

CHAPTER 1

INTRODUCTION

1.1 THE BURDEN OF DIABETES

Type II Diabetes Mellitus (T2DM) is a serious and escalating health burden in the world. According to the International Diabetes Federation (IDF) Diabetes Atlas (International Diabetes Federation, 2019b), the worldwide estimate of individuals with diabetes is 463 million in the year 2019, and it is expected to increase to 578 million by 2030 and to 700 million by 2045. Table 1, extracted from the IDF Diabetes Atlas 2019, shows the major regions of the world and their current and expected diabetes numbers.

Table 1: Worldwide prevalence of diabetes in millions of people (age-adjusted comparative prevalence)

Region	2019	2030	2045
Worldwide	463 (8.3%)	578 (9.2%)	700 (9.6%)
South-East Asia (incl. India)	88 (11.3%)	115 (12.2%)	153 (12.6%)
Europe	59 (6.3%)	66 (7.3%)	68 (7.8%)
North America and Caribbean	48 (11.1%)	56 (12.3%)	63 (13%)
South and Central America	32 (8.5%)	40 (9.5%)	49 (9.9%)
Africa (excl. North Africa)	19 (4.7%)	29 (5.1%)	47 (5.2%)
Middle East and North Africa	55 (12.2%)	76 (13.3%)	108 (13.9%)
Western Pacific (includes China, SE Asia, Japan, Korea, Australia and NZ)	163 (11.4%)	197 (12.4%)	212 (12.8 %)

The human impact of diabetes is dire. It is estimated that 4.2 million adults aged 20 – 79 years will die as a result of diabetes and its complications in 2019 – equivalent to one death every 8 seconds. Diabetes is estimated to be associated with 11.3% of global deaths from all causes among people in this age group.

The economic impact of diabetes is equally huge. In 2019, IDF estimates that the total diabetes related health expenditure worldwide is USD 760 billion (International Diabetes Federation, 2019a). The indirect cost of diabetes – from labour-force drop out, mortality, etc. – is estimated to be 34.7% of the direct cost (Bommer et al., 2017), which brings the total to USD 1.16 trillion. This represents 1.3% of the world GDP.

To summarize: in 2019, approximately one in 12 people in the world would have had diabetes; one in 9 deaths would have been from diabetes, and USD 1.30 of every USD 100 produced in the world would have been spent on diabetes care.

India is home to the second largest number of adults with diabetes in the world, with an age-adjusted comparative prevalence of 10.74%. Over 77 million people have been diagnosed with the disease, with more than 1 million deaths attributable to diabetes or related complications. Over USD 7 billion was spent in direct costs relating to diabetes care (International Diabetes Federation, 2019a), which constitutes 0.26% of the national GDP. Each of these numbers is expected to increase.

Recognizing this, the National Health Policy 2017 of India aimed to increase screening and treatment of 80% of people with diabetes and reduce premature deaths from diabetes by 25% by 2025 (Govt of India, Ministry of Health. National Health Policy 2017). In order to bring this vision to fruition, there is need for rapid progress along four dimensions.

The first dimension is **prevalence**. It is imperative that we have a robust estimate of the magnitude of diabetes and its risk factors across the country so that proper policies can be setup to respond to this epidemic. The second dimension is **screening**, to determine individuals that are at high risk. While screening is an essential component of any policy level response to diabetes, it is especially important for the Indian population, as it has been reported in multiple studies that Asian Indians have one of the highest global rates of progression from prediabetes

to diabetes (Dutta & Mukhopadhyay, 2016). The third dimension is **prevention**. There is urgent need for evidence based interventions for diabetes risk reduction that are effective in a large community based setting. The final dimension is **treatment**. In addition to standard care, there is need for a cost effective lifestyle intervention which helps bring about glycemic control for individuals with diabetes.

The practice of Yoga, comprising *āsanas* (physical exercises), *prāṇāyāma* (breathing techniques) and meditation, along with strong behavioral components of self-regulation derived from ethical concepts of *Yamas* and *Niyamas* (Gard, Noggle, Park, Vago, & Wilson, 2014) has the potential to be universally available, cost-effective, and sustainable intervention strategy for prevention and treatment of diabetes. The impact of yoga on various risk factors that lead to insulin resistance (a precursor to type 2 diabetes) has been studied extensively (a complete review of these studies is done in Chapter 3 of this report); taken together these studies provide a strong basis to assert that Yoga can reduce diabetes risk. In addition, a few studies have directly explored the extent of diabetes risk reduction effected by Yoga practices (Jyotsna, 2014; McDermott et al., 2014). Several studies have also investigated the impact of yoga practice on the health of adults with T2DM and have found significant improvements in multiple health outcomes including glycemic control (Vizcaino & Stover, 2016).

While there is preponderance of evidence indicating that Yoga can be a very effective intervention to reduce diabetes risk among high-risk populations and to effect glycemic control among individuals with diabetes, there are no large scale studies that have proven the its efficacy in a large community setting. As a result, two key questions lack satisfactory answers: (a) while Yoga positively impacts several diabetes risk-factors, does it in fact reduce risk of diabetes progression? (b) is Yoga suitable as an intervention in the setting of a large community, in the sense of being accessible to most people, doesn't require specialized

equipment or setting, can be practiced with minimal instruction, and is safe for most body types?

In this report, we will explore these two questions and offer evidence that not only does Yoga reduce diabetes risk reduction and effect glycemc control but is also suitable as an intervention in a large community setting.

1.2 DEFINING THE PROBLEM

To understand the scope of the problem, it useful to delineate the populations that are of interest to us. This is shown in the left side of Fig 1. The blue square is the entire Indian population. The red circle marked **A** is the population of individuals with diabetes. Within this population are a number of people who've already been

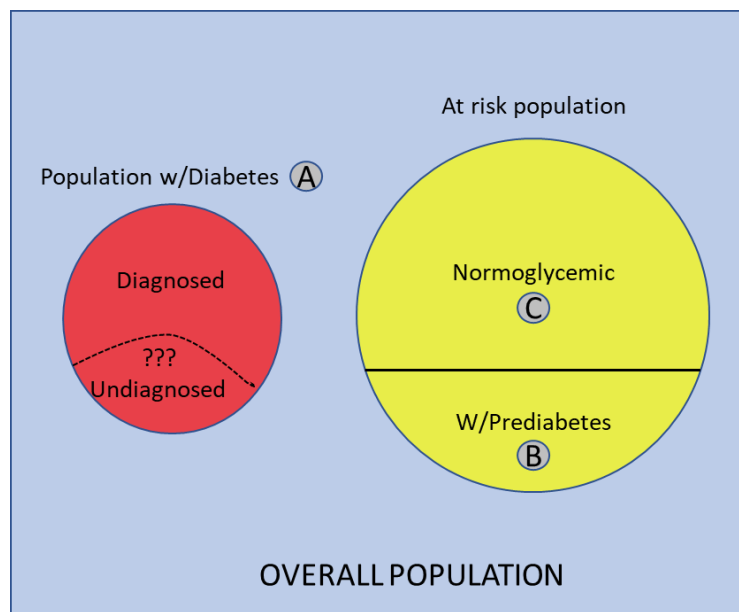


Figure 1: Various populations involved in tackling the problem of diabetes

diagnosed; but there remain a number of people who are undiagnosed. This is of course always the case within any population; but given that the pace of diabetes testing has not kept up with the spread of the epidemic, it is suspected that the number of undiagnosed individuals is high enough that the true magnitude of diabetes burden is unknown. This is the problem of prevalence determination: to have a robust nationwide estimate of the area of circle **A**.

The yellow circle on the right in Fig 1 is the population that is at risk of getting diabetes. This population falls into two categories: (a) those who have normal levels of serum glucose but have risk factors for diabetes (e.g. family history, obesity, sedentary lifestyle, etc.) – this is the

area marked **C** (b) those for whom serum glucose is in prediabetes range – this is the area marked **B**. The working assumption is that people progress from **C** to **B** to **A**. Given that Asian Indians are known to be at higher risk of progression from prediabetes (**B**) to diabetes (**A**), and it is not practical to test the entire population for prediabetes, there is need for an effective screening test to determine who is at high risk (**C**).

Once we have estimated the area of **A** (prevalence) and determined accurate ways of determining who belongs in **C** (screening), then the next step is to find cost-effective interventions to reduce the risk of progression from **C** or **B** to **A** (prevention). For individuals who are already in **A**, there is need to find evidence-based lifestyle protocols that form an effective complement to standard care to maintain glycemic control (treatment).

1.3 NIYANTRITA MADHUMEHA BHĀRATA ABHIYĀN (DIABETES

FREE INDIA) STUDY

To tackle all four dimensions of the public health challenge facing India's diabetes epidemic, a large study was conducted in 2017. Known as *Niyantrita Madhumeha Bhārata Abhiyān* (Diabetes Free India) and commonly abbreviated as **NMB 2017**, its objectives were (a) estimate the prevalence of diabetes simultaneously in all zones of India; (b) to use the pan-Indian data to improve existing diabetes screening methods; (c) to conduct a cluster randomized controlled trial (RCT) to document the efficacy of a yoga-based lifestyle module for both diabetes prevention among high-risk individuals, and as an adjunct to standard treatment for bringing about normoglycemic outcome in individuals with diabetes (Nagarathna, et al., 2019; Nagendra et al., 2019).

NMB used several innovative approaches to preserve accuracy and ensure cost-effectiveness. It employed a cluster sampling method in the screening stage, followed by selection of at risk candidates at the ward or village level for the lifestyle intervention trial. This approach enabled

researchers to answer more than one research question at once. NMB also employed parallel sampling to increase sampling rate; to reduce interrater variation, the volunteers involved in data gathering underwent specialized training, with consistency checks built into various levels.

The sophisticated design of NMB 2017 allowed researchers to investigate the following:

1. What is the prevalence of diabetes in India (i.e. an estimate of the area of **A** in Fig 1)?
2. How to increase the accuracy of existing diabetes screening scores (i.e. inclusion criteria for region **C** in Fig 1)
3. The efficacy of Yoga to prevent diabetes
 - a. Does it reduce the risk of progressing from prediabetes to diabetes (**B** → **A**)?
 - b. Does it accelerate regression to normoglycemia among people with prediabetes? (**C** → **B**)
 - c. Does it reduce the risk of progressing from high-risk to diabetes (**C** → **A**)?
4. The efficacy of Yoga as a complement to standard care for individuals with diabetes: when so implemented, does it help bring about glycemic control among individuals with diabetes?

1.4 SCOPE OF THIS THESIS

Among individuals with prediabetes, the efficacy of Yoga in reducing the risk of progression to diabetes (3.a) and the accelerated regression to normoglycemia (3.b) have been reported elsewhere (Nagarathna, Venkata S Ram, et al., 2019).

In this thesis, we consider the following 3 questions:

- Improving existing screening methods to determine diabetes risk (question 2)
- The ability of yoga in reducing risk of progression from high risk (but still normoglycemic) to diabetes (question 3.c);

- The efficacy of yoga as an adjunct modality to standard care bringing about glycemic control (question 4)

1.5 DIABETES SCREENING

Many screening models have been developed to assess diabetes risk. Some common models include the German Diabetes Risk Score (Schulze et al., 2007), Cambridge Risk Score (Griffin, Little, Hales, Kinmonth, & Wareham, 2000), Framingham Offspring Diabetes Risk Score (Wilson et al., 2007), and the Finnish Diabetes Risk Score (Lindström & Tuomilehto, 2003). In India, the most commonly used screening model is the Indian Diabetes Risk Score (IDRS) (Mohan, Deepa, Deepa, Somannavar, & Datta, 2005).

Each of these is a multivariate score derived from several diabetes risk factors. Most of them include family history, physical activity, age, and obesity. A review of some of the used scores is provided in section 3.2.

Incorporating age and physical activity into these risk scores is straightforward; there also exist well established methods for how to categorize levels of physical activity and measure risk from these categories. However, measurement of obesity has turned out to be much harder. Specifically, it is unclear whether Waist Circumference (WC) or Body Mass Index (BMI) is a better measure of obesity in terms of capturing diabetes risk, as various studies in this area report conflicting results regarding the efficacy of each (Alperet, Lim, Mok-Kwee Heng, Ma, & van Dam, 2016; Hartwig et al., 2016; He et al., 2015; Kobayashi, Chan, & Fuller-Thomson, 2018; McKeigue, Shah, & Marmot, 1991; Nyamdorj, 2008; Okosun, Liao, Rotimi, Choi, & Cooper, 2000; Qiao & Nyamdorj, 2010; Wannamethee et al., 2010; Yang et al., 2018).

The screening scores mentioned above use either WC or BMI as the obesity component (Ahirwar & Mondal, 2019). But given that there are conflicting results as to which of these measures is a better determinant of diabetes risk, it stands to reason that having an improved

obesity metric is a very effective way of improving these screening scores. Furthermore, the requirement is that the improved obesity metric be a *field measure* – i.e. one that can be easily measured without resorting to specialized equipment and/or needing specialized training. In other words, it should be anthropometric in nature. We started with the assumption that *both* WC *and* BMI were effective, but were incomplete when used in isolation. Thus, our aim was to combine them into a composite measure which, we reasoned, would better capture the risk of diabetes. To this end, we had the dual objectives of doing a risk analysis of the new obesity measure (which was called BMI_{WC}), and also to incorporate this measure into IDRS and determine if the modified IDRS (which we called IDRS_{BMIWC}) was a better diabetes screening score as compared to the original IDRS.

1.6 DIABETES PREVENTION AND GLYCEMIC CONTROL

1.6.1 Current Approaches

Among the population that has been determined to be high-risk for diabetes, including those that are in the prediabetes stage, a large variety of pharmacological agents have been tried in order to halt or at least slow down the progress to diabetes. These include pioglitazone, acarbose, voglibose, valsartan, orlistat, colesvelam, glucagon-like peptide analogues, curcumin, and vitamin-D (Chuengsamarn, Rattanamongkolgul, Luechapudiporn, Phisalaphong, & Jirawatnotai, 2012; Dutta et al., 2013, 2014; Handelsman, 2009; Smith-Marsh, 2013). However, they lack convincing evidence for reducing the risk of progression to diabetes. Currently, lifestyle interventions followed by metformin are the best established options for the prevention of T2DM among high-risk individuals (Knowler et al., 2002).

For individuals diagnosed with T2DM, glycemic control is one of the most important outcomes of treatment. In addition to pharmacological agents, exercise and nutrition are important adjuncts to achieving and maintain glycemic control. Exercise – a specific form of physical

activity that is structured and designed to improve physical fitness – has been shown to improve glycemic control among individuals with T2DM (American Diabetes Association, 2017). Nutritional therapy, including portion control, plant based diets, emphasis on whole grains, avoidance of sugar sweetened beverages, have shown great benefit in achieving glycemic control (American Diabetes Association, 2017). These lifestyle modifications need robust behavioral change strategies in order to sustain clinical outcomes (Baker, Simpson, Lloyd, Bauman, & Singh, 2011)

Diabetes prevention and treatment, when limited solely to pharmacological agents, represents a significant financial burden on both the individual and on the public health coffers. Exercise and nutrition therapy, while proven adjuncts to pharmacological agents in bringing about glycemic control, are often out of reach for many segments of the population and/or have proven difficult to sustain over the long run. As a result, it is of urgent need to implement additional evidence-based interventions that are cost-effective, accessible, and can offer preventative and glycemic control benefits.

1.6.2 The role of Yoga

Yoga is an ancient practice whose goal is to transcend body-consciousness, silence the mind, and still the waves of feeling. As Maharshi Patanjali says at the beginning of the *Yoga Sūtras* (Satchidananda, 2004):

योगस्चीत्त वृत्ति निरोधः

Yogascitta vṛitti nirodhaḥ

(Yoga Sūtras 1:2)

Yoga is the mastery over modifications of mind.

While this is the larger goal of Yogic practices, Yoga has been shown to have many benefits related to physical health and mental well-being. In fact, a careful study of Yogic scriptures

show that the core practices of Yoga, namely *āsanas* (physical postures), *prāṇāyāma* (practices to control vital energy), *ṣaṭ-karmas* (purification practices), *mudras* and *bandhas* (advanced practices to redirect the flow of inner vitality), and *dhyāna* (meditation) help reduce obesity, mitigate effects of chronic stress, help one become more physically active, and achieve sustained habit change towards better nutrition – each of which is a reduction of a diabetes risk factor.

Scientific studies have validated these scriptural claims, reporting salutary effects of Yogic practices on reducing obesity (Cramer, Thoms, Anheyer, Lauche, & Dobos, 2016; Kristal, Littman, Benitez, & White, 2005; Rshikesan, Subramanya, & Nidhi, 2016; Seo et al., 2012; Telles, Naveen, Balkrishna, & Kumar, 2010), sustaining an active lifestyle (Lian et al., 2017; Petracovschi, 2017; Watts, Rydell, Eisenberg, Laska, & Neumark-Sztainer, 2018), improving dietary habits (Monk-Turner & Turner, 2010; Palasuwan, Margaritis, Soogarun, & Rousseau, 2011; Ross, Friedmann, Bevans, & Thomas, 2012; Satin, Linden, & Millman, 2014; Watts et al., 2018), reducing levels of glucocorticoids which in turn have a salutary effect on the levels of serum glucose in the blood (Banasik, Williams, Haberman, Blank, & Bendel, 2011; García-Sesnich, Flores, Ríos, & Aravena, 2017; Jevning, Wilson, & Davidson, 1978; Katuri et al., 2016; Sudsuang, Chentanez, & Veluvan, 1991; Thirthalli et al., 2013; Vadiraja et al., 2009), and increasing insulin sensitivity (Innes, Bourguignon, & Taylor, 2005; Nidhi, Padmalatha, Nagarathna, & Ram, 2012; S. Singh, Kyizom, Singh, Tandon, & Madhu, 2008). A comprehensive review of 46 controlled trials (Nagendra, More, Kumar, Jagannathan, & Raghuram, 2017) concluded that Yoga practice demonstrated a significant improvement in primary outcome measures such as blood glucose levels, along with significant improvements in cardiac autonomic variables, lipid profile, liver enzymes, respiratory variables, quality of life, anxiety, and depression.

Taken together, there is preponderance of scriptural and scientific evidence that Yoga can be very effective in both diabetes risk reduction and glycemic control. However, as mentioned in the introductory section, there are no studies to date that actually demonstrate this small cohorts and/or controlled settings. From a public health perspective, it is important for a lifestyle intervention to be accessible, simple, and inexpensive (in addition to being clinically effective) in order for it to be useful. Our sister study demonstrated the effectiveness of Yoga in in a large community setting for individuals with prediabetes (Nagarathna, Venkata S Ram, et al., 2019) Our aim was to demonstrate this for high risk individuals with normal glycemic levels, and for individuals with diabetes.