Original Article

Identification of risk factors for targeted diabetic retinopathy screening to urgently decrease the rate of blindness in people with diabetes in India

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Purpose: There is an exponential rise in the prevalence of diabetes mellitus (DM) in India. Ideally all people with DM should be periodically screening for diabetic retinopathy (DR) but is not practical with current infrastructure. An alternate strategy is to identify high-risk individuals with vision-threatening diabetic retinopathy (VTDR) for priority screening and treatment. **Methods:** We reanalyzed four population-based studies, conducted in South India between 2001 and 2010, and reclassified individuals above 40 years into known and newly diagnosed diabetes. Multiple regression analysis was done to identify risk factors in people with known and new DM. **Results:** The prevalence of DR in 44,599 subjects aged ≥40 years was 14.8% (18.4 and 4.7% in known and new DM, respectively), and the prevalence of VTDR was 5.1%. Higher risk factors of VTDR were older age >50 years, diabetes duration >5 years, and systolic blood pressure >140 mm Hg. Targeted screening of people with diabetes using high-risk criteria obtained from this study was able to detect 93.5% of all individuals with VTDR. **Conclusion:** In a limited resource country like India, a high-risk group-based targeted screening of individuals with DM could be prioritized while continuing the current opportunistic screening till India adopts universal screening of all people with DM.

Key words: Diabetic retinopathy, high-risk, risk factors, targeted screening, vision-threatening DR

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Diabetes mellitus (DM) is one of the common noncommunicable diseases (NCDs) in the world. The global prevalence has increased nearly 8 times in the last five decades, from 1.2% in 1971 to 9.3% in 2019.[1] The increase in prevalence is disproportionately high in low- and middle-income countries. In India, the prevalence of DM in people aged 20–79 years has increased from 61.3 million in 2011 to 77 million in 2019, and another 77 million are considered prediabetic, raising a significant public health burden.[1,2] By the year 2030, approximately 101 million people in India are estimated to have diabetes.[3-5] Recent studies in India have shown a lower prevalence of DM in rural India (5.2% rural and 11.2% urban) and higher prevalence in certain Indian states (South – Kerala, Tamil Nadu, and Karnataka; North – Punjab, and Delhi; West – Goa).[2,6] We suspect, with rapid urbanization, this disparity may blur over time, and hence this must be factored into future planning for resources.[1,6]

Diabetic retinopathy (DR) is the most common complication of diabetes and is usually asymptomatic until late. Therefore, DR screening, either by fundus examination or fundus photography, is needed. This requires trained health personnel and retina specialists. The current infrastructure and human resources for health (HRH) in India are underprepared, and people with diabetes have suboptimal knowledge-attitude-practice.[7] These factors are mainly responsible for a high proportion of patients presenting with irreversible and advanced diabetic eye disease to India's eye care facilities.[8] The two most common causes of vision-threatening DR (VTDR) are diabetic macular edema (DME) and proliferative diabetic retinopathy.[9] According to the National Diabetes and Diabetic Retinopathy Survey report 2015–2019, the prevalence of DR is 16.9% in the population ≥50 years, and the prevalence of VTDR is 3.6% in India.[10] Ideally, every individual with diabetes needs regular screening for VTDR. However, in India, the DR screening is predominantly opportunistic. Indian data indicates that we would need to identify 2,772,000 people with VTDR from 77 million people with diabetes through opportunistic screening and treat them to reduce the rate of blindness urgently. Left untreated, 26% of people with VTDR are likely to be severely vision impaired in 2 years, and this risk could decrease by 11%

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by timely retinal laser photocoagulation.[11] Ideally, an effective screening program should result in a 20% risk reduction of the clinical sequelae.[12] An opportunistic screening *per se* is unlikely to meet this target, and many people in urgent need of treatment could be left out. Hence, there is an urgent need to identify a more vulnerable population segment where a targeted screening could be more rewarding in reducing cost of care and impact in reducing DR-related blindness.

There is no primary care data of DM and DR, which could identify the high-risk group for targeted DR screening in India. Hence, we examined the population-based studies conducted from 2001 to 2010 in India that had required information to assess temporal trends in the prevalence of DM, DR, and VTDR.[13-16] Similar studies in large numbers have not been conducted in India thereafter.

Methods

Summary of selected studies

Six large population-based studies have been conducted in India between 2001 and 2014 on the prevalence of DR and its risk factors.[13-18] Four of these studies, conducted between 2001 and 2010, had patient-level data.[13-16] [Table 1]. These studies had included both known and newly diagnosed individuals with diabetes. There were two levels of differences in recruitment into these studies: age (≥ 20 years,[13] ≥30 years,[15] and ≥40 years); [14,16] and level of fasting blood sugar, FBS (≥100 mg/dL[16], ≥110 mg/dL[14], and >126 mg/dL) [Table 1].[13,15] Oral glucose tolerance test and glycated hemoglobin (HBA1c) were not performed in all studies. New diabetes in the individuals was confirmed after the second level of confirmatory test in two study groups (CURES and SN-DREAMS) [Table 1]. A history of antidiabetic medications was obtained to confirm people with known diabetes.

To obtain uniform data for analysis in this study, we included data on people aged 40 years and older to compare the studies. In the current study, the diagnosis of new diabetes was defined as FBS >7 mmol/L or >126 mg/dL at the time of initial screening.[19,20] Overweight was defined as a body mass index (BMI) between 25 and 29.9 and obese as BMI ≥30.[21] Sociodemographic and clinical parameters common to all studies were collated; these included age at presentation, duration of diabetes (for known individuals with diabetes), gender, history of hypertension, obesity, cardiovascular disease (CVD), and history of smoking.

Statistical analysis

Data from all four studies were entered in a Microsoft Excel spreadsheet and analyzed using Stata Statistical Software (Release 16, StataCorp, 2019, College Station, TX). Results were summarized as mean (± SD) for continuous variables or median (IQR) and percentages for categorical variables. A comparison of variables was performed using an independent *t*-test for continuous variables and Pearson Chi-square test for categorical variables. Univariate and multivariate logistic regression analyses were performed to evaluate risk factors, using DR, DME, and VTDR as dependent variables. A P value of < 0.05 was considered significant.

Results

Fig. 1a summarizes the reclassified total screened population's overall results in each study based on the redefined age criteria of 40 years or older. A total of 44,599 of 71,048 individuals (62.8% of the original cumulated cohort) satisfied the reanalysis criteria. In this study, the prevalence of DM was 12.9% (9.6% having known diabetes and 3.3% having new diabetes). Study-specific prevalence of diabetes was 14.0% (2001–2004, CURES), 23.1% (2003–2006, SN-DREAMS I), 12.0% (2005–2006, ATDRES), and 8.6% (2005–2010, SN-DREAMS III). The residential classification originally considered in the studies was used to label each subject as belonging to a rural or urban household [Fig. 1b]. A total of 31.7% (1838/5784) subjects were from rural households, and the rest, 68.2%, were urban.

Demography and diabetes

Table 2 summarizes the demographic details of the study populations. In the studied cohort, 5,784 people had DM. The average age of patients was 54.98 ± 9.9 years (range, 53.9–56.4 years). The highest proportion of patients (34.5%; $n = 1997$) were in the 50–59 years age group; one-third patients were in the 40–49 years age group, and one-fourth patients were in the 60–69 years age group. Three of four studies had a higher proportion of females. Around 10% of each study population was obese, and 30–40% was overweight (even in a rural population cohort, SNDREAMS-III). There was no change in individuals who were smokers throughout the studies. A significant proportion of each cohort gave no history of previously diagnosed CVD. Hypertension was present in 40% of the participants and was higher in the

Table 1: Summary of DR prevalence studies from South India

Study	Duration of study	Setting	Sampling technique	Age	Screening of DM	Confirmation of DM
CURES[13]	2001-2004	Urban + Rural	Systematic random sampling	>20 years	FBS ≥126 mg/dL	OGTT
SNDREAMS-I[14]	2003-2006	Urban	Multistage systematic random sampling	>40 years	FBS ≥110 mg/dL	2nd FBS >110 mg/dL
ATDRES[15]	2005-2006	Urban + Rural	Randomly selected clusters	>30 years	FBS ≥126 mg/dL	-
SNDREAMS-III[16]	2005-2010	Rural	Multistage cluster sampling	>40 years	FBS ≥100 mg/dL	OGTT

CURES: Chennai Urban Rural Epidemiology Study; SNDREAMS-I: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study for Urban Population; ATDRES: Aravind Theni Diabetic Retinopathy Epidemiology Study; SNDREAMS-III: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study for Rural Population; FBS: Fasting blood sugar; OGTT: Oral glucose tolerance test

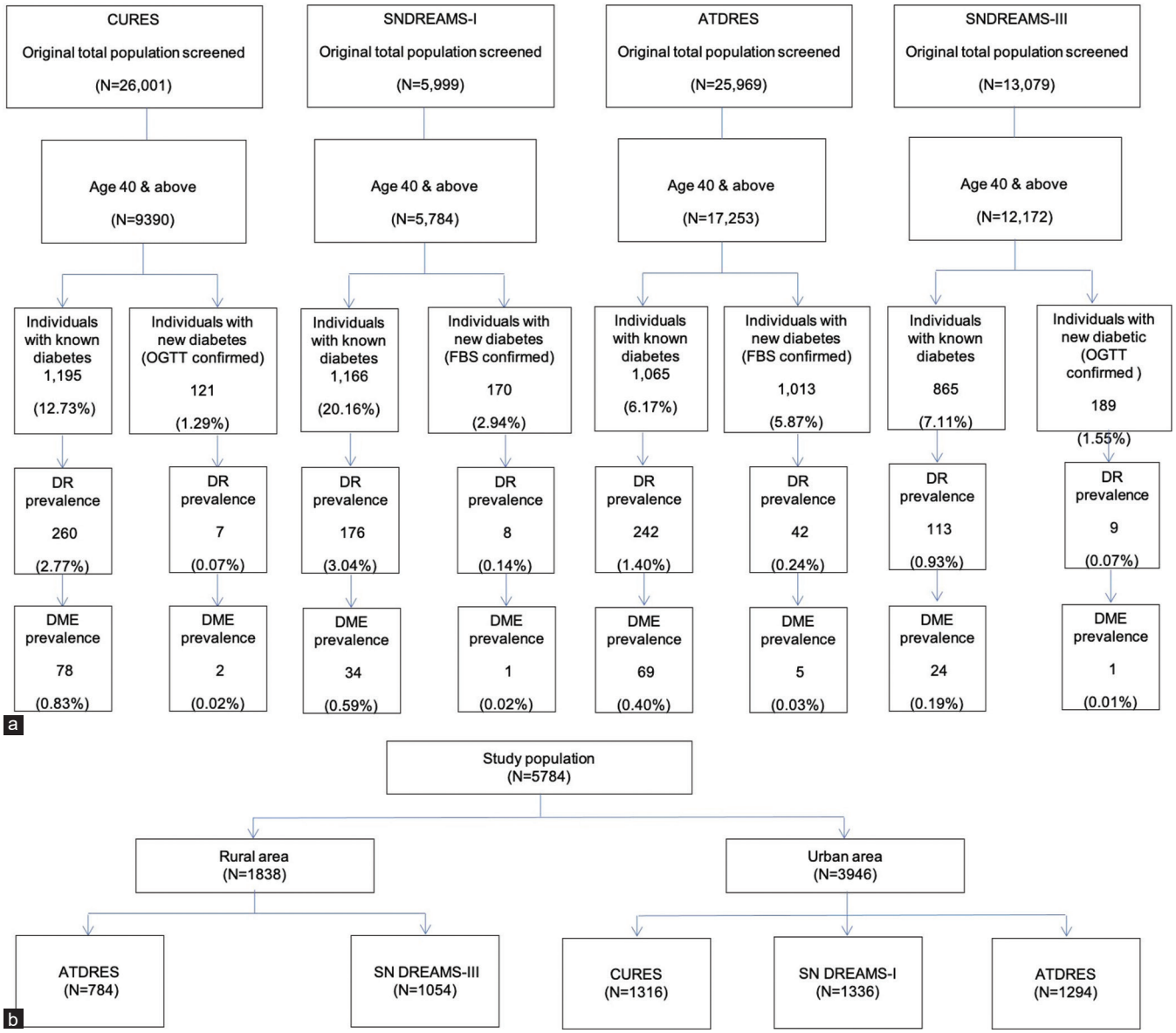

Figure 1: (a) Summary and reclassification of known and newly diagnosed individuals with diabetes, diabetic retinopathy (DR), and diabetic macular edema (DME). (**b)** Summary of study individuals categorized based on urban or rural household status

purely urban SN-DREAMS-I cohort [Table 2]. Considering data from SNDREAMS-I as an outlier, the overall prevalence of hypertension was 30% (26.8% in rural, 43.9% in urban).

The mean duration of diabetes in the subjects with known DM was around 5 years or more in three of the four studies (except the rural SN-DREAMS-III study with a mean of about 1 year) [Table 2]. In all the studies, about 60% of subjects with known DM had received their diagnosis within the last 5 years (except 95.6% in the rural cohort of SN-DREAMS-III). Overall, around 60% of the rural population received their diagnosis within the previous 5 years, with a mean duration of diagnosis being 2.38 years. However, the urban population seemed to have an earlier diagnosis of DM, with around 50% diagnosed within 5 years and about 20% diagnosed 6–10 years ago, with a mean duration of DM 6.24 years. In this cohort, 74.2% people were known DM.

Prevalence of DR

Fig. 1 summarizes the prevalence of DR and DME in people with diabetes recruited in each study based on the status of diabetes (known or new). The overall range of DR prevalence in the studies was 11.6– 20.3% [Table 2]. After combining the data of all studies, the prevalence of DR was 14.8% (known diabetes: 18.4% and new diabetes: 4.7%); the prevalence of DME was 3.7% (known diabetes: 4.8%; new diabetes, 0.6%); and the prevalence of VTDR was 5.1% (known diabetes: 6.5%; new diabetes: 0.8%) [Table 3]. The prevalence of DR was higher in the urban than rural population as follows: any DR – urban: 16.4%, rural: 11.5%; DME – urban: 4.2%, rural: 2.6%; and VTDR – urban: 5.3%, rural: 4.6%.

Table 4 shows that DR, DME, and VTDR prevalence was the highest in 50–59 years. In this age group, any DR was 17.0% (all ages: 14.8%), DME was 4.8% (all ages: 3.7%), and VTDR was 6.2% (all ages: 5.1%). The prevalence increased with

Table 2: Descriptive statistics of subjects with diabetes in individual studies

Parameters	Centre-wise				Area of residence		Overall (*n*=5784)
	CURES (*n*=1316)	SNDREAMS-I (*n*=1336)	ATDRES (*n*=2078)	SNDREAMS-III (*n*=1054)	Rural (*n*=1838)	Urban (*n*=3946)	
Age in years							
Median (IQR)	53 (47-60)	55 (49-64)	54 (47-62)	55 (46-61)	55 (47-62)	54 (47-62)	54 (47-62)
Age groups (years) (%)#							
40-49	439 (33.4)	367 (27.5)	687 (33.1)	333 (31.6)	567 (30.9)	1259 (31.9)	1826 (31.6)
50-59	511 (38.8)	476 (35.6)	666 (32.0)	344 (32.6)	602 (32.7)	1395 (35.3)	1997 (34.5)
60-69	288 (21.9)	338 (25.3)	509 (24.5)	291 (27.6)	491 (26.7)	935 (23.7)	1426 (24.7)
>70	78 (5.9)	155 (11.6)	216 (10.4)	86 (8.2)	178 (9.7)	357 (9.1)	535 (9.2)
Gender (%)#							
1. Male	589 (44.8)	714 (53.4)	911 (43.8)	489 (46.4)	862 (46.9)	1841 (46.6)	2703 (46.7)
2. Female	727 (55.2)	622 (46.6)	1167 (56.2)	565 (53.6)	976 (53.1)	2105 (53.4)	3081 (53.3)
BMI categories* (%)#							
1. Normal	663 (50.4)	465 (34.8)	1057 (50.9)	566 (53.7)	995 (54.1)	1756 (44.5)	2751 (47.6)
2. Overweight	432 (32.8)	415 (31.0)	638 (30.7)	285 (27.0)	490 (26.7)	1280 (32.4)	1770 (30.6)
3. Obese	160 (12.2)	123 (9.2)	213 (10.3)	97 (9.2)	152 (8.3)	439 (11.1)	593 (10.3)
BMI values							
Median (IQR)	24.6 (22.1-27.4)	23.6 (18.6-26.7)	24.0 (21.5-27.1)	23.4 (20.6-26.5)	23.4 (20.7-26.3)	24.7 (22.3-27.5)	23.9 (21.2-26.9)
Smoking status (%)#							
1. Nonsmokers	1077 (81.8)	1075 (80.5)	1648 (79.3)	904 (85.8)	1505 (81.9)	3199 (81.1)	4704 (81.3)
2. Smokers	239 (18.2)	261 (19.5)	426 (20.5)	150 (14.2)	331 (18.0)	745 (18.9)	1076 (18.6)
Cardiac comorbidity (%)#							
1. No	358 (27.2)	1175 (87.9)	1956 (94.1)	1033 (98.0)	1765 (96.0)	2757 (69.9)	4522 (78.2)
2. Yes	59 (4.5)	161 (12.1)	122 (5.9)	21 (2.0)	73 (4.0)	290 (7.3)	363 (6.3)
Hypertension#							
1. No	796 (60.5)	488 (36.5)	1440 (69.3)	791 (75.1)	1346 (73.2)	2169 (55.0)	3515 (60.8)
2. Yes	476 (36.2)	848 (63.5)	638 (30.7)	263 (24.9)	492 (26.8)	1733 (43.9)	2225 (38.5)
Duration of diabetes in subjects with known diabetes (years) Mean (SD)	6.23 (5.47)	6.69 (6.29)	5.29 (5.39)	1.17 (2.09)	2.38 (3.81)	6.24 (5.83)	5.10 (5.60)
Duration of diabetes in subjects with known diabetes (years) Median (IQR)	5 (2-9)	5 (2-10)	4 (2-7)	0.4 (0.2-1)	0.83 (0.17-3.0)	4.5 (2-10)	3 (1-7)
Diabetic status (%)#							
1. subjects with known diabetes	1195 (90.8)	1166 (87.3)	1065 (51.3)	865 (82.1)	1267 (68.9)	3024 (76.6)	4291 (74.2)
2. subjects with new diabetes	121 (9.2)	170 (12.7)	1013 (48.7)	189 (17.9)	571 (31.1)	922 (23.4)	1493 (25.8)
Duration of known diabetes categories (%)#							
≤ 5 years	708 (59.3)	686 (58.8)	721 (67.7)	827 (95.6)	1109 (60.3)	1833 (46.5)	2942 (68.6)
6-≤10 years	311 (26.0)	260 (22.3)	232 (21.8)	33 (3.8)	116 (6.3)	720 (18.2)	836 (19.5)
>10 years	172 (14.4)	220 (18.9)	112 (10.5)	5 (0.6)	42 (2.3)	467 (11.8)	509 (11.9)
SBP							
Median (IQR)	130 (115-141)	138 (124-150)	130 (120-140)	120 (120-130)	120 (120-138)	130 (120-148)	130 (120-140)

Contd...

Table 2: Contd...

Parameters	Centre-wise				Area of residence		Overall (*n*=5784)
	CURES (*n*=1316)	SNDREAMS-I (*n*=1336)	ATDRES (*n*=2078)	SNDREAMS-III (*n*=1054)	Rural (*n*=1838)	Urban (*n*=3946)	
SBP categories (%)#							
<120	387 (29.4)	150 (11.2)	418 (20.1)	234 (22.2)	414 (22.5)	775 (19.6)	1189 (20.6)
120-139	518 (39.4)	519 (38.9)	801 (38.6)	666 (63.2)	977 (53.2)	1527 (38.7)	2504 (43.3)
140-159	259 (19.7)	414 (30.9)	611 (29.4)	116 (11.0)	322 (17.5)	1078 (27.3)	1400 (24.2)
160-179	110 (8.4)	183 (13.7)	185 (8.9)	26 (2.5)	88 (4.8)	416 (10.5)	504 (8.7)
180 and above	41 (3.1)	70 (5.2)	63 (3.0)	12 (1.1)	37 (2.0)	149 (3.8)	186 (3.2)
DBP							
Median (IQR)	78 (70-83)	80 (72.5-90)	80 (80-90)	80 (78-86)	80 (76-90)	80 (70-90)	80 (70-90)
DBP categories (%)#							
<80	712 (54.1)	421 (31.5)	511 (24.6)	287 (27.2)	503 (27.4)	1428 (36.2)	1931 (33.4)
80-89	365 (27.7)	515 (38.6)	788 (37.9)	544 (51.6)	853 (46.4)	1359 (34.4)	2212 (38.2)
90 and above	238 (18.1)	400 (29.9)	779 (37.5)	223 (21.2)	482 (26.2)	1158 (29.4)	1640 (28.4)
FBS							
Median (IQR)	150 (111-206)	135 (103-186)	159 (134-216)	137 (102-197)	147 (118-206)	150 (119-204)	149 (118-205)
Diabetic retinopathy prevalence	267 (20.3%)	184 (13.8%)	284 (13.7%)	122 (11.6%)	211 (11.5%)	646 (16.4%)	857 (14.8%)
Diabetic macular edema prevalence	80 (6.1%)	35 (2.6%)	74 (3.6%)	25 (2.4%)	47 (2.6%)	167 (4.2%)	214 (3.7%)
Vision-threatening diabetic retinopathy prevalence	100 (7.6%)	40 (3.0%)	101 (4.9%)	51 (4.8%)	85 (4.6%)	207 (5.3%)	292 (5.1%)

*Categories defined, #frequencies - data missing for some subjects - available data reported and analyzed

Table 3: Prevalence of stages of diabetic retinopathy (DR) in known (*n*=4291) and new (*n*=1493) individuals with diabetes

Parameters	*n*	Prevalence (%)
Overall (*n*=5784)		
Any DR	856	14.8
Mild/moderate NPDR	718	12.4
Severe NPDR	80	1.4
PDR	58	1.0
DME	214	3.7
VTDR	292	5.1
Known individuals with diabetes (*n*=4291)		
Any DR	790	18.4
Mild/moderate NPDR	658	15.3
Severe NPDR	77	1.8
PDR	55	1.3
DME`	205	4.8
VTDR	280	6.5
New individuals with diabetes (*n*=1493)		
Any DR	66	(66/1493)×100=4.4
Mild/moderate NPDR	60	4.0
Severe NPDR	3	0.2
PDR	3	0.2
DME	9	0.6
VTDR	12	0.8

DR: Diabetic retinopathy; NPDR: nonproliferative DR; PDR: proliferative DR; DME: diabetic macular edema; VTDR: vision-threatening DR

the duration of diabetes and was maximum in people with the duration of diabetes 10 years or longer. Subjects with systolic blood pressure (SBP) >140 mm Hg had a higher prevalence of DR, DME, and VTDR. The prevalence of DR and VTDR increased with increasing SBP of risk factor analysis [Table 4].

Logistic regression was performed to evaluate the risk of DR, DME, and VTDR [Table 4]. In multivariable logistic regression analysis for any DR, a significant positive association with risk of DR was observed with age group 50–59 years, male gender, urban residence, duration of diabetes ≥6 years, and SBP ≥140 mm Hg. A positive association of DME risk was found with age group 50–59 years, CVD, duration of diabetes ≥6 years, and SBP ≥140 mm Hg. A positive association of risk of VTDR was found with age range 50–59 years, duration of diabetes ≥6 years, and SBP ≥140 mm Hg. In this study cohort, overweight/obesity and newly diagnosed DM did not carry significant risk for any DR, DME, and VTDR.

Table 5 calculates the number of people included or excluded by a targeted screening of people with VTDR. In universal screening, i.e., if all people with diabetes would be screened, then one is expected to examine 292 people with VTDR. By priority screening of people with known DM in the vulnerable 50–69 years age group (61.5% of people with known DM), it would decrease to 198, which is 67.8% of all VTDR cases (from 292 to 198). Our analysis also indicated that people with SBP ≥140 mm Hg and duration of DM above 5 years are equally vulnerable. By adding these groups of people, the targeted screening detection would increase to 273 people (from 198), i.e. 93.5% of all people with VTDR.

Table 4: Univariate and multivariate logistic regression for diabetic retinopathy, diabetic macular edema and vision-threatening diabetic retinopathy (Severe NPDR, PDR, DME)

Parameter	Diabetic Retinopathy					
	Total population	(*n*=857) Prevalence (%)	Univariate model		Multivariable model	
			Risk Ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*
Age in years						
1. Age 40-49*	1826	217 (11.9%)	1		1	
2. Age 50-59	1997	340 (17.0%)	1.3 (1.1-1.5)	<0.001	1.2 (1.0-1.4)	0.034
3. Age 60-69	1426	229 (16.1%)	1.3 (1.1-1.5)	0.005	1.0 (0.8-1.2)	0.91
4. Age 70 +	535	71 (13.3%)	1.1 (0.9-1.4)	0.339	0.8 (0.6-1.1)	0.199
Gender						
1. Male*	2703	473 (17.5%)	1		1	
2. Female	3081	384 (12.5%)	0.8 (0.7-0.9)	<0.001	0.8 (0.7-0.9)	0.002
BMI						
1. Normal*	2751	482 (17.5%)	1		1	
2. Overweight	1770	230 (12.9%)	0.7 (0.6-0.8)	<0.001	0.7 (0.6-0.8)	<0.001
3. Obese	593	55 (9.3%)	0.5 (0.4-0.7)	<0.001	0.5 (0.4-0.7)	<0.001
Area of residence						
Rural*	1838	211 (11.5%)	1		1	
Urban	3946	646 (16.4%)	1.2 (1.1-1.4)	0.004	1.2 (1.0-1.4)	0.025
Smoking status						
1. Nonsmokers*	4704	664 (14.1%)	1		1	
2. Smokers	1076	193 (17.9%)	1.2 (1.0-1.4)	0.024	0.9 (0.8-1.2)	0.81
Cardiac status						
1. No*	4522	618 (13.7%)	1		-	-
2. Yes	363	63 (17.4%)	1.1 (0.9-1.4)	0.309		
Hypertension#						
1. No*	3027	415 (13.7%)	1		1	
2. Yes	1377	243 (17.6%)	1.2 (1.1-1.4)	0.004	1.1 (0.9-1.2)	0.716
Duration of diabetes						
1. Up to 5 years*	2942	379 (12.9%)	1		1	
2. 6-10 years	836	225 (26.9%)	2.0 (1.8-2.4)	<0.001	1.9 (1.7-2.3)	<0.001
3. Above 10 years	509	187 (36.7%)	2.5 (2.2-2.9)	<0.001	1.3 (1.2-1.6)	<0.001
SBP categories						
<120*	1189	155 (13.0%)	1		1	
120-139	2504	333 (13.3%)	0.9 (0.8-1.2)	0.71	1.1 (0.9-1.4)	0.28
140-159	1400	216 (15.4%)	1.3 (1.1-1.6)	0.005	1.5 (1.2-1.9)	0.001
160-179	504	114 (22.6%)	1.6 (1.3-1.9)	<0.001	1.8 (1.4-2.3)	<0.001
180 and above	186	39 (20.6%)	1.5 (1.1-2.0)	0.008	1.6 (1.1-2.3)	0.013
DBP categories						
<80*	1931	317 (16.4%)	1		1	
80-89	2212	277 (12.5%)	0.9 (0.7-0.9)	0.041	0.9 (0.7-1.0)	0.09
90 and above	1640	263 (16.0%)	1.2 (1.1-1.4)	0.003	1.1 (0.9-1.3)	0.4

Parameter	Diabetic Macular Edema (DME)					Vision-threatening diabetic retinopathy (VTDR)				
	(*n*=214) Prevalence (%)	Univariate model		Multivariable model		(*n*=292) Prevalence (%)	Univariate model		Multivariable model	
		Risk ratio (95% CI)	*P*	Risk Ratio (95% CI)	*P*		Risk Ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*
Age in years										
1. Age 40-49*	43 (2.4%)	1		1		63 (3.5%)	1		1	
2. Age 50-59	95 (4.8%)	2.0 (1.4-2.9)	<0.001	1.7 (1.1-2.8)	0.024	123 (6.2%)	1.8 (1.3-2.4)	<0.001	1.8 (1.2-2.7)	0.005
3. Age 60-69	58 (4.1%)	1.7 (1.1-2.4)	0.01	1.4 (0.8-2.3)	0.193	83 (5.8%)	1.7 (1.2-2.3)	0.001	1.5 (0.9-2.2)	0.093

Contd...

Table 4: Contd...

Parameter	Diabetic Macular Edema (DME)					Vision-threatening diabetic retinopathy (VTDR)				
	(*n*=214) Prevalence (%)	Univariate model		Multivariable model		(*n*=292) Prevalence (%)	Univariate model		Multivariable model	
		Risk ratio (95% CI)	*P*	Risk Ratio (95% CI)	*P*		Risk Ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*
Gender										
1. Male*	98 (3.6%)	1		-	-	144 (5.3%)	1		-	-
2. Female	116 (3.8%)	1.1 (0.8-1.4)	0.703			148 (4.8%)	0.9 (0.7-1.1)	0.364		
BMI										
1. Normal*	129 (4.7%)	1		1		172 (6.3%)	1		1	
2. Overweight	50 (2.8%)	0.6 (0.4-0.8)	0.002	0.5 (0.4-0.8)	0.001	68 (3.8%)	0.6 (0.5-0.8)	0.001	0.6 (0.5-0.8)	0.002
3. Obese	11 (1.9%)	0.4 (0.2-0.8)	0.004	0.4 (0.2-0.8)	0.009	15 (2.5%)	0.4 (0.2-0.7)	0.001	0.3 (0.2-0.6)	0.001
Area of residence										
Rural*	47 (2.6%)	1		1		85 (4.6%)	1		-	-
Urban	167 (4.2%)	2.4 (1.8-3.3)	<0.001	1.1 (0.7-1.5)	0.847	207 (5.3%)	1.1 (0.9-1.5)	0.316	-	-
Smoking status										
1. Nonsmokers*	175 (3.7%)	1		-	-	243 (5.2%)	1		-	-
2. Smokers	39 (3.6%)	0.7 (0.5-1.0)	0.077			49 (4.6%)	0.9 (0.6-1.2)	0.41		
Cardiac status										
1. No*	140 (3.1%)	1		1		198 (4.4%)	1		1	
2. Yes	23 (6.3%)	2.2 (1.4-3.4)	<0.001	1.8 (1.2-2.9)	0.01	27 (7.4%)	1.7 (1.2-2.5)	0.007	1.4 (0.9-2.0)	0.164
Hypertension#										
1. No*	105 (3.5%)	1		1		147 (4.9%)	1		1	
2. Yes	72 (5.2%)	1.7 (1.2-2.2)	0.001	1.3 (0.9-1.9)	0.144	102 (7.4%)	1.5 (1.2-1.9)	0.0.001	1/2 (0.9-1.6)	0.276
Duration of diabetes										
1. Up to 5 years*	84 (2.9%)	1		1		98 (4.0%)	1		1	
2. 6-10 years	58 (6.9%)	2.6 (1.8-3.6)	<0.001	2.8 (1.9-4.2)	<0.001	72 (10.0%)	2.5 (1.9-3.3)	<0.001	2.6 (1.8-3.8)	<0.001
3. Above 10 years	63 (12.4%)	1.3 (0.9-1.8)	0.084	1.3 (0.9-1.9)	0.12	116 (7.2%)	1.8 (1.4-2.3)	<0.001	1.6 (1.2-2.3)	0.004
SBP categories										
<120*	37 (3.1%)	1		1		49 (4.1%)	1		1	
120-139	72 (2.9%)	0.8 (0.5-1.2)	0.27	1.5 (0.8-2.7)	0.2	104 (4.2%)	1.0 (0.7-1.4)	0.963	1.5 (0.9-2.5)	0.134
140-159	64 (4.6%)	1.2 (0.8-1.8)	0.287	2.9 (1.5-5.5)	0.002	80 (5.7%)	1.4 (0.9-1.9)	0.065	2.5 (1.4-4.5)	0.002
160-179	33 (6.6%)	1.8 (1.2-2.9)	0.01	4.9 (2.4-10.1)	<0.001	47 (9.3%)	2.3 (1.5-3.3)	<0.001	4.3 (2.3-8.3)	<0.001
180 and above	8 (4.3%)	1.2 (0.6-2.6)	0.608	2.3 (0.8-6.9)	0.1	12 (6.5%)	1.6 (0.8-2.9)	0.151	2.5 (0.9-6.3)	0.056
DBP categories										
<80*	79 (4.1%)	1		1		107 (5.5%)	1		1	
80-89	64 (2.9%)	0.6 (0.4-0.8)	<0.001	0.6 (0.4-0.9)	0.15	90 (4.1%)	0.7 (0.6-0.9)	0.027	0.9 (0.6-1.2)	0.41
90 and above	71 (4.3%)	0.8 (0.6-1.1)	0.175	0.9 (0.5-1.4)	0.5	95 (5.8%)	1.0 (0.8-1.4)	0.746	1.1 (0.8-1.7)	0.524

*Reference category; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; #outlier data excluded

Table 5: Comparison of numbers screened in universal versus targeted screening (model prepared from risk factors identified in the current study)

	n	Numbers of VTDR detected	Numbers of VTDR missed
All patients screened (Universal screening model)	5784 (all DM)	292 (5.1% of all DM)	0%
Risk groups (targeted screening model)			
1. Only age group 50-69 years with known DM	2640 (61.5% of known DM; 45.6% of all DM)	198 (3.4% of all DM; 67.8% of all VTDR)	94/292 (32.2%)
2. Others outside of 50-69 years age group Systolic BP >140 mm Hg	358 (6.2% of all DM)	26 (8.9% of all VTDR)	266/292 (91.1%)
3. Others outside of 50-69 years age group with known DM duration >5 years	810 (18.9% of known DM; 14% of all DM)	49 (16.8% of overall VTDR)	243/292 (83.2%)
Total numbers screened by targeted screening	3808 (65.8% of all DM)	273 (93.5% of all VTDR)	19/292 (6.5%)

Discussion

The temporal trends of DR over a decade [2001–2010; Table 1] in South India show that the prevalence of DR and VTDR has not changed much.[22,23] Our study showed that 74.2% of people had known diabetes [Table 3], with an overall prevalence of DR and VTDR of 14.8 and 5.1%, respectively [Table 3]. Targeted screening of people with high-risk factors [Table 4] would identify 93.5% of people with VTDR by screening nearly one-third lesser population than a universal screening strategy [Table 5].

Extrapolating these findings to the current population of 77 million people with diabetes in India, 57 million people would have known diabetes (74.2% of 77 million), and 3.9 million people would have VTDR (5.1% of 77 million). Considering that a potential targeted screening program is put in place in the country according to the high-risk groups identified in our analysis, as of today, 93.5% of the total VTDR population would be detected by the same; this amounts to 3.7 million people (93.5% of 3.9 million) with VTDR. Thus, a targeted screening may result in a reduction of 200,000 individuals. But equally important is that it could be pooled from 51 million people [65.8% of all people with DM – Table 5]; the reduction of 26 million fewer people screened to obtain 93.5% of people with VTDR who need urgent care is cost-effective. With the current infrastructure for both screening and treatment and available HRH in India, striking a balance between missed diagnoses of VTDR and the possibility of detecting reasonably high numbers of VTDR by screening a lesser number of individuals would result in a faster reduction of DR-related blindness and visual impairment.

The prevalence of DR was higher in the urban than rural population. This urban–rural difference has been reported in many studies with low prevalence of diabetes in the rural population. The increased urban prevalence of diabetes probably reflects economic transition and westernization of diet. With increasing affluence and changes in diet in rural populations, along with better access to healthcare, rural areas are also facing an epidemiological shift towards a higher prevalence of DM. Ramachandran *et al*.[22] showed that between 1989 and 2003, prevalence of DM in rural areas had increased 3-fold from 2.2 to 6.3%, similar to other reports.[23] There was higher prevalence of undiagnosed diabetes in the oldest of the studies (ATDRES) again highlighting improving rates of diagnosis of diabetes over the last decade. Considering the rising population with diabetes in India, a lower prevalence of DR in India compared to the West does not signify lesser number of patients. A major reason for the large proportion of VTDR cases in spite of lower prevalence of DR may be a later diagnosis of DR in patients with DM or a later diagnosis of DM with advanced stages of DR. This may be attributed to lesser penetration of healthcare or lack in easy access to healthcare services. Despite the lower prevalence of DR, the high prevalence of VTDR in India is a significant public health burden.

Experience from the DR screening program in the UK has shown that a well-implemented program may result in timely detection and treatment of all people with VTDR; this reduces the need for vitrectomy and eventual blindness.[24] With the proper execution of the screening program, the annual incidence of screen positive for retinopathy has reduced from 4.4 – 4.6% in 2007–2009 to 2.3 – 2.9% in 2013–2017, and the rate of VTDR being consistently below 2% after 2008–2009.[24] Identifying VTDR early is important, not just for providing prompt treatment but also for spacing of screening intervals tailored to patients' clinical needs. Stratton *et al*.[25] have observed that the rate of progression to VTDR was 0.7% for patients with no DR and 1.9% for patients with mild NPDR at least in one eye. Hence, risk stratification in the screening programs is an important strategy; and it is an accepted strategy in many developed countries.[26] A Liverpool-based study has demonstrated that targeted risk-factor-based screening for patients based on the duration of known disease, HbA1c, age, systolic BP, and total cholesterol helped optimize the screening intervals. This helped reduce the proportion of people becoming screen positive before the allocated screening date by >50% and allowed targeting resources toward the patients more at risk.[27]

While we acknowledge the necessity of universal screening for detection of DR and VTDR, our study provides evidence that in a resource restraint situation like India, targeted screening of people in high-risk of developing VTDR such as older age (50–69 years), known diabetes of longer duration (more than 5 years), and high SBP (>140 mm Hg) should be a priority. While this strategy in no way undermines the importance of screening every individual with diabetes for DR, we understand that we might be able to detect higher numbers of VTDR by the targeted strategy; this may reduce the burden of future blindness as a priority. The recommendations are to obtain high-quality retinal images and measure both glycated hemoglobin and blood pressure. This is not always possible at every point of care, particularly the measurement of glycated hemoglobin. The Government of India has created a dedicated program, the NPCDCS (National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease, and Stroke) in 2010 with objectives of health promotion, opportunistic screening, setting up of NCD clinics, capacity building, health financing, and a robust surveillance system. By March 2016, the program had set up 298 district NCD cells and 293 district NCD clinics (India has 718 districts).[28] These new facilities could be equipped with all recommendations for high-risk population screening. We suggest a basic eye examination and a fundus photography system in the NCD cells/clinics, risk-based referral to a district hospital for reconfirmation of diabetes status (glycated hemoglobin test) and retinopathy (repeat fundus examination/photography), followed by treatment of all eligible patients immediately, till India develops enough resources to practice routine and systematic screening of all people with diabetes.

Post hoc analysis of decade or longer old data is a major weakness of the study. However, a recent population-based study in India done in 2019 showed no difference in the prevalence of DR (14.3%) or VTDR, despite a high prevalence of diabetes (21.9%), substantiating a near stable prevalence of DR in India.[29] The strength of this study is our ability to derive the main risk factors of DR in India that could be used for priority screening, be it opportunistic or otherwise.

We recognize that there is limited data from other parts of India on the prevalence of DR and VTDR. There may be regional variations of DR and VTDR in India, given the diverse lifestyles in each state. We hope the multicenter SMART-India (Statistical Modelling And Risk assessment of Type 2 diabetes in India) study currently underway in 11 states and one union territory would bridge this knowledge gap.[30]

Conclusion

In India, the number of people with diabetes is increasing, so would the people with DR and VTDR, despite the prevalence rate remaining relatively stable. Given the resource limitations, one could prioritize screening the high-risk group while not ignoring others. From the results of this study, we can infer that prioritizing the detection of VTDR, alongside opportunistic screening, which aims at detecting any DR, may be more

useful for India till we have an appropriate number of qualified vitreoretinal specialists or till all ophthalmologists become sufficiently trained in indirect ophthalmoscopy and conversant with medical management of DR. This study also does not deny the current practice of opportunistic screening for DR in India and recommends universal systemic screening in the coming years.

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Conflicts of interest

There are no conflicts of interest.

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