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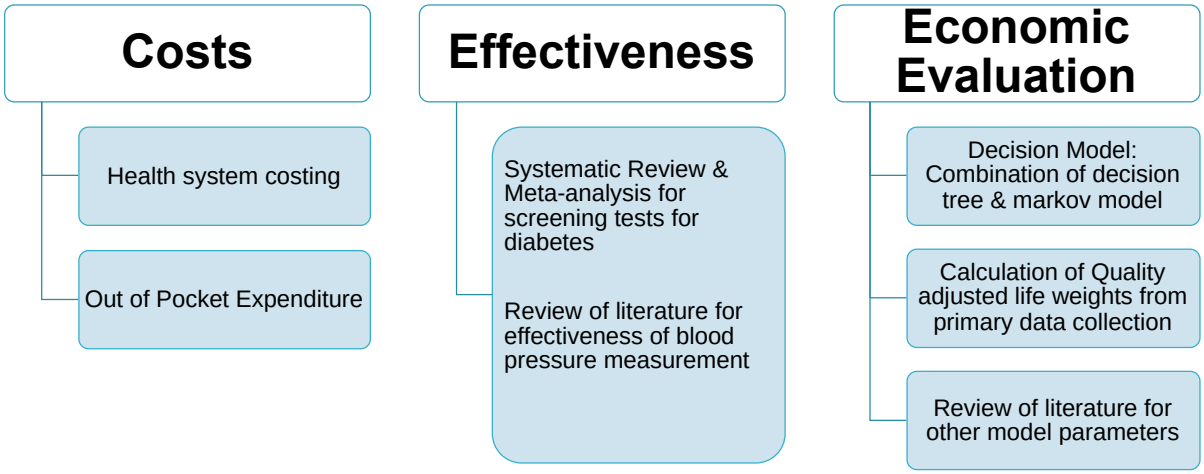
Health Technology Assessment of Population Based Screening for Type 2 Diabetes & Hypertension in India

National Institute of Research in Tuberculosis, Chennai

Contents

Executive Summary of HTA undertaken



The present study involved Health Technology Assessment of population-based screening for diabetes and hypertension in India. A systematic review and meta-analysis was undertaken to assess the diagnostic accuracy of screening tests in previously undiagnosed population. Primary data was collected using standard bottom-up costing methods, from Haryana and Tamil Nadu states, to assess the cost of screening. The National Health System Cost Database was used to determine the cost of diagnostic tests as well as the health system cost of treatment for diabetes and hypertension. The cost of treating complications in tertiary care setting was obtained from the Cost of Health Services in India (CHSI) study. Out-of-pocket expenditure for treatment in public and private sector was assessed by analysing the 71st round of National Sample Survey data on Health and Morbidity. Primary data was collected from 954 patients to assess the OOP expenditure in tertiary hospital and quality of life among those affected with diabetes, hypertension, co-morbidity, as well as different complications.

A hybrid decision model comprising of 3 parts was used to assess the incremental cost per quality adjusted life year (QALY) gained as a result of screening. The first part comprised of the decision tree which predicted the number of individuals who would be detected with either prediabetes, diabetes, hypertension, and a co-morbid state. These cases were further classified into true positives, false negative, true negative and false negative based on sensitivity and specificity of screening methods. The second part used a markov model to track the transition of diseased individuals over annual cycles to identify occurrence of disease-related complication. The third part comprised of five separate markov models for the complications (retinopathy, nephropathy, foot ulcer, coronary heart disease, stroke) which predicted the life course in terms of life years, QALYs and costs. Several alternative screening scenarios were considered depending on the methods used (random blood glucose, fasting blood

glucose), frequency of screening (annual, every three or five or ten or fifteen or twenty years and one-time) and population age group to be screened (30-65 years or 45-65 years).

In the absence of screening, there are 9267, 28,206, 2982, 3030 and 1239 cases of stroke, myocardial infarction, end stage renal disease (ESRD), amputation and blindness due to diabetes and hypertension per 1 lakh population respectively. With the implementation of annual population based screening with random blood glucose test followed by fasting glucose test (as compared to no screening), there is reduction in 23% (n=2123), 13% (n=3753), 27% (n=807), 40% (1224) and 35% (n=429) cases of stroke, myocardial infarction, end stage renal disease (ESRD), amputation and blindness per 1 lakh population respectively.

In the scenario of no screening, for a cohort of 1 lakh population, the lifetime treatment cost of complicated cases comprised of around 96.5% (INR 7794 million) of the total cost, followed by cost of treating uncomplicated cases (3.37%; INR 271 million). In the case of annual screening, treatment cost of uncomplicated cases constitutes the major component (64.5%; INR 10929 million), followed by the cost of treating complicated cases (35%; INR 5980 million). The cost of implementing screening comprised of 0.5% (INR 65 million) of the total cost.

Implementation of annual population-based screening with random blood glucose test followed by fasting glucose test (as compared to no screening), lead to gain in 6387 life years, 19,656 quality adjusted life years and reduction in 1259 deaths (due to diabetes and hypertension) per one lakh population respectively.

Only screening with once in a lifetime at 30 years of age is cost effective. Any increase in frequency of screening to every 5 year or 3 year or annually is not cost effective at the current level of health care utilization pattern for diabetes and hypertension. However, if the share of treatment for uncomplicated diabetes and hypertension at the proposed health and wellness centres (HWCs) rises, population-based screening for diabetes and hypertension starts to become cost effective. Once the HWCs treat at least 50% of the total uncomplicated cases of diabetes and hypertension, annual population-based screening starts to become cost effective.

In addition, a feasibility and landscape analysis was undertaken to explore the challenges and opportunities with regard to population-based screening for diabetes and hypertension in India. The results of various aspects of HTA undertaken are presented in the subsequent sections.

Effectiveness of Screening Tests: Evidence for Diagnostic Accuracy of Blood Glucose Detection Tests for Type 2 Diabetes and Prediabetes: Systematic Review and Meta-analysis

Abstract

Aim

This systematic review aimed to ascertain the diagnostic accuracy (sensitivity and specificity) of screening tests for early detection of type 2 diabetes and prediabetes in previously undiagnosed adults.

Methods

This systematic review included peer-reviewed journal articles related to one or more than one test (random and fasting blood glucose tests, HbA1c) for glucose detection, with Oral Glucose Tolerance Test (75-gram OGTT) as a reference standard (PROSPERO ID CRD42018102477). Databases like Medline (Ovid), Embase, Cinhal, Web of Science, Cochrane and Scopus were explored. Quadas-2 tool was used to undertake quality assessment of included studies. Meta-analysis was done using hierarchial summary receiver operating curve random model using Stata 14.0. Exploratory analysis to find the optimal cut-offs was done using R software.

Results

Of 3,338 records assessed by title and abstract, a total of 40 peer reviewed articles were included in this systematic review. The pooled sensitivity, specificity, diagnostic odds ratio, positive likelihood ration (LR+) and negative (LR-) for diagnosing diabetes with HbA1c (6.5%; venous sample; n=17 studies) was 51% (95% CI: 43-59), 97% (95% CI: 95-98), 33 (95% CI: 19–56), 16.4 (95% CI: 10.1–26.7) and 0.50 (95% CI: 0.43–0.60), respectively. However, the optimal cut-off for diagnosing diabetes in previously undiagnosed adults with HbA1c was 6.1% (pooled sensitivity of 76% (95% CI: 70-81) and specificity of 87% (95% CI: 82-91).

Conclusion:

Our findings suggest that at present recommended threshold of 6.5%, HbA1c is less sensitive and more specific in diagnosing the newly detected diabetes in undiagnosed population from community settings.

Introduction

In 2012, United Nation's resolution titled "Future We Want" recognized diabetes as a priority disease under non-communicable diseases (NCDs) and a global challenge to sustainable development (1). Owing to its growing burden across the globe, diabetes is also part of World Health Organization Global Action Plan for NCDs (2). To this end, the Sustainable Development Goal 3.4 target envisions to achieve one-third reduction in premature mortality from the major NCDs including diabetes by year 2030 (3). With the rising trajectory of diabetes worldwide, the International Diabetes Federation estimated that there would be 642 million people with diabetes by 2040 (4).

The cardinal characteristic of type 2 diabetes is chronic hyperglycemia subsequent from shortcomings in either secretion or action of insulin, or maybe both. Further, pre-diabetes characterized by impaired glucose tolerance (IGT) and/or impaired fasting glycaemia (IFG), is considered as a risk category that may progress to diabetes and cardiovascular disease (CVD) (5). Diabetes may also lead to microvascular and macrovascular complications that can have effect on eyes, kidney, nerves, feet and heart. The main drivers of this rising type 2 diabetes are associated with rapid urbanization and inadequate or lack of physical activity due to transitions in lifestyles (4, 6). Nevertheless, type 2 diabetes not only has an effect at individual level, but due to chronic nature of the condition has implications at health system and economic level as well.

Globally, cost of diabetes including its related complications was US$ 548 billion in 2013 (7). Estimates indicate that a person with diabetes utilizes twice as much resources than with non-diabetes and experiences a significantly higher predicted risk of catastrophic medical spending 17.8% (people with diabetes) vs. 13.9% (people with no-diabetes); (95% C.I. 0.2–7.7; p-0.05) (7). Moreover, this increasing prevalence of diabetes and its related complications may contribute to increase in healthcare costs (6). Undeniably, the direct costs (including diabetes treatment and complications) and indirect costs arising from productivity losses are huge (8). Approximately one-fifth of worldwide health spending in case of diabetes is being spent in the economies of low- and middle-income countries (9). Majority of these health systems are oriented towards provision of acute care and thus insufficiently organized for providing for long term conditions of chronic care of non-communicable disease (NCD) (10).

The rising burden of type 2 diabetes, its long asymptomatic period, long term and short-term complications of the disease are adding on to increasing resource strain on health systems. In such an instance, promoting health interventions such as lifestyle modifications are few of the many criteria that

accord appropriate for public policy support for screening of diabetes including pre-diabetes. Moreover, diabetes fulfils the seven screening criteria under the widely used Wilson-Jugner criteria 1968 (11) for suitability to be part of screening programs. Benefits of screening for diabetes on mortality are not directly proven (12). But indirect benefits of screening involve early detection of condition in apparently well individuals. This early detection of the condition in turn leads to lesser incidence of complications than those who were routinely diagnosed. Further ramifications can be on aspects like better quality of life, lesser health care expenditures on complications and health system preparedness in terms of availability of specialist health workforce, medicines including insulin and infrastructure to handle type 2 diabetes.

Across the globe, most of the screening programs for diabetes and prediabetes employed questionnaires/risk scoring tools and tests namely fasting blood glucose (FBG), HbA1c and random blood glucose (RBG) (5). However, a systematic review by Engelgau summarized that risk scores do not perform well as stand-alone tests in screening programs and use of biochemical tests was encouraged (13). The present guidelines adopted the cut off of HbA1c as 6.5% based on the findings of DETECT-2 study (14). Further the International Expert Committee report also concluded that for identifying people at risk of developing complication like retinopathy, HbA1c 6.5% level provided sufficiently sensitive and specific evidence to capture the same. There have been attempts previously to report on diagnostic accuracy of these blood tests separately (15, 16). A systematic review narratively presented the findings on the same for HbA1c for diabetes and did not undertake meta-analysis (15). Another published meta-analysis reported on the pooled estimates for sensitivity and specificity for HbA1c for prediabetes (16). However, little information is available about diagnostic accuracy of these most commonly used tests compared with a common comparator for detection of type 2 diabetes and pre-diabetes in previously undiagnosed cases. We aimed to bridge this gap in evidence by undertaking this systematic review. The primary objective of this review was to assess the diagnostic accuracy (sensitivity and specificity) of screening tests for early detection of type 2 diabetes and prediabetes in individuals not previously diagnosed with diabetes. Our specific objectives focussed on summarising the evidence for various types of screening tests used to detect blood glucose levels and determining the optimal cut-offs for these tests from the evidence collated. Our findings will be useful to clinicians, health care managers and policy-makers involved in provision of health care for diabetes and prediabetes worldwide.

Methods

The present systematic review is reported based on PRISMA protocol (17) and Meta-analysis and guided by "Cochrane Handbook of Diagnostic Accuracy Reviews (18). It was registered on the International prospective register of systematic reviews PROSPERO with CRD ID CRD42018102477.

Eligible Studies

We sought studies that reported the diagnostic accuracy of blood glucose tests for detecting type 2 diabetes (T2DM) in adults aged 18 years or more, recruited from community settings and without any previous history of type 2 diabetes. Based on previous knowledge through a review of literature (5), the blood glucose tests (venous or capillary sample) considered for screening for type 2 diabetes were random blood glucose, fasting blood glucose, HBA1c and post prandial glucose. Oral Glucose Tolerance Test (2-hr post load glucose through venous route) was taken as the comparator. No restrictions on study design, time period or language were considered. Any study in non-English language was only excluded at time of analysis if English translation from either author or web sources was unavailable.

Data Sources and Searches

Search strategies were developed (Refer Supplementary file) and modified accordingly to examine electronic databases from their inception to July 7, 2018. These databases were MEDLINE (OVID), EMBASE, Web of Science, CINAHL, Scopus and Cochrane (Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, Cochrane Central Register of Controlled Trials). Websites like World Health Organization and International Diabetes Federation were also searched for relevant records.

Study Selection

The titles and abstracts of searched records were independently screened by two reviewers, and subsequently the full text of retrieved articles was reviewed. Reference lists of systematic reviews and included records were also reviewed to look for relevant articles. Further, disagreements at any stage of this systematic review were resolved by discussion with third reviewer as arbitrator.

Data Extraction and Quality Assessment

Two reviewers independently extracted data using a data extraction form and further did quality assessment of included studies. Information on study setting, year of publication, sample size, prevalence of the disease condition, methods of testing used, route of sample, reference test were sought. Further, the data on diagnostic accuracy (sensitivity and specificity) were extracted as two by

two tables by comparing the index tests against the reference standard for all the cut offs reported in the included studies.

For the quality assessment, each included study was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [19]. This tool has set of questions in each of 4 sections-patient selection, index tests, reference test and applicability of studies to assess for quality. Each question had options related to risk of bias and applicability in terms of low, unclear and high risk. In order to assign a risk status to a particular section, we referred to the guiding points reported elsewhere (19). The GRADEPro approach was used for assessing the quality of evidence collated for reporting on the optimal thresholds for the index test (20).

Data Synthesis and Analysis

We undertook descriptive analysis to report on the number of studies by methods, year and country of publication, condition being diagnosed, and guidelines used for diagnosis of diabetes/prediabetes. Moreover, the included studies were tabulated by the index and reference tests. We undertook quantitative synthesis for the included studies that used the same diagnostic test with similar route of sample collection. We then pooled results based on a single data point from each study with regard to the most commonly reported threshold, as per the World Health Organization and American Diabetes Association guidelines for diabetes/prediabetes. This meta-analysis was done where a minimum of four or more studies was available for that particular test, by fitting hierarchical random effects model using STATA (version 14, STATACORP) with commands- midas (as primary package) and metandi. For studies with zero values in unit data, the model convergence was achieved with the use of metandi gllam command (FPG test). The resulted outcomes were summary points for sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-) and diagnostic odds ratios (DOR), with 95% confidence interval (CI). In addition, on the basis of LR+ and LR- obtained from the meta-analysis undertaken, we generated Fagan nomograms for estimating the clinical value of the index test (21). R software (package diagmeta) (22) was used for undertaking the analysis on the optimal cut-offs for the index test, using more than one pair of sensitivity and specificity per study.

Results

Screening and Selection of Literature

Figure 1 shows the detailed study selection process based on PRISMA reporting guidelines (23). All the searches yielded a total of 3,338 records. Subsequent to title and abstract screening, forty (excluding awaiting classification) studies were considered for the final selection. In case of insufficient information or non-English articles, the corresponding authors were contacted through electronic mail; however only studies with adequate information were included in the review. A total of twenty-eight studies included HbA1c and seven studies had FPG as the biochemical test for detecting diabetes and

prediabetes. To this end, a total of seventeen studies were included in meta-analysis for generating pooled estimates of sensitivity and specificity of HBA1c at the common threshold of 6.5% for diabetes. While five studies were considered for meta-analysis to arrive at pooled estimates of diagnostic accuracy for FPG (126 mg/dl) with respect to diabetes. Two studies reported on FCG test (24, 25). One study each was on PPG (26), RCBG (27) and RPG test (28). The reasons of exclusion for the first and subsequent screening are provided in the supplementary file. In order to arrive at the pooled results and optimal cut-offs for these tests, we included the information that was either provided in the study or was derived true and false (positives and negatives) pertaining to all the cut-offs as our domain of interest.

Figure 1: PRISMA Chart

Characteristics & Methodological Aspects of the included studies

A total of 90,490 patients for diabetes, 1,402 for prediabetes and 29,831 for both diabetes and prediabetes were included in this systematic review. These studies spanned over 21 countries in Africa, Americas, East Mediterranean, South-East Asia and Western Pacific regions. Most studies were conducted in China (22.5%), India and USA (10% each), Italy (7.5%); Brazil, Korea, Netherlands, South Africa and Thailand (5%); Bangladesh, Bulgaria, Finland, Germany, Japan, Norway, Oman, Poland, Singapore and Sri Lanka (2.5% each). Most studies were prospective, cross-sectional in design with mean sample size of 2,983. Many studies included dual reference standard (OGTT/FPG) but we only sought information related to OGTT (2hr post load glucose) for our review.

Close to one-third (74%) of the studies were on diabetes, 21% on both diabetes and prediabetes and rest 5% on prediabetes alone. For diagnosing diabetes/prediabetes, majority (47%) of these studies followed American Diabetes Association (ADA) guidelines, 36% used World Health Organization guidelines while 17% studies used both. The key characteristics of the included studies can be seen in Table 1.

Table 1: Key Characteristics of Included Studies

S No.	Author	Country of study	Journal	Year of publication	Condition studied	Sample analysed (n)	Diagnosis Criteria used	Blood glucose Test	Reference test (OGTT /2hrPG)	Prevalence (%) of diabetes with OGTT /2hr PG	No. (n) of diabetes diagnosed with OGTT /2hr PG	Prevalence of prediabetes based on OGTT	No. of prediabetes based on OGTT
1	Little (29)	USA	Diabetes	1988	Diabetes	381	WHO	HBA1c	OGTT	34	112	NA	NA
2	Husseini (24)	Norway	Scand J Clin Lab Invest	2000	Diabetes	445	WHO	FCBG	OGTT	2.7	12	NA	NA
3	Snehalatha (30)	India	Diabetes Research and Clinical Practice	2000	Diabetes	1261	WHO & ADA	HBA1c	OGTT	44	555	NA	NA
4	Mannucci (31)	Italy	Acta Diabetol	2003	Diabetes	1215	WHO	FPG	OGTT	8.8	107	NA	NA
5	Nakagami (32)	Finland	Diabetes Research and Clinical Practice	2003	Diabetes	17512	ADA	FPG	OGTT	6	1051	NA	NA
6	Al Lawati (33)	Oman	Diabetes Research and Clinical Practice	2006	Diabetes	4917	ADA (1997) & WHO (1998)	FPG	OGTT	9.9	489	NA	NA
7	Ziemer (28)	USA	Journal of General Internal Medicine	2008	Diabetes	989	ADA (2005)	RPG	OGTT	5	50	NA	NA
8	Somnnavar (34)	India	Diabetic Care	2009	Diabetes	1333	WHO & ADA	RCBG	OGTT	13.8	185	NA	NA
9	Zhou (35)	China	Diabetic Medicine	2010	Diabetes & prediabetes	903	WHO (1999)	HBA1c	OGTT	11.1	100	NA	NA

10	Araneta (36)	Japan	Diabetic Care	2010	Diabetes	933	ADA	HBA1c	OGTT	15.5	145	NA	NA
11	Kramer (37)	Brazil	Diabetic Care	2010	Diabetes	2107	ADA	HBA1c	OGTT	9.3	198	NA	NA
12	Mohan V (17)	India	Diabetic Care	2010	Diabetes	2188	ADA &WHO	HBA1c	OGTT	10.1	220	NA	NA
13	Riet (38)	Netherlands	Diabetes Care	2010	Diabetes	2753	WHO (2006)	HBA1c	OGTT	4	107	NA	NA
14	Cavagnolli (39)	Brazil	Diabetic Medicine	2011	Diabetes	498	WHO (2006)	HBA1c	OGTT	NG	54	NA	NA
15	Peter (40)	Germany	Exp Clin Endocrinol Diabetes	2011	Diabetes	2036	ADA	HBA1c	OGTT	6.5	126	NA	NA
16	Lin (41)	Singapore	Diabetes Research and Clinical Practice	2011	Diabetes	90	ADA	HBA1c	OGTT	44.4	40	NA	NA
17	Adamaska (42)	Poland	Advances in medical sciences	2012	Diabetes & prediabetes	441	ADA	HbA1c	OGTT	8	37	-	91
18	Bhowmik (43)	Bangladesh	Diabetic Medicine	2012	Diabetes	2293	WHO(1999)	HBA1c	OGTT	7.9	181	NA	NA
19	Bumverraj (26)	Thailand	Primary Care Diabetes	2012	Diabetes	874	WHO	PPG	OGTT	4.6	41	NA	NA
20	Yu (44)	China	The Korean Journal of Internal Medicine	2012	Diabetes	497	ADA(2010)	HBA1c	OGTT	46.3	155	NA	NA
21	Tankova (45)	Bulgaria	Acta Diabetol	2012	Diabetes	2231	ADA	HBA1c	OGTT	17.4	390	NA	NA NA
22	Zhao (25)	China	Journal of Endocrin	2013	Diabetes &	993	WHO	FCG	OGTT	5.7	57	14.6	145

			ological Investigations		prediabetes								
23	Wu (46)	China	Journal of Diabetes	2013	Diabetes & prediabetes	3354	WHO (1999)	HBA1c	OGTT	21.26	725	40.16	1347
24	Huang (47)	China	Preventive Medicine	2013	Diabetes	6989	ADA(2012)	HBA1c	OGTT	6.04	422	NA	NA
25	Lee (48)	Korea	Diabetes Research and Clinical Practice	2013	Diabetes	4616	ADA	HBA1c	OGTT	39.9	1846	NA	NA
26	Vlaar (49)	Netherlands	BMC Endocrine Disorder	2013	Diabetes & prediabetes	944	ADA	HBA1c	OGTT	3.7	35	20.2	191
27	Chilelli (50)	Italy	Acta Diabetol	2014	Prediabetes	501	ADA (2013)	HBA1c	OGTT	4.6	23	4.6	23
28	Liang (51)	China	Diabetes Technology and Therapuetics	2014	Diabetes & prediabetes	8239	WHO (1999)	HBA1c	OGTT	10.7	880	19	1564
29	Huang (52)	USA	Endocrine	2015	Diabetes	5782	ADA	FPG	OGTT	6.8	394	NA	NA
30	Aekplakorn (53)	Thailand	Journal of Diabetic Research	2015	Diabetes & prediabetes	6884	ADA	FPG	OGTT			-	4922

31	Zemlin (54)	South Africa	Clinica Chimica Acta	2015	Prediabetes	901	ADA	HBA1c	OGTT	25	226	27.7	226
32	Zhang	China	PLOS ONE	2015	Diabetes	7464	WHO (1993) & ADA (2003)	FPG	OGTT	9.3	696	NA	NA
33	Incani (55)	Italy	Journal of Diabetes Investigation	2015	Diabetes & prediabetes	462	ADA (2013)	HBA1c	OGTT	11	300	-	21
34	Aviles Santa (56)	USA	Endocrine Practice	2016	Diabetes	15507	ADA	HBA1c	OGTT	4.4	682	NA	NA
35	Hird (57)	South Africa	PLOS ONE	2016	Diabetes	1077	WHO	HBA1c	OGTT	5.4	59	NA	NA
36	Liu (58)	China	Journal of Diabetes Investigation	2016	Diabetes & prediabetes	7611	WHO (1999)	HBA1c	OGTT	12.71	967	-	2237
37	Mohan A (59)	India	Indian Journal of Medical Research	2016	Diabetes	683	ADA 2010	HBA1c	OGTT	38.7	264	NA	NA
38	Zou (60)	China	Diabetes Technology and Therapeutics	2016	Diabetes	3050	WHO (1999)	HBA1c	OGTT	10.2	52	22.4	202
39	Herath (61)	Sri Lanka	Diabetes & metabolic Syndrome: Clinical Research and Review	2017	Diabetes	254	ADA & WHO	HBA1c	OGTT	16.1	41	NA	NA

40	Joung (62)	Korea	Diabetes & Metabolism Journal	2018	Diabetes	515	ADA (2015)	FPG	OGTT	52.8	272	NA	NA

Overall, these included studies varied in quality as shown in Figure 2. Half of the selected studies had unclear risk of bias in the domain on patient selection and index test. Low risk of bias was seen for the questions listed under reference standard and the applicability domain in the tool.

Figure 2 a) Risk of bias graph b) Risk of bias Summary


Risk of Bias
Applicability Concerns
Patient Selection
Index Test
Reference Standard
Flow and Timing
Patient Selection
Index Test
Reference Standard
Adamska 2012
Aekplakorn et al 2015
Al Lawati 2006
Araneta 2010
Aviles Santa 2016
Bhowmik 2012
Bumrerraj 2012
Cavagnolli 2010
Chilelli 2014
Herath 2017
Hird 2016
Huang 2014
Huang et al 2013
Husseini 2000
Incani 2015
Joung 2018
Kramer 2010
Lee 2013
Liang 2014
Lin 2011
Little 1988
Liu 2016
Mannucci 2003
Mohan A 2016
Mohan V 2010
Nakagami 2001
Peter 2011
Riet 2010
Snehlatha 2000
Somannavar 2009
Tankova 2012
Vlaar 2013
Wu et al 2013
Yun Yu 2012
Zeimer et al 2008
Zemlin 2015
Zhang 2015
Zhao et al 2013
Zhou et al 2009
Zou 2016
High
Unclear
Low

Pooled Diagnostic Accuracy of Blood Glucose Tests (Meta-analysis)

For estimating the diagnostic accuracy like sensitivity, specificity, DOR, LR+ and LR- for diabetes HbA1c at a common cut off of 6.5% (venous sample) for diabetes, the following values were obtained: 51% (95% CI: 43-59), 97% (95% CI: 95-98), 33 (95% CI: 19–56), 16.4 (95% CI: 10.1–26.7) and 0.50 (95% CI: 0.43–0.60), respectively. The pooled results generated for other cut offs for HbA1c for diabetes and prediabetes are shown in Table 2. Similarly, for the FPG test (cut off as 126 mg/dl) the corresponding values are 68% (95% CI: 43-85), 97% (95% CI: 93.7-99), 78 (95% CI: 50-124), 26 (95% CI: 14-48) and 0.33 (95% CI: 0.17-0.65). Figure 3 and 4 show the SROC plots for these two tests HbA1c (6.5%) and Fasting Plasma Glucose (126 mg/dl) respectively. The SROC plots and forest plots for various other cut-offs for HbA1c and FPG for diabetes and prediabetes are shown in supplementary file.

Table 2: Pooled estimates (meta-analysis) at various cut-offs for diagnostic accuracy of HbA1c for diabetes and prediabe

Threshold value for HbA1c used for diabetes	**Condition studied**	**Number of studies**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
5.7	Diabetes	5	90 (83-94)	68 (53-80)
5.9	Diabetes	6	78 (69-85)	82 (70-90)
6.0	Diabetes	6	82 (74-88)	88 (76-94)
6.1	Diabetes	7	76 (64-85)	92 (86-95)
6.3	Diabetes	6	74 (62-83)	92 (86-96)
6.5	Diabetes	17		

Figure 3: SROC plot of HbA1c (6.5%)

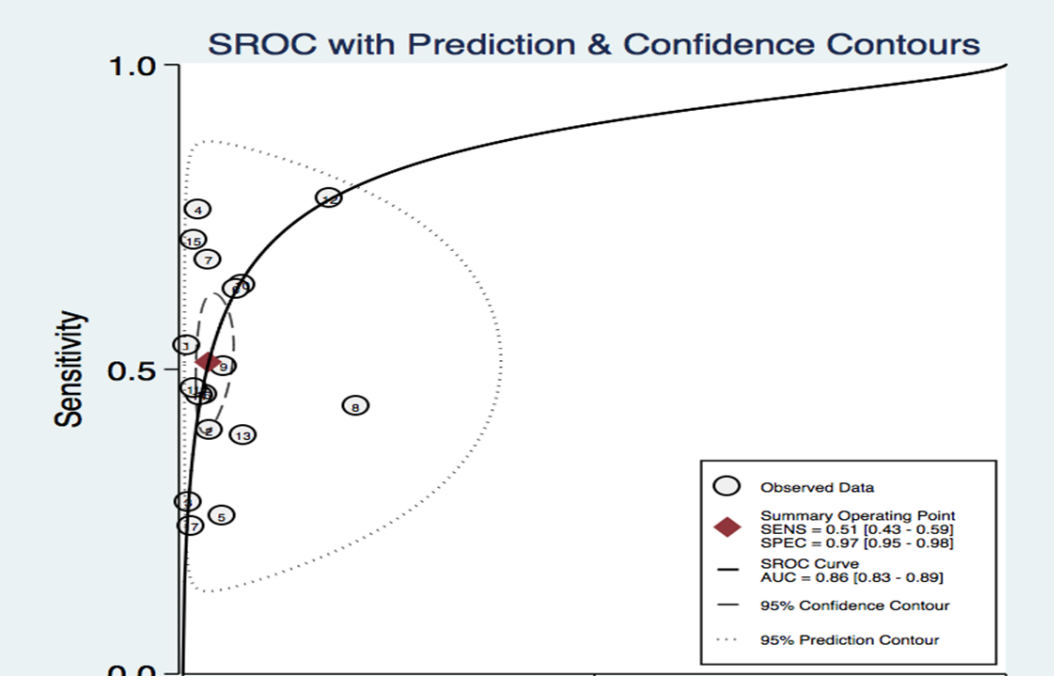
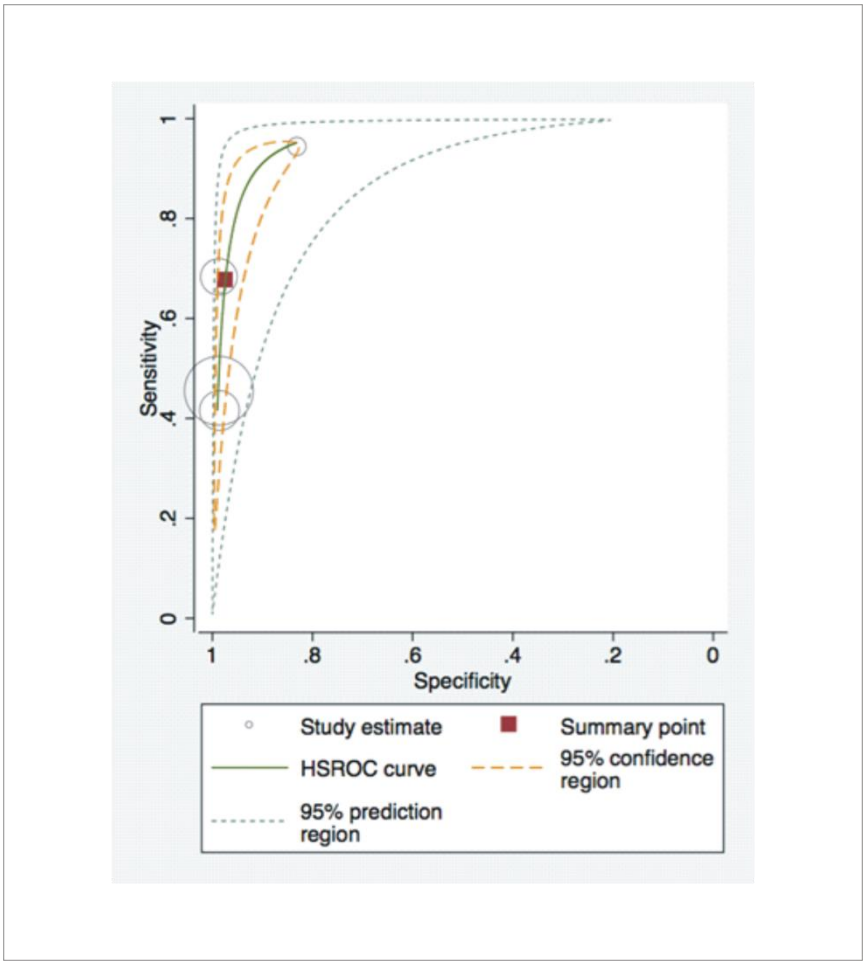
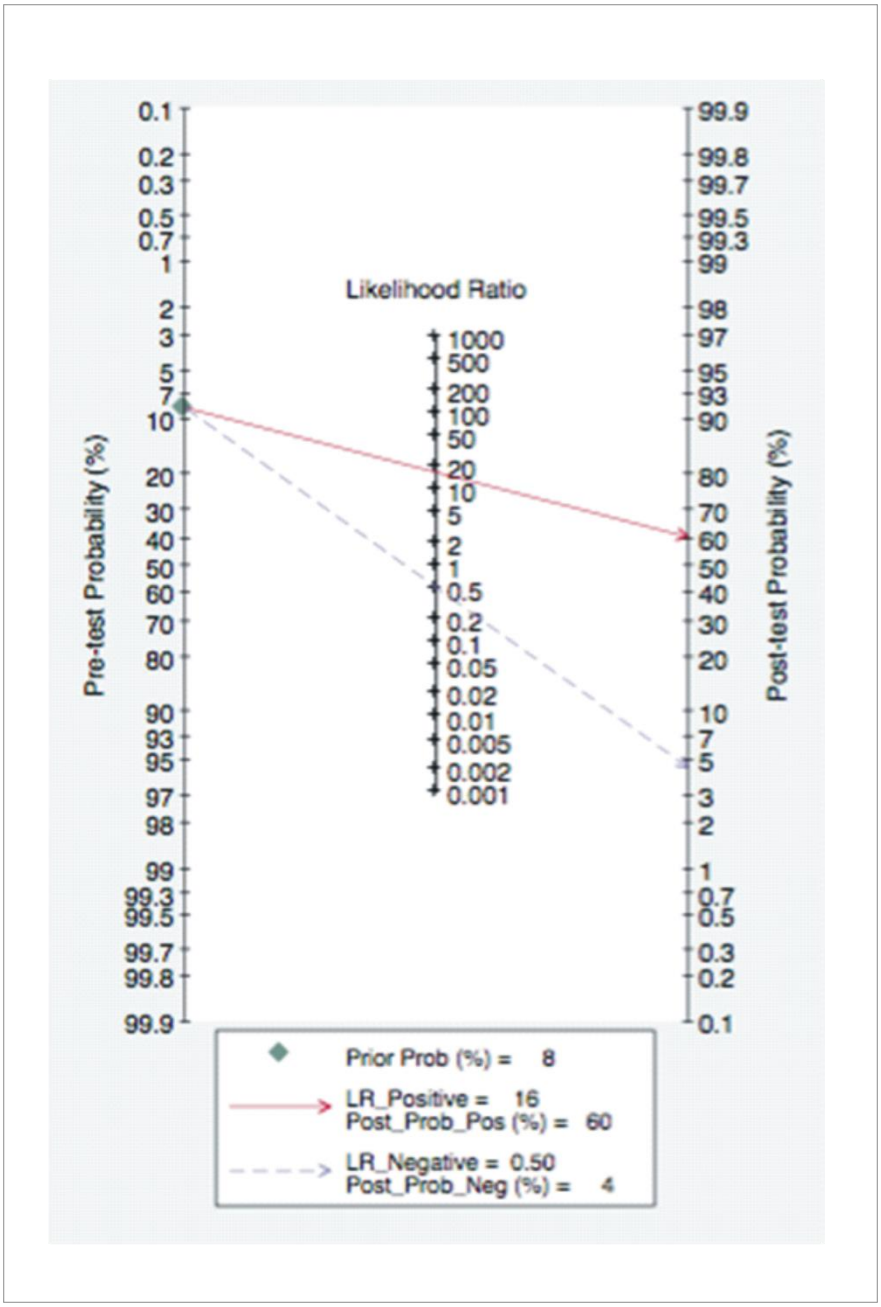


Figure 4: SROC plot of FPG (126 mg/dl)



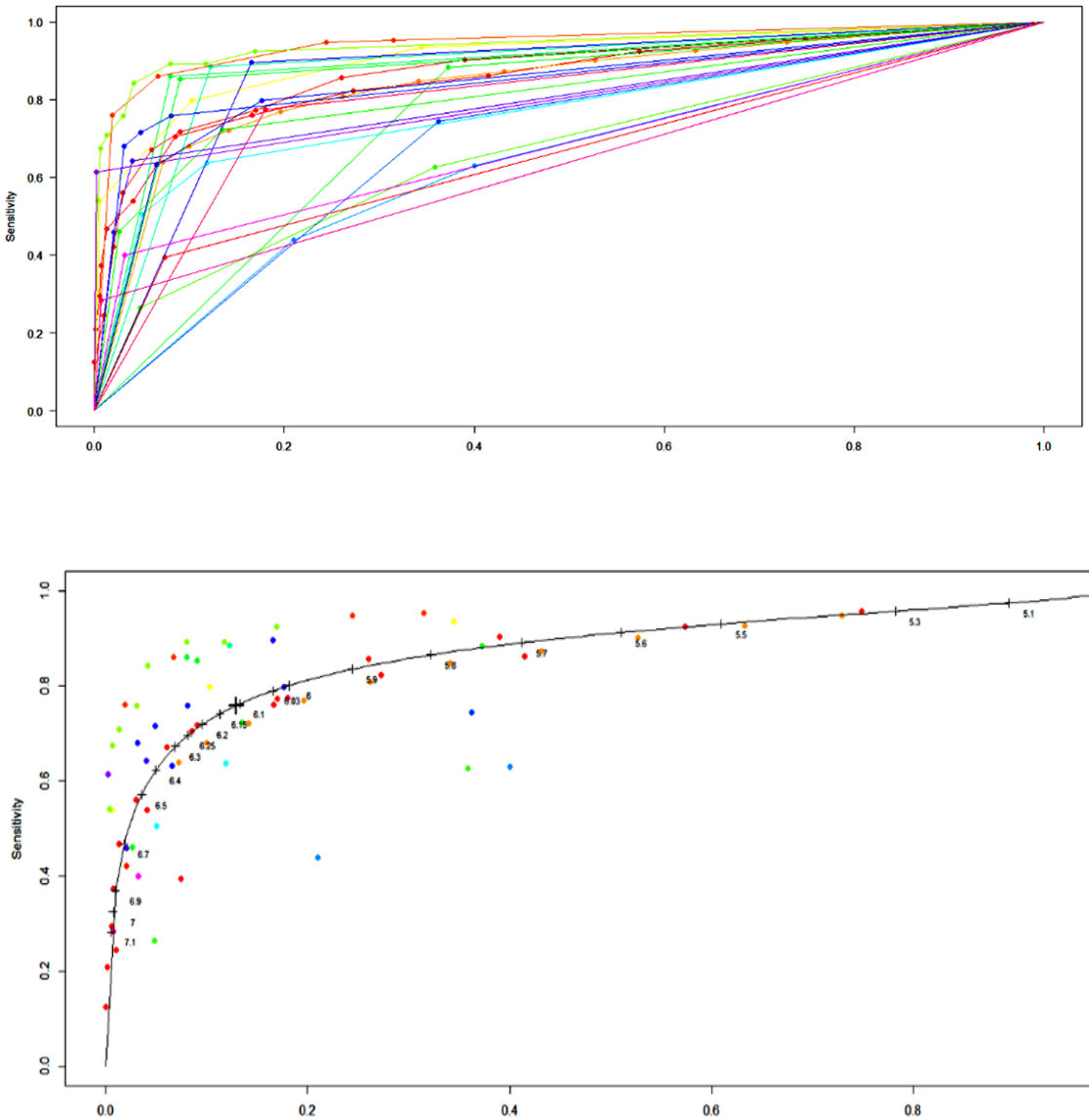
For determining the post-test probability, Fagan's nomogram with prevalence of diabetes (pre-test probability) as 8.5%, based on global estimates, for the most commonly used cut offs for HbA1c (6.5%) for diabetes was generated. Henceforth, the probability of someone having the disease and not being detected by the HbA1c (6.5%) was 4% (Figure 5).

Figure 5: Fagan Plot for HbA1c (6.5%)



Based on methodology reported elsewhere (63) and using more than one pair of sensitivity and specificity with their corresponding cut offs reported per study (mixed thresholds), the optimal cut off value estimated for HBA1c for diagnosing diabetes in previously undiagnosed population was 6.108 ≈ 6.1 (Figure 6). Using the GRADE approach, the evidence collated was of moderate quality (Refer Supplementary file). The pooled sensitivity and specificity at this optimal threshold for HbA1c for diabetes were 76% (95% CI: 70-81) and 87% (95% CI: 82-91). Similarly, for diagnosing pre-diabetes with HbA1c, the optimal cut off estimated was 5.702 ≈5.7 (Figure 7); with pooled sensitivity and specificity as 61% (95% CI:50-72) and 67% (95% CI:59-74) respectively (Refer supplementary file).

Figure 6: a) Study specific ROCs for diabetes b) Summary Receiver Operating Curve for optimal cut off of HbA1c for diagnosis of diabetes



Discussion

This meta-analysis summarizes the evidence on both paired outcomes (sensitivity and specificity) and global measures of diagnostic accuracy (diagnostic odds ratio) for the blood glucose detecting tests (HbA1c, FPG) used in the screening of diabetes and prediabetes in previously undiagnosed population. The most relevant finding of our meta-analysis was presence of higher values for pooled specificity than sensitivity for both HbA1c and FPG at the common thresholds recommended by WHO and ADA guidelines for diagnosis of diabetes. However, there was inconclusive evidence for deriving pooled estimates for diagnostic accuracy for detecting prediabetes as per present guidelines.

To this end, this is the first meta-analysis that provides a comprehensive overview regarding pooled estimates of diagnostic accuracy of these tests for an early diagnosis for diabetes in previously undiagnosed population. Based on the evidence collated the sensitivity and specificity ranged from 25% to 76.2% and 79% to 99.5% for HbA1c (6.5%) for diagnosis of diabetes respectively (Refer Supplementary file). Regarding HbA1c (6.1%), the sensitivity and specificity ranged from 42% to 88.9% and 73.8% to 98% respectively. Variation in sensitivity from 41.3% to 94.4% and specificity from 98.4% to 100% for FPG as per included studies. These are the two most frequently used blood glucose tests recommended for screening for type 2 diabetes across high income country settings. Based on pooled results at common thresholds as per the present guidelines, both the above tests are less sensitive in detecting for diabetes, implying that more number of people who are truly diabetic remain undiagnosed, giving false impression to them that they are not diabetic.

There are several strengths of the present systematic review and meta-analysis. Firstly, a thorough search was done in all relevant electronic databases, irrespective of any filters based on time, design, country or language of records on diagnostic accuracy. Secondly, the studies included are representative of individuals (≥ 18 years) without any previously diagnosed diabetes, primarily recruited from community settings across the globe and of mixed ethnicities. Thirdly, only those studies were chosen wherein the index and reference test were done on all the sampled population. Fourthly, we analysed and demonstrated the pooled estimates of diagnostic accuracy of the index tests with the use of hierarchial random model, addressing inherent heterogeneity in these diagnostic accuracy studies. The random models most commonly recommended methods of synthesis for diagnostic accuracy meta-analysis (64). These models have an advantage that, unlike previous methods, they account for both within-study and between-study variability (64). Finally, our estimates of optimal cut-offs are based on newer approach reported elsewhere that makes use of all the available information reported on thresholds in case of continuous biomarkers and avoids any overestimation of results (63). In general,

while undertaking a meta-analysis for diagnostic accuracy, each study contributes only one pair of sensitivity and specificity. However, if studies present more than one threshold, as in our case, reducing the data and selecting a specific threshold per study to find out optimal cut-off may lead to inadequate use of information and thus introduce a bias. To prevent this and report on the optimal cut-off through summary receiver operating curve, we used the novel approach given by Steinhauser 2016 (63), when diagnostic accuracy studies report on multiple thresholds and their corresponding sensitivity and specificity for a continuous bio-marker. One of the key advantages with this approach is that all the given information in the study can be used; without any need to specifically restrict to one pair of sensitivity and specificity per study (63).

Our present work had several limitations. Most of the included studies are observational data, mainly cross-sectional and cohort studies. We did not undertake any further translations of the studies that were in non-English. No indirect comparisons between the different index tests to establish the best test for diagnosing diabetes and prediabetes were done. Also, due to insufficient number of studies, the pooled estimates for other tests like random plasma & capillary glucose could not be estimated in this review. We did not undertake sub-group analysis based on the ethnicity, classification of country region by income or methods due to insufficient number of studies. However, exploring the role of ethnicity in estimation of optimal thresholds for these index tests and which is the best test to diagnose can be taken as future area of research. We could not estimate optimal cut-off for FPG test due to insufficient number of observations to achieve model convergence. Further, the optimal cut-off estimated for HbA1c is chiefly from statistical perspective. Economic modelling for various screening strategies with these tests can be another future area of research.

Our findings in terms of estimates of pooled sensitivity and specificity for HbA1c (6.5%) are similar to those reported elsewhere (65) but higher than in (66). Two other published systematic reviews did not undertake meta-analysis and narratively reported on diagnostic accuracy of HbA1c for diabetes screening (15, 67). Moreover, the latter systematic review took into account both people with and without diabetes and reviewed performance of HbA1c for prediction of microvascular complications (67). As for FPG test (126mg/dl or 7mmol/l), our results found a higher sensitivity but lower specificity for detecting diabetes in undiagnosed persons than estimated in another meta-analysis (66). The finding of this present meta-analysis for optimal cut-off of HbA1c as ≥ 6.1% for diagnosis of diagnosis in previously undiagnosed population is aligned with a previous systematic review (15) and a number of cross-sectional studies (17),(45),(48). Likewise, the prediabetes optimal cut point for HbA1c as 5.7% suggested by our review is like proposed by ADA. However, based on our value the proposed range to

diagnose people with prediabetes comes out to be 5.7-6.0 %, unlike the present guidelines for prediabetes.

Considering the rising prevalence of diabetes worldwide, our findings have important implications from both clinical and policy perspective. There is an ever-going debate on the cut-offs proposed for diagnosing diabetes and prediabetes (68). The present cut-off value for diagnosing diabetes as proposed by ADA and WHO of HbA1c 6.5% is less sensitive than FPG 126 mg/dl in capturing the true numbers of people with diabetes. In addition, with assuming global prevalence of diabetes to be 8.5%, at population level, for every 1000 positively screened individuals, HbA1c 6.5% would miss 47 individuals and under-diagnose while HbA1c 6.1% would miss 24 individuals and report more false positives and over-diagnose. Henceforth, HbA1c with 6.5% cut-off underestimates the prevalence and at 6.1% overestimates the prevalence of diabetes. But FPG 126mg/dl is neither underestimating nor overestimating the prevalence of diabetes. There exists trade-off between sensitivity and specificity and a highly specific test is important as it improves the positive predictive value by reducing the number of false positives and prevents any over-diagnosis.

As known, HbA1c level values are indicator of long term glucose control and also provide a link to development of microvascular complications (68). Henceforth, the growing epidemic of diabetes warrants for early identification of the disease and for thresholds that facilitate the same. Even 25% of people with newly developed diabetes can manifest with microvascular complications (69). Evidence from another systematic review concluded that screening individuals who are at high risk for developing diabetes through targeted approach may prove beneficial and cost-effective (70). Thus, an early institution of preventive interventions for people at high risk and treatment control for newly diagnosed can help in reducing the incidence of complications in people with diabetes. It is noteworthy to mention here that the risk of complications like mortality risk from cardiovascular disease starts in the prediabetic stage even before clinical diabetes sets in and may also lead to significant morbidities as well (5, 71). Similarly, people with diabetes are at about twice the risk of premature mortality than those without it (72). Diabetes is also risk factor for other conditions like end-stage renal disease, retinopathy, peripheral vascular disease, cerebrovascular disease and other disabling conditions like depression. All these complications magnify the cost of care for both the health provider and the individual. Further, these costs can be substantial in countries with low resource settings that face the dual challenge of communicable and non-communicable diseases.

Our findings on the pooled estimates of diagnostic accuracy like sensitivity and specificity can be useful to researchers and policy makers for undertaking health technology assessments (HTA) for various screening strategies for diabetes. We accounted for the dependency between these primary outcomes and the threshold used with the robust methods of statistical analysis through HSROC random model, as recommended by the Cochrane diagnostic test accuracy group (64). To conclude, our meta-analysis reports that HbA1c is less sensitive than FPG to diagnose newly diagnosed diabetes. FPG neither underestimates nor overestimates the prevalence of diabetes, unlike HbA1c (6.5%) and HbA1c (6.1%). The optimal cut-off of HbA1c 6.1% can be considered as an alternative diagnostic criterion for diagnosing diabetes and HbA1c 5.7-6.0% for identifying people with prediabetes in previously undiagnosed individuals. More research is warranted on cost implications and the relationship to prevalence to optimal thresholds for type 2 diabetes in adult population.

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Cost of Management and Health Related Quality of Life for Diabetes and Hypertension in India

Abstract

Background

Non-communicable diseases (NCDs) currently pose a formidable threat to global public health. The Government of India has initiated a population based screening (PBS) for non-communicable diseases like diabetes, hypertension and common cancers (oral, breast and cervix) for early detection and treatment. The Health Technology Assessment agency in India – HTAIn, has commissioned a study to assess the cost-effectiveness of screening diabetes and hypertension.

Objective

The present study was undertaken to estimate the cost of PBS for Type II diabetes (diabetes) and hypertension. Secondly, we estimated the out-of-pocket expenditure (OOPE) for outpatient care and health related quality of life (HRQoL) among patients of diabetes and hypertension.

Methods

Economic cost of population based screening of diabetes and hypertension was assessed using bottom-up costing methods from a health system perspective in Haryana and Tamil Nadu states. Data on all capital and recurrent resources utilized for the screening during 2017-18 was collected. Capital costs were annualized for their useful lifespan using a discount rate of 3%. Secondly, 234 diabetic, 300 hypertensive and 428 patients with both diabetes and hypertension attending outpatient clinic at a tertiary care hospital in north India were recruited to collect data on out-of-pocket expenditures and HRQoL. HRQoL was evaluated using the Euro Quality of Life Questionnaire, with five dimensions and five-level scale (EQ-5D-5L).

Results

At a coverage of 50%, the population based screening of diabetes and hypertension incurs a cost of INR 45.17 (US$ 0.65) per person screened. Individually, the cost of screening diabetes and hypertension was found to be INR 38.4 (US$ 0.55) and INR16.2 (US$ 0.23) per person respectively. The mean OOPE per outpatient consultation at a tertiary care public sector hospital among patients of diabetes, with and without complications was INR 6,837 (5,308-8,288) and INR 4,646 (3,907-5,348) respectively. The mean OOPE among patients of hypertension, with and without complications was INR 1,710 (1,197-2,197) and INR 1,392 (1,237-1,539) respectively. Similarly, mean OOPE for outpatient care among patients with both diabetes and hypertension, with and without complications was INR 6,904 (5,906-7,851) and INR 5,188 (4,447-5,891) respectively. The prevalence of catastrophic health expenditure

was found to be 15.8%, 0% and 16.4% among patients with diabetes, hypertension and both diabetes and hypertension respectively. The mean HRQoL score of patients with uncomplicated diabetes, hypertension and those with both diabetes and hypertension, was 0.80 (0.77-0.84), 0.90 (0.88-0.92) and 0.72(0.69-0.75) respectively, while for those with complications the mean HRQoL was 0.61 0.52-0.70), 0.78(0.70-0.86) and 0.62(0.57-0.67) respectively.

Conclusion

Estimates of screening and treatment cost as well as quality of life are useful for assessing cost effectiveness of screening strategies for diabetes and hypertension, planning the expansion of population based screening, and add to the existing cost database for healthcare services in India.

Introduction

Given the rising burden, early age of onset and the associated economic burden of Non Communicable Diseases (NCDs), the Government of India launched the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular diseases and Stroke (NPCDCS) aimed at prevention as well as early detection and treatment of diabetes, hypertension and common cancers. The objectives of the program were to prevent and control common NCDs through behaviour and life style changes, provide early diagnosis and management of common NCDs, build capacity at various levels of health care for prevention, diagnosis and treatment of common NCDs, and establish and develop capacity for palliative & rehabilitative care. (1)

The focus of NPCDCS was to enable opportunistic screening for common NCDs at secondary care level, through the setting up of NCD clinics. Further, population based screening (PBS) for NCDs including diabetes, hypertension and the three common cancers was initiated to complement the NPCDCS at primary care level. PBS was envisaged to address issues of low levels of care seeking, limited access to health services, reaching marginalized groups, in addition to increasing awareness in the community about NCDs and the need for periodic screening. The process of screening included active population enumeration, risk scoring on the Community Based Assessment Checklist (CBAC) by Accredited Social Health Activist (ASHA), allocation of unique ID, followed by screening of all individuals above the age of 30 years at on a fixed day camp at a facility or outreach. (2)

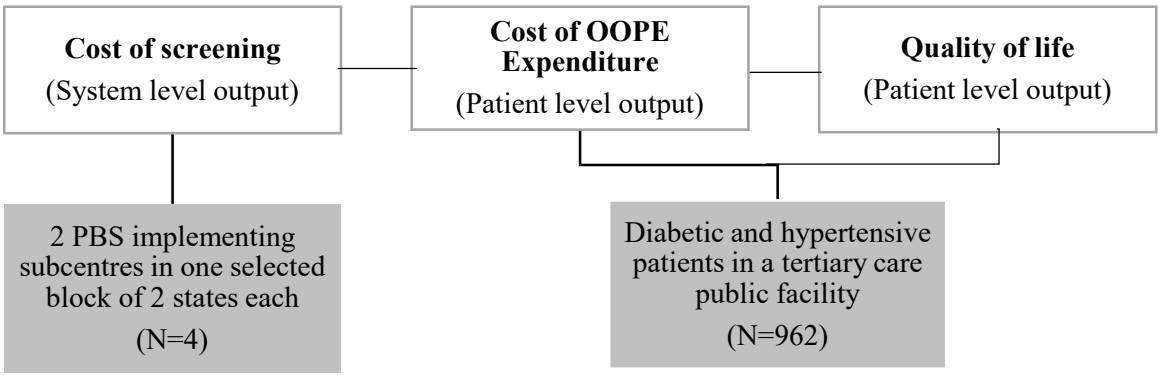
While screening of NCDs has been initiated at a national level, there are questions related to the most efficient or cost-effective screening methodology. In order to build evidence for these policy decisions, economic evaluations of different strategies need to be undertaken. The Government of India has established a health technology assessment agency called Health Technology Assessment India (HTAIn) to strengthen evidence-based policy making. (3) A study was commissioned by the HTAIn, to assess the cost effectiveness of screening for diabetes and hypertension in India. A pre-requisite for such a study involving an economic evaluation for screening strategies for diabetes and hypertension, is data on health system costs of screening, out-of-pocket expenditure (OOPE) of patients and quality of life of patients of diabetes and hypertension. While a few studies have been conducted in different parts of the country to assess the implementation of the NPCDCS program (4,5), cost of implementing the PBS has not been assessed. Secondly, while the National Sample Survey (NSS) estimates the nationally representative OOPE for outpatient and inpatient care for different illnesses, it is not possible to classify the diabetes and hypertension into those with and without complication. Thirdly, the NSS data does not specifically provide OOPE for those with comorbidity, i.e. diabetes and hypertension, as well as those visiting a tertiary level hospital. Finally, there is no Indian study on HRQoL of diabetic and hypertensive patients using the EQ5D tool which is recommended by the HTAIn for use in economic evaluations.

To address this evidence gap this study was designed at determining the health system cost of implementing PBS for diabetes and hypertension, disaggregated OOPE expenditure and HRQoL of patients with diabetes, hypertension, both diabetes and hypertension – both uncomplicated and complicated.

Methods

The study comprised of three parts namely costing of population based screening of diabetes and hypertension, OOPE and QoL of diabetic and hypertensive patients.

Figure 1: Overview of study methods



Data Collection

Health system costing

An economic costing for PBS of diabetes and hypertension under the NPCDCS was undertaken using bottom-up costing methodology and health system perspective. (6-8) The data were collected from 1 randomly selected district of Haryana and Tamil Nadu states. Within each district, one primary health centre (PHC) and two sub-centres (SCs) were randomly selected for data collection. The main activities in the PBS included, active enumeration and line listing of target population, risk scoring using the community based assessment checklist (CBAC), followed by screening of the target population.

The mode of implementation of PBS varied in both the states. In Tamil Nadu, population enumeration and first screening was done door-to-door by a Woman Health Volunteer (WHV) appointed for this purpose. Random blood sugar assessment using glucometer and blood pressure measurement using aneroid blood pressure apparatus was done in community setting at household level. On the contrary, in Haryana, the population enumeration and risk scoring using CBAC forms was performed by

Accredited Social Health Activists (ASHAs) at household level. Subsequently, the screening was done for the enumerated population in a camp mode on a single day which involved ANMs and ASHAs.

The data on all resources (capital and recurrent) utilized for the screening of diabetes and hypertension were collected for a 1 year period using a standardized tool used for economic costing studies of health facilities in India. (9-12) The data on human resources involved in screening in terms of number of personnel, designation, number of leaves in the reference period and gross annual salary, time was collected for all staff involved in service provision. The time contribution towards screening was determined through a personal interview. Time allocation interview was performed for each of the staff member and further validated using actual observation on the day of survey. A detailed time motion study was also done to determine the time contribution of different personnel for individual activities at a screening camp. Data on consumables including quantity used, unit price etc. was obtained from the stock register. All the equipment (medical as well as non-medical) used to deliver screening services were noted along with quantity, unit price, expected life and maintenance charges during last 1 year. The procurement price of each of the inputs was obtained from appropriate sources in the facility or state health department. In a few items where data was not available, market price was used.

Out-of-pocket (OOPE) Expenditure and Health Related Quality of Life (HRQoL)

Assessment of OOPE and HRQOL was done by recruiting patients from the outpatient clinic of a tertiary care hospital from North India. Patients who had at least one previous visit, i.e. who were known diseased, and had been on treatment since 1 month were included in the study. A total of 234 diabetic, 300 hypertensive and 428 patients with both diabetes and hypertension were recruited.

Patients were interviewed to collect data in routine demographic information, consumption expenditure, medical diagnosis, number of facility visits, and treatment regimen. Detailed information on out-of-pocket expenditure incurred during the last OPD consultation was collected using standard questionnaires used in previous Indian studies. (13-16) This included expenditure incurred on medicines, diagnostic test, supportive care, procedures, user fees in hospital, informal payment and, travel and boarding/food in the last visit to the facility in the last one month.

HRQoL was evaluated using the Euro Quality of Life Questionnaire (EuroQoL), with five dimensions and five-level scale (EQ-5D-5L) (17). Quality of Life (QoL) score was also captured using the Visual Analogue Scale (VAS).

Data Analysis

Health system costing

Costs were categorized into two types, namely capital and recurrent costs. In the case of capital items, the cost annualized was estimated using the average lifespan of item and a discount rate of 3%. Recurrent costs such as personnel salaries, medicines, consumables, overhead expenses etc. were estimated by multiplying price/wage rate and quantity of resource used. Shared costs were apportioned for individual services using appropriate allocation statistics. (Table 1)

Table 1: Data for health system costing

Input resources	Source of data	Form of data	Methods used to annualize/annual cost	Allocation criteria used for Joint Costs
Capital items				
Building/space	Facility observation and measurement	Observation	Estimated the floor size of constructed area multiplied by local commercial rental price	Shared areas apportioned on the basis of duration for which space was used for screening activities
Equipment	Record review (stock register), facility observation	Stock registers	Annualization factor multiplied by purchase price plus annual maintenance cost	Shared equipment costs were apportioned on the basis of number of individuals screened
Non-consumables (includes table, chair, water cooler, tube lights etc.)	Record review (stock register), facility observation	Stock registers	Annualization factor multiplied by purchase price plus annual maintenance cost	Shared non-consumable items were apportioned on the basis of number of individuals screened
Recurrent items				
Human resources	Record review, interview, facility observation	Pay slips, interviews	Salary multiplied by the proportion of time spent in a year on screening activities	Proportional time spent on various activities
Drugs and consumables (stationery, sanitary items etc.)	Record review	Stock register	Annual amount of drugs/consumables and price data	Proportion of individuals screened
Overheads utilities				

Input resources	Source of data	Form of data	Methods used to annualize/annual cost	Allocation criteria used for Joint Costs
Electricity	Record review	Monthly electricity bills	Annual consumption of electricity in cardiac centre	Proportional time for which the space was used for screening activities
Water supply	Record review	Monthly water bills	Annual consumption of water in each cost centre	Floor area

Unit costs were calculated for screening of individuals for hypertension and as per PBS. Further cost of screening for diabetes and hypertension alone was calculated by bifurcating costs into the two types of screening. Costs of equipment and consumables for each type of screening were considered separately. Costs such as human resource time and supervisory, training and IEC cost was assumed to be same irrespective of type of screening. Once the unit costs were generated for each service facility, pooled unit cost was generated by standardizing for coverage. While adjusting for coverage, equipment, human resources, training cost, IEC cost and supervisory cost was considered as fixed cost and hence kept constant, while the variable cost such as consumables and overheads were varied with number of people screened.

Out-of-pocket expenditure (OOPE)

Mean OOPE expenditure per outpatient consultation was computed. Multiple Linear regression was performed to assess the factors associated with OOP on outpatient care amongst diabetic and hypertensive patients. The independent variables included in regression were age of the patient, gender, marital status, educational status, employment status, insurance status, wealth quintiles, disease status, presence of complications and disease control status. Results are reported as beta coefficient, confidence intervals for odds ratio, t test value and p-value.

The ratio of annual OOPE on outpatient care to the annual non-food consumption expenditure was estimated. Annual OOPE was estimated by taking into account median number of outpatient visits and OOPE on medicine and non-medicine expenses (such as travel, lodging, user free etc.). Frequency of outpatient visits was as reported by patients was used to estimate the annual number of visits. OOPE on medicine was assumed to be incurred on a regular monthly basis, while the non-medicine OOPE was incurred only at each OPD visit.

$$\boldsymbol{Annual\ OOP\ on\ outpatient\ care} = (\boldsymbol{OOPE\ for\ Medicine} * \mathbf{12}) + (\boldsymbol{Non-medicine\ related\ OOPE} * \boldsymbol{Median\ OP\ visits\ per\ year})$$

A threshold of 40% was used to determine the extent of catastrophic health expenditure (CHE). (18) Binary logistic regression was performed to assess the independent factors determining CHE amongst diabetic and hypertensive patients. The variables included in regression were age of the patient, gender, marital status, educational status, employment status, insurance status, wealth quintiles, disease status, presence of complications and disease control status. Enter method was used to run the regression model. Results are reported as odds ratio, confidence intervals for odds ratio, Wald's statistic and p-value.

Quality of life

Health states generated from the scoring on the EQ5D5L were converted into utility scores using the Thailand value set. (19) Scoring on the VAS was converted into utility scores by dividing by 100. Mean scores were generated individually from EQ5D5L and VAS, for patients with diabetes, hypertension and those with both diabetes and hypertension. Scores were also generated for those with and without complications (such as retinopathy, nephropathy, neuropathy, heart disease, stroke and amputation).

Ethical Approval

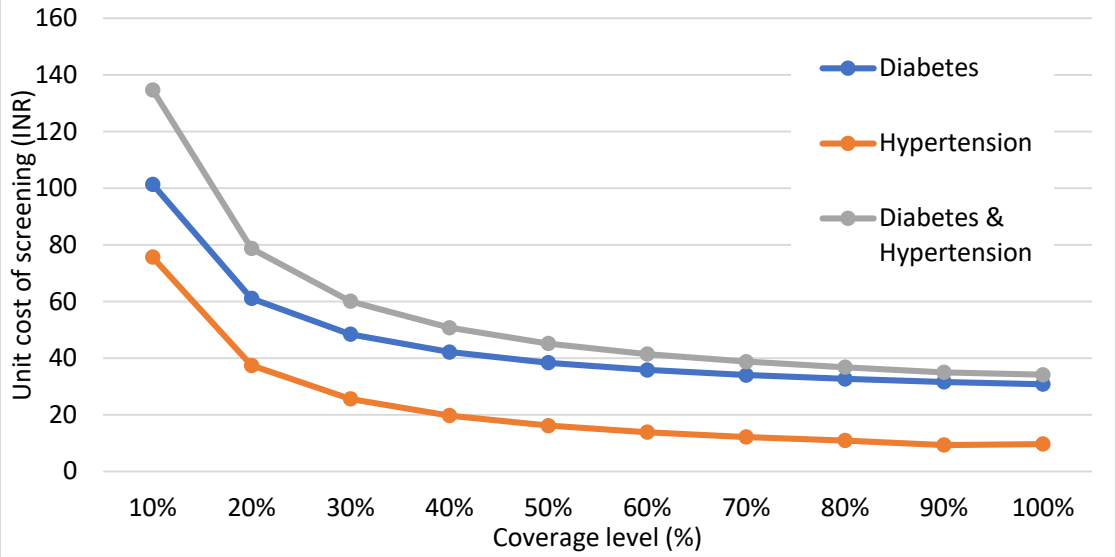
The study was approved by the ethics committee of the institute.

Results

Health system cost of screening

The per-capita health system cost of population based screening for diabetes, hypertension and both diabetes and hypertension at sub-centre level in Haryana was found to be INR 92 (US$1.32), INR 70 (US$1.00) and INR 130 (US$1.86) respectively. Similarly, the per-capita cost of screening for diabetes, hypertension and both diabetes and hypertension at sub-centre level in Tamil Nadu was estimated to be INR 22 (US$0.31) , INR 13 (US$0.19), and INR 25 (US$0.36) respectively. Figure 1 depicts the variation of the cost of screening for diabetes, hypertension and both diabetes and hypertension, with changes in coverage levels of the screening. The pooled unit cost of diabetes, hypertension and both diabetes and hypertension screening at 50% screening coverage was INR 38.4 (US$0.55), INR 16.2 (US$0.23) and INR 45.2 (US$0.65) respectively.

Figure 2: Unit cost of screening by level of population-wide coverage



Out-of-pocket Expenditure

Table 2 outlines the OOPEE per OPD consultation by socioeconomic and clinical factors. The mean out-of-pocket expenditure of a diabetic patient visiting a tertiary care facility was INR 5,170 (4,490-5,850) . The mean OOPE for a diabetic patient with complications (such as retinopathy, neuropathy, nephropathy, heart disease or stroke) was INR 6,836 (5,111-8,561) and INR 4,646(3,907-5,385) for those without complications. Similarly, for hypertension patients the OOPE on OPD consultation was INR 1,422 (1,273-1,571), with complications was INR 1,710 (1,197-2,223) and without complication was INR1,386 (1,231-1,541). The OOPE was markedly higher for patients with both diabetes and hypertension with mean OOPE INR 5,770 (5,175 – 6,165) and INR 6,904 (5,906-7,902) and INR 5,188 (4,447-5,929) for those with and without complications respectively.

Table 2: Out-of-pocket expenditure for outpatient care among Diabetes and Hypertension patients

Factors	N	Mean OOPE per OPD Consultation	95% Confidence Intervals	Catastrophic Health Expenditure (%)
Socioeconomic factors				
Gender				
Male	494	4272	3768 - 4750	9.11
Female	464	4261	3810 - 4689	13.36
Age				
18-35	66	2261	1547 - 2939	3.03

36-45	158	3188	2483 - 3858	7.59
46-55	246	4337	3664 - 4976	10.98
56-65	304	4974	4235 - 5676	12.83
>65	183	4609	4048 - 5141	14.21
Wealth Quintile				
I (Poorest)	299	3369	2983 - 3736	19.40
II	301	4088	3572 - 4578	8.97
III	163	5298	4252 - 6290	7.98
IV	79	4876	3995 - 5713	1.27
V (Richest)	28	5872	3408 - 8209	3.57
Clinical factors				
Diabetes	234	5171	4491 - 5816	15.81
Complications absent	178	4646	3908 - 5348	13.48
Complications present	56	6837	5308 - 8288	23.21
Hypertension	300	1427	1278 - 1569	0.00
Complications absent	267	1392	1238 - 1539	0.00
Complications present	33	1710	1198 - 2197	0.00
D&HTN	428	5770	5176 - 6335	16.36
Complications absent	273	5188	4448 - 5891	14.65
Complications present	151	6904	5906 - 7851	19.21
Complications				
Absent	718	3642	3279 - 3987	8.91
Present	240	6174	5416 - 6894	17.50
Disease Control Status				
Controlled	309	3931	3444 - 4392	8.74
Uncontrolled	634	4393	3943 - 4820	12.30
	962	4270	3932 - 4591	11.12

Catastrophic health expenditure (CHE) was estimated to have been incurred among 15.8% and 16.4% of patients with diabetes, and both diabetes and hypertension patients respectively. None of the patients with hypertension alone was found to have incurred CHE. Further, the percentage of patients experiencing CHE was higher in patients suffering from complications and among those with

uncontrolled disease, across the three conditions. An increasing pattern was observed with increase in number of complications suffered by patient in both OOP and CHE.

Wealth quintile and presence of complications was found to be associated with higher OOPE (p-value <0.05) (Table 3). OOPE was significantly lower in patients with hypertension as compared to diabetic patients and patients with both diabetes and hypertension (p-value<0.05).

Table 3: Determinants of OOPE for outpatient care among diabetes and hypertension patients

Variable	Beta Coefficient	95% Confidence Interval for Beta Coefficient		T value	p-value
		Lower Bound	Upper Bound		
Demographic variables					
Gender	-.038	-1107.684	415.960	-.891	0.373
Age Group	.015	-213.653	330.009	.420	0.675
Marital Status	.045	-54.798	551.373	1.369	0.171
Education	.058	-309.585	1737.760	1.608	0.108
Employment status	-.051	-1306.822	357.290	-1.120	0.263
Financial variables					
Insurance status	-.029	-1050.641	457.285	-.772	0.440
Wealth Quintile	.127	265.840	805.270	3.898	<.001
Clinical variables					
Diabetes	.026	-482.752	1046.811	.724	0.469
Hypertension	-.334	-3967.793	-2469.375	-8.433	<0.001
Presence of complications	.174	1148.241	2555.119	5.167	<0.001
Control status	.013	-501.711	758.943	.401	0.689

The odds of incurring CHE was two times higher in females as compared to males, and 1.5 times in patients with complications (Table 4). The odds of incurring CHE was highest amongst patients with diabetes and hypertension both and least in patients with hypertension. The odds of incurring CHE were 12 times higher in the poorest quintile as compared with the richest quintile (p-value 0.019).

Table 4: Association of socio-demographic and clinical factors with catastrophic expenditure for outpatient care

Variable	Categories	Wald's Statistic	p-Value	Odds Ratio	Odds Ration 95% CI	
					Lower	Upper
Demographic variables						
Gender	Male			Reference		
	Female	4.529	.033	1.977	1.055	3.704
Age Group	18-35	.592	.964	Reference		

	36-45	.028	.867	1.162	.201	6.731
	46-55	.056	.812	1.224	.232	6.465
	56-65	.212	.646	1.475	.282	7.724
	>65	.127	.722	1.361	.250	7.408
Marital Status	Married			Reference		
	Unmarried	0.002	.968	1.020	.396	2.624
Education	Illiterate	4.981	.289	Reference		
	Up to Primary	1.489	.222	.468	.138	1.584
	Up to Secondary	.895	.344	1.430	.682	2.999
	Graduation	.134	.714	1.185	.477	2.949
	Post-Graduation	.976	.323	1.775	.569	5.539
Employment status	Employed			Reference		
	Unemployed	.003	.960	1.017	.520	1.989
Financial variables						
Insurance status	Insured			Reference		
	Uninsured	.763	.382	.763	.415	1.401
Wealth Quintile	Richest	36.276	.000	Reference		
	Poorest (I)	5.471	.019	12.214	1.500	99.444
	II	1.441	.230	3.623	.443	29.651
	III	.676	.411	2.471	.286	21.352
	IV	.226	.634	.500	.029	8.697
Clinical variables						
Disease condition	Diabetes	.211	.900	Reference		
	Diabetes + Hypertension	.211	.646	1.131	.668	1.918
	Hypertension	.000	.993	.000	.000	.
Presence of complications	Complications absent			Reference		
	Complications present	1.615	.204	1.413	.829	2.407
Control status	Controlled			Reference		
	Uncontrolled	.519	.471	1.225	.706	2.126

Health Related Quality of life

The mean HRQoL score for diabetic patients with and without complications was 0.61 (±0.09) and 0.80 (±0.04) respectively using time-trade off valuation based on Thai value set. The HRQoL based on VAS scores was found to be 0.66 (±0.05) and 0.71 (±0.03) for uncomplicated and complicated diabetic patients respectively. The mean HRQoL score for hypertensive patients with and without complications was 0.78 (±0.08) and 0.90 (±0.02) respectively on the EQ-5D-5L scale. The mean HRQoL score for patients with both diabetes and hypertension with and without complications was 0.62 (±0.05) and 0.72 (±0.03) respectively on the EQ-5D-5L scale.

Table 5: Health Related Quality of life of Diabetes and Hypertension patients

Factors	N	QoL_{EQ5D5L}	95% CI	QoL_{VAS}	95% CI
Socioeconomic factors					
Gender					
Male	494	0.81	0.79 - 0.27	0.71	0.70 - 0.73
Female	464	0.72	0.69 - 0.31	0.7	0.68 - 0.71
Age					
15-35	66	0.93	0.90 – 0.97	0.76	0.73 – 0.80
36-45	50	0.86	0.82 - 0.89	0.75	0.72 - 0.77
46-55	158	0.77	0.73 - 0.80	0.72	0.70 - 0.74
56-65	246	0.74	0.70 - 0.77	0.68	0.66 - 0.70
>65	183	0.67	0.63 - 0.71	0.67	0.64 – 0.70
Wealth Quintile					
I (Poorest)	299	0.77	0.73 - 0.80	0.71	0.70 - 0.73
II	301	0.76	0.73 - 0.79	0.72	0.70 - 0.73
III	163	0.78	0.74 - 0.83	0.70	0.67 - 0.72
IV	79	0.72	0.67 - 0.77	0.66	0.62 - 0.70
V (Richest)	28	0.74	0.65 - 0.84	0.71	0.67 - 0.75
Clinical factors					
Diabetes	234	0.76	0.72 - 0.79	0.7	0.68 - 0.72
Complications absent	178	0.80	0.77 - 0.84	0.71	0.69 - 0.74
Complications present	56	0.61	0.52 - 0.70	0.66	0.61 - 0.71
Hypertension	300	0.89	0.87 - 0.91	0.77	0.76 - 0.78
Complications absent	267	0.9	0.88 - 0.92	0.78	0.76 - 0.79
Complications present	33	0.78	0.70 - 0.86	0.72	0.67 - 0.78
D&HTN	428	0.68	0.66 - 0.71	0.66	0.65 - 0.68
D&HTN- No complications	273	0.72	0.69 - 0.75	0.68	0.66 - 0.70
D&HTN- One Complication	151	0.62	0.57 - 0.67	0.62	0.59 - 0.65
Complications					
Absent	718	0.81	0.79 – 0.83	0.72	0.71 – 0.74
Present	240	0.64	0.60 – 0.68	0.64	0.62 – 0.67

Disease Control Status					
Controlled	309	0.804896	0.78 - 0.83	0.72	0.70 - 0.74
Uncontrolled	634	0.747901	0.73 - 0.77	0.70	0.69 - 0.71
OVERALL	962	0.77	0.75 - 0.78	0.7	0.69 - 0.72

QoL scores and OOPE of patients with different complications is provided in the Table S1 (Annexures)

Discussion

Overview of present study findings

NCDs present a significant public health challenge, especially with their health and economic burden. They not only put a burden on the health system but also push households into poverty owing to the requirement of long term management and treatment. In order to build evidence to inform policies on screening of diabetes and hypertension, information on cost borne by the health system and patient is required. The first year target of the PBS was 50% coverage of target population. (2) The pooled screening cost for diabetes and hypertension at 50% coverage was found to be INR 45. The unit cost of screening declined with rise in coverage, with plateauing of unit cost once a 70% population coverage was achieved.

A wide variation was observed in screening cost in the two states. The difference is attributable to the mode of operation in both states. Firstly, the primary screening in Tamil Nadu is done at household level as compared to a camp or facility-based mode in Haryana, greatly reducing the infrastructure cost in screening cost in the former. Secondly, Human resource cost contributed to 75-90% cost in Haryana as compared to 27-35% in Tamil Nadu (Table S2, Annexures). This is because Tamil Nadu employed a single Woman Health Volunteer who performed population enumeration, filling of family register and first screening at the household level while in Haryana, ASHAs perform population enumeration at household level followed by screening at camps involving both ANMs and ASHAs. Also, the salary of the WHV in Tamil Nadu was INR 3100 per month as compared to salary of ANMs ranging from INR 24000 (contractual) to INR 63000 (permanent) in Haryana, in addition to ASHAs who were remunerated on incentive basis. Thirdly, the screening coverage was much higher in Tamil Nadu (71%) as compared to Haryana (30%), further reducing per capita cost of screening in Tamil Nadu.

Our study also estimated the burden of diabetes and hypertension in terms of loss of quality of life. The HRQoL for diabetic patients with and without complications was estimated as 0.80(95% CI: 0.79 - 0.27) and 0.61(95% CI: 0.52 - 0.70), which was found to be consistent with other studies which assessed HRQoL of diabetic patients using EQ-5D-5L tool. A study by Solli et al (2010, Norway) and W. Ken

(2002, Netherlands) reported utility score of 0.85 (0.82-0.87) and 0.81(0.80-0.82) respectively among uncomplicated Type 2 diabetic patients (20) (21). They also reported the QoL score of 0.73 (95% CI: 0.69-0.78) and 0.61(95% CI: 0.59-0.63) respectively, among diabetic patients with complications. W. Ken et al (2002, Netherlands) also assessed the QoL using Visual Analog scale as done in our study, the utility score of 0.72 (95% CI: 0.71-0.73) and 0.62(95% CI: 0.61-0.62) has been reported among diabetic patients without complications and with complications respectively (20). These utility scores were found to be in line with our study findings reporting VAS scores of 0.71 (95% CI: 0.69 - 0.74) and 0.66 (95% CI: 0.61-0.71) among diabetic patients without complications and with complications respectively. In addition, the present study also assessed the HRQoL of hypertensive patients wherein utility scores of 0.90(95% CI: 0.88 - 0.92) and 0.78(95% CI: 0.70 - 0.86) among uncomplicated and complicated cases respectively were estimated. These estimates are found to be in line with a study by Ghimire et al (2017, Nepal) reporting the HRQoL of 0.87(95% CI: 0.86-0.89) and 0.64 (95% CI: 0.51 – 0.77) among 180 hypertensive patients on EQ-5D-3L and visual analogue scales respectively (22). Similarly, another study by Wong et al (2019, China) assessed the HRQoL of patients with hypertension using EQ-5D-5L tool and reported utility score of 0.85 ranging from -0.864 to 1. (23) This study also evaluated the HRQol of patients with hypertension and diabetes and stated the utility score of 0.83 as compared to 0.68 (95% CI: 0.66 - 0.71) found in our study.

The present study has also assessed OOPE per OPD consultation for diabetic and hypertensive patients. It was found that OOPE was highest among patients having both diabetes and hypertension (INR 5770, 95% CI: 5176 – 6335) as compared to patients having only hypertension (INR 1427, 95% CI:1278 – 1569) and diabetes (INR 5171, 95% CI: 4491 – 5816). These findings are found to be comparable to a study by Tharkar et al (2009, India) which found that on an average, a diabetic patient with hypertension spent 1.4 times more than a diabetic subject without hypertension (24). Furthermore, the distribution of OOPE was assessed and majority (71%) of the expenditure was found to be incurred on medicines, which is consistent with NSSO 71st round findings (72.8%). (25)

Policy implications

This paper highlights a number of operational and programmatic considerations in regard to PBS of diabetes and hypertension. The Tamil Nadu model was observed to be more effective in terms of implementation in limited resources, learnings from the model could be useful in streamlining implementation of PBS in other states. The role of the recently announced Health and Wellness Centres under the Ayushman Bharat program (26,27), could help in smooth implementation of PBS with better coverage and existence of more resources at the centre. The adverse effects of comorbidity of diabetes and hypertension was clearly established in the present study, with the observed trends in HRQoL and OOPE, highlighting the importance of screening for both conditions together and continued treatment for both in order to prevent progression to complications.

Strengths

Our study provides valuable inputs including cost of screening, HRQoL and OOPE of diabetic and hypertensive patients which maybe utilized in undertaking cost-effectiveness analysis of screening of diabetes and hypertension in India. The cost of screening has been estimated using micro-costing approach which is known to produce robust estimates. All estimates were generated through primary data collection at various levels of the health system.

Limitations

We would also like to note certain limitations of the present study. Firstly, the OOP and HRQoL estimates were generated from a cross sectional sample drawn from one tertiary level public health care facility in north India and study results cannot be generalized. However, this facility has patient footfall from more than 6 Indian states and as a result represents the heterogeneity in terms of geography, rural and urban distribution, severity of disease, and socio-economic status. As a result, there is little possibility of any selection bias resulting from a hospital-based sample. Secondly, the EQ-5D-5L health states were covered into utility scores using the Thailand tariff value set due to absence of an Indian value set. Thirdly, health system cost data on resources such as training, IEC, supervision was collected using a top down approach from the state level and apportioned to the facility at which the costing was being performed.

Conclusion

The current study findings can be used to further undertake cost effectiveness analysis to determine the ideal interval of screening, mode of screening and diagnostic test. The cost estimates may be used for determining the reimbursement package rates under various publically financed health insurance schemes in India. Further, the cost estimates may add to the existing cost database in Indian settings. The present study also highlights the rising economic burden of NCDs, largely borne by the patients which calls for steps in the direction of health system strengthening such as establishment of health and wellness centres. These HWC will contribute in better implementation of screening programme, treatment and follow up patients with chronic diseases.

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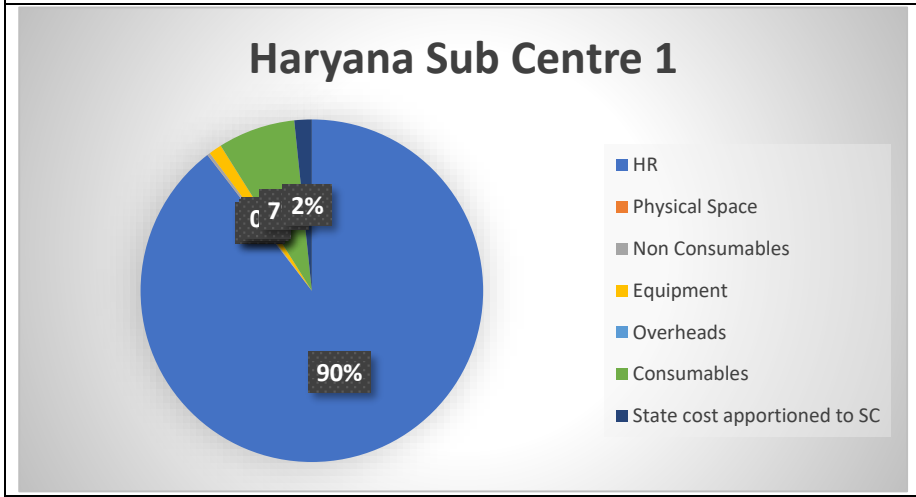
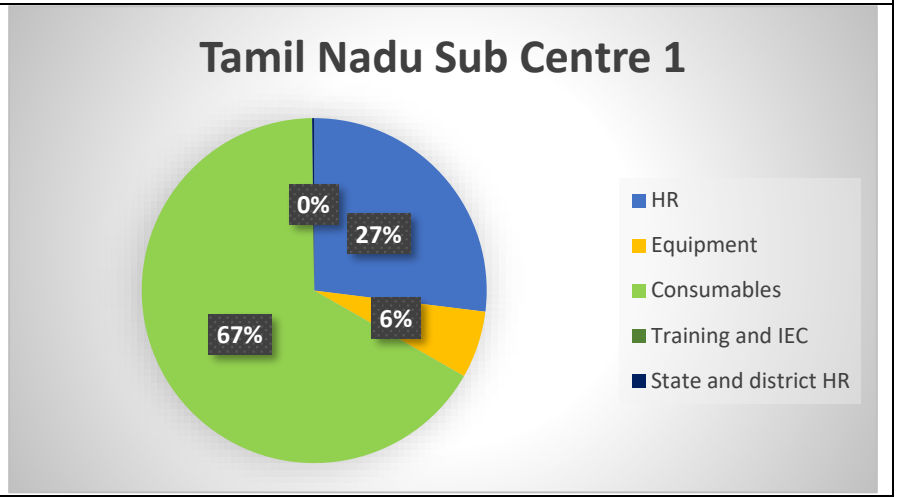
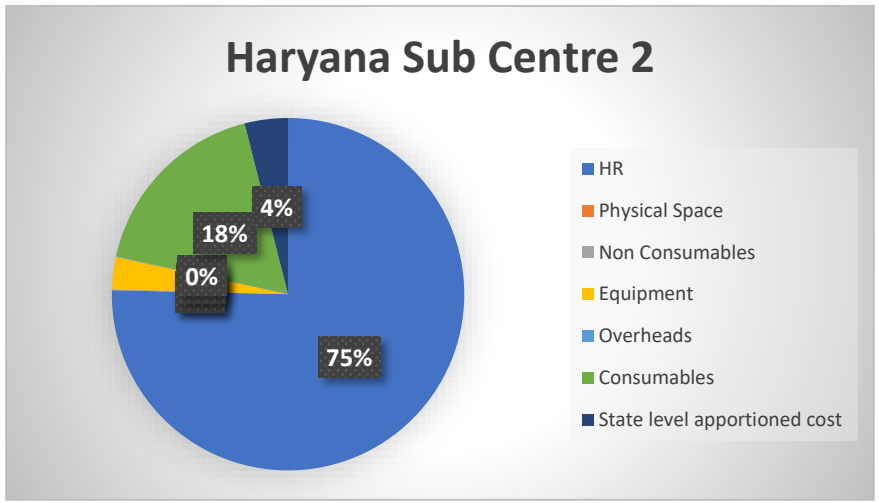
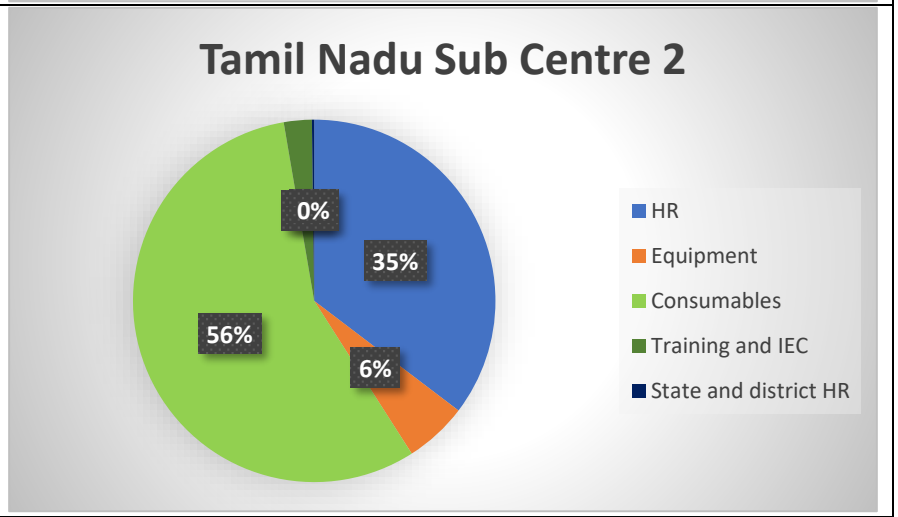
Annexure

Table S1: Mean OOPE and QoL of diabetes and hypertension patients with complications:

Complication	N	Mean OOPE	Lower limit	Upper limit	Mean HRQoL (EQ5D5L)	Lower limit	Upper limit
ONE COMPLICATION							
Retinopathy	63	4953	4316	5590	0.71	0.68	0.74
Neuropathy	16	3969	2767	5171	0.55	0.48	0.62
Heart Disease	56	4881	4322	5440	0.71	0.68	0.74
Stroke	3	7040	5448	8632	0.67	0.45	0.88
Nephropathy	41	7833	6397	9269	0.64	0.59	0.70
Foot Ulcer	17	7255	6065	8444	0.48	0.42	0.55
Foot Amputation	2	6210	4690	7730	0.49	0.52	0.65
TWO COMPLICATIONS							
Heart, Retinopathy	1	5460	-	-	0.31	-	-
Amputation, Foot Ulcer	1	1350	-	-	1.00	-	-
Foot Ulcer, Retinopathy	3	8267	6245	10286	0.75	0.50	1.00
Heart, Foot Ulcer	1	3200	3200	3200	0.39		
Heart, Nephropathy	3	10707	3553	17860	0.50	0.23	0.78
Heart, Neuropathy	1	6500	-	-	0.17	-	-
Heart, Retinopathy	4	5865	3104	8626	0.61	0.37	0.86

Heart, Stroke	3	6590	4912	8268	0.74	0.60	0.89
Nephropathy, Heart	2	9055	5010	13100	0.63	0.27	1.00
Nephropathy, Neuropathy	3	7523	5327	9719	0.44	0.35	0.53
Nephropathy, Retinopathy	6	12350	9790	14911	0.62	0.56	0.67
Neuropathy, Retinopathy	3	4840	4400	5280	0.71	0.57	0.86
MORE THAN TWO COMPLICATIONS							
Heart, Amputation, Foot Ulcers	1	9110	-	-	-0.14	-	-
Heart, Nephropathy, Retinopathy	2	15470	15110	15830	0.53	0.51	0.55
Heart, Nephropathy, Stroke	1	16200	-	-	-0.17	-	-
Heart, Neuropathy, Retinopathy	1	5000	-	-	0.59	-	-
Nephropathy, Neuropathy, Retinopathy	3	8333	6369	10297	0.60	0.57	0.63
Nephropathy, Neuropathy, Stroke	1	3010	-	-	0.26	-	-
Nephropathy, Retinopathy, Amputation	1	3750	-	-	0.27	-	-
Nephropathy, Retinopathy, Heart, Amputation, Foot Ulcer	1	16000			0.41		

Table S2: Input wise distribution of screening cost in Sub centers of Tamil Nadu and Haryana:

HARYANA	TAMIL NADU
	
	

Cost-effectiveness of India's National Program for Population Based Screening for Diabetes & Hypertension

Introduction

Addressing the non-communicable diseases (NCDs) which accounts 71% of global deaths has emerged as a public health priority (1). India is no exception to this, with 63% of overall mortality attributable to NCDs (2). Close to 4 million deaths in adults in India in 2017 were due to diabetes (3). Hypertension alone contributes to approximately 1.6 million deaths annually in India, due to ischemic heart disease and stroke. Hence, it is the number one health related risk factor in India, with the largest contribution to burden of disease and mortality (4, 5). Co-existence of hypertension and diabetes enhances the risk of developing complications which has health and economic implications (6)

Low awareness and poor care seeking are the two major deterrents for timely detection and treatment of diabetes and hypertension. As a result, several countries have initiated screening programs for early detection, which vary from facility based targeted and opportunistic screening to –whole of population community-based implementation (7-10). However, roll out of such large public programs has significant health and economic consequences. One-time screening for diabetes and hypertension has been reported to be cost-effective in United Kingdom (11), USA (12, 13), Bhutan (14) and Indonesia (15). On the other hand, diabetes screening was found to be not cost-ineffective in Brazil (16). A previous population level microsimulation-model analysis from India concluded that with current set of screening instruments community level screening is unlikely to be cost-effective (17). However, majority of the previous analyses assess the cost-effectiveness of a single once in a lifetime screening, rather than periodic screening for early detection of diabetes and hypertension.

India has implemented population-based screening (PBS) of diabetes and hypertension as part of the National Programme for Prevention and Control of Cancers, Diabetes, Cardiovascular Diseases and

Stroke (NPPCDCS) (18). All the people between 30-65 years are being screened at sub health centre level using random capillary blood glucose as the first screen. A confirmatory diagnosis is performed using fasting blood glucose at primary health centre level. In light of this, the Health Technology Assessment Board of the Government of India commissioned the present cost-effectiveness analysis for screening for diabetes and hypertension. In this paper, we report the incremental costs per quality adjusted life year gained (QALY) gained of alternative scenarios of screening diabetes and hypertension as compared to the current scenario.

Methods

A hybrid (decision tree and markov model) model was developed to estimate the costs and consequences for several alternative scenarios of population-based screening, among a hypothetical cohort of 1000 population starting at the age 30 years, for diabetes and hypertension compared against a counterfactual of no screening (routine diagnosis) in India.

The model comprised of 3 compartments. The first part comprised of the decision tree which predicted the number of individuals who would be detected with either prediabetes, diabetes, hypertension and co-morbid state, and classified each of these individuals into true positive, false negative, true negative and false negative based on sensitivity and specificity of screening methods. The second part tracked the transition of the diseased individuals over annual cycles to identify occurrence of disease-related complication. The third part (along with the second part), which comprised of five markov models for individual complications, predicted the life course in terms of life years, QALYs and costs. Several alternative screening scenarios were considered depending on the methods used (random blood glucose, fasting blood glucose), frequency of screening (annual, every three or five or ten or fifteen or twenty years and one-time) and population age group to be screened (30-65 years or 45-65 years). The analysis was undertaken using a societal perspective, wherein we included both health system and out-of-pocket expenditures for both screening and treatment of disease and its complications (19). Future costs and consequences were discounted at 3% considering both international and national Indian guidelines (19, 20).

Intervention & Comparator

The base case choice for intervention (screening) arm was based on the population-based screening (PBS) for diabetes and hypertension under the NPPCDCS program (18). Under this program, random capillary blood glucose test and blood pressure measurement is performed on the eligible population (30 years and older) by the Auxilliary Nurse Midwife in the outreach setting. Those with blood glucose level ranging between 101&140 mg/dl are offered lifestyle modification and advised a yearly test in subsequent years. Those who with the blood glucose equal to or more than 140 mg/dl and/or blood pressure screening equal to or more than 140/90 mmHg are referred to public sector health facility for the confirmatory testing using fasting plasma glucose and/or blood pressure measurement. At the facility level, those who are confirmed to be with diabetes/hypertension/both are put on their respective treatments by the medical officer. An annual screening for diabetes and hypertension is recommended based on the program guidelines. Besides annual screening, we developed scenarios for once in every three, five, ten, fifteen, twenty years, as well as once in a lifetime screening scenario. Additional scenarios with other screening methods, frequency and population age groups were also modelled (Refer Supplement). The comparator scenario comprised of the usual practice of detection for diabetes and hypertension based on coverage of opportunistic screening or detection based on onset of symptoms as per the current care seeking behaviour (21-23). The existing treatment seeking behaviour once detected for diabetes or hypertension, as per current practice, was modelled in both intervention (PBS screening) and comparator (no PBS screening).

Model Assumptions

It was assumed that the movement from healthy to diabetes occurs through pre-diabetes dysglycemic state. Similarly, a healthy person was assumed to have an annual risk to develop hypertension. Age wise incidence of pre-diabetes and hypertension as reported in CURES study (24) and CARRS study (25) respectively was used for the model. A co-morbid condition of pre-diabetes or diabetes with diabetes and hypertension, we used the annual probability of developing microvascular and macrovascular complications from Indian study (26) and UKPDS clinical trial (27, 28) respectively. Published literature from UKPDS trial reported risks of developing complications stratified by glycated haemoglobin (HBA1c) values (28) and systolic blood pressure (27). We assumed risks of developing complications for HBA1c values less than 7% and systolic blood pressure less than 140 mm Hg for controlled health state for diabetes and hypertension. These cut-offs were chosen in concurrence with previous published Indian literature (22, 29, 30). A differential of risks (mean difference) was computed from the average risk of developing complications to estimate risks for controlled and uncontrolled health states using the abovementioned cut-offs. This mean difference was applied on an Indian study (26) reporting on incidence values for microvascular complications to arrive at average risk of developing microvascular complications (retinopathy, neuropathy & nephropathy) for controlled and uncontrolled health states for diabetes and hypertension. However, the sample size was very small in this study for macrovascular complications (stroke & coronary heart disease). Henceforth, risk estimates were used from UKPDS and differentials were calculated for risks for developing macrovascular complications in controlled and uncontrolled health states for diabetes and hypertension (27, 28).

Based on previously published models and their transition parameters of progression, markov models for complications including retinopathy, nephropathy, foot ulcer, coronary heart disease and stroke were developed (31-33). In order to account for a probability of more than one e complication (microvascular and macrovascular), a combination of nephropathy and coronary heart diseasedisease was considered. This was assumed that due to irregular follow-ups, low care-seeking for treatment and subsequent low control; there was increased preponderance to develop nephropathy (incidence rate of 4.5 per 100 person years) and coronary heart disease (0.8 per 100 person years) than other closely associated combination of retinopathy (4.4 per 100 person years) and coronary heart disease (0.8 per 100 person years. Death due to any cause (age specific) as per Indian Sample Registration Survey data was assumed to occur from all health states (34) Disease specific mortality was assumed to occur as a result of complications including myocardial infarction, stroke, end stage renal disease and more than one complication state, as per the available clinical evidence on disease progression and mortality (35, 36). Fig 2 illustrates the schematic diagram of the Markov model.

In this decision model, the effect of intervention arm was assumed to be based on the early detection of the cases through screening and henceforth putting the patients on subsequent treatment and delaying the onset of complications. A systematic review and meta-analysis to assess the diagnostic accuracy of blood glucose tests (random blood glucose, fasting blood glucose, HBA1c) was undertaken (37). In absence of sufficient number of studies to carry out meta-analysis for random blood glucose test, we used the sensitivity and specificity as reported in a community-based study Indian study (38).

Costing

The cost of screening, cost of treatment of diabetes mellitus and hypertension, as well as the cost of treating complications were considered for intervention scenarios. The control scenario costs included

cost of diagnosis at facility level (either opportunistic screening or detection based on symptoms) as well as cost of treatment for both disease (diabetes mellitus and hypertension) and its complications. The cost of screening was ascertained through primary data collection in Haryana and Tamil Nadu states in India using bottom-up costing methods. The choice of states was based on the premise of differing geography, health care infrastructure as well as sufficient duration of program implementation. All the resources used in the delivery of screening program in the randomly selected sub centres from 2 districts were identified, measured and valued. Details of data collection and analysis are available in the supplementary material (….). The expenditures borne at the state level for screening related activities like information education communication, trainings of staff (involving auxiliary nurse midwife and medical officers), routine administration and supervision were apportioned to the level of service delivery. The cost of screening was adjusted for coverage of the screening. The cost of confirmatory testing for diabetes in the laboratory, as well as hypertension at primary health centre level was estimated using the primary data collected as part of the study and Indian health system cost database which comprises of data on 33 PHCs from six states in India (39-41).

The health system cost of treatment of DM and HTN at different levels of health care delivery was also derived by analysing the data from 15 district hospitals, 19 community health centres, 33 PHCs and 100 sub health centres using the cost database. The treatment seeking rates for DM and HTN in public and private sector was obtained based on analysis of the National Sample Survey 71st round data (21). For individuals with complications, it was assumed that treatment for specialised care would be sought at the tertiary level of health care. Costs for treatment of complications were derived from a large ongoing pan-India costing study (42) and the provider payment rates under national social insurance scheme in India (43). All costs were updated to 2017 value using consumer price index and reported in Indian

National Rupee (INR) and United States Dollar (USD). Out of pocket expenditure for treatment of DM and HTN in different levels of public as well as private facilities was obtained by analysing the data from the NSSO 71st round(21). A primary survey was done on 962 patients to assess the out of expenses of patients of diabetes and/or hypertension seeking treatment at a public sector tertiary care hospital that caters to more than 6 North Indian states.

Quality of Life

Health related quality of life was assessed using Euro Quality of Life Questionnaire with five dimensions and five-level scale (EQ-5D-5L) for 234 patients with diabetes, 300 with hypertension and 428 patients with both diabetes and hypertension at a publics sector tertiary care hospital in North India. Separate utility scores were generated for those without and with complications (such as retinopathy, nephropathy, foot ulcer, stroke and cardiac condition). Estimates from published international and national literature (32, 33, 44, 45) on quality of life utility scores (using EQ5D5L) for markov states in various complications were used to calculate percentage difference amongst them. This percentage difference was applied to quality of life utility scores generated for complications as part of primary data collection in this study to arrive at Indian values for each markov state. It was assumed that the patients with complications, who sought outpatient care in the study, were more representative of least severe health states in their respective complications.

Sensitivity Analysis

To test the uncertainty in the parameter values, we undertook multivariate probabilistic sensitivity analysis (PSA) to account for joint parameter uncertainty (46). Under PSA, each of the parameters was

assigned specific distribution based on its nature. Specifically, gamma distribution was assigned to cost parameters and beta distribution was used for HRQoL estimates and other parameters reported as rates, proportion and probabilities. All the health system cost estimates were varied from half to double of the base value. Standard error for OOP expenditure and HRQoL was based on the results of the primary data. Epidemiological parameters in the form of prevalence, incidence and mortality were varied by 20% on either side of base case value. Similarly, annual probabilities of progression and regression were varied by 40% on either side of the base value. Given the extent of variation seen in the sensitivity of screening tests among studies included in the meta-analysis, we varied it by 20% on either of the base value. Further, since the estimate of specificity was already more than 90% (for fasting plasma glucose and blood pressure measurement) and in view of small variation in its estimates among various studies, it was varied by 5% of the base value. Finally, the median value of incremental cost effectiveness ratio (ICER) along with 2.5^{th} and 97.5^{th} percentile was computed using 999 Monte Carlo simulations.

Results

Health Outcomes

The lifetime risk of development of prediabetes, diabetes, and hypertension in the non-screened population was estimated to be 60% (56% - 63%), 48.4% (44% - 53%) and 81.8% (80% – 83.3%). We found an incidence of 0.027 per person for diabetes under the routine scenario, with a mean age of diagnosis at 59.75 years. In the absence of screening, there are 9267, 28,206, 2982, 3030 and 1239 cases of stroke, myocardial infarction, end stage renal disease (ESRD), amputation and blindness due to diabetes and hypertension per 1 lakh population respectively. With the implementation of population based screening with random blood glucose test followed by fasting glucose test in the age group of 30-

65 years (as compared to no screening), there is reduction in 0.3% (n=227) to 23% (n=2123) , 0.2% (n=58) to 13% (n=3753), 1% (n=15) to 27% (n=807), 1% (n=24)to 40% (1224) and 1% (n=10) to 35% (n=429) cases of stroke, myocardial infarction, end stage renal disease (ESRD), amputation and blindness per 1 lakh population respectively among various frequencies of screening as shown in Table 1.

The number of deaths averted were highest in the annual screening (12.5 per 1000 population) followed by every 3-year (6.5 per 1000 population), every 5-year (4 per 1000 population) and least in one-time screen (0.2 per 1000 population). As compared to no screening, screening for diabetes beginning at 30 years results in a gain of life years and QALY per person which ranged from 0.0014 to 0.063 and 0.005 to 0.196 respectively under scenarios of different frequency intervals (Table 1). The detailed results with different combination of screening test are provided in the supplementary material (Table Supplement 2-16).

Costs

In the routine care scenario (no organized screening), lifetime cost of management of those diagnosed with DM and HTN among a cohort of 1lakh 30-year old population was estimated to be INR 8075 million. In the scenario of no screening, the cost of treatment of complicated cases comprised of around 96.5% (INR 7794 million) of the total cost, followed by cost of treating uncomplicated cases (3.37%; INR 271 million). While, in the case of annual screening (age group 30-65 years), cost of uncomplicated cases constitutes the major component (64.5%; INR 10929 million), followed by the cost of treating complicated cases (35%; INR 5980 million). The cost of implementing screening comprised of a minute component of 0.5% (INR 65 million). More details are shown in Table 2.

Cost-effectiveness

The incremental cost per QALY gained (ICER) with once in a lifetime screening was INR 4650 (-760,810 to 730,46). For all other scenarios of frequency, the ICER ranged from 2 to 3 times the per-capita gross domestic product (GDP) under different scenarios. This implies that only once in a lifetime screening scenario is cost-effective at one-time per capita GDP threshold in India. These findings are in the context of current health care utilization.

In case the health and wellness centres (sub health centres and primary health centres) together cater t at least 50% of the total uncomplicated cases of diabetes and hypertension, annual population-based screening (age group 30-65 years) starts to become cost effective. The total cost borne in case of HWC with various frequencies of screening is shown in Supplement Table 17. Further, lifetime per cent reduction in OOPE in a cohort of 1 lakh population due to shift in utilization of treatment of uncomplicated cases from the current scenario for diabetes and hypertension is shown in Supplement Table 18.

Discussion

To our knowledge, this is the first study assessing the cost-effectiveness of a population-based screening program for diabetes and hypertension in Indian context. Additionally, our analysis also reports on a range of screening scenarios to inform on evidence informed decision-making in context of weighing the lifetime benefits and the resources invested in them.

In sensitivity analysis, we found that incremental cost-effectiveness ratios were most sensitive to cost of treatment of uncomplicated cases, prevalence, coverage of treatment, utilization patterns for access to health care and quality of life weights. This is true in real world as chronic diseases like diabetes and hypertension once diagnosed warrant for life-long treatment and henceforth associated costs. High

prevalence of disease impacts on the costs and may lead to lower costs per case. The findings of our study may serve as a guidance to similar resource constrained settings with comparable prevalence estimates. ICERs are also affected by probabilities of development of risk of complications in treated and untreated/undiagnosed cases in diabetes and hypertension. Higher screening costs did/did not have any impact on ICERs. We ran scenario analysis considering recent initiatives to strengthen and promote comprehensive primary health care in the country. In this sense, increase in access to health care and greater availability of drugs at health and wellness centres can be an important tennet for individuals with diabetes and hypertension and improve coverage of treatment

Our findings indicate that the intervention increases the detection of undiagnosed cases as compared to routine diagnosis and delays the incidence of developing of complications in comparison to no screening arm. A 10-year retrospective examination of health maintenance administrative data suggested that diabetes detected through screening was associated with a 13.0% reduction in the risk of complications compared with routine diagnosis (hazard ratio 0.87, 95% CI 0.38–1.98) (47). Our modelled value of incidence of diabetes is in line other Indian cohort studies on diabetes (24, 48-50) The predicted life expectancy of the cohort in the model is in range to those reported by the sample registration system for Indian population. In addition, the lifetime risks for individual complications in diabetes and hypertension seem plausible in comparison with international literature, given the fact the latter studies had populations ranging in age-group 50-55 years. Only one study from China reported lifetime risks in age group 35-40 years, closer to ours age group of 30 years. The findings in terms of lifetime risk of stroke in diabetes in our study are similar/conservative to this study. In terms of cost of screening with random blood glucose, our estimates are conservative than another Indian study (17). This could be due to bottom up micro-costing method and the subsidized public sector costs for various

drugs and consumables used in our study; while the other study had relied on estimates from WHO-Choice databases for the same.

Strengths and limitations

There are several strengths of this study. Firstly, this is the first cost effectiveness analysis that evaluates the lifetime costs and benefits of introduction of a population-based screening program for diabetes and hypertension and does not limit to screen only strategy in a resource-constrained setting. Secondly, it reports on varying screening intervals and age of initiation of screening for both diabetes and hypertension. Thirdly, comprehensive search and meta-analysis were done to arrive at the effectiveness (diagnostic accuracy) estimates for screening tests in previously undiagnosed individual for diabetes. A previously published systematic review on health economic analyses of screening programs for diabetes reported that 48% of the included studies did not consider sensitivity and specificity parameters (51) . Fourthly, the estimates for the cost of screening, treatment of disease and its complications as well as QoL were based on local data. The out of pocket estimates for treatment were taken from a public sector tertiary hospital that caters to individuals from 7 states for diabetes and hypertension care. The cost of treatment for complications were taken from a pan India study covering 13 states on costing of health services for various conditions (refer supplement) and recently constituted national costing database(41). Standard approaches of bottom-up costing and cost of illness methods were used to generate these cost estimates(39, 52). However, normative costing approach was used to arrive at the annual cost of treatment for the scenario related to health and wellness centre.

There are few limitations to the present study. Firstly, our study relied on international literature for the probabilities of developing macrovascular complications stratified by HBA1c or age due to lack of any empirical Indian data. The latter holds true for sub-models of nephropathy and foot ulcer as well. Secondly, we assumed that an individual who develops a complication enters the sub-model in the first clinical event and moves to next more severe states based upon the transition probabilities assigned thereof. Thirdly, we did not consider opportunity costs in terms of time spent by the patient for screening and confirmatory testing. Fourthly, we did not include productivity losses and it may have an impact on the cost-effectiveness ratios. Lastly, mortality estimates are likely to be conservative as we did not consider increased mortality in undiagnosed cases. Moreover, registration system of deaths may not report on underlying condition of diabetes or hypertension as the predominant cause.

Conclusion

Our findings indicate that one-time population level screening at age 30 years with current patterns of utilization of health care for diabetes and hypertension in India is cost-effective, considering the lifetime benefits and costs.

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Table 1: Modelled population health benefits of screening for DM & HTN in India

Screening scenario		Health outcomes gained/averted per 1 lakh population							
		Complications averted (%)					Deaths averted (%)	Life year gained	QALYs gained
Age of screening	Frequency of screening	Stroke	Myocardial Infarction	End stage renal disease	Amputation	Blindness			
30 – 65 years	Annually	2123 (23)	3753 (13)	807 (27)	1224(40)	429 (35)	1259 (21)	6387	19656
	Every 3 years	1136 (12)	1993 (7)	448 (15)	683(23)	237 (19)	647 (11)	3179	9463
	Every 5 years	756 (8)	1364 (5)	297 (10)	457(15)	159 (13)	428 (7)	2097	6231
	Every 10 years	388 (4)	724 (3)	160 (5)	240(8)	85 (7)	222 (4)	1093	3326
	Every 15 years	285 (3)	541 (2)	120 (4)	176(6)	63 (5)	164 (3)	815	2431
	Every 20 years	176 (2)	338 (1)	75 (3)	116(4)	41 (3)	104 (2)	523	1637
	Once at 30 years of age	27 (0.3)	58 (0.2)	15 (1)	24(1)	10 (1)	18 (0.3)	114	573
45 – 65 years	Annually	1762 (19)	3120 (11)	568 (19)	930 (31)	312 (25)	990 (16)	4366	11615
	Every 3 years	896 (10)	1581 (6)	321 (11)	512 (17)	175 (14)	497 (8)	2148	5866
	Every 5 years	610 (7)	1079 (4)	222 (7)	354 (12)	122 (10)	341 (6)	1496	4178
	Every 10 years	378 (4)	672 (2)	142 (5)	224 (7)	78 (6)	215 (4)	972	2801
	Every 15 years	275 (3)	492 (2)	111 (4)	171 (6)	61 (5)	163 (3)	781	2309
	Once at 45 years of age	163 (2)	296 (1)	83 (3)	119 (4)	44 (4)	109 (2)	620	1913

Table 2: Cost of screening and treatment for diabetes and hypertension under different scenarios

Screening scenario		Life time cost per 1 lakh population (INR million)					
			Health system cost of treatment		OOP Expenditure		
Age of screening	Frequency of screening	Screening	Uncomplicated cases	Complicated cases	Uncomplicated cases	Complicated cases	Total cost
Control		0.93 (0.75-1.15)	3 (2.3 - 3.8)	419 (329 – 528)	269 (213 – 330)	7375 (6732 – 8034)	8075 (7372 – 8764)
30 – 65 years	**Annually**	65 (51 – 85)	133 (95 – 181)	321 (248 – 415)	10797 (8425 – 13087)	5659 (5294 – 6266)	16978 (14825 – 19050)
	Every 3 years	32 (24 – 43)	68 (47 – 94)	368 (288 – 471)	5588 (4029 – 7379)	6424 (5845 – 7027)	12511 (11026 – 14191)
	Every 5 years	22 (16 – 28)	46 (31 – 65)	386 (301 – 489)	3779 (2697 – 5072)	6518 (5949 – 7105)	10772 (9604 – 12094)
	Every 10 years	12 (9 – 16)	26 (18 – 37)	402 (315 – 507)	2150 (1359 – 2890)	6788 (6198 – 7375)	9380 (8500 – 10335)
	Every 15 years	10 (7 - 12)	19 (13 – 27)	406 (319 – 513)	1588 (1152 – 2122)	6862 (6266 – 7455)	8896 (8118 – 9705)
	Every 20 years	7 (5 – 10)	14 (10 -19)	411 (323 – 518)	1182 (880 – 1555)	6942 (6340 – 7540)	8565 (7836 – 9311)
	Once at 30 years of age	5 (3 – 6)	7 (5 – 10)	418 (328 – 527)	593 (463 – 742)	7054 (6446 – 7673)	8079 (7411 – 8789)
45 – 65 years	**Annually**	30	77	329	6652	6153	13241
	Every 3 years	16	39	363	3432	6686	10536
	Every 5 years	11	39	363	3432	6686	9692
	Every 10 years	8	19	381	1660	6973	9040
	Every 15 years	6	16	384	1352	7027	8785
	Once at 45 years of age	5	13	387	1061	7083	8549

* Values in parenthesis represent 2.5^{th} and 97.5^{th} percentile

Table 3: Incremental Cost effectiveness Ratios by age and frequency of screening

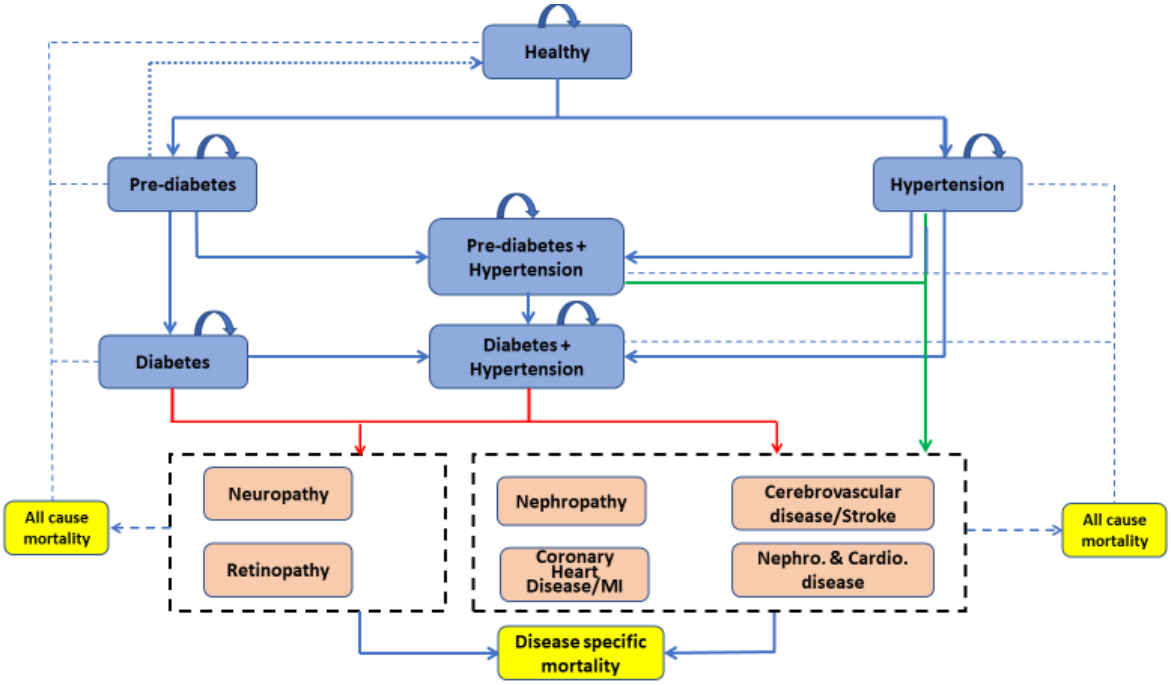
Screening scenario	At Current level of health care utilization	
	30 - 65 years of age	**45 - 65 years of age**
Annually	444,813 (296,372 – 1,249,966)	452,259
Every 3 years	461,703 (304,817 – 1,511,159)	434,478
Every 5 years	419,366 (275,278 – 1,541,405)	407,911
Every 10 years	381,181 (234,220 – 1,499,724)	375,827
Every 15 years	323,371 (164,542 – 1,235,414)	345,380
Every 20 years	281,077 (-564,755 to 1,112,456)	
Once	4650 (-760,810 to 730,460)	293,637

* Values in parenthesis represent 2.5th and 97.5th percentile

Table 4: Incremental Cost effectiveness Ratios by health and wellness centres (HWC) utilization and frequency of screening

Share of HWCs	Incremental cost (INR) per QALY gained						
	Annually	**Every 3 years**	**Every 5 years**	**Every 10 years**	**Every 15 years**	**Every 20 years**	**Once**
Current	439,639	452,605	410,827	365,002	299,361	244,709	-172,174
10%	391,794	381,440	320,191	218,602	110,514	-28,493	-931,972
20%	313,998	265,725	172,815	-19,448	-196,555	-472,723	-2,167,416
30%	236,202	150,010	25,440	-257,498	-503,624	-916,953	-3,402,860
40%	158,407	342,95	-121,936	-495,549	-810,694	-1,361,183	-4,638,304
50%	806,11	-81,420	-269,312	-733,599	-1,117,763	-1,805,413	-5,873,747
60%	2815	-197,135	-416,687	-971,649	-1,424,832	-2,249,643	-7,109,191
70%	-74,981	-312,850	-564,063	-1,209,699	-1,731,901	-2,693,873	-8,344,635

Figure 2: Model Schematic



Feasibility & Landscape Analysis of Population Based Screening for Diabetes & Hypertension in India

Introduction

Rising burden of Type 2 diabetes India is a cause of concern. Diabetes not only has an effect at individual level but due to chronic nature of the condition has implications at health system and economic level as well. Hypertension is the number one health related risk factor in India, with the largest contribution to burden of disease and mortality (1, 2). Majority of health systems are oriented towards provision of acute care and thus insufficiently organized for providing for long term conditions of chronic care of non-communicable diseases (NCD) (3). Especially in context of LMICs, role of health system becomes paramount as these nations face dual burden of diseases-communicable and non-communicable. Further, another concern is that majority of treatment costs for NCD like diabetes and hypertension are lifelong and are borne by the patients as out of pocket expenditures (OOPE) (4). Recognizing the importance of burden of non-communicable diseases, the Government of India started National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPPCCDCS) (2010) that aimed at integration of non-communicable disease interventions with in National Rural Health Mission (now referred as National Health Mission) framework for optimization of scarce resources and health care interventions. Under NPPCCDCS, framework for population-based screening (PBS) for NCD like diabetes (DM), hypertension (HTN) and common cancers (oral, breast and cervix) has been outlined.

By the WHO "Principles of Screening" document 30 (September 2001 draft): “Screening is the process of identifying those individuals who are at sufficiently high risk of a specific disorder to warrant further investigation or direct action (5). Measure of diagnostic accuracy like sensitivity, specificity, positive predictive value of a biochemical test used for screening are an important tennet for a screening programme. The sensitivity of a screening test is the proportion of people with the disorder who test positive on the screening test. The specificity of a screening test is the proportion of people who do not have the disorder who test negative on the screening test. There exists a trade-off between the sensitivity and specificity, since an inverse relationship exists between the two. Most of screening programs employ questionnaires/risk scoring tools and biochemical tests namely fasting blood glucose (FBG), HbA1c and 75-g oral glucose tolerance test (OGTT) in various combinations (6). For blood pressure measurement, guidelines like NICE (7) ASH/ISH (8), ESC (9), now suggest the use of electronic BP measurement instruments based on the oscillometric approach to record BP in both clinic as well as home based settings.

However, there is no firm consensus on the most accurate screening test for detection of diabetes (10). The ultimate onus of selection of any screening test depends upon the choice of cut-offs, the purpose of the screening programme and availability of resources required to perform this testing. The aim of this landscape analysis was to explore current process of PBS for DM and HTN, and on health systems challenges and opportunities affecting the provision of population-based screening for DM and HTN. The subsequent sections in this chapter outline on factors related to screening tests and program followed by policy recommendations, based upon drawings from published literature and primary data.

I. Factors related to screening tests

Various tests can be used to screen for hyperglycemia including in developing countries [5,34,35]. These include biochemical tests like random blood glucose (RBG), fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and the 75 g oral glucose tolerance test (OGTT). Based on their advantages and limitations, some of the screening tests may be more suitable for use in developing countries settings.

Random blood glucose

Although RBG is easy to obtain, as it does not require to be in fasting condition; but its performance as a screening tool is limited by the low sensitivity as compared to OGTT (11). There have been previous considerations of diabetes screening via RPG. The Australian Diabetes Screening concluded that a cut off of 99 mg/dl should be used for screening, but did not report sensitivity, specificity, or AROC (12, 13). A study by Johnson et al reported that a RPG of 130 mg/dl would provide 87% specificity and 63% sensitivity (14). Zhang et al. (15) reported that a capillary glucose of 120 mg/dl would provide 89% specificity and 68% sensitivity. The cut-offs for this test are dependent on the background characteristics of specific populations (e.g., age and gender) and factors like time since last meal, and there may be no universally applicable cut-off (16). The simplicity and potentially low cost of capillary blood testing make it appealing for use in low resources settings in developing countries. Nonetheless, the utility of capillary blood testing for screening remains unclear, largely because of concerns of imprecision in the few existing studies and the lack of standardization (16).

Fasting Blood Glucose

Measurement of glucose in plasma of fasting subjects is widely accepted as a diagnostic criterion for diabetes and highly correlated with the risk of diabetic complications (17, 18). Advantages include not

expensive assays on automated analyzing instruments which are available across most of the laboratories. At FPG threshold of 7 mmol/l, 55.7% of people with diabetes would be detected and specificity would be 100% as per study (19). Sensitivity for hyperglycemia screening is considered modest (20). Nevertheless, this test has some limitations. Lack of reproducibility is one such example. Biological variation, differential in its concentrations at different times in day and persons has been noted. A healthy person is reported have variability between 5.7–8.3%, whereas between individuals variation of up to 12.5% can be seen (21, 22). Further other factors preceding sample measurement like use of medications, venous stasis, handling of sample and posture can influence the results of blood tests (18). Results get affected with long fasting hours, practicing exercise before the test or any episodes of illness or factors that can induce stress. Most importantly, stringent control in terms of not eating anything for 8 hours is preferred as if not done this can affect the results of the test (23) (18). A study on Fasting blood glucose as test at medical centre reported that because of this reason screening participation for diabetes at facility was 69% of eligible participants (24). This test reflects glucose homeostasis at a single point of time (18). Mostly handheld devices are used to measure glucose through capillary blood. However, a plasma equivalent glucose value is also reported usually (25). An India based study on diabetes and prediabetes comparing capillary fasting and 2-h post-load blood glucose measurements with fasting and 2-h post-load venous plasma glucose measurements reported a moderate-to-acceptable correlation between a capillary and venous values in fasting condition. It further concluded that capillary blood glucose offers an acceptable alternative for screening for diabetes and impaired glucose tolerance where feasibility of venous samples is difficult (26). Another population based study in China reported strong positive correlation and high concordance between capillary and plasma values of fasting blood glucose and recommended its use as suitable strategy for screening for diabetes and prediabetes in rural areas (25).

Glycated Hemoglobin (HBA1c)

At a cut off of 6.5% and absence of medical conditions that may affect its accurate measurement, HBA1c is recommended to diagnose diabetes as an alternative to other glucose measurements by WHO or ADA. However, feasibility of use of this test necessitates use of standardized assays and criteria aligned to the international reference values. Further, if a person gets value lesser than 6.5% it does not deny diabetes diagnosed using glucose tests. However, there are no clear cut recommendations by WHO on the interpretation of HbA1c levels lesser than 6.5% (27). Conditions like hemolytic disease, those where erythrocyte survival is shortened or there is more number of young red blood cells as in acute blood loss may show a substantial reduction in A1c values (28). On the contrary, conditions like hypertriglyceridemia, uremia, chronic alcoholism, hyperbilirubinemia may report a false increase in

A1C (29). Selecting a right method which does not interfere with the test may overcome the quality assurance challenges.

Advantages of HbA1c as a screening tool is appealing being a good indicator of long-term glycemic control, not needing fasting health state samples, no effect by short-term lifestyle changes, simple sample, and low within-individual variability unlike fasting glucose (16). However, some of the challenges associated for low resource settings are the costs, unavailability of the test at all levels of health care due to specific standardization guidelines for the assays and associated equipment. These limitations can be addressed to some extent by conducting large scale educational programs on HbA1c standardization with involvement of various stakeholders like clinicians, biochemists, external quality assessment checks, patient groups and other manufacturers (30). Furthermore, initiatives like strategic purchasing by the government may help to bring down the cost of diagnostic set up requirements for HbA1c tests and ensure proper quality assurance protocols in place.

Oral Glucose Tolerance Test (75-gram OGTT)

This test has been used as the "gold standard" for diagnosis of diabetes. In principle, there is an increase in postprandial glucose level before an increase in fasting glucose. Therefore, postprandial glucose is a sensitive indicator to know for risk of developing diabetes and early marker of impaired glucose homeostasis.

The OGTT evaluates the efficiency of the body to metabolize glucose and for many years has been used as the. An increase in postprandial glucose concentration often occurs before fasting glucose increases. Therefore, postprandial glucose is a sensitive indicator of the risk for developing diabetes and an early marker of impaired glucose homeostasis. Further, an increased 2-h plasma glucose during an OGTT is a better predictor of both all-cause mortality and cardiovascular mortality or morbidity based on published evidence (31, 32). Though this test is accepted as a diagnostic modality by the American Diabetes Association, World Health Organization and other organizations; an extensive patient preparation is necessary to perform an OGTT. Pre-requisites include ingestion of at least 150 g of dietary carbohydrate per day for 3 days prior to the test, a 10- to 16-h fast, and commencement of the test between 7:00 A.M. and 9:00 A.M. (18). Consistent with this, a high degree of intraindividual variability (21) and resulting in poor reproducibility of the OGTT has been documented (33, 34). Limitations of OGTT namely, lack of reproducibility, cost of testing and inconvenience led to the recommendation of FPG as the preferred glucose-based diagnostic test (35). Availability of anhydrous glucose is also limiting factor in low-resource settings like India and undermines the usefulness of test.

Table 1: An overview of screening tests for assessing glycemic status (6)

Test for assessing glycemic status	Random Blood Glucose	Fasting Blood Glucose	75-g OGTT	HbA1c
State of individual	No fasting Recommended when symptoms of hyperglycemia present	Single plasma glucose level, requires fasting	8-hr fast	Any time
Cost	Inexpensive	Inexpensive	Relatively costly	More expensive
Advantages	Easy to obtain	Highly correlated with complications	Gold standard; most sensitive to IGT	Stable marker of long-term glycaemic index
Limitations	Require prompt processing (error)	Patient compliance	Lengthy, overall retest reproducibility low	Vary with assay used

Screening for hypertension can be done with various devices like electronic, mercury and aneroid. However, India being signatory to Minamata Declaration on phasing out of mercury devices globally, the mercury-based sphygmomanometers which were considered gold standard are now being discontinued. Semiautomatic devices are being considered the most reliable as they allow readings even when their batteries run low. The latter may be a common problem encountered in low resource settings (36) .

In addition to screening tests, key components of any screening programmes include equipment, trained health professionals, patient education and effective implementation of program, ood relationships between health professions (which are beneficial for referral processes between different healthcare facilities or services). These components make screening for hypertension (across an entire population) a costly intervention, because of the lengthy time to diagnosis and the human and financial resources required.

Factors related to screening program

This section focusses on the assessment of population-based screening program from the health system perspective. The findings are collated on the basis key informant interviews from two states (Haryana and Punjab), inputs from stakeholders' (clinicians, program officers and implementers), assessments at facility and community level, and review of literature. A semi-structured interview guide, focussing on the six building blocks of health system (37) (Figure 1), was made to elicit information on implementation and feasibility of PBS for diabetes and hypertension from the health system perspective.

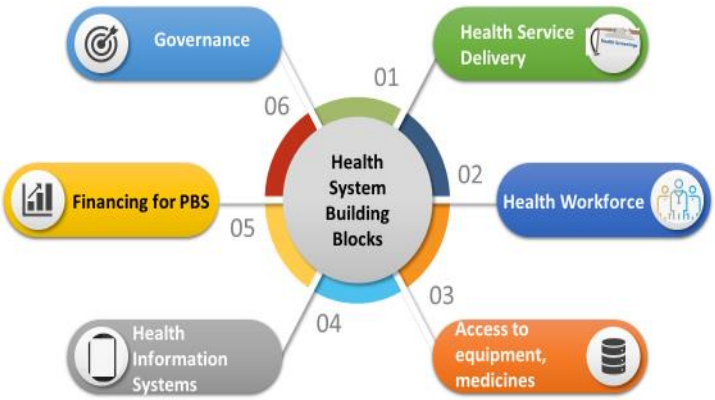


Figure 1: Health System Building blocks, World Health Organization

1. Health Service Delivery

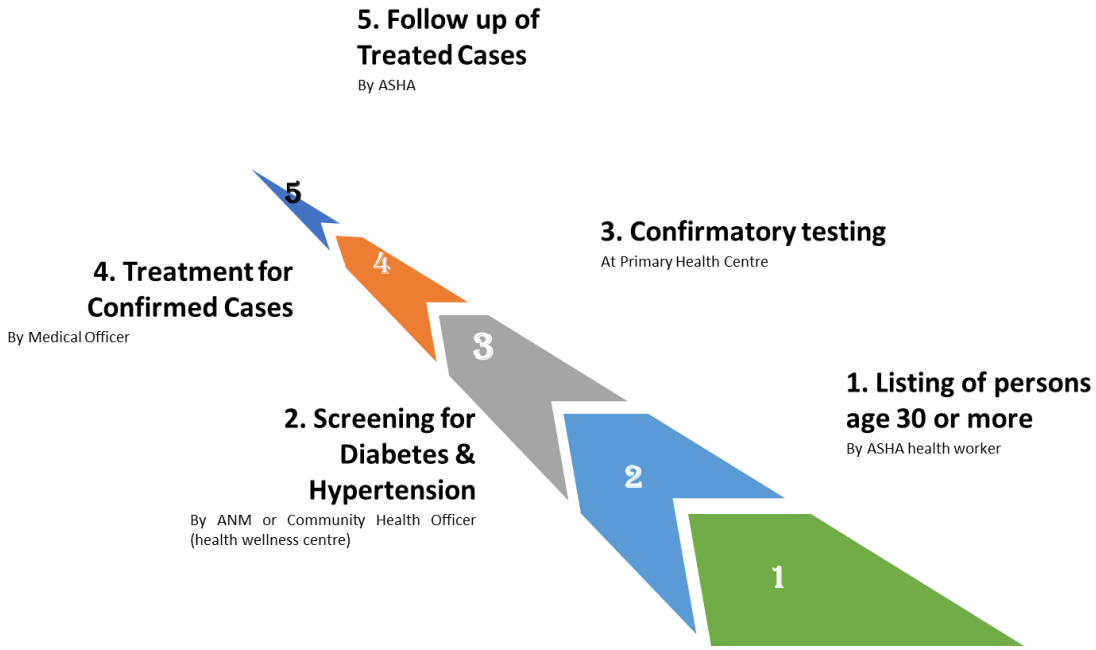


Figure 2: Process of Population based Screening for Diabetes & Hypertension

Both the states surveyed have PBS program for diabetes and hypertension in place. The implementation of PBS program started in a phased manner, with districts having longest span of NPCDCS program selected first followed by others in every subsequent year. However, there is some variation on how, when and the extent to which PBS program started in these states. The PBS program comes under the premise of NPCDCS program. However, with recent initiatives like Ayushman Bharat, there is a renewed focus on providing comprehensive primary health care (CPHC) through upgradation of sub health centres to health and wellness centres (HWCs). In lieu of this, the PBS for diabetes and hypertension also falls under CPHC. PBS started in Haryana in 2016 while PBS under NPCDCS program was in initial phase in Punjab and mainly implemented under HWC presently. It was told that the mode of service delivery for screening being followed is either through organization of camps or at sub health centres or both, depending upon the approach followed by PBS districts. Similarly, as outlined in the PBS guidelines, enumeration of persons aged 30 years or older based on community-based assessment checklist is being carried out by the Activated Social Health Activists (ASHAs) in both the states. Subsequently, persons aged 30 and older or with risk score greater than four are referred for screening to Auxiliary Nurse Midwife (ANM) to camps being organized in the outreach. In terms of information, education and communication for PBS for diabetes and hypertension, multitude of activities in the form of pamphlets, folders, leaflets, booklets are designed at the state level and distributed by ASHAs in the community. In Haryana, special radio jingles were broadcasted to mark the world diabetes day to promote awareness about the disease condition. Further, it was told that all

districts in the state have bus passenger system where audio support advertisement on preventive aspects related to disease conditions as well as information on screening is given. In the state of Punjab, a camp mode approach is being pilot tested in one of the districts wherein the persons mobilized through ASHAs attend the camp, get screened for diabetes and hypertension and as required are started on treatment by the medical officer who is also part of this camp. This model is being named as Kalanaur model, after one of the blocks in that district. As part of HWCs, screening is also being done at the sub health centre level by the Community Health Officers. There is a provision of every 6 month follow up through ASHAs of those who were started on treatment after being screened and confirmed at primary health centre for DM and/ HTN. Increased awareness in community and health staff regarding PBS and the disease conditions was observed during the monitoring visits in the state of Haryana. However, there was not any data to corroborate on the same. However, since the PBS program was in initial phases of implementation in Punjab state, it was noted that it was too soon to comment on the same.

Common challenges noted with respect to the health service delivery aspect were broadly related to access to screening and loss to follow up. It was observed that since enumeration and screening activity happens at day-time during week days, it was difficult to involve male population for the same as they were usually unavailable due to their working schedules. This led to more rounds of visits for ANM towards weekends to include this population for screening. It was reported that despite the efforts, there was substantial loss to follow up at every step of the program- screening followed by confirmatory testing and treatment and subsequently maintain good control and compliance after treatment. Similar findings were observed from national survey and previous studies (38, 39) (40). Further, it was noted that better mechanisms and algorithms were necessary to minimize these losses so as to make screening effective. Effective patient tracking and referral tracking can be possible solution. At the same time, it is necessary to ensure that availability of services like further testing for confirmation and treatment are available at public sector facilities. There was no data on whether PBS and its processes involved any specific initiatives to reach out to vulnerable populations except that as per guidelines no person had to travel more than 30 minutes to get screened. Thus, equity perspective of PBS is yet to be ascertained in terms of socio-economic status, rural/urban access.

2. Health Workforce

It was reported that at the initial phase of PBS implementation, trainings were done for ASHAs, ANMs and Medical officers as per the guidelines of PBS program. The trainer of trainers at national level further trained the persons at state and subsequently at districts selected for PBS program. In addition, it was told that refresher trainings occur from time to time during monthly meetings at district level in Haryana. At the health and wellness centres level, it was told that during the last one year, Community Health Officers (CHOs) had been appointed in Punjab. These CHOs were appointed after a 6-month

Bridge Course in Community Health, organized by the Department of Health Services under Indira Gandhi National Open University (IGNOU). The state had to prepare extensive roadmap from getting this bridge course in place till training and appointment of CHOs. The latter undergo CHO Induction training and as part of these trainings on blood glucose testing are done. However, under HWC, it was reported that more clarity on roles and responsibilities in terms of who does what for PBS for ANM and CHO was required. Both these health providers ANM and CHOs are present at sub health centres upgraded to HWC. But their roles are overlapping and not well-defined as both are involved in PBS. They both have to implement, monitor, supervise and report on the PBS but under different portals and it leads to duplication of work to some extent. Similar findings were noted in a baseline assessment of 26 HWCs in a block in Punjab (41). This study also consisted of questions to enquire about the satisfaction levels and major issues faced by community health officers in the service delivery. Lack of clarity in the duties and responsibilities of CHOs, difficulties in cooperation between different personnel at the HWC and lack of clarity on records to be maintained were some of the key findings noted in this assessment. Nonetheless, increased workload due to too many data registers activities and further uploading to web portals were other perceived potential challenges. This may further lead to lack of time to provide comprehensive and quality services to patients (42).

3. Health Information Systems

Respondents reported that there was both paper-and web-based mechanisms of gathering information about screening. The ASHA collected information regarding listing of individuals aged 30 years and older through CBAC forms. While ANM was the primary health provider involved in gathering and maintaining information in regard to screening under NCD program. Under HWCs, the same role was being performed by both ANM and CHO. In the recent past, they were also provided tablets to further upload this information on day-to-day basis on the web-based interfaces- NCD portal (by ANM) and HWC portal (by CHO). One-time induction trainings were held to familiarize the ANM and CHO with the use of tablets. Medical Officers were also trained to upload the data pertaining to suspected cases that were put on treatment or referred by PHC to higher facilities. These dashboards can be accessed real time at the district, state and national level to check the status of PBS by MO, district, state or national officials.

It was informed that there is monthly reporting for PBS where information is filled manually. Further, under section 5B of NPCDCS form, this information is sent by the state to the centre every month. Under web-based portal, the manually filled information is also uploaded to NCD portal by ANM and HWC portal by CHO. In terms of satisfaction with the introduction of tablets and app-based system, it was perceived that this increases the workload for ANM who has to upload the information on the portal. In terms of how data generated for PBS is being used, it was told by the respondents that the web-based systems provided the opportunity of real time monitoring of PBS through dashboards that

can be accessed at district, state and national level. Delays in provision of tablets for all PBS districts, time lag between uploading of manually entered data to the NCD and HWC portal, low back up time for tablets and perceived difficulties due to frequent upgradation were some of the challenges reported. It was told that there is huge gap in data collected and data uploaded on the web portals in regard to screening. The difference in pace of collecting and uploading was told due to the reason that tablets were introduced at a later stage in the program and due to increased workload of ANM due to this digitization. Based on block level assessment of HWC in Punjab (41), it was noted that ASHA were not able to capture household information at the time of form filling. NCD camps according to the risk scoring are not being initiated in the block. Some HWCs have already started organizing camps, however population-based screening as envisaged under the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) is yet to be initiated in the block. Other key findings from this study were that daily reporting on the online portal is not streamlined and is not being done in all HWCs. Some CHOs are facing connectivity and technical issues in daily reporting. Apprehensions about data sharing between ASHAs/ANMs and CHOs were also noted.

4. Access to equipment, medicines & supplies

It was reported that the key equipment used in PBS for DM and HTN are provided under the NPCDCS program and renewed depending upon the demand of PBS districts. The maintenance expenditures of equipment are also covered. Respondent told that apart from NPCDCS, there is provision for these equipment's under the funds for HWC as well. It was told that medicines for DM and HTN are covered as part of essential drug list and available at health facilities. It was explained that as and when required the demand for these medicines is put by either pharmacist or MO. However, procedural delays in the supply chain of equipment were mentioned as a challenge. Based on block level assessment of HWCs in Punjab (41), screening for diabetes was being performed at nearly 50% of the HWCs, the others were not able to perform diabetes screening due to lack of glucometers or testing supplies. To further assess the provision of diabetes and hypertension screening, the status of availability of glucometers and blood pressure apparatus was checked. It was found that while BP apparatus was available at most HWCs (in 3 it was available at the collocated SHC), glucometer was not available at 50% centres. Even within the 13 where it was available, in 2 it was used only by the ANM, in 1 it was available at SHC and in 1 it was outsourced from a private laboratory. Another important challenge noted was related to procurement to medicines, noted in many of other studies (40, 43-45). Conditions like diabetes and hypertension require life-long treatment and hence warrant continued access to medicines. Ensuring uninterrupted supply of medicines and laboratory supplies is one of key pillar for any screening program (46).

5. Health Financing for PBS

No challenges in regard to funding for PBS were reported by the respondents in their interviews from any of the two states. It was told that PBS received funds under NPCDCS program and usually the funds budgeted in program implementation plan (PIP) for the states were approved by the centre on a yearly basis. In case any new activity was to be planned under PBS for example IEC then a justification for the same was provided by the state for the same in PIP. However, in an assessment study of ASHA in a district in Punjab (47), it was found that performance-based incentives are primary method of payment being followed in the state. These incentives are given for multiple health activities including screening related activities like listing for population-based screening, follow-up. Low satisfaction levels regarding payment system by ASHA (65.5%) was noted in this study. Another key finding was that 96% of ASHA reported despite ever-increasing work load and efforts, the amount of incentives received by them were very low. Lack of clarity regarding team incentives was also reported in assessment on HWC in Punjab (41).

6. Governance

Monitoring of the PBS process is done through monthly meetings at various levels of care, uploading of information in the web portals of NCD and HWC. Supportive supervision is also done at sub health centres for PBS. At block level, Block SMO is the nodal person that monitors and does regular follow ups with CHO for PBS under HWC. Further, District Family Planning Officers monitor PBS process at district level. While program officers at state level for NCD and HWC oversee the subsequent levels for PBS program. Feedback mechanisms for PBS health providers occur through monthly review meetings at district and state level. As part of quality assurance, SOPs for PBS are distributed by the state to various levels of facilities for ASHA and ANM. It was noted that PBS is being carried out under NCD and under camp mode in HWC. CHOs are encouraged to conduct camps and integrate with existing process of PBS being done by ANM. However, there is no clarity on how this is to be done as noted in block assessment study on HWC by CHO as the HWC needs to be open as well. Moreover, the supply of equipment and supplies is mainly with ANM under NCD program so at times this may lead to discord between the ANM and CHO. Further, it was told that lack of clear guidelines on their roles and responsibilities leads to inter-personal altercations between the ANM and CHO at times. Lack of clear guidelines for parallel programs of NCD and HWC at the state level also leads to overlap in work and may promote discord. Lack of proper monitoring and reporting systems was also noted as one of the key challenges in our study. This finding was in concurrence with other studies with similar settings (48). The Medical Officer at PHC is also provided reporting formats for patient and referral tracking for those who were screened; gaps in reporting on the same had been noted.

II. Policy Implications & Conclusion

This study explored potential health system challenges and opportunities that need to be considered for PBS from the health system perspective. There are potential challenges existing in various aspects of PBS; however, some focus areas as opportunities were also recognized:

- Improving coverage rates for screening, subsequent referral for confirmatory testing and put on treatment
- Focussing on follow up of those who started on treatment and how to achieve control for the disease conditions
- Assessing cost-effectiveness of annual screening
- Assessing on screening for complications
- Promoting the prevention programs and increasing awareness for diabetes and hypertension
- Improving the reporting formats to avoid the multiplicity in reporting
- Functioning of NCD clinics to ensure early treatment
- Incorporating formats that facilitate in capturing data regarding incidence and can be of subsequent policy use
- Understanding the PBS with equity lens to assess any improvement in access to vulnerable populations

In summary, we report on the current scenario of PBS implementation and explored on the health system challenges and opportunities in regard to the existing program. Given the escalating dual burden of DM and HTN, and the current challenges noted in the provision of PBS program, there is a need to focus on addressing the same for providing quality services to patients with effective strengthening of primary health care. However, there is little empirical information about the benefits of such population based screening within current health care systems in developing countries (16).

Interventions that focus on the primary prevention like lifestyle management, health education and counselling should be the mainstay focus to ensure healthy lives. However, this may require further research to fully understand the factors responsible in detail as it has implications for additional resource allocations and other commitments. Our findings may be useful to policy-makers and implementers for future planning and assessment of the program.

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