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Casey Costello Date

Exploration of differences of fasting-glucose, 2-hours oral glucose tolerance, and HbA1c Levels for prediabetes and T2 diabetes from the D-CLIP study

By

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Master of Public Health

Global Health

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Unjali Gujral
Chair

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By

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Bachelor of Arts
Emory University
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Thesis Committee Chair: Unjali Gujral, MPH, PhD

An abstract of a thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

Exploration of differences of fasting-glucose, 2-hours oral glucose tolerance, and HbA1c Levels for prediabetes and T2 diabetes from the D-CLIP study

By Casey Costello

AIMS:
Provide additional insight at to the utility of common diagnostic and screening methods for prediabetes and T2DM: fasting plasma glucose, oral glucose tolerance, and HbA1c, in an urban Indian population.
METHODS:
The prevalence of prediabetes and type 2 diabetes by HbA1c, fasting glucose, and 2 h glucose was compared in 1,285 participants from Chennai, India from the community screening for the D-CLIP Study. T2DM and prediabetes were classified by fasting plasma glucose, 2-hour plasma glucose, and HbA1c measures from the clinic-based screening using the American Diabetes Association criteria. Characteristics were compared across prediabetes and diabetes strata diagnosed by differing glycemic measures. Polytomous logistic regression models compared the odds of prediabetes or diabetes by each diagnostic criteria and assessing the association of demographic, behavioral, biochemical, and anthropometric covariates.
RESULTS:
743 individuals were identified with prediabetes, 23.8% by A1c only, 7.3% by 2-hour glucose only, and 6.7% by fasting glucose only. 380 individuals were diagnosed with T2DM, 32.6% by A1c only, 15.8% by 2-hour glucose only, and 2.1% by fasting glucose only. After adjusting for all covariates of interest, HOMA-IR was significantly associated with prediabetes by isolated A1c (OR: 1.21, 95% CI: 1.001-1.47), fasting glucose (OR:1.46, 95% CI: 1.17-1.83), and 2-hour glucose (OR: 1.46, 95% CI: 1.17-1.82), and HOMA-B was significantly associated with prediabetes by isolated fasting glucose (OR: 0.99, 95% CI: 0.984-0.997) and 2-hour glucose (OR: 1.005; 95% CI: 1.001-1.01). After adjusting for all covariates, there was a significant association between HOMA-IR and T2DM by isolated 2-hour glucose (OR: 1.21, 95% CI: 1.10-1.35) and with isolated A1c (OR: 1.11, 95% CI: 1.01-1.23), and HOMA-B and T2DM by isolated A1c (OR: 0.995, 95% CI: 0.991-0.998) and isolated fasting glucose (OR: 0.97, 95% CI: 0.94-0.99).
CONCLUSIONS:
With these results, there is not enough compelling evidence to use A1c as the primary test for identifying prediabetes or T2DM in Indian populations. In this population, the use of HbA1c for prediabetes and T2DM diagnosis could result in a higher prevalence, leading to mis- or over-diagnosis.

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INTRODUCTION:

The prevalence of non-communicable diseases has been quickly outpacing infectious diseases around the world. In fact, non-communicable diseases have become the leading cause of death, attributed to about 41 million annual deaths globally, with over 1.5 million deaths from diabetes mellitus (DM) alone.[1] The World Health Organization (WHO) has estimated that nearly 80% of deaths due to DM occur in lower-middle income countries (LMIC).[2] The estimated deaths due to DM is also expected to increase rapidly, potentially doubling by 2030, even after taking into consideration population growth and aging as well as the effects of urbanization.[3] One country in particular has become known as the diabetes capital of the world: India. Currently, India has the most people with type 2 diabetes (T2DM) globally.[4] The estimated number of people with T2DM in India ranges from 40 to 72 million,[5] with more affluent states experiencing greater prevalence rates.[6]

There are high economic costs associated with a high burden of diabetes, as managing this disease can be very costly.[7] Due to the complex nature of T2DM, continual care is necessary; and complications tend to arise over time.[8] Lower income individuals in India can spend nearly a quarter of their income on managing their T2DM, whether on doctor visits or medication.[9] In addition to economic costs, there are social costs for those with T2DM, as it is a chronic condition with no curative options. Having a chronic health condition can put a large strain on an individual's quality of life and can contribute to added difficulty in holding a job or managing a household. As time passes, it is also possible for T2DM complications to develop, including both microvascular and macrovascular complications.[10] These complications can lead to lower quality of life, a social cost that has been linked to financial stress and concern.[11] Both

economic and social costs due to T2DM are only expected to increase as the prevalence of T2DM rises in India.

With this growing epidemic, there is increased need for testing and screening at risk populations. The current methods of testing for T2DM can be expensive and time-consuming.[12] Finding the most effective and efficient method is a priority for many researchers around the world. Given the high costs associated with managing and treating T2DM, finding a cost-effective method for screening is necessary.[13] Researchers in India are therefore looking for low-cost and accurate methods of testing. Screening can help identify high risk individuals who may be asymptomatic to help prevent T2DM development as well as to better identify tools to reduce diabetes risk before it develops into hard outcomes.[14] Additionally, screening can help identify people who do have the disease to ensure they receive adequate care and treatment.[15] This paper therefore aims to provide additional insight at to the utility of common diagnostic and screening methods for prediabetes and T2DM: fasting plasma glucose, oral glucose tolerance, and HbA1c, in an urban Indian population. HbA1c as a method of identifying T2DM and prediabetes is relatively new, only becoming a recommended method by the American Diabetes Association (ADA) in 2009.

There is much existing research on the effectiveness of fasting glucose and oral glucose tests within this population, but additional research as to the prognostic utility of HbA1c is still needed, especially in different populations. While HbA1c is seen as a less expensive and more convenient alternative to fasting and oral glucose tests, past research has shown that HbA1c levels can differ by ethnicity as well as by external factors such as nutrition and hemoglobinopathies.[16,17] This paper will help fill in some of the gaps in understanding how effective HbA1c is for identifying people at risk of diabetes. Additionally, by focusing on both

prediabetes and type 2 diabetes, this paper will not only inform future type 2 diabetes research but also methods of screening for diabetes prevention. We therefore compared the prevalence of diabetes and prediabetes by three different diagnostic tests: fasting plasma glucose, 2-hour post challenge oral glucose tolerance, and HbA1c in an urban population of adults living in Chennai, India. We also compared the association of clinical factors with a diabetes and prediabetes diagnosis by fasting glucose, 2-hour glucose, and HbA1c in this population. The goal of this research is to better understand how HbA1c categorizes and identifies people with prediabetes and T2DM and what other factors may impact this identification, in comparison to the gold standard measures of fasting glucose and 2-hour glucose in a high-risk population.

There are three types of DM: type 1, type 2, and gestational diabetes, with about 90% of DM cases in the world being T2DM.[18] T2DM is a chronic condition that usually manifests during adulthood and it impacts the ability to metabolize glucose and maintain normal glucose levels, often due to insulin resistance or insufficient insulin production.[19] With T2DM, many potential complications can arise, including retinopathy, neuropathy, and cardiovascular disease.[20] It has been shown that T2DM can be prevented with lifestyle modification and early intervention.[21] The interest of this paper is T2DM, as type 2 is much more common worldwide than the other forms of DM and there is a need for additional research on managing and preventing T2DM. For the purposes of this paper, any mention of diabetes will refer solely to T2DM.

Prediabetes is the precursor to a T2DM diagnosis; and individuals with prediabetes are at high risk for developing T2DM in the future.[22] Prediabetes is considered intermediate hyperglycemia, where blood glucose levels are higher than the normal range, but not considered high enough to for a diabetes diagnosis. With prediabetes, there is still an increased risk of

cardiovascular disease, early mortality, cancer, and retinopathy, among other complications.[23] Without intervention, the ADA estimates that nearly 70% of people with prediabetes will eventually advance to a T2DM diagnosis.[24] With lifestyle modifications and additional interventions, it is possible to reverse prediabetes and significantly reduce risk of developing T2DM and the resulting complications.[25]

LITERATURE REVIEW:

Globally, the prevalence of T2DM in adults has been increasing steadily over the last several decades. In 1964, the global estimation of diabetes prevalence was 30 million.[26] As of 2019, the estimated number of adults with diabetes worldwide has reached 463 million, and the prevalence of diabetes has increased by more than tenfold in the last 5 decades.[27] It is estimated that the global prevalence of T2DM will reach 700 million by 2045.[28] Type 2 diabetes is a leading cause of death and disability globally.[29] Approximately 75% of adults with diabetes live in LMIC. Additionally, over 80% of deaths in LMICs are attributed to diabetes.[30] In particular, India, the "diabetes capital of the world," has been facing a diabetes epidemic over recent decades.[31] Due to the large number of people with diabetes in India, it is not surprising that the socio-economic burden related to diabetes in India is extremely high. People are diagnosed with diabetes at increasingly younger ages in India, which contributes to increased financial burdens for the healthcare system,[32,33] as well as for individuals. In lower income households, the cost of diabetes care can consume nearly a quarter of household income.[34] With the predicted increase in diabetes diagnoses over the next two decades, this national and personal burden will only continue to increase.

There is also a similar trajectory for the burden of prediabetes. The International Diabetes Federation (IDF) has estimated that nearly 320 million people worldwide are considered to have

prediabetes. In the next 20 years, that number is expected to increase to an estimated 500 million.[35] Furthermore, it is estimated that globally, a quarter of individuals with prediabetes will develop diabetes within 5 years; that estimate jumps to approximately 70% over a lifetime.[36]

In India, the estimated prevalence of prediabetes is approximately 14% or 80 million individuals.[37] A study examining the prevalence of diabetes and prediabetes in 15 out of 31 states in in India found that prevalence of prediabetes was higher than T2DM, which implies a large number of people who could develop T2DM in the future.[38] It has been estimated that without intervention, 40-55% of people with prediabetes in India will develop T2DM within 5 years.[39] Since most individuals with prediabetes are asymptomatic, it can be a challenge to identify those at risk of developing T2DM.[40] To help slow the exponential growth of T2DM in India, it will be necessary to find methods of identifying prediabetes to allow for early intervention. The gold standard screening and diagnostic methods for the last several decades have been fasting glucose and oral glucose tolerance tests. However, these tests have limitations, including cost, accessibility, and participant burden. Fasting plasma glucose is measured using a venous blood sample after overnight fasting for approximately 8 hours.[41] This is the most common method for diagnosing T2DM and is usually considered the cheapest test. However, the requirement of an overnight fast can create participant burden and the timing of the test has to be well planned.[42] In addition, there is a risk of inaccurate results because fasting is self-reported.

Conversely, the oral glucose tolerance test (OGTT) measures how an individual processes glucose over time, usually 2 hours. This requires an individual to fast for 8 to 10 hours prior to the test and a fasting sample to be drawn for baseline glucose levels. After the fasting blood draw, individuals are required to drink a standard amount of glucose, 75g of glucose[43] and

complete a second blood draw after two hours. This test indicates how efficiently the person is able to clear the glucose from their blood and can help inform levels of insulin resistance and β-cell function.[44] However, there are limitations with OGTT, including uncertain fasting state, significant variability of glucose levels, the time-consuming nature, participant burden, as well as reproducibility. Additionally, having access to the requisite 75g of glucose can be a barrier for many communities around the world.[45] In particular, LMICs may not have the resources necessary to use OGTT for large populations. Another issue with both FPG and OGTT is that they struggle to capture chronic hyperglycemia, as these tests only provide information on glucose levels at the time of the test.[46] Additionally, other factors can play a role in FPG and OGTT glucose levels, including stress, exercise, and illness.

An important consideration of FPG and OGTT is that they identify different physiological measures. With regards to prediabetes, FPG allows for testing impaired fasting glucose, while OGTT tests for impaired glucose tolerance. Both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are intermediate states, where glucose levels are higher than normal but not high enough for a T2DM diagnosis. Risk factors of IFG include β-cell dysfunction and decreased insulin secretion.[47] IFG initially was considered to be analogous to IGT, but additional research showed that IFG and IGT identify different individuals. IGT is associated with slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin sensitivity. Where insulin resistance manifests can impact intervention methods. Muscle insulin resistance benefits from increased physical activity while metformin is a more effective treatment for hepatic insulin resistance.[48]

Recently, both the ADA and the WHO have moved to include A1c measures as a method of testing glucose levels in the blood. A1c levels are not a direct measure of glycemia, but instead a

proportion of hemoglobin proteins bound by glucose.[49] A1c indicates chronic glycemic levels and is not heavily impacted by day-to-day variability.[50] The use of A1c to estimate glycemia levels has become increasingly popular, as it offers advantages that FPG and OGTT lack. For example, no fasting is required for A1c samples, making it a much more convenient test.[51] Furthermore, these samples provide a broader perspective of glycemic control and are better for measuring chronic glycemia as opposed to acute glycemia.[52] Additionally, with less day-to-day variability, A1c is less impacted by acute disruption to a normal routine, such as high stress or illness. The low biological variability and less preanalytical instability makes A1c a good method of determining overall glycemic exposures and the long-term effects. As A1c becomes a more common method of monitoring glucose levels for people with T2DM, it may be beneficial to have the same measure for diagnosis. While A1c may not be the least expensive test option, the flexibility of taking a sample at any time removes many barriers to getting screened or tested. People can get screened at their own convenience, when they can be driven to the clinic, outside of work hours, or even during a lunch break.[53] This increased access could allow for more people to get screened and indicate high-risk people for early intervention. Currently, A1c has higher agreement in diagnosis with FPG for T2DM, but less so for identifying prediabetes.[54]

However, there are limitations to A1c as an isolated measure of glycemic levels, especially in lower-resource populations. Because it is a not a direct measure of glucose, A1c can be impacted by a variety of factors, including iron-deficient anemia, pregnancy, and abnormalities of hemoglobin.[55,56] Hemoglobin abnormalities are still common in many parts of the world, especially in LMICs. These abnormalities would impact A1c levels and render it an unreliable measure for diagnosing diabetes.[57] Furthermore, using A1c as a replacement to OGTT would limit the information on important physiological processes that are important in treating

T2DM, including insulin response and secretion. There is also evidence of ethnic differences impacting A1c levels and A1c has been shown to have poor sensitivity in diagnosing diabetes.[58] In addition, cost is also a concern, as having high quality, standardized samples of A1c can be an expensive undertaking. In India, an A1c test costs about 5-15 USD whereas a plasma glucose test is between 0.5-1.5 USD.[59] If used for screening, the cost of an A1c detecting one new case of diabetes would cost about 40 USD, compared to 10 USD for OGTT and 16 USD for FPG.[60] When used in a limited resource context, the cost of A1c tests can be debilitating. However, it should always be remembered that the cost of screening is much smaller than the cost of treating and caring for undiagnosed diabetes and resulting complications.

With the recent addition of A1c to identify at risk individuals, there has been concern over how effective it is at accurate diagnosis of diabetes and prediabetes. One of the largest concerns with using A1c as a method of screening and diagnosing T2DM and prediabetes is that it could mis- or reclassify millions of people.[61] This could have large epidemiological ramifications and could completely alter the diabetic landscape. A1c alone has also been seen to miss about a third of people with diabetes, considering them to be normal by isolated A1c measures but as having diabetes by FPG and OGTT.[62] There is little overlap between diagnoses from A1c and FPG and OGTT, however elevated A1c levels are still cause for concern.[63] In fact, high A1c has a stronger association with diabetic retinopathy than FPG or OGTT.[64] For prediabetes, there is also limited overlap between the three different diagnostic criteria. A study in Finland shows that a prediabetic level of A1c detects different groups of people than FPG or OGTT and may provide different prevalence estimates.[65] Not using A1c as a test would cause a missed opportunity for early intervention of risk reduction for those with elevated A1c levels but normal FPG and OGTT.

However, there is also the risk of overdiagnosis when using the A1c criteria. Overdiagnosis is a concern of the A1c test, particularly for populations who are not predominantly white, or who do not live in higher income countries.[66] Overdiagnosis gives the illusion that the burden of T2DM is inflated. This is a concern for a variety of reasons, one of which is that overdiagnosis for a patient means getting a false positive which is associated with the repercussions that follow a diabetes diagnosis. In certain countries, like the United States, a diabetes diagnosis can add restrictions and requirements to having a driver's license[67]. Restrictions on licenses can dramatically impact how individuals live their life and what jobs they can hold. Additionally, overdiagnosis can lead to overtreatment; while an argument can be made that high A1c means prediabetes and early intervention and treatment is useful, it can be problematic to misdiagnose individuals. Especially for vulnerable populations, a T2DM diagnosis can be life-altering and extremely expensive. An escalation of treatment for an improperly diagnosed individual is also not without consequence.

Overdiagnosis can also lead to more people being labeled as having prediabetes than is actually the case. This in itself can cause unintended consequences. Being identified as having prediabetes can cause anxiety about health and disease management and often comes with stigma.[68] Even without a T2DM diagnosis, a diagnosis of prediabetes tends to require additional follow-up and potential treatment. The idea of treating prediabetes can be a slippery slope, especially when there is potential of over- or misdiagnosis. For example, Metformin has been used as a preventative treatment to slow the development of T2DM from prediabetes. With overdiagnosis, people who are improperly categorized as having prediabetes can be prescribed medication that may not be medically necessary, which in itself can have negative repercussions.[69] While A1c is a simple method to test for T2DM, there is risk of overdiagnosis

and associated consequences, which illustrates the need for additional research as to the diagnostic utility of A1c for diabetes and prediabetes in different populations.

Some of the discrepancies between A1c classification and the other methods of identifying those at risk of T2DM can be attributed to ethnicity. These differences are especially apparent when comparing South Asian and Black individuals to White individuals.[70] In one study, the prevalence of T2DM diagnosed by A1c in Indians living in Chennai, India was 110% higher than by FG, and 27% higher than by OGTT.[71] The potential consequence of including A1c criteria in diagnosing this population would mean the present estimated prevalence of T2DM in India would increase from about 60 million to nearly 80 million.[72] While there may be limited overlap between classification of prediabetes and diabetes by A1c and OGTT, there is evidence that both those identified with elevated isolated A1c and isolated OGTT have poor metabolic profiles. It could be beneficial to use A1c and OGTT simultaneously to have a wider reach for the target population of preventative interventions.[73]

Additionally, A1c levels have been found to be a quarter to a full percentage point higher in Black Americans compared to White Americans.[74] This difference may not necessarily indicate elevated glucose levels, but rather that the baseline A1c is different between ethnic groups or that other ethnic-specific factors are impacting it. This difference has been seen outside of Black Americans, and is often mirrored in Asian Americans and Hispanic populations.[75] Much of the research on A1c and diabetes has taken place in higher income countries like the United States, however discrepancies between diabetes prevalence as diagnosed by A1c compared to fasting or two-hour measures have been observed in lower-middle income countries like India. In fact, one study found that 19% of participants from Chennai India, 27% from Delhi, India, and 11% of Indian Americans in the United States were classified with T2DM by A1c but

not by FPG or OGTT.[76] With such differences in classifications, it is necessary to continue researching the effectiveness of A1c in different populations, especially in the Indian context.

It is also possible that nutrition-related deficiencies, such iron-deficiency anemia, can impact A1c levels and render the measure a poor indicator of glycemic load. Iron-deficiency anemia is an ongoing issue in India, particularly in adolescents and reproductive-aged women. It is estimated that approximately 50% of reproductive-aged women and 85% of pregnant women in India have abnormal hemoglobin levels.[77] Effects of iron-deficiency anemia can increase the glycation of hemoglobin, producing falsely elevated levels of A1c. With both iron-deficiency anemia and T2DM being common issues in India, attention to this relationship will be necessary when using A1c as a measure of glycemic load. Addressing the anemia and taking repeat A1c samples could help address these discrepancies.

Lastly, current research has focused attention around diabetes management and diagnosis, but less research has been done on prediabetes, especially when it comes to the utility of A1c as a screening criteria. There is a clear need for additional and robust research to be done on prediabetes diagnoses and early detection of those at high risk of developing diabetes. Additional comparisons between A1c levels and the gold standard measures of FG and OGTT will be beneficial, as its accuracy has not been well tested for multiple populations. Specifically, more research on the utility of A1c to identify prediabetes in people from India is essential, as this is a group with a particularly high risk of diabetes. It will be necessary to have additional comparisons of A1c as a diagnostic tool for both prediabetes and diabetes with FG and OGTT.

This paper works to fill these gaps in research, delving deeper into HbA1c as a method of identifying prediabetes and T2DM. It will offer more evidence in how A1c compares to the other measures of FG and OGTT for an Indian population. The data used is from a community

screening program for people living in Chennai, India. By exploring the similarities and differences of each diagnostic criteria, this paper strives to help inform future use of A1c as a method of testing prediabetes and T2DM in a high risk population.

METHODS:

This is a secondary analysis of data gathered during community screening in Chennai, India for the Diabetes Community Lifestyle Improvement Program (D-CLIP) study. To identify individuals with prediabetes, most participants went through a two-step screening process. The first was a field-based screening including a short screening questionnaire, anthropometric measures, and a random capillary glucose measurement. If participants were identified from the first screening process to be at high risk, they underwent a second screening. This entailed a clinic-based screening process, where a 3-sample Oral Glucose Tolerance Test (OGTT) after an 8 hour overnight fast was conducted. A smaller portion of participants were identified at the study site by electronic medical records and records of other trials. These identified individuals went in for clinic-based screening only. Both the Emory University Institutional Review Board and the Ethics Committee of the Madras Diabetes Research Foundation approved the D-CLIP study.

Study participants were recruited from a variety of sources, including community-based screening camps, direct referrals, newsletters and other print media, advertisement at the study clinic, and health records at the study site. The community screening method aimed to identify high-risk individuals and bring them in to the clinic for confirmatory testing. Community screenings were conducted mostly in housing colonies or residential complexes, that included a group of apartment buildings or homes within a specific boundary. Other community screenings were held in corporate offices or worksites for employees and their families, private and

government schools for faculty and staff, and at public locations like beaches, parks, or places of worship, to highlight special days including World Health Day and World Diabetes Day. Each community screening regardless of location included a survey to gather socio-demographic information and family history of diabetes, anthropometric data such as height, weight, and waist circumference, and a random capillary blood glucose test. All potential participants were provided leaflets to outline the screening procedures and the purpose of the study prior to screenings.

These screening sites were selected as a method to maximize reach of the study, and typically included apartments and colonies with at least 200 potential participants. Corporate office screening sites were included if they had 500 potential participants at minimum. Screening camps were held at site-specific times, in order to maximize accessibility to the populations being sampled. At school screening sites, evening camps were held to ensure availability of both teaching and non-teaching professionals. Screening camps during the special health days were held in the morning for maximum participation rates.

Originally, individuals identified through community based screening were invited to clinic-based screenings for baseline testing if they had a fasting capillary blood glucose of 100-125 mg/dl (5.6-6.9 mmol/l) or random capillary blood glucose of 120-199 mg/dl (6.7-11.0 mmol/l), were between 20 and 65 years old, and had a waist circumference of ≥90 cm for males and ≥80 cm for females or a BMI of >22 kg/m2. After the first few screenings, it appeared that these cut-offs were insufficient in capturing a large enough group of individuals with prediabetes. Therefore, later screening camps had expanded capillary glucose cut-offs to include those with fasting levels of 90-126 mg/d; (5.0-7.0 mmol/l) or random levels of 110-200 mg/dl (6.1-11.0 mmol/l). Those who were pregnant, breastfeeding, had a history or current evidence of

heart disease, or any other serious illness were excluded from the study. All participants provided informed consent. Clinic-based screening took place between 2008 and 2011.

The clinic based screening site was a tertiary care diabetes clinic. In addition to those identified through community based screenings, patients from the diabetes clinic with prediabetes were identified by electronic medical records and invited to participate in the study. Family members of patients at the clinic were also screened. An additional method of recruitment was to identify individuals from past research study databases. If such individuals met the current criteria, were outside of the window period of the past trial, and had consented to future trials held at the study site they were invited to participate in the study. With this multipronged approach, 19,377 individuals were screened in the field and 1,285 individuals participated in clinic-based screening.

Limitations of this study include the cross-sectional design, which limits the ability to understand temporality, and the representation of populations in the sample. Additionally, the study population is a middle class cohort from southern India. These results may lack generalizability to other populations, such as other racial or ethnic groups and socioeconomic status. It is probable that other regions of India and other countries have their own sets of challenges. Also, each subject had a random blood glucose level of 6.1 mmol/L before the oral glucose tolerance test, which means the normal glucose tolerance group may not be completely representative of normoglycemia. Despite these limitations, the methods to recruit and the nature of participants from different sources still provide enough information to inform effective screening and recruitment strategies.

Diabetes and prediabetes were classified by fasting plasma glucose, 2-hour plasma glucose, and HbA1c measures from the clinic-based screening using the American Diabetes

Association criteria.[78] Individuals were identified with isolated A1c prediabetes if A1c was ≥5.7% and <6.5%, FPG <5.6 mmol/L, and OGTT <7.8 mmol/L. Isolated fasting prediabetes was defined as FPG ≥5.6 mmol/L and <7.0 mmol/L, A1c <5.7%, and OGTT <7.8 mmol/L. Isolated 2-hour glucose prediabetes was defined as OGTT ≥7.8 mmol/L and <11.1 mmol/L, A1c <5.7%, and FPG <5.6 mmol/L. Individuals were diagnosed with isolated A1c T2DM if A1c ≥6.5%, FPG <7.0 mmol/L, and OGTT < 11.1 mmol/L. Isolated fasting T2DM was defined as FPG≥7.0 mmol/L, HbA1c < 6.5%, and OGTT < 11.1 mmol/L. Isolated 2-hour glucose T2DM was defined as OGTT≥11.0 mmol/L, FPG < 7.0 mmol/L, and A1c < 6.5%. Normal glucose tolerance was defined as those who had FPG<5.6 mmol/L, OGTT<7.8 mmol/L, and A1c<5.7%.

Beta-cell function was determined by homeostasis model assessment of beta-cell function (HOMA-B) and was calculated by: [20*I0(mIU/ml) / G0(mmol/l)- 3.5].[79] Insulin resistance was estimated using homeostasis model assessment of insulin resistance (HOMA-IR), calculated by: [fasting insulin × fasting glucose]/22.5.[80]

STATISTICAL ANALYSIS

Participant characteristics were compared across prediabetes and diabetes strata diagnosed by differing glycemic measures. Differences in these characteristics were assessed using χ^2 tests and ANOVA as appropriate. The prevalence values and 95% confidence intervals were estimated by glucose diagnostic measures. Polytomous logistic regression models were used to compare the odds of prediabetes or diabetes by each diagnostic criteria and assessing the association of demographic, behavioral, biochemical, and anthropometric covariates. Initially, a limited polytomous regression model was run to compare the odds of prediabetes or T2DM diagnosis by isolated HbA1C, isolated IFG, and isolated IGT, compared to those without T2DM, while controlling for age and sex. The subsequent multivariable models were used to adjust for other covariates, including BMI, waist circumference, family history of diabetes, cholesterol and

triglycerides, insulin resistance, and beta-cell function. Due to the collinearity of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR), these variables were run in separate models. For final model selection, regression analysis using backward selection was performed. All analyses were performed using SAS Version 9.4.

RESULTS:

Fig. 1

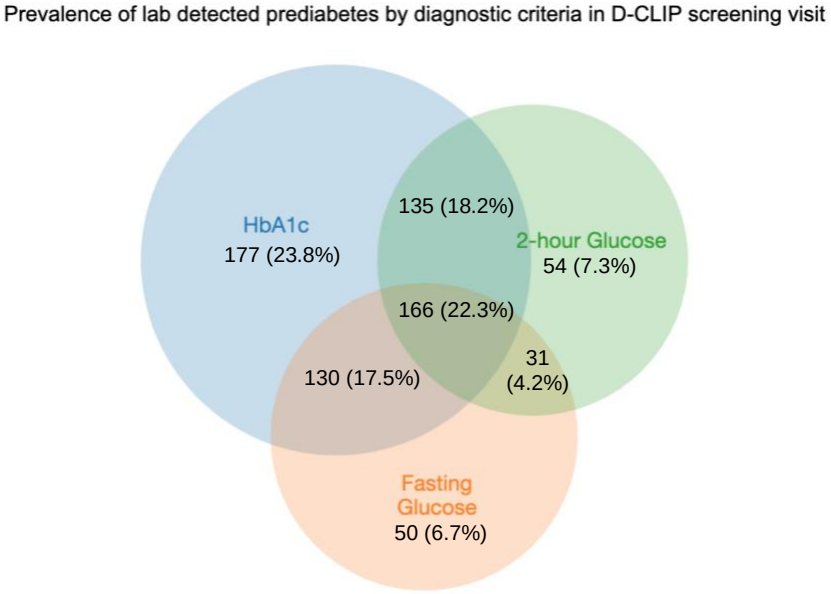
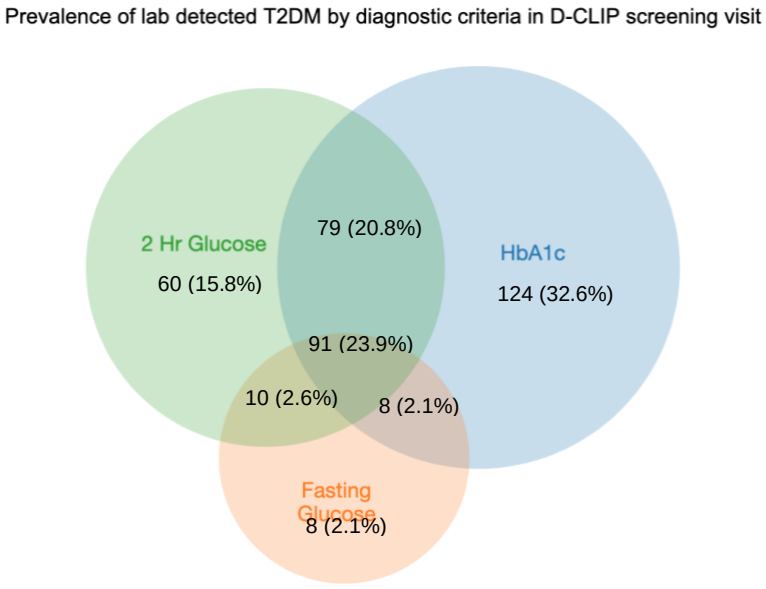


Fig. 2



Figures 1 and 2 provide prevalence details of those identified with prediabetes and T2DM by A1c, fasting glucose, and 2-hour glucose tests. Out of the 743 individuals identified with prediabetes, 23.8% (n=177) were by A1c only, 7.3% (n=54) by 2-hour glucose only, and 6.7% (n=50) by fasting glucose only. 22.3% (n=166) were identified with prediabetes by all three tests. There were 380 individuals diagnosed with T2DM, with 32.6% (n=124) by A1c only, 15.8% (n=60) by 2-hour glucose only, and 2.1% (n=8) by fasting glucose only. 23.9% (n=91) individuals were diagnosed with T2DM by all three measures.

Table 1 provides prevalence of prediabetes by diagnostic criterion and characteristic details for this population and normal glucose tolerance. Of the entire study population of 1,285, the prevalence of prediabetes diagnosed by isolated A1c was 13.8%, isolated fasting glucose was 3.9%, and isolated 2-hour glucose was 4.2%. The prevalence of normal glucose tolerance was 12.6%. Those identified with prediabetes by isolated fasting glucose and isolated 2-hour glucose as well as those with normal glucose tolerance were significantly more likely to be male in comparison to those with prediabetes by isolated A1c. When compared to the isolated A1c prediabetes group, those identified by isolated 2-hour glucose were significantly younger, had lower A1c levels, and better beta-cell function. However, they also were more insulin resistant, had lower HDL, and higher triglycerides levels in comparison to isolated A1c. Those identified with prediabetes by isolated fasting glucose had significantly lower A1c levels and lower LDL, but were more insulin resistant and had poorer beta-cell function, in comparison to those with prediabetes by isolated A1c.

Table 1. Clinical and Biochemical Characteristics of Participants Diagnosed with Prediabetes by isolated HbA1c, Fasting Glucose, and 2-hour Glucose Glycemic Status

	Normal Glucose Tolerance		Prediabetes diagnosed by isolated HbA1c		Prediabetes Diagnosed by isolated Fasting Glucose		Prediabetes Diagnosed by isolated 2-hour Glucose	
	n=162	12.61%	n=177	13.77%	n=50	3.89%	n=54	4.20%
Male (n, %)	109	67.28%	98	55.37%	36	72%	39	72.22%
	p=0.0246				p=0.0347		p=0.0273	
Age (years)	40.18	sd=8.95	43.73	sd=8.81	41.90	sd=10.42	39.35	sd=9.23
	p=0.0003				p=0.2150		p=0.0018	
Height (cm)	165.19	sd=9.24	162.90	sd=9.55	165.64	sd=9.86	164.99	sd=8.25
	p=0.0252				p=0.0764		p=0.1466	
BMI (kg/m2)	26.43	3.85	27.05	sd=3.34	26.89	sd=3.49	26.59	sd=3.24
	p=0.1138				p=0.7653		p=0.3786	
Waist (cm)	92.04	sd=9.84	92.22	sd=8.71	92.94	sd=9.80	92.38	sd=8.82
	p=0.8587				p=0.6167		p=0.9060	
Blood Pressure (mm Hg)								
Systolic	121.69	sd=16.57	122.45	sd=14.33	124.10	sd=14.30	121.23	sd=11.97
	p=0.6510				p=0.4740		p=0.5696	
Diastolic	72.92	sd=10.39	72.84	sd=8.83	74.43	sd=9.94	73.69	sd=8.35
	p=0.9404				p=0.2767		p=0.5358	
FPG (mg/dL)	90.02	sd=5.16	92.52	sd=5.04	103.78	sd=3.38	92.31	sd=5.39
	p<.0001				p<.0001		p=0.7971	
2hPG (mg/dL)	109.62	sd=15.68	114.45	sd=17.10	115.14	sd=19.58	155.65	sd=14.23
	p=0.0072				p=0.8081		p<.0001	
HbA1c (%)	5.36	sd=0.23	5.92	0.19	5.42	sd=0.18	5.39	sd=0.21
	p<.0001				p<.0001		p<.0001	
HOMA-IR Median (IQR)	2.35	1.33-2.66	2.57	1.79-3.09	3.18	2.27-3.89	3.14	1.95-3.81
	p=0.2366				p=0.0028		p=0.0058	
HOMA-B Median (IQR)	136.56	80-159.65	141.67	91.41-174.16	110.09	78.81-132.59	171.22	105-226.45
	p=0.0871				p=0.0058		p=0.0147	
LDL (mg/dL)Median (IQR)	111.84	93-126	117.35	99-135	108.12	93-123	114.25	93-136
	p=0.0201				p=0.0311		p=0.4756	
HDL (mg/dL)Median (IQR)	39.62	34-44	41.70	35-47	39.64	34-45	38.28	33-41
	p=0.0467				p=0.1375		p=0.0089	
Triglycerides (mg/dL) Median (IQR)	145.11	87-175	131.79	87-161	140.26	88-165	152.65	110-175
	p=0.1153				p=0.4215		p=0.0410	

Data are given as %, geometric mean (SD), or median (IQR). Normal glucose tolerance was tested during screening process. P-values are as compared to HbA1C.

Table 2 provides prevalence of those diagnosed with T2DM by each diagnostic criterion and the characteristics of these individuals. The prevalence of individuals diagnosed with T2DM was 9.7% by isolated A1c, 0.62% by isolated fasting glucose, and by 4.7% for isolated 2-hour glucose. Those diagnosed with T2DM by 2-hour glucose only were significantly more likely to

be male, younger, with lower A1c levels, but greater mean insulin resistance in comparison to those diagnosed by A1c only. Individuals diagnosed by isolated fasting glucose had significantly lower BMI, smaller waist circumference, lower A1c levels, and lower LDL but also had poorer beta-cell function, in comparison to individuals diagnosed with T2DM by isolated A1c

Table 2. Clinical and Biochemical Characteristics of Participants Diagnosed with T2 DM by isolated HbA1c, Fasting Glucose, and 2-hour Glucose Glycemic Status

	Normal Glucose Tolerance		T2DM diagnosed by isolated HbA1c		T2DM diagnosed by isolated Fasting Glucose		T2DM diagnosed by isolated 2-hour Gluocse	
	n=162	12.61%	n=124	9.65%	n=8	0.62%	n=60	4.67%
Male (n, %)	109	67.28%	70	56.45%	5	62.5%	45	75%
	p=0.0606				p=0.5194		p=0.0148	
Age (years)	40.18	sd=8.95	47.83	sd=8.80	47.25	sd=8.05	44.95	sd=10.04
	p<.0001				p=0.8560		p=0.0484	
Height (cm)	165.19	sd=9.24	161.54	sd=8.68	161.99	sd=10.85	163.62	sd=7.51
	p=0.0008				p=0.8884		p=0.1128	
BMI (kg/m2)	26.43	3.85	28.50	sd=4.42	25.00	sd=3.52	27.97	sd=3.65
	p<.0001				p=0.0303		p=0.4203	
Waist (cm)	92.04	sd=9.84	96.09	sd=9.71	88.09	sd=9.26	96.87	sd=9.79
	p=0.0006				p=0.0253		p=0.6106	
Blood Pressure (mm Hg)								
Systolic	121.69	sd=16.57	127.96	sd=14.35	118.38	sd=10.15	125.91	sd=14.49
	p=0.0009				p=0.0658		p=0.3670	
Diastolic	72.92	sd=10.39	77.54	sd=9.56	74.69	sd=6.75	76.12	sd=9.50
	p=0.0001				p=0.4090		p=0.3453	
FPG (mg/dL)	90.02	sd=5.16	108.48	sd=9.01	130.13	sd=5.80	110.07	sd=9.82
	p<.0001				p<.0001		p=0.2798	
2hPG (mg/dL)	109.62	sd=15.68	159.19	sd=29.52	156.88	sd=32.31	229.72	sd=35.07
	p<.0001				p=0.8313		p<.0001	
HbA1c (%)	5.36	sd=0.23	6.73	sd=0.31	5.89	sd=0.43	6.07	sd=0.31
	p<.0001				p<.0001		p<.0001	
HOMA-IR Median (IQR)	2.35	1.33-2.66	3.64	2.41-4.61	3.58	2.28-4.10	4.29	2.62-5.34
	p<.0001				p=0.9122		p=0.0233	
HOMA-B Median (IQR)	136.56	80-159.65	114.70	66-142	61.05	37.65-68.15	130.82	75.87-181.84
	p=0.0134				p=0.0203		p=0.1227	
LDL (mg/dL)Median (IQR)	111.84	93-126	125.30	103-149	103	94-114.5	122.20	98-149
	p=0.0002				p=0.0484		p=0.5581	
HDL (mg/dL) Median (IQR)	39.62	34-44	39.44	34-43	41.88	36-49	41.12	35-44
	p=0.8501				p=0.3555		p=0.1683	
Triglycerides (mg/dL) Median (IQR)	145.11	87-175	153.15	96-178.5	129	57.5-160.5	149.47	106-179
	p=0.5672				p=0.4465		p=0.7787	

Data are given as %, geometric mean (SD), or median (IQR). Normal glucose tolerance was tested during screening process. P-values are as compared to HbA1C.

Two separate polytomous logistic regression models were run to assess the association between relevant covariates and the estimated odds of having prediabetes and T2DM by different diagnostic criteria, one including HOMA-IR and one including HOMA-B. For the prediabetes models (Table 3), HOMA-IR had strong associations with all three diagnostic criteria. The associations of HOMA-IR with fasting glucose and 2-hour glucose were stronger than with isolated A1c. After controlling for age, sex, height, waist circumference, family history, and all three cholesterol measures, for every unit increase in HOMA-IR, the odds of a prediabetes diagnosis by isolated A1c was 21% higher (95% CI: 1.001-1.47), the odds of prediabetes by isolated fasting glucose was 46% higher (95% CI: 1.17-1.83), and the odds of prediabetes by 2-hour glucose was 46% higher (95% CI: 1.17-1.82) compared to NGT. For HOMA-B, there was only significant association with fasting glucose and 2-hour glucose, but not A1c. With a one unit increase in HOMA-B, the odds of prediabetes by isolated fasting glucose was 1% less (95% CI: 0.984-0.997) and the odds of prediabetes by isolated 2-hour glucose was 0.5% higher (95% CI: 1.001-1.01) compared to NGT.

For the T2DM models (Table 4), HOMA-IR was significantly associated with both A1c and 2-hour glucose, but not with fasting glucose, while HOMA-B was associated with both A1c and fasting glucose, but not 2-hour glucose. There was a stronger association between HOMA-IR and T2DM by isolated 2-hour glucose than with isolated A1c. For a one unit increase in HOMA-IR, the odds of a T2DM diagnosis by isolated A1c was 11% higher (95% CI: 1.01-1.23) whereas the odds of a T2DM diagnosis by isolated 2-hour glucose was 21% higher (95% CI: 1.10-1.35) than those without T2DM. For every unit increase in HOMA-B, the odds of a T2DM diagnosis by isolated A1c was 0.5% less (95% CI: 0.991-0.998) and the odds of a T2DM diagnosis by isolated fasting glucose was 3% lower (95% CI: 0.94-0.99) compared to those

without T2DM. It was less likely for someone to receive a T2DM diagnosis by isolated fasting glucose due to HOMA-B than by isolated A1c. Additionally, there was a similar significant association between waist circumference and a T2DM diagnosis by both isolated A1c and with isolated 2-hour glucose. For a one centimeter increase of waist circumference, the odds of a T2DM diagnosis by isolated A1c was 6% higher (95% CI:1.03-1.09) and the odds of T2DM by 2-hour glucose was 5% (95% CI: 1.02-1.09) higher than those without T2DM.

Table 3. Factors associated with prediabetes diagnosed by HbA1c, fasting glucose, and 2-hour glucose using multivariate regression

Model		HbA1c		Fasting Glucose		2-hour Glucose	
		OR Est.	95% CI	OR Est.		OR Est.	95% CI
Full model with HOMA-IR							
	Age	1.04	1.02-1.07	1.03	0.99-1.07	0.998	0.96-1.04
	Sex	0.56	0.27-1.16	1.56	0.51-4.64	1.76	0.60-5.13
	Height	0.994	0.96-1.03	0.995	0.94-1.05	0.98	0.93-1.03
	WC	1.01	0.98-1.04	0.99	0.95-1.03	0.97	0.93-1.02
	Family History	1.26	0.74-2.15	1.26	0.65-3.41	1.09	0.52-2.29
	Triglycerides	1.00	0.997-1.004	0.999	0.993-1.004	1.001	0.996-1.01
	HDL	1.02	0.98-1.05	1.01	0.96-1.05	0.98	0.94-1.03
	LDL	1.01	0.998-1.02	0.995	0.98-1.01	1.004	0.99-1.02
	HOMA-IR	1.21	1.001-1.47	1.46	1.17-1.83	1.46	1.17-1.82
Full model with HOMA-B							
	Age	1.044	1.02-1.07	1.004	0.97-1.04	1.00	0.96-1.04
	Sex	0.52	0.26-1.07	1.29	0.42-3.92	1.50	0.52-4.32
	Height	0.995	0.96-1.03	0.98	0.93-1.04	0.99	0.94-1.04
	WC	1.02	0.99-1.05	1.04	0.99-1.09	0.98	0.93-1.02
	Family History	1.25	0.73-2.13	1.58	0.69-3.66	1.08	0.51-2.26
	Triglycerides	1.001	0.997-1.005	1.000	0.994-1.01	1.001	0.996-1.01
	HDL	1.02	0.98-1.05	1.000	0.96-1.05	0.98	0.94-1.03
	LDL	1.0	0.998-1.015	0.993	0.981-1.01	1.004	0.993-1.02
	HOMA-B	1.002	0.999-1.005	0.990	0.984-0.997	1.005	1.001 1.01

OR=Odds Ratio, CI=Confidence Interval

Table 4. Factors associated with T2 DM diagnosed by HbA1c, fasting glucose, and 2-hour glucose using multivariate regression

Model		HbA1c		Fasting Glucose		2-hour Glucose	
		OR Est.	95% CI	OR Est.		OR Est.	95% CI
Full model with HOMA-IR							
	Age	1.06	1.03-1.08	1.06	0.97-1.14	1.01	0.98-1.05
	Sex	0.75	0.40-1.41	3.80	0.38-37.99	3.46	1.40-8.55
	Height	0.97	0.94-1.01	0.98	0.88-1.10	0.95	0.91-0.99
	WC	1.04	1.01-1.06	0.91	0.83-1.00	1.03	0.99-1.06
	Family History	0.82	0.52-1.30	1.12	0.21-5.93	0.97	0.51-1.85
	Triglycerides	0.999	0.996-1.003	1.00	0.988-1.012	0.999	0.994-1.003
	HDL	0.96	0.93-0.99	1.02	0.94-1.12	1.02	0.98-1.05
	LDL	1.01	1.00-1.02	0.98	0.96-1.01	1.00	0.99-1.01
	HOMA-IR	1.11	1.01-1.23	1.20	0.99-1.45	1.22	1.10-1.35

Full model with HOMA-B	Adjusted						
	Age	1.05	1.02-1.07	1.03	0.94-1.12	1.01	0.98-1.04
	Sex	0.66	0.35-1.25	1.72	0.18-16.35	2.83	1.18-6.82
	Height	0.96	0.93-0.996	0.96	0.86-1.08	0.94	0.90-0.98
	WC	1.06	1.03-1.09	0.98	0.89-1.07	1.05	1.02-1.09
	Family History	0.87	0.55-1.38	1.47	0.26-8.25	1.05	0.56-2.00
	Triglycerides	1.00	0.996-1.003	1.003	0.991-1.014	0.999	0.995-1.004
	HDL	0.96	0.93-0.99	1.01	0.92-1.10	1.01	0.98-1.05
	LDL	1.01	1.00-1.02	0.98	0.96-1.010	1.004	0.995-1.01
	HOMA-B	0.995	0.99-0.998	0.97	0.94-0.99	0.998	0.994-1.002

OR=Odds Ratio, CI=Confidence Interval

DISCUSSION:

In a community based sample of urban adults from Chennai, India, we found the highest proportion of those identified as having prediabetes and T2DM were diagnosed by isolated A1c, followed by isolated 2-hour glucose, with isolated fasting glucose diagnosing the fewest individuals. Additionally, we found that 13.77% of the entire sample population were identified as having prediabetes by isolated A1c and 9.65% of the population was considered to have T2DM by A1c levels alone. These results are similar to past studies showing that A1c tends to identify more individuals, especially in non-white populations, as having prediabetes or T2DM than other diagnostic methods.[81,82,83]

We also found that more women were more likely to be diagnosed as having prediabetes by A1c only, but more men were diagnosed by isolated fasting glucose and isolated 2-hour glucose. This is an interesting result, as another study looking at age and gender in a Chinese population found that women tend to have significantly lower A1c levels in comparison to men.[84] Those with prediabetes by isolated A1c also tended to be older than those with prediabetes by isolated 2-hour. A1c levels have been seen to increase with advancing age, which may be playing a role in the differences in A1c levels between those with prediabetes by A1c and 2-hour glucose.[85] Both the those with prediabetes by isolated 2-hour glucose and isolated fasting glucose were more insulin resistant than those with prediabetes by isolated A1c. Past

research has shown that A1c levels may not be a good predictor of insulin resistance,[86] and these results add further evidence to that claim.

Interestingly, those with prediabetes by isolated 2-hour glucose have better beta-cell function, compared to those diagnosed by isolated A1c group, but those with prediabetes by isolated fasting glucose had poorer beta-cell function than the A1c group. In a past study, both IFG and IGT were associated with poorer insulin secretion than being identified with prediabetes by A1c.[87] Our results seem to match past evidence, with those with isolated IFG having lower insulin secretion, as seen by the HOMA-B statistic. However, it is important to note that HOMA-B for those with prediabetes by A1c alone was not significantly different than NGT, thereby indicating that those diagnosed with prediabetes by isolated A1c may have better metabolic profiles than those diagnosed by other measures.

Cholesterol and triglyceride levels were also seen to be different by each diagnostic group for prediabetes. Those with prediabetes by isolated 2-hour glucose had significantly lower HDL and higher triglycerides, in comparison to the isolated A1c group, thereby indicating that in this population, those with prediabetes by isolated A1c may show less dyslipidemia than those with prediabetes by 2-hour glucose alone. Comparatively, those with prediabetes by isolated fasting glucose had significantly lower LDL than those in the isolated A1c group, but HDL and triglycerides were not significantly different. High triglycerides have been positively linked to IFG and IGT in past studies, which is relatively consistent with our findings, but shows the necessity of additional research on the association between triglycerides and A1c.[88,89]

With regards to T2DM, we found that those diagnosed by isolated A1c were significantly more likely to be female and older than those diagnosed by isolated 2-hour glucose. These results are similar to the results from the population with prediabetes, where those identified by isolated

A1c had significantly fewer males than the 2-hour glucose counterpart. Additionally, the isolated 2-hour glucose T2DM group was more insulin resistant than the isolated A1c group, which follows the pattern seen in those with prediabetes. Those identified to have T2DM by 2-hour glucose alone were significantly also younger than those by A1c alone. This adds to existing research on how age and sex may also play a role in elevated A1c levels.[90]

More significant differences were seen between those diagnosed by A1c alone and fasting glucose alone. Those diagnosed with T2DM by fasting glucose alone had lower BMI and waist circumference than those diagnosed by isolated A1c. This result may be something that needs additional research, as there is much evidence that BMI and waist circumference have ethnic variability, especially for the Indian population.[91] As seen already in the prediabetic population, those diagnosed with T2DM by isolated fasting glucose also had lower LDL than those diagnosed by isolated A1c. This pattern between lower LDL and fasting glucose should be studied further in Indian populations. Also, those with T2DM by fasting glucose alone had poorer beta-cell function than those diagnosed by A1c alone, which adds to existing research that elevated fasting plasma glucose is associated with poorer insulin secretion.[92]

From the characteristic tables 1 and 2, there are significant differences between those identified with prediabetes or T2DM by isolated A1c and those identified via isolated fasting glucose and isolated 2-hour glucose. With much higher prevalence rates in the isolated A1c groups, it appears that A1c diagnostic criterion may be identifying different types of people with prediabetes and T2DM than the other two tests. Especially in the case of prediabetes, there are more significant differences between the isolated A1c, isolated fasting glucose, and isolated 2-hour glucose groups than there is between isolated A1c and NGT. When it comes to insulin resistance and secretion, there is a much wider range of median values between the three

diagnostic groups, while the isolated A1c group does not differ significantly from NGT. This leads us to believe that A1c may not be the most discerning test for identifying those with prediabetes and may be over-diagnosing individuals with prediabetes. There are also several significant differences between all of those diagnosed with T2DM by isolated measures. These results show the need for additional research on how A1c as a test compares to the standing gold-standard tests, especially in this population. A1c has been seen to have high specificity but limited sensitivity for T2DM in certain populations, but in Asian populations, A1c may be overly sensitive and may lead to more false positives.[93]

When looking at the regression models for prediabetes, the significant association between insulin resistance and isolated A1c was smaller than the associations between insulin resistance and isolated fasting glucose and isolated 2-hour glucose, 23% compared to 43% and 41% respectively. The odds of a prediabetes diagnosis due to increased insulin resistance was much lower for isolated A1c than the other two tests. A past study found that higher levels of A1c, above the prediabetic level, were significantly associated with insulin resistance, but it may be that HOMA-IR is not as good of a predictor for a prediabetes diagnosis by A1c alone, when compared to the other methods of testing.[94] Beta-cell function was associated only with isolated fasting glucose (estimated odds: 1%) and isolated 2-hour glucose (estimated odds: 0.5%). With isolated A1c not having a significant association, it may be concluded that beta-cell functioning is not the most effective method of estimating a prediabetes diagnosis by A1c.

For the models exploring the relationships between T2DM diagnosis by each test, the association between insulin resistance and isolated A1c (11%) was smaller than that of insulin resistance and 2-hour glucose (22%). These associations add to the scholarship that insulin resistance plays a significant role in increased T2DM prevalence in India.[95] However, these

results also suggest that insulin resistance is a better predictor of T2DM by isolated 2-hour glucose than T2DM by isolated A1c. It is probable that there was not a significant association between isolated fasting glucose and most of the covariates, including HOMA-IR, due to the small sample size for this group (n=8). There was one significant association with isolated fasting glucose, where increased beta-cell function was linked to 6% lower odds of a T2DM diagnosis, compared to 0.5% lower odds of a T2DM diagnosis by isolated A1c. These results are not unsurprising, as with better beta-cell function and increase insulin secretion, there is often better glycemic control.[96] Another interesting comparison was between the association with waist circumference and a T2DM diagnosis by isolated A1c and isolated 2-hour glucose. With increased waist circumference, there was increased odds of T2DM by both of these tests. This only emphasizes evidence waist circumference being an effective of a predictor of T2DM in Indian population.[97]

From these results, it can be concluded that A1c appears to identify different individuals to have prediabetes and T2DM, compared to fasting glucose and 2-hour glucose diagnostic criteria. Generally speaking, it appears that those identified to have prediabetes by A1c alone are healthier than their counterparts identified by fasting or 2-hour glucose measures, especially when it comes to cholesterol and triglycerides. Outside of HDL and LDL levels, the characteristics between those with prediabetes diagnosed by isolated A1c and those with NGT were not significantly different. There is a need to further explore A1c levels in Indian populations, as it may be over-identifying individuals with prediabetes who are actually more similar to individuals with normoglycemia. However, the results suggest that A1c may be a better method for identifying those with T2DM than for identifying prediabetes. There were more similarities between those diagnosed with T2DM by isolated A1c and those diagnosed by

isolated 2-hour glucose, especially when comparing the odds of a T2DM diagnosis due to increased insulin resistance and insulin secretion.

A limitation in the analysis of the T2DM data was the significantly smaller sample size of T2DM by isolated fasting glucose. With a sample of only 8 individuals, it is difficult to generalize the results to the larger fasting glucose T2DM population. These data may not be representative of most people diagnosed with T2DM by fasting glucose. However, it is still apparent that there is a higher prevalence of T2DM by A1c than either of the two other tests. Due to this small sample size, it will be necessary to continue researching the relationships between T2DM by A1c, fasting glucose, and 2-hour glucose in order to get a better understanding of how these diagnostic criteria function in an Indian population. This study is also limited by the cross-sectional nature, where these data were gathered at a singular time point and were not replicated. Additionally, with most participants coming from a middle-class community in Chennai, India, it can be difficult to generalize these results, even to the rest of India. Given that A1c can be impacted by nutritional deficiencies, it will be necessary to explore different socioeconomic groups and both rural and urban areas to develop more insight on how A1c may fluctuate depending on the population. Also, there are regional and state differences throughout India and additional research will need to be done in order to see how A1c functions in those populations.

With these results, there is not enough compelling evidence to use A1c as the primary test for identifying prediabetes or T2DM in Indian populations. There is still concern of overdiagnosis by using A1c as a screening method for at-risk individuals. Furthermore, there should be caution in considering replacing OGTT with A1c, as there were significant differences in characteristics between those diagnosed with prediabetes and T2DM by A1c alone and by 2-hour glucose alone. By using A1c instead of OGTT, many high-risk individuals would not be

diagnosed or identified for early intervention and it is possible that many people will be incorrectly presumed to be prediabetic or have T2DM. Mis- or re-classifying individuals could have negative health effects, both physically and emotionally. There needs to be caution in recommending a test that has the potential of misclassifying many individuals in an area where there is limited health system capacity.

APPENDIX:

Appendix A. Full multivariate regression models: Factors associated with prediabetes diagnosed by HbA1c, fasting glucose and 2-hour glucose

Model		HbA1c		Fasting Glucose		2-hour Glucose	
		OR Est.	95% CI	OR Est.	95% CI	OR Est.	95% CI
MV-adjusted Model 1							
	Age	1.05	1.02-1.07	1.02	0.99-1.06	0.990	0.96-1.02
	Sex (male)	1.27	0.64-2.51	1.24	0.62-2.49	0.59	0.37-0.92
MV-adjusted Model 2							
	Age	1.04	1.02-1.07	1.02	0.99-1.06	0.99	0.95-1.02
	Sex	0.53	0.27-1.06	1.18	0.42-3.29	1.82	0.67-4.98
	Height	0.99	0.96-1.03	0.99	0.95-1.05	0.97	0.93-1.02
	WC	1.02	0.99-1.05	1.01	0.97-1.05	1.00	0.96-1.04
MV-adjusted Model 3							
	Age	1.04	1.02-1.07	1.02	0.99-1.06	0.99	0.95-1.02
	Sex	0.56	0.28-1.12	1.28	0.46-3.59	1.87	0.68-5.14
	Height	0.99	0.95-1.03	0.99	0.95-1.05	0.97	0.92-1.02
	WC	1.02	0.99-1.05	1.01	0.96-1.05	1.00	0.96-1.04
	Family history	1.30	0.77-2.20	1.64	0.73- 3.71	1.14	0.55-2.36
MV-adjusted Model 4							
	Age	1.04	1.02-1.07	1.02	0.99-1.06	0.99	0.95-1.02
	Sex	0.57	0.29-1.15	1.30	0.46-3.67	1.85	0.67-5.10
	Height	0.99	0.95-1.03	1.00	0.95-1.05	0.97	0.92-1.02
	WC	1.02	0.99-1.06	1.01	0.97-1.05	1.00	0.96-1.04
	Family History	1.29	0.76-2.18	1.63	0.72-3.68	1.15	0.56-2.39
	Triglycerides	0.999	0.996-1.002	0.999	0.996-1.003	1.000	0.998-1.003
MV-adjusted Model 5							
	Age	1.04	1.01-1.07	1.02	0.98-1.06	0.99	0.95-1.02
	Sex	0.60	0.30-1.22	1.29	0.62-4.84	1.73	0.62-4.84
	Height	0.99	0.95-1.03	0.996	0.95-1.05	0.97	0.92-1.02
	WC	1.03	0.99-1.06	1.01	0.97-1.05	0.999	0.96-1.04
	Family History	1.27	0.75-2.15	1.63	0.72-3.68	1.16	0.56-2.41
	Triglycerides	0.999	0.997-1.002	0.999	0.995-1.003	1.00	0.997-1.003
	HDL	1.01	0.98-1.04	0.998	0.96-1.04	0.98	0.94-1.03
MV-adjusted Model 6							
	Age	1.04	1.02-1.07	1.02	0.98-1.06	0.99	0.95-1.03
	Sex	0.54	0.27-1.11	1.42	0.48-4.15	1.51	0.53-4.32
	Height	0.99	0.96-1.03	0.99	0.94-1.04	0.98	0.93-1.03
	WC	1.02	0.99-1.05	1.01	0.97-1.05	0.997	0.96-1.04
	Family History	1.27	0.75-2.16	1.55	0.68-3.52	1.11	0.53-2.30
	Triglycerides	1.001	0.997-1.004	0.999	0.994-1.005	1.002	0.997-1.01
	HDL	1.01	0.981-1.04	1.00	0.96-1.05	0.98	0.94-1.03
	LDL	1.01	0.998-1.02	0.99	0.98-1.01	1.00	0.99-1.02
MV-adjusted Model 7							
	Age	1.04	1.02-1.07	1.03	0.99-1.07	0.998	0.96-1.04

	Sex	0.56	0.27-1.16	1.56	0.51-4.64	1.76	0.60-5.13
	Height	0.994	0.96-1.03	0.995	0.94-1.05	0.98	0.93-1.03
	WC	1.01	0.98-1.04	0.99	0.95-1.03	0.97	0.93-1.02
	Family History	1.26	0.74-2.15	1.26	0.65-3.41	1.09	0.52-2.29
	Triglycerides	1.00	0.997-1.004	0.999	0.993-1.004	1.001	0.996-1.006
	HDL	1.02	0.98-1.05	1.01	0.96-1.05	0.98	0.94-1.03
	LDL	1.01	0.998-1.02	0.995	0.98-1.01	1.004	0.99-1.02
	HOMA-IR	1.21	1.001-1.47	1.46	1.17-1.83	1.46	1.17-1.82
MV-adjusted Model 8	Adjusted						
	Age	1.044	1.02-1.07	1.004	0.97-1.04	1.00	0.96-1.04
	Sex	0.52	0.26-1.07	1.29	0.42-3.92	1.50	0.52-4.32
	Height	0.995	0.96-1.03	0.98	0.93-1.04	0.99	0.94-1.04
	WC	1.02	0.99-1.05	1.04	0.99-1.09	0.98	0.93-1.02
	Family History	1.25	0.73-2.13	1.58	0.69-3.66	1.08	0.51-2.26
	Triglycerides	1.001	0.997-1.005	1.000	0.994-1.005	1.001	0.996-1.007
	HDL	1.02	0.98-1.05	1.000	0.96-1.05	0.98	0.94-1.03
	LDL	1.0	0.998-1.015	0.993	0.981-1.006	1.004	0.993-1.016
	HOMA-B	1.002	0.999-1.005	0.990	0.984-0.997	1.005	1.001 1.010

Appendix B. Full multivariate regression models: Factors associated with prediabetes diagnosed by HbA1c, fasting glucose and 2-hour glucose

Model		HbA1c		Fasting Glucose		2-hour Glucose	
		OR Est.	95% CI	OR Est.	95% CI	OR Est.	95% CI
MV-adjusted Model 1							
	Age	1.06	1.04-1.08	1.05	0.97-1.14	1.02	0.99-1.05
	Sex (male)	0.74	0.50-1.09	0.96	0.23-4.05	1.77	0.97-3.22
MV-adjusted Model 2							
	Age	1.01	0.98-1.04	1.05	0.97-1.14	1.05	1.03-1.08
	Sex	0.82	0.45-1.50	1.18	0.29-20.26	2.78	1.19-6.51
	Height	0.96	0.932-0.995	0.98	0.88-1.10	0.94	0.90-0.99
	WC	1.05	1.03-1.07	0.92	0.84-1.01	1.04	1.01-1.08
MV-adjusted Model 3							
	Age	1.05	1.03-1.08	1.05	0.97-1.14	1.01	0.98-1.04
	Sex	0.56	0.44-1.45	2.47	0.29-21.05	2.78	1.18-6.53
	Height	0.96	0.933-0.995	0.98	0.88-1.10	0.94	0.90-0.99
	WC	1.05	1.03-1.08	0.92	0.84-1.01	1.04	1.01-1.08
	Family history	0.82	0.53-1.29	1.12	0.22-5.74	1.04	0.55-1.95
MV-adjusted Model 4							
	Age	1.05	1.03-1.08	1.058	0.97-1.14	1.01	0.98-1.04
	Sex	0.78	0.43-1.43	2.51	0.29-21.46	2.79	1.18-6.59
	Height	0.96	0.932-0.996	0.96	0.88-1.10	0.94	0.90-0.99
	WC	1.05	1.03-1.07	0.92	0.84-1.01	1.04	1.01-1.08
	Family History	0.84	0.53-1.31	1.11	0.22-5.72	1.03	0.55-1.95
	Triglycerides	1.001	0.999-1.003	0.999	0.987-1.010	1.000	0.996-1.003
MV-adjusted Model 5							

	Age	1.06	1.03-1.08	1.05	0.97-1.14	1.01	0.98-1.04
	Sex	0.71	0.38-1.30	2.57	0.29-22.50	3.00	1.26-7.15
	Height	0.96	0.933-0.996	0.98	0.88-1.10	0.94	0.90-0.99
	WC	1.05	1.02-1.07	0.92	0.84-1.01	1.04	1.01-1.08
	Family History	0.83	0.53-1.30	1.11	0.22-5.72	1.04	0.55-1.96
	Triglycerides	1.001	0.999-1.003	0.999	0.99-1.01	1.00	0.997-1.003
	HDL	0.97	0.95-1.00	1.01	0.92-1.10	1.02	0.99-1.06
MV-adjusted Model 6							
	Age	1.06	1.031-1.08	1.05	0.97-1.14	1.01	0.98-1.04
	Sex	0.68	0.36-1.27	2.88	0.31-26.92	2.87	1.20-6.88
	Height	0.97	0.94-1.00	0.98	0.87-1.09	0.94	0.90-0.99
	WC	1.04	1.02-1.07	0.93	0.85-1.02	1.05	1.01-1.08
	Family History	0.84	0.53-1.32	1.12	0.21-5.92	1.03	0.54-1.94
	Triglycerides	1.00	0.996-1.003	1.00	0.99-1.01	0.999	0.995-1.004
	HDL	0.96	0.93-0.99	1.02	0.94-1.11	1.01	0.98-1.05
	LDL	1.01	1.00-1.02	0.98	0.96-1.01	1.00	0.995-1.01
MV-adjusted Model 7							
	Age	1.06	1.03-1.08	1.06	0.97-1.14	1.01	0.98-1.05
	Sex	0.75	0.40-1.41	3.80	0.38-37.99	3.46	1.40-8.55
	Height	0.97	0.94-1.01	0.98	0.88-1.10	0.95	0.91-0.99
	WC	1.04	1.01-1.06	0.91	0.83-1.00	1.03	0.99-1.06
	Family History	0.82	0.52-1.30	1.12	0.21-5.93	0.97	0.51-1.85
	Triglycerides	0.999	0.996-1.003	1.00	0.988-1.012	0.999	0.994-1.003
	HDL	0.96	0.93-0.99	1.02	0.94-1.12	1.02	0.98-1.05
	LDL	1.01	1.00-1.02	0.98	0.96-1.01	1.00	0.99-1.01
	HOMA-IR	1.11	1.01-1.23	1.20	0.99-1.45	1.22	1.10-1.35
MV-adjusted Model 8	Adjusted						
	Age	1.05	1.02-1.07	1.03	0.94-1.12	1.01	0.98-1.04
	Sex	0.66	0.35-1.25	1.72	0.18-16.35	2.83	1.18-6.82
	Height	0.96	0.930-0.996	0.96	0.86-1.08	0.94	0.90-0.98
	WC	1.06	1.03-1.09	0.98	0.89-1.07	1.05	1.02-1.09
	Family History	0.87	0.55-1.38	1.47	0.26-8.25	1.05	0.56-2.00
	Triglycerides	1.00	0.996-1.003	1.003	0.991-1.014	0.999	0.995-1.004
	HDL	0.96	0.93-0.99	1.01	0.92-1.10	1.01	0.98-1.05
	LDL	1.01	1.00-1.02	0.98	0.96-1.010	1.004	0.995-1.01
	HOMA-B	0.995	0.991-0.998	0.965	0.938-0.992	0.998	0.994-1.002

Appendix C. Factors associated with prediabetes diagnosed by HbA1c, fasting glucose and 2-hour glucose using backwards stepwise selection

Backwards Selection Model		HbA1c		Fasting Glucose		2-hour Glucose	
Model with HOMA-B	Adjusted						
	Age	1.05	1.02-1.08	1.01	0.97-1.05	0.999	0.96-1.04
	Sex	0.55	0.35-0.87	1.27	0.62-2.58	1.14	0.57-2.28
	HOMA-B	1.002	0.999-1.005	0.990	0.984-0.997	1.005	1.001-1.010
Model with HOMA-IR	Adjusted						
	Age	1.05	1.02-1.08	1.03	0.99-1.05	0.998	0.96-1.03
	Sex	0.56	0.35-0.88	1.13	0.55-2.30	1.17	0.59-2.34
	HOMA-IR	1.23	1.03-1.47	1.43	1.17-1.75	1.41	1.15-1.72

Appendix D. Factors associated with T2DM diagnosed by HbA1c, fasting glucose and 2-hour glucose using backwards stepwise selection

Backwards Selection Model		HbA1c		Fasting Glucose		2-hour Glucose	
Model with HOMA-B	Adjusted						
	Age	1.04	1.02-1.07	1.02	0.94-1.111	1.02	0.99-1.05
	Height	0.95	0.93-0.98	0.98	0.90-1.07	0.97	0.94-1.01
	Waist Circ.	1.06	1.03-1.09	0.98	0.90-1.08	1.06	1.02-1.09
	HOMA-B	0.995	0.991-0.998	0.96	0.94-0.99	0.998	0.99-1.00
Model with HOMA-IR	Adjusted						
	Age	1.06	1.04-1.09	1.06	0.98-1.14	1.02	0.99-1.05
	Sex	0.53	0.33-0.85	2.81	0.48-16.46	1.81	0.88-3.71
	Waist Circ.	1.03	1.00-1.05	0.91	0.83-0.996	1.02	0.98-1.05
	HDL	0.96	0.94-0.99	1.02	0.94-1.11	1.02	0.98-1.05
	LDL	1.01	1.00-1.02	0.98	0.96-1.01	1.00	0.995-1.01
	HOMA-IR	1.12	1.02-1.23	1.21	0.99-1.46	1.23	1.11-1.36

Appendix E. Clinical and Biochemical Characteristics of Participants Diagnosed with Prediabetes by aggregated HbA1c, Fasting Glucose, and 2-hour Glucose Glycemic Status

	Normal Glucose Tolerance		Prediabetes diagnosed by HbA1c		Prediabetes Diagnosed by Fasting Glucose		Prediabetes Diagnosed by 2-hour Glucose	
	n=344	26.77%	n=608	47.32%	n=377	29.34%	n=386	30.03%
Male (n, %)	210	61.05%	360	59.21%	234	62.07%	253	65.54%
	p=0.0800				p=0.0354		p=0.0045	
Age (years)	42.05	sd=9.07	44.49	sd=8.81	44.21	sd=9.41	43.56	sd=9.27
	p<.0001				p=0.0014		p<.0001	
Height (cm)	163.96	sd=9.43	163.13	sd=9.44	163.78	sd=9.65	164.24	sd=9.18
	p=0.0432				p=0.0145		p=0.0089	
BMI (kg/m2)	26.77	sd=3.6	27.60	sd=3.62	27.67	sd=3.82	27.71	sd=3.71
	p=0.0001				p=0.1306		p=0.0136	
Waist (cm)	92.20	sd=9.27	93.80	sd=9.04	93.99	sd=9.42	94.75	sd=9.22
	p=0.0026				p=0.8066		p=0.0015	
Blood Pressure								
Systolic (mm Hg)	122.04	sd=15.35	123.93	sd=14.92	124.70	sd=15.44	125.38	sd=15.39
	p=0.0788				p=0.4692		p=0.0057	
Diastolic (mm Hg)	72.95	sd=9.65	74.90	sd=9.70	75.47	sd=10.32	76.05	sd=10.09
	p=0.0003				p=0.2519		p=0.0005	
FPG (mg/dL)	91.37	sd=5.23	99.51	sd=9.09	106.32	sd=5.71	100.02	sd=9.33
	p<.0001				p<.0001		p<.0001	
2hPG (mg/dL)	112.15	sd=16.60	138.65	sd=27.44	142.10	sd=28.02	160.53	sd=15.72
	p<.0001				p<.0001		p<.0001	
HbA1c (%)	5.67	sd=0.37	5.99	sd=0.22	5.90	sd=0.33	5.89	sd=0.34
	p<.0001				p<.0001		p<.0001	
HOMA-IR Median (IQR)	2.18	1.50-2.87	3.15	1.97-3.87	3.50	2.22-4.14	3.46	2.11-4.22
	p<.0001				p<.0001		p<.0001	
HOMA-B Median (IQR)	120	86.18-170.31	131.75	80.23-162.00	112.14	70.64-132.98	141.90	84.27-174.24
	p=0.0871				p<.0001		p=0.0133	
LDL (mg/dL) Median (IQR)	112	96-132	118.70	100-137	116.51	96-136	117.57	99-136
	p=0.0201				p=0.0240		p=0.2751	

HDL (mg/dL Median (IQR)	40	35-45	40.75	35-45	40.11	35-45	39.79	35-44
	p=0.0467				p=0.1520		p=0.0108	
Triglycerides(mg/dL) Median (IQR)	121	87-165.5	143.21	96.5-174.5	149.69	101-179	155.60	105-190
	p=0.1153				p=0.0706		p=0.0001	

Appendix F. Clinical and Biochemical Characteristics of Participants Diagnosed with T2DM by aggregated HbA1c, Fasting Glucose, and 2-hour Glucose Glycemic Status

	Normal Glucose Tolerance		Diabetes diagnosed by HbA1c		Diabetes Diagnosed by Fasting Glucose		Diabetes Diagnosed by 2-hour Glucose	
	n=344	26.77%	n=302	23.5%	n=117	9.11%	n=240	18.68%
Age (years)	42.05	sd=9.07	47.46	sd=8.61	46.84	sd=8.29	46.50	sd=8.96
	p<.0001				p=0.57		p=0.07	
Male (n, %)	210	61.05%	195	60.47%	73	62.39%	171	71.25%
	p=0.3477				p=0.72		p=0.013	
Height (m)	163.96	sd=9.43	162.60	sd=8.77	163.33	sd=9.58	163.25	sd=8.31
	p=0.0665				p=0.595		p=0.254	
BMI (kg/m2)	26.77	sd=3.6	27.75	sd=3.97	27.27	sd=3.85	27.41	sd=3.61
	p=0.0012				p=0.207		p=0.026	
Waist (cm)	92.20	sd=9.27	95.37	sd=9.23	94.25	sd=9.89	95.24	sd=9.18
	p<.0001				p=0.067		p=0.464	
Blood Pressure								
Systolic (mm Hg)	122.04	sd=15.35	128.24	sd=15.43	127.41	sd=14.75	127.83	sd=15.87
	p<.0001				p=0.595		p=0.652	
Diastolic (mm Hg)	72.95	sd=9.65	77.31	sd=9.77	76.84	sd=8.86	77.08	sd=9.71
	p<.0001				p=0.715		p=0.878	
FPG (mg/dL)	91.37	sd=5.23	121.95	sd=21.79	143.39	sd=20.40	126.07	sd=22.47
	p<.0001				p<.0001		p<.0001	
2hPG (mg/dL)	112.15	sd=16.60	216.16	sd=63.97	263.10	sd=61.68	251.98	sd=46.05
	p<.0001				p<.0001		p<.0001	
HbA1c (%)	5.67	sd=0.37	7.08	sd=0.87	7.35	sd=1.09	6.98	sd=1.08
	p<.0001				p<.0001		p<.0001	
Median (IQR) HOMA-IR	2.18	1.50-2.87	3.79	2.65-5.34	4.63	3.03-6.78	4.19	2.72-5.61
	p<.0001				p<.0001		p=0.0005	
Median (IQR) HOMA-B	120	86.18-170.31	86.25	54.4-121.94	60.35	39.94-94.90	82.12	51.6-124.87
	p<.0001				p<.0001		p<.0001	
Median (IQR) LDL (mg/dL)	112	96-132	120	100-142	117	97-135	118	98-143
	p=0.0197				p=0.342		p=0.122	
Median (IQR) HDL (mg/dL0	40	35-45	38	33-44	38	38-45	38	33.5-44
	p=0.0065				p=0.41		p=0.083	
Median (IQR) Triglycerides (mg/dL)	121	87-165.5	143	108-186	149	112-198	145	110-194.5
	p=0.0019				p=0.078		p=0.125	

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