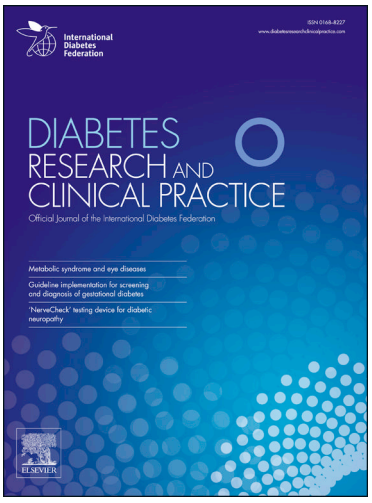

Isolated HbA1c identifies a different subgroup of individuals with type 2 diabetes compared to fasting or post-challenge glucose in Asian Indians: The CARRS and MASALA Studies

U.P. Gujral, D. Prabhakaran, R. Pradeepa, N.R. Kandula, D. Kondal, M. Deepa, N.A. Zakai, R.M. Anjana, G. Rautela, V. Mohan, K.M.V. Narayan, N. Tandon, A.M. Kanaya

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Isolated HbA1c identifies a different subgroup of individuals with type 2 diabetes compared to fasting or post-challenge glucose in Asian Indians: The CARRS and MASALA Studies

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Abstract

Aims: Guidelines recommend hemoglobin A1c (HbA1c) as a diagnostic test for type 2 diabetes, but its accuracy may differ in certain ethnic groups.

Methods: The prevalence of type 2 diabetes by HbA1c, fasting glucose, and 2 hour glucose was compared in 3,016 participants from Chennai and Delhi, India from the CARRS-2 Study to 757 Indians in the U.S. from the MASALA Study. Type 2 diabetes was defined as fasting glucose ≥ 7.0 mmol/L, 2-hr glucose ≥ 11.1 mmol/L, or HbA1c ≥ 6.5%. Isolated HbA1c diabetes was defined as HbA1c ≥ 6.5% with fasting glucose <7.0 mmol/L and 2hr glucose < 11.1 mmol/L.

Results: The age, sex, and BMI adjusted prevalence of diabetes by isolated HbA1c was 2.9% (95% CI: 2.2-4.0), 3.1% (95% CI: 2.3-4.1), and 0.8% (95% CI: 0.4-1.8) in CARRS-Chennai, CARRS-Delhi, and MASALA, respectively. The proportion of diabetes diagnosed by isolated HbA1c was 19.4%, 26.8%, and 10.8% in CARRS-Chennai, CARRS-Delhi, and MASALA respectively. In CARRS-2, individuals with type 2 diabetes by isolated HbA1c milder cardio-metabolic risk than those diagnosed by fasting or 2-hour measures.

Conclusions: In Asian Indians, the use of HbA1c for type 2 diabetes diagnosis could result in a higher prevalence. HbA1c may identify a subset of individuals with milder glucose intolerance.

Keywords: Type 2 Diabetes, HbA1c, diagnostic criteria

Introduction

Measurement of fasting plasma glucose (FPG) and/or 2-hour post challenge glucose (2hPG) levels have traditionally been the cornerstone of the diagnosis of diabetes mellitus (DM) [1]. In 2009 an international expert committee recommended the use of HbA1c as an additional diagnostic criterion for DM [2] and it is now recommended as a diagnostic tool by both the American Diabetes Association and the World Health Organization [3,4]. While HbA1c is now often used in clinical practice, it is possible that the pathophysiological mechanisms of type 2 diabetes development may differ in those identified by HbA1c compared to fasting or 2-hour glucose measures, and its accuracy as a diagnostic tool has not been well tested in populations such as Asian Indians, a group with particularly high type 2 diabetes risk [5,6]. We aimed to compare HbA1c as a diagnostic tool with fasting plasma glucose and 2-hour post-challenge glucose measurements in assessing the prevalence of type 2 diabetes in two South Asian populations. One population was from two geographic centers in India (from the **C**enter for c**A**rdio-metabolic **R**isk **R**eduction in **S**outh Asia (CARRS-2) study) [7], and the other from two geographic centers in the United States (from the **M**ediators of **A**therosclerosis in **S**outh **A**sians **L**iving in **A**merica (MASALA) study) [8].

Methods

We conducted a cross-sectional analysis of data from two large, population-based cohorts, one in India and one in the United States. In total, 1,568 participants living in Chennai, India and 1,448 participants living in New Delhi, India from the CARRS-2 Study were compared with 757 Asian Indian immigrants in the MASALA Study.

Description of Participants

The CARRS-2 Study

In brief, CARRS-2 is a multi-site cross-sectional study recruiting participants from the cities of Chennai and New Delhi in India and Karachi in Pakistan. Study design and recruitment for CARRS-2 was methodically akin to that of CARRS-1 which was conducted in 2010-2011 [7]. For the purposes of this study we analyzed data only from the Chennai and New Delhi sites in order to limit our analysis to Asian Indians. This was done in order to remain in accordance with MASALA which had very few participants with origins from Pakistan. Recruitment occurred between September 2014 and March 2016. A multi-stage random sampling technique was used to select households for participation in order to be representative of Delhi and Chennai. In order to reduce selection bias, two adults, one male and one female, aged 20 years or older were selected from each household. In households with more than two eligible members, the "Kish method" was applied to determine enrollment [9]. Recruitment, enrollment, and data collection were collected through three visits to each participant's place of residence. In order to maintain valid comparisons with MASALA, we excluded participants who were younger than age 40 and/or who had existing cardiovascular disease as ascertained through self-report. Pregnant women and bed-ridden individuals were excluded from study enrollment [7].

Demographic and behavioral information including language use, medical history, current medication use, and use of alcohol and tobacco were obtained using standardized questionnaires administered by trained interviewers. Physical activity was assessed using the Global Physical Activity Questionnaire (GPAQ). Blood pressure was assessed using an electronic sphygmomanometer (Omron HEM-7080 and HEM-7080IT-E; Omron Corporation,

Tokyo, Japan). Three seated measurements were taken, and an average of the three was used to assess systolic and diastolic blood pressure. After an 8-12 hour overnight fast, a 75g oral glucose tolerance test (OGTT) was administered to participants without previously diagnosed diabetes who were willing and able to participate. Blood samples were obtained from a peripheral vein just before glucose ingestion (fasting) and at 30 minutes and 2-hours post glucose challenge for plasma glucose measurements. The samples were transported from field sites in cold chain to the laboratories for analysis. Both accredited laboratories in Delhi and Chennai participated in a Randox International Quality Assessment Scheme (RIQAS) that standardized findings to a central laboratory at the All India Institute of Medical Sciences (AIIMS) in Delhi. Blood samples were analyzed on the same day as they were collected. For the three cities together (including Karachi, Pakistan), response rates were 94.7% for questionnaire completion and 84.3% for bio-specimens. Total cholesterol was measured by enzymatic colorometric cholesterol oxidase peroxidase method, high-density lipoprotein cholesterol by direct method, and triglycerides by enzymatic methods using Roche/Boehringer-Mannheim Diagnostics. Low-density lipoprotein cholesterol cholesterol was calculated using Friedewald's formula.

Plasma glucose was measured by hexokinase/kinetic method, and glycated hemoglobin (HbA1c) was measured by high performance liquid chromatography (HPLC). Insulin was measured using the electro chemiluminescence immune assay (ECLIA). Participant weight was measured using body composition analyzers (Tanita BC-601), and height was measured using a portable stadiometer (SECA-213). BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured using a non-stretch measuring tape

(SECA-201) at the site of maximum circumference halfway between the lower ribs and the anterior superior iliac spine.

MASALA Study

The design, sampling strategy, recruitment, enrollment, and both questionnaire and examination components of the MASALA study have been described previously [8]. Briefly, MASALA is a community-based sample of South Asian Americans living in the greater San Francisco Bay and Chicago areas. Participants were aged 40-84 years, and are without previously known cardio-vascular disease. Recruitment occurred between October 2010 and March 2013. All participants were screened by telephone and were invited to either the University of California, San Francisco, or the Northwestern University clinical field center for a 6-hour baseline clinical examination [8].

South Asian ethnicity was self-reported and defined as having 3 or more grandparents born in either India, Pakistan, Nepal, Bangladesh, or Sri Lanka. However, for the purposes of this study in order to remain in accordance with CARRS, we limited our sample to the 757 individuals who were born in India specifically. Individuals with previous diagnosis of heart attack, stroke, transient ischemic attack, heart failure, angina, nitroglycerin medication use, any prior cardiovascular procedures, current arterial fibrillation, cancer treatment, shortened life expectancy, impaired cognition, plans to move out of the geographic area of the study site in the next five years, living in a nursing home, or weight > 300 pounds were excluded from study enrollment [8].

Demographic and behavioral information including language use, medical history, current medication use, and use of alcohol and tobacco were obtained using standardized

questionnaires administered by trained interviewers. Physical activity was assessed using the Typical Week's Physical Activity Questionnaire [10]. After a 5-minute seated rest, blood pressure was assessed using an automated blood pressure machine (V100 Vital Sign Monitor; GE Healthcare, Fairfield, CT, USA). Three seated measurements were taken, and an average of the last two readings was used to assess systolic and diastolic blood pressure. After at least a 9 hour overnight fast, a 75g oral glucose load was administered to participants without previously diagnosed diabetes who were willing to participate. Blood samples were obtained from a peripheral vein just before glucose ingestion (fasting) and at 30 minutes and 2-hours post glucose challenge. Plasma glucose was measured using the hexokinase method. Fasting serum samples were batched for insulin measured by the sandwich immunoassay method (Roche Elecys 2010; Roche Diagnostics, Indianapolis, IN). HbA1c was measured using the immunoturbidimetry assay. Total cholesterol, triglycerides, and high density lipoprotein cholesterol were analyzed using enzymatic methods and low-density lipoprotein cholesterol was calculated using the Friedewald equation.

Participant weight was measured using a standing balance beam scale or digital weighing scale, and height was measured using a stadiometer. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured by trained study staff using a non-stretch tape measure at the site of maximum circumference halfway between the lower ribs and the anterior superior iliac spine. Two measures were taken and the average was used for analysis. Computed tomography (CT) scans of the abdomen (Philips Medical Systems, Andover, MA; Toshiba Medical Systems, Tustin, CA; Siemens Medical Solution Malvern, PA) were used to assess visceral, subcutaneous, and intermuscular fat mass. Non-contrast cardiac CT

images using a cardiac-gated CT scanner (UCSF: Phillips 16D scanner or Toshiba MSD Aquillion 64; NWU: Seimens Sensation Cardiac 64 Scanner) were obtained to assess pericardial fat volume and hepatic fat attenuation.

Informed consent and ethics committee approval

The CARRS-2 study was approved by the Institutional Review Boards of the Public Health Foundation of India, New Delhi, All India Institute of Medical Sciences, New Delhi, Madras Diabetes Research Foundation, Chennai, India, Aga Khan University, Karachi, Pakistan, and Emory University, Atlanta, USA [7]. The MASALA Study was approved by both the Univeristy of California San Francisco and Northwestern University Institutional Review Boards [8].

Definition of Type 2 Diabetes

In order to assess the prevalence of newly diagnosed type 2 diabetes by glycemic measure, we excluded individuals with a previously known diagnosis of diabetes who were taking any glucose lowering medication (n= 1,728 for CARRS and n= 124 for MASALA). We further excluded those who were missing fasting glucose, 2-hour glucose or HbA1c data from the CARRS-2 (n=6,880) and the MASALA (n=28) cohorts. A new laboratory diagnosis of type 2 diabetes was made if fasting glucose ≥ 7.0 mmol/L, 2-hr post challenge glucose ≥ 11.1 mmol/L and/or HbA1c ≥ 6.5%. Isolated fasting type 2 diabetes was defined as fasting glucose ≥ 7.0 mmol/L; HbA1c < 6.5%; and 2hr glucose < 11.1 mmol/L. Isolated 2-hr post challenge type 2 diabetes was defined as 2hr glucose ≥ 11.0 mmol/L; fasting glucose < 7.0 mmol/L, HbA1c < 6.5%. Isolated HbA1c type 2 diabetes was defined as HbA1c ≥ 6.5%; fasting glucose <7.0 mmol/L and 2hr glucose < 11.1 mmol/L [3]. Normal glucose tolerance was defined as those

participants who had both fasting plasma glucose <5.6 mmol/l and a 2 hour post-challenge glucose <7.8 mmol/l, as well as HbA1c < 5.7% [3].

Calculations

Beta-cell function was estimated by the oral disposition index (DI_o) and was calculated as $(\Delta I_{0-30}/\Delta G_{0-30})$*(1/fasting insulin) [11], and by HOMA-β, [20*I_0(μIU/ml) / G_0 (mmol/l)- 3.5] [12]. HOMA-IR was used to measure insulin resistance and calculated as [I_0(μIU/ml) * G_0 (mmol/l)/22.5] [12]. Given that fasting and 30-minute insulin measures were not available for the CARRS-2 Chennai site, we calculated disposition index, HOMA-β and HOMA-IR for the CARRS-2 Delhi and MASALA sites only.

Statistical Analysis

Prevalence values and 95% confidence intervals were estimated by glucose measure and study site. Participant characteristics of those with type 2 diabetes were stratified by glycemic measure and study site and were compared by study using chi-squared test or ANOVA as appropriate. The non-normally distributed variables were log transformed. The effect of isolated HbA1c on the odds of type 2 diabetes compared to normal glucose tolerance or prediabetes was assessed using standardized logistic regression. Initially, a regression model was created to compare the odds of having diabetes diagnosed by isolated HbA1c compared to no diabetes after adjusting for age and sex. Subsequent multivariable models were then created to adjust for additional variables including education physical activity smoking status, body mass index, blood pressure, cholesterol triglycerides, insulin resistance, beta-cell function, and vegetarian diet. In MASALA, an additional model was run to adjust for adiponectin, resistin, and ectopic fat. All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Table 1 provides details on the prevalence of type 2 diabetes by diagnostic criterion and study site. The age, sex, and BMI adjusted prevalence of any newly diagnosed type 2 diabetes was 18.2% (95% CI: 15.8-20.9) in CARRS-2 Chennai, 14.0% (95% CI: 12.0-16.4) in CARRS-2 Delhi, and 12.5% (95% CI: 9.6-16.4) in MASALA. If using isolated elevated HbA1c to define type 2 diabetes, the age, sex, and BMI adjusted prevalence was 2.9% (95% CI: 2.2-4.0), 3.1% (95% CI: 2.3-4.1), and 0.8% (95% CI: 0.4-1.8) in CARRS-Chennai, CARRS-Delhi, and MASALA, respectively. In both sites in India, the prevalence of type 2 diabetes diagnosed by HbA1c was greater than the prevalence as diagnosed by fasting glucose or 2-hr post challenge glucose. Figure 1 provides details about the proportion of diabetes diagnosed by each glycemic measure by study site. In CARRS-2 Chennai, 19.4% of type 2 diabetes cases were diagnosed by isolated HbA1c, while 26.8% of type 2 diabetes cases were diagnosed by isolated HbA1c in CARRS-2 Delhi. In MASALA, 10.8% of the new type 2 diabetes cases were diagnosed by isolated elevated HbA1c.

Participant characteristics by glycemic status and study population are shown in Tables 2 and 3. In CARRS-2, compared to those with type 2 diabetes diagnosed by either the fasting or 2-hour glucose criteria, those with type 2 diabetes as diagnosed solely by HbA1c were significantly older, with a greater proportion consuming a vegetarian diet. They also had lower mean systolic and diastolic blood pressure, fasting glucose, 30-minute glucose, 2-hour post challenge glucose, HbA1c value and triglycerides. In a subset of individuals from the Delhi site only, those with type 2 diabetes diagnosed by isolated HbA1c had significantly lower HOMA-IR, higher HOMA-β, and higher mean disposition index compared to those with type 2 diabetes diagnosed by either

of the glucose measures. We compared the characteristics of type 2 diabetes diagnosed by isolated elevated HbA1c to type 2 diabetes diagnosed by HbA1c and with either glucose criterion in CARRS-2 participants (Supplemental Table 1). Those diagnosed by HbA1c and a glucose criterion more closely resembled those diagnosed by fasting or 2-hour glucose measures compared to those diagnosed by isolated elevated HbA1c.

In MASALA (Table 3), we compared the clinical characteristics of those with type 2 diabetes by either the fasting or 2-hour glucose criteria to those with type 2 diabetes as diagnosed by isolated HbA1c. Those with type 2 diabetes classified by isolated HbA1c had a significantly lower mean fasting glucose, 30-minute post-challenge glucose, 2-hour glucose, , lower cholesterol, and greater mean HOMA-β and resistin than those diagnosed by fasting or 2-hour measures. HOMA-IR was significantly lower in those with type 2 diabetes diagnosed by isolated HbA1c compared to those diagnosed by fasting glucose, however it was not significantly different in those diagnosed by 2-hour glucose. Fasting insulin was significantly higher in those with type 2 diabetes diagnosed by fasting glucose, but was not significantly different in those diagnosed by 2-hour glucose compared to those diagnosed by HbA1c. There were no significant differences in ectopic fat measures between those with type 2 diabetes diagnosed by isolated HbA1c compared to fasting or 2-hour glucose measures. As with CARRS, those diagnosed by HbA1c and another glucose criterion in MASALA more closely resembled those diagnosed by fasting or 2-hour glucose measures compared to those diagnosed by isolated HbA1c. (Supplemental Table 2)

In the CARRS-2 study, using backwards stepwise regression models including age, sex, education, physical activity, smoking status, vegetarian diet, BMI, waist circumference, systolic

and diastolic blood pressure, and HDL, LDL, and triglycerides, only age (OR 1.03; 95% CI: 1.01, 1.06) and waist circumference (per cm, OR 1.02; 95% CI: 1.00, 1.04) were significantly associated with type 2 diabetes diagnosed by isolated HbA1c compared to no diabetes. In a subset of individuals from the Delhi site only, after additional adjustment for HOMA-IR, HOMA-β, and Disposition Index, only waist circumference (OR 1.03; 95% CI: 1.01, 1.06), HOMA-IR (OR 1.31; 95% CI: 1.06, 1.62), and HOMA-β (OR 0.99; 95% CI: 0.98, 0.99) were associated with having type 2 diabetes diagnosed by HbA1c as opposed to not having diabetes.

Despite the small sample with isolated elevated HbA1c in MASALA (n=8), waist circumference (OR 1.09; 95% CI: 1.01, 1.68), HOMA-IR (OR: 2.30, 95% CI: 1.13, 4.67), and HOMA-β (OR 0.97; 95% CI: 0.94, 0.99) were significantly associated with the odds of having type 2 diabetes diagnosed by HbA1c after adjusting for all other relevant covariates in the model.

DISCUSSION

In two population-based studies of Asian Indians living in India and the United States, we found that the prevalence of type 2 diabetes was highest when diagnosed by HbA1c, followed by 2-hour post challenge glucose, and then fasting glucose measures in those living in India, and was highest by 2-hour post challenge glucose in those living in the United States. We also found that between 1.3% to 3.5% of Asian Indians met type 2 diabetes criteria solely due to an elevated HbA1c.

The prevalence of type 2 diabetes diagnosed by isolated elevated HbA1c varies by race/ethnicity, and may be higher in populations of Asian descent. In our two Asian Indian populations, we found a prevalence between 1.3 to 3.5%. Studies in other Asian populations also found a prevalence of isolated HbA1c diagnosed type 2 diabetes, similar to the range we

found in our study. A study from Korea found a type 2 diabetes prevalence of 2.1% when using isolated HbA1c as the diagnostic criterion [13], while a study in Filipino Americans, Japanese Americans, and Native Hawaiians noted a type 2 diabetes prevalence of 2.7% by isolated HbA1c [14].

The results of our study are similar to those of a previous study comparing the prevalence of type 2 diabetes by glycemic measures in Asian Indians living in Chennai [15]. In this study, the prevalence of type 2 diabetes diagnosed by HbA1c was 110% and 27% higher than the prevalence of type 2 diabetes as diagnosed by the fasting glucose and 2-hour post challenge glucose criteria respectively [15]. The current study adds to these findings by including a population from another city in India as well as a migrant Asian Indian population to the United States, thereby indicating that these findings are associated with race/ethnic background rather than geographical location. Furthermore, a study examining the effects of type 2 diabetes definition on global diabetes prevalence using a pooled analysis of 96 population-based studies found that while in general type 2 diabetes prevalence based on HbA1c was lower than the prevalence based on fasting or 2-hour plasma glucose measures , in the subgroup of studies from South Asia, the prevalence of type 2 diabetes based on HbA1c was higher than those based on fasting or 2-hour measures [16]. Similarly, a supplemental analysis of South Asians, Blacks, and Whites from a study in the U.K. showed that South Asians had a higher prevalence of HbA1c diagnosed type 2 diabetes as opposed to OGTT diagnosed type 2 diabetes when compared to other ethnic groups [17] thereby indicating that this particularly high type 2 diabetes prevalence based on the HbA1c assay may be a phenomenon unique to Asian populations.

Furthermore, while HbA1c has been shown to have high specificity but limited sensitivity for type 2 diabetes diagnosis in White, African American, Mexican American, and Brazilian populations compared to fasting and 2-hour post challenge glucose measures, [18,19], this may not be the case in certain Asian populations, where HbA1c may be overly sensitive with higher false positives.

It is also possible that in populations of Asian Indian decent, the isolated HbA1c criteria for diabetes diagnosis may identify individuals with milder glucose intolerance compared to those diagnosed with fasting or 2-hour measures. In CARRS-2, participants with isolated HbA1c had significantly lower fasting and 30-minute, and 2-hour glucose measures as well as lower mean triglyceride, lower HOMA-IR, and higher HOMA-β and disposition index measures compared to those with type 2 diabetes diagnosed by fasting or 2 hour glycemia. In MASALA, individuals with type 2 diabetes diagnosed by isolated HbA1c had lower 2-hour glucose, total cholesterol, and Apo-B and higher HOMA-β compared to those with type 2 diabetes diagnosed by fasting or 2 hour glucose measures. In addition, they also had lower fasting and 30-minute glucose as well as lower HOMA-IR compared to those with type 2 diabetes diagnosed by fasting glucose. These results are similar to a study from Chennai, India which found that participants diagnosed by the HbA1c criterion had milder glucose intolerance and lower serum triglyceride levels than those diagnosed by fasting or 2-hour post challenge measures [15]. In aggregate, these findings suggest that individuals with isolated elevated HbA1c may represent either a different subgroup of type 2 diabetes, an earlier phase in the natural history of type 2 diabetes development, or a possible misdiagnosis. Furthermore, recognizing that the relationship between

HbA1c and glucose measures may differ by race/ethnicity has clinical relevance for minimizing the risks of over or under-treatment of diabetes and related complications [20].

Our study directly compared differences in type 2 diabetes prevalence by diagnostic criteria using two populations of Asian Indians. While there were differences in the sampling frames and socio-demographic characteristics between MASALA and CARRS-2, both studies are large population-based samples with similar laboratory and anthropometric measures and are representative of Asian Indians in large urban centers in India or the United States. However, the results of our study should be interpreted in the context of several limitations. Given that our study directly compares two distinct Asian Indian populations from large metropolitan cities (the greater San Francisco and Chicago areas of the U.S. and Chennai and Delhi India) the results cannot be generalized to Asian Indians living in other parts of the U.S. or India. Additional limitations to our study include the exclusion of participants under the age of 40 and also those with pre-existing cardiovascular disease. Furthermore, the primarily cross-sectional nature of our study makes it impossible to determine temporality between the prevalence of type 2 diabetes as diagnosed by isolated HbA1c and the associated covariates. Measures of insulin sensitivity and secretion were assessed by fasting surrogate measures, and therefore may not be completely accurate. However, these results suggest milder defects in insulin secretion and resistance in Asian Indians diagnosed with diabetes by HbA1c compared to fasting or 2 hour glucose measures, and should be tested in further studies using gold-standard procedures. In addition, HbA1c was measured by different methods in the CARRS and MASALA studies, which may possibly explain the somewhat different prevalence of diabetes diagnosed by isolated HbA1c in the two cohorts. However, since that the pattern of a higher prevalence of diabetes

diagnosed by isolated HbA1c compared to other measures was seen in both cohorts, it is not likely that the different assay measures affected the overall results. HbA1c measures are also influenced by several conditions such as the presence of iron deficiency anemia [21]. Therefore, the lack of data regarding circulating iron and vitamin B12 in our study is an important limitation, and future studies should examine the influence of iron and B12 levels on the prevalence of HbA1c diagnosed diabetes in Asian Indian populations. Lastly, various factors such as hemoglobin variants may affect the accuracy of HbA1c measurements according to the assay method used [22]. Therefore knowledge and awareness of hemoglobin variants affecting HbA1c measurements in a given population is critical when determining whether this measure is appropriate as a diagnostic tool [22].

Our findings suggest that while the prevalence of type 2 diabetes diagnosed by isolated elevated HbA1c is fairly low, this is still a substantial proportion of all type 2 diabetes that is identified by this method. Furthermore, individuals diagnosed with type 2 diabetes by isolated HbA1c had milder glucose intolerance, and significantly lower serum triglycerides than those diagnosed by fasting or 2-hour post challenge measures. While HbA1c is generally considered a more specific test for type 2 diabetes screening then fasting or 2 hour glucose measures, this may not be the case in Asian Indian individuals. Furthermore, the use of a solo test may not be the best strategy to diagnosed diabetes. While the combination of a 2-hour glucose test and HbA1c would likely capture the highest number of people with diabetes, this strategy may not be practical given the burdensome nature of the oral glucose tolerance test. Given that HbA1c is becoming an increasingly utilized tool clinically for type 2 diabetes diagnosis, these results prompt the need for comprehensive studies examining the diagnostic accuracy and outcomes of

the different glycemic measures, particularly in Asian Indian populations. In addition, future longitudinal studies are needed in order to ascertain the long-term implications of a high prevalence of elevated isolated HbA1c on type 2 diabetes related morbidity and mortality.

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Author Contributions: U.P.G. analyzed data, wrote the manuscript, drafted tables and figures, and revised the manuscript and approved the final manuscript for submission. D.P., N.T., V.M., and R.M.A. contributed to concept, design, and interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript for submission. R.P., M.D., GR, and D.K. oversaw the CARRS research operations and contributed to the design, and data collection of the CARRS study. N.R.K contributed to the concept, design, discussion and interpretation of the data and reviewed and revised the manuscript, and approved the final manuscript for submission. K.M.V.N. contributed to concept, design, analysis, and interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript for submission. N.A.Z. contributed to the discussion and interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript for submission. A.M.K. obtained the funding for the MASALA study, collected the data, contributed to concept, design, analysis, discussion, and interpretation of the data, and reviewed and revised the manuscript, and approved the final manuscript for submission. U.P.G. is the guarantor of this work and has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data Availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Table 1. Age, Sex, and BMI Adjusted Prevalence of Glycemic Status in the CARRS-2 and MASALA study

	CARRS-2 Chennai	CARRS-2 Delhi	MASALA
n	1568	1448	608
Lab diagnosis of DM	n=242 18.2% (95% CI: 15.8-20.9)	n=190 14.0% (95% CI: 12.0-16.4)	n=74 12.5% (95% CI: 9.6-16.4)
FPG ≥126 mg/dl	n=136 9.4% (95% CI: 7.8-11.2)	n=99 7.0% (95% CI: 5.7-8.7)	n=19 3.3% (95% CI: 2.1-5.4)
PPG ≥200 mg/dl	n=172 12.3% (95% CI: 10.5-14.5)	n=108 7.6% (95% CI: 6.2-9.3)	n=63 11.2% (95% CI: 8.4-14.1)
HbA1c ≥6.5%	n=181 12.9% (95% CI: 11.0-15.1)	n=139 9.6% (95% CI: 8.0-11.5)	n=35 5.4% (95% CI: 3.7-7.8)
Isolated FPG ≥126 mg/dl	n=10 0.6%	n=19 1.3%	n=0 0.0%

	(95% CI: 0.3-1.1)	(95% CI: 0.8-2.1)	(95% CI: 0.0-0.0)
Isolated PPG ≥200 mg/dl	n=40 2.7% (95% CI: 1.9-3.6)	n=26 1.8% (95% CI: 1.2-2.6)	n=36 5.8% (95% CI: 4.0-8.6)
Isolated HbA1c ≥6.5%	n=47 2.9% (95% CI: 2.2-4.0)	n=51 3.1% (95% CI: 2.3-4.2)	n=8 0.8% (95% CI: 0.3-1.9)

Table 2. Age, Sex, and BMI Adjusted Participant Characteristics by Glycemic Status-CARRS-Combined Chennai and Delhi

	Normal Glucose Tolerance	***DM by FPG***	***DM by 2-hr Glucose***	***Isolated HbA1c% ≥ 6.5%***
N (%)	1054 (49.9)	235 (8.2)	280 (10.0)	98 (3.0)
Age (years)	48.7 (8.1)*	50.4 (7.5)*	50.9 (8.3)*	53.6 (8.6)
Men (%)	47.2	52.3	56.6	53.4
Vegetarian Diet	28.0	20.6*	20.8*	32.3
Bachelor's degree or higher (%)	18.7*	13.3	10.7*	20.9
Income Category (%)				
Tertile 1	38.7*	39.0	35.8	29.4
Tertile 2	23.7	28.1	28.7	23.0
Tertile 3	37.6*	32.9*	35.1*	47.7
Physical Activity Category (MET-min/week) (%)				
<600	23.8	20.7	24.4	27.5
600-4000	60.7	69.8*	65.4	56.1
4,000-8000	13.1	8.0	8.2	13.7
>=8,000	2.3	1.5	2.0	2.7
Current Smoker (%)	21.7	25.5	22.3	24.0
Blood Pressure Lowering Medication Use (%)	12.7*	15.4	18.4	20.4
Lipid Lowering Medication Use (%)	3.5	2.6	2.6	3.1
BMI, kg/m^2	25.1 (0.1)*	27.5 (0.3)	27.8 (0.3)	28.3 (0.5)
Waist Circumference, cm	88.4 (0.2)*	91.0 (0.5)	91.2 (0.4)	90.8 (0.7)

Systolic blood pressure, mmHg	128.5 (0.6)	137.2 (1.3)*	138.0 (1.1)*	130.0 (2.0)
Diastolic blood pressure, mmHg	81.9 (0.4)	86.1 (0.8)*	86.4 (0.7)*	83.0 (1.2)
Fasting glucose, mmol/L	5.0 (0.05)*	10.0 (0.07)*	9.1 (0.8)*	6.1 (0.2)
30 minute glucose, mmol/L	7.8 (0.08)*	15.6 (0.1)*	14.8 (0.1)*	10.8 (0.3)
2-hour glucose, mmol/L	5.5 (0.1)*	16.5 (0.2)*	16.8 (0.1)*	7.9 (0.4)
HbA1c, %	5.3 (0.03)*	8.1 (0.05)*	7.8 (0.04)*	6.6 (0.1)
HbA1c, mmol/L	34.6 (0.3)*	65.3 (0.5)*	61.5 (0.5)*	49.1 (1.1)
†‡Fasting Insulin, pmol/L	58.3 (0.03)*	99.6 (0.1)*	92.3 (0.1)*	84.2 (0.1)
Median (IQR)	56.2 (35.4-84.3)	114.9 (76.7-116.7)	114.8 (70.2-166.7)	103.2 (72.0-146.3)
†‡HOMA-IR	1.9 (0.03)*	5.8 (0.1)*	4.9 (0.06)*	3.3 (1.2)
Median (IQR)	1.8 (1.2-2.7)	6.2 (4.2-10.5)	5.8 (3.9-9.0)	4.1 (2.7-5.9)
†‡HOMA-β	111.3 (0.03)*	53.0 (0.1)*	60.2 (0.1)*	97.4 (0.1)
Median (IQR)	105.5 (66.6-159.3)	64.0 (36.3-96.1)	74.0 (39.4-131.2)	127.3 (78.9-164.4)
†‡Disposition Index	3.0 (0.05)*	0.3 (0.1)*	0.3 (0.1)*	1.0 (0.2)
Median (IQR)	2.8 (1.7-4.8)	0.3 (0.2-0.5)	0.3 (0.2-0.5)	0.8 (0.5-1.3)
†‡Total Cholesterol	4.6 (0.01)*	5.1 (0.01)*	5.0 (0.01)*	4.9 (0.02)
Median (IQR)	5.2 (5.1-5.3)	5.3 (5.1-5.4)	5.3 (5.1-5.4)	5.3 (5.1-5.4)
†‡HDL, mmol/L	1.1 (0.01)	1.0 (0.04)	1.0 (0.01)*	1.1 (0.07)
Median (IQR)	1.1 (1.0-1.3)	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.1 (0.9-1.2)
†‡LDL, mmol/L	2.8 (0.01)*	3.0 (0.02)	3.0 (0.02)*	2.9 (0.03)
Median (IQR)	2.8 (2.3-3.3)	3.1 (2.5-3.7)	3.0 (2.5-3.7)	3.0 (2.6-3.9)

†‡Triglycerides, mmol/L	1.3 (0.01)*	2.0 (0.03)*	1.9 (0.3)*	1.6 (0.05)
Median (IQR)	1.2 (0.9-1.7)	2.0 (1.3-2.8)	1.9 (1.3-2.7)	1.5 (1.2-2.1)

Data are given as %, mean (SD), or †geometric mean (SD) with median and interquartile range.

* $P < 0.05$ vs. isolated HbA1c ≥ 6.5.

‡Data are from a subset that includes the Delhi site only

Table 3. Age, Sex, and BMI Adjusted Participant Characteristics by Glycemic Status-MASALA

	Normal Glucose Tolerance	*DM by FPG*	*DM by 2-hr Glucose*	*Isolated HbA1c% ≥ 6.5%*
N (%)	134 (28.3)	19 (3.3)	63 (11.4)	8 (1.9)
Age (years)	51.6 (8.9)	56.3 (8.3)	55.8 (8.2)	54.5 (9.6)
Men (%)	49.4	83.5	46.1	64.5
Vegetarian Diet (%)	47.6	23.3	43.6	37.4
Bachelor's degree or higher (%)	93.1	98.9	81.7	83.7
Income Category (%)				
<$40k	10.0*	6.2*	16.7*	48.4
$40-75k	11.1	10.4	12.2	15.4
$75-100k	12.3	18.1	12.0	0.1
>100k	66.6	65.4	59.1	36.0
Physical Activity Category (MET-min/week) (%)				
600-4000	4.0	0	0	0
4,000-8000	36.4	32.0	29.1	13.6
>=8,000	59.5	67.8	71.3	87.6
Current Smoker (%)	3.1	3.7	1.7*	15.5
Blood Pressure Lowering Medication Use (%)	26.1	30.6	29.9	26.8

Lipid Lowering Medication Use (%)	12.7	10.1	20.1	14.5
AHEI-2010 Component Score	70.3 (0.6)	69.6 (1.6)	69.9 (0.9)	70.1 (2.7)
BMI, kg/m^2	25.2 (0.4)	27.9 (1.0)	26.9 (0.6)	27.9 (1.8)
Waist Circumference, cm	90.1 (0.6)*	93.1 (1.5)	93.1 (0.8)	97.8 (2.6)
Systolic blood pressure, mmHg	121.7 (1.5)	127.2 (3.7)	128.5 (2.0)	126.8 (6.4)
Diastolic blood pressure, mmHg	71.8 (0.9)	75.9 (2.3)	75.4 (1.3)	78.0 (3.9)
Fasting glucose, mmol/L	5.0 (0.08)*	8.4 (0.1)*	6.5 (0.1)*	5.7 (0.3)
30 minute glucose mmol/L	7.8 (0.2)	13.1 (0.4)*	11.1 (0.2)*	9.2 (0.7)
2-hour glucose, mmol/L	5.7 (0.3)	15.3 (0.6)*	13.6 (0.3)*	7.7 (1.2)
HbA1c, %	5.4 (0.05)*	7.3 (0.1)	6.5 (0.1)	6.9 (0.2)
HbA1c, mmol/L	35.8 (0.5)*	56.3 (1.2)	47.8 (0.7)	51.7 (2.3)
†Fasting Insulin, pmol/L	45.9 (0.05)*	78.8 (0.1)*	63.7 (0.07)	64.1 (0.2)
Median (IQR)	46.0 (35.0-61.0)	90.1 (56.0-132.0)	71.7 (44.7-111.0)	72.1 (50.3-83.1)
†HOMA-IR	1.7 (0.05)*	4.8 (0.1)*	3.0 (0.07)	2.7 (0.2)
Median (IQR)	1.7 (1.3-2.3)	5.5 (3.4-8.6)	3.4 (1.9-5.5)	3.1 (2.4-3.7)
†HOMA-β	108.4 (0.05)*	57.4 (0.1)*	81.4 (0.07)*	97.4 (0.2)
Median (IQR)	114.5 (76.5-154.1)	63.0 (35.4-92.6)	93.4 (59.7-126.6)	93.6 (73.0-126.2)
†Disposition Index	3.6 (0.08)*	0.3 (0.2)	0.8 (0.1)	1.0 (0.3)
Median (IQR)	3.4 (2.3-5.7)	0.3 (0.2-0.6)	0.9 (0.5-1.3)	0.8 (0.7-1.3)
†Total Cholesterol, mmol/L	4.7 (0.02)	5.2 (0.04)*	5.0 (0.02)*	4.8 (0.07)

Median (IQR)	4.8 (4.3-5.3)	5.4 (4.5-5.9)	5.1 (4.5-5.6)	4.6 (4.3-5.2)
†HDL, mmol/L	1.3 (0.02)	1.2 (0.05)	1.2 (0.03)	1.2 (0.09)
Median (IQR)	1.3 (1.1-1.6)	1.0 (1.0-1.6)	1.2 (1.0-1.4)	1.2 (0.9-1.4)
†LDL, mmol/L	2.8 (0.02)	2.9 (0.07)	2.9 (0.04)	2.8 (0.1)
Median (IQR)	2.8 (2.4-3.4)	3.0 (2.6-3.5)	3.0 (2.6-3.4)	2.8 (3.3-2.5)
†Triglycerides, mmol/L	1.1 (0.04)*	1.8 (0.1)	1.6 (0.05)	1.4 (0.2)
Median (IQR)	1.2 (0.8-1.5)	1.8 (1.4-2.6)	1.6 (1.3-2.1)	1.6 (1.1-1.8)
†Apo-B, g/L	0.8 (0.02)	0.9 (0.05)	0.9 (0.03)	0.8 (0.09)
Median (IQR)	0.8 (0.7-0.9)	0.9 (0.8-1.0)	0.9 (0.7-1.0)	0.8 (0.7-0.9)
†‡Adiponectin (ng/ml)	11.9 (0.06)*	8.5 (0.2)	8.2 (0.08)	7.8 (0.3)
Median (IQR)	12.9 (7.8-17.0)	6.5 (4.4-10.3)	8.5 (6.0-12.1)	7.9 (4.9-11.4)
†‡Resistin (ng/ml)	17.2 (0.07)*	19.9 (0.2)*	19.8 (0.1)*	26.7 (0.3)
Median (IQR)	18.8 (16.4-24.6)	19.6 (17.7-23.6)	18.7 (16..5-23.5)	17.7 (16.3-25.8)
Subcutaneous fat area (cm^2)	229.6 (7.3)	259.2 (18.2)	251.9 (10.0)	270.3 (32.3)
‡Visceral fat area (cm^2)	113.5 (4.0)*	128.6 (10.3)	130.9 (5.7)	146.7 (17.1)
‡Hepatic fat attenuation (HU)	59.4 (0.9)	51.8 (2.3)	50.8 (1.3)	54.4 (3.9)
‡Pericardial fat volume (cm^3)	49.2 (2.1)	63.1 (5.4)	61.8 (3.0)	52.6 (9.0)
‡Intramuscular fat area (cm^2)	19.6 (0.7)	16.4 (1.9)	20.1 (1.1)	23.5 (3.1)
‡Total lean mass area (cm^2)	91.0 (1.5)	92.2 (3.9)	93.6 (2.2)	86.7 (6.4)

Data are given as %, mean (SD), or †geometric mean (SD) with median and interquartile range.
* $P < 0.05$ vs. isolated HbA1c $\geq$ 6.5.
‡ Data are from a restricted sample that includes only participants with adiponectin, resistin, and visceral fat mass measurements (N=516 participants)

Figure 1. Proportion of diabetes diagnosed by glycemic measure and study site.

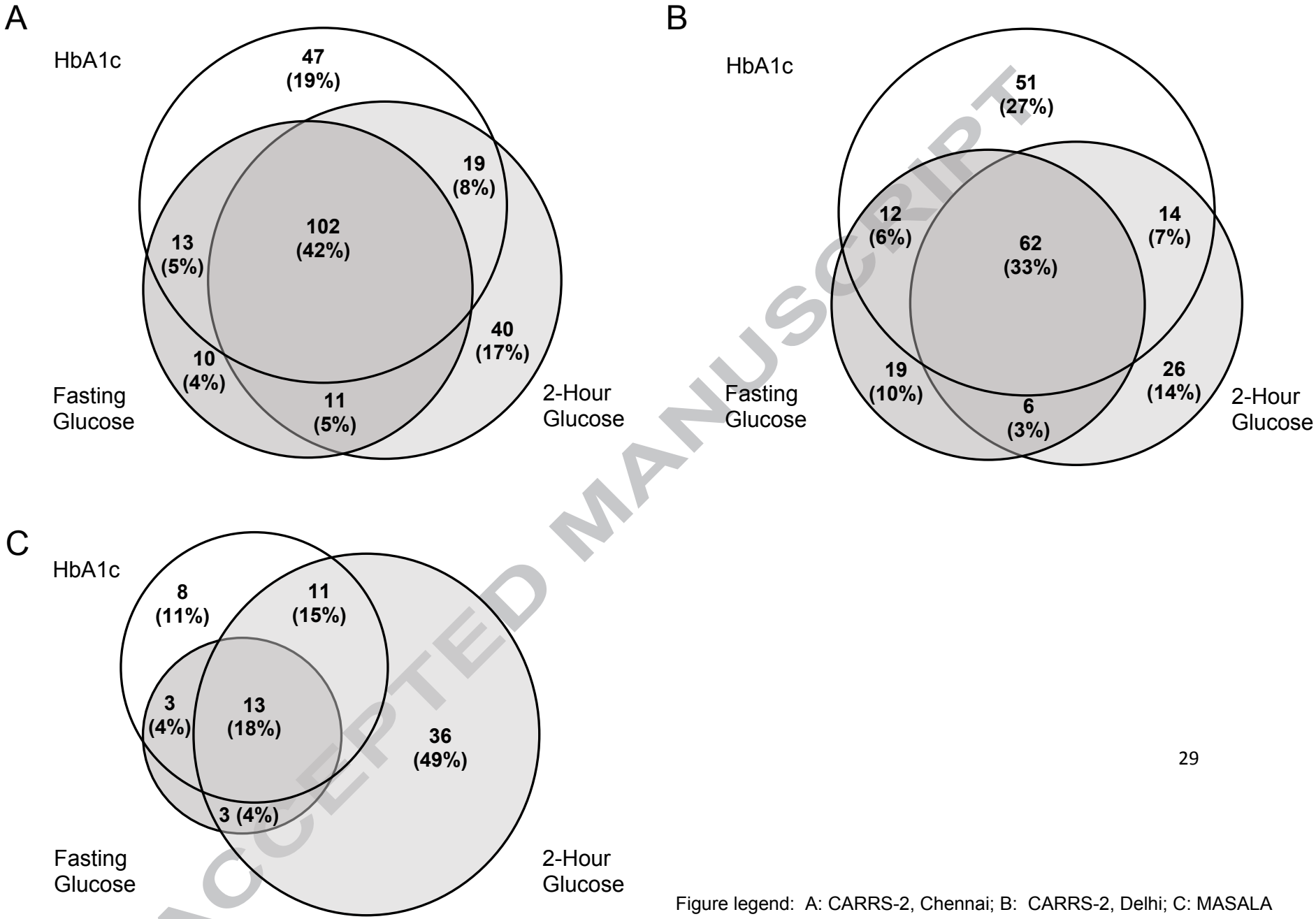

Figure legend: A: CARRS-2, Chennai; B: CARRS-2, Delhi; C: MASALA

Highlights:

- Hemoglobin A1c is becoming a widely used tool for identifying type 2 diabetes.
- However, Hemoglobin A1c may not accurately identify diabetes cases in all populations.
- In South Asians, Hemoglobin A1c identifies a substantially higher proportion of individuals with diabetes compared to fasting or two hour measures.
- Hemoglobin A1c also identified individuals with milder cardio-metabolic risk, lower triglyceride, and lower glucose levels.
- Future longitudinal studies are needed in order to ascertain the long-term implications of a high prevalence of elevated isolated HbA1c on type 2 diabetes related morbidity and mortality.