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Incident Type 2 Diabetes Among Individuals With CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study

Christopher Jepson, PhD^{a,b}, Jesse Y. Hsu, PhD^{a,b}, Michael J. Fischer, MD^{c,d}, John W. Kusek, PhD^e, James P. Lash, MD^c, Ana C. Ricardo, MD^c, Jeffrey R. Schelling, MD^f, Harold I. Feldman, MD, MSCE^{a,b}, and on behalf of the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators*

^aDepartment of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

^bCenter for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA, USA

^cDepartment of Medicine, University of Illinois College of Medicine, Chicago, USA

^dCenter of Innovation for Complex Chronic Healthcare, Edward Hines Jr. VA Hospital, Hines, IL and Jesse Brown VAMC, Chicago, IL

^eDivision of Kidney, Urologic and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

^fDivision of Nephrology and Hypertension, Case Western Reserve University, Cleveland, Ohio, USA

Abstract

Rationale & Objective: Few studies have examined incident type 2 diabetes mellitus (T2DM) in chronic kidney disease (CKD). Our objective was to examine rates of and risk factors for T2DM in CKD, using several alternative measures of glycemic control.

Study Design: Prospective cohort study.

Setting & Participants: 1,713 participants with reduced glomerular filtration rate and without diabetes at baseline, enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study.

Corresponding Author: Christopher Jepson, PhD, Senior Research Investigator, Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, 821 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104, 215-746-4274 (phone), 215-573-2265 (fax) cjepson@pennmedicine.upenn.edu.
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Predictors: Measures of kidney function and damage, fasting blood sugar (FBS), hemoglobin A1c (HbA1c), insulin resistance (HOMA-IR), demographics, family history of DM, smoking status, medication use, systolic blood pressure, triglycerides, high-density lipoprotein, body mass index, and physical activity.

Outcome: Incident T2DM (defined as FBS ≥ 126 or prescription of insulin or oral hypoglycemic agents).

Analytical Approach: Concordance between FBS and HbA1c was assessed using kappa. Cause-specific hazards modeling, treating death and ESRD as competing events, was used to predict incident T2DM.

Results: Overall T2DM incidence rate was 17.81 cases per 1000 person-years. Concordance between FBS and HbA1c was low (kappa for categorical versions of FBS and HbA1c = 0.13). Unadjusted associations of measures of kidney function and damage with incident T2DM were non-significant ($P = 0.4$). In multivariable models, T2DM was significantly associated with FBS ($P = 0.002$) and family history of DM ($P = 0.03$). The adjusted association of HOMA-IR with T2DM was comparable to that of FBS; the association of HbA1c was non-significant ($P = 0.1$). Harrell's C for the models ranged from 0.62 to 0.68.

Limitations: Limited number of outcome events; predictors limited to measures taken at baseline.

Conclusions: The T2DM incidence rate among individuals with CKD is markedly higher than in the general population, supporting the need for greater vigilance in this population. Measures of glycemic control and family history of DM were independently associated with incident T2DM.

Keywords

Diabetes; type 2 diabetes mellitus (T2DM); glycemic control; chronic kidney insufficiency; chronic kidney disease (CKD); kidney function; renal damage; fasting blood sugar (FBS); hemoglobin A1c (HbA1c); insulin resistance (HOMA-IR); prediabetes

Introduction

Patients with chronic kidney disease (CKD) and type 2 diabetes mellitus (T2DM) share common risk factors,^{1,2} suggesting that CKD may increase risk for T2DM. Few studies have been conducted in patients with CKD prior to end-stage renal disease (ESRD) to determine whether the risk for incident T2DM is increased. In the clinical trial and cohort phases of the African American Study of Kidney Disease and Hypertension (AASK), an incidence rate for T2DM of 38 cases per 1000 person-years was observed in African Americans with presumed hypertension-attributable CKD.³ This rate significantly exceeds the rates observed in most cohort studies in the general population, which typically range from 4 to 14 cases per 1000 person-years.⁴⁻⁹

A number of models predicting T2DM risk in the general population have been developed.¹⁰⁻¹³ These models typically include a number of well-established risk factors that are obtained either in the course of a normal clinical visit or by standard blood tests. Models of T2DM risk incorporating measures of kidney function and damage have not been developed

for persons with CKD prior to ESRD. In addition, the issue of which measure of glycemic control – fasting blood sugar (FBS), hemoglobin A1c (HbA1c), or insulin resistance -- is best to use both to define and to predict T2DM has not been addressed extensively in the setting of CKD.

We examined the rates of new cases of (incident) T2DM among persons with CKD enrolled in a long-term, observational cohort study. Our goals were: (a) to estimate the unadjusted incidence of T2DM; (b) to examine the concordance among several measures of glycemic control; (c) to identify factors associated with incident T2DM; and (d) to examine the predictive performance of multivariable models of incident T2DM, including measures of kidney function and damage in addition to established T2DM risk factors, and using various measures of glycemic control.

Methods

Study Design

The Chronic Renal Insufficiency Cohort (CRIC) Study is an ongoing, multicenter observational cohort study of individuals with CKD. Details of the rationale and design, and baseline characteristics of participants, have been described previously.^{14,15} All participants provided written informed consent for participation. The CRIC Study was approved by the institutional review boards at all clinical centers (see Table S1 for approval numbers). The first cohort of 3,939 participants was recruited from July 2003 to September 2008. Primary eligibility criteria were age (21–74 years) and age-based estimated glomerular filtration rate (eGFR) (range 20 to 70 ml/min/1.73m²).

Approximately one-half of the participants had diabetes at baseline and were excluded from the current analysis. After an initial eligibility screening visit, participants completed a baseline clinic visit; follow-up consisted of annual clinic visits and annual telephone calls halfway between each clinic visit.

Measurements

Glycemic control.—Blood glucose (in mg/dL) was measured in blood obtained at the screening visit (non-fasting), at the baseline visit (fasting), and at each annual clinic visit (fasting) thereafter. At baseline only, blood levels of HbA1c, as % of total hemoglobin, were measured, in addition to Homeostatic Model Assessment insulin resistance (HOMA-IR),¹⁶ calculated as [glucose (in mg/dL) × insulin (in μU/mL)] / 405.

Diabetes status at baseline.—Participants were categorized as having diabetes at baseline and excluded from the analyses if they either: (a) were prescribed insulin or an oral hypoglycemic medication at baseline; (b) had a FBS level ≥ 126 mg/dL, or a nonfasting level ≥ 200, at either screening or baseline; or (c) had a blood HbA1c level ≥ 6.5% at baseline.

Pre-diabetes status at baseline.—Participants with a baseline FBS between 100 and 125 mg/dL were categorized as having pre-diabetes, reflecting American Diabetes Association (ADA) criteria.¹⁷

Incident T2DM during follow-up.—At each follow-up point, participants were categorized as having diabetes if they either were: (a) taking insulin or oral hypoglycemic agents, or (b) had a FBS level ≥ 126 (clinic visits only).

Incident ESRD during follow-up.—Self-reported date of initiation of renal replacement therapy was used as the date of ESRD, supplemented by information obtained from queries implemented through the United States Renal Data System.

Measures of kidney function at baseline.—Participants' eGFR at baseline was estimated using an equation derived from CRIC Study data.¹⁸ Urinary albumin-creatinine ratio (UACR) was also measured from a 24-hour urine sample at baseline.

Other characteristics at baseline.—Other measures used in the analyses included: (a) Demographics (age, gender, race); (b) self-reported history of diabetes in parents or siblings; (c) smoking status; (d) use of blood pressure medications (ACE inhibitors/ARBs, diuretics, other) and lipid-lowering medications (statins, other); (e) systolic blood pressure (SBP) (in mmHg); (f) triglycerides (in mg/dL); (g) high-density lipoprotein (HDL) (in mg/dL); (h) body mass index (BMI) (in kg/m²); and (i) self-reported physical activity, assessed using the Typical Week Physical Activity Survey (TWPAS).¹⁹ The measure used was the total MET score, which is the sum of self-reported number of hours/week spent in each of 27 activities, weighted by each activity's MET value (1 MET = energy expenditure at rest).

Statistical analysis

Descriptive statistics were calculated for all variables. Unadjusted T2DM incidence rates were calculated in the overall sample of participants without diabetes at baseline and within deciles of baseline FBS, HOMA-IR, and HbA1c. Cumulative incidence functions for T2DM were obtained separately among participants who were normoglycemic (baseline FBS < 100) and participants with pre-diabetes; Gray's test was used to compare incidence in the two groups.

Concordance among baseline measures of glycemic control was examined using simple kappa for cross-tabulations of glycemic control status (normoglycemia vs. prediabetes).

Risk of incident T2DM was modeled using cause-specific hazards models, treating competing events as censoring. All models were performed on the subset of participants who were normoglycemic at baseline, to avoid including individuals who either had undiagnosed T2DM or were at a point where T2DM was imminent. First, unadjusted models were performed, each using one of five baseline indicators of glycemic control (FBS, HOMA-IR, and HbA1c) and renal function (eGFR and UACR). A multivariable cause-specific model was then performed, including baseline FBS (continuous) plus other baseline predictors widely employed in diabetes risk assessment tools developed in the general population: SBP, triglycerides, HDL, age, BMI, physical activity, and eGFR (all continuous); gender; race (Black vs. other); family history of diabetes (yes vs. no/don't know); smoking status (current smoker vs. other); and use of ACE inhibitors/ARBs, diuretics, other BP medications, statins, and other lipid-lowering medications. Hispanic ethnicity was not included as a predictor because the analysis sample contained few Hispanic participants, and among those, there

was almost no outcome variance (4 events total); Hispanic participants were included according to self-identified racial category. For all time-to-event analyses, follow-up ended at the earliest of the following events: (a) incident T2DM; (b) ESRD; (c) loss to follow-up (including death); (d) cut-off date (mid 2014). Thus, participants developing T2DM post-ESRD or post-study cut-off were not counted as incident cases. Death and ESRD were competing events.

We performed several repetitions of the original model to compare the adjusted effects of different indicators of glycemic control, using HOMA-IR and HbA1c either instead of, or in addition to, FBS.

Finally, we used Harrell's C statistic to compare the overall predictive performance of the various models described above (except those including eGFR and UACR), plus a model including all the predictors in the original model except FBS.

For the purposes of the cause-specific models, a transformation (square root or natural logarithm) was applied to all continuous predictor variables with skewness > 1.0, and all continuous variables were standardized so that the hazard ratios derived from the models would refer to an increase of one standard deviation on the variable in question. Research site was included in the models as a latent random effect (frailty models).

Some of the analyses described above were repeated with certain variations as sensitivity analyses. Unadjusted incidence rates, cumulative incidence functions, and cause-specific hazards models were repeated without censoring at ESRD. The multivariable models were also repeated using backwards selection (P -to-retain = 0.05). Finally, the multivariable models were repeated stratifying by baseline eGFR (< 45 vs. ≥ 45 ml/min/1.73m²); in addition, each model was repeated including terms representing the interaction of dichotomized eGFR with each measure of glycemic control included in the model.

Results

Study participants

Among the 3939 participants recruited, 2064 were categorized as having diabetes at baseline. Of the remaining 1875 participants, 1713 (91.4%) had complete data on all variables included in the final multivariable models. These 1713 participants and the 162 with partial data were compared on baseline characteristics and unadjusted risk of incident T2DM. The two groups did not differ significantly on sex, family history of diabetes, use of blood pressure or lipid-lowering medications, BMI, triglycerides, age, eGFR, UACR, HOMA-IR, or HbA1c, and did not differ in unadjusted risk of incident T2DM ($P = 0.9$); the full set of comparisons is presented in Table S2. The 1713 participants with full data were used as the analysis sample.

Among these 1713 participants, 1402 (81.8%) were categorized as normoglycemic, and 311 (18.2%) as pre-diabetic, at baseline. Baseline characteristics of participants are given in Table 1.

Crude rates of incident T2DM

In the overall sample of 1713 participants, 203 (11.85%) developed incident T2DM during a mean of 6.65 years of follow-up (median = 7.69 years), over a total of 11,399 person-years. The overall unadjusted incidence rate of incident T2DM was 17.81 cases per 1000 person-years. (With individuals who developed T2DM after onset of ESRD included as cases, the rate was 18.95 per 1000 person-years.) Among participants with baseline FBS levels below 100, the rate was 12.17 (116 events over 9530 person-years); among those with levels between 100 and 125, it was 46.55 (87 events over 1869 person-years).

Figure 1 shows the unadjusted rates of incident T2DM by deciles of baseline FBS, HbA1c, and HOMA-IR. The overall pattern was similar across the three measures, showing a gradual increase over the first nine deciles (with some fluctuations due to small numbers of events in some deciles), and very high rates in the top decile, particularly in the top decile of FBS (105–124 mg/dL), which corresponds roughly to the category of participants with pre-diabetes (≥ 100 mg/dL). Figure 2 shows the cumulative incidence functions for T2DM; the unadjusted rate of T2DM was greater among participants with baseline FBS ≥ 100 compared to those with values <100 (Gray's test $\chi^2 = 98.0$, $P < 0.001$). As shown in Figures S1 and S2, the results were very similar when not censoring at ESRD.

Concordance among baseline measures of glycemic control

Using the ADA definitions of pre-diabetes (HbA1c 5.7–6.4%, FBS 100–125 mg/dL),¹⁷ a higher percentage of the sample was classified as having pre-diabetes at baseline by a single measurement of HbA1c (47.3%) than by a single FBS measurement (18.2%), as shown in Table 2. The simple kappa coefficient for these two measures was 0.13. HOMA-IR was not included in the analysis of concordance, as no standard criteria for pre-diabetes and diabetes have been established for this measure.

Among the 1402 participants classified as normoglycemic at baseline by FBS, those classified as having pre-diabetes by HbA1c (609, or 43.4%) scored significantly lower than those classified as normoglycemic by HbA1c on measures of baseline glycemic control (FBS and HOMA-IR), and significantly higher on numerous baseline measures of T2DM risk factors; they also had significantly ($P = 0.05$) greater unadjusted risk of incident T2DM. However, when the indicator of baseline glycemic control status based on HbA1c was added to a cause-specific hazards model of incident T2DM including only baseline FBS, neither its main effect nor its interaction with FBS were significant; the same was true for models including the full set of predictors. Accordingly, the two groups were not analyzed separately; however, as described in Methods, certain multivariable models did include both FBS and HbA1c as predictors.

Associations of T2DM with indicators of glycemic control and kidney function and damage

As shown in the upper portion of Table 3, for each of three indicators of glycemic control (FBS, HOMA-IR, and HbA1c), higher values were significantly ($P < 0.01$) associated with higher unadjusted rates of incident T2DM. Neither of the two indicators of kidney function and damage (eGFR and UACR) were significantly associated with incident T2DM ($P = 0.8$ and 0.4 respectively).

Table 4 shows the results for the multivariable cause-specific hazards model containing baseline FBS and other accepted T2DM risk factors. Even though the analysis was restricted to normoglycemic participants, FBS was the predictor with the most significant contribution to the model; the hazard ratio associated with a 1-sd increase in FBS was 1.407 (95% CI, 1.135–1.744; $Z = 3.12$, $P = 0.002$). Family history of DM was the only other predictor that contributed significantly (HR, 1.50; 95% CI, 1.033–2.172; $Z = 2.13$, $P = 0.03$).

To compare the adjusted effects of different indicators of glycemic control, we repeated the model shown in Table 4 five times, with HOMA-IR and HbA1c used either instead of, or in addition to, FBS, as described in Methods. As shown in the lower portion of Table 3, the adjusted associations of FBS and HOMA-IR with T2DM risk were comparable, while the association of HbA1c was not significant ($P = 0.1$). Moreover, the associations of FBS and HOMA-IR with T2DM each remained significant when both were included in the model, whereas the association of HbA1c did not attain significance ($P = 0.3$).

Predictive performance of models

We compared the predictive performance of the models described above, plus a model including all the predictors in the original model except FBS. As shown in Table 3, the addition of a single indicator of glycemic control (FBS, HOMA-IR, or HbA1c) to the other predictors increased predictive performance slightly (Harrell's $C = 0.652$, 0.656 , and 0.625 respectively). The addition of either HOMA-IR, HbA1c, or both to a model including the other predictors plus FBS yielded another slight increase in predictive performance (Harrell's $C = 0.672$, 0.657 , and 0.675 respectively).

Sensitivity analyses

The cause-specific hazards models shown in Tables 3 and 4 were repeated without censoring at ESRD; the results were very similar (Tables S3 and S4). When the multivariable models were repeated using backwards selection (Tables S5 and S6), measures of glycemic control and family history of T2DM remained in most models; in addition, race became significant in some models but not others, medication use variables became significant in the models not including any measure of glycemic control, and HDL became significant in several models not censored at ESRD. When the multivariable models were repeated separately among participants with $eGFR < 45$ vs. ≥ 45 ml/min/1.73m², some differences in the risk profiles appeared (Tables S6,S7,S8,S9,S10); however, the differences did not necessarily have plausible mechanistic explanations. Also, when the differences across eGFR strata in the effects of measures of glycemic control were tested formally using interaction terms, the only term that reached significance was the interaction of eGFR by HbA1c, and only in the models censored at ESRD (Table S11).

Discussion

Our unadjusted rate of incident T2DM, while lower than the rate reported in the AASK study,³ is substantially higher than rates commonly reported in the general population.^{4–9} For example, in the Tromsø Study (Norway), incidence rates (age-adjusted) per 1000 person-years were 2.6 for men and 1.6 for women;⁹ in the QDScore study (England and

Wales), the rate was 4.8;²⁰ and in the ARIC study (U.S.), which was restricted to individuals aged 45–64 and included individuals with pre-diabetes, the rate was approximately 12.7.²¹ The high rates seen in the current study and in the AASK study (which was restricted to patients with both CKD and hypertension) are not surprising, as hypertension, CKD, and diabetes share common risk factors. The relatively low level of concordance among the measures of baseline glycemic control, consistent with other studies in high-risk²² and patient (post-MI)²³ populations, raises questions about the best measure to use to characterize glycemic control status in persons with CKD. In the setting of CKD, numerous confounders may affect the legitimacy of the HbA1c assay²⁴ and HOMA-IR.²⁵ Identification of the best glycemic marker in CKD is a goal for future research.

Our measure of kidney function, eGFR, was not significantly associated with incident T2DM in our cohort, which is at odds with the high rates of reduced kidney function observed among persons with T2DM.²⁶ Some aspects of CKD may actually protect against T2DM, while others increase risk of T2DM. Specifically, CKD is associated with lower levels of gluconeogenesis, and to a lesser extent glycogenolysis, as well as a longer insulin half-life, all of which would have a tendency to lower FBS;²⁷ however, insulin resistance, a contributing factor to T2DM, is also a common alteration in CKD.²⁵

The significant association between family history of DM and incident T2DM is consistent with a well-established body of literature.^{28,29} However, it should be noted that a significant association does not necessarily imply predictive utility, which seems to be the case here (Harrell's C for the multivariable model including FBS did not change when family history was excluded), suggesting that knowledge of family history of DM is of limited incremental value in making clinical decisions related to prevention of T2DM among individuals with CKD.

The lack of significant associations of other risk factors in the multivariable models is at odds with the literature on T2DM risk tools developed in the general population, in which numerous risk factors, such as age, hypertension, smoking, and BMI typically display significant adjusted associations with T2DM risk.^{4,9,30,31} The effects of these factors may be mediated by measures of glycemic control. However, even with no measure of glycemic control included, the only factor that was significant was family history of DM.

Given the fact that the outcome measure was based on FBS, it is perhaps not surprising that baseline FBS proved to be a better predictor of outcome than did baseline HbA1c. The fact that baseline HbA1c level did not contribute significantly to any of the multivariable models of T2DM risk, however, is somewhat surprising.

The results provide clear evidence that, in a CKD population, measures of glycemic control (FBS and/or HOMA-IR) are of moderate predictive value for risk of incident T2DM, even among individuals classified as normoglycemic by FBS. This is consistent with other findings from the general population indicating that there is no clear threshold value of FBS at which risk of morbidity and mortality increases sharply.^{32,33}

The models developed here had lower predictive performance than similar models developed in non-CKD populations. Abbasi et al.,¹³ using data from the EPIC-NL cohort (N = 40,011),

performed an external validation study of 25 prediction models developed in 16 studies. Harrell's C for these models ranged from 0.71 to 0.92 in the original studies, and from 0.74 to 0.93 in the validation analyses.

The reason for the poorer predictive performance of our models is not clear. The models reviewed by Abbasi et al. do not seem to include any highly important predictors omitted by our models, other than waist circumference (included in 11 models), which had a correlation of approximately .85 with BMI in our sample. In addition, many of the models did not include FBS or a number of other predictors included in our models. The median follow-up time in our study also does not appear greatly different than that in the original studies or verification study, and the incidence rates reported in those studies are uniformly lower than the rate in the CRIC sample.

One potential reason for the discrepancy in performance is the fact that the analysis was restricted to individuals with CKD, thus excluding younger and healthier individuals. In addition, individuals with pre-diabetes were excluded; in effect, we may have been trying to predict incident T2DM within a substantially truncated range of T2DM risk. Also, the individuals in our sample with advanced stage CKD may represent a subpopulation with unidentified factors protecting against T2DM. Furthermore, CKD itself involves metabolic dysfunction that may impact the usual mechanisms of T2DM pathogenesis, suggesting that there may be other, non-traditional factors that might, if included, yield improved prediction in this specific population. Other potential reasons for the discrepancy in predictive performance relate to details of the study or of our analysis, including the relatively small number of cases and overall sample size, the use of ESRD as a censoring event, and dropout rates.

The limitations of this analysis include the relatively low number of events observed, which diminished the power of all analyses. Also, the predictors were limited to measures taken at baseline, thus excluding potentially informative changes over time. Similarly, HbA1c level was measured only at baseline, precluding its use in ascertainment of incident T2DM; among individuals not taking insulin or oral hypoglycemic agents, incident T2DM was defined entirely by a single FBS measurement, which may have resulted in some degree of misclassification. Use of FBS to define incident T2DM may also have inflated the association of baseline FBS with incident T2DM relative to other predictors. Finally, there may have been important risk factors that were not measured in the study.

In conclusion, the rate of incident T2DM among individuals with CKD is markedly higher than in the general population, supporting greater vigilance in this subpopulation. Concordance among measures of baseline glycemic control was low. In multivariable models of T2DM risk among individuals who were normoglycemic at baseline, measures of kidney function and damage were not associated with incident T2DM, and did not improve the capacity of the models to predict T2DM; baseline glycemic control and family history of DM were the only factors detected to be predictive of incident T2DM. These models displayed moderate predictive performance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Unadjusted incidence rates of type 2 diabetes mellitus (per 1000 person-years) by decile of baseline fasting blood sugar, hemoglobin A1c, and insulin resistance (HOMA-IR).

Figure 2.
Unadjusted cumulative incidence functions for new onset Type 2 diabetes mellitus among participants with baseline fasting glucose < 100 vs. 100.

Table 1.

Baseline characteristics of CRIC participants overall and separately among those with baseline fasting blood sugar <100 vs. 100–125 mg/dL

Characteristic	Overall (N = 1713)	By baseline fasting blood sugar	
		< 100 mg/dL (n = 1402)	100–125 mg/dL (n = 311)
Age, y Mean Median	56.2 (12.0) 59 (49–65)	55.4 (12.3) 58 (47–64)	59.8 (9.9) 61 (54–68)
Male sex	907 (52.9%)	717 (51.1%)	190 (61.1%)
Race-ethnicity category Non-Hispanic White Non-Hispanic Black Hispanic Other	883 (51.5%) 623 (36.4%) 136 (7.9%) 71 (4.1%)	734 (52.4%) 494 (35.2%) 112 (8.0%) 62 (4.4%)	149 (47.9%) 129 (41.5%) 24 (7.7%) 9 (2.9%)
Current smoker	226 (13.2%)	189 (13.5%)	37 (11.9%)
Diabetes in either parent or any sibling	653 (38.1%)	524 (37.4%)	129 (41.5%)
Systolic blood pressure, mm Hg Mean Median	123.0 (20.0) 120.7 (108.7–134.0)	122.4 (20.0) 120.0 (108.7–132.7)	125.7 (19.5) 122.7 (111.3–137.3)
Body mass index, kg/m ² Mean Median	30.1 (7.1) 29.2 (25.4–33.4)	29.6 (7.1) 28.6 (25.0–32.7)	32.5 (6.7) 31.7 (27.6–36.6)
Statins	683 (39.9%)	526 (37.5%)	157 (50.5%)
Lipid-lowering medications other than statins	148 (8.6%)	114 (8.1%)	34 (10.9%)
ACEi or ARB	986 (57.6%)	780 (55.6%)	206 (66.2%)
Diuretics	794 (46.4%)	602 (42.9%)	192 (61.7%)
BP medications other than ACEi/ARB or diuretic	1065 (62.2%)	832 (59.3%)	233 (74.9%)
Fasting blood glucose, mg/dL Mean Median	90.4 (10.6) 89 (83–96)	86.7 (7.4) 87 (82–92)	106.9 (6.4) 105 (102–110)
HOMA-IR, mg/dL x μ U/mL Mean Median	3.7 (3.2) 2.9 (2.0–4.4)	3.3 (2.7) 2.6 (1.9–3.8)	5.8 (4.2) 4.9 (3.4–7.0)
HbA1c, % Mean Median	5.6 (0.4) 5.6 (5.3–5.9)	5.6 (0.4) 5.6 (5.3–5.9)	5.8 (0.4) 5.8 (5.5–6.6)
Pre-diabetic by HbA1c	810 (47.3%)	609 (43.4%)	201 (64.6%)
eGFR ^a , ml/min/1.73m ² Mean Median	48.9 (18.1) 47.3 (34.8–60.4)	49.4 (18.5) 47.4 (34.6–61.3)	46.9 (16.0) 46.7 (35.8–56.7)
UACR, mg/g Mean Median	286.9 (823.7) 20.5 (5.8–187.9)	286.1 (775.6) 20.3 (5.9–193.1)	290.4 (1012.4) 23.0 (5.6–141.4)
HDL cholesterol, mg/dL Mean Median	50.4 (17.1) 47 (38–58)	51.0 (17.1) 48 (39–59)	47.7 (16.7) 45 (37–54)
Triglycerides, mg/dL Mean Median	143.6 (98.4) 120 (84–170)	138.9 (94.1) 116 (83–164)	164.6 (113.9) 139 (97–201)

Characteristic	Overall (N = 1713)	By baseline fasting blood sugar	
		< 100 mg/dL (n = 1402)	100–125 mg/dL (n = 311)
Physical activity ^b	218.6 (150.5)	221.4 (154.5)	206.4 (130.5)
Mean	182.3 (128.5–264.8)	184.2 (129.8–266.0)	175 (119.9–262.0)
Median			

Values for continuous variables given as mean (SD) or median (quartile 1-quartile 3);

values for categorical variables as count (%).

FBS = fasting blood sugar;

T2DM = Type 2 diabetes mellitus;

IQR = interquartile range;

ACEi = angiotensin-converting enzyme inhibitor;

ARB = angiotensin receptor blocker;

HOMA-IR = Homeostatic Model Assessment insulin resistance;

eGFR = estimated glomerular filtration rate;

HbA1c, hemoglobin A1C;

UACR, urinary albumin-creatinine ratio;

HDL, high-density lipoprotein.

^aEstimated using CRIC equation.

^bTotal MET sum from Typical Week Physical Activity Survey (TWPAS) instrument.

Table 2.

Concordance between baseline fasting glucose and hemoglobin A1c

Baseline Fasting blood glucose	Baseline Hemoglobin A1c		
	Normoglycemic (< 5.7%)	Pre-diabetic (5.7–6.4%)	Total
Normoglycemic (< 100 mg/dL)	793 (46.3%)	609 (35.6%)	1402 (81.8%)
Pre-diabetic (100–125 mg/dL)	110 (6.4%)	201 (11.7%)	311 (18.2%)
Total	903 (52.7%)	810 (47.3%)	1713 (100%)

All percentages are of the total N of 1713.

Table 3.

Unadjusted and adjusted associations of indicators of glycemic control with risk of new onset Type 2 diabetes mellitus (cause-specific hazards models), and predictive performance of models

Model	Statistics for measure(s) of baseline glycemic control included in model				Harrell's C
	Measure	Hazard ratio ^a	95% confidence interval	p	
Unadjusted models					
a)	FBS	1.505	1.224, 1.851	< 0.001	0.609
b)	HOMA-IR ^b	1.486	1.270, 1.740	< 0.001	0.624
c)	HbA1c	1.289	1.061, 1.567	0.01	0.570
Adjusted models ^c					
d)	None	--	--	--	0.620
e)	FBS	1.407	1.135, 1.744	0.002	0.652
f)	HOMA-IR ^b	1.442	1.208, 1.721	< 0.001	0.656
g)	HbA1c	1.183	0.966, 1.449	0.1	0.625
h)	FBS HOMA-IR ^b	1.284 1.364	1.030, 1.603 1.127, 1.650	0.03 0.001	0.672
i)	FBS HbA1c	1.385 1.144	1.117, 1.717 0.933, 1.403	0.003 0.2	0.657
j)	FBS HOMA-IR ^b HbA1c	1.268 1.355 1.124	1.016, 1.584 1.119, 1.642 0.915, 1.380	0.04 0.002 0.3	0.675

Note. Analyses restricted to participants with baseline fasting blood glucose < 100 and complete data on all variables.

FBS = fasting blood sugar.

HOMA-IR = Homeostatic Model Assessment insulin resistance.

HbA1c = hemoglobin A1c.

^aHazard ratio associated with increase of 1 standard deviation on predictor.

^bTo reduce skewness, a natural logarithm transformation was applied to this variable.

^cAdjusted models include: systolic blood pressure; use of ACE/ARB, diuretics, and other BP medication; body mass index; triglycerides; high-density lipoprotein; use of statins and other lipid-lowering medications; age in years; sex; race; smoking status; family history of DM; physical activity; and eGFR.

Table 4.

Multivariable cause-specific hazards model of risk of new onset diabetes mellitus

Predictor	Hazard ratio	Standard error	z	P > z	95% C.I.
Fasting blood sugar ^a	1.407	0.154	3.12	0.002	1.135, 1.744
Systolic blood pressure ^a	1.006	0.103	0.06	0.9	0.823, 1.230
ACEi/ARB use	1.000	0.201	-0.00	0.9	0.673, 1.484
Diuretic use	1.268	0.265	1.13	0.3	0.841, 1.910
Other BP medication use	1.108	0.244	0.47	0.6	0.719, 1.707
Body mass index ^{a,b}	1.044	0.113	0.40	0.7	0.845, 1.290
Triglycerides ^{a,b}	1.035	0.111	0.32	0.8	0.838, 1.277
High-density lipoprotein ^{a,c}	0.925	0.120	-0.60	0.6	0.717, 1.194
Statins use	1.008	0.207	0.04	0.9	0.674, 1.507
Other lipid-lowering medication use	1.577	0.453	1.59	0.1	0.899, 2.768
Age in years ^a	1.087	0.138	0.65	0.5	0.847, 1.395
Sex (female = 1)	0.870	0.194	-0.62	0.5	0.562, 1.347
Race (Black = 1)	1.420	0.309	1.61	0.1	0.927, 2.176
Smoking status (current smoker = 1)	1.334	0.369	1.04	0.3	0.775, 2.293
Family history of DM	1.498	0.284	2.13	0.03	1.033, 2.172
Physical activity ^{a,c,d}	1.093	0.105	0.93	0.4	0.906, 1.319
eGFR ^{a,e}	1.107	0.125	0.89	0.4	0.886, 1.382

Note. Analyses restricted to participants with baseline fasting blood glucose < 100 and complete data on all variables.

ACE = angiotensin-converting enzyme inhibitor.

ARB = angiotensin-renin blocker.

BP = blood pressure.

DM = diabetes mellitus.

eGFR = estimated glomerular filtration rate.

^a z-transformation was applied to these variables. Hazard ratios given reflect an increase of 1 standard deviation.

^b To reduce skewness, a natural logarithm transformation was applied to these variables prior to the z-transformation.

^c To reduce skewness, a square root transformation was applied to these variables prior to the z-transformation.

^d Total MET sum from Typical Week Physical Activity Survey (TWPAS) instrument.

^e Estimated using CRIC equation.