR GUPTA

PREVALENCE OF VISUAL IMPAIRMENT AND SEVERITY OF DIABETIC RETINOPATHY IN VARIOUS ETHNIC GROUPS IN THE UNITED KINGDOM

CRANFIELD HEALTH

DM

THESIS

Academic year: 2008-11

Academic Supervisor: Dr. T. Bailey

Clinical Supervisor Ms. S. Sivaprasad

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"Prevalence of visual impairment and severity of diabetic retinopathy in various ethnic groups in the UK"

The manufacture and use of precision tools

Academic Supervisor: Dr. T. Bailey

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April 2011

This thesis is submitted in partial fulfillment of the requirements

for the degree of Doctorate of Medicine

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ABSTRACT

Diabetic Retinopathy (DR) is a leading cause of visual impairment (VI) in the working population. Minor ethnic groups are at increased risk of diabetes. Diabetic Retinopathy In Various Ethnic groups in the United Kingdom (DRIVE UK) is a cross-sectional study to estimate the prevalence of DR, VI and associated risk factors for sight threatening diabetic retinopathy (STDR) in Afro-Caribbeans (AC) and South Asians (SA) compared to Caucasians. People with diabetes in two regions in the United Kingdom who were screened and/or treated for DR from September 2008 to September 2009 were included in this study. VI and severe visual impairment (SVI) were defined as Snellen visual acuity of $\leq$ 6/18 and $\leq$ 6/60 respectively. DR was graded according to National Screening Committee (NSC) for diabetes guidelines UK.

There were 57,144 people on the diabetic register, of which retinopathy data was available from 50,285 (88.1%) subjects (type 1 n=3,323, type 2 n=46,962). In type 1 and type 2 diabetes, any DR was detected in 53.1%, 39.5%, diabetic maculopathy in 13.1%, 8.4% and STDR in 9.91%, 4.0% of people respectively. STDR was significantly more prevalent in the SA (10.3%) and AC (11.5%) populations compared to Caucasians (5.5%). Overall VI was significantly higher in the ethnic minority population. A total of 7.5% (95% CI 7.3, 7.8) people with diabetes were not eligible for driving based on their visual acuity, 3.4% (95% CI 3.2, 3.5) were classified as VI and 0.4% (95% CI 0.33, 0.44) as SVI. Risk factors for STDR were found to include longer duration of diabetes and higher mean HbA1c.

This study provides information that could be used to help develop future service frameworks and guidelines for local health bodies responsible for delivery of end user

services. The study also supports the need to explore the role of inflammatory, genetic and epigenetic factors as markers for ethnic differences in DR and potential treatment avenues for diabetic retinopathy.

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ABBREVIATIONS

ABCD	Appropriate Blood Pressure Control in Diabetes
AC	Afro-Caribbean
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin converting enzyme
ACE-I	Angiotensin converting enzyme inhibitor
ACR	Albumin creatinine ratio
AFR	African
ANOVA	Analysis of variance
ARB	Angiotensin II receptor blocker
ARIC	Atherosclerosis Risk in Communities Study
ASDIAB	The Asian Young Diabetes Research Study
BDR	Background diabetic retinopathy
BES	Barbados Eye Study
BM	Basement membrane
BMES	Blue Mountain Eye Study
BMI	Body mass index
CABG	Coronary artery bypass graft

CCB	Calcium channel blocker
CDC	Centre for disease control and prevention
CHS	Cardiovascular Health Study
CI	Confidence interval
CSMO	Clinically significant macular oedema
CURES	Chennai Urban Rural Epidemiology Study
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complication Trial
DD	Disc diameter
DECS	Diabetic Eye Complications Screening
DiaComp	The DiaMond Substudy of Complications
DiaMond	Diabetes Mondiale
DIRECT	Diabetic Retinopathy Candesartan Trials
DM	Diabetic mellitus
DN	Diabetic nephropathy
DR	Diabetic retinopathy
DRIVE UK	Diabetic Retinopathy in Various Ethnic Groups in United Kingdom
DRS	Diabetic Retinopathy Study

DRVS	Diabetic Retinopathy Vitrectomy study
EDIC	Epidemiology of Diabetes Interventions and Complications
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
ETDRS	Early Treatment Diabetic Retinopathy Study
EUR	Europe
EURODIAB	Europe and Diabetes study
FIELD	Fenofibrate Intervention and Lowering Intervention in Diabetes study
HDL	High density lipoprotein
HES	Hospital eye services
HLA	Human leukocyte antigen
ICD	International classification of diseases
IHD	Ischemic heart disease
IRMA	Intra retinal microvascular abnormality
LALES	Los Angeles Latino Eye Study
LDL	Low density lipoprotein
M	Maculopathy
M0	No maculopathy

M1	Diabetic maculopathy present
MENA	Middle East and North Africa
MESA	Multi-Ethnic Study of Atherosclerosis
MO	Macular oedema
MSVDD	Multinational Study of Vascular Disease in Diabetes
NAC	North America and Caribbean
NPDR	Non proliferative diabetic retinopathy
NSC	National Screening Committee
NCVH	Non-clearing vitreous haemorrhage
NHANES	National health and nutrition examination survey
NVD	Neovascularisation at disc
NVE	Neovascularisation elsewhere in retina
O	Ophthalmoscopy
OCT	Optical coherence tomography
OL	Other lesion
OR	Odds ratio
P0	No photocoagulation
P1	Photocoagulation

Ph	Photography
PCT	Primary care trust
PDR	Proliferative diabetic retinopathy
PRP	Pan retinal photocoagulation
PPV	Pars plana vitrectomy
RNIB	Royal National Institute of Blind People
R0	No retinopathy
R1	Mild non-proliferative retinopathy
R2	Severe non-proliferative retinopathy
R3	Proliferative retinopathy
RCT	Randomised control trial
SA	South Asian
SACA	South and Central American
SBP	Systolic blood pressure
SD	Standard deviation
SEA	South East Asia
SN-DREAMS	Sankara Nethralaya-Diabetic Retinopathy Epidemiology and Molecular Genetic Study

STDR	Sight threatening diabetic retinopathy
SVI	Severe visual impairment
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
TRD	Tractional retinal detachment
UK	United Kingdom
UKADS	UK Asian Diabetic Study
UKPDS	UK Prospective Diabetes Study
US	United States
VA	Visual acuity
VADT	Veterans Affairs Diabetes Trial
VEGF	Vascular endothelial growth factor
VER	Vision Evaluation and research
VH	Vitreous haemorrhage
VI	Visual impairment
VIP	Visual Impairment Project
WESDR	Wisconsin Eye Study for Diabetic Retinopathy
WHO	World Health Organisation

WP	Western Pacific Region

CHAPTER I

INTRODUCTION, LITERATURE REVIEW, AIMS AND OBJECTIVES

1.1 Introduction

Increasing epidemiological evidence suggests that there is a global increase in the prevalence of diabetes. It is no longer a problem in developed nations but people with diabetes in developing countries such as India, China and Brazil will soon outnumber other nations because of increasing population and changing life styles (Wild et al., 2004). With this, the prevalence of microvascular and macrovascular complications due to diabetes, and hence that of diabetic retinopathy, is also expected to increase. Evidence from previous major epidemiologic studies in the United States (US) suggests that ethnic minorities are at increased risk of diabetes and its related complications (Harris et al., 1998, Wong et al., 2006). In the United Kingdom (UK), increasing immigration, mainly from developing countries, has resulted in a shift in the population demographics in metropolitan cities like London and other highly populated regions such as parts of Yorkshire and Birmingham.

Countries like the UK have well established national screening programmes for diabetic retinopathy (DR) and all primary care trusts (PCTs) are expected to have screening uptake rates of > 98%, ideally 100% (www.retinalscreening.nhs.uk). The service objectives of screening programmes include early detection of sight threatening disease and timely referral of these patients to medical retina services for treatment, with the primary aim to decrease the rate of blindness due to diabetes related ocular complications by offering timely treatment. It is therefore useful to identify high risks groups to enable appropriate resource allocation.

The UK Prospective Diabetic Study (UKPDS) study performed over 2 decades ago indicated that there is no difference in incident DR in newly diagnosed diabetes in

different ethnic groups (Kohner et al., 1998), but a recent study in Birmingham comparing prevalence of DR and sight threatening diabetic retinopathy (STDR) showed a much higher prevalence of DR and macular oedema (MO) in South Asians (SA) (Raymond et al., 2009). The two main minor ethnic groups in UK are Afro-Caribbeans (AC) and SA (India, Pakistan, Bangladesh and Sri Lanka) (Office for National Statistics UK, 2007). Most of the information on the prevalence of DR and its impact on visual impairment (VI) in Afro-Caribbean ethnic groups is provided by Barbados Eye Study (BES) and Multi-Ethnic Study on Atherosclerosis (MESA) performed in US.

The data on the differences in risk factors and response to treatment of DR in different ethnic minorities is also limited (Raymond et al., 2009). End stage complications of diabetic retinopathy result in severe visual impairment (SVI) which severely impacts on quality of life and leads to loss of productive life-years. Afro-Caribbeans are particularly at risk of hypertension and end-stage renal disease (ESRD). There is paucity of data on the relation of ESRD and DR with particular reference to ethnic groups (Lopes, 2009). It is therefore important to have data on the UK-specific ethnic variations in prevalence of diabetic retinopathy, risk factors and treatment response of DR to understand the impact on the already stretched health resources.

1.2 Diabetes

Diabetes is a chronic metabolic disorder caused by defects in insulin production or insulin resistance in the peripheral tissue. The two major types of diabetes are:

Type 1 diabetes mellitus (T1D) is characterized by absolute deficiency of insulin due to immune-mediated destruction of pancreatic β cells. The development of T1D is thought to be triggered by environmental factors in genetically susceptible subjects. Several

lines of evidence indicate a rather complex genetics for T1D with the strongest risk associated within the human leukocyte antigen (HLA) region (Alizadeh and Koeleman, 2008, Barrett et al., 2009). This region has both susceptible and protective haplotypes and the relative contribution of these haplotypes and their interactions with environmental determinants and other genetic loci might partially explain the ethnic variations in the frequency of this disease (Ikegami et al., 2008).

Type 2 diabetes mellitus (T2D) is a growing worldwide problem with World Health Organisation (WHO) estimates suggesting that 300 million people will be affected by 2025. It is characterised by peripheral insulin resistance (primarily imbalance between calorie intake and energy expenditure resulting in reduced whole body insulin sensitivity), impaired regulation of hepatic glucose production, and declining ß-cell function, eventually leading to ß-cell failure. Both environmental factors including changing population lifestyle (urbanisation, calorie excess, physical inactivity) and genetic factors (38 individual susceptibility loci identified via genome wide association studies) have been implicated as causative factors (Petrie et al., 2011).

Others forms include gestational diabetes, which is due to glucose intolerance in females during pregnancy. Diabetes may also result from drug-induced genetic defects in the production by beta cells, endocrinopathies or chemicals.

1.3 Prevalence of diabetes

Recent estimates indicated there were 171 million people in the world with diabetes in the year 2000 and this is projected to increase to 366 million by 2030 (International Diabetes Federation, 2009).

1.3.1 Prevalence of type 1 diabetes

T1D predominantly affects population of European ancestry, the highest rates being reported in Finland and Sardinia (Borchers et al., 2010). Asian and sub-Saharan African countries report low frequency although some Asians countries (Kuwait and China) have recently presented high rates (Moussa et al., 2005, Zhang et al., 2008a). The SEARCH for Diabetes in Youth Study provided recent prevalence rates for youths aged 0–19 years with T1D from different ethnic groups in the US. The prevalence rates per 1000 indicate that T1D remains a Caucasian dominated disease: 2.00 in non-Hispanic white subjects, 1.31 for African-Americans, 0.99 for Hispanics, 0.94 for Navajos, and 0.52 for Asians and Pacific Islander (Mayer-Davis et al., 2009, Borchers et al., 2010). Similarly Europe and Diabetes study (EURODIAB) across Europe and the Diabetes Mondiale study (DiaMond) group worldwide both have reported an increased prevalence of T1D in all countries with the exception of Central America and West Indies (EURODIAB, 1994, Karvonen et al., 2000). Prevalence among children under the age of 15 years is predicted to rise to 160,000 in 2020. Recently, a national survey in England noted that 22,947 people under the age of 18 years have diabetes and this is mostly type 1. The incidence of T1D in children younger than 15 years is also increasing. The rapid increase in the incidence of T1D has been almost a global phenomenon during the last few decades (Green and Patterson, 2001). This may represent a true increase resulting from changing environmental or lifestyle factors, or be due to improvement in case ascertainment with the existence of diabetic registers across Europe and America, and more reports from developing countries (Figure 1.1).

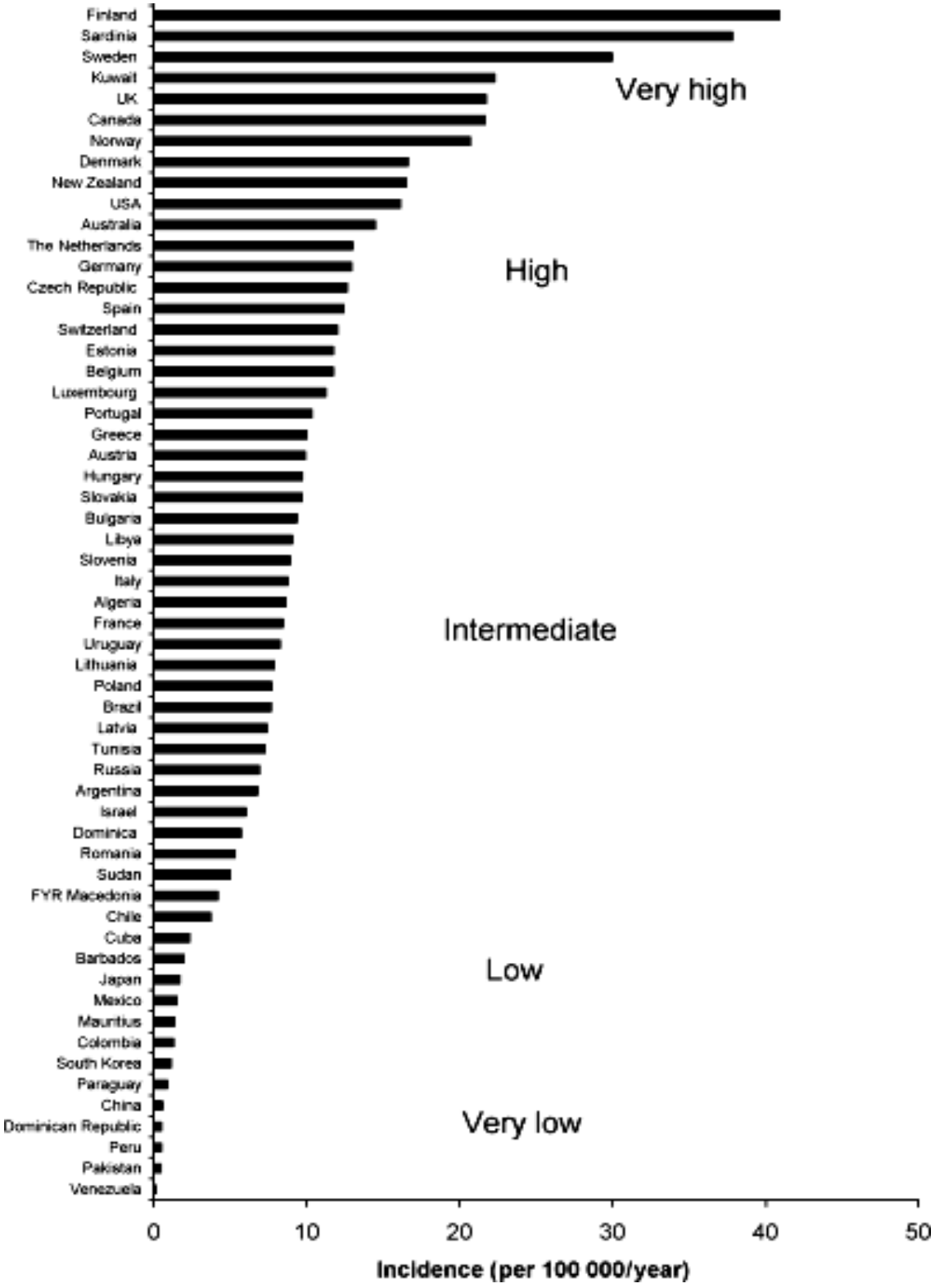


Figure 1.1: Age-standardized incidence of type 1 diabetes in children under 14 years of age (per 100 000 per year). Countries are arranged in descending order according to the incidence. ***Source: The DiaMond Project Group, Incidence and trends of childhood T1D worldwide 1990–1999 (DiaMond study group, 2006)***

1.3.2 Prevalence of type 2 diabetes

T2D was once considered a disease of the west, but is now a global health priority. The International Diabetes Federation has predicted that up to 80% of the disease burden will affect low- and middle-income countries. More than 60% of the world's population with diabetes will come from Asia, because it remains the world's most populous region (International Diabetes Federation, 2009) (Figure 1.2). The number of individuals with diabetes in each South East Asian country will increase substantially in coming decades (Table 1.1) (International Diabetes Federation, 2009). Between 70 to 90% of known diabetic patients have T2D. An estimated 50% more remain undiagnosed (Nabarro, 1988, Simmons et al., 1989). In the UK white population, rates of known diabetes range from 2 - 4%. T2D is commoner in ethnic minority peoples who also often have poor glycaemic control. They are also more likely to develop complications of the disease (Adams et al., 2008, Harris et al., 1998, Saydah et al., 2007). T2D is also common in those who are socio-economically deprived (Strodl and Kenardy, 2006).

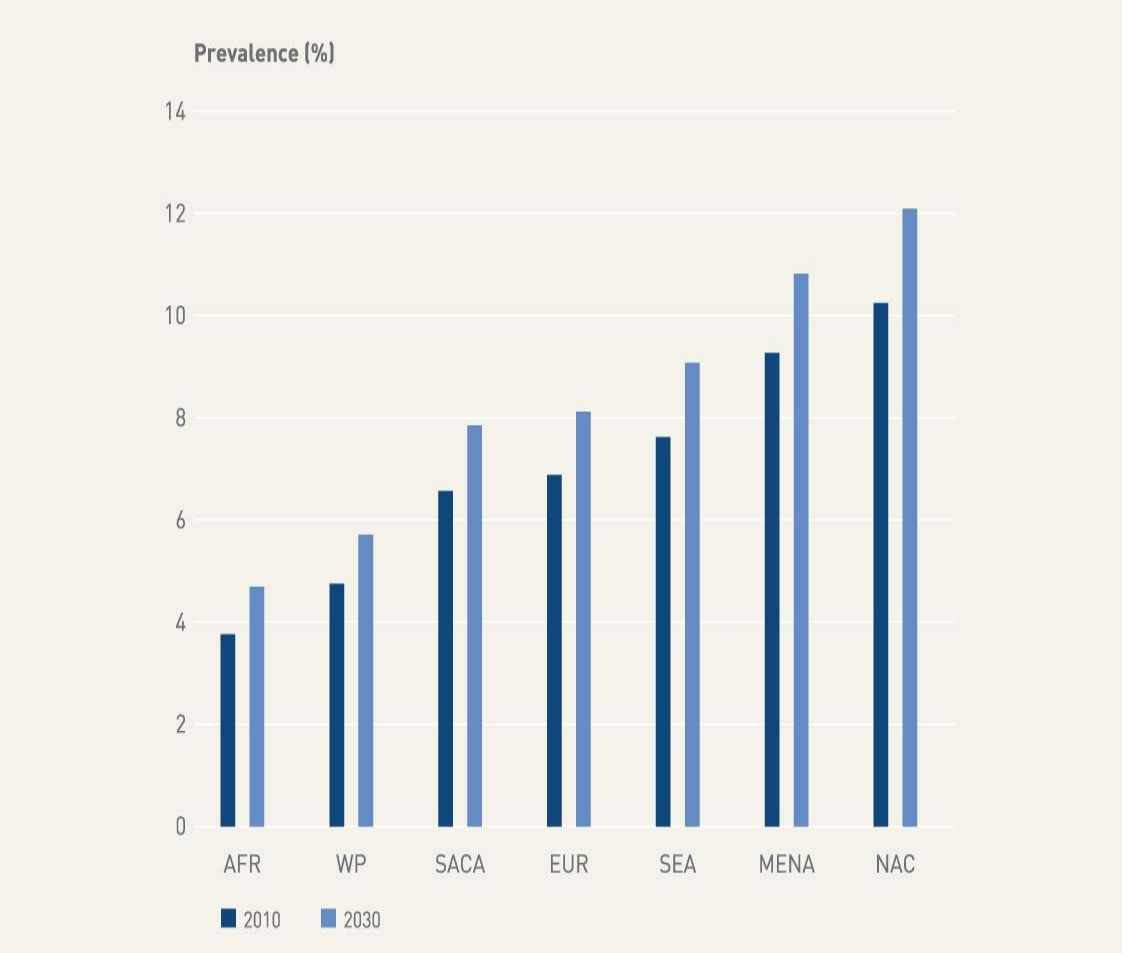


Figure 1.2: Estimated and projected global prevalence of diabetes. AFR indicates African region, EUR: Europe, MENA: Middle East and North Africa, NAC: North America and Caribbean, SACA: South and Central American, SEA: South East Asia, WP: Western Pacific Region. Source: (International Diabetes Federation, 2009)

Table 1.1: Estimated and projected per cent population prevalence of diabetes in South East Asia

	Population in 2010 (20-79)	Estimated diabetes prevalence (%)	
	000's	2010	2030
Bangladesh	93,862	6.6	7.9
Bhutan	413	3.6	4.6
India	713,498	7.8	9.3
Maldives	186	7.3	-
Mauritius	877	16.2	19.8
Nepal	15,556	3.9	5.2
Pakistan	93,644	9.1	10.5
Sri Lanka	13,339	10.9	13.5

Source: (International Diabetes Federation, 2009)

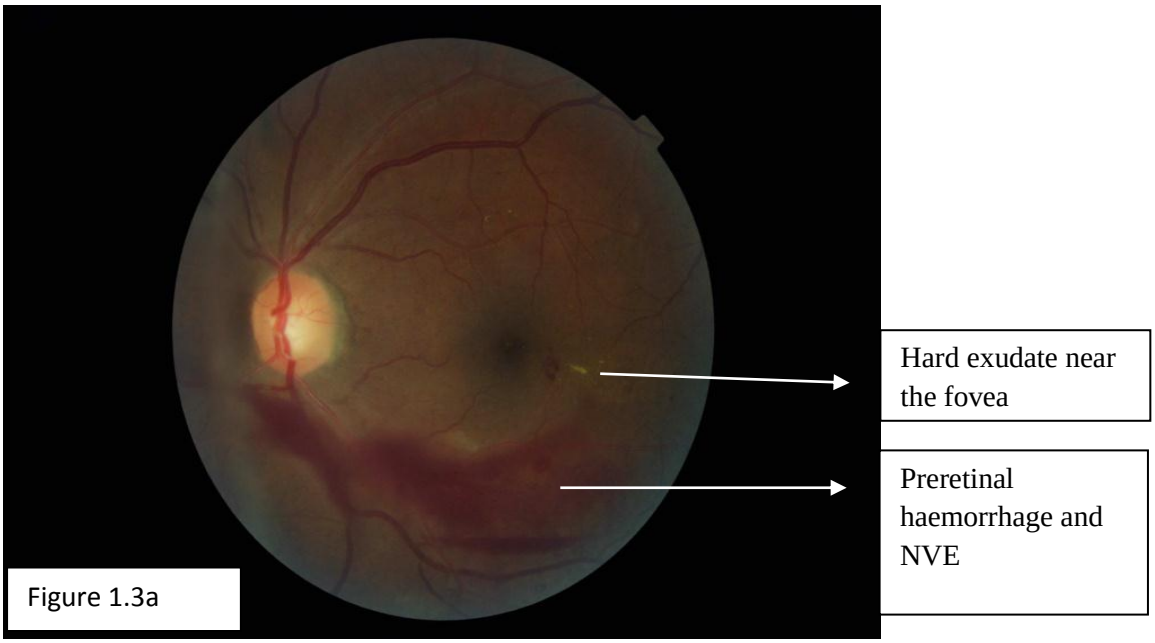
1.4 Diabetic retinopathy

Diabetic retinopathy is a chronic and progressive sight-threatening disease of the retinal microvasculature associated with the prolonged hyperglycaemia and other conditions linked to diabetes mellitus such as hypertension, impaired cholesterol and lipid profile and nephropathy.

1.4.1 Clinical signs and pathogenesis of diabetic retinopathy

Clinically two distinct changes can be identified: retinopathy and maculopathy. Retinopathy is a disorder that progresses from no retinopathy to presence of haemorrhage or microaneurysm, as seen in non proliferative diabetic retinopathy (NPDR). These changes can develop in severity with associated vascular changes such as beading and intra-retinal microvascular abnormality (IRMA) to sight threatening proliferative diabetic retinopathy (PDR) characterised by formation of new vessels around optic disc (NVD) or elsewhere (NVE) (See Figure 1.3a and 1.3b). Maculopathy

(M) can be minimal or sight threatening when it involves the centre of eye, fovea (See Figure 1.4a and 1.4b).



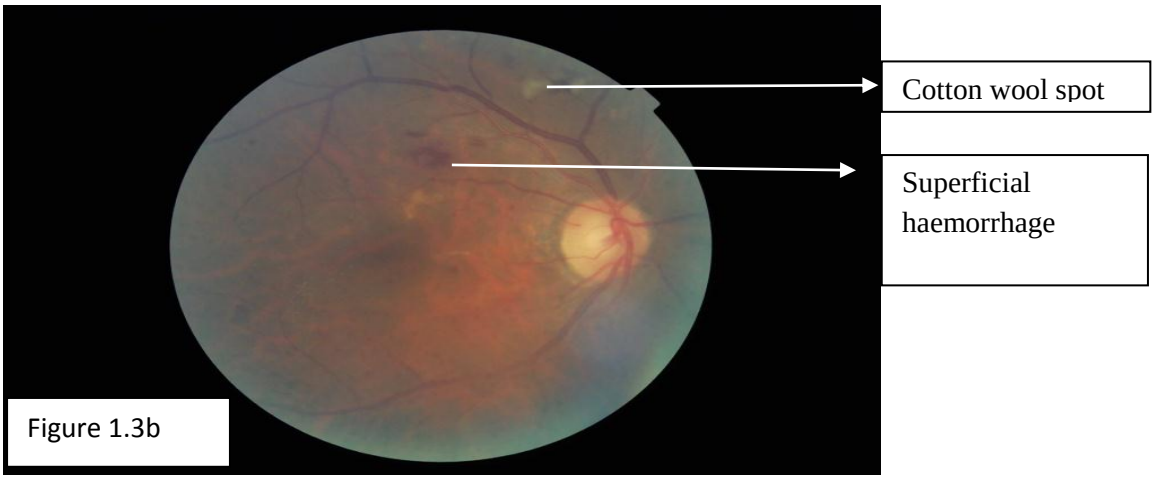


Figure 1.3 (a & b): Fundus photographs with various retinal lesions seen in retinopathy. Source: Diabetic Eye Complication Screening Services (DECS), London.

The clinical signs of the disease are (RCOPhth, 2005):

Microaneurysms: These are focal dilation of the venous end of capillaries. Histologically they represent out pouching of capillary endothelium with loss of

supporting pericytes. On clinical examination they appear as tiny red dots, most commonly temporal to the macula but can occur anywhere in retina.

Hard exudates: These are the result of precipitation of lipoproteins due to an abnormally leaky capillary bed or microaneurysms. They appear as yellow lipid deposits and appear in a circular pattern around foci of leaking capillaries.

Haemorrhages: These occur due to the rupture of weakened capillaries. They appear as small dots or larger blot haemorrhages when present within the densely packed deeper layers of the retina, or flame shaped when in the superficial retina nerve fibre layer.

Venous beading, looping and duplication: These are seen near the areas of capillary non perfusion and signify severe ischemia.

Intraretinal microvascular abnormalities (IRMA): These represent either new vessel growth or remodelling of pre-existing vessels through endothelial cell proliferation within the retinal tissues to act as shunts through areas of non-perfusion.

Cotton wool spots: These are fluffy white lesions that represent infarcts of the nerve fibre layer with associated stasis in axoplasmic flow.

New Vessel Disc (NVD) or New Vessel Elsewhere (NVE): These are the hallmarks that represent the extreme spectrum of the disease (PDR). They appear as arcade of abnormal structures which are new vessels commonly arising on the optic disc (NVD) or elsewhere on the retina (NVE). They appear at the junction of perfused and non perfused retina and cause visual disruption as they are highly fragile and permeable. They either grow along the surface of the retina or as scaffolding along the posterior

vitreous surface. Important features of proliferative retinopathy include neovascularization, and pre-retinal and vitreous haemorrhages.

Macular Oedema (MO): This is defined as the retinal thickening within one disc area of the macula. Clinically, it is diagnosed using stereoscopic fundus examination and objectively using optical coherence tomography (OCT) (Figure 1.4a and 1.4b).

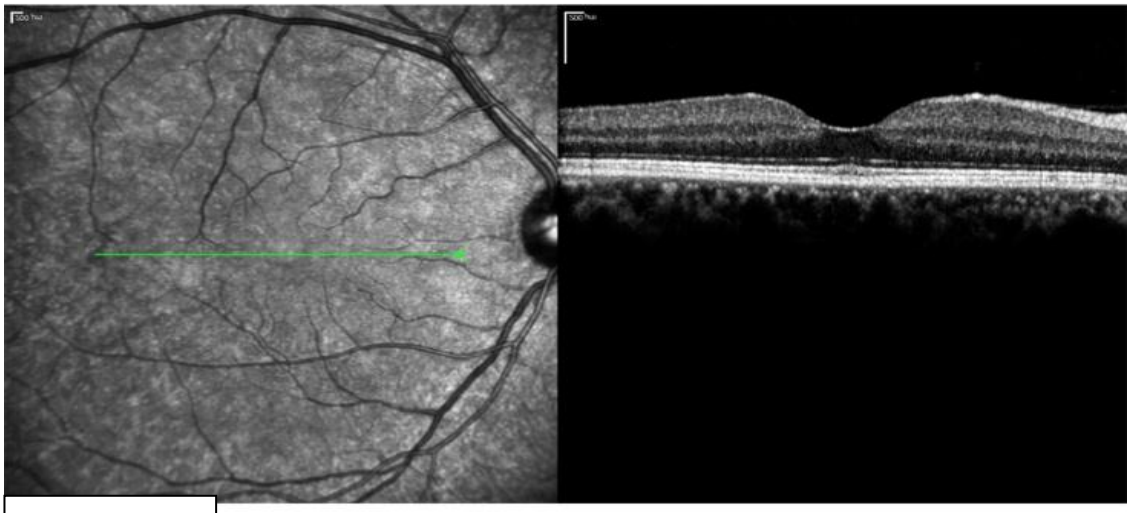


Figure 1.4a

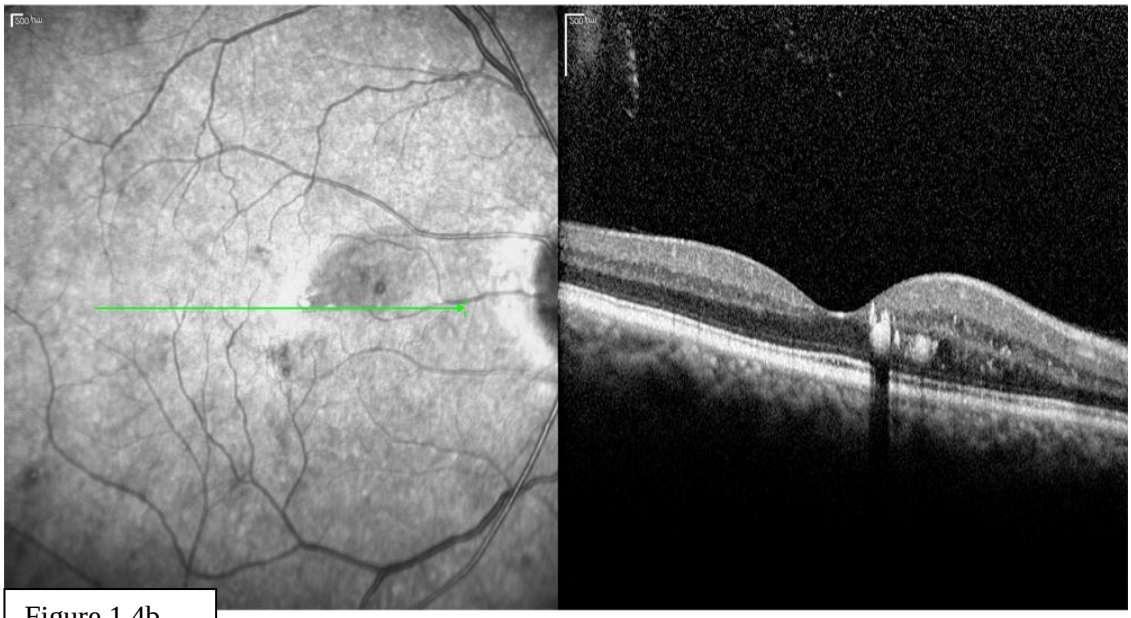


Figure 1.4b

Figure 1.4 (a & b): Fovea appearance on optical coherence tomography: a) Normal, b) With hard exudates and macular thickening

1.4.2 Classification of DR

Classification and grading of severity of DR have been based on ophthalmoscopically visible signs of increasing severity, ranked on a stepwise scale from no retinopathy through various stages of NPDR to advanced proliferative disease. These have developed from the original Airlie House classification developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) aimed at grading retinopathy in the context of overall severity of ophthalmoscopic signs (Early Treatment Diabetic Retinopathy Study Research Group, 1991). A reduced version of the ETDRS classification aimed at countries without systematic screening programmes has recently been endorsed by the American Academy of Ophthalmology Guidelines Committee (Wilkinson et al., 2003), and used in clinical trials. The latter classification was developed in recognition of the need for a clinical grading system that would reflect the vision threatening risk of DR. This describes three stages of low risk non-proliferative retinopathy, a fourth stage of severe non-proliferative retinopathy and a fifth grade of proliferative retinopathy.

In the UK there are two classification used: The National Screening Committee (NSC) for use in England and Wales (Harding et al., 2003), and the Scottish Diabetic Retinopathy Grading Scheme (Leese et al., 2003). The NSC classification adopts a simplified approach to grading retinopathy based on features which a non-ophthalmologist / accredited photographic grader might be faced with in a population of diabetic patients (table 1.2).

Table 1.2: (continued over two pages) National Screening Committee retinopathy grading standard

NSC	International Term	Symptoms	Features	Action
R0	No DR	Asymptomatic	Normal retina	Annual rescreen
R1	Mild non-proliferative (mild pre-proliferative)	None	Haemorrhages & microaneurysms only	Annual rescreen
R2	Moderate non-proliferative	None	Extensive microaneurysm, intraretinal haemorrhage, and hard exudates.	Refer HES
R2	Severe non-proliferative	None	Previously termed pre-proliferative. Venous abnormalities, large blot haemorrhages, cotton wool spots (small infarcts), venous beading, venous loop, venous reduplication, IRMA.	Urgent refer HES
R3	Proliferative retinopathy	Floaters, sudden visual loss or asymptomatic	New vessel formation either at the disc (NVD) or elsewhere (NVE). Extensive fibrovascular proliferation, retinal detachment, pre-retinal or vitreous haemorrhage.	Urgent refer HES
M0			No maculopathy	Annual rescreen
M1	Diabetic maculopathy	Blurred central vision	The macula is defined as a circle centred on the fovea, with a radius of the distance to the disc margin (section 2.3.3). If the leakage involves or is near the fovea the condition is termed clinically significant macular oedema (CSMO). Exudative maculopathy presents with leakage , retinal thickening, microaneurysms, hard exudates at the macula. Ischaemic form can have a featureless macular with	Refer HES

NSC	International Term	Symptoms	Features	Action
			NVE and poor vision. Milder Forms exudate < or = 1DD (Disc diameter) of centre of fovea circinate or group of exudates within macula any microaneurysm or haemorrhage < or = 1DD of centre of fovea only is associated with a best Snellen's visual acuity (VA) of < or = 6/12 retinal thickening < or = 1DD of centre of fovea (if stereos available)	
P	Photocoagulation	Reduced night vision, glare	Small retinal scars throughout the peripheral retina.	
OL	Other lesion / Un-gradable		Un-gradable is usually due to cataract, other lesions usually referred for assessment	

CSMO: Clinically Significant Macular Oedema, DD: Disc Diameter, HES: Hospital Eye Service, NVD: New vessel on disc, NVE: New vessel elsewhere on retina

1.4.3 Methodology of image capture in the screening programmes in UK

(Harding et al., 2003)

Each eye is dilated with a mydriatic agent such as guttae tropicamide (0.5% or 1% v/v) and guttae phenylephrine (2.5% or 10% v/v)

Photographers capture 2 x nominal 45º fields per eye (Figure 1.5a and 1.5b), 1 fovea centred and 1 disc centred.

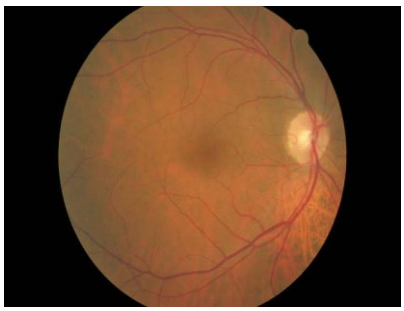
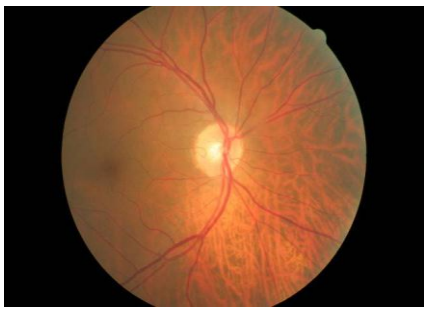
Macular image (1.5a)		Disc image (1.5b)
centre of fovea ≤1DD from centre of image vessels clearly visible within 1DD of centre of fovea vessels visible across >90% of image	**AND**	centre of disc ≤1DD from centre of image fine vessels clearly visible on surface of disc vessels visible across >90% of image
		

Figure 1.5 (a & b): Showing definition of fovea and disc centred images. Adapted from National Screening Committee guideline for diabetic retinopathy

Definitions

Fovea: The fovea lies at the centre of the image and is marked by a '+' symbol represented by big circle figure 1.6.

1DD: 1DD is defined as the horizontal diameter of the optic disc.

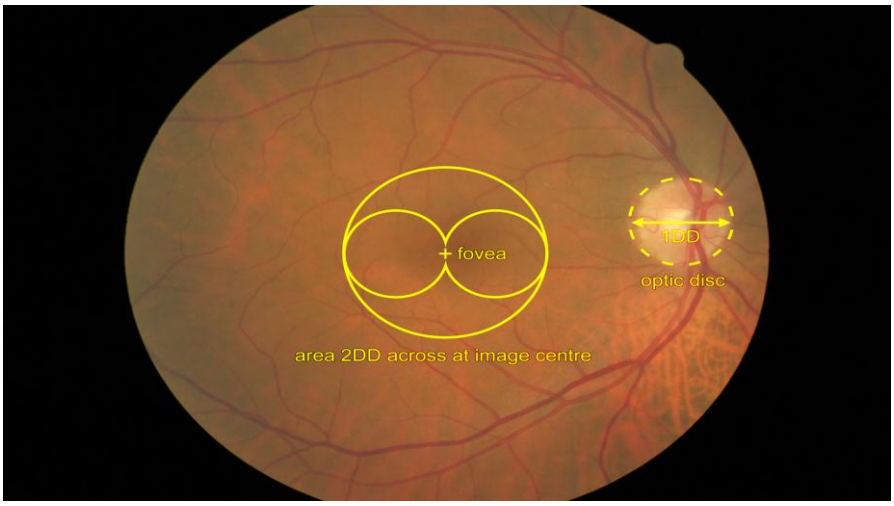


Figure 1.6: Representing fovea and 1DD shown in 2.x magnification. Adapted from National Screening Committee guideline for diabetic retinopathy

1.4.4 Prevalence of diabetic retinopathy

The purpose of this review is to address the regional and ethnic variations in DR and to review risk factors that may explain the differences.

1.4.4.a Diabetic retinopathy in type 1 diabetes

There are more epidemiological studies on T1D related DR in Caucasian population from the European countries compared to other parts of the world reflecting the disease predilection and historically better healthcare systems (Table 1.3). The prevalence rates of DR range from 10-50% depending on the methods used to screen for DR, the type of population screened, the age of the patients, and the duration of diabetes. The prevalence rates are usually lower in population-based studies compared to hospital-based populations.

Table 1.3: (continued over two pages) Studies on the rates of diabetic retinopathy in TID in Caucasians in North America and Europe

Reference and year	Methods of Examination Ph, O	Participants and mean age of cohort	Prevalence of DR in study	Population study or clinic based.
(Klein et al., 1984b)	Ph	996 < 30 years	54% Any DR 27% PDR	Population
(Arfken et al., 1994)	Ph	142 17.2±8.7 years	39% Any DR	Hospital based
(Danielsen et al., 1982)	O	212 NA	34% Any DR 6.1% PDR	Hospital based
(Sjolie, 1985)	Ph	718 3-76	30% Any DR 9% PDR	Population
(Burger et al., 1986)	O	231 17.6± 4.0	47% Any DR 4% PDR	Hospital based
(McCance et al., 1989)	O	216 26.6	56% Any DR 4% PDR	Hospital based
(Pinto-Figueiredo et al., 1992)	O	1302 24.14±12.47	42% Any DR 7% PDR	Population
(Joner et al., 1992)	Ph	369 18.3±4.9	33% Any DR	Population
(Falck et al., 1993)	Ph	194 11.8	11% Any DR	Hospital based
(Stephenson et al., 1995)	Ph	2479 32.7±10.2	46% Any DR 10% PDR	Population
(Kristinsson et al., 1994b)	Ph+O	205 32.9±0.91	52% Any DR 13% PDR 9% MO	Population
(Kokkonen et al., 1994)	Ph	80 21.6	70% any DR 10% PDR	Population
(Johansen et al., 1994)	Ph	138 25-34	59% Any DR 17% PDR	Hospital based
(Ebeling and Koivisto, 1997)	Ph	140	55% Any DR 21% PDR	Hospital based

Reference and year	Methods of Examination Ph, O	Participants and mean age of cohort	Prevalence of DR in study	Population study or clinic based.
		33.0±0.8		
(Kuiv et al., 1997)	Ph	149 34-71 (median 40 years)	77% Any DR 17% PDR	Population
(Kernell et al., 1997)	Ph+O	557 14.6	15% Any DR 2% PDR	Population
(Olsen et al., 1999)	Ph	339 (median 21.1 years)	57.6% Any DR	Population
(Larsson et al., 1999)	Ph	285 33.1±9.6	75% Any DR 22% PDR	Population
(Nordwall et al., 2006)	Ph	80 (7-22)	27% Any DR	Population

O-ophthalmoscopy, Ph-photography

The earliest signs of DR in T1D usually occur after 5-10 years of diabetes duration and the prevalence of DR is strongly correlated to duration of disease. Nearly all subjects with T1D will develop some degree of retinopathy within twenty years of diagnosis but this may change with better control of risk factors (Klein et al., 1984c, Klein et al., 2008a). So the current guidelines recommend annual screening for all patients from the age of 12 years in UK or 10 years in US (American Academy of Pediatrics, 1998, NSC, 2010).

There are limited studies on prevalence of DR in T1D from non-Caucasian dominated countries probably because T1D is more prevalent in people of European ancestry (table 1.4). Moreover, information on other ethnic groups is more recent perhaps due to better case ascertainment and improvement in the healthcare systems (Arfken et al., 1994,

Elbagir et al., 1995, Esteves et al., 2009, Gomes et al., 2000, Motala et al., 2001, Roy, 2000, Majaliwa et al., 2007, Ko et al., 1999).

Table 1.4: Prevalence rates of DR in T1D in non-Caucasian population

Author and year	Ethnic group	Methods of Examination Ph, O	Number of participants with mean age(years)	Prevalence rates	Type of study
(Arfken et al., 1994)	African American	Ph	58 20.7±10.0	36% Any DR	Hospital based
(Elbagir et al., 1995)	Sudan	O	91 15-75	43% Any DR 10% PDR	Hospital based
(Fairchild et al., 1994)	Australia	Ph	255 11.0-19.9	42% Any DR	Population
(Ramachandran et al., 2000)	Indian	Ph	617 Median 25(10-50)	13.4% Any DR	Population
(Ko et al., 1999)	China	O	150 30.7± 0.5	14% Any DR	Hospital based
(Roy, 2000)	African American	Ph + O	724	64% Any DR 19% PDR	Hospital based
(Motala et al., 2001)	African	O	36 39.9 ± 11.2	56% Any DR 17% PDR	Hospital based
(Maguire et al., 2005)	Australia	Ph	618	34% Any DR	Population
(Majaliwa et al., 2007)	Tanzania	O	99 12.6 ± 3.5	23% Any DR	Hospital based
(Scott et al., 2004)	New Zealand	Ph	237 16.7	25% Any DR	Hospital

Inter-regional differences in prevalence rates of DR are best observed in the four multinational studies: The DiaMond Substudy of Complications (DiaComp), the WHO Multinational Study of Vascular Diseases in diabetes (MSVDD), the EURODIAB

Study and the DiabCare Asia 1998 study (DiaMond study group, 2006, EURODIAB, 1994, Lee et al., 2001b, Nitiyanant et al., 2002, Walsh et al., 2006).

In the EURODIAB study of patients from 31 clinics in 16 European countries, the rate of retinopathy ranged between 25% in Austria to 60% in Portugal (EURODIAB, 1994). The DiaComp study also mirrored such variations in prevalence of self-reported retinopathy in subjects with short duration of diabetes, with highest rates noted in Lithuania (29.9% requiring laser treatment) (Walsh et al., 2006). The prevalence rates were more consistent in people with long duration of diabetes. Similarly, the WHO MSVDD found the cumulative incidence of any retinopathy to vary at least two-fold between centres, with even greater variation in the frequency of PDR.

The Asian Young Diabetes Research (ASDIAB) Study, reported the prevalence of DR in 724 young diabetic subjects of age 12-40 years with duration of diabetes of less than 12 months in 7 centres of four Asian countries. The fact that the Asian study has very few patients with DR again reflects both the low prevalence of T1D and the low rates of healthcare utilization. It is interesting to note that DR prevalence was least among Indians (5.3%) as compared to other ethnic groups such as Malays (10%) and Chinese (15.1%) (Rema and Mohan V, 2002). Higher levels of fasting and glucagon stimulated C-peptide among the Indians were postulated to partly explain the lower prevalence of DR in this group (Rema and Mohan V, 2002).

Few single-centred studies from the Indian sub-continent also show a low prevalence. A study in Pakistan amongst TID of more than 10 years duration reports a prevalence of 7.7% (Shera et al., 2007). Similarly, a study from South India in a cohort of T1D followed up over 15 years showed that despite an earlier age of onset of the disease

there was lower prevalence rates of 13.4% and 1.9% of any DR and PDR respectively (Ramachandran et al., 2000) implying despite the earlier age of onset and poorer glycaemic control, there may be other clinical and genetic factors that may determine the rate of complications in various ethnic groups (Borchers et al., 2010). The study also showed that the prevalence of T1D is increasing in India (10.5/10,000 per year) probably due to better case ascertainment and improved survival rates. These rates are similar to the incidence reported in Asian children in the UK (Ramachandran et al., 2000).

In a study comparing South African Black and Indian subjects with T1D of over 10 year duration, no ethnic differences in prevalence of DR (Blacks 55.6%, Indians 45.5%), was reported despite the fact that the prevalence of hypertension was higher in the Blacks. However, the onset of retinopathy from time of diagnosis occurred earlier in Blacks (13.0 +/- 4.6 years versus 18.0 +/- 4.6 years) (Motala et al., 2001).

Similarly, Arfken et al compared the risk of development of PDR between African-Americans and whites with T1D and showed that 17.5% of the African-Americans developed PDR compared to 10.2% in the whites but ethnicity was not a risk factor after adjusting for glycaemic control and duration of the disease (Arfken et al., 1994).

A cross-sectional study from Brazil showed comparable prevalence to European studies (Esteves et al., 2009, Gomes et al., 2000).

The prevalence of macular oedema and clinically significant macular oedema (CSMO) is also related to the duration of the disease with very low rates within five years of diagnosis to 29% showing evidence of MO at 20 years (Klein et al., 1984b, Klein et al., 1984b, Klein et al., 1984a, Klein et al., 1989d, Klein et al., 1995b, Klein et al., 2009a,

Williams et al., 2004b). However, it is crucial to note that the prevalence of MO varies depending on the period of study within the same region due to the improved healthcare experienced by the T1D subjects. Incidence studies will provide a better insight into these temporal changes.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) is the largest study with data on incidence of DR in a predominantly Caucasian population in the United States (Klein et al., 1984b, Klein et al., 1985a, Klein et al., 1985c, Klein et al., 1985b, Klein et al., 1989b, Klein et al., 1989d, Klein et al., 1990, Klein et al., 1994b, Klein et al., 1995b, Klein et al., 1998, Klein et al., 2008a, Klein et al., 2009a). Table 1.5 gives the incidence data of DR and visual impairment at different time-points. Studies in Europe at similar time-points also reveal that approximately 50% with no retinopathy develop any retinopathy by 5-7 years (Agardh et al., 1997, Burger et al., 1986) while 9% with background retinopathy develop PDR by 5 years. Higher prevalence was noted in subjects with poorer control of blood pressure and glycaemic status as confirmed by the Diabetes Control and Complications Trial (DCCT). This study involving volunteers with TID of less than 5 years duration from 29 medical centres in Canada and the USA and showed that 54.2% of patients had DR at baseline and 67.1% had DR within 5 years of diabetes duration and the rate of progression of DR decreased significantly and exponentially with better control of hyperglycaemia (DCCT, 2000). The Berlin Retinopathy study also stressed that a threshold of HbA1C of at least 9% is required to reduce the risk of progression (Danne et al., 1994).

Table 1.5: Incidence of DR at different time points in WESDR

US WESDR	N	No DR to any DR	DR to PDR	MO	CSMO	Blindness	VI
4 years (Klein et al., 1989b)	891	59%	10.5%	8.2%	4.3%	1.5%	1.5%
10 years (Klein et al., 1994b)	765	89.3%	29.8%	20.1%	NA	1.8%	9.4%
14 years (Klein et al., 1998)	634	86%	37%	26%	17%	2.4%	12.7%
25 years (Klein et al., 2008a)	567	83%	42%	29%	17%	3%	13%

N: Number

Incidence studies on other ethnic groups are limited (Arfken et al., 1994, Gomes et al., 2000, Kalter-Leibovici et al., 1997). The risk of conversion to PDR was higher in non-Ashkenazi Jewish origin versus Ashkenazi independent of the glycaemic and blood pressure parameters (Kalter-Leibovici et al., 1997). On the contrary, African-Americans have higher incidence of PDR compared to whites that is explained by poorer control of the conventional risk factors (Arfken et al., 1994). In the WHO MSVDD study complicating T1D in different ethnic groups, American Indians had a higher incidence of any retinopathy compared to the European and Asian cohorts (Lee et al., 2001b).

Incidence studies from the Scandinavian countries have observed a decline in incidence rates of nephropathy earlier than the decrease in incidence rates of severe retinopathy over the last 25 years (Bojestig et al., 1998b, Hovind et al., 2003, Nordwall et al., 2006).

This decrease in the cumulative incidence of both retinopathy and nephropathy is attributed to better control of the risk factors. A similar decline in incidence of visual impairment due to diabetes has also been reported from the same region (Hovind et al., 2003, Backlund et al., 1997). Comparatively, in the US, a similar decline in rates of PDR was not noted in the Pittsburgh Epidemiology of Diabetic Complications Study over a 25-year period of follow-up (Pambianco et al., 2007). However, annualized estimates of the 25 year WESDR study have also shown a decline in rates of PDR in the latter half of the study compared to the first 12 years (Klein et al., 2008a). The 25 year incidence study of MO in the WESDR study also observed a decrease in rates of MO from 2.3% in the first four years of the study compared to 0.9% at 25 years follow-up. The reduction in incidence rates of MO and PDR is also reflected in the lower prevalence of visual impairment (VI) in more recent period of diagnoses of T1D (Klein et al., 2009a, Klein et al., 2008a).

A similar decline in DR prevalence is also observed in children and adolescents in both European and other ethnic groups (Sano et al., 2009, Massin et al., 2007). Several authors have attributed this to advances in insulin therapy preventing or decreasing glucose excursions (Maguire et al., 2005, Massin et al., 2007, Mohsin et al., 2005).

Studies from around the world have identified a variety of predictors for the microvascular complications of T1D with disease duration and glycaemic control being the strongest risk factors. The geographic and ethnic variations in DR are largely accounted for by significantly worse glycaemic control in the minor ethnic groups (Arfken et al., 1994, Moreira, Jr. et al., 2010, Mendes et al., 2010, Svensson et al., 2009, Povlsen et al., 2005b, Povlsen et al., 2005a).

The DCCT and Epidemiology of Diabetes Interventions and Complications (EDIC) study results suggest that the risk of DR progression is higher in adolescents than in older-onset T1D subjects (Massin et al., 2007, White et al., 2010, Morales, 2009). The cumulative incidences of a progression of 3 steps or more in the ETDRS retinopathy level, from DCCT baseline to EDIC Year 4, were 65% and 32%, respectively, in the conventional and intensive groups of the original adolescent cohorts, compared to 49% and 18%, respectively, for the entire cohort of T1D. This may be due in part to globally worse glycaemic control in the original adolescent cohort than in older T1D subjects during both the DCCT and EDIC studies, but still underlines the higher risk of DR progression in these young patients.

Comparison of prevalence studies on DR in T1D between different regions should be done with caution. The approach of different healthcare systems on the management of T1D varies significantly. The DCCT demonstrated that intensive therapy was more effective when initiated during the first 5 years of diabetes as primary prevention than when introduced as secondary intervention after complications had begun to develop. Moreover, the beneficial effects of intensive therapy on the onset and progression of retinopathy were not evident until after three or four years of therapy. So the risks of DR are determined more by the 'metabolic memory' of hyperglycaemia than to the prevailing level of hyperglycaemia (The Diabetes Control and Complications Trial Research Group, 2002). This was confirmed by data from the Fulminant T1D Committee that suggested that HbA1C up to 5 years earlier made a greater contribution to progression of retinopathy than the present level (Lind et al., 2010).

It is also known that, despite adequate glycaemic and blood pressure control, DR can progress and once the disease process reaches a certain stage, its effects become

irreversible. This phenomenon of 'retinopathic momentum' was defined in the DCCT and suggests that once DR progresses far enough down the line, then the momentum carries it forward, and that any form of intervention would not affect its relentless progress. Given that glycaemic control is the one of the strongest risk factor for DR, the early implementation of intensive treatment of diabetes determines the prevalence and incidence of DR in T1D in any region in the world.

Another important risk factor in T1D is hypertension especially high systolic blood pressure (Arfken et al., 1994, Walsh et al., 2006) and high nocturnal blood pressure (Rodrigues et al., 2010). Inhibition of angiotensin converting enzyme (ACE) and angiotensin receptor blockade reduces the risk of progression of DR in normotensive T1D (Chaturvedi et al., 1998, Chaturvedi et al., 2008, Jandeleit-Dahm and Cooper, 2006) independent of the effect on hypertension. The effect of changes in clinical practice brought about by these trials are shown in the Steno Diabetes Centre Study and have contributed partly both to the recent decline in DR prevalence rates (Hovind et al., 2003, Klein and Klein, 2010) and will influence the prevalence rates of DR in future. There are no studies on other ethnic groups on the effect of these drugs on the prevalence of retinopathy.

High caloric and sodium intakes are significant and independent risk factors for progression of DR in African American patients with T1D (Roy and Janal, 2010). Risk modelling of a Thai cohort showed that serum creatinine of >2mg/dl is an added risk factor in that population (Chetthakul et al., 2006b).

Other contributing factors include high body mass index (BMI) (Ko et al., 1999, De Block et al., 2005), lack of physical activity, dyslipidemia (plasma triglycerides) in

CSMO (Miljanovic et al., 2004), microalbuminuria, smoking and socio-economic factors (Pedro et al., 2010). High haemoglobin levels predicts the incidence of PDR in T1D (Conway et al., 2010) while moderate alcohol consumption reduced the risk of PDR (Beulens et al., 2008).

Age at onset significantly modifies the long-term risk of proliferative retinopathy. The highest risk is in age-at-onset group 5-14 years, whereas the lowest risk is in age-at-onset group 15-40 years (Hietala et al., 2010). Hormonal changes induced by puberty including increased growth hormone and insulin-like growth factor and the effect of prepubertal diabetes duration in the development of DR remain controversial (Flack et al., 1996, Donaghue et al., 2003).

In a Caucasian study, increment of carotid intima-media thickness in T1D was associated with diabetic microangiopathy (Gul et al., 2010) but a similar association was not observed in a Japanese cohort (Ogawa et al., 2009).

The current evidence supports a multifactorial and polygenic aetiology. It is also possible that genetic differences contribute to the higher risk of DR in certain ethnic groups (Borchers et al., 2010, Abhary et al., 2009, Roy et al., 2009). Whether the effects of ethnicity are independent of socioeconomic status remains the matter of considerable controversy. While a few studies showed a positive association of low socioeconomic control and poor metabolic control (Bachmann et al., 2003), other studies failed to show such effects (Carter et al., 2008). Other social, cultural and behavioural factors including access to health care may also contribute to the ethnic variations in DR.

In conclusion, there is geographic and ethnic variability in the rate of retinopathy in T1D that cannot be explained by the variations in study methodologies only. Although it may be thought to parallel the prevalence of T1D, other factors may play important roles including differences in genetic risk factors, ecological differences such as socio-economic inequalities, differential distribution of known risk factors between ethnic groups and differences in healthcare systems and availability of more intensive medical care around the world to keep T1D related complications low for these people.

1.4.4.b Diabetic retinopathy in type 2 diabetes: There has been a surge in the reports on T2D related DR in the last 2 decades, especially from Asia. More multi-ethnic comparative studies are also available to better understand the variations in DR between racial groups. A breakdown of the prevalence rates of races per continent provides us with a vision on future needs per region.

Europe

Most of Europe is historically predominantly populated by Caucasians. However, in the past 20 years, migrations of other ethnic groups have converted some European cities to multiracial population. These ethnic groups are mainly Asians and Afro-Caribbeans. As diabetes and its complications are far more prevalent in these ethnic groups, data on ethnicity-specific prevalence rates are crucial to assess health needs. Table 1.6 shows the prevalence rates of predominantly Caucasian population in Europe at different time points (clinic-based studies have been included in areas where no population based studies are available). Comparison of data between regions is difficult because of different study entry criteria and methodology used. Studies employing retinal photography consistently suggest that the prevalence of DR is close to 40%, whereas

STDR account for 6-8% of all diagnosed cases in Caucasians. However, some regions in Europe report low rates, suggesting that DR is still under diagnosed in these areas (Beynat et al., 2009).Various longitudinal studies indicate an annual incidence of DR of 2-6% in the Caucasian population.

Table 1.6: (continued over two pages) Prevalence rates of diabetic retinopathy in predominantly Caucasian population with T2D in Europe

Author and year	**Region**	**Sample size**	**Methods of examination Ph, O**	**Prevalence rate**
(Kalm et al., 1989)	Sweden	185	O + Ph	39% Any DR 4% PDR 21% Macular Oedema
(Sparrow et al., 1993)	UK	148	O	52% Any DR 4% PDR 10% CSMO
(Leese et al., 1993)	Rural versus Urban UK	961 rural versus 1225 urban	Ph	Any DR 13% rural, 7% urban
(Kristinsson et al., 1994a)	Iceland	243 Hospital based	Ph	41% Any DR 7% PDR 10% Macular Oedema
(Stolk et al., 1995)	Netherland Rotterdam Study	7129	Ph	4.8% Any DR
(Hirvela and Laatikainen, 1997)	Finland	113 aged > 70 years	O + Ph	21% Any DR 2% PDR
(Cahill et al., 1997)	Ireland	150 Hospital based	O+ Ph	14% Any DR 3% PDR
(Kohner et al., 1998)	UKPDS	2964 Newly diagnosed	Ph	37% Any DR

Author and year	**Region**	**Sample size**	**Methods of examination Ph, O**	**Prevalence rate**
		T2D		
(Delcourt et al., 1998)	France	428 Hospital based	Ph	32% Any DR 3% PDR 5% Macular Oedema
(Rajala et al., 1998)	Finland	790	Ph	4% Any DR
(Younis et al., 2003)	Liverpool, UK	7615	Ph	34% Any DR 1% PDR 9% Macular Oedema 6% STDR
(Olivarius et al., 2001)	Denmark	1251	O + Ph	5% Any DR 1% Macular Oedema
(Ling et al., 2002)	UK	775	O + Ph	30% Any DR 3% PDR 6% Macular Oedema
(Giuffre et al., 2004)	Italy	1588	O + Ph	34% Any DR 5% PDR
(Hove et al., 2004)	Denmark	378	Ph	31% Any DR 3% PDR
(Beynat et al., 2009)	Rural France	1718	Ph	5% Any DR 1% Macular Oedema

UKPDS: UK Prospective Diabetes Study

Comparative studies between ethnic groups in Europe shows that sight-threatening complications of diabetes mellitus affect racial and ethnic minority populations disproportionately (table 1.7). Earlier studies on the ethnic variations in the prevalence rates of DR are conflicting. As early as 1987, Cruickshank et al reported no difference

in prevalence of mild DR between West Indians and Caucasians in UK and between West Indians in UK and Jamaica based on undilated fundus examination. However, since then the reports have been conflicting. In the U.K., blacks had an equal risk of retinopathy after adjustment for age (Cruickshank and Alleyne, 1987), and Asians had a lower risk after adjustment for risk factors like smoking or treatment.

Table 1.7: Inter-ethnic comparison of prevalence of DR in Europe

Author Year	**Ethnic groups**	**N**	**Methods of examination Ph, O**	**Prevalence of DR**	**Prevalence of MO**	**Prevalence of STDR**
(Chaturvedi et al., 1996a)	Caucasian Afro-Caribbean	889 583	Ph	37% 33%		4% PDR 1% PDR
(Das et al., 1994)	Caucasian South Asia	2241 73	O	17% 23%	- -	- -
(Raymond et al., 2009)	Caucasian South Asia	614 421	Ph	37% 45%	8% 13%	16% 12%

The prevalence of T2D is three to five times as prevalent in the South Asians and African-Caribbeans in UK compared to the Caucasians (Riste et al., 2001). Table 1.7 highlights the increased prevalence of DR and CSMO in South Asians in UK compared to the Caucasians. The reports on the African-Caribbean are conflicting. However, African-Caribbean people with diabetes have wider retinal arterioles that may contribute to enhanced microvascular damage in this ethnic group (Mahal et al., 2009). The maximal hyperaemic response of the microvascular to heat and post ischemic response is also significantly attenuated in African-Caribbeans compared to the Caucasians (Strain et al., 2005).

United States

Epidemiologic studies from the US over the past 25 years have provided the most data on the prevalence, natural history and its associated risk factors for diabetic retinopathy. The prevalence of DR in Non-Hispanic whites in the US is similar to the rates reported in the whites in Europe. Approximately 40% have evidence of retinopathy, and 8% have sight-threatening disease at any time (Kempen et al., 2004). In persons without retinopathy, studies suggest that the risk or incidence of new retinopathy is between 5% and 10% per year. One of the landmark epidemiologic studies WESDR identified the key risk factors for diabetic retinopathy in the 1980s: longer duration of diabetes, hyperglycaemia, and hypertension. These observations led to the major clinical trials that have conclusively proven the importance of adequate control for glycaemia and blood pressure levels to prevent visual loss from diabetic retinopathy (UKPDS, 1998b, UKPDS, 1998a). Findings from WESDR and subsequent epidemiologic studies have been used widely to develop guidelines for patient care around the world. The WESDR, a population-based cohort study of diabetes in which participants were first examined in 1980-82, showed that in persons with T2D, the prevalence of diabetic retinopathy ranged from 29% in those with diabetes for less than 5 years to 78% in those with diabetes for over 15 years (Klein et al., 1984c). The few studies conducted in more contemporary populations suggest significantly lower prevalence of diabetic retinopathy compared to WESDR, although differences in study design, population characteristics, and definitions of diabetes and retinopathy between earlier and newer studies make it difficult to draw definitive conclusions.

The main population groups in the US are non-Hispanic Whites, Hispanics, African-Americans and Asian Americans. Data on Native American Indian population is also available.

In the US, the most common non-Caucasian ethnic groups include Hispanics Latinos, African-Americans, Chinese and Pacific Islanders and Native Indians.

A comparative study between ethnic groups (table 1.8 and 1.9) shows that the Hispanic and the African-American have a higher risk of clinical significant macular oedema.

Table 1.8: shows the studies in different ethnic groups in the US

Author and year	**Ethnic group**	**Sample size**	**Methods of examination Ph, O**	**Prevalence rate**
(Kahn and Milton, 1980)	Predominantly Caucasian	2477	Ph+O	3.1% Any DR
(Klein et al., 1984c)	Predominantly Caucasian	1370	Ph	54% Any DR 9% PDR
(Klein et al., 1992)	Predominantly Caucasian	416	Ph	68% Any DR 11%PDR 11% Macular Oedema
(Nagi et al., 1997)	Pima Indian	991	Ph	38% Any DR
(Schulz et al., 1997)	Oneida Indian	345	O	9% Any DR
(Smith et al., 2007)	Vanuatu	83	Ph	52.9% Any DR 1% PDR

The Hispanic/Latinos comprise 15.1% of the population of the United States. The prevalence of DR and MO in Latinos ranges from 30 to 50%. The prevalence of DR in Hispanics has not changed significantly over time. The prevalence of DR in Hispanics was 41.8% compared to 54.1% in non-Hispanic whites in the San Luis Valley Study

conducted from 1984-1992 (Hamman et al., 1989). Data from the recent Los Angeles Latino Eye Study (LALES), which comprised of only Latinos ≥ 40 years, showed an overall prevalence of 46% (Varma et al., 2004). Although there are noted ethnic differences in the phenotype of DR, large scale population based studies are needed to confirm this observation. Several studies show a prevalence of hard exudates in the Black population and a prevalence of intra-retinal haemorrhages in the Latino population (Klein et al., 1992, Lim et al., 2008a, Varma et al., 2004). It is also interesting to note that the severity of DR aggregates in families rather than the presence of DR itself in a study on Mexican- American T2D siblings of probands with DR (Hallman et al., 2005).

The meta-analysis of eight major US epidemiological studies conducted by the Eye Diseases Prevalence Research Group (Kempen et al., 2004) also revealed a significant prevalence of MO in the ethnic minority populations of the studies in comparison to the non-Hispanic whites. The prevalence of MO ranged from 1.2% to 5.1% in studies composed of non-Hispanic whites to 8.9% in a study composed of Hispanics (no risk factor adjustment made) (Kempen et al., 2004).

One of the major studies exploring the issue of MO was the Multi-Ethnic Study of Atherosclerosis (MESA) (Wong et al., 2006). Little or no cardiovascular disease was found in this diabetic population and the study revealed the prevalence of DR in this cohort to be 33.2%, with CSMO accounting for 5.6% and sight-threatening retinopathy accounting for 7.9%. However, ethnicity was not a risk factor when adjusted for other predictive variables, such as blood sugar and blood pressure. This indicates that a differential susceptibility to risk factors does not exist between ethnic groups in a relatively healthy T2D population.

In contrast, the Veterans Affairs Diabetes Trial (VADT) study where cardiovascular disease was found in 40% of their populace at baseline revealed an increased prevalence of sight threatening DR in Hispanics compared to non-Hispanic whites. This difference was unaccounted for by inter-ethnic differences of the established risk factors, for example, duration of diabetes, age, glycaemic control and blood pressure. There was also an ethnic variation in the increased prevalence of CSMO in Hispanics (3 times) and the Blacks (2.5 times) in comparison to the non-Hispanic white population. The presence of CSMO was also independently associated with the severity of DR, diastolic blood pressure and a history of amputation (Emanuele et al., 2009).

The annual incidence of retinopathy for the Latino study (LALES) (Varma et al., 2004) (7.1%) was similar to the rates found in the WESDR (8.6%) (Klein et al., 1989c), the black Barbados Incidence Study of Eye Diseases (Leske et al., 2003) (7.5%) but higher than the rates found in the non-Hispanic white Blue Mountains Eye Study (BMES) (Cugati et al., 2006) (4.4%), the non-Hispanic white Australian Diabetes Obesity and Lifestyle (AusDiab) (2.78%) (Tapp et al., 2003) and the Liverpool eye study (0.8%) (Broadbent et al., 1999). The LALES study also reported that the 4 year incidence of DR was 34%, MO was 5.4% and CSMO was 7.2% (Varma et al., 2004). A higher incidence of DR was associated with the younger age group and longer duration of diabetes. However, a higher incidence of MO was only associated with longer duration of diabetes ($p=0.004$) (Varma et al., 2010a).

For presenting binocular visual impairment (VI) and blindness, the 4 year incidence was 2.9% and 0.3% respectively. Also with respect to best corrected VI and blindness, the 4 year incidence was 1.2% and 0.3% respectively (Varma et al., 2010b). Cultural and socio-economic disparities may have a role to play in this finding. Appiah et al in 1991

suggested that late diagnosis of diabetes in the Latino and Black population may account for the increased severity of DR at presentation (Appiah et al., 1991). In the USA, Latinos account for one of the highest rates of visual impairment secondary to eye disease. The prevalence and risk of undetected eye disease is unquantifiable. This population access to health care is at best inconsistent and unequal and this may influence disease statistics. For example, in the Proyecto VER (Vision Evaluation and Research) study, there was a higher prevalence of PDR in the low income group which may have reflected use of healthcare (West et al., 2001). In contrast, no association was found between socio-economic status and DR in a cohort of Mexican-Americans and Caucasians with adult onset diabetes in Texas (Haffner et al., 1989).

African-American (Blacks)

Approximately 13% African-American have diabetes (Chin et al., 1998) with the prevalence and incidence of diabetes being at least twice as high as the white Americans (Centers for Disease Control and Prevention (CDC)., 2010, Harjo et al., 2010).

Earlier prevalence studies on DR in this group are limited by methodological flaws (Baker et al., 1998). The Barbados Eye Study (BES) reported a prevalence of 25.8% in the black Caribbean population (Leske et al., 1999a) while the National Health and Nutrition Examination Survey (NHANES) III reported a prevalence of 26.5% for African-Americans compared to 18.2% in non-Hispanic white Americans aged 40 or older (Zhang et al., 2008b). Nevertheless, reliable estimates based on contemporary studies on inter-ethnic comparisons also reveal significantly higher rates of DR in African-Americans. Data from the Atherosclerosis Risk in Communities Study (ARIC) indicate a prevalence of diabetic retinopathy of 27.7% in African-Americans as

compared with 16.7% in white Americans (Klein et al., 2002b) while the Cardiovascular Health Study (CHS) in adults aged 65 years and older in US reported a prevalence of 35.4% for African-Americans compared to 16.0% for white Americans (Klein et al., 2002a). The Veterans Affairs Diabetes Trial (VADT) noted that both the prevalence and severity of DR were more frequent in African Americans compared to non-Hispanic whites (29% versus 22%) and these differences could not be accounted for by an imbalance in traditional risk factors such as age, duration of diagnosed diabetes, hyperglycaemia, and blood pressure (Emanuele et al., 2005). The MESA also showed that the prevalence of any DR was higher in the African-American compared to the non-Hispanic whites (36.7% versus 24.8%) but observed that race was not an independent predictor of retinopathy (Wong et al., 2006). Recently, a 2-field non-mydriatic screening programme noted a prevalence of DR to be 15.7% with no difference between ethnic groups in an urban multi-racial population (Lim et al., 2008a). These prevalence rates may be an underestimate due to poorer ascertainment levels and higher mortality rates in African-Americans compared to their white counterparts (Baker et al., 1998).

Table 1.9: (continued over two pages) Diabetic retinopathy in Hispanics and African Americans

Author Year	Ethnic Groups	N	Methods of examination Ph, O	Prevalence of DR	Prevalence of MO	Prevalence of STDR
(Harris et al., 1998)	Non Hispanic Blacks Mexican Americans Non-Hispanic whites	261 308 345	Ph	27% 33% 18%	- - -	2% PDR 6% PDR 1% PDR
(Harris et al., 1999)	African American Non-Hispanic whites	57 49	Ph	50% 19%	- -	- -
(Hamman et al., 1989)	Hispanics Non-Hispanic whites	166 85	Ph	43% 48%	- -	7% PDR 5% PDR
(West et al.,2001)	Mexican-American	1044	Ph	48%	2%	6% PDR
(Emanuele et al., 2005)	African American Hispanic Non Hispanics Whites	2402 36 779	Ph	20% 35% 47%		29%* 36%* 22%* (*ETDRS score > 40)
(Varma et al., 2004)	Hispanics	1217	Ph	47%	10%	12% PDR 6% CSMO
(Wong et al.,	Whites African-	153 289	Ph	24.8% 37.4%	3% 11%	3% PDR 4% PDR

Author Year	Ethnic Groups	N	Methods of examination Ph, O	Prevalence of DR	Prevalence of MO	Prevalence of STDR
2006)	American Hispanics Chinese Americans	235 101		37.4% 25.7%	11% 9%	4% PDR 5% PDR
(Lim et al., 2008a)	African American Hispanic Non Hispanics Whites	216 229 127	Ph	14% 17% 14%		

More importantly, the prevalence of CSMO was 8.63% in the BES, twice higher than reported in the white population reported at the same time points (Klein et al., 1992, Klein et al., 1995b, Leske et al., 1999a). Similarly, 15.6% African-Americans were noted to have CSMO compared to 6.3% non-Hispanic whites in the Veterans Affairs Diabetes Trial (VADT) (Emanuele et al., 2005) while the Multi-Ethnic Study of Atherosclerosis (MESA) showed that the risk of CSMO is approximately 5 times in African-American than whites (11.1% versus 2.7%) (Wong et al., 2006).

There is paucity of data on incidence of DR in this group. Harris et al observed DR in 50% of African-American compared to non-Hispanic white participants (19%) after 4 years follow-up but these differences could not be explained by differences in risk factor profile (Harris et al., 1999). The BES showed that the 9-year DR incidence was 39.6% (38.0% for minimum, 9.0% for moderate, and 2.6% for severe/proliferative DR). Incidence tended to increase with diabetes duration and treatment. Of persons with pre-

existing DR at baseline, 8.2% progressed to proliferative DR. The CSMO incidence was 8.7%, and it increased with diabetes duration, accounting for most of the overall incidence of sight-threatening DR (Leske et al., 2006).

On the whole, African-Americans have higher rates of macro- and micro-vascular complications of diabetes (Harris et al., 1993) and are more susceptible to the known risk factors of DR (Harris et al., 1999, Harris et al., 1998, Wong et al., 2006). So other gene-environmental interactions have to be explored. In addition, familial clustering evidenced by increased risk of severe diabetic retinopathy among family members with diabetes (Looker et al., 2007), in siblings of affected individuals (approximately 3-fold increased risk) and the moderate heritability of diabetic retinopathy risk (0.52) have to be further investigated (Arar et al., 2008).

Native American-Indians

There are more than 2 million native Americans comprising more than 500 tribal organizations (Carter et al., 2000). A comprehensive review of complications of T2D in indigenous population revealed that high prevalence rates of diabetic retinopathy were seen for all populations with available data (Naqshbandi et al., 2008). A high rate of 40% for DR was observed in the Alberta First Nations of Canada (Oster et al., 2009) and 37.8% in Pima Indians in Arizona (Nagi et al., 1997). In the James Bay Cree in Canada, the prevalence of DR was 34% with the prevalence of NPDR and PDR being 28.5% and 2.5% respectively (Maberley et al., 2002). In Manitoba, Canada, the prevalence of diabetic retinopathy in First Nations and Métis was 17.0% (Oster and Toth, 2009). One study found a retinopathy prevalence of 24% of Carolinians and Chamorros in the Commonwealth of the Northern Mariana Islands (Zimmet et al.,

1984). The Cherokee Indians in the United States were reported to have a rate of 24.6% (Farrell et al., 1993). Two studies were carried out with the Oklahoma Indians and indicated prevalence rates of PDR and NPDR of 1.1% and 11.5%, respectively, while a follow-up later that year showed PDR and NPDR rates of 3.6% and 21.1% (Lee et al., 1992, West et al., 1982), respectively. The Strong Heart study showed that the Dakota Sioux Indians also had a high prevalence of DR (45.3%) (Berinstein et al., 1997). Elevated serum and urinary sialic acid and microalbumin concentrations have been strongly linked to the presence of microvascular complications in this ethnic group (Nayak and Bhaktha, 2005). Limited access to healthcare is also observed to be an important cause of undiagnosed and increased prevalence of microvascular and macrovascular complications in Alberta First Nations individuals with diabetes living on reserves (Oster et al., 2009).

Asian-American and Pacific Islanders

The Asian Americans are a diverse community of partial or full Asian heritage. They have the highest educational attainment level and median household income of any racial demographic in the US and they are heavily urbanized. It is projected that by 2070, the Asian population will reach 11% of the total population of the US.

The Pacific Islanders are the indigenous population of the three regions known as Melanesia, Micronesia and Polynesia. More than 50% of the population is overweight and over 40% suffered from diabetes, cardiovascular disease and hypertension resulting in high premature mortality rates.

Analyses of data from the Behavioural Risk Factor Surveillance System comparing Asian Americans/Pacific Islanders with Whites and diabetes showed that the rates of

DR in this diverse community is 2.2 times the rates reported in Whites despite comprehensive adjustment of risk factors including socio-economic status. Reports as early as 1991 indicate a high prevalence of DR among the Polynesian Western Samoans indicating that urbanization may not be the driving force for the high prevalence in this group (Collins et al., 1995). Similarly, Fijian and Indians living in the Fiji islands had more severe and more prevalent DR than Australian Indians. Differences in healthcare systems may be an important factor implicated in this difference as delay in the diagnosis of diabetes as well as poor glycaemic control are possible factors in Fiji (Brooks et al., 1999).

The overall prevalence of DR has been increasing since 1990 and the current prevalence rate is 21.9%. An increase in public awareness and improved healthcare facilities may have led to the increased diagnosis of retinopathy in subjects with either known or unknown diabetes.

ASIA

The remarkable economic achievement in Asia in the last 30 years has resulted in a great improvement in living standards and prolongation of life expectancy. The alarming prevalence of T2D in Asia is a public health and economic threat. The highest numbers of estimated cases of diabetes in 2000 and 2030 are in India and China. Most of the studies on the prevalence of DR are from India and China with a recent surge of reports from China, South East Asia and the Arab countries.

Indian Subcontinent

It is estimated that nearly 80 million people in India will have diabetes by the year 2030 (Wild et al., 2004). Several reports have suggested that T2D in Indians may differ from

their European counterpart in several aspects including younger age of onset, obesity, insulin resistance and genetic predisposition (Rema et al., 1996, Rema et al., 2000, Rema and Mohan V, 2002). Moreover, the demographic right shift of the population, urbanization and the disparity in access to healthcare may all have implications on the prevalence of diabetes and its complications in this region. Although cataract and uncorrected refractive errors remain the major causes of blindness in this region (Dandona et al., 1999), the impending diabetic epidemic in the subcontinent pose a significant public health concern (Namperumalsamy et al., 2009).

There are several clinic-based and population derived studies on DR in South Asia particularly focused on the urban-rural disparities and risk factors. Table 1.10 shows the population based studies from India.

Table 1.10: Prevalence of diabetic retinopathy in India

Author /Year	**Diagnosis of diabetes**	**N**	**Methods of examination Ph, O**	**Age (years)**	**Prevalence of DR (%)**
(Dandona et al., 1999)	OGTT	2522	O	31-86	22.4
(Ramachandran et al., 1999)	Self-reported	3010	O	52±9.7	23.7
(Narendran et al., 2002)	RBS>120mg /dl	5212	O	61.70 ± 8.0	26%
(Rema et al., 2005)	OGTT	1529	Ph	52±11	17.6
(Raman et al., 2009)	FBS>126mg /dl	1414	Ph	56.3±10	18
(Namperumalsamy et al., 2009)	FBS>126mg /dl	2802	O	47.0±12.7	12%

As undiagnosed diabetes remains a major challenge in this region, clinic-based studies are referral-biased and are not always an accurate reflection of the prevalence in this

population (Rema et al., 2005). Clinic-based detection of DR show higher prevalence rates compared to targeted screening (Agarwal et al., 2006). However, it is interesting to note that no significant difference in prevalence was noted between clinic-based and population-based screening programmes in the Hoorn Screening Study reiterating the differences in the healthcare systems (Spijkerman et al., 2003). The diagnostic criteria for diabetes also differ between studies and reports are based on self-reported diabetes, fasting blood sugar and/or oral glucose tolerance test. Similarly, only recent studies have utilized retinal photography as screening tools (Raman et al., 2009, Rema et al., 2005).

The prevalence of DR in known diabetes appears to be lower than that reported among Europeans. In contrast to the studies from Europe and US, studies that used retinal photography reveal a lower prevalence rate of DR of 18% (Raman et al., 2009, Rema et al., 2005).

Similarly, the prevalence of DR among newly diagnosed diabetes in India is low (5-7% compared to studies from neighbouring areas such as Nepal (19.3%) (Paudyal et al., 2008), Sri Lanka (15%) (Weerasuriya et al., 1998) and Pakistan (15%) (Wahab et al., 2008). In the United Kingdom Prospective Diabetes Study (UKPDS, 1994, Kohner et al., 1998) done two decades ago show that the prevalence of DR at the time of diagnosis was higher in South Asians (17.5%) compared to the Europeans (7.9%). Most of the other population based Western studies report a prevalence rate of 7%-11%. This may again reflect the differences in management of diabetes between regions. It has been observed that the actual onset of diabetes occurs much earlier (could be 9 to 12 years) before it is clinically presented and diagnosed (Harris et al., 1998). So earlier diagnosis

and optimal treatment of diabetes will potentially reduce the prevalence of DR (UKPDS, 1998a).

However, the rate of CSMO is high. The Sankara Nethralaya-Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS) study on 1414 T2D reported that one third of the patients had any MO while 6. 27% had CSMO (Raman et al., 2010b). In the Chennai Urban Rural Epidemiology Study (CURES), the prevalence of MO among the known diabetic subjects was 6.3% and 1.1% among the newly diagnosed diabetic subjects (Rema et al., 2005). Maculopathy was noted to be as high as 17.6% in a study from Pakistan (Jamal-u-Din et al., 2006) on predominantly T2D.

The two major known risk factors, the length of exposure to hyperglycaemia and the degree of glycaemic control for DR, are also observed in the studies from South Asia, consistent with findings in the Caucasian counterparts. The CURES study revealed that for every 5-year increase in duration of diabetes, the risk for DR increases by 1.89-fold, whereas a 2% increase in HbA1c results in a 1.7-fold increase in risk for DR (Rema et al., 2005).

In the UKPDS, the risk reduction in eye complications for every 1 per cent decrease in HbA1c was 40% for DR, 25% for STDR and 15% for blindness (UKPDS, 1998a).

Since microvascular complications are directly related to the duration of diabetes and the age of onset of diabetes is earlier in South Asians, it is intriguing that the DR rates are lower than the South Asian counterparts in the western world. Although underestimation and survival bias may be important reasons for these differences, genetic susceptibility indicated by familial clustering (Radha et al., 2002) and the interaction/balance of susceptibility and protective genes (Uthra et al., 2010) with the

environment may also be important parameters that need to be investigated. Environmental factors including the characteristic dietary ingredients in South Indian diet such as curcumin has been postulated to decrease the oxidative stress in diabetes (Premanand et al., 2006).

Urbanisation, obesity and adaptation to Western diet may also influence the rates of DR in urban population and the emigrant Indian population in the West. Studies in India have focused on urban-rural differences in DR because approximately ¾ of the area of India is rural (Namperumalsamy et al., 2009) and westernization is more localised to the urban area. The prevalence of DR in South Asians is more prevalent in those who live outside the Indian sub-continent (Raymond et al., 2009) and in urban cities (Raman et al., 2009) compared to rural population (Namperumalsamy et al., 2009).

Another important observation is that the prevalence of STDR is also higher in the South Asians who live in the developed countries (Raymond et al., 2009) compared to their counterparts in India. The AdREM study also noted a higher rates of DR in Asians compared to Caucasians (Stolk et al., 1995). These findings may correlate to their changes in life-style characteristics and consequent susceptibility to the risk factors for DR or merely relate to better case ascertainment and different classifications used.

Although diabetes is more likely to develop in people with higher socioeconomic status, this was not a risk factor for DR in the SN-DREAMS study that used sampling of socio-economic status based on multiple indices. However, studies that defined socio-economic status based on annual income found that the low-income group subjects showed a trend to lower prevalence of diabetes and DR (Ramachandran et al., 2002) in

contrast to the western population studies where diabetes is reported to be higher among the lower economic group (Connolly et al., 2000).

The age specific prevalence of DR show a similar trend to Western counterparts with an increased prevalence in the sixth decade compared to the previous decade with an ensuing decline in rates following that. Similar trends are also observed by the Eye Diseases Prevalence Research Group's report on the prevalence of DR in the United States, the Barbados Eye Study, the Beaver Dam Study, and the Wisconsin Epidemiologic Study of Diabetic Retinopathy and this pattern may be partly explained by survival bias (Kempen et al., 2004, Klein et al., 1984c, Klein et al., 1992, Leske et al., 1999a, Zhang et al., 2010). The prevalence of DR is almost twice more in those subjects who develop diabetes before the age of 40 years than those who develop it later (33.3% versus 16.5%) (Raman et al., 2011).

A male preponderance of DR has been reported in reports from India (Raman et al., 2009, Rema et al., 2005, Dandona et al., 1999). This observation is in agreement with other studies (Kohner et al., 1998, Nagi et al., 1997). A gender effect has also been reported in the prevalence of diabetes with UK Asian males up to the age of 60 years showing a higher prevalence of diabetes than females (Sharp et al., 1964). In older patients, the prevalence rates in males and females are similar, possibly as a result of an increase in mortality in Asian men from cardiovascular disease (Balarajan, 1998). However, contemporary data on this aspect is required to merit further investigation.

The prevalence of DR among subjects with diabetes was higher in those receiving insulin treatment in studies from India (Raman et al., 2009, Rema et al., 2005) again similar to the findings observed in the Western studies (Klein et al., 1992, Kohner et al.,

1998). This is probably because of more severe diabetes with poor glycaemic control. Similar findings were reported in the study of Pima Indians, and in the Beaver Dam study (Raman et al., 2009, Klein et al., 1992, Nagi et al., 1997). In contrast, in the WESDR, it was shown that among the older diabetic subjects, after adjustment for HbA1c level, there was no association of insulin treatment with either the incidence or progression of retinopathy.

Other reported risk factors for the prevalence of DR in the South Asian studies included anaemia (Ranil et al., 2010), isolated abdominal obesity and increased waist-hip ratio in women (Raman et al., 2010a). Hyperlipidemia (elevated serum cholesterol, serum triglycerides and low density lipoprotein (LDL) is observed as a risk factor for MO in two population based studies (Raman et al., 2010b, Rema et al., 2006). The UKPDS showed that the incidence of retinopathy was associated with systolic blood pressure but hypertension did not play a major role in the CURES study (Pradeepa et al., 2008). Akin to other western studies, prevalence of PDR was higher in patients with proteinuria compared to microproteinuria (Mohan et al., 2000). The CURES study also demonstrated that intima media thickness and arterial stiffness are significantly associated with DR (Rema et al., 2006).

Lastly, genetic susceptibility and familial clustering of DR have also been reported in South Indian population. Siblings of the probands with DR had 3.5 times higher risk of developing retinopathy (Rema et al., 2002).

CHINA

The World Health Organization estimates that over 40 million Chinese will have diabetes by 2030 (Wild et al., 2004). Studies in different Chinese populations with

similar genetic characteristics have shown substantial variations in the prevalence rates of diabetes (Chang et al., 2000). The prevalence rates of diabetes are consistently higher in Hong Kong and Taiwan than Mainland China regardless of diagnostic criteria or study periods. Moreover, the percentage of undiagnosed diabetes is 68.6% in Mainland China as compared to 52.6% in their counterparts in Hong Kong and Taiwan. Chinese in Hong Kong and Taiwan generally live in an urbanised environment (Wong and Wang, 2006) while over 800 million (64%) live in economically deprived rural regions in China (Wang et al., 2009). So as in the Indian subcontinent, it is important to note the regional variations of DR in China.

Data on DR in the Chinese population in Asia are mainly from Hong Kong, Taiwan, Mainland China and comparative studies are available on Singapore Chinese, Chinese Mauritians and Chinese Americans. In Taiwan, the prevalence of DR was reported as 35.0% while the prevalence of DM for newly diagnosed diabetics was 28.3% (Chen et al., 1992). The two studies on incidence of DR in Hong Kong Chinese patients show the prevalence of DR to be 28.4% and 39.2% baseline respectively (Tam et al., 2005, Tam et al., 2009, Wang et al., 1998). The recent Beijing Eye Study that covered both rural and urban population reported the prevalence of DR among Chinese patients aged 40+ years with a self-reported diagnosis of diabetes to be about 37% and vision-threatening retinopathy in 5% of the subjects (Xie et al., 2009). Both DR and MO in subjects with known diabetes mellitus were significantly more common in the rural group. The Handon Eye Study in rural China reported the highest prevalence rate (43.1%) (Wang et al., 2009). Although better case ascertainment should be taken into account, prolonged exposure to poor glycaemic control, undiagnosed diabetes and high rates of hypertension (74%) in rural China are possible explanatory factors.

In a multiethnic study in Mauritius, the Chinese Mauritians with known diabetes had similar rates to the Indians and Creoles in Mauritius. However, the prevalence rates of DR (43.8%) were similar to rural Chinese population in Mainland China (Dowse et al., 1998, Wang et al., 2009).

The MESA study provided the data for the Chinese Americans. The prevalence among the Chinese sample (25.7%) was similar to whites (24.8%) in the MESA. So there is a significant regional variation in the prevalence of DR among the Chinese population which may be partly explained by differences in health care access. However, gene-environmental interactions may also provide important clues to these variations.

The prevalence rate in the newly diagnosed subjects in Taiwan was 21%, which was similar to those found in newly diagnosed Hong Kong Chinese (21.9%). These rates are lower than rates in rural China (33.5%) (Chang et al., 1990, Chen et al., 1992). It is striking to note that the prevalence rate of DR in newly diagnosed patients were higher within 12 months of diagnoses than when routinely screened for DR at point of diagnoses of diabetes. Both the Chinese subjects in the Beijing study (Liu et al., 2002) and the Hong Kong study (Wang et al., 1998) showed a prevalence rate of 21% at 12 months from diagnoses. In contrast, the Da Qing study in which 110 660 individuals were screened for diabetes by glucose tolerance tests and amongst 423 newly diagnosed diabetic patients, retinopathy was found in 15.4% (Hu et al., 1991) . These studies suggest that the prevalence of DR increases within the first year of diagnoses. However, Dowse et al (Dowse et al., 1998) noted that there is a significant association between current age and retinopathy in the newly diagnosed study and suggested that current age might behave as a surrogate marker of diabetes duration in these newly diagnosed patients. Liu DP et al (Liu et al., 2002) showed that the age of onset of hyperglycaemia

is much younger in the Beijing Chinese (36 years) compared to the Fijian Indians (37 years) while the age of onset of hyperglycaemia in the Anglo-Celtic patients in Australia was much older at 54 years. This may partly explain the ethnic differences in prevalence and severity of DR (Harris et al., 1998, Liu et al., 2002).

Females and lower socioeconomic groups were more common in the newly diagnosed group. More females are undiagnosed than males indicating social, hormonal or genetic basis.

Similar to the studies in South Asia, the Beijing eye study on the survey of visual impairment in the Chinese population reported diabetic retinopathy as a minor cause of blindness (low vision 0%/ blindness 7.7%) (Jonas et al., 2009).

The incidence and progression of DR are not significantly different between Chinese and Caucasian populations. Progression to sight-threatening retinopathy was more common (7.9% versus 0.7%), and occurred more rapidly (mean 1.5 years versus 2 years) in eyes with baseline retinopathy than that without. High baseline glycosylated haemoglobin is observed as a predictor for disease onset and progression (Chen et al., 1995, Tam et al., 2005, Tam et al., 2009).

Despite different study procedures and populations, the prevalence of DR mirror the regional prevalence rates of diabetes with higher rates of diabetes in Hong Kong and Taiwan compared to Mainland China. Nevertheless, there is an upward trend within Mainland China too. The risk factors for DR are similar to those demonstrated in the Caucasian population and include duration of diabetes, age at onset of diabetes, age at examination, type of diabetes treatment, control of diabetes hypertension, proteinuria, serum creatinine level, serum cholesterol level and BMI (Xie et al., 2009). Subclinical

hypothyroidism in the Chinese population has been associated with sight threatening DR (Yang et al., 2010).

The increasing prevalence and the urban-rural differences are often attributed to urbanization especially increasing obesity, sedentary lifestyle and dietary transition towards a high-fat, high-energy-density and low-fibre diet.

South East Asia

Asian Malays are the third largest ethnic group in Asia, including 300 to 400 million people. The overall prevalence of DR was 35% and approximately 10% have sight threatening DR. The presence of DR was also associated with longer diabetes duration, poorer glycaemic and blood pressure control, and lower levels of total and LDL cholesterol. Systemic vascular diseases, including stroke and chronic kidney disease were associated with sight threatening DR (Wong et al., 2008a).

A similar rate was reported in Thailand diabetes registry project. The authors found the factors associated with DR were duration of diabetes, HbA1c level, systolic BP and diabetic nephropathy (Chetthakul et al., 2006a).

Middle-East

The number of people with diabetes mellitus in the Middle East is expected to grow three times from the 2000 to 2030 with approximately 60 million estimated to have the disease by 2030 (WHO, 2005). Numerous studies on DR in Middle East inhabitants have been published in recent years. They mainly underscore the great disease heterogeneity in North African and Asian Arab countries, probably reflecting the genetic and socioeconomic heterogeneity of the populations in these regions as well as

environmental differences. While direct comparisons with other ethnic groups are lacking, the existing data provide some indications that Arabs frequently have high rates of DR. The cross-sectional survey of DR in the United Arab Emirates has reported variable prevalence rates from a low of 19.0% (Al-Maskari and El-Sadig, 2007) to high of 54% (Saadi et al., 2007). Other studies in the region have reported variable rates of DR: Qatar (23.5%) (Elshafei et al., 2010), Saudi Arabia (16.7%- 31%) (Alwakeel et al., 2008a, Khan et al., 2010, El-Asrar et al., 1998), Oman (14.39% - 42%) (Khandekar and Mohammed, 2009, el Haddad and Saad, 1998), Egypt (42%) (Herman et al., 1998), Iran (39.3%) (Golbahar J.Rahimi M.Tabei M.B., 2008, Manaviat et al., 2008, Manaviat et al., 2004, Javadi et al., 2009), Turkey: (45.5%) (Sehnaz Karadeniz Z., 2007), and Lebanon (35%) (Salti et al., 2009). A systematic review of studies from Iran showed a prevalence of DR in known diabetics and newly diagnosed diabetes to be 30-40% and 9-11% (Amini and Parvaresh, 2009).

Visual impairment due to DR in this region highlights the need for resource allocation for systematic screening and timely treatment of this potentially avoidable complication (Chiang et al., 2010). Although the prevalence of sight threatening DR is high in this region, public awareness of eye complications remain limited (Bamashmus et al., 2009, Salti et al., 2009, Javadi et al., 2009). Gender inequality for eye care is also an issue in this region although the disparity has lessened in the last decade (Khandekar and Mohammed, 2009).

The prevalence of DR in newly diagnosed diabetes in Kuwait was 8%. The substantial heterogeneity in reported prevalence of retinopathy may partly be real, for example due to differences in the age structure of different population, but may again be due to differences in study methodology and population sample. The presence of

microalbuminuria was highly significantly associated with DR in the UAE study population.

SUB-SAHARAN AFRICA

African people with diabetes have a high complication burden, which are both difficult to treat and prevent (Gill et al., 2009). Ophthalmoscopy based studies reveal a prevalence rate of DR to be about 15-17% (Erasmus et al., 1989, Rotimi et al., 2003). However, a South African multi-ethnic photography based study showed a higher prevalence rate with no differences between ethnic groups (Black African 37%; Europeans 41%; Indians 37%). However, severe retinopathy was more frequent in African and Indians (Kalk et al., 1997). In another study that compared the rates between black African and Indians, the rates of DR were 68.8% in blacks versus 59.2% in Indians. The mean age of onset was earlier in Indians but the blacks had an earlier onset of retinopathy from time of diagnosis. Duration of diabetes and systolic hypertension were significantly associated with DR with Blacks being more prone to hypertension than Indians (Motala et al., 2001).

AUSTRALASIA

Studies from Australia dates back more than 3 decades and provides encouraging evidence of the impact of health education and resultant better glycaemic control on the prevalence and incident DR (Cugati et al., 2006, McCarty et al., 2001, Muller et al., 2007). The earliest clinic-based study of DR in Australia was the Newcastle Diabetic Retinopathy Study (1977 to 1988). The prevalence rate of DR was 35%. Since then population based studies have reported lower rates (Mitchell, 1985). The Australian Diabetes, Obesity and Lifestyle Study was a nationally representative population-based

study of 11,247 people aged ≥25 years, from 42 randomly selected urban and rural areas of Australia that reported a prevalence rate of DR of 21.9% in those with known diabetes and 6.2% in those with newly diagnosed diabetes (Tapp et al., 2003). The Blue Mountain Eye Study (BMES) is an urban based population study that was carried out in residents aged 49 years or older in Sydney in 1992–1994. The prevalence rate of DR was 35.5 %. The 5 year cumulative incident data of DR was 22.2%, lower than the 4 year cumulative incidence of 32.7% reported for non-insulin-treated predominantly Caucasian subjects with diabetes in the WESDR cohort and a clinic based Swedish study (Cugati et al., 2006, Mitchell et al., 1998). This may be a true difference due to better public awareness and better glycaemic control in Australia as elucidated in the Melbourne Visual Impairment Project in 2003 that reported the 5-year incidence of DR to be 11% with most patients with sight threatening disease receiving treatment (McCarty et al., 2001). However, similar lower incidence rates have also been reported in other ethnic groups from Japan, Korea, Taiwan, Mauritians and non-Hispanics (Chen et al., 1992, Kim et al., 1998, Tapp et al., 2003, Tudor et al., 1998, Morisaki et al., 1994) where suboptimal glycaemic control remains an issue.

The Australian Aborigines has the highest reported incidence of vision-threatening retinopathy in Australia and one of the highest ever reported incidences of CSMO in the world (Jaross et al., 2003). The Katherine Region Diabetic Retinopathy Study on the Australian Aborigines in the northern territory of Australia highlighted that data on this indigenous population is hampered with small sample size and short follow-up (Jaross et al., 2003). Access to treatment for DR is a problem for the inhabitants of Fiji, Samoa and Tonga (Brian et al., 2010). However, it is interesting to note that the Darwin Region Urban Indigenous Diabetes Study observed no difference in prevalence rates of DR in

T2D in urban Indigenous Australians and the general Australian population despite poorer glycaemic control (Maple-Brown et al., 2008).

On the contrary, the Greek-born migrants in Australia have low rates of DR that cannot be explained by the effect of established risk factors for DR (Brazionis et al., 2010).

In the New Zealand population, the ethnic composition is predominantly European, the Polynesian population, consisting of indigenous New Zealand Maori and immigrants from the other Pacific Islands. The prevalence of diabetes and obesity in these Polynesians are 2-4 times higher than Europeans, with younger age of onset of diabetes, a genetic susceptibility to nephropathy and inadequate access to healthcare (Simmons et al., 1989, Moore and Lunt, 2000). A household survey showed that the overall prevalence rates of DR did not vary between the ethnic groups but the prevalence of moderate or severe retinopathy was significantly higher in the Polynesians (4.0% in Europeans, 12.9% in Maori and 15.8% in Pacific people) (Simmons et al., 1991). Recent data indicate that the Wellington regional retinal screening programme for DR has a good coverage of the people with diabetes with low rates of DR and sight threatening disease. However, the Maoris were under-represented (Frederikson and Jacobs, 2008). Nevertheless Te Wai o Rona: Diabetes Prevention Strategy recently reported that the rate of retinopathy in newly diagnosed diabetes is also low suggesting that case detection for diabetes in the community is improving, but that other strategies among those at risk of diabetes, including those promoting smoking cessation, will be needed to reduce the risk of renal disease among Maori with diabetes (Lim et al., 2008b).

1.5 Systemic risk factors for diabetic retinopathy

1.5.1 HbA1C and glycaemia control

Long term observational studies demonstrate that improved glycaemic control reduces the development and progression of existent retinopathy (DCCT, 1993). Both the Stockholm Diabetes Interventional Study (Reichard et al., 1991) (n= 102) and Diabetic control and complication trial (DCCT, 1993) (n= 1441) have demonstrated beneficial effects in delaying the progression of diabetic retinopathy with intensive diabetic control in type I disease: There was a fivefold reduction in the DCCT study at the end of 5 years, and a 25% reduction in the Stockholm study at the end of 7.5 years.

A similar trend of 8% reduction in progression of DR was observed in the UKPDS (n= 3867) study with intensive tight control for T2D over 10 years and in a more recent study the Action to Control Cardiovascular Risk in Diabetes (ACCORD) when HbA1c was less than 6% versus 7.0-7.9% at the end of 4 years (Chew EY et al, 2010) . There is paradoxical worsening of DR seen with intensive tight control in first few years but these acute lesions resolve with time and in the long term are better off with tight diabetic control (DCCT, 1993).

1.5.2 Hypertension

Diabetes and hypertension commonly co-exist in both T1D and T2D. In WESDR 17% of T1D had hypertension at baseline and 25% incidence at 10 years (Klein et al., 1996a). Similarly in T2D this is exceedingly common with a prevalence of 80 – 85% in cohort studies (O'Connell et al., 2010, Vijayakumar et al., 2009).

Studies have shown that angiotension converting enzyme inhibitors (ACE-I) such as lisinopril or the angiotensin II type 1receptor blocker: losartan, candersartan have

significant anti-angiogenic effect, independent of their effects on systemic BP (UKPDS, 1998b, Chaturvedi et al., 1998, Chaturvedi et al., 2008, Estacio et al., 2000). In T1D patients, antihypertensive treatment with angiotensin converting enzyme (ACE) inhibitors resulted in 23% reduction in the progression of retinopathy and progression to proliferative DR by 80% in type 1 normotensive diabetes (Chaturvedi et al., 1998). However, similar effects were not mirrored in the UKPDS and the ABCD study (UKPDS, 1998b, Estacio et al., 2000).

In T2D, in the UKPDS study, tight control of blood pressure (< 150/80) versus 'less' tight control (<180/105) resulted in a 34% and 47% reduction in significant deterioration of retinopathy and visual acuity at the end of 7.5 years respectively. This reduction was seen independent of glycaemic control and the drugs used to control hypertension mainly ACE inhibitors or β blockers. However there was no difference in the progression of DR between the groups assigned to a policy of tight BP (diastolic BP goal of 75 mmHg) control versus less tight BP control (diastolic BP goal of 80-89 mmHg) in Appropriate Blood Pressure Control in Diabetes (ABCD) Trial (n =470) over a period of 5.3 years (Estacio et al., 2000).

The Diabetic Retinopathy Candesartan Trials (DIRECT) which was placebo-controlled randomised controlled trial (RCT) studied the effect of candesartan in reducing the incidence and progression of DR in both T1D and T2D (Chaturvedi et al.,2008, Sjolie et al.,2008). The trial looked at role of candesartan in prevention (Prevent 1 & 2) and progression (Protection 1& 2) of DR in T1D and T2D respectively.

In DIRECT-Prevent 1 (n= 1421), the incidence of retinopathy was 25% in patients from no retinopathy in the candesartan group compared to (31%) in the placebo group of

T1D. In the DIRECT-Protect 1 study (n=1905) progression of retinopathy occurred in 13% in both the candesartan and placebo groups. Thus candesartan reduced incidence of retinopathy in T1D with no significant benefit on retinopathy progression.

The DIRECT-Protect 2 (n=1905) 17% of patients with T2D in the candesartan group had progression of DR compared to 19% in the placebo group, with regression of retinopathy of 19% in the candesartan group compared to 14% in the control group after a median follow up 4.7 years .

ACCORD eye study found no significant difference in progression of retinopathy in patients with intensive SBP (<120mmHg) versus less these intensive SBP (<140mmHg) at the end of 4 years (Chew EY et al, 2010). In summary uncontrolled and sustained high SBP (>140mmHg) in T2D and higher DBP (>80mmHg) in T1D are significant risk factors associated with both development and progression of diabetic microvascular complication but they cease to have significant impact after adequate control. British Hypertension Society recommends in diabetic patients initiation of antihypertensive drug therapy if systolic blood pressure (SBP) is sustained at ≥140mmHg and/or diastolic blood pressure (DBP) is sustained ≥90mmHg and optimal BP goals of SBP <130mmHg and DBP of <80mmHg (Williams et al., 2004a).

1.5.3 Age

Older patients with diabetes have a greater risk of visual impairment (Hayward et al., 2002). Diabetic Retinopathy is the 3rd leading cause of severe (5.9%) and partial sight impairment (7.4%) in England and Wales after age-related macular degeneration and glaucoma (Bunce and Wormald, 2008).

1.5.4 Pregnancy

Most pregnant patients with background retinopathy will not experience a worsening of their retinopathy during pregnancy. A small and unpredictable group of patients will progress rapidly to PDR; in addition, they remain at risk for a year post-partum (DCCT, 2000). The NSC has formulated the following guidelines for screening during pregnancy (National Screening Commitee, 2008)

Annual screening is offered to women for diabetic retinopathy in the preconception period using two-field mydriatic digital photography using guttae tropicamide only for dilation. Women with T1D and T2D are offered two-field mydriatic digital photography to national standards at (or soon after) their first antenatal clinic visit and again at 28 weeks' gestation. If background diabetic retinopathy is found to be present, an additional screen is performed at 16-20 weeks gestation and post partum.

1.5.5 Renal disease

There is an association between retinopathy and all levels of abnormal renal function, from albuminuria to frank proteinuria, independent of duration of diabetes and level of glycaemic control, in both types 1 and 2 diabetes, especially in some ethnic groups (Collins et al., 1995). However this relation between renal and retinal angiopathy is complex as they share common confounding and predisposing factors mainly chronic hyperglycaemia, high HbA1c levels, duration of diabetes, and elevated BP. A recent meta-analysis has shown that all patients with T1D should receive ACE inhibitors to reduce incidence of macroalbuminuria, though this effect is not mediated by reduction in BP or structural changes associated with diabetic nephropathy (ACE Inhibitors in Diabetic Nephropathy Trialist Group, 2001).

Large cross-sectional and longitudinal population studies have demonstrated that the severity of diabetic retinopathy is indicator of risk of severe proteinuria. Elevated albumin excretion has also been found as a risk factor for retinopathy in many ethnic groups (Kofoed-Enevoldsen et al., 1987) and presence of gross proteinuria at baseline was associated with 95% increased risk of developing macular oedema among T1D patients (Klein et al., 1995a).

1.5.6 Hyperlipidemia

In the WESDR and Hoorn (Van Leiden et al., 2002) studies there was a correlation between high cholesterol blood levels and risk of retinopathy in the diabetic population. Lipid lowering drugs like Simvastatin and Atorvastatin have long demonstrated beneficial effect in reducing the hard exudates and progression of DR in clinical trials (Cullen et al., 1974, Harrold et al., 1969). Similar results were seen in the Fenofibrate Intervention and Lowering Intervention in Diabetes (FIELD) study, which was a double blind placebo controlled RCT (Keech et al., 2007). The results showed that, in the fenofibrate treatment arm (n = 4895) of the study, the need for first laser treatment for retinopathy was significantly lower (p = 0.0002) than in the placebo arm (n = 4900) [3.4% versus 4.9%].

1.5.7 BMI

There has been a global increase in obesity with changing life style. This has nearly doubled the prevalence of diabetes in last decade (Narayan et al., 2007). It is however unclear if increased BMI is independent risk factor for the development and progression of DR.

1.5.8 Smoking

The relationship between cigarette smoking and microvascular complications of diabetes is complex. However, it appears that cigarette smoking is not a risk factor for the development or progression of retinopathy in observational studies (Moss et al., 1996).

1.5.9 Alcohol

There is no clear data available about the effects of alcohol consumption and the development or progression of diabetic retinopathy (Xu et al., 2009).

1.5.10 Effect of ethnicity on risk factors

1. Haemoglobin A1c (HbA1c) is widely used as an index of mean glycaemia, a measure of risk for the development of diabetes complications, and a measure of the quality of diabetes care. HbA1c levels are significantly higher in African Americans, Hispanics, Asians, and other races and ethnicities compared to whites before and after adjusting for age, gender, BMI, duration of diabetes, oral medication use, mean fasting plasma glucose, mean postprandial glucose, insulin resistance, and β-cell function (Herman et al., 2009). So this aspect should be taken into account when comparing glycaemic control between ethnic groups.

2. Black patients have a higher prevalence and earlier onset of hypertension than other ethnic groups, with poorer prognosis than white patients. Blacks are more likely to be salt-sensitive, and to have a low plasma renin activity than are whites. They are at much greater risk of developing cardiovascular and renal complications (Kola et al., 2009).

3. The increase in diabetes in Asia differs from that reported in other parts of the world: it has developed in a shorter time, in a younger age group, and in people with lower BMI. Studies reported that for the same BMI, Asians have a higher body fat percentage, a prominent abdominal obesity, a higher intramyocellular lipid and/or a higher liver fat content compared to Caucasians. These characteristics may contribute to a higher predisposition to insulin resistance at a lesser degree of obesity than Caucasians. The differences in body composition are more pronounced depending on the region. For the same BMI, among three major ethnic groups in Asia, Asian Indians have the highest body fat, followed by Malay and Chinese. Lower insulin sensitivity is already observed in Asian Indian adolescents with a higher body fat and abdominal obesity compared to Caucasian adolescents. In general, Asian adolescents share the same feature of body composition such as higher body subcutaneous fat, lower appendicular skeletal muscle and lower gynoid fat compared to Caucasian adolescents. This unfavourable body composition may predispose to the development of insulin resistance at later age. Genetics may play a role and the interaction with environmental factors (changes in lifestyle) could increase the risk of developing the metabolic syndrome (Wulan et al., 2010).

4. Some ethnic groups including the tribal population are 2-4 times more susceptible to diabetes so the rates of DR may reflect the rates of diabetes.

5. Inequality to access to healthcare is an important issue in minor ethnic groups and in socially and economically deprived areas. A recent systematic review reported ethnic differences in quality and intermediate outcomes of diabetes care to late 2004. Intermediate clinical outcomes were worse in Blacks and inclined to be worse in Hispanics (Lanting et al., 2008, Soljak et al., 2007).

6. Ethnic differences in dietary habit may also be influential factors for the ethnic difference (Premanand et al., 2006, Takeuchi et al., 2008). Culture is a major determinant of lifestyles and corresponding health outcomes (Perez-Escamilla and Putnik, 2007).

7. Retinal arteriolar dilatation measured from retinal photographs is an important risk factor of incident diabetic retinopathy in both T1D and T2D in Caucasians and has been confirmed in both the Ausdiab and WESDR cohorts. This risk is [i]ndependent of the known risk factor of hyperglycaemia and hypertension (Klein et al., 2004, Rogers et al., 2008). However, venular dilatation is a more significant risk factor for the Hispanics, Chinese and African-Americans suggesting ethnicity dependent variations in retinal calibre patterns in diabetes (Nguyen et al., 2008, Rogers et al., 2008).

1.6 Diabetic retinopathy is a public health problem

DR is the most common cause of visual impairment in the working age group (Klein et al., 1984c, Klein et al., 1984b). Exact numbers are difficult to report as 20-30% of population have undiagnosed diabetes. According to the National Health and Nutrition Examination Survey in the USA (NHANES 1999-2004), 3.8% of subjects with diabetes had visual impairment (Vision of < 20/40 in the better eye) (Zhang et al., 2008b). Similarly DR accounted for 17.7% of all people registered as visual impaired in the age group of 16-64 years in England and Wales (Bunce and Wormald, 2008), 2.8% (Vision < 20/63 in the better eye) (Huang et al., 2009) of all adult population in China, 13.3% in India (Herse and Gothwal, 1997) and 8.7% in Barbados (Hennis et al., 2009).

There has been a global increase in the prevalence of DR and it is no longer a burden restricted to developed countries. In fact, the steepest gradient of increase in prevalence is projected to be in India and China (Klein et al., 1992, Leske et al., 1999a, Namperumalsamy et al., 2009, Raman et al., 2009, Rema et al., 2005, Simmons et al., 1989, Wang et al., 2009, Xie et al., 2009). The increased prevalence may be a true increase, or may be the result of better detection rates of DR due to the availability of more sophisticated cameras for identification of the disease. It is important to identify the rate of increase in prevalence in different regions in the world to enable appropriate resource allocation. It is also crucial for us to understand why there are significant regional differences in the prevalence rates and whether the increased prevalence of the disease equates to increasing rate of visual impairment due to DR. The most common causes of visual impairment in DR are macular oedema, non-resolving vitreous haemorrhage and tractional retinal detachment.

1.7 Treatment of diabetic retinopathy

Major population studies (DCCT, 1993; UKPDS, 1998) have highlighted that intensive control of diabetes and lifestyle modification can reduce the risk of long term microvascular complication like DR. However, this is offset by the increase in the prevalence of diabetes overall and the frequency of risk factors in different ethnic groups.

Two large multicentre randomised trials: the Diabetic Retinopathy Study (DRS, 1981) and Early Treatment for Diabetic Retinopathy Study (Diabetic retinopathy study, 1978, Early Treatment Diabetic Retinopathy Study Research Group, 1985) independently identified the beneficial effect of laser treatment in reducing the risk of moderate and

severe visual loss respectively. Xenon Arc or argon laser reduced the risk of severe visual loss (VA <5/200) by 50-60% in eyes with PDR or severe NPDR in DRS. Similarly in ETDRS chances of loss of 15 ETDRS letters was 12% in immediate treatment group compared to 24% in the deferred group for macular oedema at end of three years. The 2 year randomised control trial, Diabetic Retinopathy Vitrectomy Study (DRVS) showed that recovery of good vision (10/20 or better) was more frequent in the eyes assigned to early vitrectomy for dense recurrent vitreous haemorrhage (25% compared to 15%) in the eyes assigned to conventional observation group (The Diabetic Retinopathy Vitrectomy Study Research Group, 1985).

Laser remains the gold standard treatment for both diabetic maculopathy and PDR. However recently there has been surge in the use of steroid and anti-vascular endothelial growth factor (VEGF), either as primary treatment or in combination with laser to improve potency and efficacy or expedite its action. In a multi-centre randomised trial evaluating intravitreal 0.5 mg ranibizumab or 4 mg triamcinolone combined with focal/grid laser compared with focal/grid laser alone for treatment of MO, eyes treated with 0.5 mg ranibizumab and prompt laser had better visual results than laser or steroid with laser at the end of 2 years (Elman MJ et al., 2011). In another study by the same group addition of 1 intravitreal triamcinolone injection or 2 intravitreal ranibizumab injections in eyes receiving focal/grid laser for MO and PRP was associated with better visual acuity and decreased MO (Googe J et al., 2011).

1.8 Cost of Diabetic Retinopathy and Blindness

Data on the costs of key chronic disease like diabetes and its complication allows providing estimate of the current size of economic burden and planning future

estimates. There were approximately 2.8 million people with diagnosis of diabetes in UK in 2009 and it is likely to increase to 4 million by 2025 (www.diabetes.org.uk). In UK nearly £9 billion pounds is spent annually on treating diabetes and its complications which equates to £16,666 being spent on diabetes every minute (www.diabetes.org.uk). A report by the NHS titled *Prescribing for Diabetes in England* reported that the cost of drugs and treatments alone in order to treat people with diabetes had risen by 40% from £458.6 million in 2004/5 to £649.2 million in 2009/10 (www.diabetes.org.uk) in last 5 years.

There is a substantial expenditure associated with the management of any form of DR and a significant increase in cost incurred with increasing severity of DR due to increased inpatient, outpatient episode and cost of treatment. Delaying progression by better control of risk factors is both cost effective and improves quality of life. In a study by Schmier et al, looking at Medicare claims in US in patients with DR, average payment was 35% higher in patients with PDR versus patients with no retinopathy. Also among diabetic patients with no DR inpatient and outpatient claim was 0.05%, 38% respectively that increased to 0.39% and 94% in patients with PDR. Similarly total payments were significantly higher for cases with NPDR (>63%), PDR (>4 fold) compared to no patients with no retinopathy (Schmier JK et al., 2009)

There are an estimated 166,325 people in UK with diabetic MO in one or both eyes, and of these, 64,725 individuals had CSMO (Minassian DC et al., 2011). Patients with MO consume significantly more healthcare resources, incur higher costs compared to diabetic patients without retinal complications and have negative impact patients' health related quality of life (Chen E et al., 2010). In a study by Shea et that analysed administrative claims from a sample of US Medicare beneficiaries from 2000 to 2004 in

people with diabetic MO costs were more than 30% higher than for diabetic patients without retinal disease at 1 and 3 years after diagnosis. Inpatient costs constituted almost half of the total costs. Total costs incurred in the year of diabetic MO diagnosis were 27% higher than the previous year. After adjustment for age, sex, race/ethnicity, geographic region, and baseline comorbid conditions, MO was a significant independent predictor of total medical costs – associated with 25% higher 1-year costs and 27% higher 3-year cost (Shea AM et al, 2008). In UK the estimated cost for overall health and social care costs in 2010, on the pathway from screening to rehabilitation and care in the home in people with MO, was £116 296 038 (Minassian DC et al, 2011).

In a study commissioned by Royal National Institute of Blind (RNIB) there were approximately 1.8 million people with partial sight and blindness in UK in 2008 (Access Economics Pty Limited, 2011) and 62,000 (3.5%) of these are due to diabetic retinopathy. Of all the people with diabetic retinopathy nearly 19,000 (8.7%) were blind with a vision of < 6/60 in the better eye. There is projected 46% increase to 93,000 people with partial sight and blindness in UK by 2050 due to diabetic retinopathy and majority (> 65%) of it will be in working population (age < 65 years). In the same study estimated annual expenditure due to blindness or partially sighted in UK in 2008 was £6.4 billion which is projected to rise to in £7.9 billion by 2013. According to other study commissioned by Diabetes, UK (Diabetes.org.uk) lifetime costs to the UK government for a person with diabetic retinopathy can be £314,512 per person assuming productivity loss to 65 years of age. So if early detection or screening could potentially avoid 1000 cases it could save up to £314 million to the UK government.

1.9 Conclusion

Race- and ethnicity-related differences in prevalence of DR, CSMO and visual impairment remain an important public health issue. Understanding the epidemiology of DR in different ethnic groups is essential for more effective screening and treatment of DR. Several studies have highlighted the inter-ethnic variations in the susceptibility to known risk factors of complications of diabetes. In particular, the prevalence of metabolic syndrome illustrates the continuum of inter-ethnic variations. The studies on prevalence rates of diabetes indicates that obesity, urbanization, changes in diet and increasing sedentary life-style, the declining rate of communicable diseases and associated mortality will inevitably lead to increased health burden due to diabetes and its related complications. Although a concerted approach on prevention of these risk factors exists in several countries around the world, it is important to understand that a directed ethnic-specific approach is required to reduce the burden especially in multi-racial populated cities. Policy makers and clinicians should focus on the development of guidelines that are ethnic specific so that more effective control of risk factors is feasible. It is also important to highlight that further research on other genetic and environmental risk factors are necessary to better understand these differences. However, direct comparison of studies from individual countries are seriously hampered by differences in the definitions for the individual clinical complications and the methods used in their assessment, in addition to enormous variations in the ages of subjects at diagnosis and study entry. Educational programs aimed at the physician to facilitate cultural competence and at the patient to increase level of knowledge about their disease are appropriate and enthusiastically endorsed (Wilson and Eezzuduemhoi, 2005). In the UK, the NSC has provided guidelines on screening techniques and grading

criteria that guide all DR screening programmes. This allows for uniform grading outcome and comparative data between established programmes. In addition it is the national requirement for all screening programs to provide 95-100% coverage of screening to all patients with diabetes. There are several regions globally where screening programmes do not exist or are still in their infancy. So the regional variations in diabetic retinopathy and the differences in frequency of DR in various ethnic groups are important for different types of stakeholders. Data is difficult to obtain from some areas in the world and therefore we believe that outcomes of studies such as this may be translated to policy makers and clinicians in areas where no local data is obtainable.

Very little is known about inter-ethnic global differences in severity of DR in UK. DR is a final pathway of a complex interplay of systemic biochemical and metabolic abnormalities and local tissue effects on all cells of the retina. Established risk factors for the two types of disease are very similar. However T1D is more prevalent in Whites than Afro-Caribbeans indicating some race specific differences in risks. Risk factors for T2D can be broadly divided into modifiable and non modifiable. Non modifiable risk factors include: increasing age (Centers for Disease Control and Prevention (CDC)., 2010), ethnicity (Egede and Dagogo-Jack, 2005), genetic predisposition, history of gestational diabetes, and low birth weight. Modifiable factors include increased body mass index(BMI) (Hu et al., 2001), physical inactivity (Jeon et al., 2007), hypertension and smoking (Will et al., 2001) and psychosocial factors such as depression, increased stress, lower social support, and poor mental health status (Grandinetti et al., 2000, Strodl and Kenardy, 2006). The severity of the disease is related to the duration of diabetes (Klein et al., 2008b, Klein et al., 2009b). As mentioned previously there are differences in risk factors and access to healthcare between ethnic groups. It is also

important to focus on the prevalence and risk factors of subjects with end stage disease (PDR). Identification of risk stratification models for end-stage disease is as important as early disease. Prevention of end-stage may potentially reduce severe visual impairment more significantly than early prevention.

1.10 Aim of the study

1. There is paucity of prevalence data on diabetic retinopathy amongst ethnic minority population in UK especially Afro-Caribbeans and in people with T1D. This study aims to determine the prevalence of DR and visual impairment in three main ethnic groups. The cohorts identified for the study include one region from the North of the country (Yorkshire) and London from the South of England. South East London has a multi-racial population with a majority of the ethnic minority consisting of Afro-Caribbeans (24%). Other than London, there is a high proportion of Asians in Yorkshire and the Humber and the West Midlands. South Asian population makes up 17% of the population of North Kirklees, while Wakefield has a predominantly Caucasian population.

2. A regional difference in frequency of DR and VI will be determined from this study.

3. The differences of risk factors between ethnic groups will also be determined to assess whether ethnicity is an independent risk factor or is it the differential susceptibility to risk factors that explain any ethnic specific differences in VI and DR.

4. In addition, further investigations will include detailed analyses of subjects with end-stage diabetic retinopathy to understand inter-ethnic differences and identify any risk factors to explain any differences. The clinical details and risk factors to be collected from General Practitioners will include: age at onset of diabetes, age of patient, sex, history of hypertension, HbA1C, microalbuminuria, serum lipids, BMI (body mass index), smoking, use of statins, peripheral neuropathy, peripheral vascular disease, myocardial infarction or coronary arterial bypass and stroke (Section 2.6 & 2.7).

5. The role of renal function in the ethnic groups will also be compared and correlated to the retinopathy levels in each ethnic group. This includes subgroup of subjects with end-stage renal disease from the London cohort to determine the retinopathy grades and the relation to different ethnic groups.

This study on the prevalence of all grades of retinopathy and the associated risk factors in various ethnic groups will hopefully inform policy makers and clinicians on the need to reinforce ethnicity based screening and treatment threshold in diabetic retinopathy.

Within its overall aim the following objectives were defined:

1) To discover the prevalence of diabetic retinopathy (DR) in various ethnic groups, ethnic group as defined by Census of 2001, United Kingdom (Section 2.3) and presence of DR as National Screening Committee (NSC) UK (Sections 1.4.3 and 2.2).

2) To assess the prevalence of visual impairment in various ethnic groups as defined by NSC (Sections 2.2 and 2.4).

3) To elucidate the systemic risk factors for diabetic retinopathy in people with T1D a case control study will be done for sight threatening diabetic retinopathy (severe NPDR and proliferative diabetic retinopathy) in London cohort only. These will be matched by age, and type of diabetes to patients with no diabetic retinopathy in ratio of 1: 2.

4) To elucidate the systemic risk factors for diabetic retinopathy in people with T2D, similar data will be collected in the London cohort.

5) To determine the outcome following vitrectomy (Surgical outcome for end stage DR) including inter-ethnic differences in outcome. This part of the study will relate to the London cohort only.

6) To determine the temporal relation between end stages retinal and renal disease (diabetic population on renal dialysis) with reference to the different ethnic groups. This part of the study will relate to the London cohort only.

CHAPTER II

MATERIALS AND METHODS

2.1 Methods

2.1.1 Ethics approval

The Research Ethics Committee of King's College Hospital, London School of Hygiene and Tropical Medicine and the Clinical Effectiveness Department of the hospital also approved the study (CASS AP0861-01) (Appendix 1, 2 & 3)**.**

2.1.2 Study population

The comprehensive population based Diabetes Register keeps an up to date count of the people with diabetes in South East London and West Yorkshire. These patients are screened annually for diabetic eye disease by the regional diabetic retinopathy screening programs: in South East London, by the Diabetic Eye Complications Screening (DECS) program and in Yorkshire, the by Wakefield and North Kirklees diabetic retinopathy screening program. Both the screening programs are well established and quality-assured.

2.1.3 Digital photography-Retinal photographs

Fundus photography was performed at each site following a standardized protocol recommended by the NSC (For detailed methodology see section 1.4.3).

In short, both eyes of each participant were photographed after mydriasis. Standard software was used for image acquisition and archiving. Images were then graded for first full disease grade and second full disease grade by experienced screeners and graders. Arbitration was performed by medical retina consultants at both sites. Five percent of the patients were not fit for digital photography and were examined for retinopathy using slit-lamp biomicroscopy.

2.1.4 Grading of diabetic retinopathy

Retinopathy was considered to be present if any characteristic lesion as defined by the ETDRS severity scale were present: microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading, or new vessels. For each eye, a retinopathy severity score is assigned as recommended by the NSC (See section 1.4.2).

Presence of macular oedema (M1) is characterized by presence of any of signs vascular leakage within macular area like retinal thickening, microaneurysms, hard exudates or may be featureless as in ischemic maculopathy (section 1.4.1).

P1 signifies the presence of laser treatment. This is further classified into macular laser or pan retinal photocoagulation (PRP). In cases where macular laser was performed for macular edema, the category was termed as M1P1 to give the life-time prevalence of treated maculopathy.

2.1.5 Screen positive patients

Screen positive patients with sight-threatening retinopathy were referred to the Ophthalmology department for management. Patients requiring photocoagulation therapy were treated according to the guidelines from the ETDRS (Early Treatment Diabetic Retinopathy Study Research Group, 1985) and the DRS (Diabetic retinopathy study, 1978).

A small proportion of diabetic patients (<2%) were permanently excluded from screening because they are severely visually impaired or refused screening. These patients were not included in the analyses.

2.1.6 Visual acuity testing

The protocols for recording visual acuity in both screening programmes are similar (as recommended by the National Screening Committee). Presenting visual acuity is recorded. This is measured with the participant wearing their "walk-in" optical correction (i.e. spectacles or contact lenses) using ETDRS charts. If no letters are read at 2 metres, visual acuity is assessed as counting fingers, hand movements, perception of light, or no perception of light.

2.2 Data collection

2.2.1 Baseline demographics, vision and retinopathy status of population affected with diabetes form screening program

The diabetes register is the nearest true representation of the population with diabetes. The screening programs maintain and update their databases from the diabetes register. The screening database and computer software of the digital photography at both sites provided details on the visual acuity and grade of retinopathy of those who were screened between 1st September 2008 and 30 September 2009. The data collected from these registers included baseline demographics: date of birth, gender, ethnicity, type of diabetes, and best corrected Snellen visual acuity in both eyes, retinopathy grades in both eyes, maculopathy grades in both eyes and any photocoagulation treatment administered (Appendix 4). The number of patients that refused screening was noted.

2.2.2 Data collection from hospital eye services

The retinopathy grades obtained by slit lamp biomicroscopy or indirect ophthalmoscopy were recorded for subjects for whom it was technically difficult to acquire retinal photographs. Also the records of subjects who were exempted from the screening programme because they were under the care of the specified hospital eye service was

collected using specialist feedback forms circulated in the diabetic clinic (appendix 5) or are blind were collated from hospital records and the registers for visually impaired.

The number of subjects for which no records were obtainable was noted. In addition, there were subjects with very recently diagnosed diabetes (less than 12 weeks from referral as newly diagnosed diabetes) or who were only recently registered with family practices in the area, were excluded. The ETDRS diabetic retinopathy grades in feedback forms were converted to the NSC equivalent (section 1.4.3) Patients that are already registered severely visually impaired were also examined and their data was included.

2.3 Ethnicity data

The target population for this study includes Caucasians, and those of Afro-Caribbean and South Asian descent /origin. The study did not separately identify duration of stay, food habits and role of micronutrients in UK of ethnic minority population to analyze their impact on generations living in UK. The allocation of ethnicity for this study was defined as per the 2001 Census as follows:

A White: British; Irish or any other White background.
B Mixed: White and Black Caribbean; White and Black African; White and Asian or any other mixed background.
C Asian or Asian British: Indian; Pakistani; Bangladeshi; any other Asian background.
D Black or Black British: Caribbean; African; any other Black background.
E Chinese or other ethnic group: Chinese; any other.

The project focused on groups A, C and D. The people who are in groups B and E were excluded due to small numbers.

2.4 Definition of visual impairment

Blindness as defined by the WHO standard is the best-corrected visual acuity of <6/120 in the better-seeing eye; 6/60 or worse by the US definition and 6/60 or worse by National Screening Criteria (NSC). Low vision is defined as <6/18 to 3/60 by WHO standard, <6/12 is visual impairment by US definitions and 6/18 or worse by NSC definition {(NSC, 2010, US, 2010 WHO, 2010) (Table 2.1)}.

Table 2.1: Equivalence of visual impairment according to NSC, US and WHO criteria

	WHO	**National Screening Committee**	**US**
Visual Impairment	<6/18	6/18 or worse	< 6/12
Low Vision	Low vision: <6/18 to 3/60	6/60 or worse	< 6/60 Severe visual impairment
Blindness	Blindness: <3/60		

<6/12 is visual impairment by US definitions. Equal to ≤ 6/18 which is "Sight impairment" according to National Screening Committee programme criteria

2.5 Data Collection and statistical analysis on prevalence of DR and visual impairment

The data analysis was performed using Stata version 11.0 (Stata Corp., College Station, TX, USA). Data were analysed at the individual subject level. The eye with the worse grade was used in the analyses. Descriptive analyses include reporting the age-specific prevalence and of the different DR and visual impairment in diabetic people in the three ethnic groups. The estimates from the two areas were similar, and hence data was pooled to provide national prevalence data that can be used for resource allocation. The

association between DR and the various clinical risk factors was explored using logistic regression models.

2.6 Random sampling

A case control study was performed in London to assess clinical risk factors for sight threatening diabetic retinopathy (severe NPDR and PDR). A random sample of 3,346 people from the patients with completed ethnicity, demographics and retinopathy data from London was generated and this included all patients with severe NPDR and PDR in patients with T1D and T2D disease. These were matched by age, and type of diabetes to patients with no diabetic retinopathy in ratio of 1: 2.

2.7 Clinical risk factors

The clinical details and risk factors that collected from General Practitioners included: age at onset of diabetes, age of patient, sex, history of hypertension, HbA1C, microalbuminuria, serum lipids, BMI, smoking, use of statins, peripheral neuropathy, peripheral vascular disease, myocardial infarction or coronary arterial bypass and stroke (appendix 6) .

2.8 Risk factors for end stage DR

The study also looked at the ethnic variations in people with PDR who underwent vitrectomy secondary to PDR between January 2007 to December 2009 at King's College Hospital, London and St Thomas's Hospital, London. A dedicated vitreo-retinal electronic patient software allowed case identification from both centres from 2007-09.

This study enabled provision of evidence of anatomical and visual outcome for this complex and sight threatening disease due to diabetic retinopathy with particular reference to the ethnic differences.

The patients were divided in three groups

Group A: Tractional retinal detachment with/without haemorrhage

Group B: Non clearing vitreous haemorrhage (at least 3 month duration) secondary to proliferative diabetic retinopathy (PDR)

Group C: Others (Tractional diabetic macular oedema, epi-retinal membrane etc.)

Data collected included age, ethnicity, baseline best corrected visual acuity, indication for the procedure, complication, outcome and duration of follow up. Visual acuities were converted to LogMAR, and CF, HM and PL and no perception of light (NPL) were assigned values of 1.85, 2.3, 2.6 and 2.9 respectively (Holladay, 1997, Schulze-Bonsel et al., 2006). The primary endpoints of the study were anatomical success and eyes with visual acuity $\leq$ 0.3 LogMAR (20/40) at last follow up with reference to different ethnic groups.

2.9 The relation of retinopathy status to end stage renal disease in various ethnic groups

Data on consecutive patients with a diagnosis of diabetes related end stage renal disease (ESRD) was extracted from the renal database maintained by the hospital eye service. Further demographic and clinical data of these patients was collected as previously stated in section 2.7 (appendix 6). The study cohort was divided in two cohorts: 1) PDR with ESRD and 2) NPDR with ESRD

Diabetic nephropathy (DN) was confirmed if a chart review revealed a diagnosis by renal biopsy or the clinical criteria of diabetes duration ≥5 years prior to dialysis with proteinuria >500 mg/24 h, or urine dipstick protein >30 mg/dl, in the absence of other causes of ESRD. The date of diagnosis of ESRD was defined as the date of initiation of renal replacement therapy. Individuals with diabetes with ESRD due to other causes were excluded, typically due to short duration of diabetes prior to ESRD. Multiple logistic regression analyses were performed, in which the effects of potentially confounding variables were controlled. The following were used as independent variables: age, gender, HbA1c at the time of diagnosis of ESRD, lipid profile, hypertension, smoking, peripheral vascular disease, neuropathy, macrovascular complications and renal function tests. Comparison of disease severity between ethnic groups was done using ANOVA analysis. Kaplan Meier survival analysis was performed to assess the time to ESRD in different ethnic groups.

2.10 Statistical analysis

SPSS 17.0 software was used for statistical analysis for methods described in section 2.7, 2.8 & 2.9. All significance levels were defined at $p<0.05$. Logistic regression analyses were performed to control for potentially confounding variables.

CHAPTER III

RESULTS

3.1 Patient profile in screening program

There were 20,878 registered subjects with known diabetes in the family practices of West Yorkshire region and 36,266 in South East London (Table 3.1). The total population in these areas are 534,883 and 868,322 respectively (Yorkshire and the Humber Quality Observatory (YHQO), 2011). So the prevalence of diagnosed diabetes is 4.2%. The average national prevalence of diagnosed diabetes is 4%. The Association of Public Health Observatories model indicates that the prevalence of diabetes (defined as a total of undiagnosed and known diabetes) is significantly higher in the minor ethnic groups with estimated rates in Caucasians - 6.9%, African-Caribbean – 9.8% and Asians- 14% (Yorkshire and the Humber Quality Observatory (YHQO), 2011). The number of eligible study population with T2D were 17,332 and 29,630 and with T1D were 1211 and 2112 respectively in West Yorkshire and South East London respectively. Data on DR was available in 50,285 subjects (Table 3.1).

Table 3.1: Baseline diabetic population profile in two screening program

	West Yorkshire	South East London	Total
Total diabetic population	20,878	36,262	57,140
Total eligible population for this study	18,552	31,733	50,285
Eligible Type 1 diabetes	1,211	2112	3323
Eligible Type 2 diabetes	17341	29621	46962
Information on retinopathy or ethnicity not available*	836	2412	3248
Moved out of area*	**	242	242
Attend other screening program*	**	634	634
Patients refused screening*	83	244	327
Deceased during study period*	35	767	802
Medically unfit for screening*	161	230	391

* Population not included for further analysis. ** No information available

Overall 93.3% of the study population had T2D with a mean age of 63.6 SD13.3 years. There were more males (52.86%) in the whole population cohort and Afro-Caribbeans amongst the ethnic minority population. In all 76.9% of the population with T1D and 37% with T2D were in working age group (20-59) (Table 3.2). The age- distribution of T1D is in keeping with the disease onset before the age of 30 years and the increasing longevity associated with this disease. The fact that 80% of people with T1D are Caucasian suggests that T1D is not associated with ethnic group.

In contrast, approximately 63% of T2D is observed in persons aged 60 years and over. A greater proportion of people with T2D are of non-Caucasian origin compared to T1D in keeping with the higher prevalence of T2D in the minority ethnic groups.

Table 3.2: Characteristics of the screened population

	Type 1 diabetes N= 3,323	**Type 2 diabetes N= 46,962**
Mean age in years (SD)	39.4 (16.3)	63.6 (13.3)
	N (%)	*N (%)*
Age <20	326 (9.8)	23 (0.1)
Age 20-29	748 (22.5)	134 (0.3)
Age 30-39	755 (22.3)	1634 (3.5)
Age 40-49	680 (20.5)	5779 (12.3)
Age 50-59	382 (11.5)	9802 (20.8)
Age 60-69	235 (7.1)	12352 (26.3)
Age 70-79	152 (4.6)	11843 (25.2)
Age 80+	44 (1.3)	5366 (11.4)
Male	1764 (53.1)	24842 (52.9)
Caucasian	2682 (79.2)	30352 (64.7)
African-Caribbean	344 (10.4)	8023 (17.1)
South Asian	120 (3.6)	3397 (7.2)
Mixed race	105 (3.2)	2577 (5.5)
Other	123 (3.7)	2587 (5.5)

3.2 Prevalence of diabetic retinopathy

In people with T1D the prevalence rates of any diabetic retinopathy was 53.1%, STDR was 5.9% and these were not significantly different between ethnic groups. In T1D, the prevalence of DR was similar in the three ethnic groups. People of African/Afro-Caribbean origin had a lower prevalence of "any retinopathy" compared to Caucasian people. The numbers of people in the non-Caucasian ethnic groups with T1D were relatively small which meant the study had low power to detect differences between the ethnic groups with respect to retinopathy in T1D.

The prevalence of any DR among people with T2D in South East London and in Yorkshire was 39.52% and 39.57% respectively (table 3.3). This was not significantly different and hence the data was collated to provide overall prevalence rate and across each ethnic group.

Table 3.3: Prevalence of retinopathy

	South Asia	**Caucasian**	**Afro-Caribbean**	**Total**
South East London	37.89	36.78	51.49	39.52
Yorkshire	41.22	39.36	-	39.57
Combined	39.70	38.0	51.30	39.50

In T2D, the prevalence of any DR was significantly higher in the African-Caribbean group compared to both Caucasians and South Asians. Diabetic retinopathy was detected on the fundus photographs in 18,565 (39.5%) of people, diabetic maculopathy in 3953 (8.4%), clinically significant macular oedema in 2,220 (4.7%), and sight threatening retinopathy in 1,865 (4.0%) people. Sight threatening diabetic retinopathy was significantly more prevalent in the South Asians (4.0%) and Afro-Caribbeans (3.7%) compared to Caucasians (2.5%) with diabetic maculopathy being twice as prevalent in South Asians (11.7%) and Afro-Caribbeans (12.9%) compared to Caucasians (6%) (Table 3.4, 3.5 and Figure 3.1 (a-d).

Table 3.4: Prevalence of diabetic retinopathy by ethnic group

	Caucasians	**Afro-Caribbean**	**South Asian**	**Whole population**
	N (%)	***N (%)***	***N (%)***	***N (%)***
Type 1 diabetes	2628 (100)	344 (100)	120 (100)	3323 (100)
R1, R2 or R3	1446 (55.0)	154 (44.8)	64(53.3)	1766 (53.1)
R1 only	1177 (44.8)	116 (33.7)	51 (42.5)	1438 (43.3)
R2 only	80 (3.0)	4 (1.2)	6 (5.0)	92 (2.8)
R3 only	189 (7.2)	34 (9.9)	7 (5.8)	236 (7.1)
R2 or R3	269 (10.2)	38 (11.1)	13 (10.8)	328 (9.9)
M1	371 (14.1)	47 (13.7)	17 (14.2)	449 (13.5)
M1 and P1	171 (7.3)	35 (11.1)	12 (11.0)	225 (6.8)
(R2 or R3) and M1	164 (6.2)	20 (5.8)	7 (5.8)	196 (5.9)
Type 2 diabetes	30350 (100)	8023 (100)	3397 (100)	46959 (100)
R1, R2 or R3	11538 (38.0)	4117 (51.3)	1350(39.7)	18565 (39.5)
R1 only	10378 (34.2)	3718 (46.3)	1146 (33.7)	16700 (35.6)
R2 only	445 (1.5)	70 (0.9)	88 (2.6)	637 (1.4)
R3 only	715 (2.4)	329 (4.1)	116 (3.4)	1228 (2.6)
R2 or R3	1160 (3.8)	399 (5.0)	204 (6.0)	1865 (4.0)
M1	2249 (7.4)	1037 (12.9)	396 (11.7)	3953 (8.4)
M1 and P1	1127 (3.7)	720 (9.0)	211 (6.2)	2220 (4.7)
(R2 or R3) and M1	770 (2.5)	299 (3.7)	136 (4.0)	1274 (2.7)

Logistic regression analyses (Table 3.5) showed that the risk of DR, STDR and CSMO increased with increasing age and male gender. People with T1D had twice the risk of all grades of retinopathy compared to people with T2D. Minority ethnic groups (both South Asians and Afro-Caribbeans) were twice as likely to have CSMO and STDR

compared to their white counterparts. There were no consistent regional variations in the severity of DR

Table 3.5: Odds ratio (OR) and confidence interval for overall prevalence of diabetic retinopathy

Odds ratio* (95% CI)	**Any retinopathy R1, R2 or R3 (n=20,344)**	**Any proliferative diabetic retinopathy R2or R3 (n= 2,195)**	**CSMO M1P1 (n=2,446)**	**STDR R2 or R3 or M1P1 (n=3,426)**
Age (per year age)	1.007 (1.006, 1.008)	1.005 (1.002, 1.009)	1.019 (1.016,1.022)	1.012 (1.099,1.015)
Men	1	1	1	1
Women	0.93 (0.90,0.97)	0.77 (0.71,0.84)	0.91 (0.84,0.99)	0.84 (0.78,0.90)
DECS	1	1	1	1
Wakefield	0.91 (0.87, 0.94)	0.69 (0.63, 0.77)	1.79 (1.61, 1.99)	1.04 (0.96,1.13)
T1D	1	1	1	1
T2D	0.47 (0.43, 0.51)	0.32 (0.27, 0.37)	0.42 (0.35, 0.49)	0.35 (0.31, 0.40)
Caucasians	1	1	1	1
Afro-Caribbeans	1.79 (1.70, 1.89)	1.61 (1.42, 1.82)	2.12 (1.91, 2.35)	1.99 (1.81,2.18)
South Asians	1.10 (1.02, 1.18)	1.52 (1.31, 1.77)	1.98 (1.71, 2.30)	1.82 (1.61, 2.06)
Other	0.75 (0.70, 0.80)	0.59 (0.48, 0.72)	0.68 (0.57, 0.81)	0.68 (0.58, 0.79)

***Adjusted for all factors on the table**

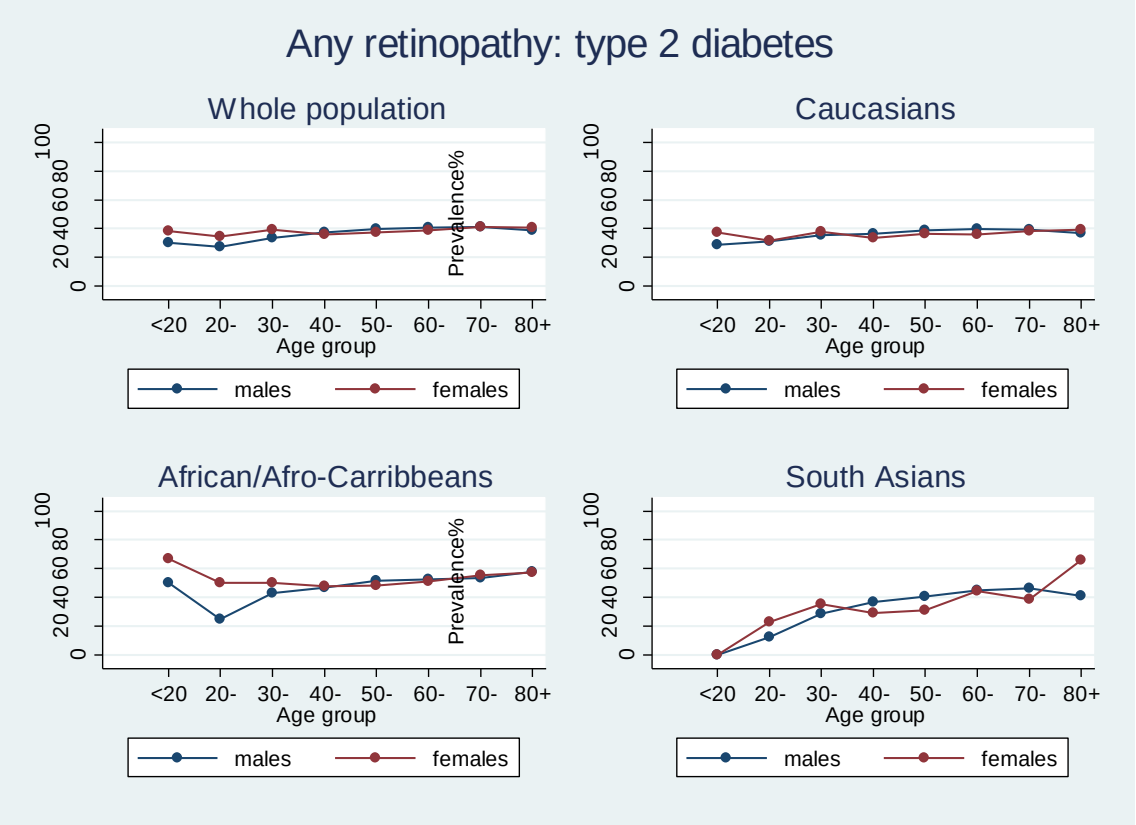


Figure 3.1a: Retinopathy in type 2 diabetes

There were 49,659 people at risk of developing retinopathy and it was present in 39.5 % of the population at given time. Afro-Caribbean had significantly high prevalence rate of retinopathy (51.3%) compared to Caucasian (38.0%) or South Asians (39.7%). The age specific prevalence was similar in South Asians to other ethnic groups. The upward trend reflects fewer people in elderly age group in South Asians

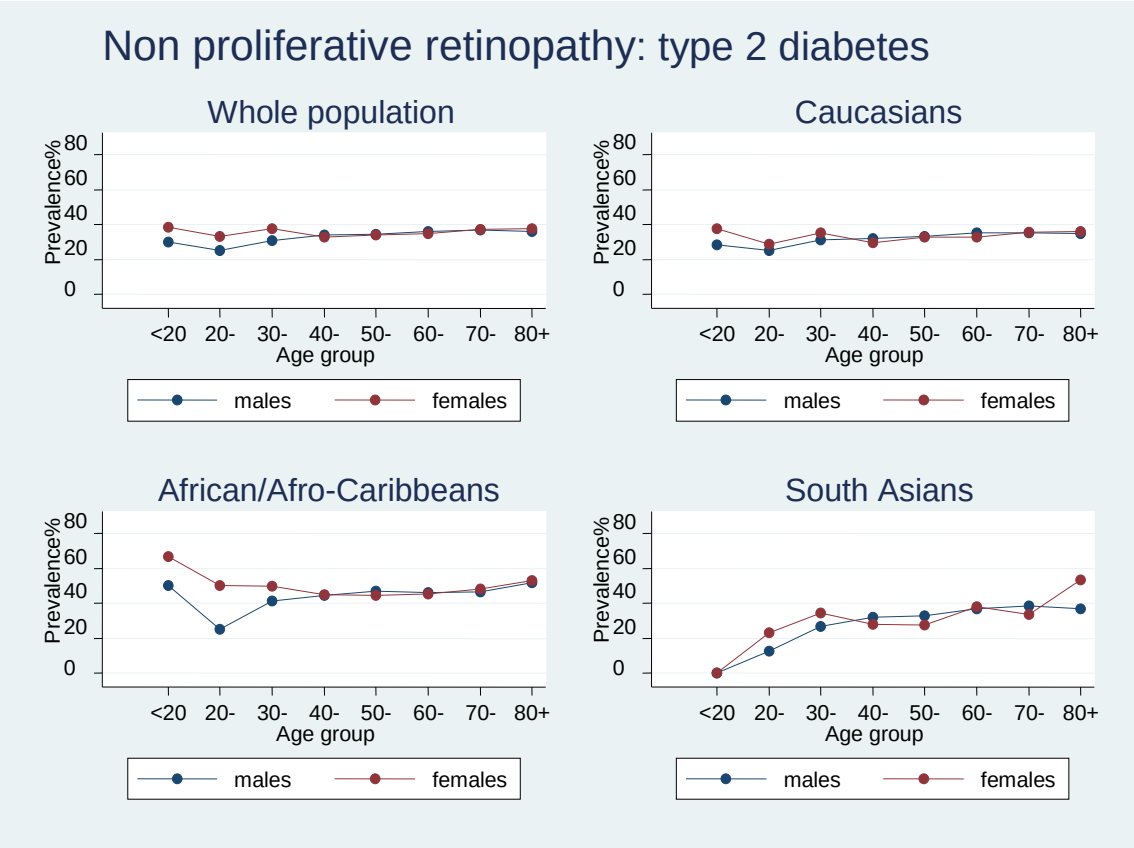


Figure 3.1b: Non proliferative retinopathy in type 2 diabetes

Overall prevalence rate was 35.6% with Afro-Caribbeans (43.6%) showing significantly highest prevalence compared to Caucasian or South Asians. In South Asians increasing prevalence was seen with increasing age where in Afro-Caribbeans and Caucasians early peak was seen in 3rd decade of life and the rates were constant thereafter. The disparity observed in South Asians is due to reasons explained previously.

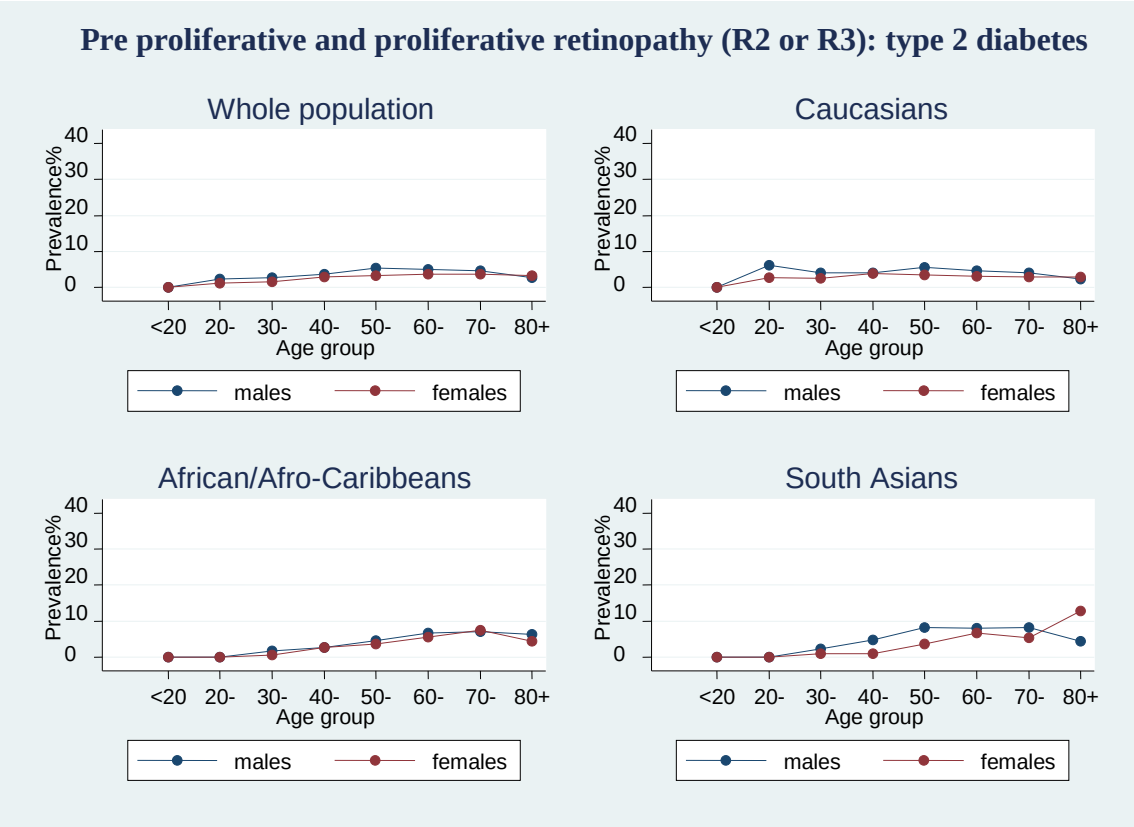


Figure 3.1c: Pre proliferative and proliferative retinopathy (R2 or R3) in type 2 diabetes

South Asians with 6.0% and Afro-Caribbean with 5.0% had higher prevalence rates of either R2 or R3 compared to Caucasians. However Afro-Caribbean had higher (4.1%) prevalence rate of proliferative (R3) compared to South Asians (3.4%) and Caucasians (2.4%). Also Afro-Caribbeans had risk of 1.79 compared to Caucasian to develop any retinopathy.

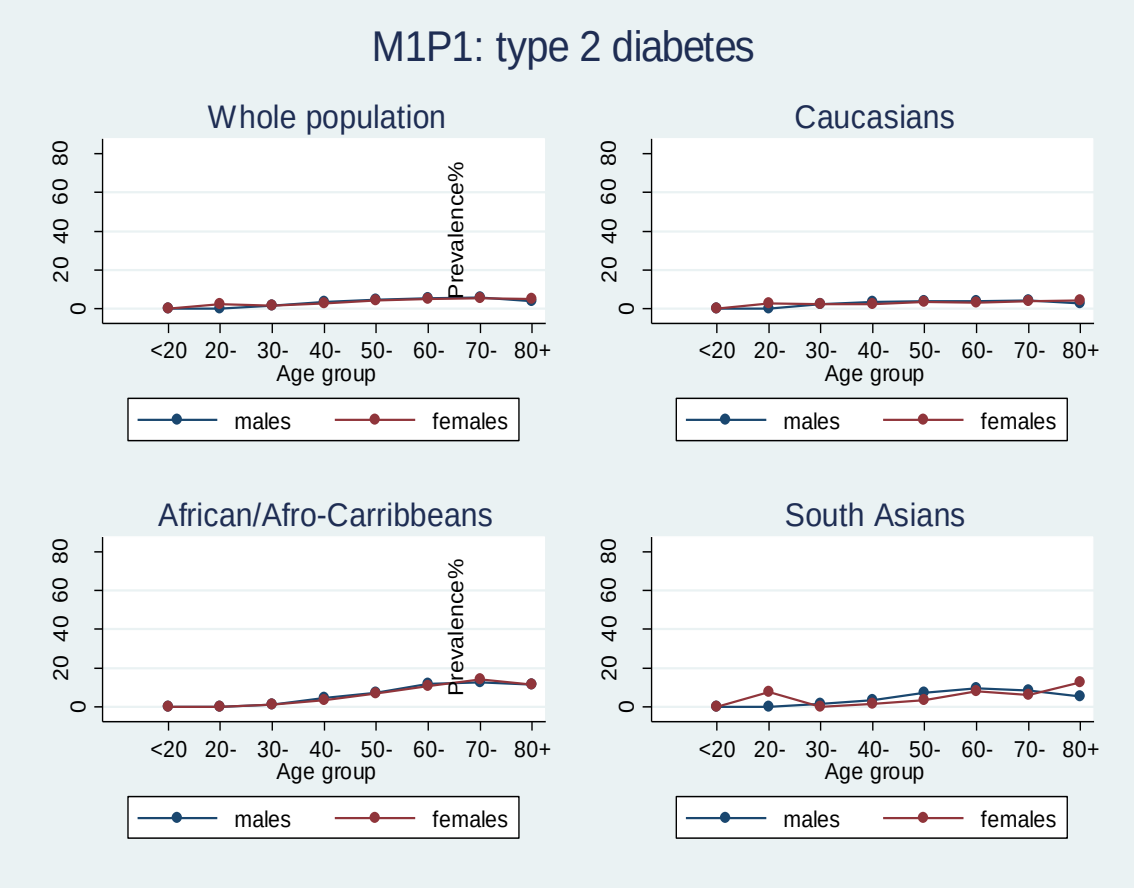


Figure 3.1d: Life time risk of maculopathy in patient with type 2 diabetes

Life time prevalence for maculopathy was 4.7% and it was significantly greater in Afro-Caribbeans (9.0%), South Asians (6.2%) than Caucasians (3.7%). Maculopathy rates did not differ with gender in any ethnic groups but a high rate in 7th decade was seen in Afro- Caribbeans compared to other population.

3.3 Prevalence of visual impairment

3.3.1 Visual acuity in the screened population

Overall, 88.9 % of the population in West Yorkshire and 94% in South East London had a visual acuity of 6/12 better in the best seeing eye. Overall prevalence of severe visual impairment (SVI) was similar accounting for 0.6% of patients in the two population cohorts Overall, 3787 (7.5%, 95% confidence intervals 7.3, 7.8) of the people with diabetes attending screening were not eligible for driving based on their presenting visual acuity and 1699 (3.4%, 95% CI 3.2, 3.5) were visually impaired (<6/12) and 195 (0.4%, 95% CI 0.33, 0.44) severely visually impaired. (Table 3.6)

Table 3.6: Vision in the screened population

	Vision in best eye	**Wakefield**			**DECS**		
		N	**%**	**Cumulative %***	**N**	**%**	**Cumulative %***
		18557*	100	100	31773	100	100
1	>=6/6	13529	72.9	100	23123	72.8	100.0
2	6/7.5	0	0.0	27.1	6737	21.2	27.2
3	6/9	3154	17.0	27.1	0	0.0	6.0
4	6/12	1052	5.7	10.1	1036	3.3	6.0
5	6/18	461	2.5	4.4	412	1.3	2.8
6	6/24	140	0.8	1.9	130	0.4	1.5
7	6/36	101	0.5	1.2	142	0.4	1.1
8	6/60	48	0.3	0.6	70	0.2	0.6
9	<6/60	72	0.4	0.4	123	0.4	0.4

*1 person had no data on vision

3.3.2 Visual acuity by ethnic group and type of diabetes

In the London cohort, visual impairment (VI) and severe visual impairment (SVI) in T2D was 9.07% and 0.63% in South Asians, 4.47% and 0.37% in Caucasians, 7.54%

and 0.53% in Afro-Caribbean respectively. The overall VI and SVI in T1D was 8.89%, 0.00% in South Asians, 3.70% and 0.13% in Caucasian, 6.15% and 0.59% in Afro-Caribbean (Table 3.7 and 3.8).

Table 3.7: Visual impairment by ethnic group

Vision in best eye	**South Asian N (%)**	**Caucasian N (%)**	**Afro-Caribbean N (%)**	**Other N(%)**
6/9 or better	3153 (89.6)	30575 (92.6)	7702 (92.0)	5088 (94.3)
<6/9 – 6/12	196 (5.6)	1345 (4.1)	364 (4.4)	180 (3.3)
<6/12-6/18	88 (2.5)	568 (1.7)	151 (1.8)	66 (1.2)
<6/18-6/60	65 (1.9)	401 (1.2)	114 (1.4)	50 (0.9)
<6/60†††	16 (0.5)	120 (0.4)	45 (0.5)	14 (0.3)
Specific cut-points				
<6/9 *	365 (10.4)	2,434 (7.4)	674 (8.1)	310 (5.7)
<6/12 or ≤ 6/18**	169 (4.8)	1,089 (3.3)	310 (3.7)	130 (2.4)
<6/18†	81 (2.3)	521 (1.6)	159 (1.9)	64 (1.2)
≤ 6/60††	27 (0.8)	194 (0.6)	67 (0.8)	25 (0.5)

*Vision required for driving

** <6/12 is visual impairment by US definitions.

† Visual impairment World Health Organisation (WHO) based on International Classification of Diseases (ICD) 10 classification

†† "Severe sight impairment" National Screening programme criteria

††† Severe visual impairment US criteria

Overall 2.0% of the population with T1D and 3.5% with T2D had VI and 0.3% with T1D and 0.7% with T2D had SVI (Table 3.7). Approximately 4% people with T1D are

not eligible for driving based on the presenting visual acuity and this figure nearly doubles (7.8%) in T2D.

Table 3.8: Visual impairment by type of diabetes

Vision in best eye	Type 1 diabetes N (%)	Type 2 diabetes N (%)
	3,323 (100)	46,962 (100)
6/9 or better	3183 (95.8)	43,317 (92.2)
<6/9 – 6/12	75 (2.3)	2,012 (4.3)
<6/12-6/18	34 (1.0)	838 (1.8)
<6/18-6/60	26 (0.8)	604 (1.3)
<6/60†††	5 (0.2)	190 (0.4)
Specific cut-points		
<6/9 *	140 (4.2)	3,644 (7.8)
<6/12 or ≤ 6/18**	65 (2.0)	1,632 (3.5)
<6/18†	31 (0.9)	794 (1.7)
≤ 6/60††	9 (0.3)	304 (0.7)

*Vision required for driving

** <6/12 is visual impairment by US definitions.

† Visual impairment World Health Organisation (WHO) based on ICD10 classification

†† "Severe sight impairment" National Screening programme criteria

††† Severe visual impairment US criteria

3.3.3. Visual acuity by severity of diabetic retinopathy

Presence of sight threatening diabetic retinopathy (STDR) severely impacted the visual outcome. Only 65.3% of patients with STDR had visual acuity of ≥ 6/9 in the better eye, 5.5% had VI and 2.8% with SVI respectively (Table 3.9). When considering the grades of DR, proliferative diabetic retinopathy remains the commonest cause of visual

impairment among the grades of retinopathy. Half of the patients with PDR are not legally eligible for driving, and a quarter of them have low vision. Approximately 6% are severely visually impaired. Treated but persistent maculopathy (a surrogate marker of clinically significant macular oedema) is also an equally important cause for all categories of visual impairment. Approximately 40 per cent of patients in this group have visual acuity below the driving standards, 20% have low vision while 3% are severely visually impaired.

Table 3.9: Visual impairment by severity of diabetic retinopathy

Vision in best eye	R1	R2	R3	M1	M1P1
	18,149 (100)	730 (100)	1,465 (100)	4,403 (100)	2,446 (100)
6/9 or better	16,717 (92.1)	606 (83.0)	686 (46.8)	3,194 (72.5)	1,421 (58.1)
<6/9 – 6/12	850 (4.7)	68 (9.3)	402 (27.4)	649 (14.7)	538 (22.0)
<6/12-6/18	357 (2.0)	28 (3.8)	95 (6.5)	211 (4.8)	165 (6.8)
<6/18-6/60	193 (1.1)	26 (3.6)	199 (13.6)	261 (5.9)	237 (9.7)
<6/60†††	32 (0.2)	2 (0.3)	83 (5.7)	88 (2.0)	85 (3.5)
Specific cut-points					
<6/9 *	1,432 (7.9)	124 (17.0)	779 (53.2)	1,209 (27.5)	1,025 (41.9)
<6/12 or ≤ 6/18**	582 (3.2)	56 (7.7)	377 (25.7)	560 (12.7)	487 (19.9)
<6/18†	225 (1.2)	28 (3.8)	282 (19.3)	349 (7.9)	322 (13.1)
≤ 6/60††	63 (0.4)	5 (0.7)	126 (8.6)	142 (3.2)	135 (5.5)

*****Vision required for driving

** <6/12 is visual impairment by US definitions.

† Visual impairment World Health Organisation (WHO) based on ICD10 classification

†† "Severe sight impairment" National Screening programme criteria

††† Severe visual impairment US criteria

3.3.4. Prevalence of Uniocular blindness

Unilateral visual impairment was present in 11.5% of the population with diabetes and 3.1% had severe unilateral visual impairment. Uniocular blindness was present in 3.2% of diabetics in London and 2.8% in West Yorkshire with greater prevalence of VI and SVI in London than Wakefield (Table 3.10).

Table 3.10: Unilateral visual impairment i.e. vision in the worst eye for people who have good vision (6/9 or better) in one eye

	Wakefield	DECS (London)	Total
Total number of people with vision 6/9 or better in one eye	16,683 (100)	29,821 (100)	46,504 (100)
<6/9 *	2,651 (15.9)	6.908 (23.2)	9,559 (20.6)
<6/12 or ≤ 6/18**	1,443 (8.7)	3,913 (13.1)	5,536 (11.5)
<6/18†	862 (5.2)	2,077 (7.0)	2,939 (6.3)
≤ 6/60††	462 (2.8)	957 (3.2)	1,419 (3.1)
<6/60†††	310 (1.6)	599 (2.0)	909 (2.0)

*Vision required for driving

** <6/12 is visual impairment by US definitions.

† Visual impairment World Health Organisation (WHO) based on ICD10 classification

†† "Severe sight impairment" National Screening programme criteria

††† Severe visual impairment US criteria

3.4 Risk factors for diabetic retinopathy

3.4.1 Characteristics of responders of the random sample from London

A total of 2348 responses were collected from a possible of 3336 people on the random sample from DECS, London giving a 70% response rate (See section 2.6 and 2.7). A series of Chi-Square and analysis of variance (ANOVA) were performed on a subsample of diabetes patients with no retinopathy (R0) to determine whether there were any differences in characteristics by ethnicity. The Chi-Square for type of diabetes was significant; Afro-Caribbean (89.1%) and South Asian (87.3%) were likely to have T2D than were Caucasians (79.8%), as opposed to T1D.

The Chi-Square for medication was also significant - Caucasians were more likely to be on just insulin (25.4) than either Afro-Caribbean (15.4) and South Asians (15.4) and less likely to be on both insulin and oral medication (10.7 for Whites compared to 13.3 for Afro Caribbeans, 14.1 for South Asians).

Diabetes duration was significant, with Whites having had diabetes longer than Afro-Caribbean or South Asian patients. Afro-Caribbeans also had higher systolic BP than Caucasians or South Asians. The same was true for diastolic BP. Afro-Caribbeans had higher LDL than Caucasians or South Asians, but there was no difference in HDL. South Asians had a lower BMI than Afro-Caribbeans or Caucasians (Table 3.11). No differences were found in smoking patterns.

Table 3.11: (continued over two pages) Characteristic of study people with no retinopathy (R0 in both eyes)

Characteristic	Total	White British	Afro-Caribbean	South Asian	Others	*F= /X2=	P
Total	1355 (100.0)	797 (58.8)	338 (24.9)	158 (11.7)	62 (4.6)		
Type of diabetes	*					X2(3) =20.42	.000
T1D, n (%)	223 (16.5)	161 (20.2)	37 (10.9)	20 (12.7)	5 (8.1)		
T2D, n (%)	1132 (83.5)	636 (79.8)	301 (89.1)	138 (87.3)	57 (91.9)		
Medication for Hyperglycaemia	*					X2(6) =27.86	.000
On tablets, n (%)	777 (57.3)	430 (54.4)	206 (62.2)	96 (61.5)	45 (73.8)		
On insulin, n (%)	284 (21.0)	201 (25.4)	51 (15.4)	24 (15.4)	8 (13.1)		
On both, n (%)	153 (11.3)	85 (10.7)	44 (13.3)	22 (14.1)	2 (3.3)		
Diabetes duration, years, mean ± SD	7.71 ± 7.00*	8.15 ± 7.59	6.92 ± 6.33	7.50 ± 5.19	6.87 ± 6.31	F(3, 1351) =2.83	.037
On treatment for hypertension, n (%)	826 (61.0)	476 (59.7)	206 (60.9)	99 (62.7)	45 (72.6)		
Systolic BP mean ± SD	131.37 ± 16.30*	130.02 ± 16.58	134.51 ± 16.50	130.24 ± 14.43	135.21 ± 13.31	F(3, 1311) =7.20	.000
Diastolic BP mean ± SD	75.92 ± 9.83*	74.58 ± 9.73	78.47 ± 9.89	75.65 ± 8.78	80.47 ± 9.43	F(3, 1311) =17.01	.000
LDL mean ± SD	2.20 ± 0.90*	2.13 ± 0.87	2.46 ± 0.83	1.92 ± 1.01	2.50 ± 0.93	F(3, 1225) =17.36	.000
HDL, mean ± SD	1.39 ± 0.75	1.37 ± 0.66	1.43 ± 0.97	1.44 ± 0.64	1.44 ± 0.83	F(3, 1233) =0.80	.494
BMI, mean ± SD	29.16 ± 7.59*	28.95 ± 8.23	30.21 ± 6.29	26.93 ± 6.31	32.11 ± 6.27	F(3, 1295) =9.93	.000

Characteristic	Total	White British	Afro-Caribbean	South Asian	Others	*F= /X2=	P
eGFR, mean ± SD	78.13 ± 54.16	78.03 ± 48.48	74.28 ± 48.5	88.26 ± 91.18	75.09 ± 26.64	F(3, 1164) =2.02	.110
Albumin Ratio, mean ± SD	8.22 ± 35.89	6.71 ± 34.85	13.04 ± 41.41	7.03 ± 34.63	5.05 ± 11.10	F(3, 943)= 1.89	.130
Smoker						X2(6) =50.43	.000
No, n (%)	619 (53.9)	319 (46.4)	203 (69.0)	67 (58.8)	30 (55.6)		
Ex-smoker, n (%)	301 (26.2)	212 (30.9)	51 (17.3)	20 (17.5)	18 (33.3)		
Current, n (%)	229 (19.9)	156 (22.7)	40 (13.6)	27 (23.7)	6 (11.1)		

*** F = ANOVA, X 2= chi-square**

In people with sight threatening diabetic retinopathy (R2 & R3), Chi-Square for Type of diabetes was significant; there were more Afro-Caribbean (88.9%) and South Asian (89.6) than Caucasians (63.3) with T2D and STDR as opposed to T1D which was more in Caucasians.

The Chi-Square for medication was also significant – more Caucasians were on just insulin (46.8) than either Afro-Caribbean (27.8) and South Asians (23.6) and less likely to be on both insulin and oral medication (26.5 for Caucasians compared to 43.3 for Afro-Caribbeans and 85.3 for South Asians).

Diabetes duration was significant, with Caucasians having had diabetes longer than Afro-Caribbeans or South Asian patients. Whites also had lower systolic BP than Afro-Caribbeans or South Asians but there was no difference in diastolic BP. Whites had lower LDL, but there was no difference in HDL. South Asians had a lower BMI than

Afro-Caribbeans or Caucasians. Caucasians were more likely to have ever been a smoker, but the rates of current smokers are the same across ethnicities (Table 3.12). So the differences in risk factors between ethnic groups in R0 & R2+R3 were similar and risk factor differences seem to be determined by ethnicity and not by severity of DR.

Table 3.12: (continued over two pages) Characteristic of study people with pre-proliferative and proliferative retinopathy (R2 and R3)

Characteristic	Total	White British	Afro-Caribbean	South Asian	Others	F/X2	P
Total	991 (100.0)	528 (53.3)	342 (34.5)	106 (10.7)	15 (1.4)		
Type of diabetes	*					X2(3) =90.13	.000
T1D, n (%)	250 (25.2)	194 (36.7)	38 (11.1)	11 (10.4)	7 (50.0)		
T2D, n (%)	741 (74.8)	334 (63.3)	304 (88.9)	95 (89.6)	7 (50.0)		
Medication for Hyperglycaemia	*					X2(6) =49.64	.000
On tablets, n (%)	257 (25.9)	125 (23.7)	96 (28.1)	32 (30.2)	3 (21.4)		
On insulin, n (%)	373 (37.6)	247 (46.8)	95 (27.8)	25 (23.6)	6 (42.8)		
On both, n (%)	338 (34.1)	140 (26.5)	147 (43.0)	48 (45.3)	3 (21.4)		
Diabetes duration, years, mean ± SD	19.82 ± 10.836 *	21.55 ± 11.86	18.48 ± 9.37	15.77 ± 7.94	17.60 ± 10.40	F(3, 986)= 11.63	.000
On treatment for hypertension, n (%)	820 (82.7)	428 (81.1)	286 (83.6)	93 (87.7)	13 (86.7)	X2(3) =3.17	.366
Systolic BP, mean ± SD	136.77 ± 19.57*	134.06 ± 18.46	140.10 ± 20.53	138.71 ± 19.13	143.60 ± 25.52	F(3, 979)= 7.80	.000
Diastolic BP, mean ± SD	74.79 ± 11.18	74.12 ± 10.44	75.53 ± 12.28	75.12 ± 10.41	79.80 ± 14.11	F(3, 979)= 2.54	.055
LDL, mean ± SD	2.11 ± 0.95*	2.03 ± 0.95	2.23 ± 0.89	2.12 ± 1.05	2.24 ± 1.11	F(3, 939)= 3.00	.030

Characteristic	Total	White British	Afro-Caribbean	South Asian	Others	F/X2	P
HDL, mean ± SD	1.50 ± 0.65	1.52 ± 0.65	1.49 ± 0.63	1.46 ± 0.75	1.09 ± 0.33	F(3, 940)= 1.92	.124
BMI, mean ± SD	29.53 ± 7.03*	29.19 ± 7.60	30.61 ± 6.34	27.91 ± 5.88	28.38 ± 4.71	F(3, 972)= 5.07	.002
eGFR, mean ± SD	63.47 ± 68.53	68.22 ± 76.55	56.94 ± 63.86	60.37 ± 35.07	63.50 ± 28.01	F(3, 910)= 1.80	.145
Albumin Ratio, mean ± SD	37.50 ± 113.87	29.09 ± 102.97	47.36 ± 122.93	40.06 ± 123.90	87.19 ± 159.45	F(3, 747) = 2.14	.094
Smoker	*					X2(6) =36.48	.000
No, n (%)	425 (54.3)	203 (47.1)	167 (64.7)	53 (66.3)	2 (14.3)		
Ex-smoker, n (%)	211 (26.9)	141 (32.7)	50 (19.4)	14 (17.5)	6 (42.9)		
Current, n (%)	147 (168.8)	87 (20.2)	41 (15.9)	13 (16.3)	6 (42.9)		

*** F = ANOVA, X 2= chi-square**

3.4.2 Risk Factor for pre-proliferative and proliferative retinopathy (R2 and R3)

Logistic regression analysis was performed to identify the significant risk factors for sight threatening diabetic retinopathy (R2 & R3) (Table 3.13). There was no increased risk with gender. Among ethnic minority groups Afro-Caribbeans were at more risk to develop R2/R3 (OR 1.53) than Caucasians. There was no effect of age. People with T2D were only 58% as likely to develop R2R3 versus T1D (table 3.13).

Treatment with insulin increased risk by 3.97 times more than for oral medication alone, and was 6.68 times as great if patients were on both insulin and oral medication compared to tablets alone. Both duration of diabetes and diabetic control (HbA1c) affected the risk for pre-proliferative and proliferative DR: 2.6 if diabetes duration was

3-10 years compared to <3; and 27 times more in people with 10+ years duration of diabetes. Increasing HbA1C also increased the risk of sight threatening retinopathy R2/R3 2.19 times if HbA1c between 7.1 – 9, 3.23 times for 9.1-11 and 2.87 times if HbA1c >11.1 compared to values of < 7.

Presence for hypertension, and both systolic BP and diastolic BP also affected the risk for retinopathy: on treatment for HT = 3.07 times more than if not. Increased blood pressure increased the risk of R2/R3, those in the 4th quartile of systolic BP (>145) had high risk (OR 2.20) compared to those in the 1st quartile (<117). Similarly trend was, seen with diastolic blood pressure, with odds ratios of 0.59, 0.55 and 0.56 in the 2nd, 3rd and 4th quartiles respectively.

People on treatment with cholesterol lowering drugs were 1.71 times as likely to develop R2R3. For total cholesterol, those in the 2nd quartile were only 70% as likely as those in the 1st, while those in the 4th are 23% more likely (1.23 times as likely). For LDL, those in the 2nd, 3rd and 4th quartiles were 0.84, 0.68 and 0.75 times as likely as the 1st quartile. For HDL, the 2nd, 3rd and 4th quartiles were 1.34, 2.38 and 1.91 times as likely (respectively) than the 1st quartile.

For BMI, the 2nd, 3rd and 4th quartiles were 1.23, 1.28 and 1.35 times as likely, respectively, than the 1st to develop R2R3. Impaired renal function also affected the development of R2R3: for eGFR, greater than 90 people were 0.48 times less likely to have R2/R3 than those with <90. Albumin ratio over 1 corresponds with a 1.65 times as likely as those <1.

Smoking status did not affect likelihood of R2R3. Presence of both microvascular and macrovascular complication severely affected the likelihood of R2R3: amputation 28

times, angioplasty patients 2.16 times, coronary artery bypass graft (CABG) 2.55 times, microalbuminuria 3.91 times, on renal dialysis 15 times, presence of foot ulcer 6.57 times, peripheral neuropathy 4.08 times, myocardial infarctions 2.46 times and cerebro-vascular accident 2.06 times respectively. Those with no symptoms were 0.25 times as likely to develop R2R3.

Table 3.13: (continued over three pages) Table showing OR and risk of developing sight threatening retinopathy versus no retinopathy

	Number at Risk	%	OR (95% CI)	P Value
Gender				
Male	531	41.4	1.00	0.42
Female	460	43.3	1.08 (0.92-1.27)	
Ethnicity				
Caucasians	528	39.8	1.00	<0.001
Afro-Caribbean	342	50.3	1.53 (1.27-1.84)	
South Asian	106	40.2	1.01 (0.77-1.33)	
Others	15	19.5	0.37 (0.21-0.65)	
Age, per year			1.00 (0.99-1.01)	0.84
Type of diabetes				
T1D	250	52.9	1.00	<0.001
T2D	741	39.6	0.58 (0.48-0.72)	
Medication for Hyperglycaemia				
On tablets	257	24.9	1.00	<0.001
On insulin	373	56.8	3.97 (3.22-4.89)	
On both	338	68.8	6.68 (5.27-8.47)	
Diabetes duration				
Less than 3 years	24	7.5	1.00	<0.001
3-10 years	148	17.6	2.62 (1.67-4.13)	
10 years or longer	819	68.9	27.12 (17.57-41.84)	
HbA1c %				
< 7	214	28.8	1.00	<0.001
7.1-9	474	46.9	2.19 (1.79-2.68)	
9.1-11	210	56.6	3.23 (2.49-4.19)	
> 11.1	73	53.7	2.87 (1.98-4.17)	
On treatment for hypertension				
No	171	24.4	1.00	<0.001

	Number at Risk	%	OR (95% CI)	P Value
Yes	820	49.8	3.07 (2.52-3.74)	
Systolic BP				
1st Quartile < 117	134	38.7	1.00	<0.001
2nd Quartile 117-131	257	34.1	0.82 (0.63-1.07)	
3rd Quartile 131-145	289	42.7	1.18 (0.91-1.53)	
4th Quartile ≥ 145	304	58.1	2.20 (1.66-2.90)	
Diastolic BP				
1st Quartile < 65	188	54.8	1.00	<0.001
2nd Quartile 65-72	235	41.7	0.59 (0.45-0.77)	
3rd Quartile 72-79	205	40.2	0.55 (0.42-0.73)	
4th Quartile ≥ 79	356	40.4	0.56 (0.43-0.72)	
Cholesterol Lowering Medication				
No	279	34.4	1.00	<0.001
Yes	709	47.2	1.71 (1.43-2.04)	
Total cholesterol				
1st Quartile < 3	94	49.5	1.00	0.01
2nd Quartile 3-5	600	40.5	0.70 (0.51-0.94)	
3rd Quartile 5-7	248	46.7	0.90 (0.64-1.25)	
4th Quartile ≥ 7	29	54.7	1.23 (0.67-2.27)	
LDL				
1st Quartile < 1.5	260	48.2	1.00	0.02
2nd Quartile 1.5-2.25	347	44.0	0.84 (0.68-1.05)	
3rd Quartile 2.25-3.00	181	38.8	0.68 (0.53-0.87)	
4th Quartile ≥ 3	156	41.3	0.75 (0.58-0.98)	
HDL				
1st Quartile < 1.5	547	39.7	1.00	<0.001
2nd Quartile 1.5-2.25	294	46.9	1.34 (1.11-1.62)	
3rd Quartile 2.25-3.00	75	61.0	2.38 (1.63-3.47)	
4th Quartile ≥ 3	30	55.6	1.91 (1.10-3.29)	
BMI				
1st Quartile < 26.4	323	39.1	1.00	0.04
2nd Quartile 26.4-29.8	251	44.1	1.23 (0.99-1.53)	
3rd Quartile 29.8-33.8	200	45.1	1.28 (1.02-1.62)	
4th Quartile ≥ 33.8	203	46.5	1.35 (1.07-1.71)	

	Number at Risk	%	OR (95% CI)	P Value
eGFR				
< 90	799	47.0	1.00	<0.001
>= 90	116	30.2	0.48 (0.38-0.62)	
Albumin Creatinine Ratio (ACR)				
< 1	205	36.2	1.00	<0.001
>= 1	546	48.3	1.65 (1.34-2.03)	
Smoker				
No	560	43.6	1.00	0.26
Ex-smoker	211	41.2	0.91 (0.74-1.12)	
Current	147	39.1	0.83 (0.66-1.05)	
Microvascular and macrovascular complication				
Amputation				
No	950	42.1	1.00	<0.001
Yes	41	95.3	28.18 (6.80-116.80)	
Angioplasty				
No	883	41.6	1.00	<0.001
Yes	108	60.7	2.16 (1.58-2.96)	
CABG				
No	881	41.4	1.00	<0.001
Yes	110	64.3	2.55 (1.85-3.53)	
Dialysis				
No	816	38.7	1.00	<0.001
Yes	175	90.7	15.37 (9.38-25.16)	
Foot Ulcer				
No	832	39.6	1.00	<0.001
Yes	159	81.1	6.57 (4.54-9.49)	
Microalbuminuria				
No	731	37.9	1.00	<0.001
Yes	260	70.5	3.91 (3.07-4.98)	
Myocardial infarction				
No	834	40.7	1.00	<0.001
Yes	157	62.8	2.46 (1.88-3.23)	
Stroke				
No	878	41.6	1.00	<0.001
Yes	113	59.5	2.06 (1.52-2.78)	
Peripheral neuropathy				

	Number at Risk	%	OR (95% CI)	P Value
No	749	38.2	1.00	<0.001
Yes	242	71.6	4.08 (3.17-5.26)	
No complication				
No	728	57.9	1.00	<0.001
Yes	263	25.2	0.25 (0.21-0.29)	

3.4.3 Risk factor for R2R3 in type 1 diabetes

South Asians were more likely to be male and were less likely to have low levels of HbA1C. Retinopathy, maculopathy and age did not differ by ethnicity. Hypertension treatment as a whole did not differ among ethnicities, nor do type of medication to control blood pressure although Afro-Caribbeans were more likely to be on calcium channel blockers (CCB). Whites had lower systolic BP, whereas Afro-Caribbeans had higher diastolic BP. Use of cholesterol lowering medication, total cholesterol, LDL, HDL, eGFR, ACR, smoking, amputation, angioplasty, CABG, dialysis, foot ulcer, microalbuminia, myocardial infarction, stroke and peripheral neuropathy, did not differ among ethnicities. Afro-Caribbeans had higher BMI (Table 3.14).

Table 3.14: (continued over four pages) Risk factors for retinopathy in people with type 1 diabetes

All except age are n (% within ethnicity)	Total	White British	Afro-Caribbean	South Asian	Other	F/X2	P
Gender	*					X2(3)= 10.43	.015
Male	247 (52.2)	185 (52.1)	31 (41.3)	22 (71.0)	9 (75.0)		
Female	226 (47.8)	170 (47.9)	44 (58.7)	9 (29.0)	3 (25.0)		
Retinopathy						X2(3)= 4.50	.212
No retinopathy (R0)	223 (47.1)	161 (45.4)	37 (49.3)	20 (64.5)	5 (41.7)		
Sight threatening retinopathy (R2 and R3)	250 (52.9)	194 (54.6)	38 (50.7)	11 (35.5)	7 (58.3)		
Maculopathy in either eye						X2(3)= 2.35	.503
No maculopathy (M0)	320 (67.8)	234 (65.9)	54 (73.0)	23 (74.2)	9 (75.0)		
Any maculopathy (M1)	152 (32.2)	121 (34.1)	20 (27.0)	8 (25.8)	3 (25.0)		
Age, mean ± SD	43.10 ± 13.58	43.22± 13.28	42.51±13.96	45.26± 17.32	37.58± 7.95	F(3, 469)=0.97	.403
Diabetes duration	*					X2(6)= 18.80	.005
Less than 3 years	31 (6.6)	23 (6.5)	6 (8.0)	1 (3.2)	1 (8.3)		
3-10 years	93 (19.7)	57 (16.1)	20 (26.7)	14 (45.2)	2 (16.7)		
10 years or longer	349 (73.8)	275 (77.5)	49 (65.3)	16 (51.6)	9 (75.0)		
HbA1c %	*					X2(9)= 38.36	.000
< 7	89 (19.2)	65 (18.5)	18 (24.7)	2 (7.1)	4 (33.3)		
7.1-9	221 (47.6)	182 (51.9)	20 (27.4)	13 (46.4)	6 (50.0)		
9.1-11	115 (24.8)	84 (23.9)	18 (24.7)	11 (39.3)	2 (16.7)		
> 11.1	39 (8.4)	20 (5.7)	17 (23.3)	2 (7.1)	0 (0.0)		

All except age are n (% within ethnicity)	Total	White British	Afro-Caribbean	South Asian	Other	F/X2	P
On treatment for hypertension						X2(3)= 6.64	.084
Yes	243 (51.4)	192 (54.1)	30 (40.0)	17 (54.8)	4 (33.3)		
No	230 (48.6)	163 (45.9)	45 (60.0)	14 (45.2)	8 (66.7)		
Medication for hypertension							
ACE						X2(3)= 4.14	.247
No	316 (67.4)	243 (68.8)	49 (65.3)	19 (65.5)	5 (41.7)		
Yes	153 (32.6)	110 (31.2)	26 (34.7)	10 (34.5)	7 (58.3)		
ARB						X2(3)= 7.06	.070
No	414 (88.3)	313 (88.7)	61 (81.3)	28 (96.6)	12 (100.0)		
Yes	55 (11.7)	40 (11.3)	14 (18.7)	1 (3.4)	0 (0.0)		
Beta blocker						X2(3)= 2.89	.409
No	422 (90.0)	322 (91.2)	64 (85.3)	25 (86.2)	11 (91.7)		
Yes	47 (10.0)	31 (8.8)	11 (14.7)	4 (13.8)	1 (8.3)		
CCB	*					X2(3)= 13.27	.004
No	393 (83.8)	304 (86.1)	53 (70.7)	24 (82.8)	12 (100.0)		
Yes	76 (16.2)	49 (13.9)	22 (29.3)	5 (17.2)	0 (0.0)		
Diurectic						X2(3)= 5.98	.113
No	416 (88.7)	319 (90.4)	62 (82.7)	26 (89.7)	9 (75.0)		
Yes	53 (11.3)	34 (9.6)	13 (17.3)	3 (10.3)	3 (25.0)		
Systolic BP	*					X2(9)= 24.74	.003
1st Quartile < 117	123 (26.2)	103 (29.2)	14 (18.9)	6 (19.4)	0 (0.0)		
2nd Quartile 117-131	172 (36.6)	135 (38.2)	21 (28.4)	10 (32.3)	6 (50.0)		

All except age are n (% within ethnicity)	Total	White British	Afro-Caribbean	South Asian	Other	F/X2	P
3rd Quartile 131-145	116 (24.7)	75 (21.2)	26 (35.1)	13 (41.9)	2 (16.7)		
4th Quartile ≥ 145	59 (12.6)	40 (11.3)	13 (17.6)	2 (6.5)	4 (33.3)		
Diastolic BP	*					X2(9)= 26.49	.002
1st Quartile < 65	70 (14.9)	59 (16.7)	6 (8.1)	5 (16.1)	0 (0.0)		
2nd Quartile 65-72	132 (28.1)	111 (31.4)	13 (17.6)	7 (22.6)	1 (8.3)		
3rd Quartile 72-79	110 (23.4)	82 (23.2)	15 (20.3)	9 (29.0)	4 (33.3)		
4th Quartile ≥ 79	158 (33.6)	101 (28.6)	40 (54.1)	10 (32.3)	7 (58.3)		
Statin for cholesterol						X2(3)= 2.05	.562
No	255 (54.4)	198 (56.1)	38 (50.7)	14 (48.3)	5 (41.7)		
Yes	214 (45.6)	155 (43.9)	37 (49.3)	15 (51.7)	7 (58.3)		
Total cholesterol						X2(9)= 5.48	.791
1st Quartile < 3	36 (7.8)	29 (8.3)	4 (5.6)	3 (10.3)	0 (0.0)		
2nd Quartile 3-5	283 (61.4)	216 (61.7)	43 (60.6)	16 (55.2)	8 (72.7)		
3rd Quartile 5-7	125 (27.1)	95 (27.1)	20 (28.2)	8 (27.6)	2 (18.2)		
4th Quartile ≥ 7	17 (3.7)	10 (2.9)	4 (5.6)	2 (6.9)	1 (9.1)		
LDL						X2(9)= 16.52	.057
1st Quartile < 1.5	108 (24.2)	84 (24.7)	15 (21.4)	8 (32.0)	1 (9.1)		
2nd Quartile 1.5-2.25	161 (36.1)	129 (37.9)	24 (34.3)	7 (28.0)	1 (9.1)		
3rd Quartile 2.25-3.00	91 (20.4)	72 (21.2)	12 (17.1)	3 (12.0)	4 (36.4)		
4th Quartile ≥ 3	86 (19.3)	55 (16.2)	19 (27.1)	7 (28.0)	5 (45.5)		
HDL						X2(9)= 8.79	.457
1st Quartile < 1.5	210 (47.1)	154 (45.3)	34 (48.6)	17 (68.0)	5 (45.5)		

All except age are n (% within ethnicity)	Total	White British	Afro-Caribbean	South Asian	Other	F/X2	P
2nd Quartile 1.5-2.25	171 (38.3)	133 (39.1)	27 (38.6)	5 (20.0)	6 (54.5)		
3rd Quartile 2.25-3.00	51 (11.4)	43 (12.6)	6 (8.6)	2 (8.0)	0 (0.0)		
4th Quartile ≥ 3	14 (3.1)	10 (2.9)	3 (4.3)	1 (4.0)	0 (0.0)		
BMI	*					X2(9)= 39.14	.000
1st Quartile < 26.4	248 (52.8)	205 (58.1)	22 (29.7)	15 (48.4)	6 (50.0)		
2nd Quartile 26.4-29.8	110 (23.4)	81 (22.9)	21 (28.4)	6 (19.4)	2 (16.7)		
3rd Quartile 29.8-33.8	63 (13.4)	40 (11.3)	12 (16.2)	9 (29.0)	2 (16.7)		
4th Quartile ≥ 33.8	49 (10.4)	27 (7.6)	19 (25.7)	1 (3.2)	2 (16.7)		
eGFR						X2(3)= 5.25	.155
< 90	299 (71.5)	223 (69.7)	54 (83.1)	15 (68.2)	7 (63.6)		
> 90	119 (28.5)	97 (30.3)	11 (16.9)	7 (31.8)	4 (36.4)		
ACR						X2(3)= 5.19	.158
< 1	123 (36.7)	96 (39.0)	16 (26.2)	9 (47.4)	2 (22.2)		
> 1	212 (63.3)	150 (61.0)	45 (73.8)	10 (52.6)	7 (77.8)		
Smoker						X2(6)= 9.21	.162
No	287 (64.9)	218 (65.1)	50 (73.5)	14 (50.0)	5 (45.5)		
Ex-smoker	76 (17.2)	57 (17.0)	7 (10.3)	9 (32.1)	3 (27.3)		
Current	79 (17.9)	60 (17.9)	11 (16.2)	5 (17.9)	3 (27.3)		
Amputation						X2(3)= 6.73	.081
No	459 (98.7)	347 (99.1)	72 (97.3)	29 (100.0)	11 (.917)		
Yes	6 (1.3)	3 (0.9)	2 (2.7)	0 (0.0)	1 (8.3)		
Angioplasty						X2(3)=	.223

All except age are n (% within ethnicity)	Total	White British	Afro-Caribbean	South Asian	Other	F/X2	P
						4.38	
No	448 (96.3)	338 (96.6)	72 (97.3)	26 (89.7)	12 (100.0)		
Yes	17 (3.7)	12 (3.4)	2 (2.7)	3 (10.3)	0 (0.0)		
CABG						X2(3)= 3.22	.359
No	453 (97.4)	343 (98.0)	70 (94.6)	28 (96.6)	12 (100.0)		
Yes	12 (2.6)	7 (2.0)	4 (5.4)	1 (3.4)	0 (0.0)		
Dialysis						X2(3)= 2.57	.463
No	407 (87.5)	311 (88.9)	61 (82.4)	25 (86.2)	10 (83.3)		
Yes	58 (12.5)	39 (11.1)	13 (17.6)	4 (13.8)	2 (16.7)		
Foot Ulcer						X2(3)= 3.81	.283
No	424 (91.2)	318 (90.9)	67 (90.5)	29 (100.0)	10 (83.3)		
Yes	41 (8.8)	32 (9.1)	7 (9.5)	0 (0.0)	2 (16.7)		
Micro-albuminuria						X2(3)= 3.08	.380
No	382 (82.2)	292 (83.4)	58 (78.4)	24 (82.8)	8 (66.7)		
Yes	83 (17.8)	58 (16.6)	16 (21.6)	5 (17.2)	4 (33.3)		
Myocardial infarction						X2(3)= 4.84	.184
No	445 (95.7)	338 (96.6)	69 (93.2)	26 (89.7)	12 (100.0)		
Yes	20 (4.3)	12 (3.4)	5 (6.8)	3 (10.3)	0 (0.0)		
Stroke						X2(3)= 6.86	.077
No	445 (95.7)	339 (96.9)	68 (91.9)	26 (89.7)	12 (100.0)		
Yes	20 (4.3)	11 (3.1)	6 (8.1)	3 (10.3)	0 (0.0)		
Peripheral neuropathy						X2(3)= 0.27	.965
No	395	297	64	24	10		

All except age are n (% within ethnicity)	Total	White British	Afro-Caribbean	South Asian	Other	F/X2	P
	(84.9)	(84.9)	(86.5)	(82.8)	(83.3)		
Yes	70 (15.1)	53 (15.1)	10 (13.5)	5 (17.2)	2 (16.7)		

*** F = ANOVA, X 2= chi-square**

3.4.4 Risk factor for type 2 diabetes

Risk factors in T2D included male gender in South Asians (Table 3.15). Caucasians were likely to be on insulin and oral medication for hyperglycemia and had diabetes for 10 years or longer. South Asians had lower HbA1C. Afro-Caribbeans had poor glycaemic control, have high systolic and diastolic blood pressure and have high BMI and LDL.

Table 3.15: (continued over four pages) Risk factors for retinopathy in people with type 2 diabetes

All except age are n (% within ethnicity)	Total	White British	Afro-Caribbean	South Asian	Other	F/X2	P
Gender	*					X2(3)= 8.21	.042
Male	1036 (55.3)	556 (57.3)	306 (50.6)	136 (58.4)	38 (58.5)		
Female	837 (44.7)	414 (42.7)	299 (49.4)	97 (41.6)	27 (41.5)		
Retinopathy	*					X2(3)= 59.90	.000
No Retinopathy (R0)	1132 (60.4)	636 (65.6)	301 (49.8)	138 (59.2)	57 (87.7)		
Sight threatening retinopathy (R2 and R3)	741 (39.6)	334 (34.4)	304 (50.2)	95 (40.8)	8 (12.3)		
Maculopathy in either eye	*					X2(3)= 42.98	.000
No maculopathy (M0)	1306 (69.8)	714 (73.6)	368 (60.9)	165 (71.1)	59 (90.8)		
Any maculopathy (M1)	565 (30.2)	256 (26.4)	236 (39.1)	67 (28.9)	6 (9.2)		
Age, mean ± SD	65.12 ±12.13	66.60± 12.05	63.66± 12.43	62.24 ±11.09	67.02 ±10.86	F(3, 1869)= 12.86	.000
Medication for Hyperglycaemia	*					X2(6)= 34.26	.000
On tablets, n (%)	1021 (54.5)	551 (56.8)	296 (48.9)	126 (54.1)	48 (73.8)		
On insulin, n (%)	228 (12.2)	117 (12.1)	84 (13.9)	23 (9.9)	4 (6.2)		
On both, n (%)	469 (25.0)	211 (21.8)	185 (30.6)	68 (29.2)	5 (7.7)		
Diabetes duration	*					X2(6)= 31.63	.000
Less than 3 years	287 (15.3)	162 (16.7)	83 (13.7)	27 (11.6)	15 (23.1)		
3-10 years	746 (39.8)	411 (42.4)	206 (34)	96 (41.2)	33 (50.8)		
10 years or longer	840 (44.8)	397 (40.9)	316 (52.2)	110 (47.2)	17 (26.2)		
HbA1c %	*					X2(9)= 37.31	.000
(4 quarters : < 7	655 (36.4)	360 (38.1)	202 (35.7)	61 (27.1)	32 (51.6)		

All except age are n (% within ethnicity)	Total	White British	Afro-Caribbean	South Asian	Other	F/X2	P
7.1-9	789 (43.9)	429 (45.4)	224 (39.6)	111 (49.3)	25 (40.3)		
9.1-11	256 (14.2)	110 (11.7)	99 (17.5)	44 (19.6)	3 (4.8)		
> 11.1	97 (5.4)	45 (4.8)	41 (7.2)	9 (4.0)	2 (3.2)		
On treatment for hypertension						X2(3)= 1.44	.697
Yes	457 (24.4)	229 (23.6)	158 (26.1)	55 (23.6)	15 (23.1)		
No	1416 (75.6)	741 (76.4)	447 (73.9)	178 (76.4)	50 (76.9)		
Medication for hypertension							
ACE						X2(3)= 5.79	.122
No	1008 (54.7)	504 (52.7)	351 (58.7)	120 (53.3)	33 (51.6)		
Yes	835 (45.3)	452 (47.3)	247 (41.3)	105 (46.7)	31 (48.4)		
ARB	*					X2(3)= 11.98	.007
No	1423 (77.2)	766 (80.1)	436 (72.9)	175 (77.8)	46 (71.9)		
Yes	420 (22.8)	190 (19.9)	162 (27.1)	50 (22.2)	18 (28.1)		
Beta blocker	*					X2(3)= 11.52	.009
No	1435 (77.9)	730 (76.4)	488 (81.6)	163 (72.4)	54 (84.4)		
Yes	408 (22.1)	226 (23.6)	110 (18.4)	62 (27.6)	10 (15.6)		
CCB	*					X2(3)= 10.85	.013
No	1210 (65.7)	658 (68.8)	363 (60.7)	148 (65.8)	41 (64.1)		
Yes	633 (34.3)	298 (31.2)	235 (39.3)	77 (34.2)	23 (35.9)		
Diuretic						X2(3)= 4.97	.174
No	1376 (74.7)	720 (75.3)	430 (71.9)	178 (79.1)	48 (75)		
Yes	467 (25.3)	236 (24.7)	168 (28.1)	47 (20.9)	16 (25)		

All except age are n (% within ethnicity)	Total	White British	Afro-Caribbean	South Asian	Other	F/X2	P
Systolic BP	*					X2(9)= 28.34	.001
1st Quartile < 117	223 (12.2)	134 (14)	53 (9.2)	32 (14)	4 (6.2)		
2nd Quartile 117-131	581 (31.8)	329 (34.4)	160 (27.6)	71 (31)	21 (32.3)		
3rd Quartile 131-145	561 (30.7)	275 (28.8)	190 (32.8)	69 (30.1)	27 (41.5)		
4th Quartile ≥ 145	464 (25.4)	218 (22.8)	176 (30.4)	57 (24.9)	13 (20)		
Diastolic BP	*					X2(9)= 35.42	.000
1st Quartile < 65	273 (14.9)	147 (15.4)	88 (15.2)	32 (14)	6 (9.2)		
2nd Quartile 65-72	432 (23.6)	245 (25.6)	120 (20.7)	56 (24.5)	11 (16.9)		
3rd Quartile 72-79	400 (21.9)	235 (24.6)	102 (17.6)	53 (23.1)	10 (15.4)		
4th Quartile ≥ 79	724 (39.6)	329 (34.4)	269 (46.5)	88 (38.4)	38 (58.5)		
Statin for cholesterol						X2(3)= 4.91	.179
No	556 (30.2)	286 (29.9)	173 (28.9)	81 (36)	16 (25)		
Yes	1287 (69.8)	670 (70.1)	425 (71.1)	144 (64)	48 (75)		
Total cholesterol						X2(9)= 12.01	.212
1st Quartile < 3	154 (8.6)	85 (9)	43 (7.6)	21 (9.5)	5 (7.8)		
2nd Quartile 3-5	1198 (66.8)	642 (68.2)	367 (64.7)	150 (67.9)	39 (60.9)		
3rd Quartile 5-7	406 (22.6)	195 (20.7)	149 (26.3)	43 (19.5)	19 (29.7)		
4th Quartile ≥ 7	36 (2)	20 (2.1)	8 (1.4)	7 (3.2)	1 (1.6)		
LDL	*					X2(9)= 68.75	.000
1st Quartile < 1.5	431 (25)	256 (28.3)	89 (16.4)	78 (36.1)	8 (13.1)		
2nd Quartile 1.5-2.25	628 (36.4)	345 (38.1)	186 (34.2)	74 (34.3)	23 (37.7)		
3rd Quartile 2.25-3.00	376 (21.8)	166 (18.3)	158 (29)	39 (18.1)	13 (21.3)		

All except age are n (% within ethnicity)	Total	White British	Afro-Caribbean	South Asian	Other	F/X2	P
4th Quartile ≥ 3	292 (16.9)	139 (15.3)	111 (20.4)	25 (11.6)	17 (27.9)		
HDL						X2(9)= 15.12	.088
1st Quartile < 1.5	1169 (67.3)	649 (71.2)	347 (63.4)	133 (61)	40 (65.6)		
2nd Quartile 1.5-2.25	456 (26.3)	209 (22.9)	162 (29.6)	68 (31.2)	17 (27.9)		
3rd Quartile 2.25-3.00	72 (4.1)	33 (3.6)	26 (4.8)	10 (4.6)	3 (4.9)		
4th Quartile ≥ 3	40 (2.3)	20 (2.2)	12 (2.2)	7 (3.2)	1 (1.6)		
Body mass index	*					X2(9)= 79.59	.000
1st Quartile < 26.4	579 (32.1)	333 (35.2)	131 (23)	106 (46.5)	9 (14.1)		
2nd Quartile 26.4-29.8	459 (25.4)	222 (23.5)	158 (27.8)	66 (28.9)	13 (20.3)		
3rd Quartile 29.8-33.8	380 (21)	178 (18.8)	147 (25.8)	33 (14.5)	22 (34.4)		
4th Quartile ≥ 33.8	388 (21.5)	212 (22.4)	133 (23.4)	23 (10.1)	20 (31.3)		
eGFR	*					X2(3)= 17.49	.001
< 90	1400 (84.1)	735 (83.3)	461 (88.7)	161 (78.5)	43 (74.1)		
> 90	265 (15.9)	147 (16.7)	59 (11.3)	44 (21.5)	15 (25.9)		
ACR	*					X2(3)= 9.21	.027
< 1	444 (32.6)	229 (32.6)	122 (28.7)	77 (41.2)	16 (33.3)		
> 1	919 (67.4)	474 (67.4)	303 (71.3)	110 (58.8)	32 (66.7)		
Smoker	*					X2(6)= 102.62	.000
No	998 (57.7)	432 (47.4)	374 (69.5)	164 (73.2)	28 (48.3)		
Ex-smoker	436 (25.2)	296 (32.5)	94 (17.5)	25 (11.2)	21 (36.2)		
Current	297 (17.2)	183 (20.1)	70 (13)	35 (15.6)	9 (15.5)		
Amputation						X2(3)= 2.13	.546

All except age are n (% within ethnicity)	Total	White British	Afro-Caribbean	South Asian	Other	F/X2	P
No	1797 (98)	929 (97.9)	586 (97.7)	220 (98.7)	62 (100)		
Yes	37 (2)	20 (2.1)	14 (2.3)	3 (1.3)	0 (0)		
Angioplasty	*					X2(3)= 37.54	.000
No	1673 (91.2)	860 (90.6)	569 (94.8)	183 (82.1)	61 (98.4)		
Yes	161 (8.8)	89 (9.4)	31 (5.2)	40 (17.9)	1 (1.6)		
CABG						X2(3)= 6.21	.102
No	1675 (91.3)	859 (90.5)	561 (93.5)	198 (88.8)	57 (91.9)		
Yes	159 (8.7)	90 (9.5)	39 (6.5)	25 (11.2)	5 (8.1)		
Dialysis						X2(3)= 0.79	.852
No	1699 (92.6)	884 (93.2)	552 (92)	206 (92.4)	57 (91.9)		
Yes	135 (7.4)	65 (6.8)	48 (8)	17 (7.6)	5 (8.1)		
Foot Ulcer						X2(3)= 5.10	.164
No	1679 (91.5)	856 (90.2)	556 (92.7)	208 (93.3)	59 (95.2)		
Yes	155 (8.5)	93 (9.8)	44 (7.3)	15 (6.7)	3 (4.8)		
Microalbuminuria						X2(3)= 2.01	.570
No	1548 (84.4)	800 (84.3)	502 (83.7)	190 (85.2)	56 (90.3)		
Yes	286 (15.6)	149 (15.7)	98 (16.3)	33 (14.8)	6 (9.7)		
Myocardial infarction	*					X2(3)= 11.47	.009
No	1604 (87.5)	819 (86.3)	543 (90.5)	185 (83)	57 (91.9)		
Yes	230 (12.5)	130 (13.7)	57 (9.5)	38 (17)	5 (8.1)		
Stroke						X2(3)= 1.33	.723
No	1664 (90.7)	855 (90.1)	548 (91.3)	203 (91)	58 (93.5)		

All except age are n (% within ethnicity)	Total	White British	Afro-Caribbean	South Asian	Other	F/X2	P
Yes	170 (9.3)	94 (9.9)	52 (8.7)	20 (9)	4 (6.5)		
Peripheral neuropathy						X2(3)= 4.29	.232
No	1566 (85.4)	810 (85.4)	516 (86)	183 (82.1)	57 (91.9)		
Yes	268 (14.6)	139 (14.6)	84 (14)	40 (17.9)	5 (8.1)		

*** F = ANOVA, X 2= chi-square**

3.4.5 Independent predictors of diabetic retinopathy and vision-threatening retinopathy

Age was a factor for T1D patients to develop R2R3 - with each year the odds increased by 5% (Table 3.16). However this was not true for T2D. Type 1 females were 43% more likely to develop R2R3- no sex differences for T2D. Ethnicity does not affect T1D patients' risk of developing R2R3, but for T2D Afro-Caribbeans are nearly twice as likely as Caucasians whites and South Asians are1.31% more likely than Caucasians.

Diabetes duration affects the likelihood of developing R2R3 for both types. For each 10 years of diabetes, odds increase fourfold for T1D and six fold for T2D. In people with T2D, for each increase of 0.5% in HbA1c results in a 16% increase in risk. There was no similar effect noted for T1D. Also for each 10-point increase in systolic BP risks of developing R2R3 increase 36% for type 1 and 20% for type 2.

Table 3.16: Independent predictors of diabetic retinopathy and vision-threatening retinopathy

	Overall (N=2346)		Type I (N=473)		Type II (N=1873)	
Risk Factor	**OR (95% CI)**	**P Value**	**OR (95% CI)**	**P Value**	**OR (95% CI)**	**P Value**
Age, per year	1.00 (0.99-1.01)	0.84	1.05 (1.04-1.07)	<0.001	1.00 (0.99-1.01)	0.44
Gender, female versus Male	1.08 (0.92-1.27)	0.36	1.43 (1.00-2.06)	0.05	0.99 (0.82-1.19)	0.91
Ethnicity						
Caucasians	1.00	<0.001	1.00	0.23	1.00	<0.001
Afro-Caribbean	1.53 (1.27-1.84)		0.85 (0.52-1.40)		1.92 (1.56-2.37)	
South Asian	1.01 (0.77-1.33)		0.46 (0.21-0.98)		1.31 (0.98-1.76)	
Others	0.37 (0.21-0.65)		1.16 (0.36-3.73)		0.27 (0.13-0.57)	
Duration of diabetes, per 10 years	4.79 (4.19-5.48)	<0.001	3.96 (3.11-5.06)	<0.001	6.02 (5.07-7.16)	<0.001
HbA1c, every 0.5% increase	1.12 (1.09-1.15)	<0.001	0.99 (0.95-1.04)	0.81	1.16 (1.12-1.19)	<0.001
Systolic BP, per 10 mmHg	1.19 (1.13-1.24)	<0.001	1.36 (1.21-1.54)	<0.001	1.20 (1.14-1.27)	<0.001
Use of diabetes medication, yes versus No	5.25 (3.21-8.56)	<0.001	-	-	7.62 (4.18-13.89)	<0.001

3.4.6 Microvascular and macrovascular complications in people with sight threatening retinopathy

There was a gradual increase in both microvascular and macrovascular complication increased with increase age and duration of diabetes (figure 3.2). Approximately 20% of people had both peripheral neuropathy and microalbuminuria whereas risk of

cardiovascular complication including angina and myocardial infarction was approximately 15%, and risk of stroke was 8%.

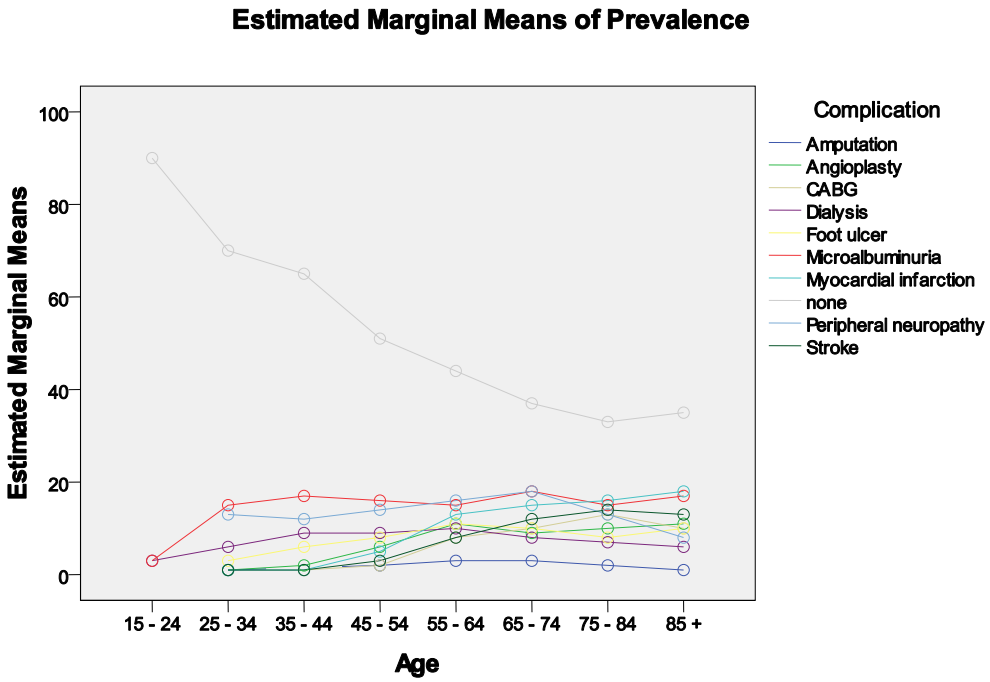


Figure 3.2: Microvascular and macrovascular complication in people with diabetes

3.5 Anatomical and visual outcome following vitrectomy in 2007-2009

3.5.1 Patient demographics

A total of 185 eyes of 158 patients had vitrectomy between January 2007 and December 2009. So 2 per 1000 diabetic patients per year required vitrectomy for diabetic eye disease. There were more Caucasians, males, and patients with T2D (Table 3.17). The mean age of the population was 54.08 (SD ± 14.15) years and duration of diabetes was 23.12 (SD± 8.82) in T1D and 17.1 ± (SD 8.12) years in T2D respectively.

A total of 110 patients were on treatment to lower blood pressure, 96 on cholesterol lowering agents, 13 patients with type I and 29 with T2D had ischemic heart disease (IHD); 13 with type I and 10 with type II were on renal dialysis and 4 each with T1D and T2D had co-existent cerebrovascular accidents respectively.

Table 3.17: Baseline Demographics

	Frequency	**%**
Ethnicity (n= 158)		
Caucasian	83	52.53
Afro-Caribbean	51	32.28
South Asian	17	10.75
Others	7	0.04
Gender (n= 158)		
Male	85	54.1
Female	73	45.9
Type of diabetes (n= 158)		
T1D	58	36.8
T2D	100	63.2
Indication for surgery (n = 185)		
Group A	117	63.24
Group B	60	32.43
Group C	8	4.32

Group A: Tractional Retinal Detachment (TRD), Group B: Non-Clearing Vitreous Haemorrhage (NCVH), Group C: Others

3.5.2 Effect of systemic factors

A logistic regression was performed to explore the baseline systemic factors that were significant predictors of visual success of the operation (Table 3.18). Group C was ignored in regression model due to very few numbers**.** The overall regression was significant, Chi-square (28) = 82.57, $p<0.001$, for a Cox & Snell $R^2=0.506$ and Nagelkerke $R^2=0.700$, meaning that the collective set of predictors were able to predict between an estimated 51 and 70% of the variance in the likelihood of an operation to be a complete success.

Duration of diabetes (p=0.01) was a significant predictor for likelihood for visual success. For each year the patient has had diabetes, the odds decreased by 0.69 for successful outcome. Likewise, if a patient was on insulin, the odds of visual success decreased by 0.04 (p=0.02). Presence of IHD was also significant negative predictor (OR: 0.047, p=0.01).

Time interval in months from decision to operate by physician as demonstrated by progressive TRD involving macular or NCVH to date of operation was also a significant negative predictor, with each month delay resulting in a decrease in likelihood of success, with an OR of 0.59, p=0.021.

Table 3.18: Logistic Regression Analysis showing the effect of various systemic variables

	B	S.E.	Sig.	Exp (B)
Group A (Tractional retinal detachment)	-20.46	24651.17	0.99	0.00
Group B (Non-Clearing vitreous haemorrhage)	-11.93	24651.17	1.00	0.00
Age	-0.05	0.06	0.39	0.95
Male	0.78	0.86	0.36	2.18
T1D	1.65	2.09	0.43	5.21
Duration	-.37	0.15	0.01	0.69
Insulin	-3.23	1.40	0.02	0.04
Duration of insulin	0.06	0.13	0.66	1.06
HbA1c	0.01	0.24	0.98	1.01
Hypertension	-2.419	1.32	0.07	0.09
Cerebro-vascular accident	-0.31	1.61	0.85	0.74
Total time interval screening positive PDR to first laser PRP (month)	-0.43	0.44	0.33	0.65
Interval (months): Clinician surgical decision to operations	-0.51	0.22	0.02	0.60
Intravitreal bevacizumab	-0.88	0.90	0.33	0.41
Appointments not attended by patient	-0.54	0.19	0.01	0.58

Group C was omitted in regression model due to very few numbers

3.5.3 Visual and anatomic outcome

Overall 93.2% eyes in group A, 100% in group B and C had stable vision (loss of <15 letters). 29.05% in group A, 65% in group B and 100% in group C had final visual acuity of better than ≥ 6/12 (LogMAR ≤0.3). Table 3.19 (a & b) shows the visual outcomes for each indication of vitrectomy. There was a mean gain of 18.08 ± 27.08 ETDRS letters in group A, 42.02 ± 27.17 ETDRS letters in group B and 17.37± 26.13 ETDRS letters in group C (Table 3.23). Overall 6.4% of the patients had best corrected

Snellen visual acuity of ≤6/60 in the better eye and were certified visually impaired as defined by National Screening Committee (NSC), UK.

Table 3.19 a: Visual outcome in patients following vitrectomy

	≥ 15 letters gain		**± 15 letters**		**≥ 15 letters loss**	
	First operated eye* N (%)	All eyes N (%)	First operated eye* N (%)	All eyes N (%)	First operated eye* N (%)	All eyes N (%)
TRD	45(46.4%)	58 (49.6%)	46 (47.4%)	51(43.6%)	6 (6.2%)	8 (6.8%)
NCVH	46 (88.6%)	51 (85.0%)	6 (11.4%)	9 (15.0%)	0 (0.0%)	0 (0.0%)
Other	3 (42.8%)	3 (37.5%)	4 (57.2%)	5 (62.5%)	0 (0.0%)	0 (0.0%)

NCVH: Non-clearing vitreous haemorrhage, TRD: Tractional retinal detachment

Overall anatomic success in this series was 84.32%. As ethnicity was found to be an independent risk factor for visual impairment and severity of diabetic retinopathy in the total cohort of people with diabetes in this region we estimated the visual outcome of vitrectomy in each ethnic group (Table 3.19b). Ethnic minorities had an average of 5.55 fewer letters than Caucasians, but minority status did not affect final visual outcome after controlling for all other factors.

Table 3.19b: Visual outcome in patients following vitrectomy by ethnicity and indication

	Tractional Retinal Detachment (TRD)			Non Clearing Vitreous Haemorrhage (NCVH)			Other		
	Baseline VA	**Final VA**	**Mean Change VA**	**Baseline VA**	**Final VA**	**Mean Change VA**	**Baseline VA**	**Final VA**	**Mean Change VA**
Afro-Caribbean (n=51)	26.91 ± 18.34	35.76 ± 27.20	8.83 ± 26.91	14.42 ± 16.71	60.52 ± 26.94	46.11 ± 26.13	58.0 ± 2.8	65.0 ± 14.14	7.0 ± 11.3
Caucasian (n=83)	19.71 ± 18.75	41.73 ± 27.53	22.03 ± 27.39	23.15 ± 18.52	66.55 ± 27.37	43.39 ± 27.41	44.2 ± 20.67	62.8 ± 29.82	18.6 ± 28.95
South Asian (n=17)	22.30 ± 16.09	53.30 ± 25.10	31.10 ± 26.05	17.86 ± 17.81	52.43 ± 27.32	34.57 ± 27.82	48.0	80.0	32.0
P value	0.435	0.064	0.045	0.104	0.248	0.167	0.604	0.681	0.294

VA: Visual Acuity

3.5.4 Ethnicity and appointments

The number of failed and attended appointments in the eye clinic from the date of decision to operate to last follow up was recorded from the hospital electronic record system. The average follow up in group A was 17.53 months, and for each missed appointment/cancelled by patient, after controlling for months, there was an estimated letter loss of 2.09 letters, significance of p=0.033. The average follow up in group B was 17.61 months, and for each missed appointment/cancelled by patient, after

controlling for months, there was an estimated letter loss of 2.40 letters, significance of p=0.033

3.5.5 Complications

a) Re-detachment and final retina status: A total of 36/117 (30.7%) of the eyes in group A had redo-vitrectomy out of which 17/36 (47.2%) for re-detachment of the retina, 14/36 (38.9%) for NCVH and 5/36 (13.9%) for epi-retinal membrane. In group B 6/60 (10.0%) underwent redo vitrectomy, with 4/6 (66.7%) for NCVH and 2/6 (33.3%) for retinal detachment. In this study, 11.35% (21/185) of the eyes had either detached retina or developed into phthisis at time of last follow up.

b) Cataract: Fewer 51 (27.57%) eyes had prior cataract extraction and 41 (22.62%) eyes required cataract operation at a mean of 8.01 months following primary vitrectomy while 26 (14.05%) eyes had combined primary vitrectomy and cataract extraction. Two eyes had subsequent zonular dialysis, while one eye had dropped nucleus during cataract extraction following vitrectomy and one eye had subluxated intra-ocular lens.

c) Post Vitrectomy Vitreous Haemorrhage and sight impairment: In this study, 43.25 % of the eyes had post vitrectomy haemorrhage with majority (31.89%) occurred on the first post operative day (Table 3.20).

Table 3.20: Frequency of post vitrectomy haemorrhage

	N (Total =185)	%	Mean episodes
Group A	59	31.89	1.23 (range 1-3)
Group B	15	8.10	1.47 (range1-2)
Group C	6	3.20	1.1 (range1-2)
No Haemorrhage	105	56.75	

Overall 23.56% of the patients had best corrected Snellen visual acuity of ≤6/18 (ETDRS of 65 letters) in the better eye and were certified visually impaired (VI).

3.6 Temporal relation of ESRD and Retinopathy

3.6.1 Prevalence of ESRD

There were a total of 167 (0.52%) patients with ESRD including Afro-Caribbean (n=59), Caucasian (n=76), South Asians (n= 19), and others (n=13) in a population of 31,773 patients with diagnosed diabetes living in the region. The prevalence of ESRD in each ethnic group was 0.45% in Caucasians, 0.71% in Afro-Caribbeans, 1.28% in South Asians. Out of 29,630 T2D, 120 (0.40%) patients were diagnosed with ESRD while 47 (2.2%) of T1D patients (n=2112) had ESRD. In patients with any form of retinopathy (n=12,788), the prevalence of ESRD increased to 1.18%.

Approximately 50% of the patients with ESRD had PDR while 8.17% of patients with PDR had ESRD. The prevalence of ESRD in patients with non –PDR was 0.58% which was not significantly different from the prevalence of ESRD in any patient with diabetes. The mean interval between diagnosis of PDR and ESRD was 3.71± 5.26 years and the interval was significantly shorter than those patients with non-PDR group with a

mean interval of 8.70 ± 5.35 years, the mean difference of 4.99 years being significant, t (148)=5.73, p<0.001.

3.6.2 Characteristics of patients with ESRD

Table 3.21 represents patient demographics, and associated microvascular and macrovascular co-morbidities and risk factors in the current cohort of diabetic patients at the time of diagnosis of ESRD.

Table 3.21: Characteristics of the patient cohort with end stage renal disease

	N	Mean	SD	Median
Age (years)	167	61.6	12.38	62
Duration of diabetes (years)	167	23.1	10.50	23
Use of insulin (years)	167	13.1	13.23	10
HbA1c	167	8.1	8.10	7.4
Interval in years (year of diagnosis of status of DR at time of ESRD- year of diagnosis of ESRD)	150	5.9	5.84	6
Systolic BP	167	138.9	20.50	140
Diastolic BP	167	71.1	10.43	70
Haemoglobin	167	11.4	1.54	11.5
BMI	165	30.4	6.88	29
Gender (female) (%)	78	46.7		
Insulin use (yes) (%)	141	84.4		
Hypertension (yes) (%)	164	98.2		
Systolic BP - Group (>141) (%)	72	43.1		
Diastolic BP - Group (y>81) (%)	24	14.4		
BMI - Group (>28) (%)	86	51.5		
Increased Cholesterol (yes) (%)	144	86.2		
Smoker (yes) (%)	15	9.0		
Stroke (yes) (%)	40	24.0		
IHD (yes) (%)	56	33.5		
Angioplasty (yes) (%)	41	24.6		
Neuropathy (yes) (%)	58	34.7		
Diabetic foot (yes) (%)	42	25.1		
Ethnicity				
SE Asian (%)	19	11.4		
Caucasian (%)	76	45.5		
Afro-Caribbean (%)	59	35.3		
Other (%)	13	7.8		

	N	Mean	SD	Median
Type of Diabetes				
T1D (%)	47	28.1		
T2D on tablets for diabetes (%)	27	16.2		
T2D 2 with insulin for diabetes (%)	93	55.7		
Stage of Retinopathy				
No Retinopathy (%)	15	9.6		
NPDR (%)	69	40.7		
PDR (%)	83	49.7		

3.6.3 Regression analyses

Using regression analysis (Table 3.22) PDR status had a beta coefficient of -6.62, $p<0.001$, if a patient was classified as PDR, he would have an ESRD onset of 6.62 years earlier than those who were not classified as PDR, above and beyond the influence of all other variables.

Table 3.22: Multiple regression analysis for all Continuous and binary predictors

	B	Standard Error	Standard Beta	T	p-value
Constant	2.134	8.806		0.242	0.809
Age	0.051	0.042	0.111	1.218	0.226
Gender	0.299	0.796	0.027	0.376	0.708
Duration of diabetes	0.188	0.064	0.355	2.937	0.004
Insulin Use	-0.023	1.254	-0.002	-0.019	0.985
HbA1C	0.161	0.274	0.048	0.589	0.557
PDR	-6.621	1.088	-0.585	-6.087	0.000
Maculopathy	2.028	1.205	0.171	1.683	0.095
HT	7.040	5.279	0.103	1.333	0.185
Systolic BP – Value	-0.023	0.024	-0.077	-0.965	0.337
Diastolic BP – Value	-0.005	0.048	-0.009	-0.108	0.914
Haemoglobin – Value	-0.356	0.269	-0.095	-1.325	0.187
BMI – Value	-0.060	0.057	-0.074	-1.058	0.292
Increased Cholesterol	-0.760	1.271	-0.044	-0.598	0.551
Smoker	1.118	1.419	0.060	0.788	0.432
Drusen	0.066	1.395	0.003	0.047	0.962
Stroke	0.521	0.986	0.040	0.529	0.598
IHD	0.678	1.292	0.057	0.525	0.601

	B	Standard Error	Standard Beta	T	p-value
Angioplasty	1.791	1.410	0.139	1.270	0.207
Neuropathy	0.526	0.977	0.045	0.538	0.591
Diabetic foot	-0.693	1.083	-0.054	-0.640	0.524
Atrial/Ventricular Fibrillation	-1.284	1.112	-0.088	-1.155	0.250

A gender predisposition was also observed. Women with non-PDR took 7 years to develop ESRD compared to women with PDR who develop ESRD in 4 years. However, a man with non-PDR took 10 years to develop ESRD but only 3 years to develop ESRD if he developed PDR. So PDR men have ESRD 7 years sooner than NPDR men – this 4 year disparity being significant (Table 3.23).

Table 3.23: Effect of gender in years on status of development of ESRD

PDR	Gender	Mean	SD	N
NPDR	Male	9.89	6.762	28
	Female	7.85	3.924	39
	Total	8.70	5.349	67
PDR	Male	3.02	4.518	52
	Female	4.87	6.228	31
	Total	3.71	5.263	83
Total	Male	5.43	6.300	80
	Female	6.53	5.249	70
	Total	5.94	5.840	150

3.6.4 Ethnicity and ESRD

The group mean differences for ESRD onset intervals between PDR and non-PDR patients was significant, there was no differences by ethnicities, and nor does ethnicity moderate the relationship between PDR and ESRD onset.

3.6.5 Duration of diabetes

Overall, the beta coefficient was 0.188, $p<0.01$. Thus for each one-year increase in duration of diabetes, the ESRD latency increased by 0.19 years above and beyond the influence of all other variables.

3.6.6 Maculopathy

Presence of co-existent maculopathy marginally increased the risk of developing ESRD ($p=0.095$). Maculopathy patients with ESRD had a latency period 2.03 years shorter than non-maculopathy patients.

3.6.7 Type of diabetes

Type of diabetes was classified into 3 main groups: T1D: young onset who required insulin from the time of diagnosis of diabetes. T2D on tablets: adult onset diabetes that required oral agents /± life style modification and T2D on insulin: adult onset diabetes that require both oral medication and insulin.

In patients with PDR type of diabetes did not affect the ESRD latency and it was significantly shorter than non-PDR patients. However, in patients with non-PDR T1D have significantly longer ESRD latencies than either kind of T2D (Table 3.24).

Table 3.24: Effect of diabetes type on ESRD latency

PDR	Type	Mean	SD	N
NPDR	T1D	14.75	9.910	8
	T2D on tablets	6.18	3.340	17
	T2D on insulin	8.57	3.890	42
	Total	8.70	5.349	67
PDR	T1D	4.15	6.584	39
	T2D on tablets	2.33	2.066	6
	T2D on insulin	3.47	3.964	38
	Total	3.71	5.263	83
Total	T1D	5.96	8.183	47
	T2D on tablets	5.17	3.473	23
	T2D on insulin	6.15	4.666	80
	Total	5.94	5.840	150

3.6.8 Survival analyses by ethnicity

A survival analysis was performed upon the latency to develop ESRD, to examine differences among ethnicities (figure 3.3). Ethnic minorities have earlier peak "proportion terminated" i.e. people who developed ESRD than Caucasians.

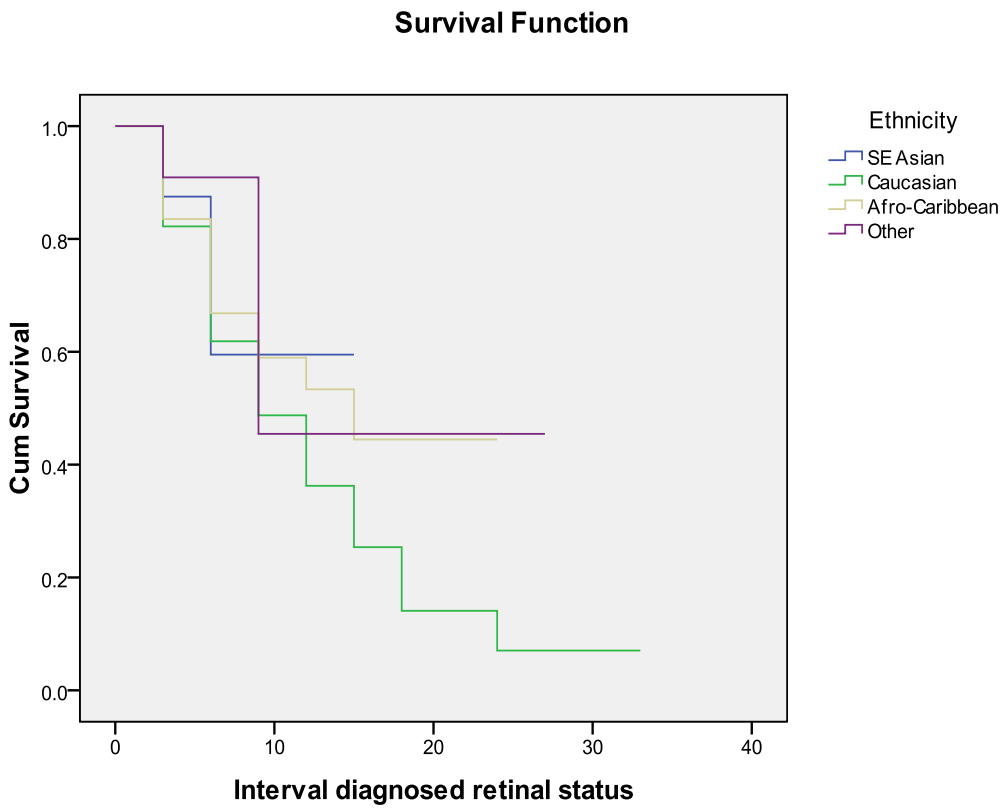


Figure 3.3: Survival Function to ESRD

CHAPTER IV

DISCUSSION

4.1 Prevalence of DR

This study highlights important differences in the prevalence of DR across all ethnic groups with more prevalent sight threatening retinopathy in ethnic minority groups. It is the largest cross-sectional study on the prevalence of DR in the various ethnic groups with diabetes in the UK. The study shows that the risks of any retinopathy in T2D are highest in people with of African descent compared to South Asians or Caucasians. Both South Asians and Afro-Caribbeans are twice as likely to have CSMO and STDR compared to the Caucasians. No ethnic variations in prevalence of DR were observed in T1D although there were proportionately very small numbers of minor ethnic groups with T1D.

The estimated population of UK in 2008 was 51.4 million of which 2.7 million were Asians (mainly South Asians) and 1.3 million were of Black ethnic background. Over the past decades there has been a significant change in the ethnic composition of the UK population. For example, there was increase from just over 6% to 10 % of foreign born people between 1981 and 2006 in the UK, with the majority of this increase occurring since 2001. Also it is predicted that net migration between 2006 and 2031 will be around 4.9 million migrants that represents nearly 69% of the population growth (Access Economics Pty Limited). Hence the current estimates on the prevalence of diabetic retinopathy and visual impairment from this study will guide health policy makers and decision making bodies to allocate adequate resources and target at risk ethnic minority population against this sight threatening complication.

This study comprised of people with diabetes in two community based diabetic retinopathy screening programme, one representing the inner city population cohort in

UK (South East London) and the other reflecting regions within UK with pockets of minor ethnic groups (West Yorkshire). So the study population is a true representation of the ethnic minority groups in the UK. Of the 57,144 people diagnosed with diabetes in the two regions, data on DR was available in 50,331 (88.1%) which is comparable to the response rates of other population-based studies.

The prevalence of diagnosed diabetes in this study is 4.2% with similar rates of diagnosed diabetes between the three ethnic groups. Based on the associations of health professionals in ophthalmology model (Yorkshire and the Humber Quality Observatory (YHQO), 2011) that shows a disproportionate burden of diabetes in South Asians and Afro-Caribbeans, this study suggests that undiagnosed diabetes and/or uptake of retinal screening remain an issue especially in the minor ethnic groups in the UK. So in absolute terms, the disparities in prevalence of DR between ethnic groups noted in this study are unlikely to be due to the differences in prevalence of the underlying diabetic disease.

In our study ethnic minority (Afro-Caribbean > South Asian> Caucasian), type of diabetes (T1D), use of insulin, long duration of diabetes (>10 years) duration, poor glycaemic control (HbA1c >11), high systolic blood pressure (>131), on treatment for cholesterol and high total cholesterol were independently related to high risk of sight threatening DR (R2 & R3) (Table 4.13).

Both ethnicity and diabetes have been reported to be risk factors for microvascular and macrovascular complication including coronary heart disease, stroke, peripheral neuropathy and nephropathy from population based and cross sectional studies. T1D, longer duration and poor control of diabetes have been recognised globally as risk

factors for diabetic retinopathy. Also the inequality in DR could be complex from greater prevalence and insulin resistance in population and poor access to health care systems (Bhopal et al., 2002, Aspinall P and Jacobson B, 2004). A recent health survey from England also reported cardiovascular disease more common among South Asians with diabetes and also higher prevalence of end stage renal disease, stroke and hypertension in Black Caribbean, Indian and Pakistani population (Zaninotto et al., 2007, Cappuccio et al., 2003).

4.1.1 Comparative prevalence of diabetic retinopathy in type 1 diabetes and systemic risk factors

The overall prevalence of DR in T1D was 53.1%, CSMO of 8.9% and STDR of 14.4%. The rates of DR was similar in both Caucasian (55.0%) and South Asians (53.3%) but was significantly lower in Afro-Caribbean's. However Afro-Caribbeans had significantly higher prevalence of R2/R3 (11.1%) compared to other ethnic groups. Maculopathy rates of (13.5%) were similar across all ethnic groups: Caucasians (14.1%), South Asians (14.2%) and Afro-Caribbeans (13.7%).

Although there is no historical comparative data in the UK, it is reassuring to note that the prevalence in this population is very similar to that observed in the Nordic countries (41.8% DR and 12.1% STDR) (Heintz et al., 2010) where there is overwhelming evidence of a decline in the incidence of STDR compared to reports published two decades ago (Bojestig et al., 1998a, Hovind et al., 2003). Much of the information on prevalence of DR in T1D is available from the WESDR in North America that was done more than 2 decade ago or multicentre European studies that were clinically based (Stephenson et al., 1995). A comparison with such studies runs the risks of comparison of different health care system and population that is more dynamic today in terms of

length of stay in one place, has a longer life span and better access to health care system.

The prevalence of DR in this study is lower than that noted in the 725 New Jersey study on type 1 African Americans that showed that 64% of the cohort have any retinopathy, 18.9% proliferative diabetic retinopathy and 12% have CSMO (Roy, 2000). Patients in New Jersey study were identified through hospital admissions and that could explain higher rates than seen in our population based study. Very limited information on DR prevalence is available from the native South Asian population. This could partly be due to lower prevalence rate of T1D, lack of screening services and health inequalities. The Diabetic Care-Asia Study reported 22% prevalence rate for any DR amongst T1D population from 230 centres in 12 Asian countries with a mean diabetic duration of 9.4 (SD7.2) years. In contrast the prevalence of any DR in native South Asians with T1D was noted to be much lower at 13.4% (Ramachandran et al., 2000). Caution should be exercised when comparing epidemiological studies using different assessment techniques and classification. Nevertheless, the observations in this study indicate that ethnicity by itself is not an independent risk factor for the prevalence of any categories of DR in T1D when the same ascertainment techniques are used.

In our study risk of sight threatening retinopathy (R2/R3) was related to duration of diabetes. For shorter duration of diabetes (3-10) years ethnic minority were at increased risk: South Asians (45.2%) > Afro-Caribbeans (26.7%) than Caucasian (16.1%). Such high prevalence rates seen in our study in ethnic minorities with shorter duration especially in South Asians could possibly be due to fewer numbers and poor glycaemic control. Studies have reported variable prevalence rates across ethnic groups with shorter duration of diabetes: 16.8% amongst South Asians with less than < 10 years of

diabetes (Ramachandran et al., 2000), 49.5% in African Americans (Roy, 2000) and 19% among Caucasians in Wisconsin county of North America (Klein et al., 1984b). Similarly diabetic control (indicated by HbA1c levels) affected the risk of developing R2/R3. A proportionally linear affect was seen for HbA1c (7.1-9.0%) across all ethnic groups but not for HbA1c > 9.0%. This could possibly be explained by fact that after a certain threshold point hyperglycaemic damage continues irrespective of the absolute numeric values. Systemic blood pressure was independent risk factor for STDR in our study. Overall 51.4 % of the patients with T1D were on medication to lower the blood pressure. This included people purely on either angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARB). ACE inhibitors and ARB's are primarily used for reno-protective function but have additional blood pressure lowering effect (Jandeleit-Dahm and Cooper, 2006) and are used in isolation or combination with other drugs. The prevalence of hypertension in our study was not statistically different across ethnic groups and was similar to previously reported by Maahs DM et al (Maahs et al., 2005) but both Afro-Caribbeans and South Asians had high systolic BP and diastolic BP (3rd and 4^{th} quartile) than Caucasians. Cross sectional and long term longitudinal studies have established that presence of hypertension and elevated diastolic blood pressure as significant risk factor for sight threatening retinopathy across all ethnic groups with T1D (Klein et al., 2008a, Leske et al., 2005). Both ethnicity and presence of diabetes has been endorsed as risk factors for hypertension. Higher prevalence of BP and high systolic and diastolic BP readings were reported amongst ethnic minorities and African Americans by SEARCH study group (Rodriguez et al., 2010). A similar trend was seen for total cholesterol and LDL. Afro-Caribbeans had higher BMI with 25.7% of the population > 33.8 (BMI) compared to 7.6% of the

Caucasians and 3.2% of the South Asians. Also Afro-Caribbeans had higher prevalence of amputation and on renal dialysis for end stage renal disease compared to Caucasians and South Asians. There is paucity of data on the actual prevalence and risk factors for foot complications including peripheral neuropathy, amputation due to T1D. African-American had nearly twice the rate of lower limb amputation compared to Non-Hispanic Americans possible due to increased prevalence of peripheral vascular disease due to diabetes in this cohort of population (Lavery et al., 1996). A similar pattern of increased prevalence in African American was seen by Chaturvedi N et al in WHO Multinational Study of Vascular Disease in Diabetes. Risk factors identified in the study included glycaemic control and increased BMI (Chaturvedi et al., 2001). Macroalbuminuria and end stage renal disease are recognised complication of diabetes and risk factors for STDR. There is no direct comparison but in a recent estimate by National Institute of Health, US it is also more prevalent in ethnic descent of Afro-American and Asians in comparison to Non-Hispanic Caucasians both due to inherited genetic risk factors and greater prevalence of systemic co-morbidities in the ethnic minority cohorts (U S Renal Data System, 2010, Gross et al., 2005).

Long duration of diabetes, higher baseline serum glucose, uncontrolled systolic pressure and high serum cholesterol levels have all been implicated as risk factors for sight threatening retinopathy (Klein et al., 1996b, Van Leiden et al., 2002, Wong et al., 2008b). Two large independent, interventional, multicentre studies have proved the beneficial effects of tight blood pressure control and glycaemic on incidence and progression of DR. (DCCT, 1993, UKPDS, 1998b, UKPDS, 1998a). DCCT study recruited 1,441 patients with T1D who were treated by either conventional therapy (defined as 1 or 2 injections per day) or intensive diabetes management (defined as 3 or

more daily injections or continuous infusion). Results showed intensive therapy reduced the risk for developing retinopathy by 76 % and slowed the progression of the disease by 54% in participants with some eye damage at the beginning of the study. Early treatment with intensive therapy was most effective; however it had a beneficial effect over the entire range of retinopathy. In addition to a beneficial effect on retinopathy it slowed development and progression of diabetic kidney disease by 50% and peripheral neuropathy by 60%. This improvement was achieved with an average 10% reduction in HbA1c from 8 to 7.2%. Studies from Caucasian population mainly WESDR, a population-based study in southern Wisconsin, in 1984 of 996 T1D, reported prevalence of diabetic retinopathy was 17% with diabetes duration of < 5 years that increased up to 97.5% with >15 years duration of diabetes. PDR was 67% in persons with diabetes for >35 years. In the same study severity of retinopathy with diabetes duration >10 years was related to longer duration, high levels of glycosylated haemoglobin, presence of proteinuria, higher diastolic BP, and male gender (Klein et al., 1984b). A another study funded by WHO, DiaComp, comprised 25 centres in 18 countries from Asia, Africa, Australia, Europe, and North and South America. In this study complications were assessed by self-report of physician diagnosis and subjects with diabetes diagnosed at <15 years of age and had duration of diabetes varied between 5–24 years when surveyed. Diabetic retinopathy was related to age, duration of diabetes, hypertension and women had a significantly higher prevalence of retinopathy and laser treatment.

The World Health Organization (WHO) Multinational Study of Vascular Disease in Diabetes (MSVDD), examined the prevalence and incidence of microvascular complications in individuals with T1D (Lee et al., 2001a). In the UK cohort of 245 patients, any retinopathy was around 37% with PDR in 6% of the cases. Women had

higher systemic blood pressure but lower risk of hypercholesterolemia. EURODIAB a clinic based cross sectional study, examined complication prevalence in T1D subjects from 16 European countries. There were 172 participants from four centres in England with mean age of 33.8 years (SD10.7), mean duration of diabetes of 16.6 years (SD10.1) and a mean HbA1c of 7.3 (SD1.7). Any retinopathy was present in 51% of the subjects, background retinopathy increased with increasing HbA1c till absolute value of 8% and with duration of diabetes between 5 and 15 years and reached plateau of 82% over 20 years , whereas PDR increased after HbA1c cut off 8% (Stephenson et al., 1995).

Diabetic care study in Asian countries found both diabetes duration (OR = 1.1) and hypertension (OR = 2.74) to be significantly associated with STDR, but it was not related to raised HbA1c (OR = 0.76) (Nitiyanant et al., 2002).

In New Jersey study by Roy et al diabetic retinopathy in African Americans was associated with presence of renal disease, poor glycaemic control, high systolic blood pressure, and long duration of diabetes. In DiaComp study any retinopathy and STR was 3%, 0.8% with mean diabetic duration of 8 years in Puerto Rica island; and was 9.4%, 0.7% with diabetes duration of 10.1 years that increased to 49.4%, 35% respectively with diabetes duration of 17.9 years in Caribbean island of Havana.

The above summary shows that in our study of people with T1D: long duration, higher HbA1c and both high systolic & diastolic blood pressure were related to sight threatening DR (R2 & R3) (Table 4.13). Also there is wide geographic variation in complication rates due to T1D and many of the data that are previously available are not derived from population-based samples. The risk factors identified amongst all studies are longer duration of diabetes, poor glycaemic and blood pressure control among

ethnic minority population remain challenging scenarios for the health providers across UK and the rest of the world. So it is necessary to develop community based educational program delivered locally to reinforce the need for better compliance with medication and adherence to screening program to reduce the burden of this preventable sight threatening complications in young and working population and improve the quality of life as population continue to live longer.

4.1.2 Comparative prevalence of diabetic retinopathy in type 2 diabetes and systemic risk factors

In T2D, the overall prevalence of DR was 39.5%, CSMO was 4.7% and STDR was 8.3% in keeping with estimates generated by contemporary studies in the US and UK (Kempen et al., 2004, Wong et al., 2006, Raymond et al., 2009, Younis et al., 2003). Though there has been a global increase in the prevalence of diabetes (Wild et al., 2004) and anticipated increase in the prevalence of diabetic retinopathy, the prevalence of DR in UK have remained constant over last 2 decades despite the changing population composition and the improved diagnostic criteria and examination techniques. This could be due to both greater awareness and better management of risk factors and systemic co-morbidities associated with DR like hypertension and hypercholesterolemia both by health providers and end users.

Overall, the prevalence rate of retinopathy is similar in both Caucasian and South Asian populations to previously reported population based studies in UK. However, there is a marked increase in prevalence in people of Afro-Caribbeans origin. This could be multi-factorial from increased population, true increased prevalence of diabetes and known risk factors for DR like poor control, hypertension, cholesterol and increased BMI seen in this population cohort.

A significant percentage of people suffer from sight threatening retinopathy (R2, R3, M1 or P) in people with T2D. The prevalence of STR was 12.4% in this population cohort with significantly higher rates among Afro-Caribbean (17.9%) and South Asians (17.7%) compared to Caucasians (11.2%) $p< 0.001$.

Studies conducted before the UKPDS era that compared the prevalence of DR between Afro-Caribbean and Caucasians in the UK did not reveal significant differences between the two groups (Chaturvedi et al., 1996a, Cruickshank and Alleyne, 1987). However, comparative data in the US show higher rates in people on African descent (Emanuele et al., 2005, Klein et al., 2002b, Klein et al., 2002a, Zhang et al., 2010).

The increased prevalence of CSMO in Afro-Caribbeans in this study was consistent with other studies that show at least twice higher rates than that reported in the white population (Leske et al., 1999a, Wong et al., 2006). The MESA showed that the risk of CSMO was approximately 5 times in African-American than whites (11.1% versus 2.7%) (Wong et al., 2006).

When considering the South Asian population, our observations of increased STDR and CSMO are consistent with the reports of a recent cross-sectional study in the Midlands in UK comparing the prevalence of DR between the UK South Asians and white Europeans with T2D (Raymond et al., 2009). However, well-conducted population based studies from South India (Rema et al., 2005, Wong et al., 2006) reported very low prevalence rates in DR. It may be argued that ascertainment bias, non-availability of screening services and health inequities may account for the lower prevalence in native South Asians. However, these differences may also suggest that prevalence of DR within the various ethnic groups defined as ‘South Asians’ in the UK may be different

and future studies should attempt to report the prevalence of DR in each ethnic group within the Indian subcontinent to better understand these regional differences. Furthermore, these observations imply a role of environmental and epigenetic factors that may be responsible for higher prevalence in ethnic minority population in developed nations compared to the native South Asians.

The study also showed that increasing age is a risk factor for all categories of DR. Though this is a recognised risk factor for T1D, the age effect in T2D remains controversial (Kempen et al., 2004, Wong et al., 2006, Klein et al., 1984c). The age-specific prevalence of diabetes in this study mirrors the APHO diabetes prevalence model that indicates that there are a rising number of people with diabetes in the older age group. Earlier report on inequalities in uptake of diabetic retinopathy screening showed that non-attendance for screening was high among those aged 85 years or greater (Gulliford et al., 2010). So this study highlights another priority group that has to be focussed to promote equity in DR screening and treatment.

Male gender was also noted to be a risk factor in this study. Pooled data from 8 epidemiological studies showed no consistent association of gender with DR or STDR in Caucasians and African-Americans (Kempen et al., 2004). However, both the CURES (Rema et al., 2005) and SN-DREAMS (Raman et al., 2009) study showed significantly higher prevalence in South Asian males. More than 90% of the population with diabetes have T2D. Most of the studies reporting inter-ethnic differences in DR were performed in developed states of United States and Europe with predominantly native Caucasian population and immigrant ethnic minority groups. High reported figures of DR in ethnic minorities are not replicated in population based studies from native countries. In UK only two population based studies with identifiable ethnicity of

the study cohort have looked at prevalence and inter-ethnic differences in diabetic retinopathy. Most of this comparison has been between native Caucasians and people of South Asian origin but the data on the Afro-Caribbean population is limited. The UKPD was a multicentre, randomized, controlled clinical trial of therapy in patients with newly diagnosed T2D looking at the effect of tight blood pressure and diabetic control on microvascular and macrovascular complications due to diabetes. Baseline examination at recruitment entry from 1977 to 1991 and reported results in 1994 revealed similar rates of 37% for any retinopathy among three ethnic groups mainly Caucasian, Afro-Caribbean and South Asians (UKPDS, 1994). However in a more recently study, overall prevalence of any retinopathy was 40% and it was significantly higher among South Asians (45%) than in Caucasians (37%) from a randomised community cluster sample of 1035 patients (Raymond et al., 2009). However, the results from clinic based studies are in contradiction to population based studies. A clinic based study from Leicester, UK in 1984-86 reported prevalence of 11.6% for any retinopathy in South Asian Versus 32.3% in Caucasians (Samanta et al., 1991).

Most of the data from population based studies in the Indian subcontinent report a lower prevalence rate of 17-27% for any DR (Ramachandran et al., 1996, Raman et al., 2009, Rema et al., 2005). Much of the information on prevalence of DR amongst people of Afro-Caribbean ethnicity comes from studies done in the USA. The Barbados Eye Study (BES) reported a prevalence of 25.8% in the black Caribbean population (Leske et al., 1999a) and similar rates were reported in NHANES III survey with a prevalence of 26.5% for African-Americans compared to 18.2% in non-Hispanic white Americans aged 40 or older (Zhang et al., 2008b). Other studies reporting prevalence information in Afro-Caribbean with T2D include the Atherosclerosis Risk in Communities Study

(ARIC) with a prevalence of 27.7% (Klein et al., 2002b), Cardiovascular Health Study (CHS) in adults aged 65 years and older with a prevalence of 35.4% (Klein et al., 2002a), the Veterans Affairs Diabetes Trial (VADT) of 29% (Emanuele et al., 2005) and MESA study of 36.7% respectively (Wong et al., 2006). Rotimi et al reported a prevalence rate of 18% for any DR from Nigeria and Ghana (Rotimi et al., 2003).

In our study more Afro-Caribbean than South Asians and Caucasians had high risk retinopathy (50.2%, 40.8%, 34.4% respectively), presence of maculopathy (39.1%, 28.9%, 26.4%) and were on treatment with both insulin and oral hypoglycaemic medication (30.6%, 29.2%, 23.2%) respectively (Table 3.14), higher HbA1C: > 3rd quartile (24.7, 23.6%, 16.5%), higher systolic BP: > 3rd quartile (63.2%, 55%, 51.6%), higher Diastolic BP: > 3rd quartile (64.1%, 61.5%, 59%) respectively. South Asians had a lower BMI, total cholesterol and HDL compared to Afro-Caribbeans and Caucasians.

In our study logistic regression analysis revealed ethnicity, diabetes duration, higher systolic BP and higher HbA1C as independent risk factors for developing high risk DR (R2/R3) ($p< 0.001$). Afro-Caribbeans (OR1.92) and South Asians (1.31) compared to Caucasians were more likely to develop R2/R3. Also, with every 10 year increase in duration of diabetes, there was 6 fold increase; every 0.5% in HbA1c increased the risk by 1.16 times and every 10 mmHg increase in SBP increased the risk by 1.20 times of developing high risk DR (R2/R3) (Table 3.15).

Population based studies have proved that diabetic retinopathy is related to duration of diabetes, uncontrolled hyperglycaemia and systemic blood pressure (Klein et al., 1989c, Raman et al., 2009, UKPDS, 1994, Leske et al., 1999a). The UKPDS was a multicentre study that looked at the beneficial effects of tight blood pressure and diabetic control on

microvascular complication in people with T2D (UKPDS, 1998b, UKPDS, 1998a). The relative risk of two step progression of DR was reduced by 21% with intensive glucose control and 17% by intensive blood pressure control (<150/85mm Hg). Randomised controlled trials have also demonstrated the beneficial effects of lipid lowering agents on hard reducing exudates at the macula and progression of retinopathy with fewer eyes requiring laser treatment for sight threatening retinopathy (Cullen et al., 1974, Harrold et al., 1969, Keech et al., 2007, Van Leiden et al., 2002). Analysis of clinical and biochemical variables in UKPDS study revealed Asians were younger, shorter and had a lower BMI than both the white Caucasian and Afro-Caribbean patients but a higher waist-hip ratio after taking age and obesity into account. Blood pressure levels were lower in the Asian patients than in the other groups but AC patients had significantly higher diastolic blood pressure than the white Caucasians. Also AC patients had significantly higher fasting plasma glucose than in other groups.

Similar findings were reported from UKADS with people of South Asian ethnicity had significantly higher systolic, diastolic blood pressure, HbA1C and total cholesterol compared to white Caucasians.

In our study both mean systolic and diastolic blood pressure was higher in Afro-Caribbean and South Asian than Caucasian population. Similarly higher prevalence pattern of macrovascular complication were seen in ethnic minority patients (Table 4.13. 4.14). Stricter targets for systemic risk factors control, ethnically oriented programs delivered locally and measures to motivate patients may achieve desired health-care outcomes in such diverse ethnic groups. This will reduce the burden of sight threatening retinopathy to the state and loss of working life years in this young people with T2D.

In summary in our study of people with T2D: male, presence of maculopathy, long duration, higher HbA1c, use of insulin, higher low LDL, higher systolic & diastolic blood pressure and low eGFR (impaired kidney function) were related to sight threatening DR (R2 & R3) (Table 4.14).

South East London and Yorkshire are two distinct geographic areas, under the two independent strategic health authorities and diabetic screening programme. Similar prevalence rate allowed us to collate the information, and provide overall prevalence rates for diabetic retinopathy. The study found significant differences in the prevalence of DR and VI in ethnic minority population in both T1D and T2D. This information possibly represents the overall prevalence rates of DR in UK and could be used by health bodies in identifying the high risk ethnic groups in the region, and appropriate service design and resource allocation to meet the challenges of rising diabetic epidemic and reducing burden of blindness due to DR. Sustained delivery of health information and awareness programmes delivered locally and using incentivised scheme have shown to improve the success of DR screening programs (Beynat J et al., 2009; Lester H et al., 2010). Such models could be used to address the systemic comorbidities associated with diabetes. There were differences in glycaemic control, cholesterol and blood pressure control across all ethnic groups in this study and far from ideal but were better controlled in comparison to seen in UKPDS study. Thus the differences observed in this study prevalence of DR cannot be solely explained on known systemic diseases. Diabetes has long been recognised as a low grade inflammation with increased levels and association seen between circulating and locally produced inflammatory biomarkers, such as cell adhesion molecules (vascular adhesion cell molecule-1, VCAM-1; intracellular adhesion molecule-1, ICAM-1), pro-inflammatory cytokines

(interleukin-6, IL-6; tumour necrosis factor-alpha, TNF-α; C-reactive protein, CRP) with the development and progression of diabetic micro-vascular complications (Kaul K et al., 2010). Clinically it is seen as beneficial effect of steroids in management of MO and improvement in DR (Elman MJ et al., 2011). Other possible causes could be due to differential susceptibility and in genetic polymorphism involved in final metabolic pathways of diabetes and DR like seen are in aldose reductase and VEGF A (Doria A., 2010). These factors need further exploration and may hold keys to design of future management strategies of DR.

4.2 Visual Impairment

This study on a substantial dataset demonstrates that the prevalence of visual impairment (<6/12) and severe visual impairment (<6/60) are 3.4% and 0.4% in a multiracial population of people with diabetes attending screening in the UK. A further 10.7% people are unilaterally visually impaired. The study merely reports the overall visual prevalence and does not separately identify other coexistent disease such as age related macular degeneration, cataract, or glaucoma that can independently affect the visual status.

In addition, the study provides overwhelming evidence of inequities in vision healthcare in people with diabetes in the UK. People of South Asian and African descent are twice at risk of visual impairment in all 3 categories (driving vision, low vision and severe visual impairment) compared to Caucasians.

This study highlights that even though people with diabetes participate in screening of DR using digital fundus photography, visual impairment remain a significant public health problem in the UK. On the contrary, loss of vision is uncommon in studies from

Iceland where the stable and predominantly Caucasian population is carefully screened for diabetes mellitus and provided with regular screening for DR since 1983 (Olafsdottir et al., 2007, Stefansson et al., 2000). It is still too early for the national systematic screening programme for DR in England and Wales to produce such an effect on prevalence of visual impairment. Only time will tell if such findings could be translated to a multiracial and mobile population.

The analyses of severity of DR between ethnic groups in this cohort showed that the risk of sight threatening DR is also two times higher in the minority groups compared to the Caucasian counterpart. People with PDR and persistent maculopathy despite laser treatment are especially vulnerable to visual impairment. These observations are consistent with the findings of the UKADS study on South Asians that showed that the risk of sight threatening retinopathy is significantly higher than Caucasians and that this disparity could partly be explained by differential susceptibility to systemic risk factors (Raymond et al., 2009). Previous studies evaluating ethnic differences in certifications of visual impairment also showed similar results with the proportion of South Asians registered blind due to DR being three times that of the Caucasians in the UK (Hayward et al., 2002, Pardhan et al., 2004). So DR may contribute significantly to the higher prevalence of visual impairment in this minority population. There is very limited data on visual impairment in people of African descent with diabetes in the UK. Nevertheless, Kahn et al indicated that blacks suffer from a proportionate burden of blindness due to diabetes in the United States (Kahn et al., 1977). A similar higher prevalence rate of visual impairment has been reported in people of African origin with 8.9% annual incidence of blindness (WHO criteria) due to DR in the Barbados Eye Study (Leske et al., 2010) but a lower rates of 0.17% (Low vision: <6/12) was reported

from Bangladesh (Dineen et al., 2003). Cataract and uncorrected refractive error still continue to be major cause of visual impairment in native states of ethnic minority groups (Dineen et al., 2003).

Current digital photographic retinal screening for DR may not be sufficient to reduce the prevalence of visual impairment in diabetes. Uncorrected refractive error, cataract and glaucoma are more common in people with diabetes than the non-diabetic population and contribute more to visual impairment than diabetic retinopathy (Congdon et al., 2004, Congdon et al., 2003, Leske et al., 1991, Leske et al., 2010, Scanlon, 2008). Although people with diabetes are offered free eye-sight test in UK, the spectacles are often unaffordable. Studies from around the world also indicate that the threshold to correct one's refraction varies considerably between ethnic groups. Furthermore, some of these ocular co-morbidities are more prevalent in certain ethnic groups such as cataract in South Asians and glaucoma in the Afro-Caribbean population (Miki et al., 2001, Nwosu, 2000b, Nwosu, 2000a, Rotimi et al., 2003). These factors may also explain the ethnic differences in visual impairment observed in this study.

The other risk factors in minor ethnic groups include an earlier age of onset of diabetes and poorer health care utilization rates (Broadbent et al., 1999, Harris et al., 1993, Riste et al., 2001, Hanif et al., 2008). These findings are of concern, as patients who are at highest risk seem to have poorer outcomes. Previous studies on education levels and socio-economic status have shown that people with low income and those with lower levels of education are at higher risk of visual impairment, cataract and PDR (Klein et al., 1994a, Hansson-Lundblad et al., 2002, Chaturvedi et al., 1996b). The effect of race on ocular diseases was highlighted as early as 1990 in the United States (Tielsch et al., 1990) in the Baltimore Eye Survey that showed that people of African descent had, on

average, a twofold greater prevalence of blindness and visual impairment compared to Caucasians. This effect of race was reduced after adjustment of the socio-economic factors. However, previous studies on the South London cohort showed that socio-economic inequalities based on the Index of Multiple Deprivation score 2007 did not determine the rate of retinopathy in those who attended the screening programme (Gulliford et al., 2004). So further research into differences observed due to ethnic disparity is warranted.

This study also shows that increasing age is a risk factor for visual impairment in diabetes. Although DR is reported to be the commonest cause of visual impairment in the working age-group, people aged 65 years and older with diabetes are three times more likely to be visually impaired (in all 3 categories- driving vision, low vision and severely visually impaired) compared to those between 16-64 years. In the UK there was an increase of 5.8% in blind registrations due to DR between 1990-91 to 1999-2000 in the working age group (16-64 years) (Bunce and Wormald, 2008). Similar high prevalence rates of 3.2% for VI and 6.2% for SVI were reported from Cambridgeshire in UK with 1.4% of VI affecting the working age group (Gordon-Bennett et al., 2009). However, Bunce et al observed that the rates of registration (both low vision and blindness) due to DR in the elderly have increased significantly in the last two decades (Bunce and Wormald, 2008, Bunce et al., 2010). Although this rise is often attributed to increased public, professional and political awareness of certifications and support provided as part of the VISION 2020 strategy, this study highlights the fact that visual impairment is definitely a significant public health issue in the older population and it may be postulated that these figures may only reflect the increasing prevalence of

diabetes in the older people who mainly suffer from other causes of visual impairment especially age related macular degeneration.

Visual impairment also occurs more frequently in people with T1D compared to T2D. Screening and timely management of DR has been shown to reduce the risk of visual impairment in people with T1D (Agardh et al., 1993, Stefansson et al., 2000). A similar reduction in T2D is more difficult to achieve unless diabetes is diagnosed promptly (de Fine et al., 2001, Olafsdottir et al., 2007). In the present study, in people with T1D, VI and SVI was 1.0% and 0.2% respectively. Recently Klein et al from Wisconsin eye study reported 25 year cumulative incidences rates of 13% and 3%, of any VI and severe VI respectively. The cumulative incidence rates were lower and people with recently diagnosed T1D had lower prevalence rates of vision impairment when controlled for duration of diabetes. This has been independently reported from two population based studies (Hovind et al., 2003, Klein et al., 2009c). The diminishing incidence could be due to better glycaemic and risk factor control, effective screening (Arun et al., 2009) and timely laser treatment in sight threatening retinopathy from proliferative diabetic retinopathy and maculopathy (The Diabetic Retinopathy Study Research Group, 1981).

In summary, this study identifies priorities to reduce the prevalence of visual impairment in people with diabetes in the UK. With the increasing population, the demographic right shift of the populace and the emerging racial-mix in most cities in the UK, it is important that human and financial resources be allocated to implement ethnic-specific strategies to reduce this burden. The observed inequalities have a substantial impact on the already compromised quality of life of people with diabetes

and its complications. They also represent a considerable drain on resources, both of the NHS and of care providers.

Reducing disparities and promoting equity in vision health care in diabetes will require several changes at various levels: (1) increase public, professional and political awareness of disparities, (2) eliminate barriers to optometric care and correction of refractive errors, (3) facilitate efficient eye care services with particular focus on the vulnerable groups, and (4) increase the uptake rate of DR screening(Baker et al., 2005, Biello et al., 2010).

The data presented from the DRIVE-UK study could be utilised in planning and prioritising strategies for prevention, treatment, and management of this chronic eye disease within the UK context.

4.3 Vitrectomy

End-stage diabetic eye disease is the most important cause of severe visual impairment in the working age-group, both globally, in the USA (Resnikoff et al., 2004) and in the UK (Bunce and Wormald, 2008). Both the prevalence and severity (Klein et al., 1989a, Leske et al., 1999b) of diabetic retinopathy is increasing. Tractional retinal detachment (TRD) and non-clearing vitreous hemorrhage (NCVH) are two complications of proliferative diabetic retinopathy (Fine and Patz, 1987) which are treated with vitreo-retinal surgical repair. Improvements in surgical techniques such as the use of wide angled viewing systems, use of endolaser during vitrectomy (Flynn, Jr. et al., 1992, Williams et al., 1989a) should have improved visual outcome since the first reported

randomized controlled diabetic vitrectomy study (DRVS, 1988b, DRVS, 1988a) but this requires further investigation.

Anatomical and visual outcome are quite often unpredictable in vitrectomy for proliferative diabetic retinopathy. Anatomical results are often limited by the extent and degree of fibrous tissue (Eliott et al., 2006), vitreo-retinal adhesion (Eliott et al., 2006) and high rates of iatrogenic tears which complicate surgery (Schrey et al., 2006, Yorston et al., 2008). Functional visual outcome are also limited due to severe macular dysfunction from a long duration of macular traction and preceding ischemic maculopathy (Schrey et al., 2006, Williams et al., 1989b, Miller et al., 1980).

In our study eyes that underwent vitrectomy overall anatomic success was 87.53%, 60.5% of all eyes showed ≥ 3 ETDRS line improvement from the baseline and 38.38% of all cases had final visual acuity of ≥ 6/12 (20/40). These results represents an improvement from DRVS study where 25% achieved ≤ 0.3 logMAR following vitrectomy for VH and TRD (Williams et al., 1989b, Yorston et al., 2008). These improved results could be attributed to both improvement in surgical techniques and instrumentation and possible early detection of severe sight threatening disease through screening programs. These programs are well established in UK and provide uptake (www.retinalscreening.nhs.uk) of up to 78% in most regional screening program. Also it could be due to improved control in diabetes and better control of systemic factors like blood pressure, cholesterol, intensive glycaemic control after the lessons learned from DCCT study (DCCT, 1993). When controlled for all other factors ethnicity alone did not affect the final outcome implying once the subject had reached end stage retinal disease it ceased to be modifying factor.

Preoperative visual acuity improved with time suggesting a move to earlier intervention and this correlated with improved postoperative visual results. Patients with lower pre-operative baseline visual acuity achieved greater amount of improvement in LogMAR at time of last post-operative visit however patients with better pre-operative visual acuities had better final visual acuities. This suggests that patients should be operated upon before severe visual loss has occurred. The gradual improvement seen in preoperative visual acuities seen in this study may have been as a result of a realization of this factor clinically. The early vitrectomy study (DRVS, 1988b, DRVS, 1988a) suggested that the results of surgery were better with earlier vitrectomy. The surgical method has changed significantly with smaller gauge instruments, better viewing system and availability of surgical adjuvants like anti-vascular endothelial growth factors since the EVS and there could be a justification for repeating that study with modern methods. Both the EVS and our study suggest earlier intervention is preferable, our study because patients with better pre-operative vision perform better and the EVS because of the better outcomes from surgery performed more quickly after presentation.

To summarise, surgical management of the late complications of PDR remains a common but challenging vitreoretinal procedure and the visual results remain unpredictable. The surgical outcome after diabetic vitrectomy has continued to improve with advances in vitreoretinal surgical instrumentation and technique. There was a trend for operating patients with better vision over the ten years and this was associated with better visual outcomes.

4.4 End Stage Renal Disease and Retinopathy

Diabetic nephropathy (DN) is rarely diagnosed using invasive kidney biopsies, the case definition of this complication is typically based on the presence of albuminuria (Ng et al., 2005). When applying this case definition, it is plausible that there is a substantial number of patients who are classified as having DN that actually have non-diabetic kidney disease instead (Parving et al., 1988). Several investigators have proposed that to diagnose DN the subject should also have diabetic retinopathy (Canani et al., 2005, Remuzzi et al., 2002). Nevertheless, a recent meta-analyses of DN related genetic studies showed that the presence of diabetic retinopathy may be of limited practical value for defining cases of DN in both T1D and T2D (Ng et al., 2005). It could be hypothesized that the mere presence of retinopathy does not provide sufficient information to define DN or its progression and that the severity of retinopathy may be a better tool to understand the prognosis of DN.

The relationship between DR and DN is a complex. Several cross-sectional and longitudinal studies suggest that the microvascular complications in the retina and kidney are closely related as they share the same risk factors including length of diabetes, high HbA1c, hypertension and hyperlipidemia (Girach et al., 2006, Orasanu and Plutzky, 2009, Romero-Aroca et al., 2010). However, the temporal relation between these two microvascular complications remains unclear. Cross sectional studies on T1D and T2D indicate that PDR is associated with microalbuminuria (Boelter et al., 2006, Chun and Li, 2010). In fact, after 30 years of T1D, half of the patients develop PDR and approximately a quarter develop macroalbuminuria. So it does suggest that although microalbuminuria may precede retinopathy, the progression of retinopathy to

PDR is faster than the development of macroalbuminuria. This concept is however contraindicated in other studies. Mosier et al found no congruence between stages of retinal and renal disease (Mosier et al., 1997). Several studies have highlighted severity of diabetic retinopathy as an indicator of the risk of gross proteinuria. In WESDR of all patients with T1D and diabetes of 10 or more years half of the patients with PDR had concomitant proteinuria. Similar findings were noted in a longitudinal population studies in American Indians, Asians and Joslin Clinic Study. In our study amongst patients with T1D in London cohort 30% of the patients with PDR had ESRD and nearly 50% of the patients with ESRD had PDR. Conversely in another study of 211 patients with T1D the prevalence of PDR was 7% at onset of microalbuminuria that increased to 29%, 4 years after onset of microalbuminuria as compared to 5% increase over same period in patients without microalbuminuria. In WESDR with T1D presence of gross proteinuria at baseline was associated with 95% increased risk of developing macular oedema.

If any patient with diabetes is considered, the risk of ESRD is 0.52% or 5 in a 1000. The risk is not higher in patients with non-PDR. However, if one develops PDR, the risk increases 16 times and the time to ESRD is shortened to approximately 4 years from date of diagnosis of PDR. The risk of PDR has been observed in other studies (Cruickshanks et al., 1993, Cusick et al., 2005), However this is the first study to our knowledge that investigated the factors that determine the time to ESRD.

Although ethnic difference in the prevalence of diabetic retinopathy and ESRD is increasingly recognised with higher prevalence reported among Afro-Caribbean and Asians, this study on a multiracial community in a metropolitan city shows that the rate

of conversion to ESRD once a person develops PDR is not influenced by ethnicity (Deshpande et al., 2008, Lopes, 2009) .

In fact, gender seemed to be a more important risk factor in that a male with non-PDR takes nearly 10 years to develop ESRD but once a male convert from non-PDR to PDR, the rate of progression to ESRD is faster than in females (3 years versus 5 years). Alwakeel et al also noted that male gender was associated with a higher risk of ESRD (Alwakeel et al., 2008b) but no obvious cause could be found.

There is no relationship between type of diabetes and ESRD latency as observed in other studies (Hasslacher et al., 1993). However the longer the duration of diabetes, the higher is the prevalence of ESRD.

The presence of maculopathy marginally increases the risk of ESRD. The link between PDR and the development of ESRD is not clearly understood. Anemia is associated with an increased risk of PDR (Davis et al., 1998) and renal insufficiency (Breyer et al., 1996). A recent study showed that the severity of retinopathy have increased following the use of recombinant erythropoietin (EPO) for chronic renal failure (Diskin et al., 2007). Recombinant EPO is used routinely in our patients with ESRD. Our study did not assess the use of recombinant EPO or the circulating EPO levels but it is useful to note that the mean haemoglobin of these patients with ESRD was 11.4%. The present day practice is to administer recombinant EPO to patients with ESRD and pre-ESRD anaemia to target a haemoglobin level of 12.5g/dl. So a combination of anaemia related retinal hypoxia and the direct angiogenic drive of EPO may help explain the high prevalence of PDR in our ESRD cohort. This study warrants the need for a multi-disciplinary approach of patients with ESRD and diabetic retinopathy.

In conclusion, although ESRD and PDR share several common risk factors the shorter time to ESRD in patients with PDR will help to better identify the high risk group that could potentially develop ESRD and preventive strategies may be focussed on this group to facilitate global assistance to slow the progression of chronic kidney disease and indirectly reduce cardiovascular risks in diabetes.

4.5 Strength and weakness of the study

The strength of our study is the use of a substantial dataset of a representative multi-ethnic population with physician diagnosed diabetes and the use of standard national quality-assurance protocols for post-mydriatic 2-field high-resolution digital photographs and grading of DR.

The limitation of this study is the use of a grading system that is not universally used in epidemiologic studies making it difficult to compare the prevalence of CSMO. However, the prevalence of DR in T2D in the white population in DRIVE UK (38%) was similar to that found other recent studies in the world that used either the interim or final ETDRS scale. Secondly, this study is limited to those who attend screening and treatment for DR so it likely that the rates may be an underestimation. Additionally, we have not considered retinopathy rates in undiagnosed diabetes. After adjusting for age, gender, type of diabetes, ethnicity and region: glycaemic control, duration of diabetes and higher blood pressure were found to be other traditional risk factors of high risk diabetic retinopathy. It would be useful to observe whether ethnicity remains an independent risk factor. Reports on this aspect are conflicting.

In summary, this study provides data on the frequency of different categories of DR in various ethnic groups in the UK. We showed that while one in three Caucasian and South Asians with T2D has any retinopathy, one in two persons of African-Caribbean have retinopathy. The risk of STDR and CSMO is two times higher in the Afro-Caribbeans and South Asians compared to the white counterparts. In T1D, ethnicity was not found to be a risk factor for DR.

We have focused on presenting vision—that is, visual acuity as used in everyday life by the people taking part in DR screening. This measure of visual impairment is the most relevant for public health purposes (Evans et al., 2002). Despite that our prevalence may be an underestimate of visual impairment in people with diabetes because the study did not include non-attenders to the screening programmes and associated eye clinics. Previous study on the South London cohort indicated that screening uptake rates were particularly poor among the young adults aged 18-34 years and those aged 85 years or greater (Gulliford et al., 2010).

Another limitation of our study is that approximately 30% of the non-participants were those referred to hospital eye services for referable DR or unclassifiable retinopathy using digital photography due to ungradable images. So it is likely that the actual prevalence of visual impairment may again be underestimated. However, the results of our study compare well with other studies that examined patients from the local diabetic retinopathy screening programmes in predominantly Caucasian-inhabited regions in the UK. The Liverpool Eye study in 1999 observed that 3.4% had visual acuity of ≤6/24 and 0.8% had visual acuity of ≤6/60 (Broadbent et al., 1999). Prasad et al noted that the prevalence of low vision and blindness as per WHO classification in Wirral were 2 % and 0.75% in 2000 (Prasad et al., 2001) and in Gloucestershire, Scanlon et al reported these to be 2.9% and 0.45% respectively in 2008 (Scanlon, 2008). It is useful to note that whatever be the source of data collection (survey of DR screening database or register of certifications of visual impairment), the prevalence of visual impairment in people with diabetes has been stable in the last decade (Broadbent et al., 1999, Bunce and Wormald, 2008, Bunce et al., 2010, Gordon-Bennett et al., 2009, Hayward et al., 2002, Kumar et al., 2006, Pardhan et al., 2004, Prasad et al., 2001, Scanlon, 2008).

Another limitation is the retrospective nature of the diabetic vitrectomy outcome arm of the study. However this information is useful for counselling patients before surgery of the risks, complications and the likely outcomes of this sight threatening condition. It will also help to council patients the need to keep up with their future appointment to ensure visual success and reduce the costs of visual impairment to state**.**

Again the study highlighting temporal relation between ESRD and PDR was retrospective in nature, the date of ESRD and PDR are recorded from the first documentation in the medical records and not determined by a standardized protocol and at definite time–points. The results of this study may also be affected by the different treatment thresholds maintained by different physicians. Lastly, both PDR and ESRD are indicators of mortality and mortality was not censored in this study so it is likely that the prevalence of both end-points may be higher.

CHAPTER V

CONCLUSION AND SUGGESTION FOR FUTURE WORK

5.1 Conclusion

Diabetic retinopathy is a multifactorial disease. Diabetic Retinopathy in various ethnic groups (DRIVE-UK) is a cross sectional population based study that looked at the prevalence of diabetic retinopathy and visual impairment in different ethnic groups. Both London and Wakefield are cosmopolitan cities with high immigrant populations particularly with respect to individuals of Afro-Caribbean and South Asia origin respectively.

There was found to be an increased prevalence of diabetes and with that there was a projected increase in prevalence and severity of diabetic retinopathy. However the overall prevalence rates for any DR are similar to reported previously reported in UKPDS study over a decade ago. There is a decreased prevalence in younger age group possibly due to overall better glycaemic control and other risk factors from the lessons learnt from DCCT and UKPDS study. This decreased prevalence in native Caucasian population is offset by higher rates in ethnic minority and elderly population in these two cities. The increase rate in elderly could be due to increased life span and benefits of improved risk factor control offset by longer and natural history of the disease. The prevalence rates in ethnic minority population is nearly 2 times than reported in large population based studies from India and Africa.

The study also highlights increased prevalence of significantly low vision below the driving requirements (< 6/12) in ethnic minority (Southeast Asian> Afro-Caribbean> Caucasian) in both T1D and T2D. This could be due to health disparity and poor risk factor control amongst this group of population (Gulliford et al., 2010, Nsiah-Kumi et al., 2009).

The visual and anatomical results have continuously improved across all ethnic groups over the last decade following surgical intervention in end stage retinal disease. This is been mainly due to improvement in pre-operative vision highlighting possible beneficial effects of early identification through national screening programmes and better risk factor control. However the uptake rate in most screening program is around 80% and there is continuous need to improve and provide services accessible locally in community or at GP practices to decrease the incidence from this preventable cause of blindness. There is an overall increased prevalence of visual impairment due to DR in ethnic minority population but it ceased to be factor in patients undergoing vitrectomy for end stage retinal disease. This highlights the importance of better diabetic and risk factor control before the disease momentum pushes it to point of no return. Patients who were non-compliant with appointments had poor visual outcome following surgery for end stage retinal disease. This information could be used for patient counselling at the time of operation and informed consent with the use of information leaflets at the time.

Lastly the study explores the temporal relation between end stage eye disease and renal disease secondary to diabetes. The microvascular complications in the retina and eye are closely related and share the pathogenic process and same risk factors. The temporal relation of shorter time to ESRD in patients with PDR will help to better identify the high risk group that could potentially develop ESRD and preventive strategies may be focussed.

This study highlights the need of to deliver diabetic education program at grassroots level locally and possibly integrating with local cultural and religious beliefs.

5.2 Future Work

1) Further research work is needed to address socio-economic and health inequalities that possibly contribute to differences in prevalence rates of DR between ethnic groups.

2) The study did not address the role of environmental and dietary components in disease phenotype as higher rates were seen in ethnic minority groups than previously reported in native population. There is need to look into modifiable factors like monitoring of life style, food habits, nutrients, vitamins and other environmental factors.

3) This was a cross-sectional study looking at the prevalence rates of diabetic retinopathy however longitudinal studies are needed to understand the incidence of DR. Also this will help to study temporal changes in prevalence and incidence of DR over decade.

4) There is need to understand the role of novel risk factors- genetics and circulatory biomarkers that may explain these ethnic differences. So future studies may look at inflammatory markers, mitochondrial factors in patients with high risk retinopathy in various ethnic groups.

5) Future studies are needed to look into the lack of disease awareness in community in general and ethnic minority population in particular. This could involve use of questionnaire based model to look into health utilisation within community.

Appendix 1

NHS
National Research Ethics Service

King's College Hospital Research Ethics Committee
Camberwell Building
King's College Hospital
94 Denmark Hill
London
SE5 9RS

Tel: 0203 299 3923
Fax: 0203 299 5085

27th November 2008

Dr Sobha Sivaprasad
Consultant Opthalmologist
Diabetic Eye Complications Service
1st Floor Normandy Building

Dear Dr Sivaprasad

Full title of project: Ethnic variations in the severity of diabetic retinopathy and the prevalence of visual impairment in diabetic people in the UK

Thank you for seeking the Committee's advice about the above project.

You provided the following documents for consideration:

Protocol

This document has been considered by the Chair who has advised that the project is not one that is required to be ethically reviewed under the terms of the Governance Arrangements for Research Ethics Committees in the UK. Providing that the KCH patient data is fully anonymised before being sent to Wakefield and vice versa.

Although review by a Research Ethics Committee is not required, you should check with the R&D Department for King's College Hospital whether management approval is required before the project starts.

Yours sincerely,

Will Bowen
Committee Co-ordinator

E-mail: William.bowen@kch.nhs.uk

Appendix 2

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

ETHICS COMMITTEE

APPROVAL FORM
Application number: **5684**

Name of Principal Investigator	**Dr Sobha Sivaprasad**
Department	**Infectious and Tropical Diseases**
Head of Department	**Professor Simon Croft**

Title: **Ethnic variations in the severity of diabetic retinopathy and prevalence of visual impairment in diabetic people in the UK**

This application is approved by the Committee.

Chair of the Ethics Committee ..... T. W. Meade .....

Date .....11 June 2010.....

Approval is dependent on local ethical approval having been received.

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form.

Appendix 3

From: Cook Simon (King's College Hospital NHS Foundation Trust) (simon.cook@nhs.net)
To: gupta_bhaskar@yahoo.com;
Date: Thu, September 24, 2009 12:34:10 PM
Cc:
Subject: CASS AP0861-01: Vitrectomy Outcome for Diabetic retinopathy

To Bhaskar Gupta

Your Project has now been reviewed. Please open the Project Details form and click on the acknowledgement check box to enable you to continue.

Regards,

Simon Cook
Clinical Effectiveness Project Co-ordinator
King's College Hospital NHS Foundation Trust
2nd Floor, Jennie Lee House
34 Love Walk, London SE5 8AD
tel: 020 3299 1934 fax: 0203 299 6310

Appendix 4

Baseline Information

Date of Birth

Gender

Ethnicity

Best Corrected Snellen Visual Acuity		
Grade of Retinopathy	A B C D	A B C D
Macular oedema	M0 M1	M0 M1
Laser	Macular PRP None	Macular PRP None

Type of diabetes

Right Eye **Left Eye**

Any other Ocular Co-morbidity

Comments

A. R0
• No Retinopathy
B. R1
• Background Retinopathy present.
C. R2
• Pre-proliferative diabetic Retinopathy
D. R3
• Proliferative diabetic Retinopathy
M0: No maculopathy
M1

Ay macular oedema

DMO: Diabetic maculae oedema

Appendix 5

DECS –Specialist Care Feedback System

Sticker of Patient Date

Has the patient been seen in DECS in 2008/2009 Yes/No

Has the patient been seen in DECS Yes/No

	Right Eye	**Left Eye**
Visual Acuity		
Grade of Retinopathy	A B C D E F	A B C D E F
Macular edema	M0 CSMO DMO	M0 CSMO DMO
Laser	Macular PRP None	Macular PRP None
Vitrectomy		
IVTA		
Anti-VEGF		

Ethnicity

Any other Ocular Co-morbidity

Comments

Diabetic Care: KCH GSTT UHL GP Other

Was OCT done in this Visit Yes/No

Was FFA done in this visit Yes/No

A. Mild NPDR
• At least one microaneursym
B. Moderate NPDR
• Hemorrhages or microaneurysms (H/Ma)
• Soft exudates, Venous beading (VB), and intraretinal microvascular abnormalities (IRMAs) definitely present.
C. Severe NPDR
• H/Ma in all 4 quadrants
• VB in 2 or more quardrants
• IRMA in at least 1 quadrant
D. **Very Severe NPDR**
• Any two or more of C
E. Early PDR
• New vessels on the retina
• Definition not met for F
F. High-Risk PDR
• New vessels on the disc (NVD) of 1/4 to 1/3 or more of the disc area or
• Any NV and vitreous or preretinal or vitreous hemorrhage
M0: No maculopathy

CSMO: Clinically Significant macular edema

DMO: Diabetic maculae edema

Appendix 6

DRIVE-UK

Diabetic **R**etinopathy **i**n **v**arious **e**thnic groups in **UK**

Please complete the following form and return in the envelope provided to:

Name and address of where to return to:

Dr Sobha Sivaprasad

DRIVE-UK

Ophthalmology

Normanby Building

King's College Hospital

Identification details (this page to be removed before data entry:

NHS number: _____

Study Randomisation Number: _____

THANK YOU

ID number: (pre-printed)

Question		Please complete data or tick which applies.	
1	Year of birth(leave blank if not known)	☐☐☐☐	
2	Gender	☐Male ☐Female	☐Not known
3	Ethnic group	☐White British ☐African-Caribbean ☐ South Asian[1] ☐Other	☐Not known
4	Smoker	☐Current ☐Ex smoker ☐No	☐Not known
5	Type of diabetes	☐Type I ☐Type II ☐ Other	☐Not known
6	Year of diagnosis of diabetes (leave blank if not known)	☐☐☐☐	
7	Medication for hyperglycaemia	☐Tablets ☐Insulin ☐Both ☐None	☐Not known
8	Medication for cardiovascular disease	☐ ACE ☐Anti-platelets ☐ARB ☐Aspirin ☐Beta-blockers ☐Calcium blockers ☐ Diuretics ☐ Statins ☐ No medication	☐Not known
10	Diabetes related health problems	☐ Amputation ☐Angioplasty ☐ CABG ☐ Dialysis ☐Foot ulcer ☐Microalbuminuria ☐ Myocardial infarction ☐Stroke ☐Peripheral neuropathy ☐ None	☐Not known
For the following items, please record the measurement taken on the date nearest to JUNE 30th 2009			
11	Body mass index (BMI)	Date: _____/_____/_____☐☐.☐kg/m^2	
12	Blood pressure mmHg	Date: ___/___/____☐☐☐/☐☐☐	
13	HbA1c%	Date: ____/____/____ ☐☐.☐	
14	LDL (mmol/litre)	Date: ____/____/____ ☐☐☐.☐	
15	HDL (mmol/litre)	Date: ____/____/____ ☐☐☐.☐	
16	Total cholesterol (mmol/litre)	Date: ____/____/____ ☐☐☐.☐	
17	eGFR (ml/min)	Date: ____/____/____ ☐☐☐.☐	
18	Albumin:creatinine ratio (ACR)	Date: ____/____/___ ☐☐.☐	

* South Asian: people of origin from India, Pakistan, Sri Lanka or Bangladesh

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PRESENTATIONS ARISING FROM THIS STUDY

ARVO: 2010: **Poster**

Ocular manifestations in patients with diabetes-related end stage kidney disease in various ethnic groups (DRIVE UK Study)

Bhaskar Gupta, Ian MacDougall, Claire Sharpe, Satish Jayawardene, Tracey Bailey, Sobha Sivaprasad

EURETINA: Paris Sep 2nd 2010: **Free Paper**

Visual Impairment in Various Ethnic Groups in Diabetic population (DRIVE UK Study)

Bhaskar Gupta MRCOphth, Jennifer Evans PHD, Sobha Sivaprasad FRCS

Shankar Netralaya, Chennai, India: Joint ARVO-SN diabetic update(9-11th September,2010)

Free Paper

Proliferative Diabetic Retinopathy predicts the onset of diabetes-related end stage kidney disease.

Bhaskar Gupta, Claire Sharpe, Sobha Sivaprasad

Poster

1) **Visual Impairment in Various Ethnic Groups in Diabetic population (DRIVE UK Study)**

   Bhaskar Gupta MRCOphth, Jennifer Evans PHD, Sobha Sivaprasad FRCS

2) **Visual and anatomical outcomes following Vitrectomy for complication due to diabetic retinopathy. (DRIVE UK Study)**

   Bhaskar Gupta MRCOphth, Tom H Williamson FRCS, FRCOphth, Roger Wong FRCOphth, Alistair Laidlaw FRCOphth, Tim Jackson FRCOphth, Dominic McHugh FRCOphth, Sobha Sivaprasad FRCS.