Non-Traditional Risk Factors are Important Contributors to the Racial Disparity in Diabetes Risk: The Atherosclerosis Risk in Communities Study

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BACKGROUND: Traditional risk factors, particularly obesity, do not completely explain the excess risk of diabetes among African Americans compared to whites.

OBJECTIVE: We sought to quantify the impact of recently identified, non-traditional risk factors on the racial disparity in diabetes risk.

DESIGN: Prospective cohort study.

PARTICIPANTS: We analyzed data from 2,322 African-American and 8,840 white participants without diabetes at baseline from the Atherosclerosis Risk in Communities (ARIC) Study.

MAIN MEASURES: We used Cox regression to quantify the association of incident diabetes by race over 9 years of in-person and 17 years of telephone follow-up, adjusting for traditional and non-traditional risk factors based on literature search. We calculated the mediation effect of a covariate as the percent change in the coefficient of race in multivariate models without and with the covariate of interest; 95 % confidence intervals (95 % CI) were calculated using bootstrapping.

KEY RESULTS: African American race was independently associated with incident diabetes. Body mass index (BMI), forced vital capacity (FVC), systolic blood pressure, and serum potassium had the greatest explanatory effects for the difference in diabetes risk between races, with mediation effects (95 % CI) of 22.0 % (11.7 %, 42.2 %), 21.7 % (9.5 %, 43.1 %), 17.9 % (10.2 %, 37.4 %) and 17.7 % (8.2 %, 39.4 %), respectively, during 9 years of in-person follow-up, with continued effect over 17 years of telephone follow-up.

CONCLUSIONS: Non-traditional risk factors, particularly FVC and serum potassium, are potential mediators of the association between race and diabetes risk. They should be studied further to verify their importance and to determine if they mark causal relationships that can be addressed to reduce the racial disparity in diabetes risk.

KEY WORDS: non-traditional risk factors; diabetes; racial disparity.

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INTRODUCTION

African Americans are disproportionately affected by the diabetes epidemic. Estimates from the National Health and Nutrition Exam Survey (NHANES) 2005–2006 found that the prevalence of diabetes among African Americans is 70 % higher than that of non-Hispanic whites after adjustment for differences in sex and age.¹ Many factors are thought to contribute to the higher incidence of diabetes among African Americans, including differences in socioeconomic status, diet, behavioral factors, as well as related comorbidities, particularly obesity.² Prior analysis of data from the Atherosclerosis Risk in Communities (ARIC) Study found that, among traditional risk factors, obesity accounted for almost 50 % of the excess risk of diabetes among African Americans compared to whites, particularly in women.³ However, excess risk of diabetes is not completely explained by traditional risk factors, and there are likely other environmental, cultural, metabolic, and genetic factors that contribute to the increased risk. (online Appendix Fig. 1)

Recent studies have identified newer or non-traditional risk factors for diabetes. These non-traditional risk factors include measures related to chronic inflammation and hemostasis, metabolic abnormalities, anthropometric measures, as well as genetic markers.⁴ These non-traditional risk factors vary in their relevance to diabetes—some may be related to the pathogenesis of diabetes, such as measures indicating chronic inflammation and endothelial dysfunction, while others may only be markers of diabetes risk.

These non-traditional risk factors of diabetes have generally been identified through analysis of prospective cohort studies, including the ARIC cohort, but have not

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been systematically and simultaneously investigated as potential mediators of the racial disparity in diabetes risk. Determining if and which non-traditional risk factors mediate the racial disparity in diabetes risk may suggest biological or environmental causes of this disparity. Identification of mediators of the racial disparity in diabetes risk may help target areas for further research and development of tailored interventions for diabetes prevention. Therefore, utilizing the available data from the ARIC Study, we sought to test the hypothesis that non-traditional risk factors explain a substantial portion of the excess risk of diabetes in African Americans compared to whites, and to determine which of these non-traditional risk factors have the greatest impact on this excess risk.

METHODS

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective cohort of 15,792 adults between the ages of 45 and 64 years of age at baseline. The participants were recruited from four US communities—Forsyth County, North Carolina, Jackson, Mississippi, Minneapolis, Minnesota, and Washington County, Maryland. All participants from Jackson were African American, while participants from Forsyth County included both African Americans and whites. The other 2 communities recruited primarily white participants. All participants attended an initial baseline visit between 1987 and 1989. Three subsequent visits took place at approximately 3-year intervals for 9 years of in-person follow-up. Follow-up was subsequently conducted yearly, primarily through telephone contact, with an additional 8 years (through 2006) of data included for these analyses. Details of the design and conduct of the ARIC study have been published previously.⁵ Institutional review boards at each of the participating institutions approved the study, and informed consent was obtained from each participant.

Exclusions

We excluded participants sequentially from this analysis if, at the baseline visit, they had diabetes ($n=1870$), defined similarly as the main outcome.⁶ We further excluded participants with abnormally high serum potassium (> 5.5 mEq/L; $n=156$) who potentially had abnormal homeostatic mechanisms of potassium handling; ethnicity other than African American or white ($n=44$); African American race from centers with minimal minority representation ($n=36$); fasting less than 8 h ($n=257$); a serum creatinine >1.7 mg/dL ($n=75$), given that potassium handling is different in those with renal disease compared with

those with normal renal function; or missing information on incident diabetes or other relevant covariates ($n=2192$). Our final study sample consisted of 11,162 (2322 African American and 8,840 white) participants.

Incident Type 2 Diabetes Mellitus

The main outcome was incident diabetes, defined as 1) fasting glucose ≥ 126 mg/dL, 2) non-fasting glucose ≥ 200 mg/dL, 3) participant report of a physician diagnosis, or 4) use of medications, including oral agents and insulin, to treat diabetes during the 9 years of in-person follow-up.⁶ For this definition, the date of onset of diabetes was estimated by linear interpolation using fasting glucose values at the visit at which diabetes was ascertained and the immediately preceding visit.⁶

To confirm the robustness of the main findings, we conducted analyses with an alternative definition of incident diabetes and longer duration of follow-up. First, we limited the definition of diabetes to self-report of physician diagnosis or use of diabetes medications through visit 4 (year 9 of follow-up), thereby excluding cases of undiagnosed diabetes. This interview-based approach allowed us to extend follow-up beyond the final in-person clinic visit to include data from annual telephone calls. For our second analysis using self-report as our definition of incident diabetes, we use data through 2006 (years 17–20 of follow-up). For both analyses using outcome of self-reported diabetes, the date of onset of diabetes was defined as the date of the interview in which diabetes was first reported.

Race

The main exposure in our assessment of mediation was self-reported race, African American or white, obtained at an in-person interview at the baseline visit.

Covariates

We evaluated traditional demographic and lifestyle risk factors, including age; sex; leisure, work, and sports-related physical activity levels;⁷ parental history of diabetes; presence of hypertension; use of antihypertensive medications that may affect potassium (K⁺) levels or diabetes risk, including beta-blockers, angiotensin-converting-enzyme inhibitors (ACE-I), and diuretics; combined family income; education; and smoking history. These variables were obtained at an in-person interview at the baseline visit. Other traditional risk factors that we evaluated included anthropometric and blood pressure measurements and laboratory measurements, all of which were

Table 1. Selected Baseline Characteristics^a (Traditional and Non-traditional Risk Factors) in 11,198 Participants with Diabetes by Race, the Atherosclerosis Risk in Communities (ARIC) Study, 1987–89

Baseline Characteristic	African Americans	Whites
n	2,322	8,840
Traditional risk factors		
Age	53 (5.7)	54 (5.7)
Sex (% female)	63 %	53 %
BMI (kg/m ²)	29.2 (6.0)	26.7 (4.6)
Waist-to-hip ratio	0.91 (0.07)	0.92 (0.08)
Parental history of diabetes (%)	24 %	22 %
Hypertension (%)	51 %	25 %
Systolic blood pressure (mmHg)	126 (19)	118 (16)
Serum creatinine (mg/dL)	1.11 (0.20)	1.09 (0.17)
Glucose (mg/dL)	99 (10)	99 (9)
Insulin (pmol/L)	96 (68)	72 (53)
Physical activity ^b	2.2 (0.5)	2.4 (0.5)
Pack-years of smoking	11 (18)	16 (21)
Combined family income >\$50,000 (%)	8 %	32 %
Education ≤ 12 years (%)	37 %	15 %
Non-traditional risk factors		
Serum potassium (mEq/L)	4.2 (0.5)	4.5 (0.4)
Serum magnesium (mEq/L)	1.6 (0.2)	1.7 (0.1)
Cereal dietary fiber	3.2 (2.0)	3.7 (2.5)
Uric acid (mg/dL)	6.2 (1.6)	5.9 (1.5)
Heart rate	66 (10.2)	66 (9.7)
Activated partial thromboplastin (aPTT)	29.4 (3.2)	29.2 (3.1)
von Willebrands Factor (vWF)	128.6 (54.5)	110.0 (41.3)
Factor VIII:C value	140.8 (41.8)	123.1 (32.1)
Hematocrit	40.1 (4.2)	42.1 (3.7)
White blood cell count (WBC)	5.5 (2.0)	6.2 (1.9)
Actual forced vital capacity (FVC) (L)	3.3 (0.8)	4.0 (1.0)
Number of years at residence	33.5 (14.3)	31.4 (17.4)
Occupation held longest (%)		
Management	22 %	26 %
Technician	7 %	17 %
Service	22 %	4 %

^aValues are mean (SD) or percentages

^baverage score of leisure, sports, and work-related physical activity; Index ranges from 1 (least active) to 5 (most active)

obtained by trained personnel and processed in a standardized fashion. (Table 1)^{3,5,8}

We searched PubMed and the ARIC publications repository, through July 2010, for observational cohort and case-cohort studies identifying significant non-traditional risk factors of diabetes. We selected non-traditional risk factors that were measured in a majority of ARIC participants at the baseline exam using standardized procedures described above. The variables included in our analyses were: serum electrolytes—potassium, magnesium, and calcium;^{8,9} serum uric acid;^{10,11} serum albumin;¹² dietary factors, including total fiber, cereal fiber, and coffee intake;^{13,14} resting heart rate;¹⁵ coagulation measurements, including activated partial thromboplastin time (aPTT), von Willebrand factor (vWF), factor VIII:C;¹⁶ hematologic measurement of white blood cell count (WBC) and hematocrit;^{17,18} actual forced vital capacity (FVC);¹⁹ leg length;²⁰ and non-traditional measures of socioeconomic status including

dental care use patterns, occupation held longest, and number of years at current residence, which were variables collected during ARIC interviews and thought ‘a priori’ to be important variables to consider, in addition to education and income, to account for socioeconomic differences by race.

All covariates considered were obtained at the baseline visit except for the non-traditional measures of socioeconomic status that were obtained at different visits, but which were considered unlikely to change over the time of the study.

Statistical Analyses

We compared the mean and standard deviation or frequency of baseline characteristics of the study population by race using Student’s t-tests for continuous variables, which were normally distributed and Pearson’s chi-square tests for categorical variables. We used Cox proportional hazard regression models to quantify the association between race and risk of incident diabetes, adjusting for the traditional and non-traditional risk factors mentioned above. Models were checked for multicollinearity using variance inflation factors.

We calculated the mediation effect of each continuous covariate on the association between race and risk of diabetes if the variable met the following two criteria for being a potential mediator: 1) race was associated with the variable; and 2) the variable was significantly associated with incident diabetes after adjustment for race (P value < 0.05). We calculated the mediation effect of a covariate as the percent change in the coefficient of race in models without and with the covariate of interest, initially including all mediators. In our final models, we included only those traditional risk factors, as well as those non-traditional risk factors which had statistically significant mediation effects, either positive or negative. Confidence intervals of 95 % (95 % CI) were calculated using bootstrapping with replacement (1000 samples).²¹ All P values were two-sided, and a P value of < 0.05 was considered to be statistically significant. All statistical analyses were conducted using SAS 9.1.3 (SAS Institute, Cary, NC) and STATA/SE 10.1 (College Station, TX).

We conducted a sensitivity analysis restricting our analyses to participants from Forsyth County ($n=2,944$), which is the only center that had a significant racially-mixed population (whites, $n=2,689$; African Americans, $n=255$). We performed the same mediation analyses as in the full cohort to determine if the mediation effects of risk factors followed a similar pattern in this community as in the full cohort.

RESULTS

At baseline, there were statistically significant differences between African Americans and whites in all covariates,

traditional and non-traditional, except for parental history of diabetes, baseline fasting glucose, and aPTT level (Table 1). For our base case analysis over 9 years of in-person follow-up, in this population of 11,162 persons, the relative hazard (RH) (95 % CI) of incident diabetes in African Americans compared to whites was 2.07 (1.84, 2.32), adjusting for age and sex only (Table 2). In a model adjusting for traditional risk factors [age, sex, body-mass-index (BMI), waist-to-hip ratio (WHR), physical activity, parental history of diabetes, systolic blood pressure (SBP), and smoking pack-years], approximately 42 % of the excess risk in African Americans was explained [HR (95%CI) 1.62 (1.42, 1.85)], while further adjustment with the non-traditional risk factors explained an additional 26 % of the excess risk [HR (95 % CI) 1.34 (1.15, 1.57)] (Table 2).

In our initial model including all covariates, only a few variables had statistically significant positive or negative mediation effects (online Appendix Table 5). Our final model included traditional risk factors and those non-traditional risk factors that had statistically significant positive or negative mediation effects on the association between race and incident diabetes (Table 3). BMI and FVC had the greatest mediation effect (95 % CI) of 22.0 % (11.7 %, 42.2 %) and 21.7 % (9.5 %, 43.1 %), respectively, followed by SBP and serum potassium, which had mediation effects (95 % CI) of 17.9 % (10.2 %, 37.4 %) and 17.7 % (8.2 %, 39.4 %) respectively. Factor VIII:C had a statistically significant but smaller mediation effect (95 % CI) of 13.1 % (5.5 %, 28.8 %) (Table 3).

We found that adjustment for certain variables, including WHR, smoking pack-years, and WBC, strengthened the association between African American race and incident diabetes, rather than explaining and attenuating risk compared to whites.

Sensitivity Analyses

In analyses using a diabetes outcome based on self-report over both a 9-year period and a 17-year period, FVC, BMI, systolic blood pressure, and serum potassium continued to be the variables with the greatest mediation effects. (Table 4)

In our sensitivity analysis limited to African American and white participants who were recruited from Forsyth County,

Table 2. Incidence Rates and Partially and Fully Adjusted Hazard Ratios (HR) for Incident Diabetes by Race

	African Americans	Whites
N	2,322	8,840
Incident cases of diabetes	434	922
Incidence rate (per 1000 person-years)	27.0	13.4
Age and sex-adjusted HR (95 % CI)	2.07 (1.84, 2.32)	1.00 (ref)
Traditionally-adjusted HR (95 % CI) ^a	1.62 (1.42, 1.85)	1.00 (ref)
Fully-adjusted HR (95 % CI) ^b	1.34 (1.15, 1.57)	1.00 (ref)

^aadjusted for age, sex, BMI, waist-to-hip ratio, systolic blood pressure, parental history of diabetes, physical activity, pack-years smoking

^badjusted for the above as well as non-traditional risk factors of serum K⁺, VIII:C, WBC, FVC (actual forced vital capacity), occupation held longest

Table 3. Mediation Effects (%) (95 % CI) of Covariates with Positive Mediation Effects on the Association Between Race and Risk of Incident Diabetes^a

Baseline Characteristic	Mediation Statistic (%) (95 % CI) ^b
BMI (kg/m ²)	22.0 (11.7, 42.2)
Actual FVC (L)	21.7 (9.5, 43.1)
Systolic blood pressure (mmHg)	17.9 (10.2, 37.4)
Serum K ⁺ (mEq/L)	17.7 (8.2, 39.4)
Factor VIII:C value	13.1 (5.5, 28.8)
Occupation held longest	11.6 (−3.4, 33.8)
Physical activity	7.0 (−2.5, 26.1)

^aFull model adjusted for age, sex, BMI, waist-to-hip ratio, systolic blood pressure, parental history of diabetes, physical activity (combined effect of leisure, work, and sports-related physical activities), pack-years smoking, serum K⁺, VIII:C, WBC, FVC (actual forced vital capacity), occupation held longest

^bWe calculated the mediation effect of a covariate as the percent change in the coefficient of race in models without and with (full-model) the covariate of interest

African Americans were at a similarly higher risk of diabetes compared to whites as in the total population [age-adjusted and sex-adjusted HR (95% CI) 2.46 (1.83, 3.32)]. In this subsample, the pattern of mediation was similar to that found in the total population for our final model, with mediation effects (95 % CI) being greatest for FVC, 22.6 % (−4.9 %, 133.0 %); however, none of the variables had statistically significant mediation effects in this small subcohort.

DISCUSSION

Analyses of these longitudinal data on a community-based biracial cohort of middle-aged adults confirm that African Americans are at higher risk for incident type 2 diabetes compared to their white counterparts, and that racial differences in adiposity and other traditional risk factors only partially explain their excess risk. Two non-traditional risk factors in particular—low FVC and low serum potassium—appear to play as significant a role as adiposity as mediators of excess diabetes risk in African Americans.

While an association between lung function and diabetes risk has clearly been found, the direction of this association is not clear.²¹ The mechanism(s) through which reduced lung function, and specifically reduced FVC, may increase risk of diabetes is unclear. One possibility is that FVC, as measured in most contexts, is reduced by central adiposity.²¹ Low measured FVC would, under this hypothesis, simply be a proxy for central adiposity in its role, above and beyond BMI and even WHR, both of which were adjusted for in our final model, as a risk factor for incident diabetes. Another possibility is that low FVC has also been linked to markers of adverse environmental factors in early development, including maternal socioeconomic status and birth-weight, which have also been found to be linked to increased diabetes risk.²¹ Finally, persistent diabetic-range hyperglycemia re-

Table 4. Mediation Effects (%) (95 % CI) of the Four Main Mediators of the Association Between Race and Risk of Incident Diabetes in Our Main Model and Sensitivity Analyses

Model	BMI	FVC	Systolic Blood Pressure	Serum Potassium
Main model ^a	22.0 (11.7, 42.2)	21.7 (9.5, 43.1)	17.9 (10.2, 37.4)	17.7 (8.2, 39.4)
Self-reported diabetes outcome (9-year follow-up) ^b	26.7 (12.6, 134.0)	29.5 (11.0, 92.8)	6.6 (−5.1, 63.9)	19.8 (4.3, 107.2)
Self-reported diabetes outcome (17 year follow-up) ^b	30.1 (17.8, 62.6)	40.4 (25.1, 72.6)	18.4 (10.0, 49.1)	17.6 (5.6, 45.5)
Main model for Forsyth County participants only ^a	15.7 (−26.5, 85.7)	22.6 (−4.9, 133.0)	5.2 (−4.7, 60.0)	12.8 (−12.3, 123.5)

^aFull model adjusted for age, sex, BMI, waist-to-hip ratio, systolic blood pressure, parental history of diabetes, physical activity, pack-years smoking; serum K⁺, VIII-C, WBC, FVC, occupation held longest. Diabetes outcome based on lab measures, medication use, and self-report of physician diagnosis of diabetes

^bDiabetes outcome based on self-report of physician diagnosis or use of diabetes medications

duces lung elasticity,^{21,22} and it is plausible that racial disparities in glycemia in the non-diabetic range may also adversely affect FVC.²² In none of these three scenarios does FVC emerge unequivocally as a causal risk factor, but rather as subclinical marker for other adverse exposures.

Racial disparities in FVC are well recognized. Data from the Third National Health and Nutrition Examination Survey demonstrate FVC about 12 % lower in African American men and women compared to their white counterparts.²³ Pulmonologists routinely use a racial correction factor in lung function measurement to fit race-based norms.²³ Several studies have identified obesity, socioeconomic status, low birth-weight, and inappropriate standard references for measurements among the causes for this racial disparity in lung function.^{21,23} It is important to clarify the nature of this association to determine if low FVC can simply be used for prediction of diabetes risk, if interventions should be developed to target lung function specifically, or if efforts should be directed towards promoting weight loss, particularly amongst African Americans to help reduce the racial disparity in diabetes risk.

The association between risk of diabetes and lower serum potassium has been studied primarily among users of thiazide diuretics. Studies re-analyzing data from antihypertensive trials have found that serum potassium may mediate the association between exposure to thiazide diuretics and diabetes risk, with lower serum potassium being associated with higher glucose levels.^{22–25} Two cohort studies have found that low-normal serum potassium was associated with increased risk of diabetes compared to higher serum potassium independent of diuretic use.^{9,26} Studies utilizing glucose clamps revealed that induction of low serum potassium in healthy participants induced impaired glucose tolerance through a reduction in sensitivity of pancreatic beta-cells to glucose loads and decreased insulin secretion.^{27,28}

Potassium homeostasis appears to differ by race: hypertensive African Americans have a greater blood pressure-lowering effect with potassium supplements compared to whites, decreased urinary excretion of potassium with similar dietary potassium intake, and a faster decline of total potassium stores with age compared to whites.^{29–36} African Americans also tend to have reduced dietary intake of potassium compared to whites.^{9,37} Further study is needed to determine the mechanism of effect of potassium on glucose metabolism and long-term diabetes risk and

to determine if and how this differs by race. Further study is needed to determine if interventions to raise serum potassium might be beneficial at reducing the risk of diabetes, particularly in African Americans.

Several limitations of this study deserve to be mentioned. First, there may be measurement error in the assessment of our exposures as well as outcome of incident diabetes, which did not include measurements of 2-hour oral glucose tolerance tests or hemoglobin A1c levels. Measurement techniques for most of the variables assessed have been validated, however, including the use of self-reported data for determining incident diabetes.³⁸ Secondly, although this study has a biracial population, the African Americans and whites in this cohort may not be representative of all African Americans and whites, and so results may not be generalizable. The majority of African Americans in this study came from one study site, so even within this cohort, there may be confounding of the association between race and diabetes risk by geography. We did, however, analyze data separately from the Forsyth County, North Carolina field center and found a similar pattern of mediation effects as in the larger cohort, although results were not statistically significant, likely due to the small sample size.

A limitation of mediation analyses is that we assume a direct causal relationship between the exposure and outcome, which may be incorrect. There are also likely other mediators of the association between race and diabetes risk. We limited our analyses to the variables available in a majority of the cohort in our data set and did not include other potential mediators available in a small subset of the cohort, including other markers of inflammation and measures of oxidative stress; we also did not include any genetic markers associated with diabetes. Additional follow-up, replication of our results in other cohorts, and assessment of other risk factors measured in other cohorts should be pursued. We excluded many participants who had incomplete data, and this may limit the generalizability of our results. The confidence intervals for our mediation statistics were quite wide; however, a similar pattern of significant mediators emerged with our sensitivity analyses. Also, given that we were exploring the mediation effect of several variables in each model, we cannot exclude the possibility of a type I error based on multiple comparisons. However, to try to minimize this potential error we used a final

model that included only those non-traditional risk factors that had statistically significant positive or negative mediation effects, thus limiting the number of variables in our model.

This study has several implications. First, despite several decades of epidemiologic work on the subject, we have not yet identified key causal factors behind the excess risk of type 2 diabetes in African Americans. Second, systematic racial differences in FVC appear to mediate a significant proportion of excess diabetes risk and warrant more scientific attention in regards to causation. Third, the finding that low serum potassium, a potentially modifiable risk factor, is a strong mediator of racial disparities warrants confirmation, both in other cohort studies and possibly in trials of potassium supplementation designed to raise serum potassium levels in African Americans at risk for type 2 diabetes. Finally, non-traditional risk factors of diabetes should be studied further to verify their importance and to determine if they mark causal relationships that can be addressed to reduce the racial disparity in diabetes risk.

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REFERENCES

1. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. *Diabetes Care*. 2009;32(2):287–94.
2. Signorello LB, Schlundt DG, Cohen SS, et al. Comparing diabetes prevalence between African Americans and Whites of similar socioeconomic status. *Am J Public Health*. 2007;97(12):2260–7.
3. Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M. Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. *JAMA*. 2000;283(17):2253–9.
4. Raynor LA, Pankow JS, Duncan BB, Schmidt MI, Hoogeveen RC, Pereira MA, et al. Novel risk factors and the prediction of type 2 diabetes in the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care*. 2013;36(1):70–6.
5. The ARIC. Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol*. 1989;129(4):687–702.
6. Duncan BB, Schmidt MI, Pankow JS, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes*. 2003;52(7):1799–805.
7. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr*. 1982;36(5):936–42.
8. Kao WH, Folsom AR, Nieto FJ, Mo JP, Watson RL, Brancati FL. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. *Arch Intern Med*. 1999;159(18):2151–9.
9. Chatterjee R, Yeh H, Shafi T, et al. Serum and dietary potassium and risk of incident type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Arch Intern Med*. 2010;170:1745–51.
10. Kodama S, Saito K, Yachi Y, et al. Association between serum uric acid and development of type 2 diabetes. *Diabetes Care*. 2009;32(9):1737–42.
11. Kramer CK, von Muhlen D, Jassal SK, Barrett-Connor E. Serum uric acid levels improve prediction of incident type 2 diabetes in individuals with impaired fasting glucose: the Rancho Bernardo Study. *Diabetes Care*. 2009;32(7):1272–3.
12. Folsom AR, Ma J, Eckfeldt JH, Nieto FJ, Metcalf PA, Barnes RW. Low serum albumin. Association with diabetes mellitus and other cardiovascular risk factors but not with prevalent cardiovascular disease or carotid artery intima-media thickness. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Ann Epidemiol*. 1995;5(3):186–91.
13. Stevens J, Ahn K, Juhaeri, Houston D, Steffan L, Couper D. Dietary fiber intake and glycemic index and incidence of diabetes in African American and white adults: the ARIC study. *Diabetes Care*. 2002;25(10):1715–21.
14. Paynter NP, Yeh HC, Voutilainen S, et al. Coffee and sweetened beverage consumption and the risk of type 2 diabetes mellitus: the atherosclerosis risk in communities study. *Am J Epidemiol*. 2006;164(11):1075–84.
15. Carnethon MR, Yan L, Greenland P, et al. Resting heart rate in middle age and diabetes development in older age. *Diabetes Care*. 2008;31(2):335–9.
16. Duncan BB, Schmidt MI, Offenbacher S, Wu KK, Savage PJ, Heiss G. Factor VIII and other hemostasis variables are related to incident diabetes in adults. The Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care*. 1999;22(5):767–72.
17. Vozaeva B, Weyer C, Lindsay RS, Pratley RE, Bogardus C, Tataranni PA. High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes*. 2002;51(2):455–61.
18. Tamariz LJ, Young JH, Pankow JS, et al. Blood viscosity and hematocrit as risk factors for type 2 diabetes mellitus: the atherosclerosis risk in communities (ARIC) study. *Am J Epidemiol*. 2008;168(10):1153–60.
19. Yeh HC, Punjabi NM, Wang NY, Pankow JS, Duncan BB, Brancati FL. Vital capacity as a predictor of incident type 2 diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care*. 2005;28(6):1472–9.
20. Weitzman S, Wang CH, Pankow JS, Schmidt MI, Brancati FL. Are measures of height and leg length related to incident diabetes mellitus? The ARIC (Atherosclerosis Risk in Communities) study. *Acta Diabetol*. 2010;47(3):237–42.
21. Vittinghoff E, Shiboski SC, McCulloch CE, Glidden DV. Regression Methods in Biostatistics: Linear, Logistic, Survival and Repeated Measures Models. New York, NY: Springer Science Business Media, Inc.; 2005.

22. Klein OL, Krishnan JA, Glick S, Smith LJ. Systematic review of the association between lung function and Type 2 diabetes mellitus. *Diabet Med*. 2010;27(9):977–87.
23. van den Borst B, Gosker HR, Zeegers MP, Schols AMWJ. Pulmonary function in diabetes: a metaanalysis. *Chest*. 2010;138:393–406.
24. Harik-Khan RI, Fleg JL, Muller DC, Wise RA. The effect of anthropometric and socioeconomic factors on the racial difference in lung function. *Am J Respir Crit Care Med*. 2001;164(9):1647–54.
25. Shafi T, Appel LJ, Miller ER, Klag MJ, Parekh RS. Changes in serum potassium mediate thiazide-induced diabetes. *Hypertension*. 2008;52:1022–9.
26. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension*. 2006;48(2):219–24.
27. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007;369(9557):201–7.
28. Taylor EN, Hu FB, Curhan GC. Antihypertensive medications and the risk of incident type 2 diabetes. *Diabetes Care*. 2006;29(5):1065–70.
29. Heianza Y, Hara S, Arase Y, et al. Low serum potassium levels and risk of type 2 diabetes: the Toranomon Hospital Health Management Center Study 1 (TOPICS 1). *Diabetologia*. 2011;54(4):762–6.
30. Rowe JW, Tobin JD, Rosa RM, Andres R. Effect of experimental potassium deficiency on glucose and insulin metabolism. *Metabolism*. 1980;29(6):498–502.
31. Helderma JH, Elahi D, Andersen DK, et al. Prevention of the glucose intolerance of thiazide diuretics by maintenance of body potassium. *Diabetes*. 1983;32(2):106–11.
32. He Q, Heo M, Heshka S, et al. Total body potassium differs by sex and race across the adult age span. *Am J Clin Nutr*. 2003;78(1):72–7.
33. Turban S, Miller ER, Ange B, Appel LJ. Racial differences in urinary potassium excretion. *J Am Soc Nephrol*. 2008;19(7):1396–402.
34. Langford HG, Cushman WC, Hsu H. Chronic effect of KCl on black-white differences in plasma renin activity, aldosterone, and urinary electrolytes. *Am J Hypertens*. 1991;4(5 Pt 1):399–403.
35. Panel on Dietary Reference Intakes for Electrolytes and Water. Chapter 5. Potassium. In: *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate*. Washington, DC: National Academies Press; 2004:186–268.
36. Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA*. 1997;277(20):1624–32.
37. Newby PK, Noel SE, Grant R, Judd S, Shikany JM, Ard J. Race and region are associated with nutrient intakes among black and white men in the United States. *J Nutr*. 2011;141(2):296–303.
38. Schneider AL, Pankow JS, Heiss G, Selvin E. Validity and reliability of self-reported diabetes in the atherosclerosis risk in communities study. *Am J Epidemiol*. 2012;176(8):738–43.

APPENDIX

Figure 1. Conceptual model of the association between race and diabetes risk.

Table 5. Mediation Effects of All Potential Mediators^a Considered on the Association Between Race and Risk of Incident Diabetes

Potential Mediator	Mediation Effect (%)	95 % Confidence Interval
BMI (kg/m ²)	8.18	2.64, 18.9
Parental history of diabetes (%)	-3.05	-11.34, 1.88
Presence of hypertension (%)	-2.87	-8.91, 0.73
Potassium (mEq/L)	10.19	4.17, 20.70
Calcium (mg/dL)	-1.09	-6.42, 3.93
Magnesium (mEq/L)	-1.09	-6.12, 3.87
Creatinine (mg/dL)	-1.95	-8.99, 3.47
Glucose (mg/dL)	-20.40	-57.37, 2.41
Insulin (pmol/L)	0.12	-2.93, 2.88
Physical activity ^b	2.32	-2.89, 16.66
Systolic blood pressure (mmHg)	4.08	1.42, 11.11
Blood pressure medication use (%) ^c	-5.59	-14.96, -0.06
Income	-6.57	-23.49, 6.02
Education	-0.69	-4.36, 2.02
Cereal dietary fiber	-1.00	-4.91, 3.37
Uric acid (mg/dL)	-0.28	-2.94, 0.88
Pack-years of smoking	-5.09	-13.73, -1.66
Heart rate	-2.18	-8.59, 1.61
Activated partial thromboplastin (aPTT) time (aPTT)	-1.97	-6.78, 1.22
von Willebrand factor (vWF)	-0.86	-4.72, 1.52
Factor VIII:C	3.68	0.96, 9.05
Hematocrit	-6.47	-18.00, 0.83
White blood cell count (WBC)	-12.64	-26.45, -6.47
Actual forced vital capacity (L)	13.24	4.76, 27.81
Waist-to-hip ratio	-32.35	-76.31, -17.56
Use of dentist patterns	3.99	-2.77, 12.78
Occupation held longest	11.68	1.22, 25.13
Number of years at residence	-0.58	-3.69, 0.49

^aFull model included all of the covariates listed in table as well as age and sex

^bCombined effect of leisure, work, and sports-related physical activity levels

^cCombined effect of use of either beta-blockers, angiotensin-converting enzyme inhibitors, or diuretics