RESEARCH ARTICLE

Potassium Measures and Their Associations with Glucose and Diabetes Risk: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Background

Recent studies have found low-normal potassium (K) to be associated with increased diabetes risk. We sought to verify these associations in a multi-ethnic US cohort; and to determine if these associations extend to US Hispanics and Asian-Americans.

Methods

We analyzed data from Multi-Ethnic Study of Atherosclerosis (MESA) participants who were free-of-diabetes at baseline. We examined cross-sectional associations between measures of K—serum, dietary, and urine—with fasting glucose and HOMA-IR. We examined longitudinal associations between K and diabetes risk over 8 years.

Findings

In multivariable models, compared to those with higher serum K (≥4.5mmol/L), those with lower serum K (<4.0mmol/L) had significantly higher fasting glucose [1.3 mg/dL (95%CI 0.2, 2.4), P-value = 0.03]. Incident diabetes developed in 1281 of 5415 at-risk participants. In minimally-adjusted models, we found inverse associations between serum and dietary K and diabetes risk. Compared to those with higher serum K, those with lower serum K had an HR (95% CI) of incident diabetes of 1.23 (1.04, 1.47), P-value = 0.02. However, these associations were attenuated in fully-adjusted models. We found no significant interaction between potassium and ethnicity.
Conclusions

In this multi-ethnic cohort, we found a significant inverse association between serum K and fasting glucose but no significant association with longer-term diabetes risk. This inverse association between potassium and glucose must be studied further to understand the physiology and its potential impact on chronic health.

Introduction

In secondary data analyses of certain US and international cohorts, low serum and low dietary potassium have been associated with higher risk of diabetes.[1–3] Adults in the US generally consume less than the recommended amount of dietary potassium, with one study finding that less than 2% of adults consumed the recommended amount of ≥4700mg/day.[4] There are also known disparities in dietary potassium intake between African Americans and whites, with African Americans consuming lower amounts of dietary potassium compared to whites.[4] In some studies, both serum and dietary potassium (K) have shown stronger associations with diabetes risk in African Americans compared to whites.[2, 5] Low serum K has been associated with increased diabetes risk and increased prevalence of metabolic syndrome in some Asian populations.[3, 6] Experimental studies provide biological plausibility to the association between low K and abnormal glucose metabolism, by showing that thiazide-induced hypokalemia leads to diminished insulin secretion.[7, 8] Genetic mutations in K channels on pancreatic β-cells are associated with increased diabetes risk, also suggesting a potential biological basis for the association between K and glucose metabolism.

While there has been some exploration of differences in potassium and health effects in African Americans and whites, these explorations have not extended to other ethnicities in the US. Using data from the Multi-ethnic Study of Atherosclerosis (MESA) cohort, a cohort which includes Hispanics and Chinese Americans, we sought to determine the associations between potassium measures with measures of glucose metabolism and diabetes risk.

Methods

Study population

MESA is a prospective community-based cohort of adults aged 45–84 years of age at baseline. Baseline data were collected between July 2000 and August 2002 with 4 subsequent in-person exams occurring through 2012. Participants were recruited from 6 different communities: Baltimore City and County, MD; Chicago, IL, Forsyth County, NC, Los Angeles County, CA, Northern Manhattan and Bronx, NY. Four ethnicities were represented in this cohort: of the 6814 participants recruited at baseline, 38% were white, 28% were African American, 22% Hispanic, and 12% Asian, predominantly of Chinese descent. Institutional review boards (IRB) at each of the participating institutions for MESA approved the study, and written informed consent was obtained from each participant. Additionally, the IRBs at Duke University and the University of Washington approved the conduct of the data analyses presented in this manuscript.

Participants were excluded from these analyses if they had diabetes mellitus evident at the baseline exam (n = 859). Diabetes was defined as fasting serum glucose ≥126mg/dL and/or use of glucose-lowering medications. We additionally excluded any remaining participants who were missing any of the K exposures (n = 540).
Exposures

Serum K was measured utilizing indirect potentiometry with an ion-selective electrode. Dietary K intake was derived from a modified Block-style 120-item food frequency questionnaire (FFQ) administered at the baseline exam. This FFQ was initially designed for the Insulin Resistance and Atherosclerosis Study (IRAS) cohort study but was modified to accommodate the diets of the different ethnicities included in the MESA cohort. From this FFQ, individual nutrient intake was quantified using the Nutrition Data System for Research (NDS-R database; Nutrition Coordinating Center, Minneapolis, MN, USA).[9] The coordinating center updated the nutrient variables in June 2015 in order to correct a coding error. This error was found in a subset of participants, depending on participant response to a modifier question, to lead to at least some underreporting of certain food frequency, food group, and nutrient variables. Original data was used to update some of these errors when available, and single imputation methods were used to correct the remaining errors when original data was not available.

Urinary K was measured from a random spot specimen on a Beckman Coulter chemistry analyzer (DXC 600) using indirect potentiometry utilizing a potassium ion-selective electrode in conjunction with a sodium reference electrode. Fractional excretion of K (FEK) was calculated as \((\text{urine K/urine Cr)/(serum K/serum Cr)}\). This was presumed to reflect the renal handling of filtered K, as influenced by aldosterone and the delivery of sodium and K to the distal renal tubules.

All exposures were categorized for analyses. Serum K was categorized by clinically relevant cut-points of \(\geq 4.5, 4.0–4.49, \text{ and } < 4.0 \text{ mmol/L}\). Dietary K, urinary K, and FEK were categorized into quartiles.

Outcomes

For cross-sectional analyses, outcomes were fasting serum glucose and HOMA-IR, a measure of insulin resistance which was calculated as \((\text{fasting glucose}/\text{fasting insulin})/405\), both measured at the baseline exam. Serum glucose was measured using the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc, Rochester, NY). Insulin was measured by a radioimmunoassay method using the Linco Human Insulin Specific RIA Kit (Linco Research, Inc., St. Charles, MO).

For longitudinal analyses, incident diabetes mellitus was defined as fasting serum glucose \(\geq 126 \text{ mg/dL}\) and/or use of glucose-lowering medications at any of the follow-up exams through 2012 for a mean of 8 years of follow-up. Baseline exam was performed between the years 2000–2002; there were 3 additional follow-up exams between baseline exam and the year 2007, approximately 18–24 months apart; and a fifth in-person visit between 2010–2012.

Covariates

Covariate data were collected at the baseline exam through a combination of self-administered and interviewer-administered questionnaires as well as in-person measurements. Waist circumference was measured at the umbilicus using a measuring tape and rounding to the nearest centimeter. Body-mass index was calculated using height and weight measurements from a stadiometer and calibrated scale. Physical activity was measured using the MESA Typical Week Physical Activity Survey, which was adapted from the Cross-Cultural Activity Participation Survey.[10] From this survey, physical activity was quantified and categorized as minutes spent on activities of different metabolic equivalents. Systolic blood pressure was calculated as the average of the second and third blood pressure readings with patient in a seated position and with readings taken 5 minutes apart.
Statistical methods

Baseline characteristics were evaluated by categories of each exposure of interest. Correlations between exposures were assessed. Multivariable linear regression models were used to test cross-sectional associations with the outcomes of fasting glucose or HOMA-IR. Multivariable discrete Cox regression models were used to test associations with incident diabetes. We included covariates which were thought to potentially affect relationships between K and glucose metabolism based on current understanding of pathophysiology. Model 1 adjusted for age (continuous), sex, race/ethnicity, study site, total energy intake (for dietary analyses only), and log of urinary creatinine (for urine K analyses only). Model 2 additionally adjusted for waist circumference (continuous), body mass index (continuous), smoking, family history of diabetes, education (categories), income (categories), alcohol use (categories), and physical activity (categories), systolic blood pressure, and use of antihypertensive medications (as listed in Table 1). We built parallel models with and without interaction terms for race/ethnicity x K exposure in order to evaluate associations for the full population and for participants of each race/ethnicity, respectively. We also tested for statistical interactions in the full cohort between hypertension status/use of anti-hypertensive medications and K exposure. Wald tests were used to test for heterogeneity. Tests of significance were two-tailed with an $\alpha$ level of 0.05. We performed all analyses using R version 3.2.0.[11]

Results

Baseline characteristics

Table 1 shows baseline characteristics of the 5415 included participants by serum K categories. S4 Appendix Table shows baseline characteristics of the participants who were excluded from our analyses. Of the four ethnicities represented in this cohort, whites had the greatest proportion with a high-normal serum K ($\geq 4.5$mmol/L) (52%), while African Americans had the greatest proportions with a low-normal serum K ($<4.0$mmol/L) (34%). Compared to those with a high-normal serum K, participants with a low-normal serum K had a higher systolic blood pressure and greater use of the blood pressure medications that affect renal K handling. Participants in all 3 categories of serum K had similar mean BMI. Correlations between exposures were found to be fairly low. The correlation between serum K and dietary K was 0.04; the correlation between serum K and urinary K was 0.15; and the correlation between dietary K and urinary K was 0.03.

Fasting glucose and HOMA-IR

In cross-sectional analyses using the baseline data, we did find a significant inverse association between serum K and fasting glucose.(Table 2) In our fully-adjusted model (model 2), compared to those with a high-normal serum K ($\geq 4.5$mmol/L), those with a low-normal serum K ($<4.0$mmol/L) had a higher fasting glucose (95% CI) of 1.3mg/dL (0.2, 2.4), $P$-value = 0.03. There was no statistical interaction between serum K and ethnic group on this outcome ($P = 0.53$) There was also no statistical interaction between serum K and hypertension status on this outcome ($P = 0.46$). The direction of the association was consistent in all ethnic groups, except for the Chinese Americans.(Table 2) In minimally-adjusted models (model 1), we found significant inverse associations between dietary K and urinary FEK with fasting glucose; however, after further adjustment, these associations were no longer significant. (S1 and S2 Appendix Tables) We found no significant associations between random urinary K and fasting glucose.
| Covariate                        | All (N = 5415) | K < 4.0 (N = 804) | 4.0 ≤ K < 4.5 (N = 2844) | K ≥ 4.5 (N = 1767) |
|---------------------------------|----------------|------------------|--------------------------|------------------|
| **Demographics**                |                |                  |                          |                  |
| Age (years)                     | 61.8 ± 10.3    | 62.1 ± 10.0      | 61.5 ± 10.2              | 62.3 ± 10.5      |
| Sex                             |                |                  |                          |                  |
| Female                          | 2924 (54.0)    | 514 (63.9)       | 1574 (55.3)              | 836 (47.3)       |
| Male                            | 2491 (46.0)    | 290 (36.1)       | 1270 (44.7)              | 931 (52.7)       |
| **Race/Ethnicity**              |                |                  |                          |                  |
| White, Caucasian                | 2281 (42.1)    | 238 (29.6)       | 1117 (39.3)              | 926 (52.4)       |
| Chinese-American                | 679 (12.5)     | 160 (19.9)       | 435 (15.3)               | 84 (4.8)         |
| Black, African-American         | 1345 (24.8)    | 270 (33.6)       | 707 (24.9)               | 368 (20.8)       |
| Hispanic                        | 1110 (20.5)    | 136 (16.9)       | 585 (20.6)               | 389 (22.0)       |
| **Site**                        |                |                  |                          |                  |
| Wake Forest                     | 828 (15.3)     | 131 (16.3)       | 395 (13.9)               | 302 (17.1)       |
| Columbia                        | 827 (15.3)     | 85 (10.6)        | 392 (13.8)               | 350 (19.8)       |
| Johns Hopkins                   | 807 (14.9)     | 104 (12.9)       | 400 (14.1)               | 303 (17.1)       |
| Minnesota                       | 869 (16.0)     | 91 (11.3)        | 437 (15.4)               | 341 (19.3)       |
| Northwestern                    | 1044 (19.3)    | 219 (27.2)       | 651 (22.9)               | 174 (9.8)        |
| UCLA                            | 1040 (19.2)    | 174 (21.6)       | 569 (20.0)               | 297 (16.8)       |
| **Anthropometric measures:**    |                |                  |                          |                  |
| Body mass index (kg/m²)         | 27.9 ± 5.3     | 28.0 ± 5.7       | 27.8 ± 5.3               | 28.0 ± 5.0       |
| Waist circumference (cm)        | 96.8 ± 14.0    | 96.6 ± 14.9      | 96.3 ± 13.8              | 97.7 ± 13.7      |
| **Lifestyle and family history:** |            |                  |                          |                  |
| Smoking status                  |                |                  |                          |                  |
| Never                           | 2762 (51.0)    | 450 (56.0)       | 1509 (53.1)              | 803 (45.4)       |
| Former                          | 1967 (36.3)    | 265 (33.0)       | 1004 (35.3)              | 698 (39.5)       |
| Current                         | 679 (12.5)     | 87 (10.8)        | 328 (11.5)               | 264 (14.9)       |
| Family history of DM            | 2086 (38.5)    | 316 (39.3)       | 1096 (38.5)              | 674 (38.1)       |
| Education                       |                |                  |                          |                  |
| Less than high school degree    | 881 (16.3)     | 135 (16.8)       | 448 (15.8)               | 298 (16.9)       |
| High school to some college     | 1821 (33.6)    | 265 (33.0)       | 941 (33.1)               | 615 (34.8)       |
| College degree or higher        | 2705 (50.0)    | 402 (50.0)       | 1451 (51.0)              | 852 (48.2)       |
| Family history of DM            | 2086 (38.5)    | 316 (39.3)       | 1096 (38.5)              | 674 (38.1)       |
| Total gross family income, $    |                |                  |                          |                  |
| < 20,000                        | 1850 (34.2)    | 272 (33.8)       | 995 (35.0)               | 583 (33.0)       |
| 20,000–49,999                   | 2099 (38.8)    | 340 (42.3)       | 1064 (37.4)              | 695 (39.3)       |
| ≥ 50,000                        | 1290 (23.8)    | 160 (19.9)       | 691 (24.3)               | 439 (24.8)       |
| Number of alcoholic drinks/week |                |                  |                          |                  |
| 0                               | 1313 (24.2)    | 185 (23.0)       | 706 (24.8)               | 422 (23.9)       |
| 1–7                             | 1539 (28.4)    | 213 (26.5)       | 801 (28.2)               | 525 (29.7)       |
| ≥ 7                             | 549 (10.1)     | 45 (5.6)         | 284 (10.0)               | 220 (12.5)       |
| Physical activity               |                |                  |                          |                  |
| High activity                   | 1312 (24.2)    | 183 (22.8)       | 650 (22.9)               | 479 (27.1)       |
| Moderate activity               | 2796 (51.6)    | 405 (50.4)       | 1496 (52.6)              | 895 (50.7)       |
| Light activity                  | 1302 (24.0)    | 214 (26.6)       | 696 (24.5)               | 392 (22.2)       |
| Medical history:                |                |                  |                          |                  |
| Systolic blood pressure (mmHg)  | 125.4 ± 21.2   | 132.1 ± 23.4     | 124.4 ± 20.6             | 124.0 ± 20.5     |
| Diastolic blood pressure (mmHg) | 71.8 ± 10.2    | 74.1 ± 11.1      | 71.7 ± 10.1              | 70.8 ± 9.9       |
| Fasting serum glucose (mg/dL)   | 89.5 ± 10.5    | 90.7 ± 11.4      | 89.4 ± 10.5              | 89.2 ± 10.2      |
| Antihypertensive medication use  | 1789 (33)      | 431 (54)         | 850 (30)                 | 508 (29)         |
For all 4 measures of K, in minimally-adjusted models (model 1), we found significant inverse associations between K and HOMA-IR, with lower levels of K associated with higher HOMA-IR. However, none of these associations remained significant in fully-adjusted models. (data not shown)

Incident diabetes

In longitudinal analyses, of the 5415 participants who were free from diabetes at baseline, 1281 participants developed diabetes during a mean follow-up of 8 years. During this time, there was a higher crude incident rate of diabetes (cases per 1000 person-years) among Hispanics (41.6) compared to Chinese Americans (34.0), African Americans (29.2), and whites (26.0).

Serum K was inversely associated with diabetes risk, but this association was attenuated in fully-adjusted models. (Table 3) Compared to those with a higher serum K (>4.5 mmol/L), after adjustment for age, sex, race, and study site, for those participants with a low-normal serum K (<4.0 mmol/L), there was a significantly increased risk of diabetes, with an HR (95% CI) of 1.23 (1.04, 1.47), P-value = 0.02; however this association was no longer significant with further adjustment. There was no statistical interaction between serum K and ethnic group on this association (P = 0.25, model 2). There was also no statistical interaction between serum K and hypertension status in this association (P = 0.53) This pattern of association was similar for all ethnic groups except for Chinese Americans.

Dietary K was also inversely associated with diabetes risk, but this association, again, was attenuated in fully-adjusted models. For each standard deviation (SD) decrease in dietary K, after adjustment for age, sex, race, and study site, and total energy intake, there was a significantly increased risk of diabetes, with an HR (95% CI) of 1.11 (1.00, 1.24), P-value = 0.04. (Table 4) We found no significant associations between random spot urinary K measures and diabetes risk. However, in our minimally-adjusted model, we did find an inverse association between FEK and diabetes risk. (S3 Appendix Table) Compared to those in the highest quartile of FEK, in models adjusted for age, sex, race, and study site only, those in the lowest quartile (<8%), had a higher risk of diabetes (HR) (95% CI) of 1.19 (1.01, 1.39), P-value = 0.03; however, this association was attenuated in model 2. There were no significant interactions between dietary K, urinary K or FEK and ethnic group on these associations for any of the models evaluated. Patterns of association between urinary K or FEK with diabetes risk were similar for all 4 ethnic groups.

Table 1. (Continued)

| Covariate                                      | All (N = 5415) | K < 4.0 (N = 804) | 4.0 ≤ K < 4.5 (N = 2844) | K ≥ 4.5 (N = 1767) |
|------------------------------------------------|----------------|-------------------|--------------------------|--------------------|
| ARB or ACE-I use                                | 749 (13.8)     | 157 (19.5)        | 337 (11.8)               | 255 (14.4)         |
| Thiazide diuretics w/o K-sparing agents         | 351 (6.5)      | 164 (20.4)        | 132 (4.6)                | 55 (3.1)           |
| Thiazide diuretics w/ K-sparing agents          | 203 (3.7)      | 80 (10.0)         | 84 (3.0)                 | 39 (2.2)           |
| Loop diuretics                                 | 79 (1.5)       | 18 (2.2)          | 31 (1.1)                 | 30 (1.7)           |
| Potassium supplements                           | 97 (1.8)       | 50 (6.2)          | 36 (1.3)                 | 11 (0.6)           |
| Potassium-sparing agents                        | 28 (0.5)       | 7 (0.9)           | 12 (0.4)                 | 9 (0.5)            |
| eGFR CKD-EPI (mL/min/1.73m²)                    | 77.8 ± 15.5    | 79.0 ± 16.2       | 79.1 ± 14.9              | 75.3 ± 15.9        |
| Dietary potassium intake (mg/day)               | 2847 ± 1458    | 2676 ± 1407       | 2827 ± 1466              | 2956 ± 1459        |

Entries are mean ± standard deviation or number (%)

ARB- angiotensin II receptor antagonists; ACE-I- angiotension converting enzyme-inhibitors

GFR = glomerular filtration rate

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Discussion

In these analyses of a multi-ethnic US cohort, we found a significant inverse association between serum K with fasting glucose. We also found crude inverse associations between K measures, insulin resistance, and diabetes risk; however, these associations were not significant with multivariable-adjustment of confounders. We found no statistical interaction between measures of K and ethnic group on the outcomes of either fasting glucose or diabetes risk. Some of the effect estimates of these associations, particularly involving serum K, appeared to differ by ethnicity in direction and/or magnitude, but these differences were not statistically

Table 2. Associations Between Serum Potassium and Fasting Glucose, by Ethnicity (N = 5415).

| Serum K (mmol/L) | N     | Mean glucose (mg/dL) | Adjusted difference (95% CI) (mg/dL) |
|-----------------|-------|----------------------|--------------------------------------|
|                 |       |                      | Model 1 | Model 2 |
| All participants| 5415  | 89.5 (10.5)          | 1.7 (0.8, 2.6) | 1.3 (0.2, 2.4) |
| < 4.0           | 1767  | 90.7 (11.4)          | 0.4 (-0.2, 1.0) | 0.3 (-0.5, 1.0) |
| 4.0–4.49        | 804   | 89.4 (10.5)          | 0 (Ref.) | 0 (Ref.) |
| ≥ 4.5           | 2844  | 89.2 (10.2)          | 1.1 (0.7, 1.5) | 0.6 (0.1, 1.0) |
| per 0.5 lower   |       |                      | < 0.0001 | 0.03 |
| White           | 2281  | 87.8 (10.1)          | 2.4 (1.0, 3.9) | 1.8 (0.3, 3.3) |
| < 4.0           | 238   | 89.2 (11.4)          | 0.4 (-0.4, 1.3) | 0.6 (-0.3, 1.5) |
| 4.0–4.49        | 1117  | 87.6 (10.2)          | 0 (Ref.) | 0 (Ref.) |
| ≥ 4.5           | 926   | 87.7 (9.7)           | 1.2 (0.6, 1.8) | 0.8 (0.2, 1.4) |
| per 0.5 lower   |       |                      | < 0.0001 | 0.01 |
| Chinese-American| 679   | 91.5 (9.9)           | 0.92    | 0.52 |
| < 4.0           | 160   | 90.9 (10.1)          | -0.7 (-3.4, 1.9) | -1.6 (-6.0, 2.7) |
| 4.0–4.49        | 435   | 91.5 (9.7)           | -0.8 (-3.2, 1.6) | -1.7 (-5.5, 2.1) |
| ≥ 4.5           | 84    | 92.5 (10.7)          | 0 (Ref.) | 0 (Ref.) |
| per 0.5 lower   |       |                      | 0.1 (-1.3, 1.5) | -0.7 (-2.9, 1.5) |
| p-value         |       |                      | 0.002   | 0.56 |
| African-American| 1345  | 90.2 (10.8)          | 1.7 (0.0, 3.3) | 0.6 (-1.7, 2.8) |
| < 4.0           | 270   | 91.3 (11.4)          | 0.0 (-1.3, 1.3) | -1.0 (-2.8, 0.7) |
| 4.0–4.49        | 707   | 89.7 (10.7)          | 0 (Ref.) | 0 (Ref.) |
| ≥ 4.5           | 368   | 90.5 (10.4)          | 1.2 (0.5, 1.9) | 0.3 (-0.7, 1.4) |
| per 0.5 lower   |       |                      | 0.002   | 0.56 |
| Hispanic        | 1110  | 91.0 (10.9)          | 2.0 (-0.3, 4.2) | 1.7 (-1.2, 4.5) |
| < 4.0           | 136   | 92.2 (12.5)          | 0.9 (-0.4, 2.2) | 0.9 (-0.9, 2.6) |
| 4.0–4.49        | 585   | 90.9 (10.8)          | 0 (Ref.) | 0 (Ref.) |
| ≥ 4.5           | 389   | 90.8 (10.3)          | 1.1 (0.2, 2.1) | 0.6 (-0.6, 1.7) |
| per 0.5 lower   |       |                      | 0.02    | 0.35 |

Model 1: adjusted for age (continuous), sex, race, and study site.
Model 2: M1 + waist circumference (continuous), BMI (continuous), smoking, family history of diabetes, education, income, alcohol use, physical activity, systolic blood pressure, antihypertensive medication use and use of other medications listed in Table 1.

Significant associations in bold.
Race*serum potassium, \( P = 0.53 \)

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These differences were most notable among the Chinese Americans, a population in whom these associations have not been well-studied before.

The finding of a significant inverse association between serum K and fasting glucose is consistent with other cross-sectional studies which evaluated associations between K and measures of glucose metabolism. In analyses of the Cardiovascular Health Study (CHS), compared to those with higher levels, those with lower serum and dietary K had reduced insulin sensitivity; this study did not evaluate the association between K and fasting glucose.[12] A cross-sectional study of a German cohort found that participants with a low-normal serum K had a higher prevalence of prediabetes among the participants with hypertension.[13]

### Table 3. Associations Between Serum Potassium and Incident Diabetes, by Ethnicity (N = 5415).

| Serum K (mmol/L) | Number at risk | Number of events | Unadjusted incidence ratio (per 1000 yrs) | Model 1 (95% CI) | Model 2 (95% CI) |
|------------------|----------------|------------------|------------------------------------------|-----------------|-----------------|
|                  |                |                  |                                          | Hazard ratio    | Hazard ratio    |
| All participants | 5415           | 1281             | 30.8                                     |                 |                 |
| < 4.0            | 1767           | 208              | 35.0                                     | 1.23 (1.04, 1.47)| 0.96 (0.75, 1.24)|
| 4.0–4.49         | 804            | 662              | 29.8                                     | 0.99 (0.87, 1.12)| 1.05 (0.89, 1.23)|
| ≥ 4.5            | 2844           | 411              | 30.5                                     | 1.0 (Ref.)      | 1.0 (Ref.)      |
| per 0.5 lower    |                |                  |                                          | 1.11 (1.02, 1.20)| 1.01 (0.91, 1.12)|
| p-value          |                |                  |                                          | 0.02            | 0.86            |
| White            |                |                  |                                          |                 |                 |
| < 4.0            | 2281           | 477              | 26.0                                     | 1.22 (0.89, 1.68)| 0.98 (0.66, 1.45)|
| 4.0–4.49         | 1117           | 235              | 25.5                                     | 1.02 (0.84, 1.23)| 1.13 (0.91, 1.42)|
| ≥ 4.5            | 926            | 191              | 25.9                                     | 1.0 (Ref.)      | 1.0 (Ref.)      |
| per 0.5 lower    |                |                  |                                          | 1.14 (0.99, 1.30)| 1.05 (0.91, 1.22)|
| p-value          |                |                  |                                          | 0.06            | 0.49            |
| Chinese-American |                |                  |                                          |                 |                 |
| < 4.0            | 679            | 175              | 34.0                                     | 0.85 (0.51, 1.40)| 0.47 (0.21, 1.08)|
| 4.0–4.49         | 435            | 107              | 32.2                                     | 0.75 (0.48, 1.18)| 0.50 (0.26, 0.97)|
| ≥ 4.5            | 84             | 26               | 43.0                                     | 1.0 (Ref.)      | 1.0 (Ref.)      |
| per 0.5 lower    |                |                  |                                          | 0.96 (0.74, 1.25)| 0.85 (0.52, 1.39)|
| p-value          |                |                  |                                          | 0.77            | 0.52            |
| African-American |                |                  |                                          |                 |                 |
| < 4.0            | 1345           | 290              | 29.2                                     | 1.17 (0.84, 1.63)| 0.77 (0.46, 1.30)|
| 4.0–4.49         | 707            | 148              | 27.9                                     | 0.96 (0.72, 1.26)| 0.95 (0.64, 1.40)|
| ≥ 4.5            | 368            | 79               | 29.8                                     | 1.0 (Ref.)      | 1.0 (Ref.)      |
| per 0.5 lower    |                |                  |                                          | 1.05 (0.89, 1.23)| 0.88 (0.70, 1.11)|
| p-value          |                |                  |                                          | 0.56            | 0.27            |
| Hispanic         |                |                  |                                          |                 |                 |
| < 4.0            | 1110           | 339              | 41.6                                     | 1.51 (1.09, 2.08)| 1.27 (0.81, 1.98)|
| 4.0–4.49         | 585            | 172              | 39.4                                     | 1.02 (0.80, 1.29)| 1.08 (0.79, 1.49)|
| ≥ 4.5            | 389            | 115              | 40.9                                     | 1.0 (Ref.)      | 1.0 (Ref.)      |
| per 0.5 lower    |                |                  |                                          | 1.19 (1.00, 1.41)| 1.08 (0.88, 1.33)|
| p-value          |                |                  |                                          | 0.04            | 0.46            |

Model 1: adjusted for age (continuous), sex, race, and study site.
Model 2: M1 + waist circumference (continuous), BMI (continuous), smoking, family history of diabetes, education, income, alcohol use, physical activity, systolic blood pressure, antihypertensive medication use and use of other medications listed in Table 1.

Significant associations in bold. Race*serum potassium, P = 0.25

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The finding of no significant associations between measures of K and diabetes risk differs from some studies which did show a significant inverse association between serum or dietary K and diabetes risk.[1–3] In the analyses of the Atherosclerotic Risk in Communities (ARIC) and Coronary Artery Risk Development in Young Adults (CARDIA) cohorts, significant associations

Table 4. Associations Between Dietary Potassium (mg/day) and Incident Diabetes, by Ethnicity (N = 5415).

| Dietary K (mg/Day) | Number at risk | Number of events | Unadjusted incidence ratio (per 1000 yrs) | Hazard ratio (95% CI) |
|-------------------|----------------|-----------------|-----------------------------------------|----------------------|
|                   |                |                 |                                         | Model 1 | Model 2  |
| All               | 5415           | 1281            | 30.8                                    | 1.21 (0.96, 1.53) | 0.93 (0.68, 1.27) |
| <1820             | 1384           | 309             | 31.7                                    | 1.05 (0.86, 1.28) | 0.95 (0.74, 1.22) |
| 1820–2600         | 1322           | 305             | 29.2                                    | 1.04 (0.88, 1.24) | 0.92 (0.74, 1.14) |
| 2600–3550         | 1335           | 325             | 30.2                                    | 1.0 (Ref.)      | 1.0 (Ref.)      |
| >3550             | 1374           | 342             | 32.1                                    | 1.11 (1.00, 1.24) | 0.99 (0.86, 1.13) |
| per SD decrease   |                |                 |                                         | 0.04      | 0.86     |
| White             | 2281           | 477             | 26                                      | 1.28 (0.92, 1.79) | 1.17 (0.79, 1.75) |
| <1820             | 356            | 68              | 24.8                                    | 1.11 (0.85, 1.45) | 1.04 (0.76, 1.43) |
| 1820–2600         | 583            | 115             | 24.4                                    | 1.19 (0.93, 1.51) | 1.12 (0.85, 1.48) |
| 2600–3550         | 690            | 154             | 27.6                                    | 1.0 (Ref.)      | 1.0 (Ref.)      |
| >3550             | 652            | 140             | 26.2                                    | 1.18 (1.04, 1.34) | 1.08 (0.91, 1.27) |
| per SD decrease   |                |                 |                                         | 0.009     | 0.38     |
| Chinese-American  | 679            | 175             | 34                                      | 1.19 (0.72, 1.96) | 0.88 (0.34, 2.25) |
| <1820             | 328            | 84              | 34.9                                    | 0.98 (0.56, 1.69) | 0.98 (0.36, 2.61) |
| 1820–2600         | 147            | 35              | 31                                      | 1.02 (0.59, 1.76) | 0.88 (0.33, 2.37) |
| 2600–3550         | 128            | 35              | 34.6                                    | 1.0 (Ref.)      | 1.0 (Ref.)      |
| >3550             | 76             | 21              | 34.9                                    | 1.18 (0.96, 1.45) | 1.20 (0.82, 1.77) |
| per SD decrease   |                |                 |                                         | 0.11      | 0.36     |
| African-American  | 1345           | 290             | 29.2                                    | 1.38 (0.94, 2.01) | 0.75 (0.43, 1.30) |
| <1820             | 401            | 90              | 31.8                                    | 1.20 (0.83, 1.74) | 1.01 (0.62, 1.65) |
| 1820–2600         | 316            | 69              | 28.8                                    | 0.99 (0.69, 1.43) | 0.84 (0.52, 1.37) |
| 2600–3550         | 307            | 62              | 26.5                                    | 1.0 (Ref.)      | 1.0 (Ref.)      |
| >3550             | 321            | 69              | 29.3                                    | 1.15 (0.99, 1.34) | 0.98 (0.81, 1.17) |
| per SD decrease   |                |                 |                                         | 0.07      | 0.79     |
| Hispanic          | 1110           | 339             | 41.6                                    | 0.99 (0.70, 1.39) | 0.74 (0.47, 1.16) |
| <1820             | 237            | 67              | 37.9                                    | 0.92 (0.67, 1.25) | 0.71 (0.47, 1.06) |
| 1820–2600         | 289            | 86              | 39.3                                    | 0.89 (0.65, 1.21) | 0.61 (0.40, 0.93) |
| 2600–3550         | 249            | 74              | 40.1                                    | 1.0 (Ref.)      | 1.0 (Ref.)      |
| >3550             | 335            | 112             | 47.7                                    | 0.99 (0.87, 1.14) | 0.87 (0.74, 1.01) |
| per SD decrease   |                |                 |                                         | 0.93      | 0.07     |
| p-value           |                |                 |                                         |           |           |

Model 1: adjusted for age (continuous), sex, race, study site, and total energy intake.
Model 2: M1 + waist circumference (continuous), BMI (continuous), smoking, family history of diabetes, education, income, alcohol use, physical activity, systolic blood pressure, antihypertensive medication use and use of other medications listed in Table 1.
Significant associations in bold.
Race*dietary potassium, P = 0.46

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were found between serum K and dietary K intake with diabetes risk, respectively.[1, 2] In the ARIC cohort, compared with those with a high-normal serum potassium level (5.0–5.5 mmol/L), adults with serum K < 4.0 mmol/L, 4.0 – < 4.5 mmol/L, and 4.5 – < than 5.0 mmol/L had an adjusted HR (95% confidence interval [CI]) of incident DM of 1.64 (95% CI, 1.29–2.08), 1.64 (95% CI, 1.34–2.01), and 1.39 (95% CI, 1.14–1.71), respectively.[1] In the CARDIA cohort, there was a statistical interaction between dietary K intake and race (black/white). The association between dietary K intake and diabetes risk was not significant for whites; however, the association between dietary K intake, based in diet histories, and diabetes risk was non-linear but significant for blacks. In the CARDIA cohort, compared with black participants in the highest quintile of dietary K intake, and with adjustment for dietary factors and diabetes risk factors, those in the lowest to higher dietary K intake quintile had adjusted HRs (95% CI) of incident diabetes of 1.72 (0.87, 3.42), 1.99 (1.04, 3.78), 2.10 (1.14, 3.87), and 1.46 (0.79, 2.68) respectively.[2] In a sub-cohort of CARDIA, a significant inverse association was also found between 24-hour urinary measures and diabetes risk.[2] Compared to both ARIC and CARDIA cohorts, the participants of the MESA cohort were, on average, older in age. The MESA cohort has the strength of having a diverse population, but the number of participants in each specific minority ethnic group is smaller than the number of African Americans in either ARIC or CARDIA.[1, 2] In the analyses of the ARIC and CARDIA cohorts, respectively, over 2700 and 2300 African Americans were included in the analyses, while in these analyses of the MESA cohort, there were half this number of African Americans and even fewer Hispanics and Chinese Americans. The smaller population sizes could have limited the detection of a significant association between K measures and diabetes risk in the higher risk populations of MESA. Further study is needed to determine the potential differences in these cohorts that could account for these differing results.

This study extends prior studies by examining associations of K with glucose and diabetes among Hispanics and Chinese Americans. Among Hispanics, inverse associations between serum K with fasting glucose and diabetes risk were similar to those among white and black MESA participants. In contrast, among Chinese Americans, these associations were reversed; however, these associations were also not significant and sample size was small. These potential variations in associations by ethnic group deserve further study.

In multivariate models, urinary K was not significantly associated with fasting glucose or incident diabetes. However, in minimally-adjusted models, there was an inverse association between urine K with HOMA-IR. Random spot urine specimens are easy to collect during study visits, but their use for study measures likely needs further study for validation. 24-hour urinary potassium measurements have been found to be a fairly accurate reflection of dietary potassium intake;[14] however, 24-hour urine samples are very difficult to collect and have their own measurement problems.[15, 16] In the CARDIA study, three consecutive 24-hour urine specimens were collected in a sub-cohort of the participants. In this sub-cohort, those in the lowest quintile of 24-hour urinary K had a significantly increased diabetes risk compared to those participants in the highest quintile of 24-hour urinary K (HR 2.45; 95% CI 1.08, 5.59; p for trend = 0.04).[2] Recently in an international cohort, 24-hour urinary K levels were estimated from morning fasting midstream urine samples.[17, 18] In this study, investigators found a significant association between lower urinary K levels and increased systolic blood pressure an increase in a composite outcome of all-cause mortality and major cardiovascular events. This study did not evaluate the associations of urinary K with diabetes risk or measures of glucose metabolism. In our analyses of MESA participants, random samples were used for measurement of urinary K. Given the diurnal variation in urinary K excretion, the use of spot urine samples may need to be standardized to yield the best estimate of 24-hour urinary K measures.[19, 20]
In theory, FEK should reflect the renal handling of filtered potassium, as influenced by aldosterone as well as dietary K and sodium intake as well as serum K. In minimally-adjusted models only, our analyses did reveal inverse associations between FEK with fasting glucose, HOMA-IR, and diabetes risk, which may reflect these influences. In future studies, it may be important to assess the individual effect of these influences, such as measures of aldosterone, directly on measures of glucose, insulin, and diabetes risk, to help determine if and how FEK can be used in future studies.

There are several limitations of these analyses that should be mentioned. Limitations of this study include the measurement of serum and urine K at a single time point. Serum K and indeed all biological analytes have inherent variability that can lead to misclassification of exposures. While serum K is tightly regulated with homeostatic mechanisms within a fairly tight range, there is within-person variation that is significant with within-person coefficients of variation of about 5%.[21, 22] While this within-person variability is reasonably low, the within-population range is relatively small, and so persons could easily fluctuate between categories. Another limitation of this study is in the definition of the diabetes outcome which is limited by the dataset to use of fasting glucose and use of medications; post-challenge glucose and hemoglobin A1c measures were not available. Compared to the participants included in our analyses, the baseline characteristics of the participants who were excluded from our analyses differed somewhat with regards to demographics. We found no significant differences in K measures or fasting glucose. Other differences were modest and would be unlikely to bias the conclusions drawn from our analyses.

Given that this is a prospective cohort study, a post-hoc power calculation is generally not appropriate. However, given the relatively large number of events of incident diabetes and the large population, while modest associations, particularly within each ethnic sub-group, could be missed, it is unlikely that large associations would be missed. While there were no significant associations found between measures of K and diabetes risk in this cohort, there have been significant associations found in other cohorts. There could be other factors that mediate associations between K and glucose metabolism that we were unable to determine from this dataset, including the presence of genetic susceptibility. Further study may be warranted to take into account genetic susceptibility particularly with regards to the presence of mutations within genes of K-channels such as KCNJ11.

**Conclusions**

In conclusion, these analyses of the MESA cohort identified significant although small inverse associations between serum K and fasting glucose. There was no significant association between K and diabetes risk. While we found no statistical interaction between K and ethnicity, we did find differences in these associations that varied in magnitude and direction by ethnic group. Given the potential importance of K measures on not only diabetes risk, but also cardiovascular health, further study is needed to describe, more precisely, the relationship of potassium with glucose metabolism and potential effects on longer-term health outcomes. Also further study is needed to determine if these associations are similar in different ethnic groups.

**Supporting Information**

S1 Appendix Table. Associations Between Dietary Potassium and Fasting Glucose, by Ethnicity (N = 5415).

(DOCX)
S2 Appendix Table. Associations Between Fractional Excretion (%) (FEK) of Potassium and Fasting Glucose, by Ethnicity.

(DOCX)

S3 Appendix Table. Associations Between Fractional Excretion (%) of Potassium (FEK) and Incident Diabetes, by Ethnicity.

(DOCX)

S4 Appendix Table. Baseline Characteristics of non-diabetic MESA participants included and excluded from analysis population.

(DOCX)

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Author Contributions
Conceived and designed the experiments: RC DE IHdB. Performed the experiments: LZ. Analyzed the data: RC LZ DE IHdB JAN. Wrote the paper: RC LZ DE IHdB LPS KJM JAN BRK DSS JHI RT ANH.

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