HHS Public Access

Author manuscript

Diab Vasc Dis Res. Author manuscript; available in PMC 2017 December 13.

Published in final edited form as:

Diab Vasc Dis Res. 2014 January ; 11(1): 11–18. doi:10.1177/1479164113514239.

Association of prediabetes by fasting glucose and/or haemoglobin A1c levels with subclinical atherosclerosis and impaired renal function: Observations from the Dallas Heart Study

Frank YF Xing[1,2], **Ian J Neeland**[1], **M Odette Gore**[1], **Colby R Ayers**[3], **Andre RM Paixao**[1], **Aslan T Turer**[1], **Jarett D Berry**[1], **Amit Khera**[1], **James A de Lemos**[1], and **Darren K McGuire**[1,3]

[1]Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

[2]School of Medicine, University of Missouri-Kansas City, Kansas City, MO, USA

[3]Department of Clinical Science, University of Texas Southwestern Medical Center, Dallas, TX, USA

Abstract

Background—Prediabetes defined by fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA1c) predicts incident diabetes, but their individual and joint associations with micro- and macro-vascular risk remain poorly defined.

Methods—FPG, HbA1c, coronary artery calcium (CAC), carotid wall thickness, estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) were measured in adults free from prior diabetes or cardiovascular disease (CVD) in the Dallas Heart Study 2 (DHS-2), a population-based cohort study. Prediabetes was defined by FPG 100–125 mg/dL and/or HbA1c 5.7%–6.4%. Multivariable logistic regression was used to analyse associations of HbA1c and/or FPG in the prediabetes range with subclinical atherosclerosis and renal measures.

Results—The study comprised 2340 participants, median age = 49 years; 60% women and 50% black. Those with prediabetes were older (52 vs 48 years), more often men (63% vs 53%), black (53% vs 47%) and obese (58% vs 40%; $p < 0.001$ for each). Prediabetes was captured by FPG alone (43%), HbA1c alone (30%) or both (27%). Those with prediabetes by HbA1c or FPG versus normal HbA1c/FPG had more CAC [odds ratio (OR) = 1.8; 95% confidence interval (CI) = 1.5–2.2], higher carotid wall thickness (1.32 vs 1.29 mm, $p < 0.001$), eGFR < 60 mL/min [OR = 1.6

Corresponding author: Darren K McGuire, Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA. darren.mcguire@utsouthwestern.edu.

Declaration of conflicting interests

Dr McGuire serves as a consultant to Boehringer Ingelheim, Genentech, Sanofi Aventis, Takeda, Janssen Pharmaceuticals and Regeneron, and also receives research support from Eli Lilly, Daiichi Sankyo, Roche, Genentech, Merck, Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, Takeda, GlaxoSmithKline, Orexigen, Eisai and Omthera. James A de Lemos has received honoraria from AstraZeneca and serves as a consultant for Novo Nordisk.

No conflicts of interest are reported by Frank YF Xing or Colby R Ayers and Ian J Neeland, M Odette Gore, Andre RM Paixao, Amit Khera, Jarett D Berry or Aslan T Turer.

(95% CI = 1.1–2.4)], UACR > 30 mg/dL [OR = 1.8 (95% CI = 1.2–2.7)] and a higher odds for the composite eGFR + UACR [chronic kidney disease (CKD) ≥ 2] [OR = 1.9 (95% CI = 1.5–2.6)]. After multivariable adjustment, none of these associations remained significant.

Conclusion—Prediabetes defined by HbA1c and/or FPG criteria is crudely associated with markers of diabetic macro- and micro-vascular disease, but not after statistical adjustment, suggesting the relationships are attributable to other characteristics of the prediabetes population.

Keywords

HbA1c; impaired fasting glucose; prediabetes; subclinical atherosclerosis; nephropathy

Introduction

Glycosylated haemoglobin (HbA1c) has been recently endorsed for screening and diagnosis of type 2 diabetes mellitus (T2DM) and to identify those at increased risk of T2DM (so-called prediabetes). Glucose thresholds for the diagnosis of T2DM have historically been established and validated in relation to micro-vascular disease risk, while prediabetes thresholds have been defined based on risk of progression to T2DM.[1,2] In addition, associations of prediabetes and T2DM with subclinical atherosclerosis and renal function risk have also been assessed, with T2DM robustly associated with these risk factors but with less consistent associations among those with prediabetes as defined by impaired fasting glucose (IFG = 100–125 mg/dL).[3–10] In this context, the degree to which IFG and the more recently established HbA1c diagnostic thresholds for prediabetes individually and jointly associate with subclinical atherosclerosis and abnormal renal measures as antecedents to clinical complications of T2DM remains poorly defined.

We sought to evaluate the individual and joint associations of prediabetes defined by HbA1c and/or fasting plasma glucose (FPG) criteria with prevalent subclinical coronary and carotid atherosclerosis, as well as markers of nephropathy in a large population-based cohort of adults without T2DM.

Methods

Study population

The Dallas Heart Study 2 (DHS-2) is a longitudinal follow-up study of a subset of participants who completed the DHS-1, a probability-based population sample of Dallas County adults enrolled in 2000–2002 with study methods previously described, and participants who volunteered to undergo a second comprehensive clinical study assessment with repeat data collection between September 2007 and December 2009.[11] In addition to DHS-1 participants, the DHS-2 cohort was supplemented by recruitment of participants' spouses or significant others. These assessments included an extensive health survey, laboratory testing and imaging studies during a single-day visit to the University of Texas (UT) Southwestern Medical Center.

The present analyses are limited to DHS-2 participants without prevalent diabetes, defined by patient self-report accompanied by use of at least one prescription of glucose-lowering

medication, or incident diabetes, defined by FPG and/or HbA1c values above the diabetes threshold in the absence of previously diagnosed diabetes. The analysis cohort was further restricted to those who had complete clinical data collection including fasting blood samples, HbA1c measurements, urine samples, carotid magnetic resonance imaging (MRI) and coronary multi-detector computed tomography (MDCT) scans.

Blood and urine testing

After an overnight fast, venous blood was collected into ethylenediaminetetraacetic acid (EDTA) tubes, centrifuged at 1430*g* for 15 min at 4°C, and plasma was stored in aliquots at −80°C until analysis. Samples were thawed and measured in batch at study conclusion, except for HbA1c that was measured on whole blood at the time of specimen collection using an Ultra-2 affinity high-performance liquid chromatography assay (Trinity Biotech, Kansas City, MO, USA) at the UT Southwestern HbA1c reference laboratory. Detection limits and coefficients of variation of this assay have been previously published.[12]

Glomerular filtration rate [mL/min/1.73 m^2 bovine serum albumin (BSA)] was estimated [estimated glomerular filtration rate (eGFR)] using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula: GFR = 141 × min [serum creatinine (Scr)/κ,1]$^{\alpha}$ × max (Scr/κ,1) − 1.209 × 0.993^{age} × 1.018 (if female) × 1.159 (if black), where κ is 0.7 for females and 0.9 for males; α is −0.329 for females and −0.411 for males; min indicates the minimum of Scr/κ or 1 and max indicates the maximum of Scr/κ or 1.[13]

Urine albumin and creatinine were measured on urine samples from the first morning void, and the urine albumin-to-creatinine ratio (UACR) was calculated in milligram per gram for each participant. A Beckman Coulter analyser (Beckman Coulter, Fullerton, CA, USA) was used for all biochemical measurements. Urine albumin was quantified by the turbidimetric method. Both serum and urine creatinine concentrations were determined by the alkaline picrate method. The coefficients of variation for these urine creatinine and albumin measures have been previously published.[14]

Imaging

Coronary artery calcium (CAC) was measured by MDCT and was performed on a single scanner (Toshiba Aquilion 64-Slice MDCT) with each participant scanned in duplicate with the calcium score averaged between the two scans, as previously reported.[15] Calcium scoring followed the protocol of the Multi-Ethnic Study of Atherosclerosis, and detection of calcium was based on a focus of calcium with ≥3 contiguous pixels at ≥130 Hounsfield units.[16,17]

Carotid MRI was performed using a Phillips Achieva 3.0T MRI system. In brief, the index carotid artery was imaged using four contrast weightings (T1, T2, proton density and time of flight) covering 20 slices (2 mm thickness) centred at the bifurcation. A trained technologist blind to study population characteristics interpreted the images using semi-automated software (VesselMASS). All imaging interpretation was performed with the reader blinded to all participant data.

Study variables and definitions

There were a total of 3401 DHS-2 participants, of whom 2676 were classified as normal or pre-DM. Of these 2676 participants, 2340 had CAC measurements and 1644 had carotid measurements. A history of gestational DM was not defined as DM in these analyses, unless the participant also was medically treated with a glucose-lowering drug at the time of study entry or had fasting glucose > 126 mg/dL or random glucose > 200 mg/dL or HbA1c > 6.5% in line with the overall definition of DM used in this dataset.

Race/ethnicity, history of cardiovascular diseases (CVDs) and smoking status were self-reported. Hypercholesterolaemia was defined as calculated low-density lipoprotein cholesterol (LDL-C) ≥ 160 mg/dL on a fasting sample, direct LDL-C ≥ 160 mg/dL on a non-fasting sample, total cholesterol ≥ 240 mg/dL or use of statin medication. Hypertriglyceridemia was defined as a fasting triglyceride concentration ≥200 mg/dL, and low high-density lipoprotein cholesterol (HDL-C) was defined as HDL-C < 40 mg/dL in men and <50 mg/dL in women. Blood pressure was measured in the sitting position with five sequential measurements averaged. Hypertension was defined as an average systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication. Framingham 10-year coronary heart disease (CHD) risk estimates were calculated according to the National Cholesterol Education Program – Adult Treatment Panel III report.[18] Prevalent CAC was defined as Agatston score > 10 as a data-derived threshold to maximise the signal-to-noise ratio and the reproducibility of the imaging studies. Mean common carotid wall thickness was defined as the mean thickness of the index common carotid artery 1 cm below the carotid bifurcation. CKD was categorically defined as eGFR < 60 mL/min/1.73 m^2, corresponding to CKD stage ≥ 3.[19] Albuminuria was categorically defined as an UACR > 30 mg/g.[20] Given the small sample sizes within each subgroup, an additional composite definition of CKD ≥ 2 was also defined as eGFR < 60 or UACR > 30.

Statistical analyses

Baseline characteristics were compared between participants with normal glucose and those with prediabetes using the Kruskal–Wallis test for continuous variables and Pearson's chi-square test for categorical variables. Those with prediabetes were further stratified by diagnosis with FPG-only, HbA1c-only or both. Univariable and multi-variable logistic and linear regression methods were used to analyse the associations between prediabetes classifications (overall and by diagnostic subsets) and prevalent CAC, carotid wall thickness, eGFR < 60 mL/min, prevalent albuminuria or meeting the categorical CKD ≥ 2 definition. Covariables included in the models were age, sex, race/ethnicity, smoking status, body mass index (BMI), hypertension, total cholesterol and LDL-C. Sensitivity analyses stratified by sex, race/ethnicity and BMI were also performed for descriptive purposes with formal interaction testing in each model for glycaemic category-by-stratum.[21,22] Additional sensitivity analyses were performed using the same modelling methods: (a) defining CAC prevalence by any Agatston score > 0 and (b) using the former classification of IFG defined by fasting glucose 110–125 mg/dL. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

The study cohort comprised 1651 original DHS participants with an additional 689 spouses/significant others enrolled to yield a total sample of 2340 adults with complete data collection for the present analyses. There were no significant differences in demographics, baseline characteristics or medical history between eligible DHS completers who did versus did not participate in the follow-up DHS-2.

The baseline characteristics of the study cohort stratified by prediabetes status, overall and by diagnostic subgroups, are shown in Table 1. Overall, there were 1585 (68%) participants with normal glucose metrics and 755 (32%) with prediabetes. Compared with the normal group [fasting blood glucose (FBG) < 100 mg/dL and HbA1c < 5.7%], individuals with prediabetes defined by either measurement had a higher CVD risk burden, including increased age, higher systolic blood pressure, Framingham-estimated 10-year CHD risk and BMI, with more family history of heart disease.

Among those with prediabetes, 329 (43%) were diagnosed by FPG alone, 222 (30%) by HbA1c alone and 204 (27%) by both FBG and HbA1c. When stratified by race/ethnicity, a significantly higher proportion of blacks were identified as having prediabetes by HbA1c alone (74%), including 61% with prediabetes criteria by both HbA1c and IFG, compared with prediabetes by IFG alone (33%). Among Caucasians and Hispanics, FPG criteria identified a higher proportion (46% and 19% by FPG alone, respectively; 19% and 17% by a combination of both, respectively) compared with those with prediabetes identified by HbA1c alone (13% and 10%, respectively).

Age was not statistically different across these three mutually exclusive prediabetes diagnostic subgroups. Those with prediabetes by IFG alone were more commonly Caucasian or Hispanic and with less adiposity and higher triglycerides, whereas those classified by HbA1c alone were more commonly African American, smokers and had increased adiposity. While several blood pressure and lipid measurements yielded statistical differences across the three subgroups, overall the values were numerically comparable with small absolute differences of little clinical relevance between the groups.

Associations of prediabetes with subclinical atherosclerosis and nephropathy measures, overall and among prediabetes diagnostic subgroups, are shown in Table 2. Compared with the normal glucose group, those with prediabetes by HbA1c and/or FPG had a higher crude prevalence of CAC (33% vs 22%; $p < 0.001$), higher mean common carotid wall thickness (1.32 vs 1.29 mm; $p < 0.001$) and higher prevalence of CKD either by eGFR < 60 alone (6% vs 3%; $p < 0.004$) or by UACR > 30 (5% vs 3%; $p < 0.008$) or by the composite CKD ≥ 2 definition (11% vs 8%; $p < 0.001$). Crude intergroup comparisons across the three prediabetes subcategories revealed no statistical difference in any of these five selected measures.

Results from multivariable analyses of associations between prediabetes categories and CAC, carotid wall thickness, CKD and albuminuria overall unadjusted and fully adjusted are shown in Table 3. After adjustment, no independent associations were observed between prediabetes, overall or by each of the diagnostic subsets, with subclinical atherosclerosis or

nephropathy measures. When analyses were stratified by race/ethnicity, sex and BMI, the results were similar to the overall cohort, yielding no statistically significant associations in any of the subgroups and with no heterogeneity of associations observed for any of the characteristics of stratification ($p_{\text{interaction}} > 0.05$ for all). Detailed subgroup analyses are presented in Supplementary Figures 1–5 online. Additional sensitivity analyses using CAC prevalence defined by Agatston score > 0 and IFG defined by FPG 110–125 mg/dL yielded qualitatively similar results, with no independent statistical associations observed (data not shown).

Discussion

The key observations of this study are as follows: (1) prevalence estimates for prediabetes vary significantly depending on whether FPG, HbA1c or both are used; (2) although race/ethnic differences were observed across the prediabetes subgroups, subjects meeting prediabetes definitions by IFG-only, HbA1c-only or both overall had generally similar cardiovascular risk profiles and similar crude associations with each of the intermediate markers of clinical disease assessed; (3) prediabetes was associated with a higher crude prevalence for CAC, greater carotid wall thickness, CKD and albuminuria compared with individuals with normal glucose, but after multivariable adjustment, prediabetes was no longer statistically associated with the preclinical phenotypes, independent of which criteria were met for prediabetes classification.

Racial differences in screening for prediabetes

Our study suggests that HbA1c and FPG perform differently by race or ethnicity in the identification of individuals in the prediabetes range with increased frequency of those meeting only the HbA1c criteria among African American participants representing almost three-quarters of this group, whereas IFG-only was most common among Caucasians representing about one-half of such participants. These observations have important clinical and epidemiologic implications. The quantitatively similar distribution of cardiometabolic risk factors and estimated CHD risk estimates between the prediabetes groups with IFG-only compared to HbA1c-only underscores the potential added value of HbA1c screening. Although without longitudinal assessment of risk of incident diabetes or clinical micro- and macro-vascular disease complications, the clinical relevance of this observation remains speculative. In the population perspective, the addition of the subset of individuals with prediabetes identified with HbA1c-only will increase population prevalence estimates that have been historically based primarily on IFG and/or glucose tolerance testing.

The observed increased prevalence of abnormal HbA1c among African American participants compared with other race/ethnic subgroups is consistent with prior reports, where the addition of HbA1c criteria for the diagnosis of T2DM captures a higher percentage of African Americans than other racial or ethnic groups across a spectrum of age ranges. These differences may be due to underlying racial and ethnic differences in red blood cell survival, genetic determinants of haemoglobin glycation or variability of correlation between fasting glucose values and overall glucose exposure.[23–25]

Prediabetes and atherosclerosis

Several previous cross-sectional studies have examined the association between fasting glucose and CAC, and a crude association has been reliably observed similar to the present findings. However, after multivariable adjustment to account for differences in patient mix, only about one-half of the reported studies demonstrate persistence of the statistical association.[26–29]

The largest of the positive population-based studies reported that in 2184 non-diabetic participants, FPG was associated with prevalent CAC in men but not in women. Additionally, an older definition of prediabetes was used, which was defined as fasting glucose 6.1–6.9 mmol/L (110–125 mg/dL), in contrast with this study using the contemporary threshold for FPG and evaluating potentially lower risk individuals given the younger age of our cohort.[26] However, variance in IFG definitions alone does not explain the discordant observations between the studies, as sensitivity analyses in the present dataset using the older definition of prediabetes yielded virtually identical results to the primary analysis, with no independent statistical associations with the clinical intermediates of interest. Our study also differs in the use of a more specific definition of CAC using Agatston score > 10 in contrast with CAC defined by any score.[27] However, sensitivity analyses in this study using the latter definition again did not alter the results. In addition, our study differs by increased representation of ethnic minorities and derives from a probability-based population sample, each of which may contribute to the discordant observations and augment the generalisability of the present observations.

The two largest studies reported to date, the Coronary Artery Risk Development in Young Adults (CARDIA) Study (n = 3043) and the Framingham Offspring Study (n = 3054), each showed no significant independent relationships between prediabetes and CAC.[28,29] The DHS population is notably younger compared with prior cohorts in which similar analyses have been executed, and associations between prediabetes categories and the outcomes of interest could be more evident in older populations. However, previous studies evaluating associations between prediabetes and CAC in the Framingham Offspring Study and the CARDIA Study, both with populations on average 10 years older than DHS, have also failed to demonstrate independent associations between prediabetes and CAC consistent with the present findings.

There are several notable differences between this study and these two prior studies. CAC prevalence was defined in the Framingham study using data-derived age- and sex-specific top 90th percentile cut-off, while the CARDIA investigators used a definition for prevalent CAC of Agatston score > 0. Previous analyses within the DHS dataset have shown that Agatston score > 10 maximises the signal-to-noise ratio and minimises the interscan variability in our population.[17] Another key difference is the lack of HbA1c measurements in both the CARDIA and Framingham studies, with prediabetes defined exclusively with FPG. Additionally, Framingham Offspring Study included a racially homogeneous population, while CARDIA only had 17% African Americans. A sensitivity analysis stratified by Caucasians and African Americans in our study did not reveal heterogeneity of associations between the group, with results similar to those in the overall cohort.

Carotid wall thickness is independently predictive of cardiovascular risk when added to conventional cardiovascular risk factors and is an intermediate measure of subclinical atherosclerosis in the carotid vasculature.[30,31] Few studies to date have assessed the associations between pre-diabetes and carotid wall thickness. In a cross-sectional study of Italian adults, no independent association was observed between prediabetes, defined by FPG and/or HbA1c criteria, with carotid intima-media thickness, similar to the present findings. Also similar to the present observations, prediabetic participants in that study whether identified by HbA1c alone or in combination with FPG had comparable cardiometabolic risk profiles.

Impaired renal function

For patients with abnormal glucose metabolism, guideline recommendations suggest screening for CKD only in individuals with diabetes. Analyses from the National Health and Nutrition Evaluation Survey (NHANES) 1999–2006 dataset revealed 17% prevalence of CKD after adjustment for age, sex and race/ethnicity among participants with prediabetes, representing an adjusted prevalence 45% higher than observed in participants with normal glucose metrics.[32] To the contrary, analyses of longitudinal data from the Framingham study found no increase in the incidence of CKD associated with prediabetes after adjustment for age, sex, BMI and conventional cardiovascular risk factors, suggesting that the crude association is accounted for by differences in patient characteristics, commensurate with observations in this study.[33]

Study strengths and limitations

The strengths of this study include the population-based sampling comprising the cohort which enhances generalisability, over-sampling of African Americans to augment analyses across a diverse race/ethnicity cohort, the granular phenotyping for subclinical micro- and macro-vascular disease intermediates and the measurement of HbA1c in a national reference laboratory. Limitations include the cross-sectional nature of the study with no ability to replicate the glycometabolic measures, lack of data from glucose tolerance testing and lack of longitudinal follow-up data to analyse incidence of diabetes and progression to clinically relevant renal and CVD.

Conclusion

We found no independent association between prediabetes diagnosed by HbA1c and/or FPG and subclinical atherosclerosis or impaired renal function. Therefore, prediabetes per se, without the presence of other cardiovascular risk modifiers, may not signify elevated atherosclerotic or renal risk in an otherwise healthy population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

This work was supported by the National Center for Advancing Translational Sciences/National Institutes of Health and UT-STAR (UL1TR000451); US Public Health Service General Clinical Research Center (M01-RR00633) and National Institutes of Health (UL1DE019584, PL1DK081182). Grant support for the Dallas Heart Study was provided by the Donald W. Reynolds Foundation. This work was further supported by a grant from the Doris Duke Charitable Foundation to the University of Texas Southwestern Medical Center to fund Frank YF Xing, Clinical Research Fellow.

References

1. Colagiuri S, Lee CM, Wong TY, et al. Glycemic thresholds for diabetes-specific retinopathy: implications for diagnostic criteria for diabetes. Diabetes Care. 2011; 34:145–150. [PubMed: 20978099]
2. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2003; 26(Suppl. 1):S5–S20. [PubMed: 12502614]
3. Kim SH, Chunawala L, Linde R, et al. Comparison of the 1997 and 2003 American Diabetes Association classification of impaired fasting glucose: impact on prevalence of impaired fasting glucose, coronary heart disease risk factors, and coronary heart disease in a community-based medical practice. J Am Coll Cardiol. 2006; 48:293–297. [PubMed: 16843178]
4. Coutinho M, Gerstein HC, Wang Y, et al. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care. 1999; 22:233–240. [PubMed: 10333939]
5. Barr EL, Boyko EJ, Zimmet PZ, et al. Continuous relationships between non-diabetic hyperglycaemia and both cardiovascular disease and all-cause mortality: the Australian Diabetes, Obesity, and Lifestyle (AusDiab) study. Diabetologia. 2009; 52:415–424. [PubMed: 19130039]
6. Cederberg H, Saukkonen T, Laakso M, et al. Postchallenge glucose, A1C, and fasting glucose as predictors of type 2 diabetes and cardiovascular disease: a 10-year prospective cohort study. Diabetes Care. 2010; 33:2077–2083. [PubMed: 20573752]
7. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. J Am Coll Cardiol. 2010; 55:1310–1317. [PubMed: 20338491]
8. Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care. 2003; 26:3160–3167. [PubMed: 14578255]
9. Hoogwerf BJ, Sprecher DL, Pearce GL, et al. Blood glucose concentrations < or = 125 mg/dl and coronary heart disease risk. Am J Cardiol. 2002; 89:596–599. [PubMed: 11867048]
10. Marini MA, Succurro E, Castaldo E, et al. Cardiometabolic risk profiles and carotid atherosclerosis in individuals with prediabetes identified by fasting glucose, postchallenge glucose, and hemoglobin A1c criteria. Diabetes Care. 2012; 35:1144–1149. [PubMed: 22399698]
11. Victor RG, Haley RW, Willett DL, et al. The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health. Am J Cardiol. 2004; 93:1473–1480. [PubMed: 15194016]
12. Neeland IJ, Turer AT, Ayers CR, et al. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. JAMA. 2012; 308:1150–1159. [PubMed: 22990274]
13. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604–612. [PubMed: 19414839]
14. Kramer H, Toto R, Peshock R, et al. Association between chronic kidney disease and coronary artery calcification: the Dallas Heart Study. J Am Soc Nephrol. 2005; 16:507–513. [PubMed: 15601745]
15. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002; 156:871–881. [PubMed: 12397006]
16. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990; 15:827–832. [PubMed: 2407762]
17. Jain T, Peshock R, McGuire DK, et al. African Americans and Caucasians have a similar prevalence of coronary calcium in the Dallas Heart Study. J Am Coll Cardiol. 2004; 44:1011–1017. [PubMed: 15337212]

18. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106:3143–3421. [PubMed: 12485966]
19. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39:S1–S266. [PubMed: 11904577]
20. Toto RD. Microalbuminuria: definition, detection, and clinical significance. J Clin Hypertens (Greenwich). 2004; 6:2–7. [PubMed: 15538104]
21. LaValley MP. Logistic regression. Circulation. 2008; 117:2395–2399. [PubMed: 18458181]
22. Slinker BK, Glantz SA. Multiple linear regression: accounting for multiple simultaneous determinants of a continuous dependent variable. Circulation. 2008; 117:1732–1737. [PubMed: 18378626]
23. Tsugawa Y, Mukamal KJ, Davis RB, et al. Should the hemoglobin A(1c) diagnostic cutoff differ between blacks and whites? A cross-sectional study Ann Intern Med. 2012; 157:153–159. [PubMed: 22868832]
24. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988–2006. Diabetes Care. 2010; 33:562–568. [PubMed: 20067953]
25. Saaddine JB, Fagot-Campagna A, Rolka D, et al. Distribution of HbA(1c) levels for children and young adults in the U.S.: Third National Health and Nutrition Examination Survey. Diabetes Care. 2002; 25:1326–1330. [PubMed: 12145229]
26. Moebus S, Stang A, Mohlenkamp S, et al. Association of impaired fasting glucose and coronary artery calcification as a marker of subclinical atherosclerosis in a population-based cohort – results of the Heinz Nixdorf Recall Study. Diabetologia. 2009; 52:81–89. [PubMed: 18979083]
27. Lim S, Choi SH, Choi EK, et al. Comprehensive evaluation of coronary arteries by multidetector-row cardiac computed tomography according to the glucose level of asymptomatic individuals. Atherosclerosis. 2009; 205:156–162. [PubMed: 19095235]
28. Loria CM, Liu K, Lewis CE, et al. Early adult risk factor levels and subsequent coronary artery calcification: the CARDIA Study. J Am Coll Cardiol. 2007; 49:2013–2020. [PubMed: 17512357]
29. Rutter MK, Massaro JM, Hoffmann U, et al. Fasting glucose, obesity, and coronary artery calcification in community-based people without diabetes. Diabetes Care. 2012; 35:1944–1950. [PubMed: 22773705]
30. Davis PH, Dawson JD, Riley WA, et al. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: the Muscatine Study. Circulation. 2001; 104:2815–2819. [PubMed: 11733400]
31. Chambless LE, Folsom AR, Clegg LX, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol. 2000; 151:478–487. [PubMed: 10707916]
32. Plantinga LC, Crews DC, Coresh J, et al. Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. Clin J Am Soc Nephrol. 2010; 5:673–682. [PubMed: 20338960]
33. Fox CS, Larson MG, Leip EP, et al. Glycemic status and development of kidney disease: the Framingham Heart Study. Diabetes Care. 2005; 28:2436–2440. [PubMed: 16186276]

Diab Vasc Dis Res. Author manuscript; available in PMC 2017 December 13.

Table 1

Baseline characteristics.

	Normal − FPG < 100 mg/dL, A1c < 5.7% (*n* = 1585)	**Pre-DM overall (*n* = 755)**	**IFG-only − 100 < FPG < 125 mg/dL, A1c < 5.7% (*n* = 329)**	**HbA1c-only − FPG < 100 mg/dL, 5.7% < A1c < 6.5% (*n* = 222)**	**Both − 100 < FPG < 125 mg/dL, 5.7% < A1c < 6.5% (*n* = 204)**	**Pre-DM versus normal**	**IFG versus HbA1c versus both**
Age (years)	47 (39, 55)	52 (44, 60)	53 (45, 60)	51 (43, 59)	53 (45, 61)	<0.0001	0.06
Men (%)	37	47	52	42	44	<0.0001	0.21
Race/ethnicity (%)							
African American	47	53	33	74	61	0.002	<0.001
Caucasian	38	28	46	13	19	<0.0001	<0.001
Hispanic	14	16	19	10	17	0.15	0.01
Other	2	2	2	2	3	0.28	<0.001
BMI (kg/m^2)	28 (25, 33)	31 (27, 37)	29 (26, 34)	32 (27, 38)	34 (30, 39)	<0.0001	<0.001
Waist circumference (cm)	91 (83, 102)	99 (89, 109)	95 (88, 105)	99 (88, 111)	104 (94, 114)	<0.0001	<0.001
Smoking (%)	24	23	20	30	20	0.04	0.004
FamHx heart disease (%)	32	35	31	41	35	<0.0001	0.40
Framingham 10-year CHD risk (%)	1 (0, 4)	3 (1, 8)	4 (1, 8)	2 (1, 6)	4 (1, 8)	<0.0001	0.03
Systolic BP (mm Hg)	126 (115, 138)	133 (121, 146)	131 (119, 146)	133 (122, 146)	133 (123, 147)	<0.0001	0.24
Diastolic BP (mm Hg)	80 (74, 86)	81 (75, 88)	80 (75, 87)	83 (77, 90)	82 (76, 88)	<0.0001	0.04
Total cholesterol (mg/dL)	190 (166, 216)	193 (170, 220)	194 (172, 223)	190 (169, 217)	193 (167, 219)	0.03	0.31
HDL-C (mg/dL)	52 (44, 62)	48 (41, 57)	49 (41, 60)	49 (42, 57)	46 (41, 55)	<0.0001	0.03
LDL-C (mg/dL)	114 (93, 137)	116 (95, 143)	117 (95, 141)	114 (99, 144)	117 (92, 145)	0.02	0.93
TG (mg/dL)	93 (68, 132)	112 (80, 159)	114 (82, 156)	99 (74, 143)	127 (87, 174)	<0.0001	0.002
HbA1c (%)	5.3 (5.1, 5.5)	5.8 (5.5, 6)	5.4 (5.2, 5.6)	5.9 (5.8, 6)	6 (5.9, 6.1)	<0.0001	<0.001
Fasting glucose (mg/dL)	89 (84, 94)	102 (96, 107)	103 (101, 107)	91 (86, 95)	106 (103, 112)	<0.0001	<0.001

Continuous variables are presented as medians with interquartile ranges. Categorical variables are presented as percent prevalence. Kruskal–Wallis test for continuous variables and Pearson's chi-square test for categorical variables.

FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; Pre-DM: prediabetes; IFG: impaired fasting glucose; BMI: body mass index; CHD: coronary heart disease; BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride.

Table 2

Outcome measurements.

	Normal – FPG < 100 mg/dL, A1c < 5.7% (*n* = 1585)	**Pre-DM overall (*n* = 755)**	**IFG only − 100 < FPG < 125 mg/dL, A1c < 5.7% (*n* = 329)**	**HbA1c only – FPG < 100 mg/dL, 5.7% < A1c < 6.5% (*n* = 222)**	**Both − 100 < FPG < 125 mg/dL, 5.7% < A1c < 6.5% (*n* = 204)**	**Pre-DM versus normal**	**IFG versus HbA1c versus both**
CAC (AU > 10) (%)	21.8	33.1	33.1	31.5	34.8	<0.0001	0.77
Mean common carotid thickness (mm)	1.27 (1.16, 1.38)	1.32 (1.18, 1.42)	1.32 (1.18, 1.44)	1.32 (1.17, 1.40)	1.32 (1.18, 1.40)	0.001	0.76
CKD-EPI eGFR < 60, *n* (%)	57 (4)	58 (8)	20 (6)	15 (7)	23 (11)	<0.0001	0.075
CKD-EPI eGFR, median (IQR)	97.21 (82.17, 111.49)	90.67 (76.19, 104.50)	89.95 (76.31, 101.58)	93.34 (78.75, 111.6)	89.58 (73.97, 102.47)	<0.0001	0.004
UACR > 30, *n* (%)	50 (3)	41 (5)	14 (4)	13 (6)	14 (7)	0.008	0.411
CKD ≥ 2, *n* (%)	134 (9)	94 (13)	34 (10)	26 (12)	34 (17)	<0.0001	0.091

Continuous variables are presented as medians with interquartile ranges. Categorical variables are presented as percent prevalence. Kruskal–Wallis test for continuous variables and Pearson's chi-square test for categorical variables.

FPG: fasting plasma glucose; Pre-DM: prediabetes; IFG: impaired fasting glucose; HbA1c: haemoglobin A1c; CAC: coronary artery calcium; AU: Agatston units; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio; CKD: chronic kidney disease.

Table 3

Overall unadjusted and fully adjusted outcome measurements.

	CAC > 10	UACR > 30	eGFR ≤ 60 (mL/min)	CKD ≥ 2	Mean carotid wall thickness
	OR (95% CI)				Beta (SE)
Unadjusted					
Pre-DM	1.8 (1.5–2.2)	1.4 (0.9–2.2)	1.8 (1.3–2.6)	1.9 (1.5–2.6)	0.038 (0.011)
IFG	1.8 (1.4–2.3)	1.5 (0.8–2.7)	1.6 (1.0–2.6)	1.8 (1.2–2.7)	0.038 (0.015)
A1c	1.6 (1.2–2.2)	1.4 (0.8–2.5)	1.4 (0.8–2.5)	1.6 (1.1–2.5)	0.03 (0.019)
Both	1.9 (1.4–2.6)	1.3 (0.7–2.5)	2.7 (1.6–4.3)	2.4 (1.6–3.6)	0.049 (0.02)
Adjusted					
Pre-DM	1 (0.8–1.3)	1.8 (1.2–2.7)	1.2 (0.8–1.8)	1.4 (1.0–1.9)	0.002 (0.012)
IFG	0.95 (0.7–1.3)	1.6 (0.9–2.8)	1.1 (0.6–1.8)	1.5 (1.0–2.3)	0.013 (0.015)
A1c	1.03 (0.7–1.5)	1.8 (1.0–3.2)	0.9 (0.5–1.8)	1.3 (0.8–2.1)	−0.01 (0.019)
Both	1.04 (0.7–1.5)	2.1 (1.2–3.7)	1.7 (1.0–3.0)	1.6 (1.0–2.6)	−0.007 (0.021)

Adjusted ORs with 95% CIs for prevalent CAC (Agatston score > 10), eGFR < 60, UACR > 30, CKD ≥ 2 and beta-estimates with SE for mean common carotid thickness across prediabetes diagnostic modalities compared against the normal glucose group, adjusted for age, sex, race/ethnicity, BMI, smoking status, hypertension, LDL cholesterol and total cholesterol.

CAC: coronary artery calcium; UACR: urine albumin-to-creatinine ratio; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; OR: odds ratio; CI: confidence interval; SE: standard error; Pre-DM: prediabetes; IFG: impaired fasting glucose.