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Type 2 Diabetes in Asian Indians on Two Continents: Insights into the Epidemic and Pathophysiology

By

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Doctor of Philosophy

Graduate Division of Biological and Biomedical Sciences

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B.A., University of California, Irvine, 2003

M.P.H., Yale University, 2010

Advisor: K.M. Venkat Narayan, MD, MSc, MBA

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Abstract

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Asian Indians are at high risk for type 2 diabetes despite having, on average, lower levels of traditional risk factors such as age and adiposity compared to other ethnic groups. As a result, it is possible that Asian Indians may experience unique biological susceptibilities to β-cell dysfunction which could be the driving factor behind diabetes risk in this population. These susceptibilities, coupled with recent nutritional transitions in India, may be resulting in a much higher prevalence of diabetes in Asian Indians living in India compared to those who have migrated to the United States as well as those from other ethnic populations. This dissertation sought to address these issues by utilizing data from four cross-sectional population based surveys representative of Asian Indians living in San Francisco or Chicago (The Mediators of Atherosclerosis in South Asians Living in America (MASALA) pilot study (n=150) and full cohort study (n=757)) Asian Indians living in Chennai, India (the **C**entre for c**A**rdiometabolic **R**isk **R**eduction in **S**outh-Asia study (CARRS) (n=2,305)), and Caucasians, Blacks, and Hispanics living in the United States (the Nutrition Examination Survey (NHANES) (n=6,512)). Major findings indicated that: (1) Compared to poor insulin sensitivity, poor β-cell function was more strongly associated with diabetes and prediabetes and was also associated with glycemic progression in a cohort of migrant Asian Indians; (2) After adjusting for age, sex, and anthropometry, adjustment for β-cell function was associated with an increased odds of diabetes in Blacks and Hispanics compared to Asian Indians living in India; (3) There is a high prevalence of diabetes and a relatively low prevalence of prediabetes in Asian Indians living in India; (4) Migration to a high income country may no longer increase diabetes risk in some populations. The work provided in this dissertation adds evidence to the idea that biological susceptibilities for β-cell dysfunction may be a stronger contributing factor to diabetes risk in Asian Indians compared to obesity driven insulin resistance and provides a basis for future studies that seek to disentangle the longitudinal contributions of β-cell dysfunction and insulin resistance on diabetes development in various ethnic groups.

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Chapter 1: Introduction

Type 2 diabetes mellitus currently affects approximately 382 million people worldwide,[1] and effects both individuals in living in developed and developing countries.[2,3,4] As noted in a recently published review article, while people of all ethnic backgrounds are at risk, Asian Indians (those who live in or have their roots in India) seem to be especially susceptible.[5] This is evidenced both by the steady increase of type 2 diabetes in India as well as the high prevalence of diabetes among Asian Indians living in diaspora countries.[2,5-16] Furthermore, this increased risk occurs even at lower levels of traditional risk factors such as age and BMI. A nationally representative study conducted in the United States showed that regardless of BMI classification, Asian Indians have the highest BMI-specific prevalence of type 2 diabetes among all ethnic groups.[10] Similar patterns have also been observed in other countries such as the United Kingdom, Fiji, Norway, and Singapore.[12-16] While the data are limited, it also appears that type 2 diabetes incidence is much higher in Asian Indians as compared to Caucasians. A study conducted in India noted an incidence rate of (20.2 per 1,000 person-years[17] which is much higher than incidence rates of 6.9 per 1,000 person-years in found in the United States,[18] 7.6 cases per 1,000 person years found in Italy,[19] and 10.8 cases per 1,000 person-years found in Spain.[20]

It is possible that the higher prevalence and incidence of type 2 diabetes in Asian Indian populations worldwide is due to underlying biological factors such as decreased insulin secretion, coupled with recent rapid changes in dietary, activity, and other

lifestyle behaviors. However, there is a paucity of data examining the relative contributions of β-cell function and insulin resistance on glycemic status in Asian Indians. Furthermore, migration to developed countries, such as the United States, has traditionally been associated with increased diabetes risk compared to individuals remaining in their home countries.[21,22] However, given the substantial increase in diabetes prevalence in India over the last four decades[2,5,6,7] as well as the accompanying nutritional and economic transitions,[23,24] it is now unclear how diabetes risk in migrant Asian Indians differs from that of Asian Indians living in urban India. Lastly, although diabetes rates have been rising worldwide,[3] few data exist to examine the differences in diabetes and prediabetes prevalence and the associated risk factors between Asian Indians in India and other ethnic groups in the United States who may have differing environmental and biological susceptibilities. The research described herein addresses these gaps in the current literature. The following chapters describe research that seeks to (A) assess the relative associations of β-cell dysfunction and insulin sensitivity with glycemic status and on the incidence of diabetes and prediabetes among Asian Indians in the United States; (B) assess the prevalence of diabetes and prediabetes and the associated risk factors in two Asian Indian populations living in different environments; and (C) compare the prevalence of diabetes and prediabetes and the associated risk factors between Asian Indians living in India to Caucasians, Hispanics, and Blacks in the United States. The aims of the research presented here are as follows:

Research Aim 1:

To analyze the relative associations of β-cell function and insulin sensitivity on glycemic status and on the incidence of diabetes and prediabetes in a population based cohort of migrant Asian Indians in the United States.

The pathophysiology of type 2 diabetes is a complex and multifactorial. Overt type 2 diabetes development is the result of both decreased insulin sensitivity and impaired insulin secretion.[25] Traditionally, the pathogenesis has been described as obesity driven insulin resistance followed by a subsequent decline in β-cell function, eventually leading to overt hyperglycemia.[25,26] However, early declines in β-cell function have also been detected as a driving factor for type 2 diabetes development.[27,28] It is therefore possible that some ethnic groups, such as Asian Indians may have an innate susceptibility for early decline in β-cell function, thereby placing them at increased risk for disease development beyond traditionally associated factors such as age, adiposity, and insulin resistance. The methodology and results of this analysis are presented in Chapter 4.

Research Aim 2:

To assess the prevalence of diabetes and prediabetes and the associated risk factors in two Asian Indian populations living in different environments (Chennai, India and the greater San Francisco and Chicago areas of the United States).

Immigration to developed countries is traditionally associated with increased type 2 diabetes risk.[9,10,11] Furthermore, several studies have indicated that Asian Indian immigrants have a higher prevalence of type 2 diabetes than the general United States population.[11,29,30] However, given that India has recently undergone rapid economic and nutrition transitions,[23,31] it is unclear whether diabetes risk among Asian Indians immigrants in the United States differs from that of Asian Indians in urban India. Therefore, a comparison of two genetically similar populations living in different environmental settings could shed light on the behavioral and environmental factors associated with increased diabetes risk in this ethnic group. Chapter 6 describes the

methodology and results of a comparative analysis assessing data from two population based studies, the **C**entre for c**A**rdiometabolic **R**isk **R**eduction in **S**outh-Asia study (CARRS, 2010-2011) and the Mediators of Atherosclerosis in South Asians Living in America study (MASALA, 2010-2013).

Research Aim 3:

To assess the prevalence of diabetes and prediabetes and the associated risk factors in Asian Indians living in a developing country setting (Chennai, India) to high risk groups living in a developed country setting (the United States).

The unique susceptibilities in Asian Indians for diabetes development, coupled with factors related to the changing landscape in urban India may be the driving factors behind the high risk in this ethnic group. However, it is unclear as to how the prevalence of diabetes in urban Asian Indians currently compares to ethnic groups in a developed country such as the United States who are also at high risk but may have differing environmental and biological susceptibilities. Chapter 7 describes the methodology and results of a comparative analysis assessing data from two population based studies, the **C**entre for c**A**rdiometabolic **R**isk **R**eduction in **S**outh-Asia study (CARRS, 2010-2011) and the National Health and Nutrition Examination survey (NHANES, 2010-2013).

Chapter 2: Background

Diabetes: The Global Burden

Type 2 diabetes is characterized by hyperglycemia that is the result of impaired insulin action, impaired insulin secretion, or both.[26] The degree of hyperglycemia may change over time, and generally begins in the precursor states of diabetes, either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).[32] If unmanaged, type 2 diabetes can eventually lead to severe complications such as blindness, kidney failure, or amputations.[32] According to recent estimates from the International Diabetes Federation, the number of people with diabetes worldwide is currently 382 million,[1] and this number is expected to increase by approximately 50% by the year 2035.[1] Furthermore, 80% of individuals currently living with diabetes live in low and middle income countries. While low and middle income countries are generally more populous than high income countries, the high diabetes burden in these nations could also be the result of rapid economic development, urbanization, and nutrition transitions that have occurred in these settings over a relatively short period of time.[33] In addition, some ethnic groups may also experience genetic susceptibilities to diabetes development which is exacerbated by recent changes in environment.

Diabetes in Asian Indians

The Asian Indian population is large, with more than 1.2 billion people living in South Asia,[34] and with an additional 25-40 million people of Asian Indian ancestry living in the Diaspora.[35] In the United States, the number of people with ancestry from India is increasing rapidly with an estimated 3.2 million people of Asian Indian descent currently living in the United States.[36] As a whole, compared to individuals from other ethnic

groups, Asian Indians are at high risk for diabetes. This is evidence by the high prevalence of the disease both in India and in Asian Indians living abroad.[8-16] A recent study covering three states and one union territory in India found a range of diabetes prevalence between 5.3 and 13.6%.[8] Additionally, Asian Indians who have migrated to the US have the highest diabetes prevalence among all ethnic groups, other than Native Americans.[37,38] Asian Indians also exhibit unique and paradoxical characteristics in regards to diabetes development in that diabetes occurs at younger ages and at lower levels of body mass indices[10,12,29,39] than other ethnic groups, thereby suggesting strong innate disease susceptibilities such as impaired β-cell function that exist in the absence of traditional risk factors such as age and adiposity.

Pathophysiology

The pathophysiology of diabetes is complex and involves both increased insulin resistance and impaired insulin secretion.[40] In general, the onset of diabetes occurs when pancreatic β-cells fail to secrete sufficient amounts of insulin to keep up with metabolic demand caused by insulin resistance in peripheral and/or hepatic tissues.[40] While it is commonly thought that that the pathogenesis of type 2 diabetes begins with adiposity-induced insulin resistance followed by a subsequent decline in pancreatic β-cell function,[25-26] recent evidence suggests that certain populations may also have innate susceptibilities to β-cell dysfunction that manifest very early in the natural history of diabetes.[41,42] Therefore these individuals may experience β-cell fatigue more rapidly and with lower levels of metabolic disruptions than those who develop diabetes through a predominantly insulin resistance induced pathway.

A study examining insulin resistance and β-cell function in a group of healthy, young, lean, East Asians, Asian Indian, Blacks, and Caucasians noted that the prevalence of insulin resistance in Asian Indian men was 3-4 times higher than lean men of other ethnic groups, despite having similar lifestyle factors and BMI.[5,43] The study went further to assess β-cell function in a subgroup of Asian Indian and Caucasian men and found that during an oral glucose tolerance test, Asian Indians had increased basal insulin secretion compared to Caucasians. However this increase in insulin was not enough to compensate for their degree of insulin resistance as evidenced by a lower disposition index in Asian Indians compared to Caucasians.[5,43] Additionally, a longitudinal study of Asian Indians living in South Africa with impaired glucose tolerance reported that participants exhibited delayed insulin responses despite similar plasma glucose levels to normal glycemic controls,[44] indicating that early β-cell dysfunction is an underlying pathophysiological abnormality of impaired glucose tolerance in this population. Therefore, an early impairment in β-cell function could be the driving factor in diabetes development in Asian Indians.

Immigration and Diabetes Risk

Several previous studies have noted that immigration from a developing to a developed country setting increases the risk of type 2 diabetes. Furthermore, this increased risk has been shown to worsen with time since arrival in the host country.[21,22] A previous study on Asian Indian immigrants in the United Kingdom indicated that migrants were more obese, more insulin resistant, and had higher levels of blood pressure, total cholesterol, and blood glucose than their siblings still residing in India.[45] A subsequent study comparing Asian Indians who immigrated from the state of Gujarat

to non-migrant Gujaratis also noted that those who had immigrated had higher measures of BMI, blood pressure, and lipids than their non-migrant counterparts.[46] Furthermore, the prevalence of diabetes in migrant Asian Indians has consistently been found to be higher than that of other ethnic groups.[9,10,11,37] In addition to innate biological susceptibilities, it has been thought that the increased availability and abundance of high fat, high calorie foods associated with migration has contributed greatly to increased diabetes risk in Asian Indian immigrants.[21] Previous studies have reported that migration to developed countries has led to a more frequent selection of non-traditional foods,[47] specifically the increased consumption of margarine, juice, chips, colas, alcohol and fast food and the decreased consumption of fruits, vegetables, and fiber.[48,49] While dietary habits among migrant Asian Indians may have shifted to include more animal fat and less traditional foods, there may be other factors associated with migration and acculturation such as access to health care and insurance, availability of healthy food choices, and improved health awareness, that can serve as protective factors against diabetes risk.[50] Furthermore, factors such as increased high fat diets and decreased physical activity that were once thought to be associated with migration may also be taking place in urban India. Therefore, it is possible that those who have migrated to metropolitan areas of the United States may now have a more favorable cardio metabolic profile than their counterparts in India.

Nutrition Transition in India

Throughout India, the prevalence of type 2 diabetes has been increasing steadily over the past 40 years. The first national study on type 2 diabetes prevalence in India was conducted between 1972 and 1975 and reported a prevalence of 2.1% in urban and 1.5%

in rural populations.[51] A study conducted approximately twelve years later in the state of Tamil Nadu reported a prevalence of 8.2% in urban and 2.4% in rural areas,[52] while a study done in the same urban area after a period of five years showed a prevalence of 11.6%.[53] More recent studies now estimate the diabetes prevalence to be 15% in an urban city in South India.[54] A large part of this increase in prevalence has occurred alongside nutritional and economic transitions that have led to rapid urbanization, changes in dietary intake, an overall decrease in physical activity,[23,24] all of which may be driving increases in diabetes risk. However, given that Asian Indians may also experience underlying biological susceptibilities to diabetes development such as an innate dysfunction in insulin production, is unclear as to how the prevalence of diabetes in urban Asian Indians currently compares to ethnic groups in a developed country that has undergone nutritional and economic transitions over many generations, and who are also at high risk but may have differing biological susceptibilities such as a tendency for obesity driven insulin resistance.

Chapter 3: Methods

The data analyzed in this dissertation came from three population based cross-sectional studies: (1) The Metabolic Syndrome and Atherosclerosis in South Asians study (MASALA), (2) The Centre for Cardio-metabolic Risk Reduction in South Asians study (CARRS), and (3) The National Health and Nutrition Examination Survey (NHANES). Data analysis methods pertinent to each study question are presented in the appropriate chapters (4-6).

The MASALA Study

The MASALA study was conducted in two parts. Initially, a pilot population based study was conducted in which 150 participants were enrolled from the San Francisco Bay area. Enrollment occurred between August 2006 and October 2007.[55] Eligibility criteria, questionnaire data, and clinical examination variables were similar to the MESA study,[56] as MASALA was designed to be similar to MESA for comparative analyses. Eligible participants were aged 45-84 years, and self-identified as Asian Indian. Excluded individuals consisted of those who had a previous physician diagnosed heart attack, stroke, transient ischemic attack, congestive heart failure, angina, past coronary artery bypass graft surgery, angioplasty, valve replacement, pacemaker or defibrillator implantation, surgery on the heart or arteries, or arterial fibrillation on electrocardiogram. Individuals using nitroglycerin, under active cancer treatment, with impaired cognitive ability, with life expectancy less than 5 years, plans to move away from the study area, or living in a nursing home were also excluded, as were those who could not speak or understand either Hindi or English.[55]

The sampling frame for the pilot study was created using the South Asian surnames list on the California Health Interview Survey. Names, addresses, and telephone numbers were obtained from randomly sampled households in the study area. From here, letters were mailed providing information about the study and phone calls were made to assess study eligibility. For the pilot study, a total of 3,484 letters were mailed and 1,587 (45%) households were reached by phone. Of these, 1,091 (69%) were not eligible and 346 (22%) were not interested. Of all eligible persons 150/248 (60.5%) were enrolled in the study.[55]

Beginning in October 2010 and concluding in March, 2013, and additional 750 participants were enrolled in the full MASALA cohort to include 900 South Asians, of which 757 self-identified as Asian Indian. Additional participants were enrolled from both the greater San Francisco Bay and Chicago areas and data were collected at either the University of California, San Francisco (UCSF) or Northwestern University (NWU) study centers. Participants were screened for eligibility by telephone and if eligible were invited for clinical examination to the pertinent study site.[57]

Eligibility criteria for the full MASALA cohort were similar to the pilot study with the additional exclusion criteria of participants weighing > 136 kg due to limitations with computed tomography scanning. Telephone based recruitment methods were used, and sampling frames were created by clinical site and included all 9 counties of the San Francisco Bay area and the 7 census tracts closest to NWU and secondary suburban locations around Chicago. Names, address, and telephone numbers were obtained for approximately 10,000 households using a list of South Asian surnames from the desired geographic locations. Similarly to the pilot study, letters were mailed detailing study

information and were followed by telephone calls to determine eligibility.[57] Questionnaire and relevant clinical components, as well as data analysis methods are detailed in the appropriate chapters (4 and 5).

Protocols for MASALA study were approved by the Institutional Review Boards at USCF and NWU. The MASALA pilot study was funded by National Institutes of Health grant no. K23 HL080026. The full MASALA study was supported by the NIH grant no. 1R01 HL093009.

The CARRS Study

CARRS is a hybrid cohort-modeled cross-sectional multi-center surveillance study to be conducted in three South Asian cities over a period of four years. However, for the purposes of this dissertation, only baseline cross-sectional data was be used from the city of Chennai, India which has an estimated population of 4.68 million.[34]

Sample Size Estimation

Assuming a response rate of 80% with a design effect factor of 1.5, an approximate sample size of 3,983 (rounded to 4,000) was determined as the minimum number of persons required in each city in order to reliably estimate one or more cardio-metabolic disease risk factors.[58]

Sampling Method

Households were selected for participation in 2010 using a multi-stage cluster random sampling technique. The city of Chennai is divided into 10 Zones and 155 wards by the Chennai Corporation. Each ward is comprised of census enumeration blocks or CEBs. From the list of wards, an initial 20 were randomly selected. Within each ward 5 CEBs were randomly selected. In each CEB, 20 households were randomly

selected from which 2 participants were eligible for participation. The initial sampling scheme for Chennai is as follows;

Chennai Municipal Corporation
↓
155 Corporation wards
↓
20 wards (randomly selected)
↓
5 census blocks per ward -randomly selected (total of 100 CEBs)
↓
20 Households per CEB randomly selected (total 2000 households)
↓
2 Participants per household (total 4000 study participants)

While 4,000 participants completed questionnaire data, after initial sampling only 2,543 (63%) gave a full 3-sample plasma glucose test. It was then determined that a full 3-sample plasma glucose test was needed from 4,000 participants in order to completely satisfy previously determined sample size criteria. Therefore additional recruitment was conducted to meet this requirement. Between 1 and 3 additional census enumeration blocks were randomly selected from 11 of the initial 20 wards sampled. In addition, 12 new wards were randomly selected. In these additional wards, between 1 and 4 CEBs were randomly selected and within these CEBs, 20 to 60 households were randomly selected for participation to yield a total sample size of 6,906 participants of which 4,051 gave a full 3 sample plasma glucose test.

Sampling Weights

Sampling weights were created in order to maximize the representativeness of the sample in terms of size, distribution, and overall characteristics of the study population.

Selection of participants for the Chennai study site was done in three phases; wards, census enumeration blocks, and households. The base weight calculations reflect the probability of selection at each phase. Sample weights were calculated taking into account probability weights for each census enumeration block and differential non-response rates at the household and individual level. Overall sample weights were then calculated as the inverse of the base weight (after adjusting for non-response), where the base weight was obtained as the reciprocal of the overall probability of selection. Detailed information regarding the sampling weight calculation is provided below.

***Step 1**:* Several equations were used to account for non-equal probability of selection at different stages i.e. ward, CEB, household level.

The probably of selecting wards was calculated using equation 1.

$$\text{Probability of selecting wards, Pi} = \frac{\text{No. of wards selected in the city}}{\text{Total number of wards in the city}}$$

The probably of selecting CEBs was calculated using equation 2.

$$\text{Probability of selecting CEB, Pij} = \frac{\text{No. of CEBs selected from the city}}{\text{Total number of CEBs in that particular ward}}$$

***Step 2**:* **Base weight** was calculated as the inverse of probability of selecting wards and CEBs. $\text{Base weight (BWij)} = \frac{1}{P_i * P_{ij}}$

***Step 3**:* To account for the differential non-response rate of household interviews in different domains, i.e. CEB levels in the respective city, the adjustment for household and individual non-response and selection of individuals was done using the KISH table. The base weight was adjusted for household non-response to get the adjusted base weight.

$$Adjusted\ base\ weight, ABW_{ij} = \frac{BW_{ij}}{HRR_{ij} * IRR_{ij}},$$

where

$$\text{Household Response rate(HRRij)} = \frac{\text{No.of households interviewed in the particular CEB/ cluster}}{\text{No.of households approached in the particular CEB/ cluster}}$$

$$\text{Individual Response rate(IRRij)} = \frac{\text{No. of individuals interviewed in the CEB}}{\text{No. of individuals approached in the CEB}}$$

Step 4: Sampling weights were calculated after adjustment for probability of selecting an individual using KISH table (when more than two eligible members were present in the household).

$\text{Weight}(W_{ij}) = \frac{ABW_{ij}}{K_{ij}}$, where K_{ij}=Probability of selecting individual using KISH method

$$\text{Probability of selecting through KISH (Kij)} = \frac{\text{No. of individuals approached in the particular CEB}}{\text{No. of individuals elilgible in the particular CEB}}$$

Surveillance Indicators and Study Instruments

Individuals were excluded from participation in the CARRS study if they were < 20 years of age, not residing permanently in the selected household, were pregnant, or were bedridden. Household data were collected using interviewer administered questionnaires. Questionnaires were given either in English or the preferred local language and were derived from English questionnaires used in the WHO Multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) study, WHO STEPS studies, and from previous Indian regional and national surveys.[58] An instrument for South Asia was thus developed and pilot tested prior to use in the CARRS study. Relevant clinical components, as well as data analysis methods are detailed in the appropriate chapters (5 and 6).

The CARRS study was approved by the Institutional Review Boards of The Madras Diabetes Research Foundation and Emory University. The CARRS study is funded in whole or in part by the National Heart, Lung, and Blood Institute, National Institutes of Health (NIH), Department of Health and Human Services, under Contract No. HHSN268200900026C, and the United Health Group, Minneapolis, MN, USA.

NHANES

NHANES is one of a series of health related surveys conducted by the Center for Disease Control (CDC) and the National Center for Health Statistics (NCHS) and is designed to provide health and nutritional information on the United States, civilian, non-institutionalized population. Only United States citizens residing in the 50 states or the District of Columbia at time of screening are considered eligible. Data collection for NHANES takes place at three levels; an initial household screening interview, an in home interview, and a physical and clinical examination.[59]

Sampling Method

NHANES is sampled using a complex, multi-stage, probability sampling design. Data are collected in two year cycles and sampling takes place in four stages. The first stage of selection is the primary sampling unit (PSU) that consists mainly of individual counties, with 15 different counties visited per year. The second stage consists of census blocks, and is designed to produce approximately equal sample sizes per PSU. The third stage consists of dwelling units or households (DUs), while the fourth stage consists of individuals within occupied DUs.[58] All eligible members within a DU are listed and a subsamples are selected based on age, sex, race, and income. Expected annual sample sizes at the design stage are:

15 PSUs
↓
360 Census blocks
↓
12,367 DUs screened
↓
11,500 Households screened
↓
6,525 Sampled persons
↓
5,000 Examined persons[60]

Sampling Weights

Sampling weights are crated in order maximize the representativeness of the sample. Sample weighting is carried out in three steps; (1) to compute weights to compensate for unequal probabilities of selection, (2) to adjust for nonresponse, and (3) to post stratify sample weights to the Census Bureau estimates of the United States population. Due to the multi-stage probability design of the survey, these steps are performed at each phase of data collection.[60] Detailed information regarding sampling weight calculation is included below.

Step 1: **Base weight** is calculated as the inverse of probability of selecting wards and CEBs.

Base weight (base) $= \frac{1}{r_k}$ ($f_{i(release)}$ $f_{i(desel)}$ $f_{i(sizeine)}$ $f_{i(year)}$)

The following briefly describes each component of this calculation.

- $f_{i(release)} = \frac{1}{D_i}$, where D_i represents the proportion of sampled DUs released for screening in the location where sampled participant *i* was selected. $f_{i(desel)} = \frac{1}{1-D_i}$, where $1 - D_i$ represents the proportion of released DUs deselected from the sample in the case when the expected number of sampled participants from released DUS would exceed the target sample size for the study location.

- $f_{i(desel)} = \frac{1}{1.2}$, where 1.2 represents a factor for study locations in cycle 2008-2010 in which the segment sizes and probability of DU selection were increased to facilitate reaching the target number of sample participants.
- $f_{i(year)} = \frac{AWF_i}{Number\ of\ years\ in\ sample}$, where AWF_i is a factor that when applied to weights converts them to annual weights.

Step 2: **Adjust for nonresponse**

Nonresponse adjustment factors $f_{i(NR)} = \frac{\sum n_{as}\, W_{i(base)}}{\sum n_{ar}\, W_{i(base)}}$,

where $W_{i(base)} =$ the base weight for the *i*th sampled participant in the *a*th cell, n_{as} is the total sample size in the *a*th adjustment cell and n_{ar} is the number of respondents in the *a*th cell.

Step 3: **Adjust for trimming**

Trimming of the weights was used to account for extreme weights that may have been created due to adjustment for nonresponse.

Trimming adjustment factors $f_{i(TR)} = \frac{\sum n_b\, t_i}{\sum n_b\, W_{i(base)} f_{i(NR)}}$,

Where n_b is the sample size of the *b*th race, Hispanic origin-income-sex-age sampling domain and t_i is equal to $W_{i(base)} f_{i(NR)}$.

Step 4: **Post-stratification**

Post-stratification factors $f_{i(PS)} = \frac{N_C}{\sum n_c\, W_{i(TR)}}$,

Where N_C is the control population total and n_c is the sample size of the poststratification cell.

***Step 5**:* **Computing Final Weights**

The final weight for each participant is calculated at each stage as the product of the base weight, nonresponse adjustment, trimming, and post-stratification factors. Specifically; the final screening weight is calculated as:

$$W_{i(S)} = W_{i(base)} f_{i(NR,S)} f_{i(TR,S)} f_{i(PS,S)}$$

the final interview weight is calculated as:

$$W_{i(I)} = W_{i(base)} f_{i(NR,S)} f_{i(TR,S)} f_{i(PS,S)} f_{i(NR,I)} f_{i(TR,I)} f_{i(PS,I)}$$

and the final examination weight is calculated as:

$$W_{i(E)} = W_{i(base)} f_{i(NR,S)} f_{i(TR,S)} f_{i(PS,S)} f_{i(NR,I)} f_{i(TR,I)} f_{i(PS,I)} f_{i(NR,E)} f_{i(TR,E)} f_{i(PS,E)}$$ [60]

Being that the data analyzed for this dissertation was a combination of three two-year cycles (2007-2008, 2009-2010, and 2011-2012), six year weights were created by multiplying the appropriate two year weights by one third.[59] Since various sample weights were assigned to each participant depending on the type of examination the individual was assigned to, the "least common denominator" approach was used when selecting the appropriate sample weight to apply. The variable of interest collected on the smallest number of persons was 2 hour post challenge glucose. Therefore the sample weight applied was the six year weight for the 2 hour post challenge subsample. Relevant questionnaire and clinical components, as well as data analysis methods are detailed in the appropriate chapters (6).

CHAPTER 4

The relative associations of β-cell function and insulin sensitivity with glycemic status and incident glycemic progression in migrant Asian Indians in the United States: The MASALA Study

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ABSTRACT

AIMS: We assessed the relative associations of β-cell dysfunction and insulin sensitivity with baseline glycemic status and incident glycemic progression among Asian Indians in the United States.

METHODS: A 5-sample oral glucose tolerance test was obtained at baseline. Normoglycemia, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes (T2DM) were defined by ADA criteria. The Matsuda Index (ISI_M) estimated insulin sensitivity, and the Disposition Index (DI_o) estimated β-cell function. Visceral fat was measured by abdominal CT. After 2.5 years, participants underwent a 2-sample oral glucose tolerance test. Standardized polytomous logistic regression was used to examine associations with prevalent and incident glycemia.

RESULTS: Mean age was 57±8 years and BMI 26.1±4.6 kg/m^2. Log ISI_M and log DI_o were associated with prediabetes and T2DM after adjusting for age, sex, BMI, family history of diabetes, hypertension, and smoking. After adjusting for visceral fat, only DI_o remained associated with prediabetes (OR per SD 0.17, 95% CI: 0.70, 0.41) and T2DM (OR 0.003, 95% CI: 0.0001, 0.03). Incidence rates (per 1,000 person-year) were: normoglycemia to IGT: 82.0, 95% CI (40, 150); to IFG: 8.4, 95% CI (0, 41); to T2DM: 8.6, 95% CI (0, 42); IGT to T2DM: 55.0, 95% CI (17, 132); IFG to T2DM: 64.0, 95% CI (3, 316). The interaction between sex and the change in waist circumference (OR 1.8, per SD 95% CI: 1.22, 2.70) and the change in log HOMA-β (OR 0.37, per SD 95% CI: 0.17, 0.81) were associated with glycemic progression.

CONCLUSIONS: The association of DI_o with baseline glycemia after accounting for visceral fat as well as the association of the change in log HOMA-β with incident

glycemic progression implies innate β-cell susceptibility in Asian Indians for glucose intolerance or dysglycemia.

KEYWORDS: type 2 diabetes mellitus, Asian Indians, insulin sensitivity, β-cell dysfunction, ethnicity, incidence, impaired glucose tolerance, impaired fasting glucose

INTRODUCTION

The pathophysiology of type 2 diabetes is a complex process involving both decreased insulin sensitivity and impaired insulin secretion.[1] Traditionally, the pathogenesis has been described as obesity driven, with progressive insulin resistance followed by a subsequent decline in β-cell function, eventually leading to overt hyperglycemia.[1,2] However, decline in β-cell function has also been detected as a driving factor early in the natural history of type 2 diabetes development.[3,4] Since several genes conferring risk for type 2 diabetes are associated with β-cell dysfunction,[5] it is possible that some ethnic groups may have an innate susceptibility for early decline in β-cell function, thereby placing them at increased risk for disease development beyond traditionally associated factors such as age, adiposity, and insulin resistance.

Asian Indians, both in India and abroad, are at a particularly increased risk for type 2 diabetes.[6-10] Several studies have noted that Asian Indians are more insulin resistant than other ethnic groups at younger ages and comparative levels of body mass index (BMI).[11-13] Recent studies have also suggested that Asian Indians exhibit lower β-cell function even with mild dysglycemia, which may suggest an early etiological factor for hyperglycemia in this population.[14,15] These studies present intriguing observations concerning the relative roles of β-cell function and insulin sensitivity in the pathophysiology of type 2 diabetes in Asian Indians in native Indian settings. However, no such studies have been conducted on Asian Indians living in a developed country environment. There is a lack of information on whether β-cell dysfunction is similarly important in Asian Indians who have migrated to developed countries where there may be additional lifestyle, environmental, and psychosocial stressors promoting obesity and

insulin resistance. Furthermore, scarce data exists regarding incidence rates of type 2 diabetes in Asian Indians and the associated risk factors responsible. Therefore, in the present study, we analyzed the relative associations of β-cell function and insulin sensitivity on glycemic status and on the incidence of prediabetes and diabetes in a population-based cohort of migrant Asian Indians in the United States.

RESEARCH DESIGN AND METHODS

Study Population

The design, sampling strategy, recruitment and enrollment of the Metabolic Syndrome and Atherosclerosis in South Asians Living in America (MASALA) study are as described elsewhere.[16] In brief, a total of 150 participants from the San Francisco Bay area were enrolled between August 2006 and October 2007, with one follow up clinical visit occurring between April 2009 and January 2010. Mean follow-up time between visits was approximately 2.5 years. Eligibility criteria were designed to be similar to that of the Multi-Ethnic Study of Atherosclerosis (MESA) study[17] and required participants to be between age 45 and 84 years and self-identify as South Asian. Those individuals with pre-existing cardiovascular disease, using nitroglycerin, undergoing cancer therapy, with impaired cognitive ability, life expectancy less than 5 years, plans to move from the area, or living in a nursing home were excluded from the study.

Study Procedures

Participant weight was measured on a standard balance beam scale, and height was measured using a stadiometer. Waist circumference was measured using a Gullick II tape at the site of maximum circumference midway between the lower ribs and the anterior super iliac spine. Three seated blood pressure measurements were taken and

mean systolic (SBP) and diastolic blood pressures (DBP) were calculated from the second and third measurements. Computed tomography was used to determine visceral and abdominal subcutaneous fat area. The correct position of the CT scan (between the L4 and the L5 vertebrae) was established by a trained radiology technician, using a lateral scout image of the spine and was conducted using standardized protocols.[16]

After a 12 hour overnight fast, a 75g oral glucose tolerance test (OGTT) was administered to all individuals at the baseline examination and to those without medication treated diabetes at the second clinical examination. At baseline, blood samples were obtained just before glucose ingestion (time 0) and then 30, 60, 90 and 120 minutes post-challenge for plasma glucose and serum insulin measurements. At the second clinical visit, approximately 2.5 years later, blood samples were obtained while fasting and at 120 minutes after the glucose challenge. Plasma glucose was measured using an automated analyzer (YSI 2300 STAT Plus, YSI Life Sciences, Yellow Sprints, OH). Serum samples were processed and stored at -80°C for batched assays of immunoreactive insulin (RIA, Millipore, St. Charles, MO).

The assessment of life expectancy and cognitive ability was similar to that of the MESA study. Potential participants were asked whether they had been diagnosed with any diseases that may limit their life expectancy to <5 years. During eligibility assessment, participants were also asked several questions to gauge their ability to respond to simple as well as more complex questions about health status. If participants were unable to respond to these questions due to inability to remember or communicate the information, they were deemed not eligible for the study.

Hypertension was defined by the use of an anti-hypertensive medication, or if their systolic blood pressure was ≥140 mmHg or if their diastolic blood pressure was ≥90 mmHg. These are the same criteria used by the MESA study. Family history of diabetes was determined by self-report and was classified as either a parent or sibling being previously diagnosed. Smoking status was also based on self-reported answers to the baseline MASALA study questionnaire.

Diabetes was defined by the use of a glucose lowering medication or fasting plasma glucose ≥7.0 mmol/l and/or 2 hour post-challenge glucose ≥11.1 mmol/l. Prediabetes was defined by fasting plasma glucose of 5.6-6.9 mmol/l (IFG) and/or 2 hour post-challenge glucose of 7.8-11.1 mmol/l (IGT). 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.[18]

Calculations

β-cell function was estimated at baseline by the oral disposition index (DI_o) and was calculated as $(\Delta I_{0-30}/\Delta G_{0-30})*(1/\text{fasting insulin})$.[19] DI_o is a product of the insulin response and a surrogate measure of insulin sensitivity, and is based on the hyperbolic relationship between these two measures.[19] The concept of a hyperbolic relationship has also been demonstrated in humans for the first-phase response to glucose and insulin sensitivity.[20] Both the oral and intravenous approaches have been proven to be useful for examining the ability of the β-cell to compensate for differences in insulin sensitivity.[21] Insulin sensitivity at baseline was also estimated using the Matsuda Index (ISI_M) calculated as $10{,}000/\sqrt{(\text{fasting glucose}*\text{fasting insulin})}*(\text{mean OGTT glucose concentration}*\text{mean OGTT insulin concentration})$.[22] ISI_M was chosen as a measure of

insulin sensitivity as it represents a composite of both hepatic and muscular tissue insulin sensitivity and correlates well with the euglycemic insulin clamp as a measure of insulin sensitivity.[22] Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of height in meters.[23]

At the follow up examination, 30-minute post-challenge glucose and insulin concentrations were not measured, therefore DI_o could not be calculated. Instead HOMA-β was used to measure β-cell function in longitudinal analysis and was calculated as [20*I_0(μIU/ml) / G_0 (mmol/l)- 3.5], and HOMA-IR was used to measure insulin resistance and calculated as [I_0(μIU/ml) * G_0 (mmol/l)/22.5].[24] Person years were calculated as the sum of years each person at risk contributed to the study between baseline and follow up. The time between the baseline and follow-up visits of those with incident cases was divided in half to arrive at total person years for all those at risk.

Statistical Analysis

Baseline characteristics of study participants were compared by glucose tolerance category using chi-squared test or ANOVA as appropriate. Non-normally distributed variables were log transformed. Standardized polytomous logistic regression was used to compare the odds of prediabetes or type 2 diabetes to normal glucose tolerance. Initially, unadjusted regression models were created to compare the individual associations of DI_o and ISI_M with prevalent glycemic status. Multivariable models were created to adjust for covariates including age, sex, smoking status, family history of diabetes, hypertension, and visceral adipose tissue area. In order to assess multi-linearity in the models, colinearity diagnostics were used to examine the condition indices and variance decomposition proportions of the variables. If it was determined that strong relationships

existed between variables that would yield the model unreliable, one of those variables was removed from the final model.[25] Backwards stepwise elimination was used to remove variables with a P >0.05 from the model to retain only the most relevant covariates.

For the longitudinal analyses, baseline and second visit characteristics were compared using chi-squared or paired t-tests as appropriate. We used standardized logistic regression models to examine the covariates associated with glycemic conversion. Since both HOMA-IR and HOMA-β are functions of fasting glucose,[24] assessing the associations of these variables with incident glycemic status from increased fasting glucose would result in fasting glucose being used as both an outcome and an association variable. We therefore restricted our analyses of glycemic conversion and assessed risk factors only from normal glycemia to IGT or type 2 diabetes, or from IGT to type 2 diabetes using only 2-hr post-challenge glucose measures, thereby eliminating the use of fasting glucose as both a predictor and an outcome variable. Bivariable models were used to assess preliminary associations, and multivariable models were used to adjust for possible confounders. Again, colinearity diagnostics were used to examine the condition indices and variance decomposition proportions of the variables to assess multi-linearity in the models, and backwards stepwise elimination was used to remove variables with a P >0.05. All analyses were performed using SAS Version 9.3 (SAS Institute, Cary, NC).

RESULTS

Baseline Visit

Of the 150 participants in the MASALA study, at baseline 58 (39%) had normal glucose tolerance, 51 (34%) had prediabetes, and 41 (27%) had type 2 diabetes. Of those with prediabetes at baseline, 8 (16%) had isolated IFG, 35 (69%) had isolated IGT, and 8 (16%) had both IFG and IGT. These results differ slightly from those published in previously because earlier MASALA studies did not use 2-hour glucose levels in their classifications of glycemic status in order to remain consistent with classifications used by the MESA study.[16] Additionally, 63 participants (42%) had hypertension at baseline, 48 of whom were using anti-hypertensive medication. Table 1.1 describes participant characteristics by glycemic status. Those with diabetes were more likely to be male, have a history of hypertension, higher levels of systolic and diastolic blood pressure, a larger body habitus based on BMI, more central adiposity assessed by waist circumference and visceral fat area, were more insulin resistant based on log HOMA-IR and log ISI_M and had poorer β-cell function based on DI_o than those with normal glucose tolerance. With regards to mean log $ISI_{M,}$ there was a significant difference between normal glycemia and prediabetes, while the mean log ISI_M between prediabetes and type 2 diabetes was not significantly different. Furthermore, while there was a difference in BMI between those with type 2 diabetes and normal glucose tolerance, there was little difference between those with prediabetes and type 2 diabetes. Waist circumference and visceral fat area were both greater in a graded fashion from normal glucose tolerance to type 2 diabetes mellitus.

Figure 1.1 shows mean glucose and insulin responses during the OGTT by glycemic status. Consistent with higher fasting and 2-hour glucose levels in those with pre-diabetes and diabetes, the values at the intermediate time points (30, 60 and 90 minutes) were greater in those with abnormal glucose tolerance compared to those with normal glucose tolerance. Mean insulin also differed amongst groups. Those with type 2 diabetes had the highest mean insulin at fasting, but the lowest mean insulin at 30, 60, and 90 minutes post-challenge. Those with normal glucose tolerance and prediabetes had similar mean insulin levels until 30 minutes post challenge. After this time point, mean insulin was significantly higher in those with prediabetes than those with normal glucose tolerance.

Table 1.2 shows the relative associations of Log ISI_M and DI_o with glycemic status both bivariately, and after multivariate adjustment. Bivariately, log ISI_M and DI_o were each associated with glycemic status. For every standardized unit increase in ISI_M the odds of prediabetes was 57% lower and the odds of type 2 diabetes was 70% lower compared to having normal glucose tolerance. For every one standardized unit increase in DI_o the odds of prediabetes was 85% lower and the odds of type 2 diabetes 98% lower compared to normal glucose tolerance. When both log ISI_M and DI_o were included in the model, after controlling for age, sex, BMI, family history of diabetes, hypertension, and smoking status, both factors, along with hypertension, remained significantly associated with prediabetes and type 2 diabetes. However, the association of ISI_M with both prediabetes and type 2 diabetes was no longer significant once visceral fat was included in the model, while the association of DI_o and glycemic status remained robust.

Follow-up Visit

Approximately 2.5 years after the baseline visit, 132 (88%) of participants returned for the second clinical examination. Of the 18 participants who did not follow-up, 2 had died, 4 had moved away from the study area, 3 had developed serious illnesses, 6 were unable to schedule an appointment for logistical reasons, and 3 refused continued study participation. There were no significant differences in the baseline characteristics of those who remained in the study and those who withdrew. At the second examination, 24 (18%) of the 132 participants were being treated with glucose lowering medication; 17 of which were on glucose lowering medication both at baseline and at the second examination and 7 of which were newly on glucose lowering medication at follow up. Oral glucose tolerance tests were not performed on these participants. Table 1.3. describes participant characteristics at baseline and second clinical examination of those at risk for developing T2DM at the second clinical exam. Only mean log HOMA-IR and mean Log HOMA-β were significantly different between visits.

Between baseline and the second examination, 11 (8%) of the 132 participants converted from normal glycemia to prediabetes, 1 (0.75%) converted from normal glycemia to type 2 diabetes, and 6 (5%) converted from prediabetes to type 2 diabetes. Of those with normal glucose tolerance who converted to prediabetes, the incidence rate of impaired glucose tolerance was 82 per 1,000 person-years; 95% CI (40, 150) while the incidence rate of conversion to impaired fasting glucose was 8 per 1,000 person-years; 95% CI (0, 41). Based on both fasting and 2-hr OGTT values at follow-up, of those with prediabetes at baseline, the incidence rate from IGT to type 2 diabetes was 55 per 1,000 person years; 95% CI (17, 132). The incidence rate of conversion from IFG to type 2

diabetes based on fasting glucose was 64 per 1,000 person years; 95% CI (3, 316), and the incidence rate of diabetes for those who had both IFG and IGT was 66 per 1,000 person years; 95% CI (33, 324).

Between baseline and visit 2, mean standardized log HOMA-IR increased by 0.92 ± 1.00 μIU/ml*mmol/l. However, mean standardized log HOMA-β also increased by 0.70 ± 1.00 μIU/ml/mmol/l. In examining the covariates associated with glycemic progression, either from NGT to IGT, from NGT to type 2 diabetes, or from IGT to type 2 diabetes, in bivariate analysis the change in log HOMA-β (OR 0.44 per SD, 95% CI: 0.21, 0.90) and the interaction between sex and change in waist circumference (OR 1.58 per SD, 95% CI: 1.13, 2.22) were associated with glycemic conversion. In multivariable models which included baseline values for HOMA-IR and HOMA-β, the change in HOMA-β (OR 0.37 per SD, 95% CI: 0.17, 0.81) between the first and second exam and the interaction between sex and change in waist circumference (OR 1.81 per SD, 95% CI: 1.22, 2.70) were significantly associated with any glycemic status conversion, while no measures of baseline insulin sensitivity, baseline β-cell function, or change in insulin sensitivity were associated either in bivariate or multivariable models.

DISCUSSION

We found that at baseline, the association between DI_o, a measure of β-cell function relative to insulin sensitivity, was more strongly associated with both prediabetes and type 2 diabetes than ISI_M, a measure of whole body insulin sensitivity, in our cohort of Asian Indians in the United States. This association remained strong even after adjustment for well-known risk factors such as age, BMI, family history and visceral adiposity. Additionally, there may be more rapid progression from normal to

impaired glucose tolerance and from impaired glucose tolerance to type 2 diabetes among Asian Indians than previously reported in other ethnic groups.[26,27] Changes in β-cell function over time were associated with glycemic progression in our cohort. Together, these findings suggest a possible independent effect of impaired β-cell function in the pathogenesis of type 2 diabetes in Asian Indians, which could be the result of an innate susceptibility.

Recent studies conducted in India have also found early reductions in β-cell function as a possible primary etiological factor for diabetes development in Asian Indians.[14,15] A cross-sectional study conducted on 1,264 individuals without known diabetes from Chennai, India noted that after adjusting for age, sex, BMI, waist circumference and family history, compared to normal glycemia, the odds of impaired fasting glucose or impaired glucose tolerance were more significant for DI_o than for HOMA-IR, thereby suggesting that reductions in β-cell function are apparent in Asian Indians even in early stages of dysglycemia, irrespective of factors known to impact disease development.[14] Another cross-sectional study from Chennai, India, compared Asian Indians with normal glucose tolerance and prediabetes with individuals in whom the onset of diabetes occurred before the age of 25 years.[15] Results of this study showed independent associations with both DI_o and Matsuda Index and type 2 diabetes and prediabetes. However, after adjusting for BMI, waist circumference, and age, DI_o remained significant for both stages of glycemia, while the Matsuda Index did not.[15] These findings of strong associations with β- cell dysfunction and hyperglycemia in Asian Indians even at very young ages suggest that the pathogenesis of type 2 diabetes in

Asian Indians in India is primarily a function of declining β-cell function rather than the development of insulin resistance.

Our current study adds additional evidence that there is a strong association between β- cell dysfunction and both prediabetes and type 2 diabetes in Asian Indians, and goes further to indicate that declines in β-cell function may be an underlying factor in type 2 diabetes development in this ethnic group regardless of the environmental setting. This is supported by the mean differences in insulin sensitivity (measured by log ISI_M) and β-cell function (measured by DI_o) between glycemic groups in our population, the associations with ISI_M and DI_o and glycemic status in polytomous standardized regression, and the association of HOMA-β with glycemic progression. While mean insulin sensitivity at baseline was only significantly different between normal glycemia and prediabetes, mean β-cell function was significantly different amongst all pairwise comparisons, thereby suggesting an early decline in β-cell function which continues to deteriorate as glucose tolerance declines. Furthermore, in bivariate standardized polytomous regression models, both insulin sensitivity and β-cell function were independently associated with both prediabetes and type 2 diabetes. However, in multivariable analyses, the association with insulin sensitivity was considerably attenuated. Furthermore, after adjusting for visceral fat area, associations with insulin sensitivity for both prediabetes and type 2 diabetes were no longer significant. This was not the case with β-cell function as DI_o remained significantly associated with both prediabetes and diabetes in multivariable models even after the adjustment of other well known risk factors. Additionally, changes in HOMA-β were associated with glycemic progression at follow up while changes in HOMA-IR were not. Our results, taken in

aggregate with similar studies from India, indicate a possible innate susceptibility to β-cell dysfunction in Asian Indians that is independent of age, BMI, and abdominal obesity, and point to early declines in β-cell function as an important contributing factor to type 2 diabetes development in this ethnic group that exists regardless of a developed or developing country setting.

While other studies have examined the relative associations of both β-cell function and insulin sensitivity across the entire spectrum of glycemia in native Asian Indians, our study is the first to do so in a cohort residing in the United States, thereby indicating that early reductions in β-cell function are apparent despite environmental, behavioral, or migratory factors and exist in both developing and developed country environments. However, the primarily cross-sectional nature of our study makes it impossible to determine when precisely during the natural history of type 2 diabetes pathogenesis the initial decline in β-cell function begins to occur. Additionally, the small sample size and short duration of follow up in our study resulted in unstable incidence rates with wide confidence intervals. A study from Chennai, India followed participants for a period of 8 years and determined that the incidence of type 2 diabetes was very high (20.2 per 1,000 person years) among Asian Indians living in an urban Indian setting.[28] While this study provides valuable insight as to the rapid rate of conversion from normal glycemic or hyperglycemic states to overt type 2 diabetes in this population, it was conducted solely on Asian Indians living in urban South India and did not include other ethnic groups for comparison. Therefore, additional large longitudinal studies, including several ethnic groups, and with a long duration of follow-up are needed in order to accurately assess rates of glycemic conversion in Asian Indians compared to other

ethnicities. Additional limitations to our study include the exclusion of participants under the age of 45 and also those with pre-existing cardiovascular disease. Lastly, 30-minute post-challenge glucose and insulin were not measured at follow up. Therefore, we could not evaluate change in log ISI_M and DI_o as measures of insulin sensitivity and β-cell function during follow up, and instead relied on HOMA-IR and HOMA-β as measures of insulin sensitivity and β-cell function respectively. Since the calculations for HOMA-IR and HOMA-β involve fasting glucose, we restricted our analyses of glycemic conversion and assessed risk factors only from normal glycemia to IGT or type 2 diabetes, or from IGT to type 2 diabetes using only 2-hr post-challenge glucose measures, thereby eliminating any potential bias caused by the use of fasting glucose as both a predictor and an outcome variable. However, as a result, we were not able to assess risk factors associated with the conversion from normal glucose tolerance to IFG or from IFG to type 2 diabetes.

In conclusion, both decreased insulin sensitivity and impaired β-cell function are associated with type 2 diabetes in Asian Indians. However, impaired β-cell function appears to have a stronger relationship with prediabetes and type 2 diabetes. This association remained robust even after adjusting for visceral adiposity and other well known risk factors such as age, family history of diabetes, and hypertension, indicating a possible excess susceptibility to β-cell dysfunction in this ethnic group. Larger longitudinal studies in migrant Asian Indians are needed to provide further insight into acquired and/or epigenetic risk factors that may play a role in the development of β-cell dysfunction and eventual overt type 2 diabetes in this population.

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No potential conflict of interest relevant to this article was reported.

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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. 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. S.E.K 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, 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.

REFERENCES

1. Kasuga M. Insulin resistance and pancreatic beta cell failure. Clin Investig. (2006) 116(7):1756-1760
2. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Charles MA, Bennett PH. A two-step model for development of non-insulin-dependent diabetes. Am. J. Med. (1991) 90(2):229-35
3. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. (2003) Diabetologia46(1):3-19
4. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M,DeFronzo RA. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. Diabetologia. (2004) 47(1):31-9
5. Florez JC. Newly identified loci highlight beta cell dysfunction as a key cause of type 2 diabetes: where are the insulin resistance genes? Diabetologia (2008) 51(7):1100-10
6. Chiu KC, Cohan P, Lee NP, Chuang LM. Insulin sensitivity differs among ethnic groups with a compensatory response in beta-cell function. Diabetes Care. (2010) 23(9):1353-8
7. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. (2010) Diabetes Res Clin Pract 87: 4-14
8. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. Diabetes Care (2004) 27:1047–1053

9. Misra R, Patel T, Kotha P, Raji A, Ganda O, Banerji M, et al. Prevalence of diabetes, metabolic syndrome, and cardiovascular risk factors in US Asian Indians: results from a national study. J Diabetes Complications. (2010) 24(3):145-53
10. Oza-Frank R, Ali MK, Vaccarino V, Narayan KM. Asian Americans: diabetes prevalence across U.S. and World Health Organization weight classifications. Diabetes Care (2009) 32:1644-6
11. Chiu M, Austin PC, Manuel DG, Shah BR, Tu JV Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. Diabetes Care (2011) 34:1741-8
12. Gupta LS, Wu CC, Young S, Perlman SE. Prevalence of diabetes in New York City, 2002-2008: comparing foreign-born South Asians and other Asians with U.S.-born whites, blacks, and Hispanics. Diabetes Care. (2011) 34:1791-3
13. Gujral UP, Pradeepa R, Weber MB, Narayan KM, Mohan V. Type 2 diabetes in South Asians: similarities and differences with white Caucasian and other populations. Ann N Y Acad Sci (2013) 1281(1):51-63
14. Staimez LR, Weber MB, Ranjani H, Ali MK, Echouffo-Tcheugui J, Phillips LS, Mohan V, Narayan KM. Evidence of reduced β-cell function in Asian Indians with mild dysglycemia. Diabetes Care (2013) Epub Ahead of Print
15. Mohan V, Anandakumar A. Ranjani H, Unnikrishnan R, Datta M, RM Anjana, Staimez LR, MK Ali, Narayan KM. Associations of β-cell function and insulin resistance with youth-onset type 2 diabetes and prediabetes among Asian Indians. Diabetes Technol Ther (2013) 15(4):315-322

16. Kanaya AM, Wassel CL, Mathur D, Stewart A, Herrington D, Budoff MJ, et al. Prevalence and correlates of diabetes in South Asian Indians in the United States: findings from the metabolic syndrome and atherosclerosis in South Asians living in America study and the Multi-Ethnic Study of Atherosclerosis. MetabSyndrRelatDisord (2010) 8(2):157–64
17. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. Multi-Ethnic Study of Atherosclerosis: Objectives and Design. Am. J. Epidemiol. (2002) 156(9): 871-881.
18. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care (2008) 31:S55-S60
19. Utzschneider K, Prigeon R, Faulenbach M, Tong J, Carr DB, Boyko EJ, et al. Oral disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. Diabetes Care (2009) 32(2):335-341
20. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, et al Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes (1993) 42(11):1663-72.
21. Bergman RN, Finegood DT, Kahn SE. The evolution of β-cell and insulin resistance in type 2 diabetes. Eur J Clin Invest 32 (2002) (Suppl. 3):35–45
22. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care (1999) 22(9):1462-70

23. WHO Expert Committee on Physical Status. The Use and Interpretation of Anthropometry: Report of a WHO expert committee. Geneva, Switzerland: World Health Organization. World Health Organization Technical Report Series. (1995) 854.
24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. (1985) Diabetologia 28:412–419
25. Kleinbaum DG, Klein M *Logistic Regression: a Self-Learning Text.* Dietz K, Gail M, Krickeberg K, Samet J, Tsiatis A, Eds. New York, NY, Springer-Verlag (2002).
26. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Meigs JB, et al. Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. Diabetes (2004) 53(7):1782-9
27. Valdes S, Botas P, Delgado E, Alvarez F, Cadorniga FD. Population-based incidence of type 2 diabetes in northern Spain: the Asturias Study. Diabetes Care (2007) 30(9):2258-63
28. Mohan V, Deepa M, Anjana RM, Lanthorn H, Deepa R. Incidence of diabetes and pre-diabetes in a selected urban south Indian population (CUPS-19). J Assoc Physicians India (2008) 56:152-7

TABLES AND FIGURES

Table 1.1. Baseline MASALA study participant characteristics by glycemic status, 2006-2007*

Characteristics	NGT	Prediabetes	T2DM	P-Value
n (%)	58 (38.7)	51 (34.0)	41 (27.3)	
Male sex (%)	31.0	54.9	70.7	<0.01
Never smoker (%)	87.9	82.4	78.1	0.43
Family history of diabetes (%)	51.7	56.9	58.5	0.77
Current hypertension (%)	17.2	45.1	73.2	<0.01
Age (years)	56.5 ±7.5	57.8 ± 9.3	57.5 ± 7.3	0.70
Years lived in the United States	23.6 ± 10.9	24.1 ± 11.1	23.8 ± 12.7	0.98
BMI (kg/m^2)	24.6 ± 3.5	27.1 ± 5.4	27.2 ± 4.5	0.01
Waist circumference (cm)	91.2 ± 10.7	97.1 ± 13.2	102.0 ± 11.0	<0.001
Visceral fat area (cm^2)	107.4 ± 45.3	136.5 ± 52.8	166.8 ± 58.4	<0.001
Subcutaneous fat area (cm^2)	233.3 ± 88.8	265.6 ± 138.4	261.3 ± 106.7	0.27
Systolic blood pressure (mmHg)	116.6 ± 15.9	126.8 ± 16.2	132.6 ± 14.4	<.001
Diastolic blood pressure (mmHg)	69.0 ± 9.0	73.8 ± 12.0	76.0 ± 11.4	0.005
Fasting glucose (mmol/l)	4.8 ± 0.4	5.3 ± 0.6	7.3 ± 1.6	<0.001
2 hr glucose (mmol/l)	6.0 ± 1.0	8.6 ± 1.3	15.7 ± 3.4	<0.001
Measures of Insulin Sensitivity:				
Log ISI_M (µIU/ml*mg/ml)	2.3± 0.5	1.9 ± 0.6	1.7 ± 0.6	<0.001
Log HOMA-IR (µIU/ml*mmol/l)	0.7 ± 0.5	0.9 ± 0.7	1.5 ± 0.7	<0.001
Measures of ß cell Function:				
Disposition Index (pmol/ mmol)*pmol	3.4 ± 3.3	1.8 ± 2.0	0.4 ± 0.3	<0.001
Log HOMA-β (µIU/ml/mmol/l)	5.0 ± 0.4	4.8 ± 0.7	4.4 ± 0.8	<0.001

*Values represent mean ± SD or %

Table 1.2. Factors associated with baseline prediabetes and/or type 2 diabetes

		Prediabetes		Type 2 Diabetes		
Model		OR	95% CI	OR	95% CI	P
Log ISI_M						
	Log ISI_M	0.43	(0.26, 0.70)	0.30	(0.17, 0.51)	<0.001
Log DI_0						
	Log DI_o	0.15	(0.06, 0.36)	0.02	(0.01, 0.02)	<0.001
MV-adjusted Model 1*						
	Log ISI_M	0.51	(0.27, 0.95)	0.35	(0.15, 0.87)	0.05
	Log DI_o	0.22	(0.09, 0.58)	0.003	(0.001, 0.03)	<0.0001
	Hypertension	4.30	(1.49, 12.41)	5.54	(1.08, 28.54)	0.02
MV-adjusted Model 2**						
	Log DI_o	0.17	(0.70, 0.41)	0.003	(0.001, 0.03)	<0.0001
	Visceral fat area	1.01	(1.00, 1.02)	1.02	(1.00, 1.04)	0.02
	Hypertension	3.9	(1.4, 11.3)	4.3	(0.88, 22.15)	0.04

*multivariate model adjusted for sex, age, BMI, family history of diabetes, smoking status, and hypertension

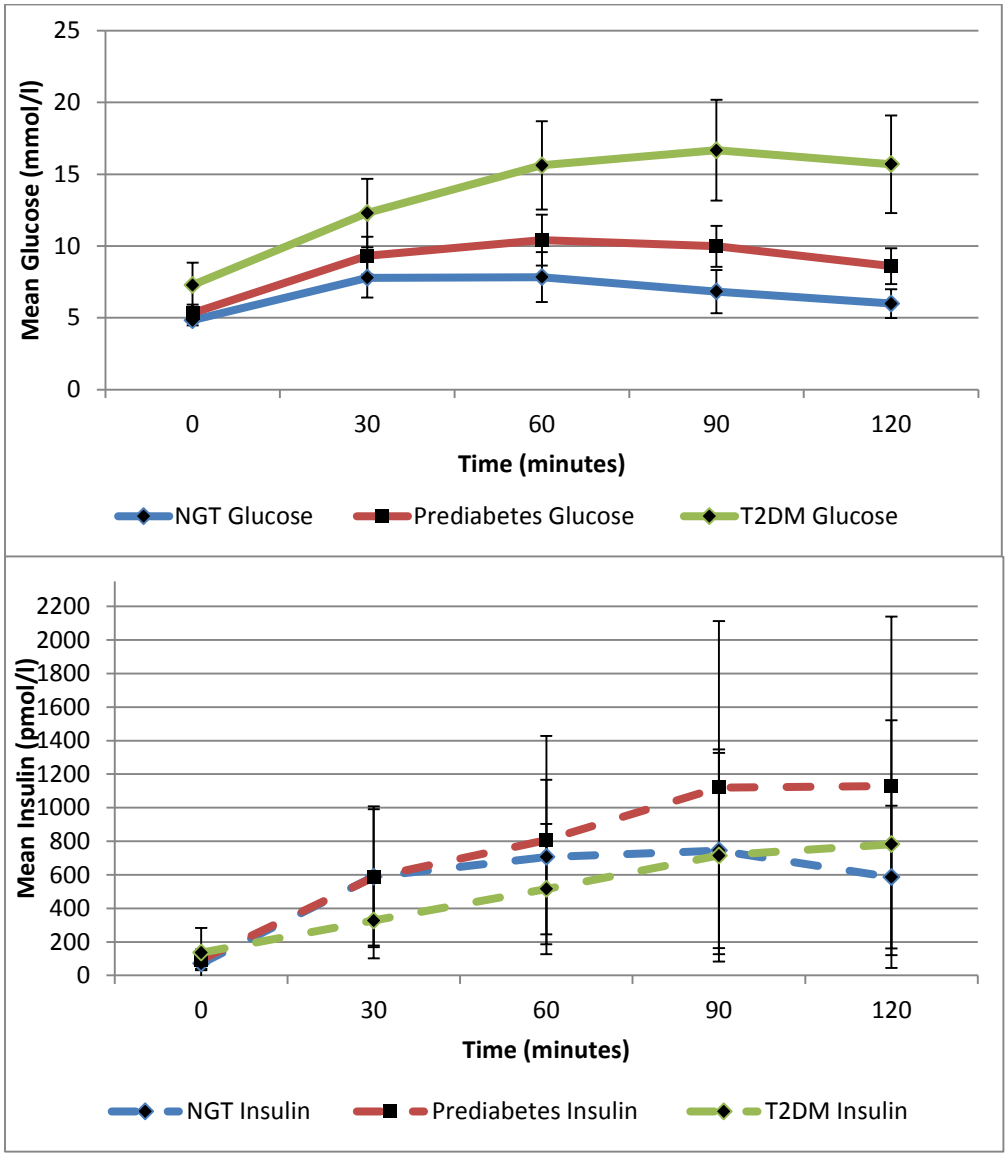
**in addition to variables in Model 1, also adjusted for visceral fat area

Table 1.3. Baseline and second clinical exam characteristics among those at risk for developing diabetes*

Characteristics	**Baseline**	**Second Visit**	**P-Value**
n (%)	97	97	
Male sex (%)	42.3	42.3	1.0
Current hypertension (%)	30.9	29.9	0.88
Age (years)	57 ± 8	59 ± 8	0.02
BMI (kg/m^2)			
Male	25.8 ± 4.2	26.0 ± 4.2	0.91
Female	25.7 ± 4.8	26.1 ± 4.9	0.66
Waist circumference (cm)			
Male	96.4 ± 9.5	95.7 ± 9.5	0.74
Female	91.6 ± 12.5	89.2 ± 12.7	0.32
Systolic blood pressure (mmHg)	122 ± 17	124 ± 14	0.25
Diastolic blood pressure (mmHg)	71 ± 11	72 ± 11	0.53
Fasting glucose (mmol/l)	5.1 ± 0.6	5.1 ± 0.7	0.96
2 hr glucose (mmol/l)	7.2 ± 1.7	7.5 ± 2.3	0.29
Log HOMA-IR (μIU/ml*mmol/l)	0.8 ± 0.6	1.2 ± 0.5	<0.001
Log HOMA-β (μIU/ml/mmol/l)	4.9 ± 0.6	5.3 ± 0.5	<0.001

*Values represent mean ± SD or %

Figure 1.1 Change in mean glucose and insulin over time by glycemic status



Values represent means ± SD

CHAPTER 5

Comparing type 2 diabetes, prediabetes, and their associated risk factors in Asian Indians in India and in the United States: The CARRS and MASALA Studies

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ABSTRACT

Objective: To assess the prevalence of diabetes, prediabetes, and the associated risk factors in two Asian Indian populations living in different environments.

Research Design and Methods: Cross-sectional analyses, using representative samples of 2,305 Asian Indians aged 40-84 years living in Chennai India, from the **C**entre for c**A**rdiometabolic **R**isk **R**eduction in **S**outh-Asia study (CARRS) (2010-2011) and 757 Asian Indians aged 40-84 years living in the greater San Francisco and Chicago areas from the U.S. Mediators of Atherosclerosis in South Asians Living in America (MASALA) Study (2010-2013). Diabetes was defined as self-reported use of glucose lowering medication, fasting glucose ≥ 126 mg/dl, or 2 hour glucose ≥ 200 mg/dl. Prediabetes was defined as fasting glucose 100-125 mg/dl and/or 2 hour glucose 140-199 mg/dl.

Results: Age-adjusted diabetes prevalence was higher in India (38% [95% CI: 36-40]) than in the US (24% [95% CI: 21-27]) Age-adjusted prediabetes prevalence was lower in India (24% [95% CI: 22-26]) than the US (33% [95% CI: 30-36]). After adjustment for age, sex, waist circumference, and systolic blood pressure, living in the US was associated with an increased odds for prediabetes (OR, 1.2 [95% CI: 9.9-1.5]) and a decreased odds for diabetes (OR, 0.5 [95% CI: 0.3.-0.6]).

Conclusions: These findings indicate possible changes in the relationship between migration and diabetes risk and highlight the growing burden of disease in urban India. Additionally, these results call for longitudinal studies to better identify the gene-environment-lifestyle exposures that underlie the elevated risk for type 2 diabetes development in Asian Indians.

INTRODUCTION

Asian Indians appear to have a higher propensity towards developing type 2 diabetes than other race/ethnic groups. India is home to the second largest population of individuals with type 2 diabetes worldwide.[1] Furthermore, immigration to developed countries is traditionally associated with higher type 2 diabetes risk,[2,3,4] and Asian Indian immigrants have a higher prevalence of type 2 diabetes than the general United States (US) population.[4,5,6] However, given that India has recently undergone rapid economic and nutrition transitions,[7,8] it is unclear whether diabetes risk among Asian Indians immigrants in the US differs from that of Asian Indians in urban India. Such a comparison of two genetically similar populations living in different environmental settings could shed light on the behavioral and environmental factors associated with increased diabetes risk in this ethnic group. We therefore compared the age-specific prevalence of type 2 diabetes and prediabetes in two current population-based studies of urban Asian Indians aged ≥40 years: n=2,305 residents of Chennai, India using data from the Centre for Cardiometabolic Risk Reduction in South-Asia study (CARRS, 2010-2011)[9] and n=757 from the US-based Mediators of Atherosclerosis in South Asians Living in America study (MASALA, 2010-2013).[10] We also analyzed the relative associations of demographic and anthropometric characteristics on prevalent glycemic status in urban Asian Indians in both India and the US.

RESEARCH DESIGN AND METHODS

The design, sampling strategy, recruitment, enrollment, and questionnaire and examination components of the MASALA and CARRS studies are described in detail elsewhere.[9,10] In brief, CARRS is a multi-site cohort study that recruited participant

populations from 3 urban mega-cities in India and Pakistan (Delhi, Chennai, and Karachi). The baseline examination for this cohort included a representative cross-sectional survey conducted in each city between 2010 and 2011. For the purposes of this study, data was analyzed from the Chennai study site only, as this site was the only one to perform an oral glucose tolerance test in order to identify diabetes accurately. Households were selected for participation using multi-stage random sampling technique in order to be representative of the city of Chennai.[9] A total of 6,920 individuals were screened for participation, of which 6906 (99%) provided questionnaire data. Fasting plasma glucose was obtained from 5952 participants (86%), and two hours post glucose challenge on 4,051 participants. For this study we limited our population to the 4,865 (70%) participants who were either previously diagnosed with diabetes as determined by questionnaire data or who provided fasting and two hour post challenge glucose measurements. Participants with existing cardiovascular disease as ascertained through self-report (n=283) and those with age <40 years (n=2,277) were excluded from the CARRS study for valid comparisons to MASALA.

MASALA is based on a community based sample of South Asians living in the greater Chicago and San Francisco Bay Areas. Data collection and assessment occurred between 2010 and 2013. The MASALA study was modeled to be similar to the Multi-Ethnic Study of Atherosclerosis (MESA) cohort study,[11] and only individuals without a known history of cardiovascular disease were eligible. Recruitment was conducted using telephone-based recruitment methods, similar to the MESA study.[11] Sampling frames were created by clinical site (either the University of California, San Francisco, or Northwestern University) and included all 9 counties of the San Francisco Bay Area and

the 7 census tracts closest to the Northwestern University medical center, as well as suburban locations around Chicago where census data revealed high proportions of Asian Indian residents. Name, address, and telephone number were obtained for approximately 10,000 households in the targeted census tracts from commercial mailing list companies (InfoUSA, Omaha, NE; and Marketing Systems Group, Horsham, PA). Random samples of South Asian surnames from the desired geographic locations were created using a specific cultural coding algorithm to identify 162 ethnicities, 16 ethnic groups, 80 language preferences, 21 countries of origin, and 12 religions using a 5-step matching process to classify a person's first and last name, thereby reducing selection bias among participants with uncommon South Asian surnames.[10] 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. In total, 9,097 households were attempted to be reached. Within these households 3,053 individuals were reached and 1,801 (59%) were eligible for participation.[10] Of all those eligible, a total of 906 individuals participated in the study. However, for the purposes of our analysis, data were analyzed only for individuals who identified as being born in India (n=757). Details regarding the eligibility criteria, questionnaire, and examination components in CARRS and MASALA are shown in Table 2.1.

In both studies, after at least a 9 hour overnight fast, a 75g OGTT was administered to participants without previously diagnosed diabetes who were willing and able to participate in the glucose challenge. Blood samples were obtained from a peripheral vein just before glucose ingestion (time 0) and at 30 and 120 minutes post glucose challenge for plasma glucose measurements. Serum glucose was measured using

the hexokinase method in both studies. Type 2 diabetes was defined similarly as self-reported use of glucose lowering medication (either an oral agent or insulin), fasting glucose ≥ 126 mg/dl, or 2 hour post-challenge glucose ≥ 200 mg/dl; prediabetes was defined as fasting glucose 100-125 mg/dl and/or a 2 hour post-challenge glucose 140-199 mg/dl.[12] BMI was classified by WHO criteria.[13] Normal weight was classified as BMI 18.5-24.99 kg/m^2, overweight was classified as BMI 25-29.99 kg/m^2, and obese was classified as BMI ≥ 30 kg/m^2. Asian specific cut-points for BMI classification were also used for sensitivity analyses.[14]

Statistical Analysis

Prevalence values and 95% confidence intervals were estimated by study site, sex, age group, and BMI category. Participant characteristics were stratified by sex and were compared by study using chi-squared test or ANOVA as appropriate. The non-normally distributed variables of fasting and 2 hour plasma glucose were log transformed. The effect of location of residence (India or the US) on the odds of prediabetes and type 2 diabetes compared to normal glucose tolerance was assessed using standardized polytomous regression. Initially, an unadjusted regression model was created to compare the individual association between study location and prevalent glycemic status. Subsequent multivariable models were then created to adjust for covariates including age, sex, blood pressure, waist circumference, educational status, and years since migration to the US. All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Table 2.2 displays participant characteristics by sex and study. Of the 2,305 participants from CARRS-Chennai 54% were women. Of the 757 participants from

MASALA, 46% were women. The mean duration of residence in the US for MASALA study participants was 27.8 ± 10.8 years for men and 26.5 ± 10.8 years for women. Participants in the MASALA Study were on average older than those in CARRS-Chennai and had higher educational attainment. On average, in both sexes, participants in MASALA were taller and had greater weight and waist circumference measurements than those in CARRS-Chennai. Additionally, men in the MASALA Study had a higher mean BMI than men in CARRS-Chennai, however this was reversed among women. In both studies, fasting glucose was obtained from all participants who were willing to provide a sample, however, a 75g OGTT was only administered to participants without a prior diagnosis of type 2 diabetes (MASALA N=617, CARRS N=1674). Participants in the MASALA Study had lower log fasting glucose values than participants in CARRS-Chennai, but higher log fasting 2 hour glucose values. Those in MASALA also had lower systolic and diastolic blood pressure levels and took more blood pressure lowering medications than participants in CARRS-Chennai. Of those with a prior diagnosis of type 2 diabetes, participants in MASALA had on average a longer duration of diagnosis

Age-adjusted type 2 diabetes prevalence was higher among Indians in CARRS-Chennai than those in the MASALA Study both overall (38% [95% CI: 36-40] vs. 24% [95% CI: 21-27]) and by sex (men: 36% [95% CI: 33-39] vs 27% [95% CI: 23-31]; women: 42% [95% CI: 39-45] vs 23% [95% CI: 19-28]) . Of those participants with type 2 diabetes, 65% of Asian Indians living in the US and 71% of Asian Indians living in India had a previous diagnosis of diabetes. Age-adjusted prediabetes prevalence was lower in Asian Indians in Chennai than in the US (overall: 24% [95% CI: 22-26] vs 33% [95% CI: 30-36]; men: 21% [95% CI: 19-24) vs 35% [95% CI: 31-40]; women 25%

[95% CI: 23-28] vs 29% [95% CI: 24-34]). These patterns were consistent across age and sex groups, but differences in type 2 diabetes prevalence by age were more significant in women (Figure 2.1). In all categories of BMI, the prevalence of diabetes was higher in Asian Indians living in India than in Asian Indians living in the US (Figure 2.2). Differences in diabetes prevalence between the groups were significant in normal and overweight participants, but were not significant in participants who were obese. In all categories of BMI, the prevalence of prediabetes was lower in native Asian Indians than those in the US and was significantly different in participants with normal BMI. The pattern of higher diabetes prevalence and lower prediabetes prevalence in Asian Indians living in Indian than Asian Indians in the US in all BMI categories was consistent using the Asian BMI cut-points. However, when using the Asian specific cut-points, the prevalence of diabetes and prediabetes was most significantly different in participants who were overweight.

Of the 757 participants from MASALA, 189 (25%) have origins from one of four the South Indian states of Tamil Nadu, Karnataka, Andhra Pradesh, or Kerala. In restricting participants from MASALA to only those with origins from South India, age-adjusted type 2 diabetes prevalence was again higher among Indians in CARRS-Chennai than those in the MASALA Study both overall (38% [95% CI: 36-40] vs. 25% [95% CI: 20-32]) and by sex (men: 36% [95% CI: 33-39] vs 27% [95% CI: 19-35]; women: 42% [95% CI: 39-45] vs 25% [95% CI: 15-34]) . Age-adjusted prediabetes prevalence was again lower in Asian Indians in Chennai than in those in the US with origins from South India specifically (overall: 24% [95% CI: 22-26] vs 33% [95% CI: 26-39]; men: 21% [95% CI: 19-24) vs 36% [95% CI: 27-45]; women 25% [95% CI: 23-28] vs 27% [95%

CI: 19-38]). These patterns were again consistent in all age and sex groups, but differences in diabetes prevalence between Asian Indians in Chennai compared to Asian Indians in the US with origins in South India were more significant than differences in prediabetes prevalence between these groups.

Table 2.3 shows the association of place of residence (either India (Chennai) or the US (greater San Francisco and Chicago areas) with glycemic status. After adjusting for age, sex, waist circumference, and systolic blood pressure, Asian Indians in the MASALA Study had a 50% [95% CI: 0.4-0.6] decreased odds of type 2 diabetes but a 20% [95% CI: 0.9-1.5] increased odds of prediabetes than those in CARRS-Chennai. The inclusion of education and years since migration in multivariable models somewhat attenuated the effect of place of residence on the odds of having diabetes compared to normal glucose tolerance. Income could not be assessed in the models as it was found to be collinear with place of residence. The inclusion of height in multivariable models as a proxy for socio-economic status prior to migration did not alter the effect of place of residence on the odds of having diabetes or prediabets compared to normal glucose tolerance between the groups. However, the inclusion of height and education together in multivariable models significantly attenuated the effect of place of residence on the odds of having diabetes.

CONCLUSIONS

Few studies have compared Asian Indians in India to those who have immigrated to the US. In this study comparing middle to older aged urban Asian Indians we found that a community-based sample of Asian Indians in the US had a lower prevalence of type 2 diabetes but a higher prevalence of prediabetes than Asian Indians living in urban

south India. This was observed despite Asian Indians in the US being older and heavier than those in India. Asian Indians in the US also had better blood pressure levels than those in India possibly explained by their higher usage of blood pressure lowering medications. However, the adjustment for age, sex, waist circumference, and systolic blood pressure, did not fully explain the increased odds of type 2 diabetes in Asian Indians in the CARRS-Chennai Study.

It is possible that India is in an early stage of the type 2 diabetes epidemic wherein those who are most susceptible to the disease develop it the earliest.[15] It is also possible that Asian Indians who have immigrated to the US have adopted more positive dietary and exercise habits, thereby lowering their risk for progression from prediabetes to overt type 2 diabetes.[16] Contrary to previous findings that Asian Indians who migrate to the US have poorer metabolic profiles than their counterparts in India,[17,18] our results indicate that while Asian Indians in India had lower BMI and waist circumference measurements than those living in the US, they still had a higher prevalence of type 2 diabetes even at normal levels of BMI and in both sexes, thereby suggesting a shift in the association between migration and type 2 diabetes risk in this population. Paradoxically, both the overall and the age specific prevalence of prediabetes was lower in Asian Indians living in India than in the US, which may be due to a more rapid conversion through the natural history of disease in Asian Indians living in India. Our results also add strength to the notion that factors besides age and central adiposity play a large role in type 2 diabetes development in Asian Indians[7] in both developed and developing country settings since the adjustment for age, sex, waist circumference, and systolic blood pressure did not explain differences in the odds of prediabetes or type 2 diabetes between the two groups.

Furthermore, while the prevalence of type 2 diabetes was lower in Asian Indians living in the US than in India, it was still considerably higher than the general US population,[19,20,21] despite Asian Indians having an overall lower BMI.

Risk factors for type 2 diabetes development such as high carbohydrate and/or fat diets and sedentary lifestyles were once considered to influence those who had migrated to developed countries leading to an increased prevalence of diabetes in migrants than those who remained in developing country settings.[17,18] The results of our study are amongst the first to highlight a higher prevalence of diabetes in individuals living in India than their counterparts who have immigrated to the United States. It is therefore possible that, given the rapid economic and nutritional transitions currently taking place in India,[7,8] these factors now exacerbate risks in Asian Indians both in India and abroad. It is also possible that with more increased knowledge of beneficial diet and lifestyle choices, migrant Asian Indians may be shifting towards more health promoting dietary patterns. A more thorough understanding of the dietary transitions taking place in India and in diaspora Indians could provide important insights into the development of type 2 diabetes in non-obese phenotypes. It is possible that in Asian Indians in the US may also have increased knowledge regarding diabetes prevention and greater access to health care than Asian Indians in India.[16,22] Such factors may serve to protect immigrant populations against type 2 diabetes risk, however further research is needed in this area.

Our study directly compared the age-specific prevalence of prediabetes, type 2 diabetes and the associated risk factors between Asian Indians living in the US and India. While there were differences in the sampling frames and socio-demographic characteristics between the two studies, both are large population based samples with

similar anthropometric and laboratory measures that are representative of Asian Indians in large urban centers either in India or the US. Additionally, while participants from CARRS are primarily of South Indian origin and participants from MASALA migrated from all parts of India, it is possible that the differences in type 2 diabetes prevalence between the groups could be attributed to differences in regional origins. However, when we restricted our analyses to participants from MASALA with origins in South India only, the finding of a high prevalence of diabetes and a relatively lower prevalence of prediabetes in Asian Indians from CARRS compared to Asian Indians from MASALA remained virtually unchanged. These results suggest that the differences in type 2 diabetes prevalence between the groups is likely not attributable to region of origin.

Furthermore, while there were large differences in education status as well as height between Asian Indians living in India and the US, adjustment for education and height in multivariable models as proxy measures for socioeconomic status prior to migration attenuated the effect of migration on the odds of diabetes between the two groups. These results suggest a possible healthy migrant effect, whereby individuals with greater access to education as well as early maternal and childhood nutrition were more likely to have the means for migration. However, while participants from the MASALA study had high levels of educational attainment, diabetes prevalence in this group was still considerably higher than that in the general US population (20, 21), thereby suggesting that factors besides education attainment play a large role in diabetes risk in Asian Indians.

Being that our study directly compares two distinct Asian Indian populations from differing geographic regions (Chennai, India and the greater San Francisco and Chicago

areas of the US) the results cannot be generalized to Asian Indians living in other parts of India or the US. However, several studies have noted an increasingly high prevalence of diabetes in urban India[23,24,25] with recent evidence indicating a rise of diabetes in rural areas of India as well.[26] Therefore, the high prevalence of diabetes in one urban Indian city as reported in this study may be indicative of an even larger burden of disease in India yet to come. Furthermore, the diabetes prevalence in MASALA study participants was similar to what was found in recently published study of Asian Indians in Michigan.[27] However, additional national level data is needed to assess the prevalence of diabetes among Asian Indians living in the US.

Our findings point to a high prevalence of type 2 diabetes in urban India with a paradoxically low prevalence of prediabetes compared to urban Asian Indians in the US. Furthermore, the increased type 2 diabetes prevalence in Asian Indians in India is evident in both sexes, in all age groups, and at all levels of BMI, and therefore cannot be explained by differences in anthropometry or age alone. These findings suggest the need for collaborative longitudinal research efforts between India and the US Such collaborations could help identify the gene-environment-lifestyle exposures that underlie the elevated risk for type 2 diabetes development in Asian Indians.

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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.

REFERENCES

1. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes. Res. Clin. Pract *2011;* 94:311–321.
2. Gupta LS, Wu CC, Young S, Perlman SE. Prevalence of diabetes in New York City, 2002-2008: comparing foreign-born South Asians and other Asians with U.S.-born whites, blacks, and Hispanics. Diabetes Care. 2011; Aug; 34(8):1791-3.
3. Oza-Frank R, Ali MK, Vaccarino V, Narayan KM. Asian Americans: diabetes prevalence across U.S. and World Health Organization weight classifications. Diabetes Care. 2009; Sep; 32(9):1644-6.
4. Misra R, Patel T, Kotha P, Raji A, Ganda O, Banerji M, Shah V, Vijay K, Mudaliar S, Iyer D, Balasubramanyam A. Prevalence of diabetes, metabolic syndrome, and cardiovascular risk factors in US Asian Indians: results from a national study. J Diabetes Complications. 2010; May-Jun; 24(3):145-53.
5. Creatore MI, Moineddin R, Booth G, Manuel DH, DesMeules M, McDermott S, Glazier RH. Age-and sex-related prevalence of diabetes mellitus among immigrants to Ontario, Canada. CMAJ. 2010; May 18; 182(8):781-9.
6. Choukem SP, Fabreguettes C, Akwo E, Porcher R, Nguewa JL, Bouche C, Kaze FF, Kengne AP, Vexiau P, Mbanya JC, Sobngwi E, Gautier JF. Influence of migration on characteristics of type 2 diabetes in sub-Saharan Africans. Diabetes Metab. 2014 Feb; 40(1):56-60.
7. Shetty, P. S. Nutrition transition in India. Public health nutrition. 2002; *5*(1a), 175-182.

8. Griffiths PL, Bentley ME. The nutrition transition is underway in India. The Journal of nutrition. 2001; 131(10): 2692-2700.
9. Nair M, Ali MK, Ajay VS, Shivashankar R, Mohan V, Pradeepa R, Deepa M, Khan HM, Kadir MM, Fatmi ZA, Reddy KS, Tandon N, Narayan KM, Prabhakaran D. CARRS Surveillance study: design and methods to assess burdens from multiple perspectives. BMC Public Health. 2012 Aug 28; 12:701.
10. Kanaya AM, Kandula N, Herrington D, Budoff MJ, Hulley S, Vittinghoff E, Liu K. Mediators of Atherosclerosis in South Asians Living in America (MASALA) study: objectives, methods, and cohort description. Clin Cardiol. 2013 Dec; 36(12):713-20.
11. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002; 156: 871–881.
12. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2008 Jan;31 Suppl 1:S55-60.
13. World Health Organization. Obesity: preventing and managing the global epidemic: Report on a WHO Consultation on Obesity, Geneva, 3-5 June, 1997. Technical Report Series No. 894. 2000, World Health Organization.
14. WHO EC (2004). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004; 363(9403), 157.
15. Qiao Q, Hu G, Tuomilehto J, Nakagami T, Balkau B, Borch-Johnsen K, Ramachandran A, Mohan V, Iyer SR, Tominaga M, Kiyohara Y, Kato I, Okubo

K, Nagai M, Shibazaki S, Yang Z, Tong Z, Fan Q, Wang B, Chew SK, Tan BY, Heng D, Emmanuel S, Tajima N, Iwamoto Y, Snehalatha C, Vijay V, Kapur A, Dong Y, Nan H, Gao W, Shi H, Fu F; DECODA Study Group. Age-and sex-specific prevalence of diabetes and impaired glucose regulation in 11 Asian cohorts. Diabetes Care. 2003 Jun; 26(6):1770-80.

16. Venkatesh S, Weatherspoon LJ, Kaplowitz SA, Song WO. Acculturation and glycemic control of Asian Indian adults with type 2 diabetes. Journal of community health. 2013; *38*(1):78-85.
17. Bhatnagar D, Anand IS, Durrington PN, Patel DJ, Wander GS, Mackness MI, Creed F, Tomenson B, Chandrashekhar Y, Winterbotham M, et al. Coronary risk factors in people from the Indian subcontinent living in west London and their siblings in India. Lancet. 1995 Feb 18;345(8947):405-9.
18. Patel JV, Vyas A, Cruickshank JK, Prabhakaran D, Hughes E, Reddy KS, Mackness MI, Bhatnagar D, Durrington PN. Impact of migration on coronary heart disease risk factors: comparison of Gujaratis in Britain and their contemporaries in villages of origin in India. Atherosclerosis. 2006 Apr; 185(2):297-306.
19. Gujral UP, Narayan KM, Kahn SE, Kanaya AM. The relative associations of β-cell function and insulin sensitivity with glycemic status and incident glycemic progression in migrant Asian Indians in the United States: The MASALA study. Journal of diabetes and its complications. 2014; 28(1): 45-50.

20. Lee JWR, Brancati FL, Yeh HC. Trends in the prevalence of type 2 diabetes in Asians versus whites results from the United States National Health Interview Survey, 1997–2008. Diabetes Care. 2011; 34(2): 353-357.
21. Kanaya AM, Herrington D, Vittinghoff E, Ewing SK, Liu K, Blaha MJ, Dave SS, Qureshi F, Kandula NR. Understanding the high prevalence of diabetes in U.S. south Asians compared with four racial/ethnic groups: the MASALA and MESA studies. Diabetes Care. 2014 Jun; 37(6):1621-8.
22. De Gagne JC, Oh J, So A, Haidermota M, Lee SY. A Mixed Methods Study of Health Care Experience Among Asian Indians in the Southeastern United States. Journal of Transcultural Nursing. 2014; 1043659614526247.
23. Mohan V, Deepa M, Deepa R, Shanthirani CS, Farooq S, Ganesan A, Datta M. Secular trends in the prevalence of diabetes and impaired glucose tolerance in urban south India – the Chennai Urban Rural Epidemiology Study (CURES-17). Diabetologia. 2006; 49:1175-1178.
24. Ramachandran A, Snehalatha C, Kapur A, Vijay V, Mohan V, Das AK, Rao PV, Yajnik CS, Prasanna Kumar KM, Nair JD. For the Diabetes Epidemiology Study Group in India (DESI). High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. Diabetologia. 2001;44:1094-1101.
25. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, Bhansali A, Joshi SR, Joshi PP, Yajnik CS, Dhandhania VK, Nath LM, Das AK, Rao PV, Madhu SV, Shukla SK, Kaur T, Priya M, Nirmal E, Parvathi SJ, Subhashini S, Subashini R, Ali MK, Mohan V. On behalf of the ICMR–

INDIAB Collaborative Study Group. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: Phase I results of the Indian Council of Medical Research–INdia DIABetes (ICMR–INDIAB) study. Diabetologia. 2011; 54:3022-3027.

26. Hwang CK, Han PV, Zabetian A, Ali MK, Narayan, KM. Rural diabetes prevalence quintuples over twenty-five years in low-and middle-income countries: a systematic review and meta-analysis. Diabetes research and clinical practice. 2012; 96(3), 271-285.
27. Wu TY, Wang J, Chung S. Cardiovascular disease risk factors and diabetes in Asian Indians residing in Michigan. Journal of community health. 2012; 37(2), 395-402.

TABLES AND FIGURES

Table 2.1. Eligibility, Questionnaire and Exam Components in CARRS and MASALA

	CARRS-Chennai	MASALA
Eligibility Criteria		
Inclusion Criteria	• Aged 20 years or older • Permanently residing in the selected household.	• Self-identify as South Asian • Age range 40-84 years. • Ability to speak/ and read English, Hindi, or Urdu.
Exclusion Criteria	• Pregnant women were excluded from the study as were bed ridden individuals.	• Those with history of physician diagnosed myocardial infarction (MI), stroke, or transient ischemic attack; heart failure, angina, use of nitroglycerin; or those with a history of cardiovascular procedures. • Current atrial fibrillation, active cancer treatment, or life expectancy <5 years, impaired cognitive ability as judged by the reviewer, plans to move out of the study region in the next 5 years, currently living in or on the wait list for a nursing home. • Individuals weighing >136 kg (300 lb) were also excluded due to limitations with the CT scanner.
Questionnaires	• Questionnaires were used to gather demographic information including language use, family history of T2DM, medical history, and current medication use.	• Questionnaires were used to gather demographic information including language use, medical history, family history of T2DM, and current medication use.
Blood Pressure	• Three seated blood pressure measurements were taken using an electronic sphygmomanometer. • An average of the last two readings were used to assess systolic and diastolic blood pressure.	• Three seated blood pressure measurements were taken using an automated blood pressure monitor. • An average of the last two readings was used to assess systolic and diastolic blood pressure.
Weight	• Participant weight was measured using a standing balance beam scale.	• Participant weight was measured using a standing balance beam scale or digital weighing scale.
Height	• Height was measured using a portable stadiometer.	• Height was measured using a stadiometer.
Waist Circumference	• Waist circumference was measured using a non-stretch measuring tape at the site of maximum circumference halfway between the lower ribs and the anterior superior iliac spine.	• Waist circumference was measured using a flexible tape measure at the site of maximum circumference halfway between the lower ribs and the anterior superior iliac spine.

Table 2.2. Baseline Participant Characteristics by Study Center*

	Men		Women	
	CARRS-Chennai N=1055	**MASALA** N=408	**CARRS-Chennai** N= 1250	**MASALA** N= 349
Age (years)	51.2 (9.2)†	56.3 (10.0)†	49.7 (8.4)†	54.6 (8.7)†
Education Bachelor's Degree or Higher	11.0%†	93.1%†	3.8%†	87.4%†
Weight (kg)	64.6 (12.6)†	74.2 (11.6)†	61.8 (11.9)†	64.0 (10.8)†
Height (cm)	163.1 (3.3)†	169.8 (4.1)†	150.1 (5.5)†	157.0 (5.9)†
BMI (kg/m^2)	24.2 (4.3)†	25.9 (4.4)†	27.4 (4.9)†	26.0 (4.0)†
Waist Circumference (cm)	88.8 (11.4)†	95.7 (9.2)†	84.2 (11.0)†	88.9 (9.7)†
Log Fasting Glucose (mg/dl)§	4.7 (0.3)†	4.6 (0.2)†	4.7 (0.3)‡	4.5 (0.1)‡
Log 2-hr Glucose (mg/dl)‖	4.7 (0.4)†	4.8 (0.3)†	4.7 (0.3)†	4.8 (0.3)†
Systolic Blood Pressure (mmHg)	131.0 (21.0)‡	126.8 (14.7)‡	127.5 (20.7)‡	123.0 (17.0)‡
Diastolic Blood Pressure (mmHg)	85.4 (12.4)†	76.6 (8.7)†	83.3 (11.7)†	70.0 (9.8)†
Use of blood pressure Lowering Medication	10.9%†	36.8%†	15.9%†	26.3%†
Self-Reported Diabetes Diagnosis	66.9	70.1	74.5†	56.8†
Years Since Diagnosis	6.4 (6.5)‡	11.2 (10.1)‡	6.0 (5.6)†	8.7 (6.3)†

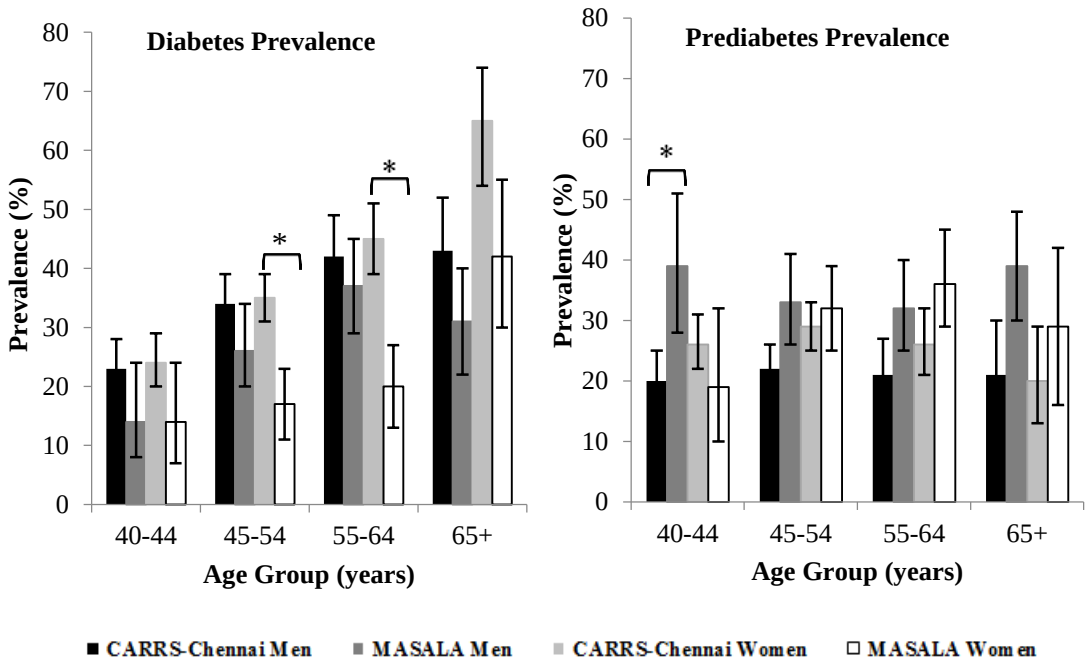
Values represented as Mean (SD) or %
*adjusted for age †$p<0.01$, ‡$p<0.0001$
§ Log Fasting Glucose: Men; CARRS-Chennai (N=1027), MASALA (N=402) Women; CARRS-Chennai (N=1215), MASALA (N=345)
‖ Log 2-hr Glucose: Men; CARRS-Chennai (N=780), MASALA (N=323) Women; CARRS-Chennai (N=894), MASALA (N=294)

Table 2.3. Risk Factors Associated with Prediabetes and Type 2 Diabetes

Model	Covariates	Prediabetes		Type 2 Diabetes		
		OR	95% CI	OR	95% CI	P
1	Migrant AI*	1.39	(1.14, 1.69)	0.73	(0.59, 0.90)	<0.01
2	Migrant AI*	1.18	(0.93, 1.50)	0.46	(0.36, 0.59)	<0.01
	Age Group (years)	1.21	(1.08, 1.38)	1.55	(1.38, 1.74)	<0.01
	Sex**	1.48	(1.18, 1.85)	1.47	(1.19, 1.84)	<0.01
	Waist Circumference (cm)	1.03	(1.02, 1.04)	1.05	(1.04, 1.06)	<0.01
	SBP (mmHg)	1.01	(1.00, 1.02)	1.02	(1.01, 1.03)	<0.01
3	Migrant AI*	1.52	(0.85, 2.73)	0.73	(0.39, 1.35)	0.07
	Age Group (years)	1.23	(1.08, 1.40)	1.55	(1.37, 1.75)	<0.01
	Sex**	1.46	(1.16, 1.84)	1.43	(1.14, 1.78)	<0.01
	Waist Circumference (cm)	1.03	(1.02, 1.04)	1.05	(1.04, 1.06)	<0.01
	SBP (mmHg)	1.01	(1.01, 1.02)	1.02	(1.01, 1.03)	<0.01
	Education	0.88	(0.60, 1.31)	0.64	(0.43, 0.94)	0.06
	Years Since Migration	0.99	(0.98, 1.01)	1.00	(0.99, 1.02)	0.81
4	Migrant AI*	1.50	(0.97, 2.32)	0.88	(0.57, 1.35)	0.05
	Age Group (years)	1.20	(1.06, 1.37)	1.51	(1.33, 1.71)	<0.01
	Sex**	1.24	(0.90, 1.72)	1.04	(0.75, 1.43)	0.41
	Height	0.99	(0.98, 1.01)	0.98	(0.96, 1.0)	0.09
	Waist Circumference (cm)	1.03	(1.02, 1.04)	1.05	(1.03, 1.06)	<0.01
	SBP (mmHg)	1.01	(1.01, 1.02)	1.02	(1.01, 1.03)	<0.01
	Education	0.83	(0.55, 1.26)	0.56	(0.37, 0.85)	0.02

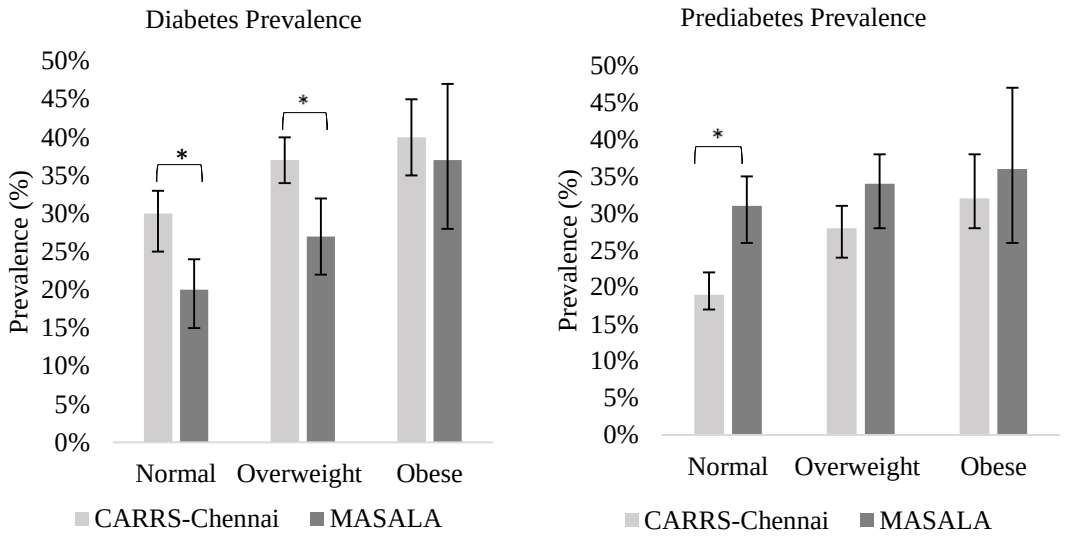
*Asian Indians living in India (CARRS-Chennai study) were used as the referent group.
**Males were used as the referent group

Figure 2.1. Age Specific Prevalence of Diabetes and Prediabetes by Study and Gender



*p < 0.05

Figure 2.2. Prevalence of Diabetes and Prediabetes by Study and BMI Category



*p < 0.05

CHAPTER 6

Comparing Type 2 Diabetes, Prediabetes, and their Associated Risk Factors in Asian Indians in India and Caucasians, Blacks, and Hispanics in the United States: The CARRS and NHANES Studies

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ABSTRACT

Background: It is unclear how the prevalence of diabetes in Asian Indians in urban India compares to that of ethnic groups in the United States. We therefore examined the age-specific prevalence of diabetes and prediabetes in a population-based sample of Asian Indians in Chennai, India, and several ethnic groups in the United States.

Methods: Cross-sectional analyses, using representative samples of 4,867 Asian Indians from the **C**entre for c**A**rdiometabolic **R**isk **R**eduction in **S**outh-Asia study (CARRS) (2010-2011) and 6,512 Caucasians, Blacks, and Hispanics from the National Health and Nutrition Examination Survey (NHANES) (2007-2012).

Findings: The prevalence of diabetes was highest in Asian Indians (men; 25.2 (95% CI: 22.4-28.2), women; (22.9 (95% CI: 20.2-25.9) and lowest in Caucasians (men; 13.1 (95% CI: 11.1-16.5), women; 10.3 (95% CI: 8.5-12.3). Asian Indians had the lowest prediabetes prevalence (men; (18.6 (95% CI: 16.9-20.4), (women (24.2 (95% CI: 20.2-28.6) and Caucasians had the highest (men; 46.9 (95% CI: (43.8-50.0), women; 35.2 (95% CI: 32.5-38.1)). The inclusion of HOMA-β in standardized polytomous logistic regression models resulted in a greater odds of diabetes in Blacks and Hispanics compared to Asian Indians.

Interpretation: The high prevalence of diabetes coupled with the lower prevalence of prediabetes in Asian Indians may be due to innate susceptibilities for β-cell dysfunction.

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INTRODUCTION

Type 2 diabetes mellitus is a complex metabolic disorder that involves both impaired insulin action and impaired insulin secretion. Traditionally, the pathophysiology has been described as age- or obesity-induced insulin resistance followed by a decrease in compensatory pancreatic β-cell response, eventually leading to overt hyperglycemia.[1,2] For the last three decades India has experienced rapid increases in the prevalence of diabetes,[3,4] that have occurred alongside concurrent economic, epidemiological, and nutritional transitions.[5,6,7] While some of the high diabetes burden in India can likely be attributed to urbanization, and the consequent obesogenic changes in patterns of food consumption, and shifts in physical activity,[6] it is also possible that Asian Indians experience unique biological susceptibilities to diabetes development, such as impaired pancreatic insulin secretion early in the natural history of disease.[8,9,10] These unique susceptibilities, coupled with factors related to the changing landscape in urban India, may be the driving factors behind the high risk in this ethnic group. However, it is unclear as to how the prevalence of diabetes in Asian Indians living in rapidly transitioning urban India currently compares to that of ethnic groups in a developed country such as the United States who are also at high risk but may develop diabetes through different physiological mechanisms such as obesity-driven insulin resistance. We, therefore, examined the age-specific prevalence of diabetes and of its precursor state, prediabetes, in a population-based sample of Asian Indians living in Chennai, India, and compared them to several ethnic groups living the United States.

RESEARCH DESIGN AND METHODS

In brief, The Center for Cardiometabolic Risk Reduction in South Asia study (CARRS) is a multi-site, cross-sectional surveillance study consisting of two urban cities in India and one urban city in Pakistan. Recruitment and data collection were conducted between 2010 and 2011.[11] For the purposes of this study, data were analyzed from the Chennai study site only, as this site was the only one to collect both fasting and two hour plasma glucose samples. Chennai is a major metropolitan city located in the South Indian state of Tamil Nadu with a population of approximately 4.68 million people.[11] Households were selected for participation using multi-stage random sampling technique in order to be representative of the city of Chennai.[12] A total of 6,920 individuals aged 20 and older were screened for participation, of which 6906 (99%) provided questionnaire data and 876 (13%) reported a previous diagnosis of diabetes. Fasting plasma glucose was obtained from 5952 participants (86%). In those not reporting a previous diagnosis of diabetes (6,030), two hour post glucose challenge glucose was obtained on 4,051 participants (67%). For this study we limited our population to the 4,867 (70%) participants who were either previously diagnosed with diabetes as determined by questionnaire data or who provided fasting and two hour post challenge glucose measurements. All participants in CARRS-Chennai were considered to be Asian Indian.

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional complex sample survey conducted by the US Centers for Disease Control and Prevention's National Center for Health Statistics. The survey is designed to be representative of the United States, civilian, non-institutionalized population on the basis of a complex multi-stage, probability sample.[13] After completing an in home

questionnaire, participants attended a mobile examination clinic where they received a questionnaire, physical and laboratory measurements. In order to generate a large enough sample for analysis and to assess diabetes and prediabetes prevalence in the United States and India at a similar time frame, we combined cycles 2007-2008, 2009-2010, and 2011-2012. A total of 24,731 participants aged ≥ 20 were screened for participation. Of those, 17,713 (72%) provided questionnaire data, and 17,085 (69%) participated in the mobile examination. A total of 1,542 (9%) of participants self-reported as "other ethnicity," 116 (0.7%) participants were currently pregnant, and 1,776 (10%) were over the age of 75, and were thus excluded from the analysis. Participants over the age of 75 were excluded to remain in concordance with the upper age group included in CARRS. Of the remaining 14,279 participants a total of 1,749 participants (12%) were previously diagnosed with diabetes according to questionnaire data. Fasting plasma glucose values were obtained from 6,399 participants and two hour post challenge glucose values were obtained from 4,763 participants. For this study, we limited our population to the 6,512 total participants who met inclusion criteria and had either a previous diagnosis of diabetes or gave both fasting and two hour post challenge glucose measurements, and self-identified as either Mexican American (Hispanic), Other Hispanic (Hispanic), Non-Hispanic Caucasian (White), or Non-Hispanic Black (Black). Details regarding the eligibility criteria, questionnaire, and examination components in NHANES and CARRS are listed in Table 3.1. Additional details of each study have been previously published.[12,13]

In both the CARRS and NHANES studies, diabetes was defined by previous physician diagnosis, the use of a glucose lowering medication, or fasting plasma glucose

≥ 126 mg/dl and/or two hour post-challenge glucose ≥ 200 mg/dl. Prediabetes was defined by fasting plasma glucose of 100-125 mg/dl and/or two hour post-challenge glucose of 140-199 mg/dl. Normal glucose tolerance was defined as those participants who had both fasting plasma glucose < 100 mg/dl and a two hour post-challenge glucose < 140 mg/dl.[14] Plasma glucose was analyzed using the hexokinase method in both studies. Sampling weights were applied to provide estimates that are representative of the U.S. non-institutionalized population (NHANES) and the city of Chennai (CARRS). HOMA modeling was done do generate estimates of inherent insulin resistance and β-cell function in participants, by computing the steady state insulin and glucose concentrations and assessing the interactions between β-cell function and insulin resistance.[14] HOMA-β was used to measure β-cell function and was calculated as [20*I_0(μIU/ml) / G_0 (mmol/l)-3·5]. HOMA-IR was used to measure insulin resistance and was calculated as [I_0(μIU/ml) * G_0 (mmol/l)/22·5].[15]

Statistical Analysis

All analyses were performed using SAS Version 9·3 (SAS Institute, Cary, NC) or SAS callable SUDAAN (version 9, Research Triangle Institute) software. Data from NHANES and CARRS were combined into a single dataset for analysis. Sampling weights for each survey were created independently in order to maximize the representativeness of each sample. Sampling weights from each respective survey were maintained upon combined analysis. Participant characteristics were stratified by gender and were compared by study using conditional marginal distributions. Weighted crude prevalence values and 95% confidence intervals were estimated by study site, gender, and age group. To obtain plots of the percent of the population in intervals of fasting plasma

glucose, two hour post challenge glucose, or fasting insulin we used the 2·5 and 97·5 percentiles of the distributions as end points to define the lowest and highest groups. We then divided the population into twelve groups of equal increments. Polytomous logistic regression was used to estimate the age- and sex-adjusted probability of an individual being classified into each group and to obtain the predicted percentages of study population.[16] Multivariable logistic regression models with either diabetes or prediabetes as the outcome were used to determine predicted marginal probabilities to determine the adjusted prevalence of diabetes or prediabetes. The models were adjusted for age, and sex as well as other well-known diabetes risk factors that differed significantly between ethnic groups. Standardized polytomous regression was used to compare the odds of prediabetes and diabetes compared to normal glucose tolerance by race/ethnic group both univariatley and after adjusting for covariates such as age, sex, anthopometry, HOMA- β, and HOMA-IR.

RESULTS

A total of 11,379 participants were included in the analysis from four ethnic groups. Table 3.2 describes the weighted mean age, anthropometric characteristics, and physiological measurements of participants by ethnic group and gender. All variables were adjusted for age. In men, Hispanics were on average younger than Asian Indians, Blacks, and Whites. In women, Asian Indians were on average younger than Blacks and Whites, however there were no significant differences in age between Asian Indian and Hispanic women (95% CI: (39.6-41.3) and (39.9-42.2)) respectively. In both males and females Asian Indians had lower height, weight, BMI, and waist circumference measurements than people from all other ethnic groups. In men, Hispanics had the

highest mean level of fasting glucose, however this was not significantly different from Asian Indians (95% CI: (110.6-116.5) and (107.2-112.6)) respectively. In women Asian Indians had the highest mean level of fasting glucose compared to all other ethnic groups. Both Hispanic men and women had the highest mean two hour glucose values. However, the difference in mean two hour glucose was not significantly different between Hispanics (95% CI: men (119.2-129.6) women (119.9-129.4)) and Asian Indians (95% CI: men (115.4-124.9) women (119.8-127.0). Both Asian Indian men and women had on average the lowest measures of fasting log insulin, and log HOMA-IR. In men, Asian Indians had the lowest mean levels of log HOMA-β, however, this was not significantly different compared to Black men (95% CI: (4.5-4.6) and (4.5-4.7) respectively. Asian Indian women had significantly lower log HOMA-β values compared to all other ethnic groups. After additional adjustment for BMI (Table 3.3), in both men and women Asian Indians had the highest mean levels of fasting glucose. However, in men, this difference was significant only when comparing Asian Indians to Whites, (95% CI: (110.6-116.3) and (104.1-107.6)) respectively. In both men and women Asian Indians also had the highest mean levels of 2 hour post challenge glucose. However, this difference was not significant when comparing Asian Indians to Hispanics; (men (95% CI: (122.3-132.3) and (118.4-128.5); women (95% CI: (121.9-128.8) and (118.8-127.6)) respectively. Asian Indian men and women again had the lowest levels of log fasting insulin and log HOMA-IR, however differences in log HOMA-IR were only significant in women. After adjustment for BMI, Asian Indian men and women had the lowest mean levels of log HOMA-β.

The crude prevalence of diabetes was highest in Asian Indians (men; 25·2 (95% CI: 22.4-28.2), women; (22.9 (95% CI: 20.2-25.9)) and lowest in Whites (men; 13.1 (95% CI: 11.1-16.5), women; 10.3 (95% CI: 8.5-12.3)) (Table 3.3). Adjustment for age resulted in a greater difference in diabetes prevalence between Asian Indians (men; 29.0 (95% CI: 25.9-31.0), women; 30.6 (95% CI: 27.5-33.9) and Whites (men; 12.2 (95% CI: 10.3-14.4, women; 9·5 (95%CI: 7.9-11.5)). Additional adjustment for BMI dramatically increased the difference in prevalence between Asian Indians and Caucasians resulting in a diabetes prevalence that was approximately 3 times as high among Asian Indians than Caucasians in both men and women. When stratified by age, diabetes prevalence increased with age in every ethnic group and in both sexes (Figure 3.1). In both men and women, Asian Indian participants had a significantly higher diabetes prevalence than White, Black, and Hispanic participants in all age categories.

In examining prediabetes prevalence, Asian Indians had the lowest crude prevalence in men (18.6 (95% CI: 16.9-20.4) and women (24.2 (95% CI: 20.2-28·6)) followed by Blacks (men; 37.8 (95% CI: 34.6-41.0), women; 29.1 (95% CI: 25.6-32.9)), Hispanics (men; 44.2 (95% CI: 40.1-48.3), women (31.4 95% CI: (26.8-36.5)) and Whites (men; 46.9 (95% CI: (43.8-50.0), women; 35.2 (95% CI: 32.5-38.1)). Adjustment for age resulted in a slight increase in prediabetes prevalence in all race/ethnic and sex groups besides White women. After this adjustment, Asian Indians still had the lowest crude prevalence in men (19.0 (95% CI: 17.2-20.8) and women (27.2 (95% CI: 22.8-32·1)) followed by Blacks (men; 38.2 (95% CI: 35.0-41.5), women; 30.2 (95% CI: 26.6-34.1)), Hispanics (men; 45.6 (95% CI: 41.4-49.8), women (34.0 95% CI: (29.1-39.3)) and Whites (men; 46.5 (95% CI: (43.5-49.6), women; 34.4 (95% CI: 31.7-37·3)). After

additional adjustment for BMI, and waist circumference, the difference in prediabetes prevalence between Asian Indians and other ethnic groups was attenuated, especially in women. In age specific analyses, the prevalence of prediabetes was significantly lower in Asian Indians in all age groups, compared to Whites, Blacks, and Hispanics (Figure 3.1). This pattern was true for both men and women.

In examining the distributions of fasting plasma glucose, two hour post challenge glucose, and fasting insulin (Figure 3.2), Asian Indians had a significantly higher probability of being classified in the lowest ranges of fasting glucose (Figure 3.3) and a significantly lower probability of being classified in the prediabetes ranges of fasting glucose compared to other ethnic groups. This remained the case after additional adjustment for BMI (Figure 3.4). Between ethnic groups, there was no difference in the distribution of two hour post challenge fasting glucose. There were also no significant differences in the distribution of fasting insulin between Whites, Blacks, and Hispanics, aside from the lowest end of the distribution where Hispanics had a significantly low probability of being classified. Asian Indians had a significantly higher probability of being classified in the lower end of the fasting insulin distribution compared to the other race/ethnic groups. After additional adjustment for BMI, the difference in the probability of being classified in the lower end of the fasting insulin distribution between Asian Indians and Whites and Blacks was no longer significant.

Table 3.4 details the odds of prediabetes and diabetes in Whites, Blacks and Hispanics compared to Asian Indians. After adjusting for age (as a categorical variable) and sex, Whites, and Blacks, were 70% less likely than Asian Indians to have diabetes, while Hispanics were 50% less likely. Compared to Asian Indians, Whites, Blacks, and

Hispanics were 74, 44, and 110% more likely to have prediabetes, respectively. When BMI was added to the model, the difference in the odds of prediabetes was attenuated in all groups while the difference in the odds of diabetes compared to Asian Indians was increased in all groups. Including waist circumference in the model instead of BMI also resulted in an even greater attenuation in the difference in odds of prediabetes as well as a greater increase in the difference in the odds of diabetes between Asian Indians and Caucasians Blacks and Hispanics. The inclusion of Log HOMA-β in the model severely attenuated the difference in odds of developing diabetes between Whites and Asian Indians and reversed the direction of the point estimate, resulting in a greater odds of diabetes in Blacks and Hispanics compared to Asian Indians. The model including Log HOMA-IR indicated no difference in the odds of prediabetes between Asian Indians and Whites. Additionally the point estimate for the odds of prediabetes was reversed from the model including only age and sex in that the inclusion of HOMA-IR resulted in a lower odds of prediabetes in Blacks and Hispanics compared to Asian Indians. With regards to the odds of diabetes, the model including HOMA-IR increased the difference in the odds of diabetes between Asian Indians and Whites and Blacks, while attenuated the difference in Hispanics.

DISCUSSION

We found an overall higher prevalence of diabetes in Asian Indians living in India than in Whites, Blacks, and Hispanics living in the U.S., despite their lower levels of adiposity. Interestingly, we also found the prevalence of prediabetes to be the lower in Asian Indians living in India compared to White, Black, and Hispanic groups in the U.S. After adjustment for age, BMI, and waist circumference, the differences in diabetes

prevalence between Asian Indians living in India and U.S. Whites, Blacks, and Hispanics became even more evident, however, the difference in prediabetes diabetes prevalence between the groups was attenuated, especially in women.

In both men and women, Asian Indians also had the highest age-specific prevalence of diabetes in all age groups, including the youngest age group of 20-34 years. Conversely, Asian Indians had the lowest prevalence of prediabetes in all age groups. These results are in concordance with other studies indicating the rising prevalence of type 2 diabetes in India alongside a stagnant or decreasing prevalence of prediabetes. A study assessing temporal changes in the prevalence of diabetes and impaired glucose tolerance using two cross-sectional studies from a rural Indian population noted that over a 14 year period, the prevalence of diabetes increased nearly three-fold. However, the prevalence of impaired glucose tolerance remained relatively stable.[17] A later study examining secular trends in the prevalence of diabetes and impaired glucose tolerance using several cross-sectional population based studies from Chennai India also noted a marked increase in diabetes prevalence over time, with an initial increase followed by a later decline in prediabetes prevalence.[3] It is possible that the high prevalence of type 2 diabetes in India relative to the low prevalence of prediabetes is due to a rapid conversion through the prediabetes state. While there are few studies examining the incidence rate of diabetes in Asian Indians, one study from Chennai, India, reported a very high incidence rate of 64·8 per 1,000 person years of diabetes from prediabetes.[17]

Results of our study also indicated that amongst all ethnic groups, Asian Indians had the lowest probability of being classified in the middle (prediabetes) range of fasting plasma glucose, while having the highest probability of being classified in the lowest

ranges of fasting insulin. Furthermore, the inclusion of Log HOMA-β in polytomous regression models decreased the difference in odds of developing diabetes between Whites and Asian Indians and also resulted in a greater odds of diabetes in Blacks and Hispanics compared to Asian Indians.

Several recent studies have suggested innate susceptibilities in Asian Indians not only for insulin resistance but also for impaired pancreatic β-cell function, which are seen even in younger adults and are evidenced early in the natural history of disease progression, even before the onset of hyperglycemia.[8,9,10] This notion was further evidenced in our study, as the inclusion of log HOMA- β in polytomous regression models resulted in a greater odds of diabetes in Blacks and Hispanics compared to Asian Indians, suggesting a large contribution of impaired β-cell function towards diabetes development in Asian Indians as compared to insulin resistance which might be the driving factor in other ethnic groups.

Our study directly compared the prevalence of diabetes and prediabetes in Asian Indians and Whites, Blacks, and Hispanics using two large, population based surveys that rely on both self-report and laboratory measures. While the laboratory measures for glucose and insulin were analyzed in different laboratories, both laboratories used the same assays for analysis, thereby reducing intra-laboratory bias. Additionally, assays from the laboratory in Chennai have been run against a reference laboratory in the US and show a high concordance of r=0·945. Furthermore, while there were differences in the sampling frames between the two studies, both studies are large, population-based samples that are representative either of the United States, or an urban city in India. While the data from CARRS is only representative of one urban city in India, and

therefore cannot be generalized to the entire Indian population, results from our study mirror those of other population-based studies in urban India that have notes an especially high diabetes prevalence.[3,18-20] Furthermore, many rural areas of India are now starting to urbanize through increases in income and improvements in basic facilities such as access to water, electricity and transportation.[21,22] Subsequently, rural areas are beginning to experience their own subsequent increases in diabetes prevalence.[4,21,22] Therefore, the high prevalence of diabetes in one urban Indian city as reported in our study may be predictive of an even larger diabetes epidemic yet to come.

In conclusion, we found that compared to Whites, Hispanics, and Blacks in the US, Asian Indians in India have a higher age-specific prevalence of diabetes in both genders and in all adult age groups. This high prevalence exists despite Asian Indians having, on average, lower BMI and waist circumference measurements, thereby suggesting the contribution of other non-obesity driven factors to the disproportionate burden of disease. In addition, the results of our study point to a lower prevalence of prediabetes in Asian Indians living in India compared to ethnic minority groups in the US. We speculate that the relatively lower prevalence of prediabetes in Asian Indians in India is due to either a rapid progression through the natural history of disease, driven by innate susceptibilities for β-cell dysfunction coupled with lifestyle factors (i.e., diet and activity), or may indicate that the epidemic in India is still evolving and not fully mature. This notion is supported by the results of a systematic review of type 2 diabetes and impaired glucose tolerance in aboriginal populations worldwide, whereby investigators noted an inverse relationship between the prevalence of type 2 diabetes and the ration of impaired fasting glucose.[23] Aboriginal populations with a very high type 2 diabetes

prevalence had a much lower prevalence of prediabetes suggesting that populations with high type 2 diabetes rates have likely moved past the prediabetes stage in the natural history of the disease.

Longitudinal studies of Asian Indians that aim to disentangle the relative contributions of genetic and environmental factors early on in the natural history of diabetes progression are necessary in order to further the understanding of and improve prevention and treatment mechanisms for diabetes and prediabetes in this high risk group.

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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. V.M. contributed to the design of the CARRS study, contributed to the discussion and interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript for submission. R.P. and M.D oversaw the CARRS research operations and contributed to the design, and data collection of the CARRS study. R.M.A contributed to the discussion and interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript for submission. N.K.M. and E.W.G contributed to the discussion and interpretation of the data, 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. 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.

REFERENCES

1. Kasuga M. Insulin resistance and pancreatic β cell failure. *Journal of Clinical Investigation* 2006; 1756-1760.
2. Saad MF, Knowler WC, Pettitt DJ, et al. A two-step model for development of non-insulin-dependent diabetes. *The American journal of medicine* 1991; ***90*(1)**: 229-235.
3. Mohan V, Deepa M, Deepa R, et al. Secular trends in the prevalence of diabetes and impaired glucose tolerance in urban South India—the Chennai Urban Rural Epidemiology Study (CURES-17). *Diabetologia* 2006; ***49*(6)**: 1175-1178.
4. Hwang CK, Han PV, Zabetian A, et al. Rural diabetes prevalence quintuples over twenty-five years in low-and middle-income countries: a systematic review and meta-analysis. *Diabetes research and clinical practice* 2012; ***96*(3)**: 271-285.
5. Griffiths PL, Bentley ME. The nutrition transition is underway in India. *The Journal of nutrition* 2001; **131(10)**: 2692-2700.
6. Shetty PS. Nutrition transition in India. *Public health nutrition* 2002; ***5*(1a)**:175-182.
7. Misra A, Singhal N, Sivakumar B, et al. Nutrition transition in India: Secular trends in dietary intake and their relationship to diet-related non-communicable diseases. *Journal of diabetes* 2011; ***3*(4)**:278-292.
8. Gujral UP, Narayan KM, Kahn SE, Kanaya AM. The relative associations of β-cell function and insulin sensitivity with glycemic status and incident glycemic progression in migrant Asian Indians in the United States: The MASALA study. *Journal of diabetes and its complications* 2014; **28(1)**: 45-50.

9. Staimez LR, Weber MB, Ranjani H, et al. Evidence of reduced β-cell function in Asian Indians with mild dysglycemia. *Diabetes care* 2013; **36(9)**: 2772-2778.
10. Mohan V, Amutha A, Ranjani H, et al. Associations of β-cell function and insulin resistance with youth-onset type 2 diabetes and prediabetes among Asian Indians. *Diabetes technology & therapeutics* 2013; **15(4)**: 315-322.
11. Registrar General I. Census of India 2011: provisional population totals-India data sheet. *Office of the Registrar General Census Commissioner, India. Indian Census Bureau*, 2011.
12. Nair M, Ali MK, Ajay VS, et al. CARRS Surveillance study: design and methods to assess burdens from multiple perspectives. *BMC public health* 2012; **12(1)**: 701.
13. NHANES Survey Methods 2014. Available from http://www.cdc.gov/nchs/nhanes/survey_methods.htm, accessed November 17, 2014.
14. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes care*, 2010; *33*(Supplement 1), S62-S69.
15. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes care* 2004; **27(6)**: 1487-1495.
16. Cheng YJ, Kahn HS, Gregg EW, Imperatore G, Geiss, LS. Recent population changes in HbA1c and fasting insulin concentrations among US adults with preserved glucose homeostasis. *Diabetologia* 2010; **53(9)**: 1890-1893.

17. Mohan V, Deepa M, Anjana RM, Lanthorn H, Deepa R. Incidence of diabetes and pre-diabetes in a selected urban south Indian population (CUPS-19). *Journal of the Association of Physicians of India* 2008; **56**: 152-157.
18. Anjana RM, Pradeepa R, Deepa M, et al. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: Phase I results of the Indian Council of Medical Research–INdia DIABetes (ICMR–INDIAB) study. *Diabetologia* 2011; **54(12):** 3022-3027.
19. Gupta A, Gupta R, Sarna M, Rastogi S, Gupta VP, Kothari K. Prevalence of diabetes, impaired fasting glucose and insulin resistance syndrome in an urban Indian population. *Diabetes research and clinical practice* 2003; **61(1)**: 69-76.
20. Deepa M, Anjana RM, Manjula D, Narayan KV, Mohan V. Convergence of prevalence rates of diabetes and cardiometabolic risk factors in middle and low income groups in urban India: 10-year follow-up of the Chennai Urban Population Study. *Journal of diabetes science and technology* 2011; ***5*(4)**, 918-927.
21. Ramachandran A, Snehalatha C, Baskar ADS, et al. Temporal changes in prevalence of diabetes and impaired glucose tolerance associated with lifestyle transition occurring in the rural population in India. *Diabetologia* 2004; **47(5)**: 860-865.
22. Misra P, Upadhyay RP, Misra A, Anand K. A review of the epidemiology of diabetes in rural India. *Diabetes research and clinical practice* 2011; ***92*(3)**: 303-311.

23. Catherine HY, Zinman B. Type 2 diabetes and impaired glucose tolerance in aboriginal populations: a global perspective. *Diabetes research and clinical practice* 2007; **78**(2), 159-170.

TABLES AND FIGURES

Table 3.1 Eligibility, Questionnaire and Exam Components in NHANES and CARRS used for Analysis

	NHANES	CARRS
Eligibility Criteria		
Inclusion Criteria	• Civilian, non-institutionalized individuals, aged 20 years or older living in the United States	• Aged 20 years or older and permanently residing in the selected household
Exclusion Criteria	• Pregnant women • Hemophilia • Chemotherapy within the last 4 weeks • The presence of rashes, gauze dressings, casts, edema, paralysis, tubes, open sores or wounds, withered arms or limbs missing, damaged, sclerosed or occluded veins, allergies to cleansing reagents, burned or scarred tissue, shunt or intravenous lines on both arms	• Pregnant women • bed ridden individuals
Questionnaires	• Demographic information including race/ethnicity, family history of type 2 diabetes mellitus medical history, and current medication use	• Demographic information including language use, family history of type 2 diabetes mellitus, medical history, and current medication use
Weight	• Digital floor scale with automated data capture and read out capabilities	• Standing balance beam scale
Height	• Wall mounted stadiometer	• Portable stadiometer
Waist Circumference	• Flexible tape measure at uppermost lateral border of the right ilium and the midaxillary line	• Non-stretch measuring tape at the site of maximum circumference halfway between the lower ribs and the anterior superior iliac spine
Phlebotomy	• Conducted by certified phlebotomists • 100 mL of blood in the fasting state to measure glucose, insulin, and lipids • After a 9 hour overnight fast, a 75g oral glucose tolerance test (OGTT) • Obtained from a peripheral vein just before glucose ingestion (time 0) and then 120 minutes post-challenge for participants who performed the (OGTT)	• Conducted by certified phlebotomists. • 15 mL of blood in the fasting state to measure glucose, insulin and lipids • After at least a 9 hour overnight fast, a 75g OGTT • Obtained from a peripheral vein just before glucose ingestion (time 0) and at 30 and 120 minutes post glucose challenge • The samples were transported from field sites in cold chain to laboratories for analysis
Glucose	• Serum glucose was measured using the hexokinase method	• Serum glucose was measured using the hexokinase method

Table 3.2. Weighted characteristics of participants aged 20-75 years by ethnicity*

	NHANES White	NHANES Black	NHANES Hispanic	CARRS Asian Indian
Men				
N	1481	736	994	2067
Age (mean year)	46.0 ± 0.6 (44.9, 47.2)	43.0 ± 0.6 (41.9, 44.1)	39.5 ± 0.5 (38.5, 40.5)	42.4 ± 0.5 (41.6, 43.8)
Height (mean cm)†	178.3 ± 0.3 (177.8, 178.9)	176.7 ± 0.3 (176.1, 177.1)	171.3 ± 0.3 (170.5, 171.7)	164.5 ± 0.2 (163.9, 164.7)
Weight (mean kg)†	91.4 ± 0.8 (90.3, 92.6)	89.9 ± 0.9 (88.0, 91.7)	85.9 ± 0.8 (84.2, 87.5)	65.5 ± 0.4 (64.8, 66.2)
BMI (mean kg/m^2)†	28.8 ± 0.2 (28.4, 29.1)	28.6 ± 0.3 (28.1, 29.4)	29.0 ± 0.2 (28.8, 29.7)	24.2 ± 0.1 (24.0, 24.5)
Waist Circumference (mean cm)†	102.6 ± 0.6 (101.3, 103.2)	97.5 ± 0.7 (96.7, 99.5)	101.4 ± 0.6 (100.2, 102.6)	87.0 ± 0.4 (86.7, 88.1)
Fasting Glucose (mg/dl)†	106.4 ± 0.9 (104.1, 107.5)	107.0 ± 2.0 (103.6, 111.6)	111.3 ± 1.4 (110.6, 116.5)	109.1 ± 1.4 (107.2, 112.6)
2-hr Glucose (mg/dl)†	111.3 ± 1.3 (107.0, 112.8)	110.5 ± 2.5 (107.3, 117.3)	119.2 ± 2.5 (119.2, 129.6)	116.8 ± 2.3 (115.4, 124.9)
Fasting Insulin (pmol/L)†	2.5 ± 0.3 (2.4, 2.6)	2.4 ± 0.4 (2.3, 2.5)	2.7 ± 0.4 (2.6, 2.8)	2.1 ± 0.2 (2.0. 2.1)
Log HOMA-IR (μIU/ml*mmol/l)†	1.1 ± 0.4 (1.0, 1.2)	1.0 ± 0.5 (0.9, 1.1)	1.3 ± 0.6 (1.2, 1.5)	0.6 ± 0.2 (0.6, 0.7)
Log HOMA-β (μIU/ml/mmol/l)†	4.8 ± 0.3 (4.7, 4.8)	4.6 ± 0.5 (4.5, 4.7)	4.8 ± 0.3 (4.7, 4.8)	4.5 ± 0.3 (4.5, 4.6)
Women	NHANES White	NHANES Black	NHANES Hispanic	CARRS Asian Indian
N	1418	818	1065	2800
Age (mean year)	46.8 ± 0.4 (45.9, 47.7)	43.7 ± 0.6 (42.5. 44.9)	41.1 ± 0.6 (39.9, 42.2)	40.4 ± 0.4 (39.6, 41.3)
Height (mean cm)†	164.0 ± 0.3 (163.6, 164.6)	164.0 ± 0.3 (163.3, 164.4)	157.8 ± 0.3 (156.9, 158.0)	150.6 ± 0.1 (150.3, 150.9)
Weight (mean kg)†	76.4 ± 0.6 (75.2, 77.5)	86.3 ± 0.9 (84.6, 88.1)	73.5 ± 0.6 (72.2, 74.7)	62.0 ± 0.4 (61.3, 62.7)
BMI (mean kg/m^2)†	28.5 ± 0.2 (27.9, 28.8)	32.0 ± 0.3 (31.4, 32.7)	29.3 ± 0.3 (29.1, 30.2)	27.3 ± 0.1 (27.0, 27.6)
Waist Circumference (mean cm)†	95.5± 0.5 (94.2, 96.3)	100.7 ± 0.7 (99.6, 102.5)	95.6 ± 0.6 (95.3, 98.0)	83.7 ± 0.4 (83.0, 84.5)
Fasting Glucose (mg/dl)†	99.3 ± 0.7 (98.0, 100.7)	105.8 ± 1.7 (102.5, 109.2)	105.6± 1.2 (103.2, 108.3)	112.7 ± 1.3 (109.9, 115.4)
2-hr Glucose (mg/dl)†	112.2 ± 1.2 (109.9, 114.5)	113.4 ± 1.9 (109.7, 117.2)	124.7 ± 2.3 (119.9, 129.4)	123.4 ± 1.1 (119.8, 127.0)
Fasting Insulin (pmol/L)†	2.4 ± 0.4 (2.4, 2.5)	2.7 ± 0.5 (2.6, 2.8)	2.6 ± 0.5 (2.5, 2.7)	2.2 ± 0.2 (2.1, 2.2)
Log HOMA-IR (μIU/ml*mmol/l)†	1.0 ± 0.5 (0.9, 1.1)	1.3 ± 0.6 (1.2, 1.4)	1.2 ± 0.5 (1.1, 1.3)	0.8 ± 0.2 (0.7, 0.8)
Log HOMA-β (μIU/ml/mmol/l)†	4.8 ± 0.4 (4.7, 4.9)	5.0 ± 0.5 (4.9, 5.0)	4.9 ± 0.6 (4.7, 4.9)	4.5 ± 0.3 (4.4, 4.5)

* Values represent mean, ± SE, and 95% CI
†Values are adjusted for age

Table 3.3 Weighted characteristics of participants aged 20-75 years by ethnicity adjusted for age and body mass index*

	NHANES White	NHANES Black	NHANES Hispanic	CARRS Asian Indian
Men				
Fasting Glucose (mg/dl)	105.9 ± 0.9 (104.1, 107.6)	107.6 ± 1.9 (103.8, 111.5)	113.1 ± 1.5 (110.1, 116.1)	113.5 ± 1.4 (110.6, 116.3)
2-hr Glucose (mg/dl)	110.0 ± 1.4 (107.2, 112.9)	112.7 ± 2.5 (107.7, 117.7)	123.4 ± 2.6 (118.4, 128.5)	127.3 ± 2.5 (122.3, 132.3)
Log Fasting Insulin (pmol/L)	2.5 ± 0.0 (2.4, 2.6)	2.4 ± 0.4 (2.3, 2.5)	2.6 ± 0.1 (2.5, 2.7)	2.4 ± 0.0 (2.3, 2.4)
Log HOMA-IR (μIU/ml*mmol/l)	1.1 ± 0.0 (1.0, 1.2)	1.0 ± 0.0 (1.0, 1.1)	1.3 ± 0.1 (1.1, 1.4)	1.0 ± 0.1 (0.9, 1.1)
Log HOMA-β (μIU/ml/mmol/l)	4.8 ± 0.0 (4.7, 4.8)	4.6 ± 0.1 (4.5, 4.7)	4.7 ± 0.0 (4.7, 4.8)	4.6 ± 0.1 (4.5, 4.6)
Women				
Fasting Glucose (mg/dl)	99.9 ± 0.6 (98.7, 101.1)	103.8 ± 1.6 (100.5, 107.1)	105.0± 1.2 (102.7, 107.4)	113.9 ± 1.4 (111.0, 116.7)
2-hr Glucose (mg/dl)	113.2 ± 1.0 (111.3, 115.1)	109.0 ± 2.1 (104.8, 113.2)	123.2 ± 2.2 (118.8, 127.6)	125.3 ± 1.8 (121.9, 128.8)
Log Fasting Insulin (pmol/L)	2.5 ± 0.0 (2.4, 2.5)	2.5 ± 0.1 (2.4, 2.7)	2.5 ± 0.0 (2.4, 2.6)	2.2 ± 0.0 (2.2, 2.3)
Log HOMA-IR (μIU/ml*mmol/l)	1.1 ± 0.0 (1.0, 1.2)	1.2 ± 0.1 (1.0, 1.3)	1.1 ± 0.0 (1.0, 1.2)	0.9 ± 0.0 (0.8, 0.9)
Log HOMA-β (μIU/ml/mmol/l)	4.8 ± 0.0 (4.8, 4.9)	4.9 ± 0.1 (4.8, 5.0)	4.8 ± 0.1 (4.7, 4.9)	4.5 ± 0.0 (4.4, 4.6)

* Values represent mean, ± SE, and 95% CI

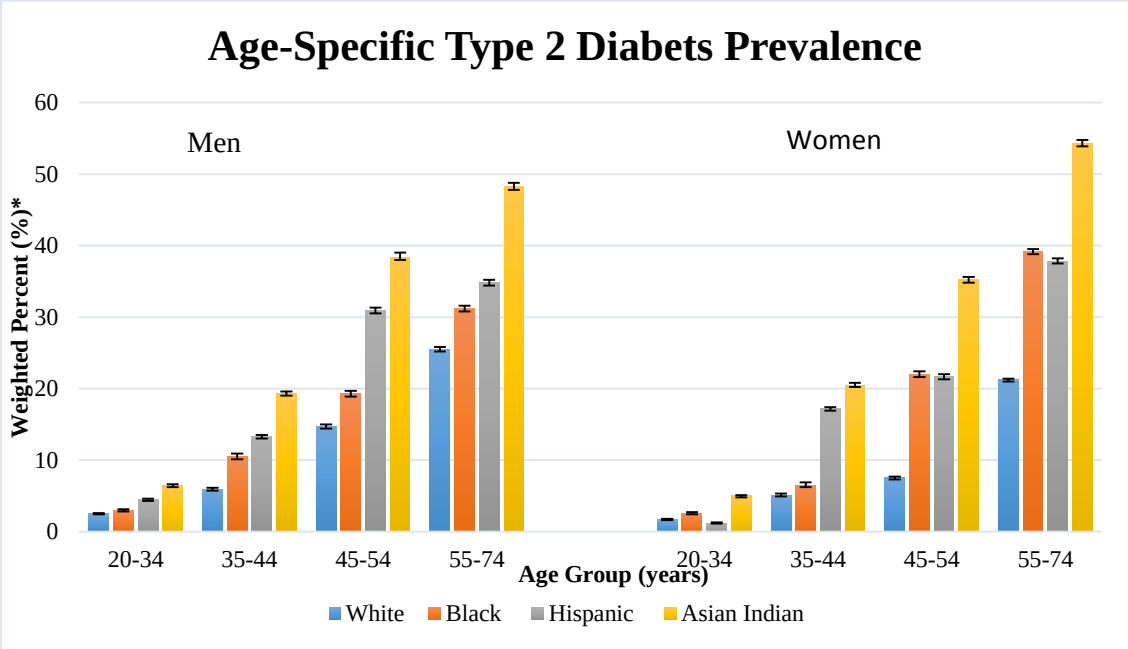
Table 3.4 Weighted Crude and Adjusted Prevalence of Diabetes and Prediabetes by Sex and Race/Ethnicity

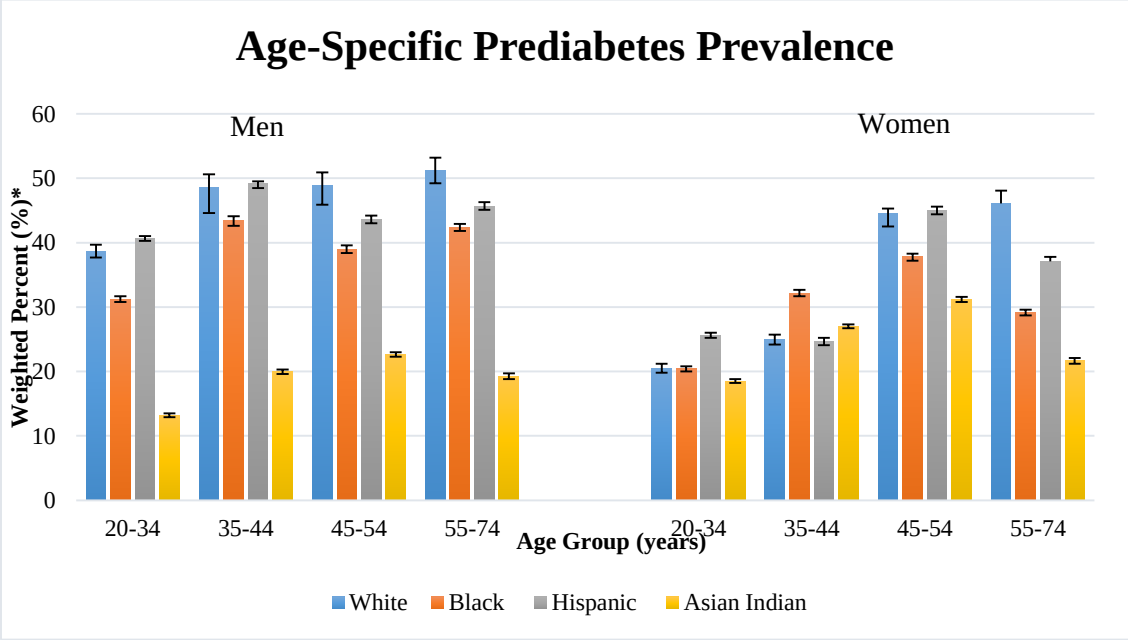
	NHANES White	NHANES Black	NHANES Hispanic	CARRS Asian Indian
Men				
Crude type 2 diabetes prevalence	13.1 (11.1, 15.5)	15.1 (12.1, 18.6)	16.2 (13.4, 19.3)	25.2 (22.4, 28.2)
Type 2 diabetes prevalence adjusted for age	12.2 (10.3, 14.4)	16.4 (13.5, 19.7)	21.3 (17.9, 25.0)	29.0 (25.9, 31.0)
Type 2 diabetes prevalence adjusted for age and body mass index	12.2 (10.3, 14.3)	16.6 (13.8, 19.8)	20.7 (17.3, 24.5)	36.9 (33.0, 40.9)
Type 2 diabetes prevalence adjusted for age, body mass index, and waist circumference	11.9 (10.0, 14.1)	17.3 (14.1, 21.0)	21.1 (17.7, 24.8)	39.0 (34.7, 43.8)
Crude prediabetes prevalence	46.9 (43.8, 50.0)	37.8 (34.6, 41.0)	44.2 (40.1, 48.3)	18.6 (16.9, 20.4)
Prediabetes prevalence adjusted for age	46.5 (43.5, 49.6)	38.2 (35.0, 41.5)	45.6 (41.4, 49.8)	19.0 (17.2, 20.8)
Prediabetes prevalence adjusted for age and body mass index	46.5 (43.6, 49.5)	38.2 (34.9, 41.5)	45.4 (41.3, 49.7)	22.1 (19.6, 24.8)
Prediabetes prevalence adjusted for age, body mass index, and waist circumference	46.2 (43.3, 49.3)	39.5 (35.8, 43.4)	46.0 (41.8, 50.3)	23.0 (20.1, 26.2)
Women				
Crude type 2 diabetes prevalence	10.3 (8.5, 12.3)	16.9 (14.0, 20.3)	15.7 (13.1, 18.8)	22.9 (20.2, 25.9)
Type 2 diabetes prevalence adjusted for age	9.5 (7.9, 11.5)	18.8 (16.0, 22.0)	20.3 (17.2, 23.9)	30.6 (27.5, 33.9)
Type 2 diabetes prevalence adjusted for age and body mass index	9.9 (8.2, 11.9)	15.1 (12.5, 18.0)	19.2 (16.2, 22.5)	33.1 (30.2, 36.2)
Type 2 diabetes prevalence adjusted for age, body mass index, and waist circumference	9.6 (7.9, 11.6)	15.3 (12.6, 18.3)	19.6 (16.7, 22.9)	41.4 (37.3, 45.7)
Crude prediabetes prevalence	35.2 (32.5, 38.1)	29.1 (25.6, 32.9)	31.4 (26.8, 36.5)	24.2 (20.2, 28.6)
Prediabetes prevalence adjusted for age	34.4 (31.7, 37.3)	30.2 (26.6, 34.1)	34.3 (29.5, 39.5)	27.2 (22.8, 32.1)
Prediabetes prevalence adjusted for age and body mass index	35.1 (32.2, 38.1)	27.8 (24.2, 31.7)	34.0 (29.1, 39.3)	29.6 (24.9, 34.8)
Prediabetes prevalence adjusted for age, body mass index, and waist circumference	35.0 (32.0, 38.1)	28.1 (24.4, 32.1)	34.4 (29.6, 39.6)	32.8 (26.8, 39.5)

Table 3.5. Weighted Risk factors Associated with Prediabetes and Diabetes

		Prediabetes		Type 2 Diabetes	
Model		OR	95% CI	OR	95% CI
Age, sex, ethnicity					
	Age Group	1.62	(1.62, 1.62)	3.09	(3.09, 3.10)
	Sex	0.51	(0.51, 0.51)	0.54	(0.54, 0.54)
	Caucasian vs. Asian Indian	1.65	(1.64, 1.67)	0.30	(0.30, 0.31)
	Black vs. Asian Indian	1.39	(1.38, 1.40)	0.51	(0.51, 0.51)
	Hispanic vs. Asian Indian	2.15	(2.13, 2.16)	0.79	(0.78, 0.80)
Age, sex, BMI, ethnicity					
	Age Group	1.54	(1.54, 1.54)	3.08	(3.07, 3.08)
	Sex	0.49	(0.49, 0.49)	0.45	(0.45, 0.45)
	BMI	1.08	(1.08, 1.08)	1.16	(1.16, 1.16)
	Caucasian vs. Asian Indian	1.38	(1.37, 1.39)	0.19	(0.19, 0.20)
	Black vs. Asian Indian	1.01	(1.00, 1.02)	0.25	(0.24, 0.25)
	Hispanic vs. Asian Indian	1.70	(1.69, 1.71)	0.47	(0.46, 0.47)
Age, sex, waist circumference, ethnicity					
	Age Group	1.45	(1.45, 1.45)	2.73	(2.73, 2.73)
	Sex	0.58	(0.58, 0.58)	0.70	(0.70, 0.70)
	Waist Circumference	1.03	(1.03, 1.03)	1.07	(1.07, 1.07)
	Caucasian vs. Asian Indian	1.11	(1.10, 1.12)	0.11	(0.11, 0.11)
	Black vs. Asian Indian	0.89	(0.88, 0.90)	0.17	(0.17, 0.17)
	Hispanic vs. Asian Indian	1.43	(1.42, 1.44)	0.30	(0.30, 0.31)
Age, sex, HOMA-β, ethnicity					
	Age	1.59	(1.59, 1.60)	3.10	(3.10, 3.10)
	Sex	0.58	(0.58, 0.58)	0.74	(0.74, 0.74)
	Log HOMA-β	1.00	(1.00, 1.00)	0.65	(0.64, 0.65)
	Caucasian vs. Asian Indian	1.55	(1.53, 1.56)	0.85	(0.84, 0.86)
	Black vs. Asian Indian	1.21	(1.20, 1.22)	1.70	(1.68, 1.72)
	Hispanic vs. Asian Indian	1.74	(1.73, 1.76)	2.93	(2.90, 2.97)
Age, sex, HOMA-IR, ethnicity					
	Age	1.69	(1.69, 1.69)	4.07	(4.06, 4.07)
	Sex	0.55	(0.55, 0.55)	0.71	(0.71, 0.71)
	Log HOMA-IR	3.85	(3.85, 3.85)	17.00	(16.97, 17.03)
	Caucasian vs. Asian Indian	0.96	(0.95, 0.97)	0.18	(0.18, 0.18)
	Black vs. Asian Indian	0.69	(0.69, 0.70)	0.34	(0.34, 0.35)
	Hispanic vs. Asian Indian	0.95	(0.94, 0.95)	0.53	(0.52, 0.54)

Figure 3.1. Weighted Age-Specific Diabetes and Prediabetes Prevalence by Sex and Race/Ethnicity





*Values represent weighted prevalence and 95% CI

Figure 3.2. Distribution of Fasting Glucose, 2 Hour Glucose, and Fasting Insulin by Race/Ethnicity

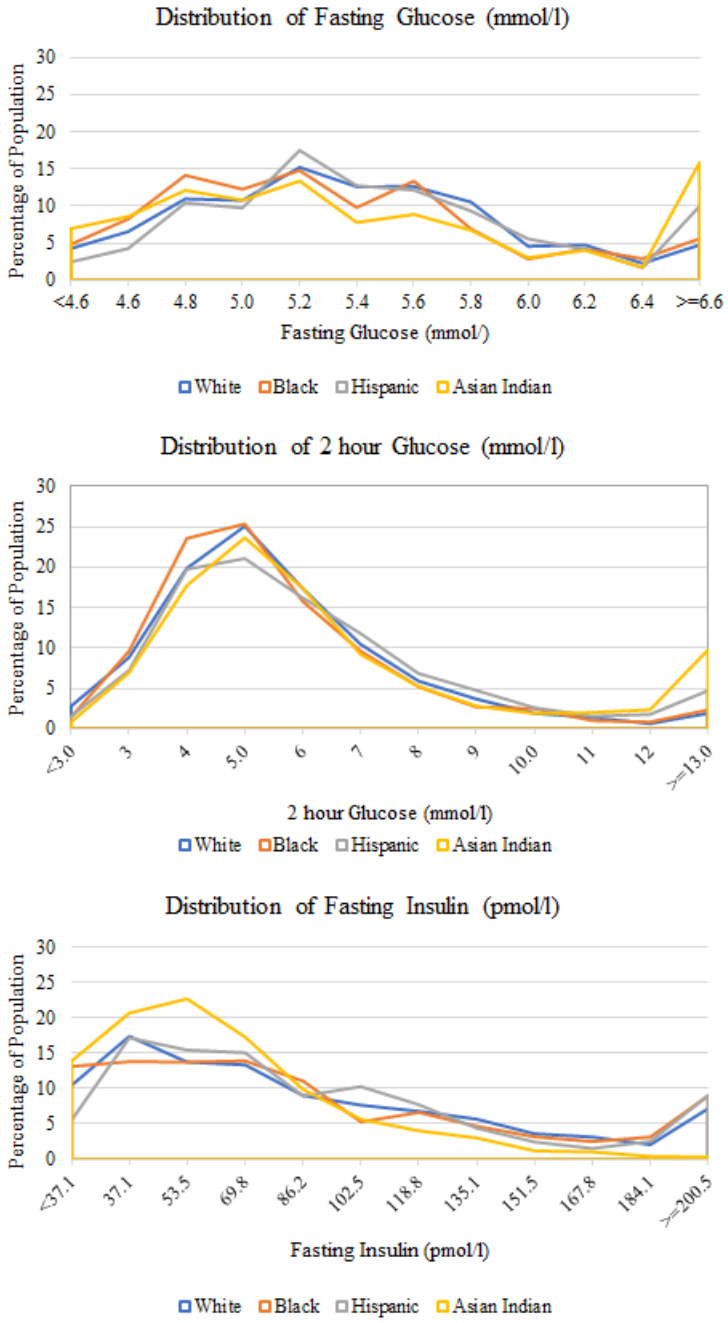


Figure 3.3. Percentages and 95% Confidence Intervals of the Distribution of Fasting Glucose, 2 Hour Glucose, and Fasting Insulin by Race/Ethnicity

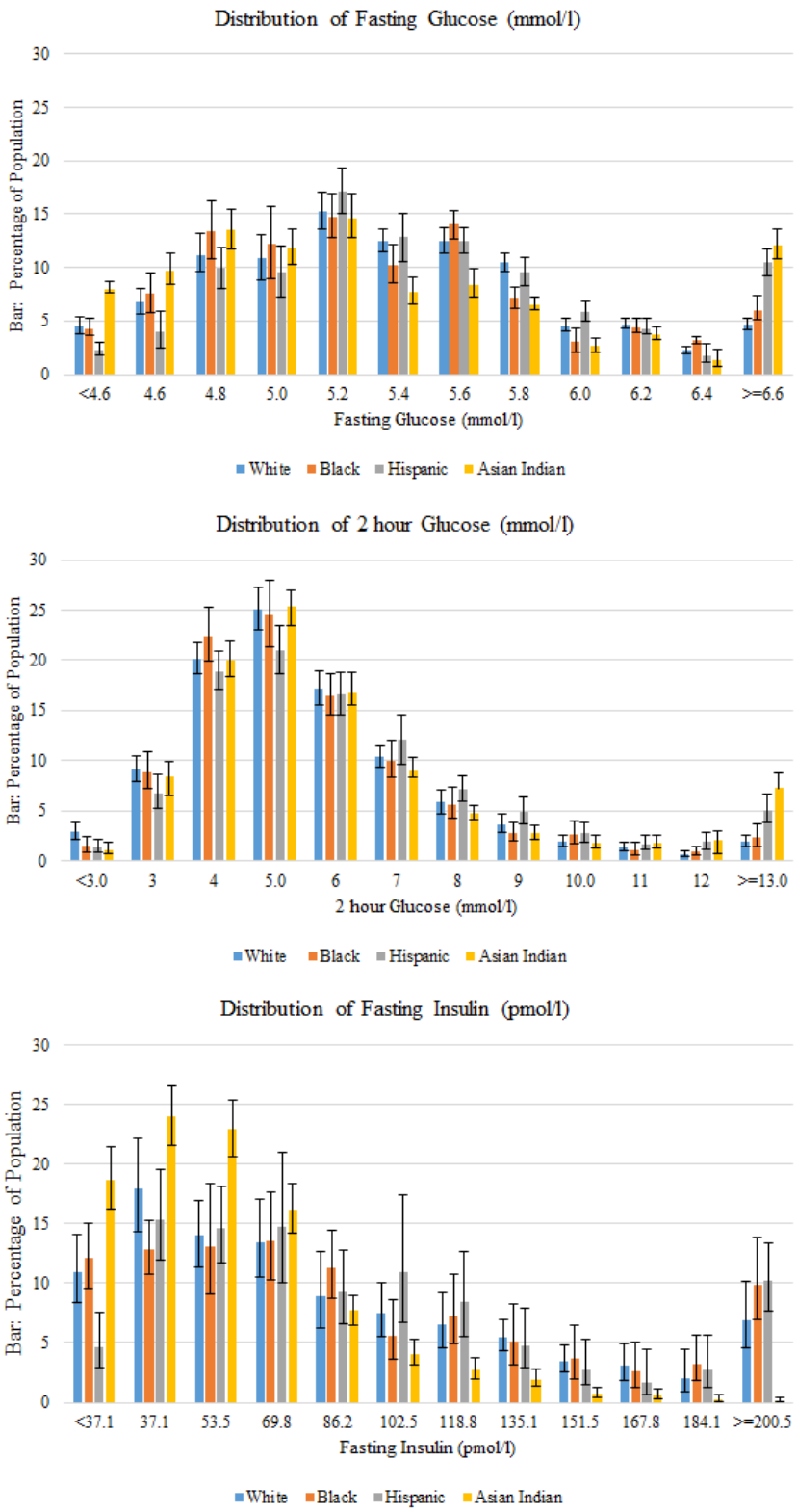
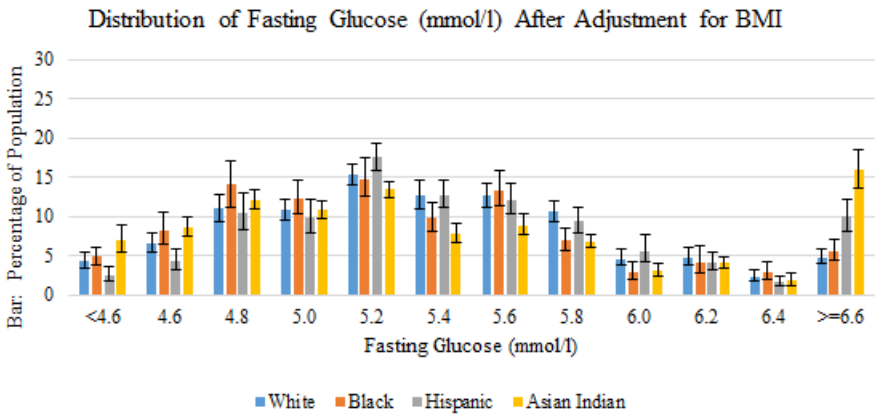
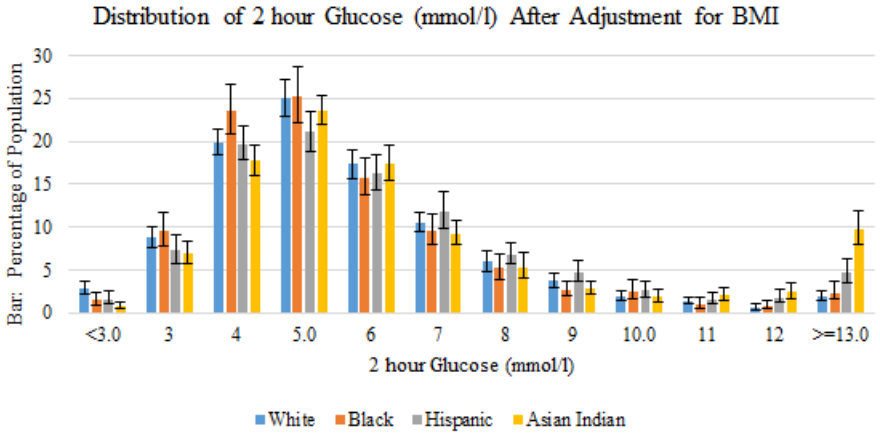
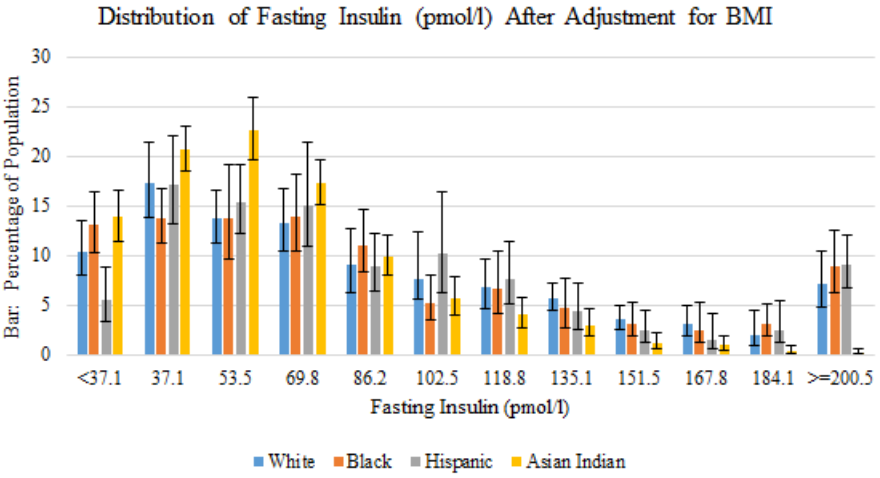


Figure 3.4 Percentages and 95% Confidence Intervals Adjusted for BMI of the Distribution of Fasting Glucose, 2 Hour Glucose, and Fasting Insulin by Race/Ethnicity







CHAPTER 7: Summary and Conclusions

Summary of Main Findings

The work presented in this dissertation is motivated by two key ideas. First, several studies have noted a higher prevalence of type 2 diabetes in Asian Indians despite lower levels of traditional risk factors such as age and adiposity.[9-16] This has given rise to the possibility that Asian Indians may experience unique biological susceptibilities to β-cell dysfunction which could be the driving factor behind diabetes risk in this population. Secondly, recent economic and nutritional transitions in India,[23,24] coupled with already existing biological susceptibilities may result in Asian Indians living in India having a high prevalence of diabetes in an international context. This dissertation sought to address some of these issues and found that β-cell dysfunction was more strongly associated with diabetes and prediabetes than insulin resistance in Asian Indians. Additionally, Asian Indians living in India had a higher prevalence of diabetes than those living in San Francisco or Chicago despite having a lower BMI. Conversely, Asian Indians living in India had a lower prevalence of prediabetes than their migrant counterparts, and migration was shown to have a protective effect on the odds of diabetes. Asian Indians living in India also had a higher prevalence of diabetes and a lower prevalence of prediabetes than Caucasians, Blacks, and Hispanics living in the United States. This occurred again despite Asian Indians having lower anthropometric measures. Additionally, a measure of β-cell function (log HOMA-β) was associated with in an increased odds of diabetes in Blacks and Hispanics compared to Asian Indians, and also severely attenuated the odds of diabetes in Asian Indians compared to Caucasians.

The results of this dissertation are in concordance with other studies conducted in Asian Indians living in India that have pointed to early reductions in β-cell function as a possible primary etiological factor for diabetes development in this ethnic group. Two recent cross-sectional studies conducted on populations in Chennai, India, both showed that after adjustment for well-known risk factors, measures of β-cell function were more strongly associated with glycemic status than were measures of insulin resistance.[41,42] The results of this dissertation contributed additional evidence to support the hypothesis that declines in β-cell function may be an underlying factor in type 2 diabetes development in Asian Indians living in India as well as those who have migrated to the United States. The findings show stronger associations of β-cell function compared to insulin resistance on glycemic status in a cohort of Asian Indians in the United States, the association of log HOMA-β with glycemic progression in this same cohort, and the severe attenuation of the odds of diabetes in Asian Indians compared to Caucasians, Blacks, and Hispanics after adjustment for log HOMA-β.

The findings presented in this dissertation also challenge previous notions regarding the role of migration on diabetes risk, as well as present paradoxical relationships between the ratio of diabetes to prediabetes prevalence in certain populations. Previous findings have noted that Asian Indians who migrate to the United States have poorer metabolic profiles than their counterparts in India.[45,46] Conversely, the results of this dissertation indicate that while Asian Indians in India had lower BMI and waist circumference measurements than those living in San Francisco or Chicago, they still had a higher prevalence of type 2 diabetes even at normal levels of BMI and in both sexes. Furthermore, in standardized polytomous logistic regression models, migration

was negatively associated with the odds of diabetes even after adjusting for well-known risk factors such as age, waist circumference, and systolic blood pressure. It is therefore possible that factors related to migration such as increased access to health care and improved awareness of diabetes prevention serve as protective factors against diabetes risk.[50] It is also possible that factors once related to migration that increase diabetes risk such as diets high in fat and low levels of physical activity are now taking place in India as well.

Recent nutrition and economic transitions occurring in India, coupled with innate susceptibilities for β-cell dysfunction may also serve to explain the high prevalence of diabetes in Asian Indians compared to the relatively low prevalence of prediabetes. The analyses presented in this dissertation found that in Caucasians, Blacks, and Hispanics, the prevalence of prediabetes relative to that of diabetes was higher in all age groups, with the exception of Black and Hispanic women aged 55-74. These results are in concordance with a study examining the prevalence of diabetes and prediabetes in Non-Hispanic Whites, Non-Hispanic Blacks, and Mexican Americans in the United States during 2005-2006.[61] The results of this study found that for all race/ethnic groups (Caucasians, Blacks, and Hispanics), and in all age categories, the prevalence of diabetes was higher than that of prediabetes. Furthermore, when compared with data from 1988-1994 the crude prevalence of diagnosed diabetes in individuals aged ≥ 20 years rose from 5.1% to 7.7% between 1988-1994 and 2005-2006. However, the prevalence of prediabetes remained relatively stable, which was surprising given the increased diabetes and obesity prevalence in these groups over time.[61] However, the work presented in this dissertation noted that unlike Caucasians, Blacks, and Hispanics, the prevalence of

diabetes in Asian Indians living in India was higher than the prevalence of prediabetes. These results were similar to those found in a study examining the prevalence of these conditions in Sri Lankan adults between 2005 and 2006 in which the prevalence of diabetes was higher than that of prediabetes in all age groups excepting those between 20 and 49 years of age.[62] Furthermore, a study from Chennai, India, that assessed the secular trends in the prevalence of diabetes and impaired glucose tolerance over time found that in a span of 14 years, diabetes prevalence increased by 72.3%. Conversely, while the prevalence of impaired fasting glucose increased by 9.6% from 1989 to 1995 and by 84.6% between 1995 and 2000, it decreased by 39.3% between 2000 and 2004.[6] Therefore, the high prevalence of diabetes prevalence relative to that of prediabetes in developing countries such as India and Sri Lanka that is not seen in developed countries such as the United States, coupled with the decline in prediabetes prevalence in urban India in more recent years could be indicative of innate susceptibilities to disease development such as impaired β-cell function being exacerbated by nutritional and economic shifts resulting in a phenomena by which those who are most susceptible progress through the natural history of disease most rapidly. Furthermore, while Asian Indians living in the United States still have a high prevalence of disease, migration to a developed country may serve to alleviate some diabetes risk in this ethnic group.

Limitations

The research presented in this dissertation has several limitations. First, the cross-sectional nature of the data sources only allows for the assessment of the relative contributions of β-cell function and insulin resistance on glycemic status at a specific point in time. While useful, it does not allow for the investigation of the influences of

each pathophysiological mechanism on the progression of type 2 diabetes through the natural history of disease. Furthermore, it is not possible to infer causality. Additionally, while it did provide some of the first data on incidence of diabetes and prediabetes in Asian Indians in the United States, the longitudinal component of this dissertation was limited by small sample size and short time of follow-up.

Secondly, in order to conduct comparisons of diabetes and prediabetes prevalence and the associated risk factors either by environmental location or by ethnic group, it was necessary to combine surveys that were conducted separately. This resulted in differing sampling frames with possible differences in sampling selection biases as well as differing socio-demographic characteristics between the studies. However, the studies used for comparison were both large population based samples with similar anthropometric and laboratory measures. In addition, the samples were representative of Asian Indians in large urban centers either in India or the United States as well as Caucasians, Blacks, and Hispanics over the age of 20 living in the United States.

While there were large differences in education status between Asian Indians living in India and the United States, Asian Indians in San Francisco and Chicago still had a higher diabetes prevalence than the general United States population[37] indicating that other factors besides educational attainment are responsible for the high prevalence of diabetes in Asian Indians regardless of environmental location. Additionally, while the laboratory measures for glucose and insulin were analyzed in different labs between the studies, all labs involved used the same assays for analysis, thereby further reducing intra-laboratory bias. Assays from the laboratory in Chennai were also run against a reference lab in the US and show a high concordance of r=0·945.

While several of the anthropometric variables used were comparable across studies, data on diet and physical activity were not collected in a similar manner between all of the datasets used. Therefore the effects of these variables on glycemic status and diabetes and prediabetes prevalence could not be assessed. Furthermore, while the MASALA and CARRS studies both collected 30 minute post challenge glucose and insulin, which allowed for the calculation of DI_O and ISI_M as measures of β-cell function and insulin sensitivity respectively, NHANES did not. Therefore, in comparisons with NHANES, HOMA-β and HOMA-IR were instead used as measures of β-cell function and insulin resistance. While products of plasma glucose and insulin were used in the calculation of DI_O, ISI_M, HOMA-β and HOMA-IR and therefore were included in both the outcome (type 2 diabetes or prediabets) and exposure variables, the relationship between insulin sensitivity and insulin response are hyperbolic in nature.[64] Therefore, an assessment of the association of DI_O with the odds of diabetes or prediabetes is appropriate as it measures the ability of the β-cell to compensate for the body's specific degree of insulin resistance.[64] Conversely, ISI_M measures the existence of an elevated plasma insulin concentration in the presence of a high fasting plasma glucose concentration and is an appropriate tool in the association of insulin sensitivity with hyperglycemia.[65] Both HOMA-β and HOMA-IR are also derived from the products of fasting glucose and insulin and assess β-cell function and insulin resistance respectively.[63] Although the gold standard for measurement of insulin secretion and sensitivity is the euglycemic hyperinsulinemic clamp, the use of this technique is long, cumbersome, and often times not practical for use in large, epidemiological studies.[66] The use of DI_O and HOMA-β as measures of β-cell function and ISI_M and HOMA-IR as

measures of insulin resistance have all been validated and correlate well with clamp techniques.[63,64,65] Furthermore, the use of 30 minute post challenge glucose and insulin in the calculation of DI_O and ISI_M provide further information beyond that of fasting and 2 hour post challenge levels, and therefore more information regarding insulin sensitivity relative to secretion may be gathered by the use of these measures.

While the sampling frames were different in each study used, both the CARRS and NHANES surveys used sampling weights to maximize the representativeness of the sample in terms of size, distribution, and overall characteristics of the study population. For CARRS, participant selection was done in three phases; wards, census enumeration blocks, and households.[58] The base weights were calculated to reflect the probability of selection at each phase of selection. Overall sample weights were then calculated as the inverse of the base weight (after adjusting for non-response) where the base weight was obtained as reciprocal of overall probability of selection. For NHANES, data were collected in two year cycles and sampling took place in four stages; the primary sampling units, census blocks, dwelling units or households, and individuals. Sample weighting was then carried out in three steps; (1) to compute weights to compensate for unequal probabilities of selection, (2) to adjust for nonresponse, and (3) to post stratify sample weights to the Census Bureau estimates of the US population.[58] The appropriate weight for the number of years surveyed overall as well as the examination component with the least number of participants (2 hour post challenge glucose) was used.[58] Once the CARRS and NHANES surveys were combined appropriate sample weights were assigned to each population. Additionally the sampling frame for MASALA was created using the South Asian surnames list on the California Health Interview Survey, whereby names,

addresses, and telephone numbers were obtained from randomly sampled households in the study area. However, the random samples of South Asian surnames from the desired geographic locations were created using a specific cultural coding algorithm which identified 162 ethnicities, 16 ethnic groups, 80 language preferences, 21 countries of origin, and 12 religions using a 5-step matching process to classify a person's first and last name, thereby reducing selection bias among participants with uncommon South Asian surname.[57]

Therefore, while the sampling frames for each study were different, the combination of the data as well as the use of appropriate sampling weights for each study likely contributed to results that were representative of each population.

The results of this dissertation are also limited by their generalizability. At the inception of this dissertation, there were no nationally representative data sets that included fasting and two hour glucose measurements in India. Furthermore, to date, there are still no nationally representative data sets that include these measures on a sample of Asian Indians in the United States. Therefore in order to achieve the aims of this dissertation, two distinct Asian Indian populations from differing geographic regions (Chennai, India and the greater San Francisco and Chicago areas of the United States) were compared, and the results cannot be generalized to Asian Indians living in other parts of India or the United States. However the results of this dissertation are in concordance with several studies noting an increasingly high prevalence of diabetes other Indian urban geographic regions besides Chennai.[8,67,68] Furthermore, the diabetes prevalence of the Asian Indians living in San Francisco and Chicago as noted in this dissertation was similar to what was found in recently published study of Asian Indians in

Michigan.[69] Additional national level data is needed to assess the prevalence of diabetes among Asian Indians living in the United States. The increased inclusion of Asian Indian participants in NHANES may serve to alleviate this issue.

Strengths and Innovations

The research presented in this dissertation has several strengths. First, diabetes was diagnosed using self-report, as well as biological measures of fasting and two hour post challenge glucose. To date, most studies examining the prevalence of diabetes in Asian Indians rely only on self-report data,[9,10,12,29,37,70] which is problematic, as it only accounts for individuals with previous knowledge of disease status, and therefore may underestimate the true prevalence of disease. Secondly, using measures of fasting and two hour post challenge glucose, the prevalence of prediabetes, which was previously not well known in Asian Indians, was also assessed. Furthermore, plasma glucose and insulin were used to calculate measures of β-cell function (DI_O and HOMA-β) and insulin resistance (ISI_M and HOMA-IR) in several different populations. Therefore, the studies presented in this dissertation were amongst the first to assess the relative contributions of β-cell function and insulin resistance on glycemic status in participants from different ethnic groups and environments.

Additionally, this dissertation utilized large population based samples with similar anthropometric and laboratory measures that are representative of Asian Indians in large urban centers either in India or the United States, as well as Caucasians, Blacks, and Hispanics in the United States. The large size of the surveys allowed for stratification by variables such as sex, BMI, age, and race. Furthermore, the combined use of surveys allowed for a comparisons between groups, (either Asian Indians in the United States and

India, or Asian Indians in India and Caucasians, Blacks, and Hispanics in the United States that would not have been possible otherwise.

Public Health Implications

Gaps in Published Literature

While several previous studies have noted the high prevalence of diabetes in Asian Indians,[8-15,28,36,69] very few have examined this in the context of pathophysiology. Seminal studies have classified the development of diabetes as obesity driven insulin resistance, followed by a subsequent decline in pancreatic β-cell dysfunction.[24,25] However, several studies have noted that Asian Indians develop type 2 diabetes at younger ages, and at lower levels of BMI and waist circumference than do members of other ethnic groups,[9,11,28,70,71] thereby suggesting possible innate susceptibilities to pancreatic β-cell function that exist beyond traditionally associated factors such as age, adiposity, and insulin resistance. The research presented in this dissertation addresses these issues, firstly by assessing the relative contributions of β-cell function and insulin resistance on glycemic status in a cohort of Asian Indians in the United States, and secondly by comparing the relative contributions of β-cell function and insulin resistance on glycemic status in participants from differing ethnic backgrounds. The results of this dissertation add further evidence to the notion that β-cell function is more strongly associated with glycemic status than insulin resistance in Asian Indians both in the United States and in India and also highlights the effect of changes in β-cell function on glycemic progression.

Additionally, for the past several decades, India has undergone rapid and substantial nutritional and economic transitions.[23,24,31] Previous data examining the

prevalence of diabetes in Asian Indians noted that the prevalence was higher in those that had migrated to developed countries compared to those still living in India.[45,46] However, few studies have examined the prevalence of disease in recent years and in light of current shifts in the Indian economic landscape. Furthermore, few studies have examined the prevalence of disease in urban Asian Indians compared to other ethnic groups such as Caucasians, Blacks, and Hispanics in the United States. This dissertation addresses these gaps by comparing the prevalence of diabetes and prediabetes in recent, population based samples, both in India and the United States. Results of this dissertation noted that Asian Indians living in India have a higher prevalence of diabetes and a lower prevalence of prediabetes than their counterparts who migrated to the United States, despite having lower levels of traditional risk factors. Migration as assessed by self-reported status of being born in India but now living in the United States, was associated with a lower odds of diabetes and prediabetes thereby challenging previous notions of the effect of migration on diabetes risk. However, Asian Indians living in the United States had higher levels of education attainment and income and likely greater access to health care and insurance. Therefore, while the results of this dissertation are among the first to highlight favorable metabolic profiles among Indians living in the United States compared to those living in India, further information is needed to disentangle the root causes behind this.

Furthermore, Asian Indians in India also had a higher prevalence of diabetes and a lower prevalence of prediabetes than Caucasians, Blacks, and Hispanics in the United States, again despite lower levels of traditional risk factors. Furthermore, a measure of β-cell function attenuated the odds of diabetes in Asian Indians compared to other ethnic

groups providing further evidence of a biological susceptibility to impaired β-cell function in Asian Indians.

Prevention

The work presented in this dissertation supports the notion that while both insulin resistance and insulin secretion are associated with diabetes and prediabetes development, individuals of Asian Indian decent are subject to innate β-cell dysfunction that occurs early in the natural history of diabetes progression. Therefore prevention strategies in Asian Indians should include aspects that focus both on the reduction of insulin resistance as well as the preservation of insulin secretion. Additionally, this dissertation highlights the high prevalence of diabetes and the relatively low prevalence of prediabetes in an urban city in India, both compared to migrant Asian Indians as well as Caucasians, Hispanics, and Blacks in the United States. Determining the prevalence of prediabetes in a population is important as evidence suggests that the most cost-effective method for diabetes prevention is to target individuals with prediabetes.[5,73] Results from both The Finish Diabetes Prevention Study and the US Diabetes Prevention Program (DPP), demonstrated that the three year risk of developing diabetes was reduced by 58% in those receiving intensive lifestyle interventions, which included lessons on behavior change, at least 150 minutes per week of physical activity, diets containing <30% total fat and no more than 10% saturated fat, and weight loss of at least 5–7%.[74,75] Randomized controlled trials are now taking place to assess the effectiveness, generalizability, and sustainability of such interventions in Asian Indians.[76] If shown to be effective, such preventative efforts need to be directed both at the individual and population levels and should start early in order to reduce the risk of type 2 diabetes in this high risk group.

Future Directions

The work presented in this dissertation suggest both a possible innate susceptibility for β-cell dysfunction in Asian Indians as well as a rapid conversion through the natural history of disease. However, the cross-sectional nature of the studies as well as a limited sample of individuals with prediabetes did not allow for the tracking of individuals from normal glycemia, through the differing states of prediabetes (impaired fasting glucose (iIFG) and impaired glucose tolerance (iIGT)), and eventually to overt type 2 diabetes. While both the precursor states, iIFG and iIGT can eventually lead to diabetes, they may represent different mechanistic processes and are characterized by different degrees of insulin resistance, insulin secretion, and hepatic glucose output,[40,77] and the predominant metabolic abnormality of each state of prediabetes is likely to track into the development of diabetes.[77] Therefore those who develop diabetes from either distinct state could exhibit different diabetes phenotypes and potentially different requirements for prevention and differing risks for complications. Longitudinal studies that follow individuals through the natural history of disease would therefore provide an improved understanding of the relative contributions of β-cell function and insulin resistance on disease incidence and provide insights into more effective prevention and treatment of diabetes and complications. Baseline data from The **C**entre for c**A**rdiometabolic **R**isk **R**eduction in **S**outh-Asia study (CARRS) were utilized in this dissertation. However, the CARRS was designed as a longitudinal follow-up cohort study, and the first phase of follow-up has recently been completed. Adding additional years of follow-up to the ongoing CARRS study would offer a unique window of scientific opportunity to objectively follow and document the physiological shifts in

disease development and the risk factors associated with these glycemic progressions. This would help to identify the most suitable periods to target interventions as well as the most appropriate mechanisms by which to do so.

Results of this dissertation also noted a lower diabetes prevalence in Asian Indians who had migrated to the United States compared to Asian Indians living in India. This could be due in part to the notion that with increased knowledge of beneficial diet and physical activity behaviors as well as diabetes prevention mechanisms, migrant Asian Indians may be shifting towards more health promoting lifestyles. It is possible that in Asian Indians in the United States may also have greater access to health care[50,78] than Asian Indians in India. However, despite having a lower prevalence of diabetes than their counterparts living in India, migrant Asian Indians still had an increased prevalence of diabetes compared to the general United States population.[38,79] It is not clear if this increased prevalence is due to factors that occurred prior to or after migration and if these factors more closely associated with lifestyle or genetics. Therefore, longitudinal studies that track individuals through the natural history of disease and compare Asian Indians born in the United States (who would have similar genetics, but differing lifelong environmental exposures than their parents who migrated) to Asian Indians living in India, as well as to Caucasians, Blacks, and Hispanics living in the United States, would serve to disentangle physiological differences in diabetes development between ethnic groups as well as highlight the environmental versus genetic components.

Lastly, the work presented in this dissertation points to impaired β-cell function as the driving factor behind type 2 diabetes risk in Asian Indians. The mechanisms causing this impairment, however, are not well known. Several animal models have noted that

under nutrition in utero impairs fetal β-cell development.[80-83] It is possible that high rates of maternal under nutrition in pregnancy in Asian Indian women result in poorer β-cell mass and function in their offspring. Furthermore, increases in circulating non-esterified fatty acids (NEFAs) have also been shown to not only contribute to insulin resistance, but also suppress the ability of the β-cell's adaptive response.[84] Other factors such as increased cytokine activity, viral infections, and the use of certain pharmacological substances may also contribute to β-cell impairment.[85] It is also possible that low intakes of dietary protein, specifically arginine, which is an insulin secretagogue, may also influence insulin release in this population. Therefore while it is apparent that β-cell defects early in the natural history of disease play a large role in diabetes development in Asian Indians, the processes by which these defects occur need to be elucidated and better understood in order to more accurately inform prevention and treatment.

Summary

In summary, the studies presented in this dissertation significantly contribute to the literature by highlighting the contribution of β-cell dysfunction to diabetes and prediabetes development in Asian Indians that exist beyond the contributions of insulin resistance and other well-known risk factors such as age and adiposity. The results of this dissertation also note the high prevalence of type 2 diabetes and the conversely low prevalence of prediabetes in Asian Indians living in India compared to Asian Indians and Caucasians, Blacks, and Hispanics in the United States and suggest a possible rapid conversion through the natural history of disease in Asian Indians, especially those living in urban India. The work presented here provides a basis for future studies that seek to disentangle the associations of β-cell function and insulin resistance on diabetes

development and examine how this might vary by ethnic group or environmental setting. Additionally, this work challenges popular paradigms regarding the negative impact of migration on diabetes risk and calls for not only the increased prevention of diabetes in urban India, but also a greater understanding of the long term, inter-generational effects of a developed country exposure on diabetes risk in migrant populations.

Literature Cited (Chapters 1-3, 7)

1. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes research and clinical practice*, 2014; *103*(2), 137-149.
2. Mohan, V. Why are Indians more prone to diabetes?. *Journal of the Association of Physicians of India*, 2004; *52*, 468-474.
3. International Diabetes Federation. *IDF diabetes atlas*, 2011; International Diabetes Federation, Executive Office.
4. Hwang CK, Han PV, Zabetian A, Ali MK, Narayan KM. Rural diabetes prevalence quintuples over twenty-five years in low-and middle-income countries: a systematic review and meta-analysis. *Diabetes research and clinical practice*, 2012; *96*(3), 271-285.
5. Gujral UP, Pradeepa R, Weber MB, Narayan KM, Mohan V. Type 2 diabetes in South Asians: similarities and differences with white Caucasian and other populations. *Annals of the New York Academy of Sciences*, 2013; *1281*(1), 51-63.
6. Mohan V, Deepa M, Deepa R, Shanthirani CS, Farooq S, Ganesan A, Datta M. Secular trends in the prevalence of diabetes and impaired glucose tolerance in urban South India—the Chennai Urban Rural Epidemiology Study (CURES-17). *Diabetologia*, 2006; *49*(6), 1175-1178.
7. Ramachandran A, Snehalatha C, Baskar ADS, Mary S, Kumar CS, Selvam S, Vijay V. Temporal changes in prevalence of diabetes and impaired glucose tolerance associated with lifestyle transition occurring in the rural population in India. *Diabetologia*, 2004; *47*(5), 860-865.

8. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, Mohan, V. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: Phase I results of the Indian Council of Medical Research–INdia DIABetes (ICMR–INDIAB) study. *Diabetologia*, 2011; *54*(12), 3022-3027.
9. Gupta LS, Wu CC, Young S, Perlman SE. Prevalence of Diabetes in New York City, 2002–2008 Comparing foreign-born South Asians and other Asians with US-born whites, blacks, and Hispanics. *Diabetes Care*, 2011; *34*(8), 1791-1793.
10. Oza-Frank R, Ali MK, Vaccarino V, Narayan, KV. Asian Americans: diabetes prevalence across US and World Health Organization weight classifications. *Diabetes Care*, 2009; *32*(9), 1644-1646.
11. Misra R, Patel T, Kotha P, Raji A, Ganda O, Banerji M, Balasubramanyam A. Prevalence of diabetes, metabolic syndrome, and cardiovascular risk factors in US Asian Indians: results from a national study. *Journal of Diabetes and its Complications*, 2010; *24*(3), 145-153.
12. Mather HM, Keen H. The Southall Diabetes Survey: prevalence of known diabetes in Asians and Europeans. *British medical journal (Clinical research ed.)*, 1985; *291*(6502), 1081.
13. Zimmet P, Taylor R, Ram P, Kimg H, Sloman G, Raper LR, Hunt, D. Prevalence of diabetes and impaired glucose tolerance in the biracial (Melanesian and Indian) population of Fiji: a rural-urban comparison. *American journal of epidemiology*, 1983; *118*(5), 673-688.

14. Omar MA, Seedat MA, Dyer RB, Motala AA, Knight LT, Becker PJ. South African Indians show a high prevalence of NIDDM and bimodality in plasma glucose distribution patterns. *Diabetes care*, 1994; *17*(1), 70-73.
15. Jenum AK, Holme I, Graff-Iversen S, Birkeland KI. Ethnicity and sex are strong determinants of diabetes in an urban Western society: implications for prevention. *Diabetologia*, 2005; *48*(3), 435-439.
16. Lee WRW. The changing demography of diabetes mellitus in Singapore. *Diabetes research and clinical practice*, 2000; *50*, S35-S39.
17. Mohan V, Deepa M, Anjana RM, Lanthorn H, Deepa R. Incidence of diabetes and pre-diabetes in a selected urban south Indian population (CUPS-19). *Journal of the Association of Physicians of India*, 2008; *56*, 152-157.
18. Geiss LS, Pan L, Cadwell B, Gregg EW, Benjamin SM, Engelgau MM. Changes in incidence of diabetes in US adults, 1997–2003. *American journal of preventive medicine*, 2006; *30*(5), 371-377.
19. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Meigs JB, Muggeo M. Population-based incidence rates and risk factors for type 2 diabetes in White individuals The Bruneck Study. *Diabetes*, 2004; *53*(7), 1782-1789.
20. Valdés S, Botas P, Delgado E, Álvarez F, Cadórniga FD. Population-Based Incidence of Type 2 Diabetes in Northern Spain The Asturias Study. *Diabetes Care*, 2007; *30*(9), 2258-2263.
21. Misra A, Ganda OP. Migration and its impact on adiposity and type 2 diabetes. *Nutrition*, 2007; *23*(9), 696-708.

22. Antecol H, Bedard K. Unhealthy assimilation: why do immigrants converge to American health status levels?. *Demography*, 2006; *43*(2), 337-360.
23. Shetty PS. Nutrition transition in India. *Public health nutrition*, 2002; *5*(1a), 175-182.
24. Misra A, Singhal N, Sivakumar B, Bhagat N, Jaiswal A, Khurana L. Nutrition transition in India: Secular trends in dietary intake and their relationship to diet-related non-communicable diseases. *Journal of diabetes*, 2011; *3*(4), 278-292.
25. Kasuga M. Insulin resistance and pancreatic β cell failure. *Journal of Clinical Investigation*, 2006; *116*(7), 1756-1760.
26. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Charles MA, H Bennett P. A two-step model for development of non-insulin-dependent diabetes. *The American journal of medicine*, 1991; *90*(1), 229-235.
27. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. *Diabetologia*, 2004; *47*(1), 31-39.
28. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia*, 2003; *46*(1), 3-19.
29. Creatore MI, Moineddin R, Booth G, Manuel DH, DesMeules M, McDermott S, Glazier RH. Age-and sex-related prevalence of diabetes mellitus among immigrants to Ontario, Canada. *CMAJ*, 2010; 82(8):781-9.
30. Choukem SP, Fabreguettes C, Akwo E, Porcher R, Nguewa JL, Bouche C, Kaze FF, Kengne AP, Vexiau P, Mbanya JC, Sobngwi E, Gautier JF. Influence of migration on

characteristics of type 2 diabetes in sub-Saharan Africans. *Diabetes Metab,* 2014; 40(1):56-60.

31. Griffiths PL, Bentley ME. The nutrition transition is underway in India. *The Journal of nutrition*. 2001; 131(10): 2692-2700.
32. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes care,* 2013; *36*(Supplement 1), S67-S74.
33. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, Hu FB. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *Jama*, 2009; *301*(20), 2129-2140.
34. Registrar General I. Census of India 2011: provisional population totals-India data sheet. *Office of the Registrar General Census Commissioner, India. Indian Census Bureau*, 2011.
35. Naujoks D. Emigration, immigration, and diaspora relations in India. *Migration Information Source*, 2009.
36. Hoeffel EM, Rastogi S, Kim MO, Hasan S. *The Asian Population: 2010*. US Department of Commerce, Economics and Statistics Administration, US Census Bureau. 2012.
37. Venkataraman R, Nanda NC, Baweja G, Parikh N, Bhatia V. Prevalence of diabetes mellitus and related conditions in Asian Indians living in the United States. *The American journal of cardiology*, 2004; *94*(7), 977-980.
38. Lee JWR, Brancati FL, Yeh HC. Trends in the prevalence of type 2 diabetes in Asians versus whites results from the United States National Health Interview Survey, 1997–2008. *Diabetes Care*, 2011; *34*(2), 353-357.

39. Decode-Decoda Study Group. Age, body mass index and type 2 diabetes—associations modified by ethnicity. *Diabetologia*, 2003; *46*(8), 1063-1070.

40. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of β-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes care*, 2006; *29*(5), 1130-1139.

41. Mohan V, Amutha A, Ranjani H, Unnikrishnan R, Datta M, Anjana RM, Narayan KM. Associations of β-cell function and insulin resistance with youth-onset type 2 diabetes and prediabetes among Asian Indians. *Diabetes technology & therapeutics*, 2013; *15*(4), 315-322.

42. Staimez LR, Weber MB, Ranjani H, Ali MK, Echouffo-Tcheugui JB, Phillips LS, Narayan KM. Evidence of reduced β-cell function in Asian Indians with mild dysglycemia. *Diabetes care*, 2013; *36*(9), 2772-2778.

43. Petersen KF, Dufour S, Feng J, Befroy D, Dziura J, Dalla Man, C., Shulman GI. Increased prevalence of insulin resistance and nonalcoholic fatty liver disease in Asian-Indian men. *Proceedings of the National Academy of Sciences*, 2006; *103*(48), 18273-18277.

44. Motala AA, Omar MAK. Evidence for impaired pancreatic beta cell function in South African Indians with impaired glucose tolerance. *Diabetic medicine*, 1994; *11*(5), 437-444.

45. Patel DJ, Winterbotham M, Britt RP, Sutton GC, Bhatnagar D, Mackness MEA, Keil JE. Coronary risk factors in people from the Indian subcontinent living in West London and their siblings in India. *The Lancet*, 1995; *345*(8947), 405-409.

46. Patel JV, Vyas A, Cruickshank JK, Prabhakaran D, Hughes E, Reddy KS, Durrington PN. Impact of migration on coronary heart disease risk factors: comparison of Gujaratis in Britain and their contemporaries in villages of origin in India. *Atherosclerosis*, 2006; *185*(2), 297-306.
47. Kulkarni KD. Food, culture, and diabetes in the United States. *Clinical Diabetes*, 2004; *22*(4), 190-192.
48. Wandel M, Råberg M, Kumar B, Holmboe-Ottesen G. Changes in food habits after migration among South Asians settled in Oslo: the effect of demographic, socio-economic and integration factors. *Appetite*, 2008; *50*(2), 376-385.
49. Garduño-Diaz SD, Khokhar S. Prevalence, risk factors and complications associated with type 2 diabetes in migrant South Asians. *Diabetes/metabolism research and reviews*, 2012; *28*(1), 6-24.
50. Venkatesh S, Weatherspoon LJ, Kaplowitz SA, Song WO. Acculturation and glycemic control of Asian Indian adults with type 2 diabetes. *Journal of community health*, 2013; *38*(1):78-85.
51. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. *The Indian journal of medical research*, 2007; *125*(3), 217-30.
52. Ramachandran A, Snehalatha C, Dharmaraj D, Viswanathan M. Prevalence of glucose intolerance in Asian Indians: urban-rural difference and significance of upper body adiposity. *Diabetes care*, 1992; *15*(10), 1348-1355.

53. Ramachandran A, Snehalatha C, Latha E, Vijay V, Viswanathan M. Rising prevalence of NIDDM in an urban population in India. *Diabetologia,* 1997; *40*(2), 232-237.

54. Deepa M, Anjana RM, Manjula D, Narayan KV, Mohan V. Convergence of prevalence rates of diabetes and cardiometabolic risk factors in middle and low income groups in urban India: 10-year follow-up of the Chennai Urban Population Study. *Journal of diabetes science and technology,* 2011; *5*(4), 918-927.

55. Kanaya AM, Wassel CL, Mathur D, Stewart A, Herrington D, Budoff MJ, Liu, K. Prevalence and correlates of diabetes in South Asian Indians in the United States: findings from the metabolic syndrome and atherosclerosis in South Asians living in America study and the multi-ethnic study of atherosclerosis. *Metabolic syndrome and related disorders*, 2010; *8*(2), 157-164.

56. Bild DE, Bluemke DA, Burke GL, Detrano R, Roux AVD, Folsom AR, Tracy RP. Multi-ethnic study of atherosclerosis: objectives and design. *American Journal of Epidemiology*, 2002; *156*(9), 871-881.

57. Kanaya AM, Kandula N, Herrington D, Budoff MJ, Hulley S, Vittinghoff E, Liu, K. Mediators of Atherosclerosis in South Asians Living in America (MASALA) Study: objectives, methods, and cohort description. *Clinical cardiology,* 2013; *36*(12), 713-720.

58. Nair M, Ali MK, Ajay VS, Shivashankar R, Mohan V, Pradeepa R, Prabhakaran D. CARRS Surveillance study: design and methods to assess burdens from multiple perspectives. *BMC public health,* 2012; *12*(1), 701.

59. Johnson CL, Paulose-Ram R, Ogden CL, Carroll MD, Kruszan-Moran D, Dohrmann SM, Curtin LR. National health and nutrition examination survey. Analytic guidelines, 1999-2010. *Vital Health Stat*, 2013; *2*, 161.

60. Mirel LB, Mohadjer LK, Dohrmann SM, Clark J, Burt VL, Johnson CL, Curtin LR. National health and nutrition examination survey: estimation procedures, 2007-2010. *Vital and health statistics. Series 2, Data evaluation and methods research*, 2013; (159), 1-25.

61. Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, Geiss LS. Full accounting of diabetes and pre-diabetes in the US population in 1988–1994 and 2005–2006. *Diabetes care*, 2009; *32*(2), 287-294.

62. Katulanda P, Constantine GR, Mahesh JG, Sheriff R, Seneviratne RDA, Wijeratne S, Matthews DR. Prevalence and projections of diabetes and pre-diabetes in adults in Sri Lanka—Sri Lanka Diabetes, Cardiovascular Study (SLDCS). *Diabetic Medicine*, 2008; *25*(9), 1062-1069.

63. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes care*, 2004; *27*(6), 1487-1495.

64. Utzschneider KM, Prigeon RL, Faulenbach MV, Tong J, Carr DB, Boyko EJ, Leonetti DL, McNeely MJ, Fujimoto W, Kahn SE. Oral disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. *Diabetes care*, 2009; *32*(2), 335-341.

65. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes care*, 1999; *22*(9), 1462-1470.

66. Ahrén B, Pacini G. Importance of quantifying insulin secretion in relation to insulin sensitivity to accurately assess beta cell function in clinical studies. *European Journal of Endocrinology*, 2004; *150*(2), 97-104.

67. Ramachandran A, Snehalatha C, Kapur A, Vijay V, Mohan V, Das AK, Rao PV, Yajnik CS, Prasanna Kumar KM, Nair JD. For the Diabetes Epidemiology Study Group in India (DESI). High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. *Diabetologia*, 2001; 44:1094-1101.

68. Gupta R, Misra A. Review: Type 2 diabetes in India: regional disparities. *The British Journal of Diabetes & Vascular Disease*, 2007; *7*(1), 12-16.

69. Wu TY, Wang J, Chung S. Cardiovascular disease risk factors and diabetes in Asian Indians residing in Michigan. *Journal of community health*, 2012; 37(2), 395-402.

70. Mohanty SA, Woolhandler S, Himmelstein DU, Bor DH. Diabetes and cardiovascular disease among Asian Indians in the United States. *Journal of general internal medicine*, 2005; *20*(5), 474-478.

71. Ramachandran A, Snehalatha C, Viswanathan V, Viswanathan M, Haffner SM. Risk of noninsulin dependent diabetes mellitus conferred by obesity and central adiposity in different ethnic groups: a comparative analysis between Asian Indians, Mexican Americans and Whites. *Diabetes research and clinical practice*, 1997; *36*(2), 121-125.

72. Chiu M, Austin PC, Manuel DG, Shah BR, Tu JV. Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. *Diabetes Care*, 2011; *34*(8), 1741-1748.

73. Narayan KV, Williamson DF. Prevention of type 2 diabetes: risk status, clinic, and community. *Journal of general internal medicine*, 2010; *25*(2), 154-157.

74. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England journal of medicine*, 2002; *346*(6), 393.

75. Lindström J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Tuomilehto J. The Finnish Diabetes Prevention Study (DPS) Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes care*, 2003; *26*(12), 3230-3236.

76. Weber MB, Ranjani H, Meyers GC, Mohan V, Narayan KM. A model of translational research for diabetes prevention in low and middle-income countries: The Diabetes Community Lifestyle Improvement Program (D-CLIP) trial. *Primary care diabetes*, 2012; *6*(1), 3-9.

77. Færch K, Borch-Johnsen K, Holst JJ, Vaag A. Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and treatment of type 2 diabetes?. *Diabetologia*, 2009; *52*(9), 1714-1723.

78. De Gagne JC, Oh J, So A, Haidermota M, Lee SY. A Mixed Methods Study of Health Care Experience Among Asian Indians in the Southeastern United States. *Journal of Transcultural Nursing*, 2014; 1043659614526247.

79. Kanaya AM, Herrington D, Vittinghoff E, Ewing SK, Liu K, Blaha MJ, Dave SS, Qureshi F, Kandula NR. Understanding the high prevalence of diabetes in U.S. south Asians compared with four racial/ethnic groups: the MASALA and MESA studies. *Diabetes Care*, 2014; 37(6):1621-8.

80. Garofano A, Czernichow P, Breant, B. In utero undernutrition impairs rat beta-cell development. *Diabetologia*, 1997; *40*(10), 1231-1234.

81. Garofano A, Czernichow P, Breant B. Effect of ageing on beta-cell mass and function in rats malnourished during the perinatal period. *Diabetologia*, 1999; *42*(6), 711-718.

82. Reusens B, Theys N, Dumortier O, Goosse K, Remacle C. Maternal malnutrition programs the endocrine pancreas in progeny. *The American journal of clinical nutrition*, 2011; *94*(6 Suppl), 1824S-1829S.

83. Dumortier O, Blondeau B, Duvillie B, Reusens B, Bréant B, Remacle C. Different mechanisms operating during different critical time-windows reduce rat fetal beta cell mass due to a maternal low-protein or low-energy diet. *Diabetologia*, 2007; *50*(12), 2495-2503.

84. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*, 2006; *444*(7121), 840-846.

85. Donath MY, Halban PA. Decreased beta-cell mass in diabetes: significance, mechanisms and therapeutic implications. *Diabetologia*, 2004; *47*(3), 581-589.

Appendices

Appendix A: CARRS Study Methodology and Sampling Frame, Chennai

CARRS Study Methodology

Introduction

A multi-stage cluster random sampling technique will be used to capture a sample representative of the urban population at the three sites. Each of the cities has its own distinctive municipal sub-divisions, encompassing municipal corporations, wards and Census Enumeration Blocks (CEB) from which households will be randomly selected. Ward/Union Council will be the primary sampling unit for Chennai, Delhi and Karachi. Site specific sampling methods are given below.

Learning objectives

After completing this chapter the field staff will be able to

1) Understand the sampling scheme for each study site– Chennai, Delhi and Karachi.

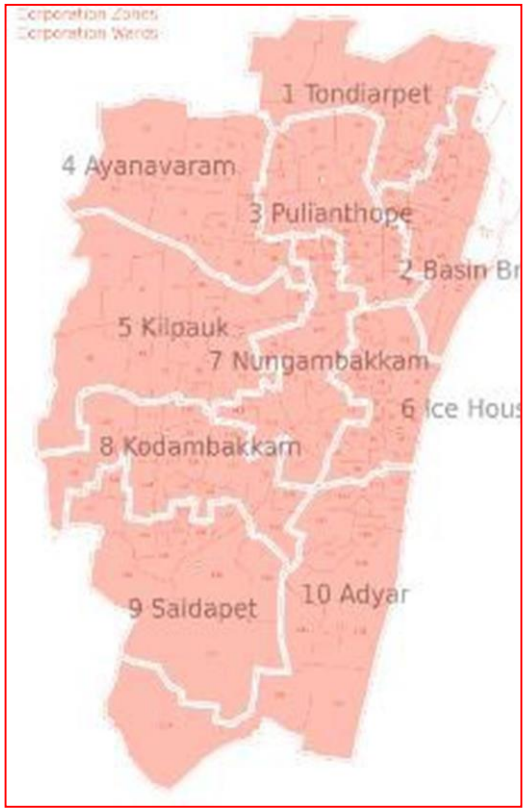
2) Understand how to capture a sample representative of the urban population in the study sites using a multi-stage cluster random sampling technique in 4 stages.

Sampling scheme

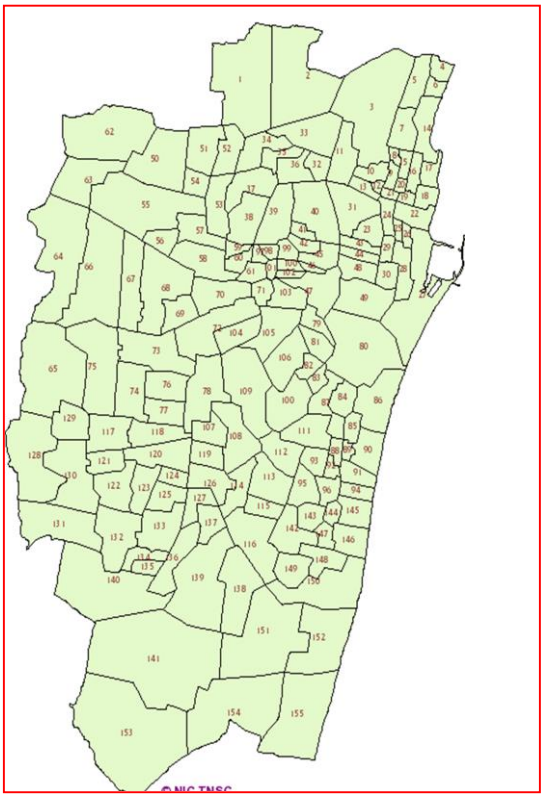
Chennai

Chennai is divided into 10 Zones and 155 wards by the Chennai Corporation. Each ward comprises of CEBs. From the list of wards, 20 were randomly selected to represent the 10 zones of Chennai. From each of these 20 wards, 5 CEBs were selected at random giving a total of 100 CEBs. From each CEB, 20 households will be selected leading to a total of 2000 households. Two participants from each of the 2000 households will provide the required sample of 4000 participants.

Zones of Chennai City



Wards of Chennai City



Chennai sampling scheme

Chennai Municipal Corporation

↓

155 Corporation wards

↓

20 wards (randomly selected)

↓

5 census blocks per ward -randomly selected (total of 100 CEBs)

↓

20 Households per CEB randomly selected (total 2000 households)

↓

2 Participants per household (total 4000 study participants)

Multistage Cluster Random Sampling

To capture a sample representative of the urban population in the three study sites a multi-stage cluster random sampling technique will be adopted in 4 stages.

Stage-1: Selection of Wards	▪ 20 wards were randomly selected for each study center from a total of 143 wards for Delhi; 155 wards for Chennai and 178 union councils for Karachi.
Stage-2: Selection of CEBs	▪ On an average each ward comprises of 120 CEBs. ▪ 5 CEBs were selected at random from each of the 20 randomly selected wards to get a total of 100 CEBs at each site (300 for all sites) ▪ CEBs which are occupied predominantly by Jhuggi Jhophri clusters and commercial establishments were excluded from this pool. ▪ Selection of wards and CEBs was done at COE-CARRS and a list has been provided to the study sites. ▪ Subsequent process of selection of households will be done at
Stage-3: Selection of Households	▪ Each CEB on an average consists of 100-150 households (HH). ▪ A house to house survey will be conducted to get the list of all HH in the 300 randomly selected CEBs. ▪ Mapping of all HHs and important landmarks will be done for each selected CEB. ▪ From this list a random sample of 20 HH (25 for Karachi) would be selected for each CEB. This will give a total of 2000 HH for each site and a total of 6000 HH for all the three study sites.
Stage-4: Selection of Participant within Households	▪ The average family size of each HH is approximately 5 ▪ We will be selecting 2 eligible participants (one male and one female) from each HH. ▪ "Kish method" used in the WHOs STEPwise surveillance will be adopted.

The final sample for the study will be composed of equal proportions of males and females in each of the three age strata (20-45 years, 45-60 years and >60 years) who have provided consent to participate in the study (both cross- sectional and three years of follow-up) leading to a sample of 4000 participants in each of the three study sites.

Central Random Sampling

A list of wards from each study site was sent to COE-CARRS (PHFI). From this list 20 wards were randomly selected and coded for each site. This list of twenty randomly selected wards was sent back to the respective sites who then obtained a list of CEBs for each of the selected wards from the 2011 Census data. The list of CEBs ward-wise was used to randomly select 5 CEBs per ward giving a total of 100 CEBs per study site. The randomly selected CEBs were coded again. This list will be used by the sites for enlisting and mapping of HHs and to finally select the required number of HHs.

Points to remember

1) Wards / union councils (UCs) are the primary sampling units
2) 20 wards / UCs were selected randomly from the districts
3) 5 CEBs were selected from each ward / UC
4) 20 households (25 for Karachi) per CEB will give a total of 2000 HH per site
5) Average 2 participants (1 male and 1 female) will be selected from each HH using within HH sampling methods

Appendix B: CARRS Study Sample Weights Calculation

Computation of Sample weights:

Sample weights

The basic objective of weighting sample data is to try and maximize the representativeness of the sample in terms of the size, distribution, and characteristics of the study population. When sample units have been selected with differing probabilities, it is common to weight the results inversely proportional to the unit selection probabilities, the design weight, so as to reflect the actual situation in the population.

Calculation of sampling weights

In CARRS surveillance study, selection of study participants for Delhi and Chennai sites were done based on three stages (Selection of wards in the first stage, CEBs in second stage and households in third stage); whereas in Karachi, sampling was done at two stages (Selection of clusters in the first stage and households in the second stage). For multi-stage designs, the base weights reflect the probabilities of selection at each stage. The sample weight for each site was calculated taking into account probability weight for each CEB and differential non-response rates at household and individual level.

Overall sample weights have been calculated as the inverse of the base weight (after adjusting for non-response) where the base weight is obtained as reciprocal of overall probability of selection. Further the sampling weights are normalized to get the weighted cases equivalent to unweight cases. Detailed step by step procedure is given below.

Step 1*:* To take care of non-equal probability of selection at different stages i.e. ward, CEB, household level in Delhi, Chennai and Karachi.

Probability of selecting clusters in Chennai, Delhi, and Karachi is calculated using equation (1) where clusters refers to wards in Chennai and Delhi whereas Union councils for Karachi.

$$\text{Probability of selecting wards, } Pi = \frac{\text{No.of wards selected in the city}}{\text{Total number of wards in the city}} \quad \ldots (1)$$

where i=Delhi, Chennai, Karachi

Probability of selecting CEBs in Delhi and Chennai is calculated as

$$\text{Probability of selecting CEB, Pij} = \frac{\text{No. of CEBs selected from the city}}{\text{Total number of CEBs in that particular ward}}$$

where j=CEB's in Delhi and Chennai and cluster in Karachi

***Step 2**:* **Base weight** was calculated as the inverse of probability of selecting wards and CEBs.

$$\text{Base weight (BWij)} = \frac{1}{P_i * P_{ij}}$$

***Step 3**:* To take care of the differential non-response rate of household interviews in different domains, i.e. CEB levels in the respective city, the adjustment for household and individual non-response and selection of individuals using KISH table was done. Base weight is adjusted for household non-response to get the adjusted base weight.

$$Adjusted\ base\ weight, ABW_{ij} = \frac{BW_{ij}}{HRR_{ij} * IRR_{ij}}$$

where,

$$\text{Household Response rate(HRRij)} = \frac{\text{No. of households interviewed in the particular CEB/ cluster}}{\text{No. of households approached in the particular CEB/ cluster}}$$

$$\text{Individual Response rate(IRRij)} = \frac{\text{No. of individuals interviewed in the CEB}}{\text{No. of individuals approached in the CEB}}$$

Step 4: Weight for each city is calculated after adjustment for Probability of selecting an individual using KISH table (when more than two eligible members were present in the household).

$$\text{Weight}(W_{ij}) = \frac{ABW_{ij}}{K_{ij}}$$

where K_{ij}=Probability of selecting individual using KISH method

$$\text{Probability of selecting through KISH } (K_{ij}) = \frac{\text{No. of individual approached in the particular CEB}}{\text{No. of eligible individual in the particular CEB}}$$

After adjustment for nonresponse, the weights are normalized so that the total number of weighted cases is equal to the total number of unweighted cases. This is done by multiplying the final weight by the ratio of total number of unweighted cases to the total number of weighted cases (obtained by applying weights before normalization to the number of cases in each CEB).

Normalization of weight is done using the following formulae

$$\text{SWij} = \frac{W_{ij} * \sum n_{ij}}{\sum W_{ij} * n_{ij}}$$

where n_{ij} = total number of individuals interviewed for each CEBs/ clusters in the respective city.

SW_{ij}= Normalized sample weight

Appendix C: Article Attachment Pending Approval of Journal

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The relative associations of β-cell function and insulin sensitivity with glycemic status and incident glycemic progression in migrant Asian Indians in the United States: The MASALA study☆,☆☆,★,★★

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ABSTRACT

Aims: We assessed the relative associations of β-cell dysfunction and insulin sensitivity with baseline glycemic status and incident glycemic progression among Asian Indians in the United States.
Methods: A 5-sample oral glucose tolerance test was obtained at baseline. Normoglycemia, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes (T2DM) were defined by ADA criteria. The Matsuda Index (ISI_M) estimated insulin sensitivity, and the Disposition Index (DI_o) estimated β-cell function. Visceral fat was measured by abdominal CT. After 2.5 years, participants underwent a 2-sample oral glucose tolerance test. Standardized polytomous logistic regression was used to examine associations with prevalent and incident glycemia.
Results: Mean age was 57 ± 8 years and BMI 26.1 ± 4.6 kg/m^2. Log ISI_M and log DI_o were associated with prediabetes and T2DM after adjusting for age, sex, BMI, family history of diabetes, hypertension, and smoking. After adjusting for visceral fat, only DI_o remained associated with prediabetes (OR per SD 0.17, 95% CI: 0.70, 0.41) and T2DM (OR 0.003, 95% CI: 0.0001, 0.03). Incidence rates (per 1,000 person-years) were: normoglycemia to IGT: 82.0, 95% CI (40, 150); to IFG: 8.4, 95% CI (0, 41); to T2DM: 8.6, 95% CI (0, 42); IGT to T2DM: 55.0, 95% CI (17, 132); IFG to T2DM: 64.0, 95% CI (3, 316). The interaction between sex and the change in waist circumference (OR 1.8, per SD 95% CI: 1.22, 2.70) and the change in log HOMA-β (OR 0.37, per SD 95% CI: 0.17, 0.81) were associated with glycemic progression.
Conclusions: The association of DI_o with baseline glycemia after accounting for visceral fat as well as the association of the change in log HOMA-β with incident glycemic progression implies innate β-cell susceptibility in Asian Indians for glucose intolerance or dysglycemia.

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★★ Author Contributions: U.P.G. analyzed data, wrote the manuscript, drafted tables and figures 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. S.E.K 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, collected the data, contributed to concept, design, analysis, discussion, and interpretation of the data reviewed and revised the manuscript, and approved the final manuscript for submission. U.P.G. is the guarantor of this work, has had full access to all the data in the study, and takes responsibility for the integrity of the data andthe accuracy of the data analysis.
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1. Introduction

The pathophysiology of type 2 diabetes is a complex process involving both decreased insulin sensitivity and impaired insulin secretion (Kasuga, 2006). Traditionally, the pathogenesis has been described as obesity driven, with progressive insulin resistance followed by a subsequent decline in β-cell function, eventually leading to overt hyperglycemia (Kasuga, 2006; Saad et al., 1991). However, decline in β-cell function has also been detected as a driving factor early in the natural history of type 2 diabetes development (Gastaldelli, Ferrannini, Miyazaki, Matsuda, & DeFronzo, 2004; Kahn, 2003). Since several genes conferring risk for type 2 diabetes are associated with β-cell dysfunction (Florez, 2008), it is possible that some ethnic groups may have an innate susceptibility for early decline in β-cell function, thereby placing them at increased risk for disease development beyond traditionally associated factors such as age, adiposity, and insulin resistance.

Asian Indians, both in India and abroad, are at a particularly increased risk for type 2 diabetes (Chiu, Cohan, Lee, & Chuang, 2010; Misra et al., 2010; Oza-Frank, Ali, Vaccarino, & Narayan, 2009; Shaw, Sicree, & Zimmet, 2010; Wild, Roglic, Green, Sicree, & King, 2004). Several studies have noted that Asian Indians are more insulin resistant than other ethnic groups at younger ages and comparative levels of body mass index (BMI) (Chiu, Austin, Manuel, Shah, & Tu, 2011; Gujral, Pradeepa, Weber, Narayan, & Mohan, 2013; Gupta, Wu, Young, & Perlman, 2011). Recent studies have also suggested that Asian Indians exhibit lower β-cell function even with mild dysglycemia, which may suggest an early etiological factor for hyperglycemia in this population (Mohan et al., 2013; Staimez et al., 2013). These studies present intriguing observations concerning the relative roles of β-cell function and insulin sensitivity in the pathophysiology of type 2 diabetes in Asian Indians in native Indian settings. However, no such studies have been conducted on Asian Indians living in a developed country environment. There is a lack of information on whether β-cell dysfunction is similarly important in Asian Indians who have migrated to developed countries where there may be additional lifestyle, environmental, and psychosocial stressors promoting obesity and insulin resistance. Furthermore, scarce data exists regarding incidence rates of type 2 diabetes in Asian Indians and the associated risk factors responsible. Therefore, in the present study, we analyzed the relative associations of β-cell function and insulin sensitivity on glycemic status and on the incidence of prediabetes and diabetes in a population-based cohort of migrant Asian Indians in the United States.

2. Subjects

2.1. Study population

The design, sampling strategy, recruitment and enrollment of the Metabolic Syndrome and Atherosclerosis in South Asians Living in America (MASALA) study are as described elsewhere (Kanaya et al., 2010). In brief, a total of 150 participants from the San Francisco Bay area were enrolled between August 2006 and October 2007, with one follow up clinical visit occurring between April 2009 and January 2010. Mean follow-up time between visits was approximately 2.5 years. Eligibility criteria were designed to be similar to that of the Multi-Ethnic Study of Atherosclerosis (MESA) study (Bild et al., 2002) and required participants to be between age 45 and 84 years and self-identify as South Asian. Those individuals with pre-existing cardiovascular disease, using nitroglycerin, undergoing cancer therapy, with impaired cognitive ability, with life expectancy less than 5 years, with plans to move from the area, or living in a nursing home were excluded from the study.

3. Materials and methods

3.1. Study procedures

Participant weight was measured on a standard balance beam scale, and height was measured using a stadiometer. Waist circumference was measured using a Gullick II tape at the site of maximum circumference midway between the lower ribs and the anterior super iliac spine. Three seated blood pressure measurements were taken and mean systolic (SBP) and diastolic blood pressures (DBP) were calculated from the second and third measurements. Computed tomography was used to determine visceral and abdominal subcutaneous fat area. The correct position of the CT scan (between the L4 and the L5 vertebrae) was established by a trained radiology technician, using a lateral scout image of the spine and was conducted using standardized protocols (Kanaya et al., 2010).

After a 12 hour overnight fast, a 75 g oral glucose tolerance test (OGTT) was administered to all individuals at the baseline examination and to those without medication treated diabetes at the second clinical examination. At baseline, blood samples were obtained just before glucose ingestion (time 0) and then 30, 60, 90 and 120 minutes post-challenge for plasma glucose and serum insulin measurements. At the second clinical visit, approximately 2.5 years later, blood samples were obtained while fasting and at 120 minutes after the glucose challenge. Plasma glucose was measured using an automated analyzer (YSI 2300 STAT Plus, YSI Life Sciences, Yellow Sprints, OH). Serum samples were processed and stored at −80 °C for batched assays of immunoreactive insulin (RIA, Millipore, St. Charles, MO).

The assessment of life expectancy and cognitive ability was similar to that of the MESA study. Potential participants were asked whether they had been diagnosed with any diseases that may limit their life expectancy to <5 years. During eligibility assessment, participants were also asked several questions to gauge their ability to respond to simple as well as more complex questions about health status. If participants were unable to respond to these questions due to inability to remember or communicate the information, they were deemed not eligible for the study.

Hypertension was defined by the use of an anti-hypertensive medication, or if their systolic blood pressure was ≥140 mmHg or if their diastolic blood pressure was ≥90 mmHg. These are the same criteria used by the MESA study. Family history of diabetes was determined by self-report and was classified as either a parent or sibling being previously diagnosed. Smoking status was also based on self-reported answers to the baseline MASALA study questionnaire.

Diabetes was defined by the use of a glucose lowering medication or fasting plasma glucose ≥7.0 mmol/l and/or 2 hour post-challenge glucose ≥11.1 mmol/l. Prediabetes was defined by fasting plasma glucose of 5.6-6.9 mmol/l (IFG) and/or 2 hour post-challenge glucose of 7.8-11.1 mmol/l (IGT). 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 (American Diabetes Association, 2008).

3.2. Calculations

β-Cell function was estimated at baseline by the oral disposition index (DI_o) and was calculated as $(\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30})^*(1/\text{fasting insulin})$ (Utzschneider et al., 2009). DI_o is a product of the insulin response and a surrogate measure of insulin sensitivity, and is based on the hyperbolic relationship between these two measures (Utzschneider et al., 2009). The concept of a hyperbolic relationship has also been demonstrated in humans for the first-phase response to glucose and insulin sensitivity (Kahn et al., 1993). Both the oral and intravenous approaches have been proven to be useful for examining the ability of the β-cell to compensate for differences in insulin sensitivity

Table 1
Baseline MASALA study participant characteristics by glycemic status, 2006–2007.*

Characteristics	NGT	Prediabetes	T2DM	P-value
n (%)	58 (38.7)	51 (34.0)	41 (27.3)	
Male sex (%)	31.0	54.9	70.7	<0.01
Never smoker (%)	87.9	82.4	78.1	0.43
Family history of diabetes (%)	51.7	56.9	58.5	0.77
Current hypertension (%)	17.2	45.1	73.2	<0.01
Age (years)	56.5 ± 7.5	57.8 ± 9.3	57.5 ± 7.3	0.70
Years lived in the United States	23.6 ± 10.9	24.1 ± 11.1	23.8 ± 12.7	0.98
BMI (kg/m^2)	24.6 ± 3.5	27.1 ± 5.4	27.2 ± 4.5	0.01
Waist circumference (cm)	91.2 ± 10.7	97.1 ± 13.2	102.0 ± 11.0	<0.001
Visceral fat area (cm^2)	107.4 ± 45.3	136.5 ± 52.8	166.8 ± 58.4	<0.001
Subcutaneous fat area (cm^2)	233.3 ± 88.8	265.6 ± 138.4	261.3 ± 106.7	0.27
Systolic blood pressure (mmHg)	116.6 ± 15.9	126.8 ± 16.2	132.6 ± 14.4	<.001
Diastolic blood pressure (mmHg)	69.0 ± 9.0	73.8 ± 12.0	76.0 ± 11.4	0.005
Fasting glucose (mmol/l)	4.8 ± 0.4	5.3 ± 0.6	7.3 ± 1.6	<0.001
2 h glucose (mmol/l)	6.0 ± 1.0	8.6 ± 1.3	15.7 ± 3.4	<0.001
Measures of insulin sensitivity				
Log ISI_M (μIU/ml*mg/ml)	2.3 ± 0.5	1.9 ± 0.6	1.7 ± 0.6	<0.001
Log HOMA-IR (μIU/ml*mmol/l)	0.7 ± 0.5	0.9 ± 0.7	1.5 ± 0.7	<0.001
Measures of β-cell function				
Disposition Index (pmol/mmol)*pmol	3.4 ± 3.3	1.8 ± 2.0	0.4 ± 0.3	<0.001
Log HOMA-β (μIU/ml/mmol/l)	5.0 ± 0.4	4.8 ± 0.7	4.4 ± 0.8	<0.001

* Values represent mean ± SD or %.

(Bergman, Finegood, & Kahn, 2002). Insulin sensitivity at baseline was also estimated using the Matsuda Index (ISI_M) calculated as 10,000/√(fasting glucose*fasting insulin)*(mean OGTT glucose concentration*mean OGTT insulin concentration) (Matsuda & DeFronzo, 1999). ISI_M was chosen as a measure of insulin sensitivity as it represents a composite of both hepatic and muscular tissue insulin sensitivity and correlates well with the euglycemic insulin clamp as a measure of insulin sensitivity (Matsuda & DeFronzo, 1999). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (WHO Expert Committee on Physical Status, 1995).

At the follow up examination, 30-minute post-challenge glucose and insulin concentrations were not measured, therefore DI_o could not be calculated. Instead HOMA-β was used to measure β-cell function in longitudinal analysis and was calculated as [20*I_0(μIU/ml)/G_0 (mmol/l)- 3.5], and HOMA-IR was used to measure insulin resistance and calculated as [I_0(μIU/ml) * G_0 (mmol/l)/22.5] (Matthews et al., 1985). Person years were calculated as the sum of years each person at risk contributed to the study between baseline and follow up. The time between the baseline and follow-up visits of those with incident cases was divided in half to arrive at total person years for all those at risk.

3.3. Statistical analysis

Baseline characteristics of study participants were compared by glucose tolerance category using chi-squared test or ANOVA as appropriate. Non-normally distributed variables were log transformed. Standardized polytomous logistic regression was used to compare the odds of prediabetes or type 2 diabetes to normal glucose tolerance. Initially, unadjusted regression models were created to compare the individual associations of DI_o and ISI_M with prevalent glycemic status. Multivariable models were created to adjust for covariates including age, sex, smoking status, family history of diabetes, hypertension, and visceral adipose tissue area. In order to assess multi-linearity in the models, colinearity diagnostics were used to examine the condition indices and variance decomposition proportions of the variables. If it was determined that strong relationships existed between variables that would yield the model unreliable, one of those variables was removed from the final model (Kleinbaum & Klein, 2002). Backwards stepwise elimination was used to remove variables with a $P > 0.05$ from the model to retain only the most relevant covariates.

For the longitudinal analyses, baseline and second visit characteristics were compared using chi-squared or paired t-tests as appropriate. We used standardized logistic regression models to examine the covariates associated with glycemic conversion. Since both HOMA-IR and HOMA-β are functions of fasting glucose (Matthews et al., 1985), assessing the associations of these variables with incident glycemic status from increased fasting glucose would result in fasting glucose being used as both an outcome and an association variable. We therefore restricted our analyses of glycemic conversion and assessed risk factors only from normal glycemia to IGT or type 2 diabetes, or from IGT to type 2 diabetes using only 2-h post-challenge glucose measures, thereby eliminating the use of fasting glucose as both a predictor and an outcome variable. Bivariable models were used to assess preliminary associations, and multivariable models were used to adjust for possible confounders. Again, colinearity diagnostics were used to examine the condition indices and variance decomposition proportions of the variables to assess multi-linearity in the models. Backwards stepwise elimination was used to remove variables with a $P > 0.05$. All analyses were performed using SAS Version 9.3 (SAS Institute, Cary, NC).

4. Results

4.1. Baseline visit

Of the 150 participants in the MASALA study, at baseline 58 (39%) had normal glucose tolerance, 51 (34%) had prediabetes, and 41 (27%) had type 2 diabetes. Of those with prediabetes at baseline, 8 (16%) had isolated IFG, 35 (69%) had isolated IGT, and 8 (16%) had both IFG and IGT. These results differ slightly from those published previously because earlier MASALA studies did not use 2-hour glucose levels in their classifications of glycemic status in order to remain consistent with classifications used by the MESA study (Kanaya et al., 2010). Additionally, 63 participants (42%) had hypertension at baseline, 48 of whom were using anti-hypertensive medication. Table 1 describes participant characteristics by glycemic status. Those with diabetes were more likely to be male, have a history of hypertension, higher levels of systolic and diastolic blood

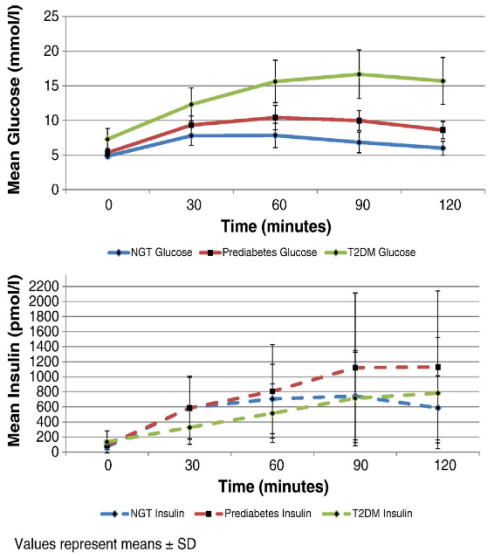

Fig. 1. Change in mean glucose and insulin over time by glycemic status. Values represent means ± SD.

pressure, a larger body habitus based on BMI, more central adiposity assessed by waist circumference and visceral fat area, were more insulin resistant based on log HOMA-IR and log ISI_M and had poorer β-cell function based on DI_o than those with normal glucose tolerance. With regard to mean log ISI_M there was a significant difference between normal glycemia and prediabetes, while the mean log ISI_M between prediabetes and type 2 diabetes was not significantly different. Furthermore, while there was a difference in BMI between those with type 2 diabetes and normal glucose tolerance, there was little difference between those with prediabetes and type 2 diabetes. Waist circumference and visceral fat area were both greater in a graded fashion from normal glucose tolerance to type 2 diabetes mellitus.

Fig. 1 shows mean glucose and insulin responses during the OGTT by glycemic status. Consistent with higher fasting and 2-hour glucose levels in those with pre-diabetes and diabetes, the values at the intermediate time points (30, 60 and 90 minutes) were greater in those with abnormal glucose tolerance compared to those with normal glucose tolerance. Mean insulin also differed amongst groups. Those with type 2 diabetes had the highest mean insulin at fasting, but the lowest mean insulin at 30, 60, and 90 minutes post-challenge. Those with normal glucose tolerance and prediabetes had similar mean insulin levels until 30 minutes post challenge. After this time point, mean insulin was significantly higher in those with prediabetes than those with normal glucose tolerance.

Table 2 shows the relative associations of Log ISI_M and DI_o with glycemic status both bivariately and after multivariate adjustment. Bivariately, log ISI_M and DI_o were each associated with glycemic status. For every standardized unit increase in ISI_M the odds of prediabetes was 57% lower and the odds of type 2 diabetes was 70% lower compared to having normal glucose tolerance. For every one standardized unit increase in DI_o the odds of prediabetes was 85% lower and the odds of type 2 diabetes 98% lower compared to normal glucose tolerance. When both log ISI_M and DI_o were included in the model, after controlling for age, sex, BMI, family history of diabetes, hypertension, and smoking status, both factors, along with hypertension, remained significantly associated with prediabetes and type 2 diabetes. However, the association of ISI_M with both prediabetes and type 2 diabetes was no longer significant once visceral fat was included in the model, while the association of DI_o and glycemic status remained robust.

4.2. Follow-up visit

Approximately 2.5 years after the baseline visit, 132 (88%) of participants returned for the second clinical examination. Of the 18 participants who did not follow-up, 2 had died, 4 had moved away from the study area, 3 had developed serious illnesses, 6 were unable to schedule an appointment for logistical reasons, and 3 refused continued study participation. There were no significant differences in the baseline characteristics of those who remained in the study and those who withdrew. At the second examination, 24 (18%) of the 132 participants were being treated with glucose lowering medication; 17 of which were on glucose lowering medication both at baseline and at the second examination and 7 of which were newly on glucose lowering medication at follow up. Oral glucose tolerance tests were not performed on these participants. Table 3 describes participant characteristics at baseline and second clinical examination of those at risk for developing T2DM at the second clinical exam. Only mean log HOMA-IR and mean Log HOMA-β were significantly different between visits.

Table 2
Factors associated with baseline prediabetes and/or type 2 diabetes.

Model	Prediabetes		Type 2 diabetes		P
	OR	95% CI	OR	95% CI	
Log ISI_M					
Log ISI_M	0.43	(0.26, 0.70)	0.30	(0.17, 0.51)	<0.001
Log DI_o					
Log DI_o	0.15	(0.06, 0.36)	0.02	(0.01, 0.02)	<0.001
MV-adjusted Model 1*					
Log ISI_M	0.51	(0.27, 0.95)	0.35	(0.15, 0.87)	0.05
Log DI_o	0.22	(0.09, 0.58)	0.003	(0.001, 0.03)	<0.0001
Hypertension	4.30	(1.49, 12.41)	5.54	(1.08, 28.54)	0.02
MV-adjusted Model 2**					
Log DI_o	0.17	(0.70, 0.41)	0.003	(0.001, 0.03)	<0.0001
Visceral fat area	1.01	(1.00, 1.02)	1.02	(1.00, 1.04)	0.02
Hypertension	3.9	(1.4, 11.3)	4.3	(0.88, 22.15)	0.04

* Multivariate model adjusted for sex, age, BMI, family history of diabetes, smoking status, and hypertension.
** In addition to variables in Model 1, also adjusted for visceral fat area.

Table 3
Baseline and second clinical exam characteristics among those at risk for developing diabetes.*

Characteristics	Baseline	Second visit	P-value
n (%)	97	97	
Male sex (%)	42.3	42.3	1.0
Current hypertension (%)	30.9	29.9	0.88
Age (years)	57 ± 8	59 ± 8	0.02
BMI (kg/m^2)			
Male	25.8 ± 4.2	26.0 ± 4.2	0.91
Female	25.7 ± 4.8	26.1 ± 4.9	0.66
Waist circumference (cm)			
Male	96.4 ± 9.5	95.7 ± 9.5	0.74
Female	91.6 ± 12.5	89.2 ± 12.7	0.32
Systolic blood pressure (mmHg)	122 ± 17	124 ± 14	0.25
Diastolic blood pressure (mmHg)	71 ± 11	72 ± 11	0.53
Fasting glucose (mmol/l)	5.1 ± 0.6	5.1 ± 0.7	0.96
2 hr glucose (mmol/l)	7.2 ± 1.7	7.5 ± 2.3	0.29
Log HOMA-IR (μIU/ml*mmol/l)	0.8 ± 0.6	1.2 ± 0.5	<0.001
Log HOMA-β (μIU/ml/mmol/l)	4.9 ± 0.6	5.3 ± 0.5	<0.001

* We have excluded those with prevalent diabetes at baseline from both columns; values represent mean ± SD or %.

Between baseline and the second examination, 11 (8%) of the 132 participants converted from normal glycemia to prediabetes, 1 (0.75%) converted from normal glycemia to type 2 diabetes, and 6 (5%) converted from prediabetes to type 2 diabetes. Of those with normal glucose tolerance who converted to prediabetes, the incidence rate of impaired glucose tolerance was 82 per 1,000 person-years; 95% CI (40, 150) while the incidence rate of conversion to impaired fasting glucose was 8 per 1,000 person-years; 95% CI (0, 41). Based on both fasting and 2-hr OGTT values at follow-up, of those with prediabetes at baseline, the incidence rate from IGT to type 2 diabetes was 55 per 1,000 person years, 95% CI (17, 132). The incidence rate of conversion from IFG to type 2 diabetes was 64 per 1,000 person years, 95% CI (3, 316), and the incidence rate of diabetes for those who had both IFG and IGT was 66 per 1,000 person years, 95% CI (33, 324).

Between baseline and visit 2, mean standardized log HOMA-IR increased by 0.92 ± 1.00 μIU/ml*mmol/l. However, mean standardized log HOMA-β also increased by 0.70 ± 1.00 μIU/ml*mmol/l. In examining the covariates associated with glycemic progression, either from NGT to IGT, from NGT to type 2 diabetes, or from IGT to type 2 diabetes, in bivariate analysis the change in log HOMA-β (OR 0.44 per SD, 95% CI: 0.21, 0.90) and the interaction between sex and change in waist circumference (OR 1.58 per SD, 95% CI: 1.13, 2.22) were associated with glycemic conversion. In multivariable models which included baseline values for HOMA-IR and HOMA-β, the change in HOMA-β (OR 0.37 per SD, 95% CI: 0.17, 0.81) between the first and second exam and the interaction between sex and change in waist circumference (OR 1.81 per SD, 95% CI: 1.22, 2.70) were significantly associated with any glycemic status conversion, while no measures of baseline insulin sensitivity, baseline β-cell function, or change in insulin sensitivity were associated either in bivariate or multivariable models.

5. Discussion

We found that at baseline, the association between DI_o, a measure of β-cell function relative to insulin sensitivity, was more strongly associated with both prediabetes and type 2 diabetes than ISI_M, a measure of whole body insulin sensitivity, in our cohort of Asian Indians in the United States. This association remained strong even after adjustment for well known risk factors such as age, BMI, family history and visceral adiposity. Additionally, there may be more rapid progression from normal to impaired glucose tolerance and from impaired glucose tolerance to type 2 diabetes among Asian Indians than previously reported in other ethnic groups (Bonora et al., 2004; Valdes, Botas, Delgado, Alvarez, & Cadorniga, 2007) Changes in β-cell function over time were associated with glycemic progression in our cohort. Together, these findings suggest a possible independent effect of impaired β-cell function in the pathogenesis of type 2 diabetes in Asian Indians which could be the result of an innate susceptibility.

Recent studies conducted in India have also found early reductions in β-cell function as a possible primary etiological factor for diabetes development in Asian Indians (Mohan et al., 2013; Staimez et al., 2013). A cross-sectional study conducted on 1,264 individuals without known diabetes from Chennai, India noted that after adjusting for age, sex, BMI, waist circumference and family history, compared to normal glycemia, the odds of impaired fasting glucose or impaired glucose tolerance were more significant for DI_o than for HOMA-IR. These results suggest that reductions in β-cell function are apparent in Asian Indians even in early stages of dysglycemia, irrespective of factors known to impact disease development (Staimez et al., 2013). Another cross-sectional study from Chennai, India, compared Asian Indians with normal glucose tolerance and prediabetes with individuals in whom the onset of diabetes occurred before the age of 25 years (Mohan et al., 2013). Results of this study showed independent associations with both DI_o and Matsuda Index and type 2 diabetes and prediabetes. However, after adjusting for BMI, waist circumference, and age, DI_o remained significant for both stages of glycemia, while the Matsuda Index did not (Mohan et al., 2013). These findings of strong associations with β- cell dysfunction and hyperglycemia in Asian Indians even at very young ages suggest that the pathogenesis of type 2 diabetes in Asian Indians in India is primarily a function of declining β-cell function rather than the development of insulin resistance.

Our current study adds additional evidence that there is a strong association between β-cell dysfunction and both prediabetes and type 2 diabetes in Asian Indians and goes further to indicate that declines in β-cell function may be an underlying factor in type 2 diabetes development in this ethnic group regardless of the environmental setting. This is supported by the mean differences in insulin sensitivity (measured by log ISI_M) and β-cell function (measured by DI_o) between glycemic groups in our population, the associations with ISI_M and DI_o and glycemic status in polytomous standardized regression, and the association of HOMA-β with glycemic progression. While mean insulin sensitivity at baseline was only significantly different between normal glycemia and prediabetes, mean β-cell function was significantly different amongst all pairwise comparisons, thereby suggesting an early decline in β-cell function which continues to deteriorate as glucose tolerance declines. Furthermore, in bivariate standardized polytomous regression models, both insulin sensitivity and β-cell function were independently associated with both prediabetes and type 2 diabetes. However, in multivariable analyses the association with insulin sensitivity was considerably attenuated. Furthermore, after adjusting for visceral fat area associations with insulin sensitivity for both prediabetes and type 2 diabetes were no longer significant. This was not the case with β-cell function as DI_o remained significantly associated with both prediabetes and diabetes in multivariable models even after the adjustment of other well known risk factors. Additionally, changes in HOMA-β were associated with glycemic progression at follow up while changes in HOMA-IR were not. Our results, taken in aggregate with similar studies from India, indicate a possible innate susceptibility to β-cell dysfunction in Asian Indians that is independent of age, BMI, and abdominal obesity. These results point to early declines in β-cell function as an important contributing factor to type 2 diabetes development in this ethnic group that exists regardless of a developed or developing country setting.

While other studies have examined the relative associations of both β-cell function and insulin sensitivity across the entire spectrum of glycemia in native Asian Indians, our study is the first to do so in a cohort residing in the United States, thereby indicating that early reductions in β-cell function are apparent despite environmental, behavioral, or migratory factors and exist in both developing and developed country environments. However, the primarily cross-sectional nature of our study makes it impossible to determine when precisely during the natural history of type 2 diabetes pathogenesis the initial decline in β-cell function begins to occur. Additionally, the small sample size and short duration of follow up in our study resulted in unstable incidence rates with wide confidence intervals. A study from Chennai, India followed participants for a period of 8 years and determined that the incidence of type 2 diabetes was very high (20.2 per 1,000 person years) among Asian Indians living in an urban Indian setting (Mohan, Deepa, Anjana, Lanthorn, & Deepa, 2008). While this study provides valuable insight as to the rapid rate of conversion from normal glycemic or hyperglycemic states to overt type 2 diabetes in this population, it was conducted solely on Asian Indians living in urban South India and did not include other ethnic groups for comparison. Therefore, additional large longitudinal studies, including several ethnic groups, and with a long duration of follow-up are needed in order to accurately assess rates of glycemic conversion in Asian Indians compared to other ethnicities. Additional limitations to our study include the exclusion of

participants under the age of 45 and also those with pre-existing cardiovascular disease. Lastly, 30-minute post-challenge glucose and insulin were not measured at follow up. Therefore, we could not evaluate change in log ISI_M and DI_o as measures of insulin sensitivity and β-cell function during follow up, and instead relied on HOMA-IR and HOMA-β as measures of insulin sensitivity and β-cell function respectively. Since the calculations for HOMA-IR and HOMA-β involve fasting glucose, we restricted our analyses of glycemic conversion and assessed risk factors only from normal glycemia to IGT or type 2 diabetes, or from IGT to type 2 diabetes using only 2-hr post-challenge glucose measures, thereby eliminating any potential bias caused by the use of fasting glucose as both a predictor and an outcome variable. However, as a result, we were not able to assess risk factors associated with the conversion from normal glucose tolerance to IFG or from IFG to type 2 diabetes.

In conclusion, both decreased insulin sensitivity and impaired β-cell function are associated with type 2 diabetes in Asian Indians. However, impaired β-cell function appears to have a stronger relationship with prediabetes and type 2 diabetes. This association remained robust even after adjusting for visceral adiposity and other well known risk factors such as age, family history of diabetes, and hypertension, indicating a possible excess susceptibility to β-cell dysfunction in this ethnic group. Larger longitudinal studies in migrant Asian Indians are needed to provide further insight into acquired and/or epigenetic risk factors that may play a role in the development of β-cell dysfunction and eventual overt type 2 diabetes in this population.

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References

American Diabetes Association. (2008). Diagnosis and classification of diabetes mellitus. *Diabetes Care, 31*, S55–S60.

Bergman, R. N., Finegood, D. T., & Kahn, S. E. (2002). The evolution of β-cell and insulin resistance in type 2 diabetes. *European Journal of Clinical Investigation, 32*(Suppl 3), 35–45.

Bild, D. E., Bluemke, D. A., Burke, G. L., Detrano, R., Diez Roux, A. V., Folsom, A. R., et al. (2002). Multi-ethnic study of atherosclerosis: objectives and design. *American Journal of Epidemiology, 156*(9), 871–881.

Bonora, E., Kiechl, S., Willeit, J., Oberhollenzer, F., Egger, G., Meigs, J. B., et al. (2004). Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. *Diabetes, 53*(7), 1782–1789.

Chiu, M., Austin, P. C., Manuel, D. G., Shah, B. R., & Tu, J. V. (2011). Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. *Diabetes Care, 34*, 1741–1748.

Chiu, K. C., Cohan, P., Lee, N. P., & Chuang, L. M. (2010). Insulin sensitivity differs among ethnic groups with a compensatory response in beta-cell function. *Diabetes Care, 23*(9), 1353–1358.

Florez, J. C. (2008). Newly identified loci highlight beta cell dysfunction as a key cause of type 2 diabetes: where are the insulin resistance genes? *Diabetologia, 51*(7), 1100–1110.

Gastaldelli, A., Ferrannini, E., Miyazaki, Y., Matsuda, M., & DeFronzo, R. A. (2004). Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. *Diabetologia, 47*(1), 31–39.

Gujral, U. P., Pradeepa, R., Weber, M. B., Narayan, K. M., & Mohan, V. (2013). Type 2 diabetes in South Asians: similarities and differences with white Caucasian and other populations. *Annals of the New York Academy of Sciences, 1281*(1), 51–63.

Gupta, L. S., Wu, C. C., Young, S., & Perlman, S. E. (2011). Prevalence of diabetes in New York City, 2002–2008: comparing foreign-born South Asians and other Asians with U.S.-born whites, blacks, and Hispanics. *Diabetes Care, 34*, 1791–1793.

Kahn, S. E. (2003). The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. *Diabetologia, 46*(1), 3–19.

Kahn, S. E., Prigeon, R. L., McCulloch, D. K., Boyko, E. J., Bergman, R. N., Schwartz, M. W., et al. (1993). Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. *Diabetes, 42*(11), 1663–1672.

Kanaya, A. M., Wassel, C. L., Mathur, D., Stewart, A., Herrington, D., Budoff, M. J., et al. (2010). Prevalence and correlates of diabetes in South Asian Indians in the United States: findings from the metabolic syndrome and atherosclerosis in South Asians living in America study and the Multi-Ethnic Study of Atherosclerosis. *Metabolic syndrome and related disorders, 8*(2), 157–164.

Kasuga, M. (2006). Insulin resistance and pancreatic beta cell failure. *The clinical investigator, 116*(7), 1756–1760.

Kleinbaum, D. G., & Klein, M. (2002). Logistic regression: a self-learning text. In K. Dietz, M. Gail, K. Krickeberg, J. Samet, & A. Tsiatis (Eds.), New York, NY: Springer-Verlag.

Matsuda, M., & DeFronzo, R. A. (1999). Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care, 22*(9), 1462–1470.

Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C. (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia, 28*, 412–419.

Misra, R., Patel, T., Kotha, P., Raji, A., Ganda, O., Banerji, M., et al. (2010). Prevalence of diabetes, metabolic syndrome, and cardiovascular risk factors in US Asian Indians: results from a national study. *Journal of Diabetes and its Complications, 24*(3), 145–153.

Mohan, V., Anandakumar, A., Ranjani, H., Anjana, R. M., Staimez, L. R., Ali, M. K., et al. (2013). Associations of β-cell function and insulin resistance with youth-onset type 2 diabetes and prediabetes among Asian Indians. *Diabetes Technology & Therapeutics, 15*(4), 315–322.

Mohan, V., Deepa, M., Anjana, R. M., Lanthorn, H., & Deepa, R. (2008). Incidence of diabetes and pre-diabetes in a selected urban south Indian population (CUPS-19). *Journal of the Association of Physicians of India, 56*, 152–157.

Oza-Frank, R., Ali, M. K., Vaccarino, V., & Narayan, K. M. (2009). Asian Americans: diabetes prevalence across U.S. and World Health Organization weight classifications. *Diabetes Care, 32*, 1644–1646.

Saad, M. F., Knowler, W. C., Pettitt, D. J., Nelson, R. G., Charles, M. A., & Bennett, P. H. (1991). A two-step model for development of non-insulin-dependent diabetes. *American Journal of Medicine, 90*(2), 229–235.

Shaw, J. E., Sicree, R. A., & Zimmet, P. Z. (2010). Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice, 87*, 4–14.

Staimez, L. R., Weber, M. B., Ranjani, H., Ali, M. K., Echouffo-Tcheugui, J., Phillips, L. S., et al. (2013). Evidence of reduced β-cell function in Asian Indians with mild dysglycemia. *Diabetes Care, 36*, 2772–2778.

Utzschneider, K., Prigeon, R., Faulenbach, M., Tong, J., Carr, D. B., Boyko, E. J., et al. (2009). Oral disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. *Diabetes Care, 32*(2), 335–341.

Valdes, S., Botas, P., Delgado, E., Alvarez, F., & Cadorniga, F. D. (2007). Population-based incidence of type 2 diabetes in northern Spain: the Asturias Study. *Diabetes Care, 30*(9), 2258–2263.

WHO Expert Committee on Physical Status. (1995). The use and interpretation of anthropometry: report of a WHO expert committee. *World Health Organization Technical Report Series*. (pp. 854)Geneva, Switzerland: World Health Organization.

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. *Diabetes Care, 27*, 1047–1053.