J Clin Endocrinol Metab. 2021 May; 106(5): e2106–e2115. PMCID: PMC8063247
Published online 2021 Jan 27. doi: 10.1210/clinem/dgaa962: 10.1210/clinem/dgaa962 PMID: 33502458

Association of Diabetes Subgroups With Race/Ethnicity, Risk Factor Burden and Complications: The MASALA and MESA Studies

Michael P Bancks,[1] Alain G Bertoni,[1] Mercedes Carnethon,[2] Haiying Chen,[1] Mary Frances Cotch,[3] Unjali P Gujral,[4] David Herrington,[1] Alka M Kanaya,[5] Moyses Szklo,[6] Dhananjay Vaidya,[6] and Namratha R Kandula[2]

[1] Wake Forest School of Medicine, Winston-Salem, NC, USA
[2] Northwestern University Feinberg School of Medicine, Chicago, IL, USA
[3] National Eye Institute of the National Institutes of Health, Bethesda, MD, USA
[4] Emory University Rollins School of Public Health, Atlanta, GA, USA
[5] University of California, San Francisco, San Francisco, CA, USA
[6] Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Correspondence: Mike Bancks, PhD, MPH, Wake Forest School of Medicine, Division of Public Health Sciences, Department of Epidemiology & Prevention, Medical Center Boulevard, Winston-Salem, NC, 27157, USA. Email: mbancks@wakehealth.edu.

Received 2020 Aug 2

Abstract

Introduction

There are known disparities in diabetes complications by race and ethnicity. Although diabetes subgroups may contribute to differential risk, little is known about how subgroups vary by race/ethnicity.

Methods

Data were pooled from 1293 (46% female) participants of the Mediators of Atherosclerosis in South Asians Living in America (MASALA) and the Multi-Ethnic Study of Atherosclerosis (MESA) who had diabetes (determined by diabetes medication use, fasting glucose, and glycated hemoglobin [HbA1c]), including 217 South Asian, 240 non-Hispanic white, 125 Chinese, 387 African American, and 324 Hispanic patients. We applied k-means clustering using data for age at diabetes diagnosis, body mass

index, HbA1c, and homeostatic model assessment measures of insulin resistance and beta cell function. We assessed whether diabetes subgroups were associated with race/ethnicity, concurrent cardiovascular disease risk factors, and incident diabetes complications.

Results

Five diabetes subgroups were characterized by older age at diabetes onset (43%), severe hyperglycemia (26%), severe obesity (20%), younger age at onset (1%), and requiring insulin medication use (9%). The most common subgroup assignment was older onset for all race/ethnicities with the exception of South Asians where the severe hyperglycemia subgroup was most likely. Risk for renal complications and subclinical coronary disease differed by diabetes subgroup and, separately, race/ethnicity.

Conclusions

Racial/ethnic differences were present across diabetes subgroups, and diabetes subgroups differed in risk for complications. Strategies to eliminate racial/ethnic disparities in complications may need to consider approaches targeted to diabetes subgroup.

Keywords: race/ethnicity, diabetes heterogeneity, diabetes subgroups, diabetes complications

---

Recent work has highlighted the potential for expansion of diabetes classification beyond traditional taxonomy (1-6). In response, the American Diabetes Association issued a charge at the 2019 Scientific Sessions to unravel the heterogeneity in diabetes mellitus, particularly among patients with type 2 diabetes (7). The advantage of further classifying diabetes into potential subgroups is that adults with type 2 diabetes may have differing underlying disease etiology and progression. By understanding these differences, it is possible to improve risk stratification and tailor clinical management strategies to reduce risk of diabetes complications. Such strategies must be equitable and effective for everyone and not perpetuate racial/ethnic disparities in diabetes prevention and treatment. As such, it is important to expand the base of evidence on potential diabetes subgroups to include multiracial populations.

One approach to identify subgroups of diabetes is to cluster cases according to phenotypic data and this approach has been undertaken by multiple groups. Two studies have characterized similar diabetes subgroups and observed differential risk for complications, but studied only European-based populations (3, 4). A third study applied similar clustering techniques to the racially diverse National Health and Nutrition Examination Survey cross-sectional sample, but was not able to assess prospective outcomes (5). Separate studies among Japanese and Asian-Indian populations observed that diabetes subgroups were differentially associated with complications (6, 8). It remains unknown whether phenotypic data and clustering approaches used previously in European-based cohorts can be applied to characterize diabetes subgroups in US-based multi-ethnic samples and whether those subgroups are associated prospectively with outcomes. Determining whether disparities in diabetes complications can be explained by subgroup clustering differs by race and ethnicity is important (9).

Our objectives were to apply methods used in prior studies to characterize potential diabetes subgroups among 5 racial/ethnic groups and assess their association with risk for complications. We hypothesized that diabetes subgroups would differ in racial/ethnic composition and risk for complications.

Methods

We included data from 2 US community-based observational epidemiological studies, the Mediators of Atherosclerosis in South Asians Living in America (MASALA) and the Multi-Ethnic Study of Atherosclerosis (MESA). The study methods and clinical measurements used in the 2 studies are similar, have been harmonized, and allow for direct comparisons between the racial/ethnic groups (10-12). All participants gave written informed consent at their baseline examination and Institutional Review Boards at each study site approved study protocols.

MASALA Study

MASALA is a prospective cohort of 906 South Asian men and women living in the greater metropolitan areas of the San Francisco Bay Area, CA and Chicago, IL and the study methods have been described (10, 11). Briefly, individuals were eligible for participation if they were between the ages 40 and 84 years and had no known cardiovascular disease (CVD) at the time of their initial clinical examination in the period from 2010 to 2013. A follow-up clinical examination occurred in 2015–2018 and 749 (83%) participants completed this second examination.

MESA Study

MESA includes 6814 men and women from 4 racial/ethnic groups including non-Hispanic white (38%), African American (28%), Hispanic (22%), and Chinese American (12%), who were recruited from 6 communities across the United States (Baltimore, MD; Chicago, IL; Forsyth County, North Carolina; Los Angeles, CA; New York, NY; and Saint Paul, MN). Individuals were eligible for participation if they were 45 to 84 years of age and free from clinical CVD at the time of their initial clinical examination in the period from 2000 to 2002 (12). Participants were contacted by telephone annually and invited to participate in 5 follow-up in-person clinic examinations (2002-2004, 2004-2005, 2005-2007, 2010-2011, 2016-2018). To match the follow-up duration of MASALA, we limited data to the first 4 MESA examinations.

Questionnaires and Clinical Measurements

Structured questionnaires were used to collect information on participant demographics, medical history and use of medications, and health behaviors, including smoking, alcohol consumption, and physical activity (metabolic equivalent, MET hours/week) (13). Resting seated blood pressure was measured 3 times with 1-minute intervals between measurements, using an automated blood pressure monitor (MASALA: V100 Vital Signs Monitor; GE Medical Systems, Fairfield, CT) or Dinamap automated oscillometric sphygmomanometer (MESA: model Pro 100, Critikon, Tampa, FL). The average of the last 2 measurements was used for analysis. Height and weight were used to calculate body mass index (BMI).

Venous blood was obtained and serum separation was performed within 30 minutes of phlebotomy with aliquots subsequently stored at −70 °C. Fasting glucose was measured from serum using a hexokinase method in MASALA (Quest Labs, San Jose, CA) and the glucose oxidase method on the Vitros analyzer in MESA (Johnson & Johnson Clinical Diagnostics). Glycated hemoglobin (HbA1c) was measured using high-performance liquid chromatography (Tosoh HbA1c 2.2 Plus Glycohemoglobin Analyzer, Tosoh Medics, Inc., San Francisco, CA) from baseline samples in MASALA and examination 2 samples in

MESA. Insulin was measured by the sandwich immunoassay method in MASALA (Roche Elecsys 2010; Roche Diagnostics, Indianapolis, IN) and by a radioimmunoassay method in MESA (Linco Human Insulin Specific RIA kit; Linco Research). Homeostatic model assessment insulin resistance (HOMA-IR) and beta cell function (HOMA-β) were calculated for individuals not taking insulin medications (14). Total cholesterol and high-density lipoprotein (HDL) cholesterol were measured by enzymatic methods (MASALA: Quest Diagnostics, San Jose, CA; MESA: Roche Diagnostics, Indianapolis, IN) with the exception that in MESA HDL-cholesterol was measured after precipitation of non-HDL-cholesterol with magnesium/dextran. Low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald equation (15). Serum creatinine was measured and calibrated to a standard reference, with a coefficient of variation of 2.2% (16). Estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation (17).

Cardiac computed tomography (CT) scans were used to measure coronary artery calcium (CAC) and scan methodology for each study has been described (11, 18). Briefly, all CT scans were completed with an electron-beam CT (EBCT) scanner or multi-detector row helical (MDCT) scanner. In MASALA, a total of 46 images at 3.0-mm slice thickness were obtained and in MESA 40 images were collimated and reconstructed (EBCT: 3.0-mm slice thickness; MDCT: 2.5-mm slice thickness). Repeat CAC scans were performed at the second MASALA clinical examination and on a random sample for half of the MESA cohort at examination 2 and the remaining half at examination 3 (19). The methodology for acquisition and interpretation of the scans for both studies has been described (20). The Agatston scoring method was used to quantify the amount of calcium: Agatston units (AU) (21). Calcium scores were adjusted with a standard calcium phantom that was scanned along with the participant (11, 18, 22). All CT scans were read independently at the Reading Center at Harbor–UCLA Medical Center using Rephot Imaging software. The intra-observer and inter-observer agreement for CAC in MESA were kappa = 0.93 and kappa = 0.90, respectively (23). While not calculated, these estimates are expected to be similar for MASALA as images were interpreted at the same reading center using identical scanning protocols as MESA.

Statistical Analysis

We restricted the study sample to individuals who were identified as having diabetes at their enrollment examination. For MESA participants, we also included diabetes ascertained at examination 2, when HbA1c was measured. Diabetes was determined by use of insulin or oral hypoglycemic medication, fasting glucose ≥7.0 mmol/L (≥126 mg/dL), or HbA1c ≥48 mmol/mol (≥6.5%). Of the 7720 combined MASALA and MESA participants, we identified 1293 individuals with diabetes to include for analysis. We did not exclude individuals with diabetes due to secondary conditions. We used two-step fully conditional specification imputation methods to generate data missing for cluster variables and covariate characteristics (24, 25). The proportion of observations with missing data before imputation was largest for HbA1c (1%). First, individuals taking insulin medications were partitioned based on whether they were younger age at onset, defined as a diabetes age at onset of 30 years or younger. Individuals taking insulin medications were not included in the k-means clustering models. We applied k-means clustering to characterize potential diabetes subgroups among individuals not taking insulin medications, as per prior studies on diabetes subgroups (3-5). Clustering variables included age at diabetes diagnosis, BMI, HbA1c, HOMA-IR and HOMA-β. On average, the cohort examination occurred 5.7 years (standard deviation: 7.8) after diabetes diagnosis. We regressed sex on the clustering variables, separately, and used the residuals as

the value for each clustering variable in the k-means models. We used cluster statistics (Pseudo F statistic and Cubic Clustering Criterion) and calculated Silhouette index (range: -1 to 1; 1 is well-matched within cluster) values to determine cluster assignment, stability, and similarity within cluster. All of these statistics supported the optimal cluster number for this data was 3 (Silhouette = 0.22). This optimal cluster number of 3 was also observed with a sensitivity analysis of which excluded HOMA-IR and HOMA-β from the clustering models, and the qualitative composition of each cluster based on profiles for age at onset, BMI, and HbA1c were consistent between the main and sensitivity analyses.

After establishing diabetes subgroups, we assessed differences by race/ethnicity and sex across and within subgroup. We compared measures of sociodemographic factors, health behaviors, and CVD risk factors, and calculated 10-year predicted risk for atherosclerotic CVD (26). We estimated differences in CVD risk factors and prevalence of diabetes complications, including chronic kidney disease (CKD, eGFR <60 mL/min per 1.73m^2) and CAC >0 Agatston units (AU) by diabetes subgroup. A sensitivity analysis assessed prevalent CAC >100 AU because this level is considered a marker of high risk for future CVD events (27). We assessed incidence of complications among individuals without the respective prevalent complication at baseline. The duration between examinations in MASALA is 5 years and we restricted the follow-up for MESA participants to examination 4 or prior (5-7 years of follow-up). We used multivariable linear regression and logistic regression models to estimate predicted marginal means and probabilities (28). Model adjustments included enrollment examination age, sex, race/ethnicity, diabetes medication use, educational attainment, smoking status, alcohol use, systolic blood pressure, LDL, metabolic equivalent (MET) moderate and vigorous physical activity, blood pressure and cholesterol-lowering medication use, and diabetes duration. Statistical analyses were done with SAS version 9.4 (SAS Institute, Cary, NC, USA) and STATA software version 13 (Stata-Corp, College Station, TX).

Results

Across both cohorts, we included 1293 participants (600 women) with diabetes, including 217 South Asians, 240 non-Hispanic whites, 125 Chinese, 387 African Americans, and 324 Hispanic Americans. The proportion of the total allocated to the 5 diabetes subgroups (clusters) ranged from 1% to 43% (Table 1). The Silhouette index was 0.21. Qualitatively, distinguishing features between the 5 subgroups included older age at diabetes onset (cluster 1), severe hyperglycemia (cluster 2), severe obesity (cluster 3), younger age at onset (cluster 4), and insulin use (cluster 5). The distributions of cohort membership and race/ethnicity differed according to subgroup, respectively. Individuals in the severe hyperglycemia cluster were least likely to be female. Diabetes duration varied markedly across diabetes subgroup.

We observed differences in cluster characteristics among race/ethnicity within subgroup (Supplementary Table 1) (29). The younger age at onset diabetes subgroup had few individuals and did not contain Chinese individuals. South Asian and Chinese individuals had lower mean BMI than other race/ethnic groups within each subgroup. Hispanic participants had greater mean BMI than other race/ethnic groups within subgroup, with exception for the older age at onset and severe hyperglycemia subgroups. South Asians had the youngest mean age at diabetes diagnosis among race/ethnic groups for all subgroups. Subgroup assignment differed by race/ethnicity; the most probable subgroup assignment was older onset for all race/ethnicities with the exception of South Asians, for whom the severe hyperglycemia subgroup was most likely.

Cardiovascular Risk Factor Levels and Progression

We estimated predicted mean value for CVD risk factor levels according to diabetes cluster before and after adjustment for potential confounders (Table 2). We included differences in estimates comparing the diabetes subgroups to the older onset subgroup, as this was the largest group, had the best profile for most of the clustering characteristics, and was not related to an underlying disease process or disease severity. The severe obesity and severe hyperglycemia subgroups had the highest adjusted systolic blood pressure. The severe hyperglycemia subgroup had the highest adjusted total cholesterol. The severe obesity subgroup had the lowest adjusted HDL-cholesterol. Adjusted mean 10-year predicted risk for atherosclerotic CVD was lowest for the younger age at onset diabetes group and highest for the severe hyperglycemia subgroup. Adjusted mean eGFR lowest for the insulin medication use subgroup and highest for the severe hyperglycemia subgroup.

Prevalent and Incident Complications

Table 3 summarizes case numbers and adjusted predicted marginal probabilities for CKD and CAC outcomes according to diabetes subgroups. Supplementary table 2 presents these estimates by race/ethnicity (29). There were 176 prevalent cases of CKD at examination 1 and the unadjusted point prevalence ranged from 19% for the older onset subgroup to 3% for the severe hyperglycemia subgroup. The prevalence of CKD was highest for whites among the racial/ethnic groups. After adjustment, the predicted probability of prevalent CKD was highest for the insulin medication use subgroup and lowest for the severe hyperglycemia subgroup. Among those without prevalent CKD at baseline, there were 176 cases of incident CKD over 5 to 7 years of follow-up and the unadjusted cumulative incidence was highest for the insulin use subgroup (34%) and lowest for the younger age at onset diabetes subgroup (12%). After adjustment, the predicted probability for incident CKD was highest for the insulin use subgroup. African Americans and Hispanics had the highest predicted probability for incident CKD, exceeding 20%.

At baseline, 782 participants had a presence of CAC >0 and 435 participants had a presence of CAC >100. After adjustment, the predicted probability for prevalent CAC >0 and CAC >100 was highest for the younger age at onset of diabetes and insulin use subgroups. The predicted probability for prevalence of CAC at baseline was lowest among African Americans. Among 465 individuals with CAC = 0 at baseline, there were 127 cases of incident CAC. The unadjusted cumulative incidence of CAC and adjusted predicted probability for incident CAC was highest for the severe hyperglycemia subgroup and lowest for the younger age at onset diabetes group; however, the number of events and individuals at risk were low. The older onset subgroup had the second lowest adjusted predicted probability for incident CAC. The predicted probability for incident CAC was highest for South Asians and lowest for Chinese and Hispanic Americans.

Discussion

In this multi-ethnic study of 2 community-based cohorts, we characterized potential diabetes subgroups based on 6 diabetes clinical characteristics and applied clustering methods similar to prior studies on this topic which were based on white populations (3, 4). Phenotypic hallmarks of the 5 diabetes subgroups in this study included older age at diabetes onset, severe hyperglycemia, severe obesity, younger age at onset, and insulin medication use. We were able to corroborate prior work showing differential risk for

complications by diabetes subgroup and we were able to extend this prior work with 2 major findings. First, we observed racial/ethnic differences in diabetes subgroups; racial/ethnic composition differed across diabetes subgroup and cluster characteristics differed by race/ethnicity within diabetes subgroup. Second, subgroup membership was associated with differences in concurrent CVD risk factors and prospective diabetes complications independent of race/ethnicity.

The findings from this study provide unique insight into the heterogeneity of diabetes, particularly with respect to race/ethnicity. Prior work to characterize diabetes subgroups and their association with risk for future complications has been limited to white European-based populations (3, 4). Our current study uses different classification variables than prior work on this topic and may not be directly comparable. Here, we include 5 distinct racial/ethnic groups and demonstrate that diabetes subgroup membership is not uniform across race/ethnicity. Furthermore, our work suggests that within each diabetes subgroup there may be considerable variation in diabetes-related clinical characteristics across race/ethnicity.

Ahlquvist et al originally identified diabetes clusters characterized by autoimmunity, severe insulin-deficiency, severe insulin resistance, mild obesity, and older age at onset (3). These findings were reproduced by Zaharia and Tanabe (4, 6). In all 3 studies, the insulin resistant cluster had the highest risk for kidney disease, determined by either eGFR or urinary albumin (3, 4, 6). Here in the MASALA and MESA cohorts, risk for incident CKD based on eGFR was highest among individuals who developed diabetes in middle adulthood and who also required insulin. In our work, membership in the older age at onset diabetes subgroup was associated with better profiles for most all CVD risk factors and 10-year predicted atherosclerotic CVD risk despite this group being on average 5 years older than any of the 4 other diabetes subgroups. Membership in the severe obesity subgroup was associated with the worst systolic blood pressure and LDL-cholesterol profiles, but this did not correspond to the highest risk for incident CKD or CAC. This is similar to other studies where a diabetes subgroup characterized by severe obesity was not associated with kidney or coronary outcomes (3, 4, 6). However, the outcomes assessed in our work are subclinical measures whereas prior work has assessed clinical events.

Prior work combining MASALA and MESA has detailed the higher prevalence of diabetes and glycemic abnormalities observed for South Asian and Chinese individuals at similar or lower adiposity levels than other racial/ethnic groups (30, 31). Our current work aligns and extends those findings. First, the diabetes subgroup related to severe obesity included few Chinese individuals. Second, for South Asian participants, membership in the severe hyperglycemia subgroup was most predominant. This subgroup had the highest HbA1c and lowest beta cell function. This is consistent with prior work observing impaired beta cell function among South Asians (32). However, there were differences between these 2 Asian American groups within subgroup for age at onset and a large proportion of Chinese individuals were members of the older diabetes onset subgroup. While the absence of obesity in diabetes may be a shared characteristic for Chinese and South Asians, our work supports disparate metabolic processes occurring in diabetes between the 2 ethnic groups.

Limitations and methodological differences in our work may explain differences in our findings from those of prior work. First, our sample included individuals with prevalent diabetes (average duration 5.7 years), and longer diabetes duration may influence cluster characteristics related to glycemia and insulin and modifiable risk factors and other clinical characteristics. Zaharia detailed how cluster characteristics change over time and may influence cluster membership at a later date (4). Furthermore, Silhoutte values

of cluster assignment and stability were modest, which may have led to misclassification. However, we observed consistent results for optimal cluster number and qualitative composition when excluding data for HOMA-IR and HOMA-β from the clustering models. Second, we were not able to include data on autoantibodies and we manually assigned individuals taking insulin medications to unique clusters. Third, our sample was older and more racially diverse than prior studies. While our goal was to assess diabetes cluster differences by race and ethnicity, these constructs encompass an array of factors, including ancestry, cultural heritage influencing such aspects as dietary preferences, differences in access and affordability of medical care, migration, and possible influence by racism. Our findings should not be interpreted as attributing different underlying genetic mechanisms to race/ethnicity. Fourth, we estimated CVD risk factors and risk for subclinical CVD (CAC), which are predictive of incident CVD, but do not directly translate to incident clinical CVD events. To this end, due to the data available in both cohorts we examined a subset of disease complications that are predominantly cardiovascular-related and do not encompass the range of complications that individuals with diabetes may experience. The definition for CKD did not include data for urinary albumin and creatinine, as these data were not available across all examinations. Acute kidney injury was not specifically ascertained in either cohort and may contribute to CKD cases. However, given that these are community-based cohorts and that participants were queried on any recent illnesses in the past 2 weeks, the prevalence of acute kidney injury in this study is likely low. Fifth, we did not have data necessary to exclude individuals with possible type 1 diabetes (eg, antibodies) or diabetes secondary to conditions (eg, monogenic diabetes) and caution should be used when interpreting these results. Lastly, although multivariable adjustment was done, South Asian participants were solely from the MASALA study and residual confounding may still be present.

In this pooled sample of US adults, we characterized potential diabetes clusters among 5 racial/ethnic groups and contrasted clinical profiles and prospective complications. Membership in the diabetes clusters was not uniform across race/ethnicity and within cluster metabolic profiles differed by race/ethnicity. Risk for renal complications and subclinical coronary disease differed by diabetes subgroup and race/ethnicity after adjustment for potential confounders.

Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MASALA and MESA studies for their valuable contributions. A full list of participating investigators and institutions can be found at https://www.masalastudy.org/ for MASALA and http://www.mesa-nhlbi.org for MESA. Dr. Bancks is the guarantor of this work. As such, he takes responsibility for the integrity of the data and the accuracy of the data analysis and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. All authors made substantial intellectual contributions participating in creating and designing the study, analyzing and interpreting the data, and reviewing this manuscript. All authors have read and approved the final report for publication. Funding for MASALA was supported by Grant Numbers R01HL093009 and R01HL131606 from the National Heart, Lung, And Blood Institute and the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 RR024131. Funding for MESA was supported by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-

95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences (NCATS).

Glossary

Abbreviations

AU	Agatston units
BMI	body mass index
CAC	coronary artery calcium
CKD	chronic kidney disease
CT	computed tomography
CVD	cardiovascular disease
EBCT	electron-beam computed tomography
eGFR	estimated glomerular filtration rate
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HOMA-β	homeostatic model assessment for beta cell function
HOMA-IR	homeostatic model assessment for insulin resistance
LDL	low-density lipoprotein
MASALA	Mediators of Atherosclerosis in South Asians Living in America
MESA	Multi-Ethnic Study of Atherosclerosis
MDCT	multi-detector row helical computed tomography

Additional Information

Disclosures: The authors have no conflicts to disclose. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, And Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request. MESA data are publicly available via the National Heart, Lung, and Blood Institute: https://biolincc.nhlbi.nih.gov/studies/mesa/ (33).

References

1. Li L, Cheng WY, Glicksberg BS, et al. . Identification of type 2 diabetes subgroups through topological analysis of patient similarity. *Sci Transl Med.* 2015;7(311):311ra174. [PMCID: PMC4780757] [PubMed: 26511511]

2. Udler MS, Kim J, von Grotthuss M, et al. ; Christopher D. Anderson on behalf of METASTROKE and the ISGC. Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: a soft clustering analysis. *Plos Med.* 2018;15(9):e1002654. [PMCID: PMC6150463] [PubMed: 30240442]

3. Ahlqvist E, Storm P, Käräjämäki A, et al. . Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol.* 2018;6(5):361-369. [PubMed: 29503172]

4. Zaharia OP, Strassburger K, Strom A, et al. ; German Diabetes Study Group . Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. *Lancet Diabetes Endocrinol.* 2019;7(9):684-694. [PubMed: 31345776]

5. Bancks MP, Casanova R, Gregg EW, Bertoni AG. Epidemiology of diabetes phenotypes and prevalent cardiovascular risk factors and diabetes complications in the National Health and Nutrition Examination Survey 2003-2014. *Diabetes Res Clin Pract.* 2019;158:107915. [PubMed: 31704094]

6. Tanabe H, Saito H, Kudo A, et al. . Factors associated with risk of diabetic complications in novel cluster-based diabetes subgroups: a Japanese retrospective cohort study. *J Clin Med.* 2020;9(7):2083. [PMCID: PMC7408659] [PubMed: 32630741]

7. American Diabetes Association. Standards of medical care in diabetes - 2019. *Diabetes Care.* 2019;42(Supplement 1):S1-S193.

8. Anjana RM, Baskar V, Nair ATN, et al. . Novel subgroups of type 2 diabetes and their association with microvascular outcomes in an Asian Indian population: a data-driven cluster analysis: the INSPIRED study. *BMJ Open Diabetes Res Care.* 2020;8(1):e001506. [PMCID: PMC7437708] [PubMed: 32816869]

9. Spanakis EK, Golden SH. Race/ethnic difference in diabetes and diabetic complications. *Curr Diab Rep.* 2013;13(6):814-823. [PMCID: PMC3830901] [PubMed: 24037313]

10. Kanaya AM, Wassel CL, Mathur D, 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. *Metab Syndr Relat Disord.* 2010;8(2):157-164. [PMCID: PMC3139526] [PubMed: 19943798]

11. Kanaya AM, Kandula N, Herrington D, et al. . Mediators of Atherosclerosis in South Asians Living in America (MASALA) study: objectives, methods, and cohort description. *Clin Cardiol.* 2013;36(12):713-720. [PMCID: PMC3947423] [PubMed: 24194499]

12. Bild DE, Bluemke DA, Burke GL, et al. . Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol.* 2002;156(9):871-881. [PubMed: 12397006]

13. Ainsworth BE, Haskell WL, Whitt MC, et al. . Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc.* 2000;32(9 Suppl):S498-S504. [PubMed: 10993420]

14. 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. *Diabetologia.* 1985;28(7):412-419. [PubMed: 3899825]

15. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972;18(6):499-502. [PubMed: 4337382]

16. Naik RP, Derebail VK, Grams ME, et al. . Association of sickle cell trait with chronic kidney disease and albuminuria in African Americans. *Jama.* 2014;312(20):2115-2125. [PMCID: PMC4356116] [PubMed: 25393378]

17. Levey AS, Stevens LA, Schmid CH, et al. ; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) . A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612. [PMCID: PMC2763564] [PubMed: 19414839]

18. Kronmal RA, McClelland RL, Detrano R, et al. . Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation.* 2007;115(21):2722-2730. [PubMed: 17502571]

19. Gassett AJ, Sheppard L, McClelland RL, et al. . Risk factors for long-term coronary artery calcium progression in the multi-ethnic study of atherosclerosis. *J Am Heart Assoc.* 2015;4(8):e001726. [PMCID: PMC4599452] [PubMed: 26251281]

20. Carr JJ, Nelson JC, Wong ND, et al. . Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. *Radiology.* 2005;234(1):35-43. [PubMed: 15618373]

21. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol.* 1990;15(4):827-832. [PubMed: 2407762]

22. Nelson JC, Kronmal RA, Carr JJ, et al. . Measuring coronary calcium on CT images adjusted for attenuation differences. *Radiology.* 2005;235(2):403-414. [PubMed: 15858082]

23. Al Rifai M, Cainzos-Achirica M, Kanaya AM, et al. . Discordance between 10-year cardiovascular risk estimates using the ACC/AHA 2013 estimator and coronary artery calcium in individuals from 5 racial/ethnic groups: comparing MASALA and MESA. *Atherosclerosis.* 2018;279:122-129. [PMCID: PMC6295226] [PubMed: 30262414]

24. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res.* 2007;16(3):219-242. [PubMed: 17621469]

25. Yuan YC. Multiple imputation for missing data: concepts and new development (Version 9.0). In: *Proceedings of the Twenty-Fifth Annual SAS Users Group International Conference*. Vol. 49. Cary, NC: SAS Institute; 2000:1-11.

26. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. ; American College of Cardiology/American Heart Association Task Force on Practice Guidelines . 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129(25 Suppl 2):S49-S73. [PubMed: 24222018]

27. Greenland P, Bonow RO, Brundage BH, et al. ; American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography); Society of Atherosclerosis Imaging and Prevention; Society of Cardiovascular Computed Tomography . ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol.* 2007;49(3):378-402. [PubMed: 17239724]

28. UCLA: Statistical Consulting Group. Using margins for predicted probabilities. Published 2020. Accessed May 2, 2020. https://stats.idre.ucla.edu/stata/dae/using-margins-for-predicted-probabilities/

29. Bancks M, Bertoni A, Carnethon M, et al. . Supplementary Material for MASALA and MESA.docx. *figshare*. Deposited December 14, 2020. https://figshare.com/articles/figure/Supplementary_Material_for_MASALA_and_MESA_docx/13079729

30. Kanaya AM, Herrington D, Vittinghoff E, et al. . 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):1621-1628. [PMCID: PMC4030091] [PubMed: 24705613]

31. Gujral UP, Vittinghoff E, Mongraw-Chaffin M, et al. . Cardiometabolic abnormalities among normal-weight persons from five racial/ethnic groups in the United States: a cross-sectional analysis of two cohort studies. *Ann Intern Med.* 2017;166(9):628-636. [PMCID: PMC5545925] [PubMed: 28384781]

32. 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. *J Diabetes Complications.* 2014;28(1):45-50. [PMCID: PMC3877179] [PubMed: 24211090]

33. National Heart, Lung, and Blood Institute. Multi-Ethnic Study of Atherosclerosis (MESA). Published 2020. Accessed August 01, 2020. https://biolincc.nhlbi.nih.gov/studies/mesa/

Figures and Tables

Table 1.

Demographic and Clustering Characteristics According to Diabetes Subgroup

Demographic characteristic	Older onset	Severe hyperglycemia	Severe obesity	Younger onset	Insulin use
N (% total sample)	554 (43%)	340 (26%)	259 (20%)	19 (1%)	121 (9%)
Women, n (%)	269 (49%)	135 (40%)	123 (47%)	11 (58%)	62 (51%)
South Asian, n (%)	62 (17%)	82 (25%)	52 (21%)	5 (2%)	16 (13%)
Non-Hispanic white, n (%)	134 (38%)	26 (8%)	56 (23%)	6 (3%)	18 (14%)
Chinese, n (%)	84 (24%)	27 (8%)	11 (4%)	0 (0%)	3 (2%)
African American, n (%)	155 (44%)	104 (32%)	76 (31%)	4 (2%)	48 (38%)
Hispanic, n (%)	119 (34%)	101 (31%)	64 (26%)	4 (2%)	36 (29%)
Examination age, years (SD)	69.5 (8.2)	60.1 (8.6)	60.1 (8.6)	55.2 (9.7)	65.0 (9.9)
Diabetes duration, years (%)	2.7 (4.2)	7.6 (7.5)	3.0 (4.5)	31.3 (13.3)	15.5 (8.4)
Any diabetes medication use, n (%)	267 (48%)	250 (74%)	124 (48%)	19 (100%)	121 (100%)
Cholesterol medication use, n (%)	189 (34%)	111 (33%)	68 (26%)	10 (53%)	53 (44%)
Blood pressure medication use, n (%)	331 (60%)	185 (54%)	165 (64%)	14 (74%)	94 (78%)
Graduate degree education, n (%)	100 (18%)	71 (21%)	49 (19%)	6 (32%)	15 (12%)

Values are means (SD), medians (interquartile range, IQR), or counts (column percentage, %), with the exception of N (% total sample)

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-β homeostatic model assessment for beta cell function; MET, metabolic equivalent; NA, not applicable

[a] HOMA measures are NA because all participants report insulin medication use

Table 2.

Cardiovascular Disease Risk Factors According to Diabetes Subgroup

	Older onset	Severe hyperglycemia	Severe obesity	Younger onset	Insulin use
Number of participants	554	340	259	19	121
Risk factors					
Systolic blood pressure, mm Hg					
Adjusted predicted mean (SE) [a]	130.4 (128.6, 132.3)	132.6 (130.4, 134.7)	134.0 (131.6, 136.4)	129.7 (119.6, 139.7)	131.8 (128, 135.6)
Difference (95% CI)	Reference	2.1 (−1.0, 5.3)	3.6 (0.5, 6.7)	−0.8 (−11.4, 9.9)	1.4 (−3.2, 6.0)
Diastolic blood pressure, mm Hg					
Adjusted predicted mean (SE) [a]	72 (71.1, 72.9)	73.7 (72.6, 74.8)	72.8 (71.7, 74)	74.2 (69.2, 79.2)	72.9 (71.0, 74.8)
Difference (95% CI)	Reference	1.7 (0.2, 3.3)	0.8 (−0.7, 2.4)	2.2 (−3.1, 7.5)	0.9 (−1.3, 3.2)
Total cholesterol, mmol/L					
Adjusted predicted mean (SE) [a]	4.73 (4.63, 4.82)	5.02 (4.91, 5.14)	4.85 (4.73, 4.97)	4.74 (4.23, 5.26)	4.91 (4.71, 5.11)
Difference (95% CI)	Reference	0.30 (0.14, 0.46)	0.12 (−0.04, 0.28)	0.01 (−0.53, 0.56)	0.18 (−0.06, 0.42)
HDL-cholesterol, mmol/L					
Adjusted predicted mean (SE) [a]	1.27 (1.24, 1.29)	1.18 (1.15, 1.21)	1.12 (1.08, 1.16)	1.18 (1.02, 1.34)	1.16 (1.09, 1.22)
Difference (95% CI)	Reference	−0.09 (−0.14, −0.04)	−0.15 (−0.20, −0.10)	−0.09 (−0.26, 0.08)	−0.11 (−0.18, −0.04)
LDL-cholesterol					

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] Adjustments include examination age, sex, race/ethnicity, diabetes medication use, educational attainment, smoking status, alcohol use, physical activity, blood pressure and cholesterol-lowering medication use, and diabetes duration

[b] Calculated using the American College of Cardiology/American Heart Association equation

Table 3.

Prevalence and Incidence of Diabetes Complications According to Diabetes Subgroup

Prevalent/incident outcome	Older onset	Severe hyperglycemia	Severe obesity	Younger onset	Insulin use
Prevalent CKD[a] at examination 1					
Cases / at risk	104 / 553	10 / 340	28 / 259	2 / 19	32 / 121
Adjusted predicted probability, % (SE) [b]	14.1 (11.3, 17.0)	5.2 (2.1, 8.2)	16.8 (11.7, 21.9)	11.5 (−6.1, 29.1)	18.8 (11.4, 26.2)
Difference, % (95% CI)	Reference	−9.0 (−13.5, −4.5)	2.7 (−3.3, 8.6)	−2.7 (−21.2, 15.9)	4.7 (−4.0, 13.3)
Incident CKD					
Cases / at risk	79 / 414	40 / 302	30 / 206	2 / 17	25 / 74
Adjusted predicted probability, % (SE) [b]	17.1 (13.2, 20.9)	15.0 (10.4, 19.6)	17.4 (11.9, 22.9)	10.6 (−4.7, 25.8)	23.3 (13.9, 32.7)
Difference, % (95% CI)	Reference	−2.0 (−8.6, 4.6)	0.3 (−6.4, 7.1)	−6.5 (−23.2, 10.2)	6.3 (−4.7, 17.2)
Prevalent CAC>0 AU at examination 1					
Cases / at risk	356 / 553	187 / 340	141 / 258	13 / 19	85 / 121
Adjusted predicted probability, % (SE) [b]	57.4 (53.0, 61.8)	61.1 (56.2, 66.0)	62.0 (56.6, 67.4)	71.7 (51.4, 92.0)	68.4 (59.8, 77.0)
Difference, % (95% CI)	Reference	3.7 (−3.4, 10.8)	4.6 (−2.3, 11.6)	14.3 (−7.4, 36.1)	11.0 (0.6, 21.4)
Prevalent CAC>100 AU at examination 1					
Cases / at risk	218 / 553	89 / 340	68 / 258	9 / 19	51 / 121
Adjusted predicted probability, % (SE) [b]	33.6 (29.5, 37.6)	31.1 (26.0, 36.3)	33.5 (27.6, 39.3)	47.7 (23.9, 71.5)	37.1 (28.3, 46.0)
Difference, % (95% CI)	Reference	−2.4 (−9.6, 4.7)	−0.1 (−7.3, 7.1)	14.1 (−11.0, 39.2)	3.6 (−6.9, 14.1)

Abbreviations: AU, Agatston units; CAC, coronary artery calcium, CKD, chronic kidney disease

[a] CKD was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2

[b] Adjustments include examination 1 values for age, sex, race/ethnicity, diabetes medication use, educational attainment, smoking status, alcohol use, systolic blood pressure, low-density lipoprotein cholesterol, physical activity, blood pressure and cholesterol-lowering medication use, and diabetes duration