

## Estimating the proportion of persons with diabetes developing diabetic retinopathy in India: A systematic review and meta-analysis

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### ABSTRACT

**Background:** Available evidence from India shows that the control of diabetes is poor in majority of the population. This escalates the risk of complications. There is no systematic review to estimate the magnitude of diabetic retinopathy (DR) in India. **Materials and Methods:** A systematic literature search was carried out in Ovid Medline and EMBASE databases using Mesh and key search terms. Studies which reported the proportion of people with diabetes with DR in a representative community population were included. Two independent reviewers reviewed all the retrieved publications. Data were extracted using a predefined form. Review Manager software was used to perform meta-analysis to provide a pooled estimate. Studies included were assessed for methodological quality using selected items from the STROBE checklist. **Results:** Seven studies (1999–2014;  $n = 8315$  persons with diabetes) were included in the review. In the meta-analysis, 14.9% (95% confidence interval [CI] 10.7–19.0%) of known diabetics aged  $\geq 30$  years and 18.1% (95% CI 14.8–21.4) among those aged  $\geq 50$  years had DR. Heterogeneity around this estimate ranged from  $I^2 = 79$ –87%. No linear trend was observed between age and the proportion with DR. The overall methodological quality of included studies was moderate. **Conclusions:** Early detection of DR is currently not prioritized in public health policies for noncommunicable diseases and blindness programs. Methodological issues in studies suggest that the proportion of diabetics with DR is underestimated in the Indian population. Future research should emphasize more robust methodology for assessing diabetes and DR status.

**Key words:** Diabetes, diabetic retinopathy, India, meta-analysis, screening

### INTRODUCTION

Worldwide, the number of persons with diabetes is expected to increase exponentially, and 80% will be living in low- and middle-income countries (LMICs),

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particularly in India and China.<sup>[1]</sup> In 2000, 31.7 million people were reported to have diabetes in India, and this number is expected to rise to 79.4 million by 2030.<sup>[2]</sup> Between 1989 and 2005, a two-fold increase in the prevalence of diabetes was observed in urban areas (from 8.3% to 18.6%) with a more than a three-fold increase in rural populations (from 2.2% to 9.2%).<sup>[3]</sup> It has been estimated that 50–70% of diabetics in India

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have poor glycemic control, which increases the risk of complications such as diabetic retinopathy (DR).<sup>[4,5]</sup>

Worldwide, DR is a leading cause of vision loss in middle-aged populations,<sup>[6]</sup> and globally 34.6% of diabetics are estimated to have DR, i.e., approximately 93 million people worldwide.<sup>[7]</sup> However, there is no regional or country specific estimate for India which could be used to inform health policies and service delivery. Our preliminary search for published reviews conducted in PubMed Medline database used the following search terms (((“Diabetic Retinopathy” [Mesh]) AND (“Prevalence” [Mesh] OR “Epidemiology” [Mesh])) OR (“Review” [Publication Type] OR “Review Literature as Topic” [Mesh])) AND “India” [Mesh]), found only one narrative review that inadequately reported the prevalence of DR in the Indian population.<sup>[8]</sup> Recent global reviews of DR neither presented country-specific estimates nor assessed the methodological quality of the prevalence studies.<sup>[7-9]</sup> Therefore, we first systematically searched the literature and synthesized the data reporting rates of DR among persons with diabetes in Indian studies. Second, data from the Indian studies was pooled to estimate the overall rate of DR among persons with diabetes. Third, a detailed quality assessment was performed to report major methodological limitations.

## MATERIALS AND METHODS

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews statement.<sup>[10]</sup> A review protocol was developed which included the search strategy, inclusion and exclusion criteria, data extraction form, plan for analysis, and outline of evidence synthesis.

### Identification of studies

The search for studies in electronic databases was conducted on May 01, 2015. Studies were identified through the following strategy:

- A search for literature was conducted in Ovid Medline and EMBASE databases to identify studies reporting rates of DR among diabetics in the Indian population. The search terms used are described in Appendix 1. No start date was specified
- Cross-referencing of eligible articles to identify additional studies that met our inclusion criteria was done
- Key informants (i.e., known DR experts, including authors of the eligible studies) were contacted to identify other studies that could be included in our review
- Bibliography of recent papers on DR<sup>[11]</sup> was hand searched to identify studies that may have been missed through the electronic database search.

### Inclusion criteria

- Population-based cross-sectional studies that provided information on the number of persons with type 1 and 2 or other forms of diabetes as well as the number of diabetics with DR
- Studies conducted among adults aged 20 years and above
- Studies which reported DR regardless of the modality used for diagnosis of DR were included.

### Exclusion criteria

- Facility based studies or studies of participants recruited through screening camps
- Studies which did not describe the study design or method of enumeration or base-population (denominator).

### Data collation and extraction

Initial screening was performed by two reviewers (NL and SN) independently to identify papers for inclusion and data extraction. Titles and abstracts of each citation were identified and inspected with reference to the inclusion and exclusion criteria. Relevant full-text papers were then assessed and reviewed by the two reviewers independently. Any disagreements were resolved by consensus and when this could not be reached, a third reviewer (ATJ) adjudicated. The quality of the studies included was assessed using the STROBE checklist. Corresponding authors of all papers were contacted to retrieve any additional or missing information.

### Data extraction

Data were extracted on the following parameters: Year of study, setting of the study (urban and rural), region, study design, sample size and sampling frame, characteristics of participants, number of persons diagnosed with DR, and methods used to diagnose diabetes and to assess and grade DR.

### Assessment of methodological quality of studies

Parameters used for quality assessment were sample size, whether peer-reviewed or not, participant response rate, study measurement, methods. The studies which mentioned these parameters clearly are categorized as at low risk of bias. Studies which mentioned these parameters vaguely and unclearly are categorized as at high risk of bias and unclear risk of bias, respectively.

### Data analysis

Meta-analysis was performed using Review Manager Version 5.1 (Cochrane Informatics and Knowledge Management Centre, London, UK) and “metan” command in STATA Version 13 (Stata Corp, Texas, US). The  $I^2$  test was used to measure statistical heterogeneity across studies. A random-effects model

was used when substantial heterogeneity was observed.<sup>[12]</sup> The uncertainty around heterogeneity was explored using subgroup analyses. Confidence intervals (CIs) for the prevalence estimate were calculated using the following formula (95% CI = prevalence ± 1.96 × standard error).<sup>[13]</sup> When standard deviations for the mean age were not reported, these were calculated using the formula (maximum – minimum/4).<sup>[14]</sup>

## RESULTS

### Search results

After removing duplicates, the electronic search identified 358 studies. Seven studies fulfilled the inclusion criteria [Figure 1].<sup>[11,15-20]</sup>

### Study characteristics

Five of the seven studies were conducted in an urban population, particularly in the South of India [Table 1]. Five out of the seven studies were conducted in an urban population.<sup>[11-15,18,20]</sup> One study recruited both urban and rural populations,<sup>[17]</sup> and another recruited a semi-rural population.<sup>[16]</sup> Three studies were conducted in Tamil Nadu: two in urban Chennai<sup>[19,20]</sup> and one in Theni district.<sup>[17]</sup> Another two studies were conducted in the state of Maharashtra; Mumbai<sup>[11]</sup> and Nagpur.<sup>[16]</sup> The other studies were from Hyderabad, Telangana,<sup>[15]</sup> and Palakkad, Kerala.<sup>[18]</sup>

### Study design

All studies were population-based cross-sectional surveys. Four of the seven studies used a two-phase study design [Table 1].<sup>[11,17,19,20,21]</sup> In phase 1, potential and known diabetics (KD) were identified and invited for phase II, when a detailed retinal examination was performed. In two studies, both phases were conducted in a community setting,<sup>[17,18]</sup> whereas, in three studies, phase II evaluation took place in hospital settings.<sup>[11,19,20]</sup> In a further study free transport was arranged for all eligible participants to the base hospital for phase I and II clinical examinations. One study conducted phase I and phase II evaluations at temporary clinics established in the study catchment area.<sup>[15]</sup>

### Characteristics of participants

Three of the seven studies recruited participants aged 30 years and above.<sup>[15,17]</sup> Two studies recruited those aged 40 years and above,<sup>[11,19]</sup> and the remaining studies recruited participants aged 50<sup>[18]</sup> and 20 years and above [Table 1].<sup>[20]</sup> The proportion of female participants ranged from 47.3% to 55.5%. One ongoing study did not provide information on the gender distribution.<sup>[17]</sup>

### Diagnosis of diabetes

Diagnostic measurement and classification of diabetes varied greatly among studies [Table 2]. Most recruited both KD and newly detected diabetics (NDD). Five studies asked about a medical history of diabetes and tested blood glucose levels for those unaware of their diabetic status.<sup>[11,16,17,19,20]</sup> One study included only KD.<sup>[18]</sup> Another study assessed diabetes status only for participants whose

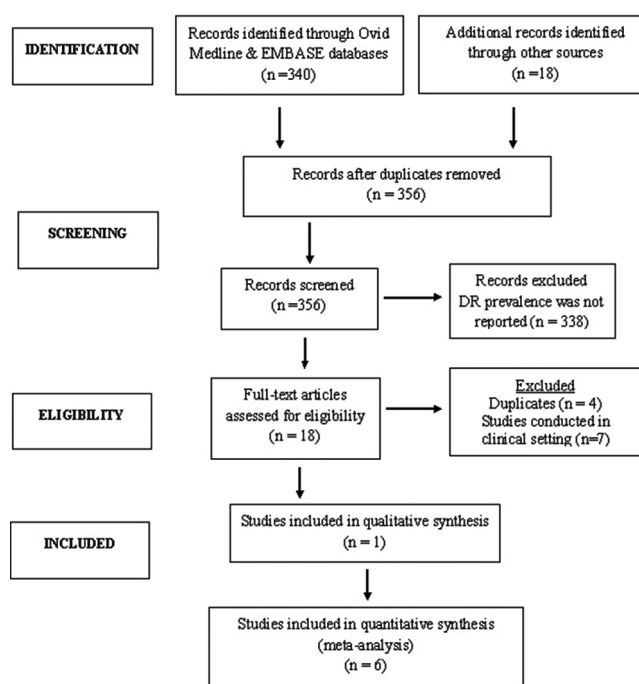


Figure 1: Preferred Reporting Items for Systematic Reviews flowchart

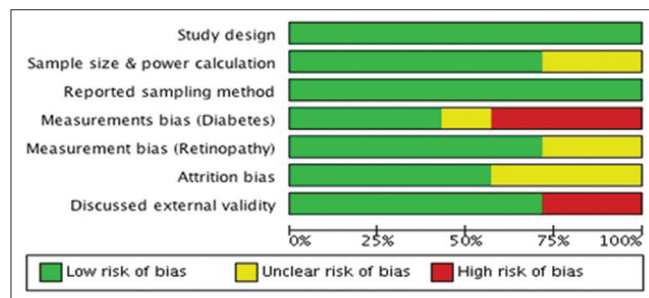
Table 1: Characteristics of studies included in the review

Reference	Study period	Region	Settings	Type of survey	Total sample	Age, (mean age)	Female %
Mohan, 2005	2001/2	Chennai (urban), Tamil Nadu	Community (Phase-I) and Hospital (Phase-II)	Two-phase	26001	≥ 20 (52±11) years	55.5
Raman, 2009	2003/6	Chennai (urban), Tamil Nadu	Community (Phase-I) and Hospital (Phase-II)	Two-phase	5784	≥ 40 (56±10) years	47.6
Narendran, 2002	2001	Palakkad district (urban), Kerala	Community/study centre	One-phase	5212	≥50 (61.7±8) years	47.3
Dandona, 1999	1996/7	Hyderabad (urban), Telangana	Clinical setting	One-phase	2522	≥30 (54±13.7) years	55.5
Namperumalsamy, 2009	2005/6	Theni district (urban and rural), Tamil Nadu	Community (Phase-I and II)	Two-phase	25969	≥30 (47.0±12.7) years	52.1
Sunita, 2014	2011/4	Mumbai (urban slum), Maharashtra	Community (Phase-I) and Hospital (Phase-II)	Two-phase	14739	≥40 years	NA
Jonas, 2013	2006/9	Nagpur (semi-rural), Maharashtra	Hospital setting	One-phase	4711	≥30 (49.1±13.2) years	53.5

fundus examination indicated the presence of DR.<sup>[15]</sup> Except one,<sup>[16]</sup> all the other studies mentioned the criteria for the diagnosis of diabetes. Study participants who reported a medical history of diabetes and were using drugs (either oral or insulin) were categorized as KD. For NDD, five of the seven studies performed fasting blood glucose (FBG) test using glucometer,<sup>[11,15,17,19,20]</sup> and of these, three studies conducted additional biochemical investigations, for example, oral glucose tolerance test, glycosylated hemoglobin estimation to confirm the diagnosis of diabetes.<sup>[11,19,20]</sup> In three out of seven studies, participants with FBG level  $\geq 126$  mg/dl were categorized as NDD;<sup>[11,17,20]</sup> whereas another study used FBG  $\geq 110$  mg/dl as the cutoff.<sup>[19]</sup> In one study, FBG was measured after the DR diagnosis and, fasting glucose level of more than 120 mg/dl was used to confirm the diagnosis.<sup>[15]</sup> One study mentioned that diabetes status was assessed by a blood glucose test and glycosylated hemoglobin, but cut-points were not presented.<sup>[16]</sup> Five out of seven studies used digital fundus cameras,<sup>[11,15,16,19,20]</sup> and two other studies used direct and indirect ophthalmoscopy alone for DR diagnosis.<sup>[17,18]</sup>

**Methodological quality of studies**

Overall, the methodological quality of the studies was moderate [Figure 2]. All included studies provided details of the sampling frame and sampling method used. In three studies the sample size calculation was unclear.<sup>[16,18]</sup> Two studies assessed FBG using a glucometer, and no further confirmatory investigations were performed for those who were not previously diagnosed as diabetic.<sup>[15,17]</sup> Another study applied self-reported information for diagnosis.<sup>[18]</sup> Two studies that applied direct and indirect ophthalmoscopy were rated as unclear for risk of bias.<sup>[17,18]</sup> In two studies, information on nonparticipants was not mentioned clearly and so were rated as having an unclear risk of bias.<sup>[11,15,16]</sup> External validity was discussed in all studies. However, in two studies, the findings were generalizable only to the study participants: One recruited participants from an urban slum,<sup>[11]</sup> and another recruited participant from an undefined catchment area that may not be representative of the target population.<sup>[18]</sup>



**Figure 2:** Risk of bias summary: Review authors' judgment about risk of bias

**Proportion of diabetics with diabetic retinopathy**

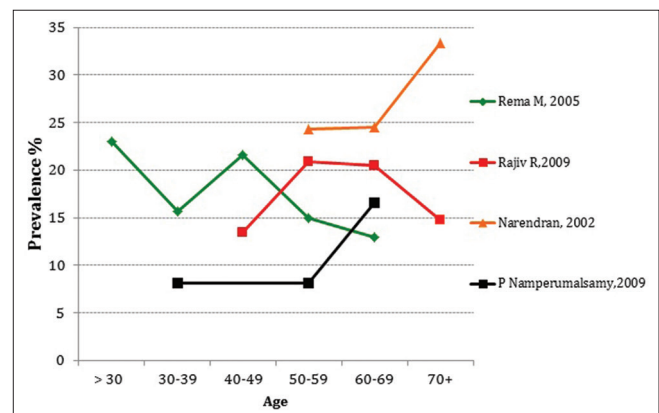
It was observed that between 9.6% and 26.8% of participants with diabetes had some degree of DR [Table 1]. Rates of DR were high among adults aged over 50 years, but there was no linear association of DR with age [Figure 3]. The prevalence was slightly higher among males as compared to females.

Although age eligibility criteria differed among studies, most presented data by age group, allowing data to be pooled in the meta-analysis. About 14.9% (95% CI: 10.7–19.0%) of the diabetics aged 30 years and above had DR compared with 16.7% (95% CI: 14.2–19.2%) of those aged 40 years and above, and 18.09% (95% CI: 14.8–21.4%) of those aged 50 years and above [Figure 4]. High heterogeneity was observed around these estimates  $I^2 = 79-87\%$ .

**DISCUSSION**

The pooled prevalence of DR among known or NDD was 14.8% in persons aged 30 years and older, 16.7% in persons aged 40 years and older, and 18.1% in persons aged 50 years and older in the Indian population. We also observed sizeable variations in the prevalence of DR reported in these studies. Putative reasons for observed heterogeneity include differences in sample size, data collection methods, the definition of diabetes used, duration of diabetes, and procedure followed for diagnosis of retinopathy.

Our review found that the overall prevalence of DR among persons with diabetes in India to be lower than in high-income countries and other LMICs.<sup>[9,22,23]</sup> The DR prevalence is influenced by the risk factors such as poor control of blood glucose, undiagnosed diabetes, and high rates of blood pressure.<sup>[1]</sup> Although these risk factors are equally or highly prevalent in the Indian population,<sup>[24,25]</sup> interestingly, Indian studies found low prevalence. One possible explanation could be the difference in life expectancy of the population; the other could be the methodology issues in the Indian



**Figure 3:** Proportion of diabetics with diabetic retinopathy by age group



included in this review where a large random sample is first screened for diabetes, with referral for detailed eye examination of those known to be diabetic/newly diagnosed as diabetic. Although there are logistical advantages to this approach, there are important limitations. The main limitation is that not all those identified as diabetic will attend for ophthalmic examination. Indeed, in the studies included in the review response rates were lower in studies using a two-phase study design (range 85.6–90%) compared with those using a one-phase design (92% and 96%). If those that do not attend differ from those who do in relation to risk factors for DR, then estimates of the proportion with DR will be biased. This seems likely, as those with other complications of long-standing, poorly controlled diabetes, such as heart disease, amputations, or renal failure are less likely to attend but more likely to have DR. Indeed, those already blind from DR may see little value in attending for ophthalmic examination. A two-phase approach is, therefore, likely to underestimate the proportion with DR. At least 10% of negatives should be invited for phase two assessment, and in case, DR is detected in 10 false negatives that number should be weighted back to the composition of the base population for precise prevalence estimates.

In phase one, none of these studies invited persons scoring negative according to the screening test in the phase one. They should have been invited for phase two clinical and laboratory examination to confirm the diagnosis of diabetes and DR. None of the included studies adequately assessed the diabetes status. In this case, the denominator, number of persons with diabetes, is imprecise: Prevalence estimated in these studies may be underestimated.

#### *Accuracy of diabetes diagnosis*

All the DR studies in the review were subject to measurement bias. We noticed two main measurement issues: (a) Self-reported assessment and (b) use of glucometer for diabetes assessment.

Studies measuring diabetes status by self-reported information are likely to yield higher prevalence of DR. In India, 20% of patients with type 2 diabetes have retinopathy at the time of diagnosis and prevalence of undiagnosed diabetes range from 4.2% to 10.5%, which is two times more than KD.<sup>[30,31]</sup> One study, recruiting only KD by self-reporting, observed a higher prevalence of DR than other studies of the same age group.<sup>[18]</sup> Possibly, in this study, self-reported assessment could have yielded only diagnosed cases; hence, the denominator (number of persons with diabetes) is likely to be smaller and result in an overestimation of DR prevalence for persons aged 50 years and older.<sup>[18]</sup>

Estimation of DR prevalence among persons with diabetes requires the inclusion of all persons with diabetes (denominator). Inaccuracy in ascertainment of diabetic status might result in either overestimating or underestimating the prevalence of DR among persons with diabetes. In four of the seven included studies, FBG was measured using a glucometer for first line screening or to confirm the diagnosis of diabetes.<sup>[15,17,19,20]</sup> Several studies which have tested the efficacy of a glucometer for diagnosis of diabetes have reported a low sensitivity and specificity as compared to the measurement of plasma glucose concentration using venous samples with enzymatic assay techniques.<sup>[32,33]</sup> Technically, a screening test that produces a considerable number of false positives or negatives would pose a major problem for prevalence estimation. In the case of DR, precise estimation of prevalence depends on an accurate denominator (total number of persons with diabetes). Hence more than sensitivity, the specificity of a screening test is arguably important. A study conducted in a South Indian population applied the WHO fasting plasma glucose (FPG)  $\geq 110$  mg/dl criteria and found that sensitivity and specificity of FBG measured by glucometer were 62.8% and 62.9%.<sup>[34]</sup> Both sensitivity and specificity were even lower (58.3% and 58.6%) for the American Diabetes Association criteria for diabetes FPG  $\geq 100$  mg/dl.<sup>[34]</sup> In another study, participants classified as having provisional diabetes using a glucometer were reassessed by a laboratory venous sample at the base hospital. Surprisingly, one-third participants received nondiabetic value in the laboratory investigations.<sup>[35]</sup> Although the impact of a diagnostic test on the prevalence of DR is difficult to judge, it is possible that DR is underestimated in the Indian population as no studies assessed false negatives.

#### **Limitations**

The literature search was conducted only in electronic databases, and we did not attempt to retrieve gray literature (university thesis, conference proceeding, and unpublished reports from services organization). Second, a database search was restricted to Ovid Medline and EMBASE databases, and other electronic databases were not extensively searched. However, expert's group consultation provided reassurance that no published eligible studies from India were excluded in this review. Third, we could not perform meta-regression (as the number of studies was  $< 10$ ) to explore factors contributing to heterogeneity around the prevalence estimate.

#### **CONCLUSIONS**

India is experiencing an unprecedented health transition as well as a demographic shift. A major public health concern is the increasing magnitude of noncommunicable diseases, which already account for 80% of the global burden of

disease.<sup>[36]</sup> While cancer and heart disease mainly contribute to mortality, conditions such as diabetes and blindness increase the number of years lived with disability.<sup>[37]</sup> In 2013, it was estimated that 20% (35.5 million) of world's population with undiagnosed diabetes live in India.<sup>[38]</sup> Compared to type 1 diabetes, people with type 2 diabetes can remain undiagnosed for many years and remain unaware of the complications caused by the disease. Therefore, early detection and management of diabetes and DR among persons with diabetes are quintessential for attenuating adverse consequences. Simultaneous efforts to bring changes at multiple levels in the health system and effective health education needed for diabetic patients would result in early detection of both DM and DR, thereby reducing the blindness due to DR.

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### Conflicts of interest

There are no conflicts of interest.

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## APPENDIX 1: SEARCH TERMS

1. Retinopathy.mp.
2. Exp diabetic retinopathy
3. Diabetic retinopathy.mp.
4. (diabet\$ adj3 retinopath\$).tw.
5. (preproliferative adj3 diabetic adj3 retinopathy).tw.
6. (proliferative adj3 diabetic adj3 retinopathy).tw.
7. Or/1-6
8. exp prevalence/
9. exp mass screening/
10. exp vision screening/
11. exp visual acuity/
12. Epidemiology.mp
13. Exp cross-sectional study/
14. Exp epidemiological studies/
15. Exp population surveillance/
16. Or/8-15
17. India.mp. or exp India/
18. 7 and 16 and 17
19. Limit 18 to human
20. Limit 19 to (comment or editorial or letter)