**RESEARCH ARTICLE**

**KCNJ11** variants and their effect on the association between serum potassium and diabetes risk in the Atherosclerosis Risk in Communities (ARIC) Study and Jackson Heart Study (JHS) cohorts

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**Abstract**

**Background**

In the Atherosclerosis Risk in Communities (ARIC) Study and Jackson Heart Study (JHS) cohorts, serum potassium (K) is an independent predictor of diabetes risk, particularly among African-American participants. Experimental studies show that serum K levels affects insulin secretion. The **KCNJ11** gene encodes for a K channel that regulates insulin secretion and whose function is affected by serum K levels. Variants in **KCNJ11** are associated with increased diabetes risk. We hypothesized that there could be a gene-by-environment interaction between **KCNJ11** variation and serum K on diabetes risk.

**Methods**

Evaluating a combined cohort of ARIC and JHS participants, we sought to determine if **KCNJ11** variants are risk factors for diabetes; and if **KCNJ11** variants modify the association between serum K and diabetes risk. Among participants without diabetes at baseline, we performed multivariable logistic regression to determine the effect of serum K, **KCNJ11** variants, and their interactions on the odds of incident diabetes mellitus over 8–9 years in the entire cohort and by race.

**Results**

Of 11,812 participants, 3220 (27%) participants developed diabetes. 48% and 47% had 1 or 2 diabetes risk alleles of rs5215 and rs5219, respectively. Caucasians had higher proportions of these risk alleles compared to African Americans (60% vs 17% for rs5215 and 60%
Introduction

Prior analyses of the Atherosclerosis Risk in Communities (ARIC) Study and Jackson Heart Study (JHS) cohorts have shown low-normal serum potassium (K) to be associated with risk of diabetes, independent of traditional risk factors [1, 2], and that this association is more robust among African Americans than Caucasians [3, 4]. The mechanism for this association remains to be elucidated. However, past experimental studies conducted in healthy adults revealed that induction of low serum K, through use of high-dose diuretics or low-potassium diet and laxatives, can lead to the development of impaired glucose tolerance, through impairments in insulin secretion from pancreatic β-cells [5–7].

Many genetic variants are associated with increased diabetes risk, and some of these genetic variants reside in or near genes encoding voltage-gated K channels of pancreatic β-cells integral to glucose-stimulated insulin secretion [8]. These K-channels are stimulated by circulating glucose levels and allow entry of serum K into the cell. The subsequent high K environment leads to channel closure and stimulates insulin secretion. The genes encoding these channels include KCNJ11, KCNQ1, and ABCC8 [8, 9]. Two variants in KCNJ11, rs5215 and rs5219, are associated with an increased risk of type 2 diabetes in Caucasians and East Asians [10]; and rs5215 has also been found to be a significant predictor of type 2 diabetes in African Americans [11]. Variants in K channel genes have been associated with functional changes [9], and serum K levels could impact the function of these channels differentially based on variations in the channels.

A previous study has evaluated the significance of certain genetic variants on diabetes risk in the entire ARIC cohort; however, this study did not include the rs5219 KCNJ11 variant [11]. There have been no studies to determine the impact of the KCNJ11 variants on diabetes risk in the JHS cohort. Direct genotyping or good quality imputation data for KCNJ11 rs5215 and rs5219 were available in both ARIC and JHS cohorts; genotype data for risk alleles of KCNQ1 and ABCC8 were not available in both cohorts.

In this study, we combined data from the ARIC and JHS cohorts to determine: 1) if there is an association between KCNJ11 variants (rs5215 and rs5219) and risk of incident type 2 diabetes; 2) if these genetic variants are significant effect modifiers of the association between serum K and incident diabetes risk; and 3) if these associations and interactions differ by race. We hypothesized that the potential impact of low-normal serum K on incident diabetes risk may be stronger among people with an increased risk of diabetes due to KCNJ11 variants. If an interaction exists between the presence of these genetic variants and serum K levels, then interventions designed to increase serum K levels may preferentially help to decrease incident diabetes risk in people with these genetic variants.
Materials and methods

Institutional review boards at each of the participating institutions approved the study. In particular, the Duke University IRB approved this study as exempt research. The ARIC study is a prospective cohort of 15,792 adults between the ages of 45 and 64 years at the baseline visit. Participants were recruited from four communities in the US—Forsyth County, North Carolina, Jackson, Mississippi, Minneapolis, Minnesota, and Washington County, Maryland. All participants from Jackson, MS were African-American, while participants from Forsyth County included both African Americans and Caucasians. The participants in the other two communities were primarily white. All participants attended an initial baseline visit between 1987–1989. Three subsequent in-person visits took place at approximately three-year intervals for nine years of follow-up. Details of the design and conduct of the ARIC study have been published previously [12]. JHS is a community-based, prospective cohort study of 5,306 African-American adults, aged 21–95 years at the baseline visit, from the Jackson, Mississippi metropolitan area. Participants had baseline data collected between 2000 and 2004. Approximately 30% of the participants had participated in the ARIC study; the rest of the cohort was recruited from community-sampling approaches, volunteers, and families of other JHS participants [13]. Participants came for in-person visits approximately every four years and had telephone follow-up annually, through 2012, for an average of eight years of follow-up. Institutional review boards at each of the participating institutions approved the study.

Study participants

We excluded 592 ARIC participants who had not fasted 8 or more hours for the baseline visit; all participants from JHS had fasted 8 or more hours for their baseline visit. The remaining, non-overlapping ARIC and JHS study populations contained 18,875 individuals. Of these participants, we excluded participants who had prevalent diabetes (defined below) at baseline exam (N = 2325); missing information on diabetes status at baseline or any follow-up (N = 862); serum K > 5.5 (N = 168) or missing information on serum K (N = 122); missing SNP data (N = 2129), evidence of kidney dysfunction (eGFR < 30 mL/min/1.73m² or serum creatinine > 1.7 mg/dL) (N = 100); race other than black/African American or white/Caucasian (N = 35); and missing other covariates (N = 1322). This left a total of 11,812 participants (27% African American) for analyses (Fig 1).

Main exposures

Genotype data for the KCNJ11 variants rs5215 and rs5219 were available in both the ARIC and JHS cohorts. Both cohorts used the same genotyping methods which were performed at the Broad Institute, Boston, MA. In the ARIC cohort, these variants were determined by direct genotyping using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affy6.0) according to the manufacturer’s recommendations. Further details regarding the genotyping protocol including quality control have been published previously [14, 15]. In the JHS cohort, these variants were either genotyped directly (rs5215, call rate 0.868); or imputed from genome wide genotyping (Affymetrix 6.0) using the 1000 Genomes cosmopolitan reference panel (phase 1 v3) (rs5219, imputation Rsq 0.985) [16]. The two variants were coded as the number of diabetes risk alleles and kept as a continuous variable in the main analyses and dichotomized into carriers (at least one minor allele) and non-carriers (no minor alleles) in sensitivity analyses. The diabetes risk allele for rs5215 was assumed to be C; the diabetes risk allele for rs5219 was assumed to be T.

Serum K (mmol/L) was measured at the baseline exam with a direct electrode potentiometric assay on undiluted serum. For the main analyses, this measure was categorized into
quartiles (with the highest quartile as the reference group). In sensitivity analyses, serum K was analyzed as a continuous variable, scaled by its standard deviation.

**Outcome**

The outcome of interest was incident diabetes during the 8 or 9 years of follow-up. A diagnosis of diabetes was based on one of the following criteria: 1) self-report history of diabetes ("Has a doctor ever said you had diabetes?"); 2) fasting glucose \( \geq 126 \text{ mg/dL} \); 3) use of diabetic medication (actual and/or self-reported) within 2 weeks prior to clinic visit; or 4) hemoglobin A1c (A1c) \( \geq 6.5\% \) (for JHS participants only). Incident diabetes was defined as evidence of diabetes based on the criteria above at any follow-up visit.
Covariates

For these analyses, all covariates were derived from the baseline exams, which took place in 1987–1989 for ARIC participants and in 2000–2004 for JHS participants. Covariates were chosen based on their potential association with diabetes risk and serum K levels. The following covariates were based on self-report: age (years), modeled as a continuous variable; sex, female or male; self-reported race, categorized as white or black, with white used as the reference category; family income, categorized into 4 groups, <12k, 12k to <25k, 25k to <50k, and ≥50k, with lowest income category used as the reference; parental history of diabetes, self-report of either parent having a history of diabetes. Other covariates included variables determined by measurements at the in-person visits as follows: body mass index (BMI) (kg/m²); systolic blood pressure (mmHg); presence of hypertension: per Joint National Committee (JNC) 7, hypertension is defined as blood pressure ≥140/90 or self-report use of blood pressure-lowering medication within 2 weeks prior to clinic visit; leisure index: a 4 item questionnaire with 5 Likert-type responses was used to measure the amount of physical activity during leisure time. The index is the average score of the 4 questions and ranges from 1 to 5, where a higher score means more active and a lower score means more leisurely. The following variables were analyzed from biological specimens collected during the baseline visit: serum creatinine (mg/dL); serum sodium (mmol/L); fasting plasma glucose (mg/dL); and fasting plasma insulin (IU/mL). Laboratory assays used for these measurements in both cohorts have been published previously [12, 17, 18]. The use of the following medications, taken individually or in a combination form, was verified by in-person assessment of medication bottles at the baseline visit: use of diuretics, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor antagonists.

Statistical methods

Baseline demographic and clinical characteristics of study participants were examined descriptively, by race/ethnicity. Exploratory logistic regression models were fit to investigate interaction effects of race and KCNJ11 variants (SNP) on the odds of incident diabetes. A likelihood-ratio test was used to determine if the race X SNP term had significant impact on odds of incident diabetes. Logistic regression was performed with minimally-adjusted and fully-adjusted multivariable models to investigate the association between incident diabetes and serum K, SNP, and serum K X SNP, respectively. A likelihood-ratio test was used to determine if the K X SNP term had significant impact on odds of incident diabetes. When these interaction terms were found not to be statistically significant, we ran the models without the interaction terms. Models were adjusted for age, sex, and race (minimally-adjusted, Model 1); additionally with either serum K or the SNP of interest (minimally-adjusted, Model 2). For multivariable models, additional adjustments were made for income, BMI, systolic blood pressure, serum creatinine, serum sodium, fasting plasma glucose, fasting plasma insulin, hypertension, parental history of diabetes, physical activity, and use of diuretics or β-blockers or ACE inhibitors, or Angiotensin II receptor antagonists, (fully-adjusted, Model 3); additionally with either serum K or the SNP of interest (fully-adjusted, Model 4).

We performed several sensitivity analyses to determine if inferences were sensitive to different assumptions. We performed analyses to determine if the inference was sensitive to serum K as a continuous variable or to combining the minor allele categories. We also examined associations within sub-groups of our total cohort. In the JHS sub-group, we performed analyses adjusting for known pedigrees in the JHS cohort. Additionally, in each sub-group, ARIC and JHS, we performed analyses adjusting for population substructure variables available for each study.
Statistical analyses were performed using R 3.3.0 (R Core Team 2016, Vienna, Austria) and SAS 9.4 (SAS Institute, Cary, NC). All hypothesis tests were 2-sided at the 0.05 level of significance. No adjustment for multiple testing for the 2 SNPs was performed.

**Results**

**Study population**

Based on eligibility criteria described above, we included 11,812 participants in the models for the overall cohort, of which 8,653 were Caucasian and 3,159 were African American. Fig 1 depicts the selection of participants for these analyses. Baseline characteristics of these participants are shown by race/ethnicity in Table 1. Compared to Caucasians, on average African Americans had a higher BMI, higher blood pressure and prevalence of hypertension, higher prevalence of a parental history of diabetes, less physical activity, lower income, and lower serum K.

The presence of 1 and 2 diabetes risk allele(s) of rs5215 was found in 38% and 11% of the entire cohort, respectively; while the presence of 1 and 2 diabetes risk allele(s) of rs5219 was found in 37% and 11% of the entire cohort, respectively. Only 17% and 13% of African American participants had 1 or 2 minor alleles for rs5215 and rs5219, respectively. Among Caucasian participants, 60% had 1 or 2 minor alleles for rs5215, and 60% had 1 or 2 minor alleles for rs5219 (Table 1). In this cohort, 3220 (27%) participants developed diabetes during the follow-up period.

**Interaction results**

In fully-adjusted multivariable models, there was no significant interaction between race and either rs5215 or rs5219 (P = 0.49 and 0.50, respectively) on odds of incident diabetes. In the fully-adjusted multivariable models, there was no significant interaction between serum K and either rs5215 or rs5219 on odds of incident diabetes (P = 0.54 and 0.69, respectively) (Table 2).

**Models 1 and 2, minimally-adjusted multivariable models**

In minimally-adjusted models, there was a significant inverse association between serum K and incident diabetes. Among all participants, after adjusting for age, sex, and race, those in the lowest serum K quartile had significantly higher odds of incident diabetes compared to those in the highest serum K quartile [OR = 1.39, 95% CI = (1.23, 1.57)]. When stratified by race, results were similar for both whites and blacks (Model 1, Table 3).

In the entire cohort, after adjusting for age, sex, and race, rs5215 was not significantly associated with odds of diabetes, with an OR (95% CI) of 0.98 (0.92, 1.05). In the minimally-adjusted model, stratified by race, similar results were obtained for whites and blacks. In the entire cohort, adjusting for age, sex, and race, rs5219 was also not associated with odds of diabetes, with an OR (95% CI) of 0.99 (0.92, 1.06); with no significant association for whites or blacks in stratified models (Model 1, Table 3). Results were similar for both serum K and each KCNJ11 variant when both serum K and each variant were included in minimally-adjusted models (Model 2, Table 3).

**Models 3 and 4, fully-adjusted multivariable models**

In multivariable models, serum K continued to be a significant predictor of incident diabetes both without adjustment for the KCNJ11 variants of interest and with adjustment for the KCNJ11 variants of interest (Models 3 and 4, Table 2). In the model adjusted for rs5215, those in the lowest quartile of serum K had higher odds of incident diabetes compared to those in...
the highest quartile of serum K, with an OR (95% CI) of 1.21 (1.05, 1.4). In the model adjusted for rs5219, compared to those in the highest quartile of serum K, those in the lowest quartile of serum K had an OR (95% CI) of incident diabetes of 1.21 (1.05, 1.4). In models stratified by

Table 1. Baseline characteristics of 11,812 ARIC and JHS participants overall and stratified by race.

|                                      | Overall       |           |           |
|--------------------------------------|---------------|-----------|-----------|
|                                      | Caucasians    | African Americans |
| n                                    | 11,812        | 8653      | 3159      |
| Age (years)                          | 53.6 ± 6.3    | 54.1 ± 5.7| 52.3 ± 7.6|
| Female sex                           | 6631 (56.1)   | 4642 (53.7)| 1989 (63.0) |
| Field center                         |               |           |           |
| Forsyth County, NC                   | 2945 (24.9)   | 2686 (31.0)| 259 (8.2)  |
| Jackson, MS                          | 2865 (23.3)   | 0 (0)     | 2865 (90.7)|
| Minneapolis, MN                      | 2957 (25.0)   | 2944 (34.0)| 13 (0.4)   |
| Washington County, MD                | 3045 (25.8)   | 3023 (34.9)| 22 (0.7)   |
| Income                               |               |           |           |
| <$12,000                             | 1396 (11.8)   | 496 (5.7) | 900 (28.5) |
| $12,000 to <$25,000                  | 2487 (21.1)   | 1619 (18.7)| 868 (27.5) |
| $25,000 to <$50,000                  | 4543 (38.5)   | 3743 (43.3)| 800 (25.3) |
| ≥ $50,000                            | 3386 (28.7)   | 2795 (32.3)| 591 (18.7) |
| BMI (kg/m²)                          | 27.5 ± 5.4    | 26.7 ± 4.6| 29.9 ± 6.5|
| Activity                             | 2.4 ± 0.6     | 2.5 ± 0.5 | 2.1 ± 0.7 |
| eGFR (mL/min/1.73 m²)                | 71.7 ± 14.4   | 67.9 ± 10.6| 82.1 ± 17.8|
| Serum creatinine (mg/dL)             | 1.1 ± 0.2     | 1.1 ± 0.2 | 1.1 ± 0.2 |
| Serum sodium (mmol/L)                | 141 ± 2.3     | 140.9 ± 2.3| 141.2 ± 2.4|
| Fasting plasma glucose (mg/dL)       | 97.9 ± 9.5    | 98.5 ± 9.0| 96.1 ± 10.5|
| Fasting plasma insulin (IU/mL)       | 11.5 ± 8.5    | 10.4 ± 7.6| 14.5 ± 10.0|
| Systolic blood pressure (mmHg)       | 119.8 ± 17.7  | 117.5 ± 16.6| 126.0 ± 19.2|
| ABD medicationsa                      | 2779 (23.5)   | 1767 (20.4)| 1012 (32.0) |
| Hypertension                         | 3773 (31.9)   | 2142 (24.8)| 1631 (51.6) |
| Parent history of diabetes mellitus  | 2567 (21.7)   | 1730 (20.0)| 837 (26.5) |
| Serum potassium (quartiles) (mmol/L) |               |           |           |
| 2.5 ≤ K < 4.1                        | 2314 (19.6)   | 1245 (14.4)| 1069 (33.8) |
| 4.1 ≤ K < 4.4                        | 3157 (26.7)   | 2124 (24.6)| 1033 (32.7) |
| 4.4 ≤ K < 4.7                        | 2946 (24.9)   | 2336 (27.0)| 610 (19.3) |
| 4.7 ≤ K < 5.5                        | 3395 (28.7)   | 2948 (34.1)| 447 (14.2) |
| Serum potassium (continuous) (mmol/L) | 4.4 ± 0.5    | 4.5 ± 0.4 | 4.2 ± 0.4 |
| rs5215                                |               |           |           |
| 0 diabetes risk alleles              | 6088 (51.5)   | 3468 (40.1)| 2620 (82.9) |
| 1 diabetes risk allele               | 4461 (37.8)   | 3949 (45.6)| 512 (16.2) |
| 2 diabetes risk alleles              | 1263 (10.7)   | 1236 (14.3)| 27 (0.9)   |
| rs5219                                |               |           |           |
| 0 diabetes risk alleles              | 6217 (52.6)   | 3466 (40.1)| 2751 (87.1) |
| 1 diabetes risk allele               | 4355 (36.9)   | 3963 (45.8)| 392 (12.4) |
| 2 diabetes risk alleles              | 1240 (10.5)   | 1224 (14.2)| 16 (0.5)   |

Continuous variables presented as mean ± SD
Categorical variables presented as n (%)

*ABD medications to include use of diuretics or β-blockers or ACE inhibitors, or Angiotensin II receptor antagonists

https://doi.org/10.1371/journal.pone.0203213.t001
race, this association between serum K and odds of incident diabetes persisted in whites but
was no longer significant in blacks (Models 3, 4, Table 3).

In sensitivity analyses, we also separated our combined cohort into ARIC and JHS sub-
groups. In the JHS sub-group, we adjusted for relatedness using generalized estimating equa-
tions in SAS 9.3 (284 out of 862 JHS participants in our analysis related to another included
participant through a known pedigree, maximum family size 13). We found that this analysis

Table 2. Interaction effects of serum K and respecti vely, rs5215 and rs5219 on inciden t diabetes in 11,812 ARIC-JHS participants , overall and by race.

| Serum K X rs5215 | Overall OR (95% CI) | P | Whites OR (95% CI) | P | Blacks OR (95% CI) | P |
|------------------|---------------------|----|-------------------|----|-------------------|----|
| Minimally Adjusted, Model 1 | | | | | | |
| 2.5 ≤ K < 4.1 | 0.88 (0.73, 1.05) | 0.162 | 0.88 (0.71, 1.1) | 0.259 | 1.05 (0.57, 1.91) | 0.884 |
| 4.1 ≤ K < 4.4 | 1.03 (0.87, 1.21) | 0.745 | 1.03 (0.85, 1.24) | 0.781 | 1.26 (0.69, 2.3) | 0.446 |
| 4.4 ≤ K < 4.7 | 1.01 (0.85, 1.19) | 0.910 | 0.96 (0.8, 1.16) | 0.691 | 1.15 (0.58, 2.28) | 0.698 |
| 4.7 ≤ K ≤ 5.5 | 1 (ref) | 1 (ref) | 1 (ref) | | |
| Serum K X rs5219 | | | | | | |
| 2.5 ≤ K < 4.1 | 0.89 (0.74, 1.07) | 0.223 | 0.9 (0.72, 1.12) | 0.325 | 0.89 (0.46, 1.74) | 0.734 |
| 4.1 ≤ K < 4.4 | 1.04 (0.88, 1.23) | 0.637 | 1.05 (0.87, 1.27) | 0.610 | 1.07 (0.56, 2.06) | 0.830 |
| 4.4 ≤ K < 4.7 | 1.02 (0.86, 1.2) | 0.826 | 0.97 (0.81, 1.16) | 0.737 | 1.11 (0.53, 2.33) | 0.782 |
| 4.7 ≤ K ≤ 5.5 | 1 (ref) | 1 (ref) | 1 (ref) | | |
| Fully Adjusted, Model 2 | | | | | | |
| Serum K X rs5215 | | | | | | |
| 2.5 ≤ K < 4.1 | 0.9 (0.73, 1.09) | 0.279 | 0.84 (0.66, 1.07) | 0.169 | 1.09 (0.57, 2.11) | 0.788 |
| 4.1 ≤ K < 4.4 | 1.03 (0.86, 1.23) | 0.773 | 0.99 (0.8, 1.21) | 0.900 | 1.42 (0.73, 2.74) | 0.302 |
| 4.4 ≤ K < 4.7 | 1.03 (0.85, 1.23) | 0.789 | 0.98 (0.8, 1.2) | 0.834 | 1.25 (0.59, 2.66) | 0.554 |
| 4.7 ≤ K ≤ 5.5 | 1 (ref) | 1 (ref) | 1 (ref) | | |

Model 1- adjusted for age, sex, race (overall only), SNP (rs5215 or rs5219), K, SNP X K
Model 2- adjusted for age, sex, race (overall only), BMI, systolic blood pressure, presence of hypertension, use of ABD medications, serum creatinine, serum sodium, fasting glucose, fasting insulin, parental history of diabetes mellitus, physical activity, income, SNP (rs5215 or rs5219), K, SNP X K

https://doi.org/10.1371/journal.pone.0203213.t002

Sensitivity analyses

In multivariable models, with serum K as a continuous value scaled by its standard deviation,
serum K continued to have an inverse association with diabetes risk. In model 2 adjusted for
rs5215 and the interaction term serum K X SNP, serum K had an OR (95% CI) of incident dia-
betes of 0.88 (0.83, 0.94); similarly, in model 2 adjusted for rs5219 and the interaction term
serum K X SNP, the OR (95% CI) for serum K was 0.89 (0.84, 0.95) (Table 4).

In our combined cohort, when modeling rs5215 and rs5219 as dichotomized variables (car-
riers or non-carriers), neither variant was a significant predictor of incident diabetes. In multi-
variable model 4, rs5215 and rs5219 had OR (95% CI) of incident diabetes of 0.62 (0.26, 1.50)
and 0.76 (0.31, 1.84), respectively.

In sensitivity analyses, we also separated our combined cohort into ARIC and JHS sub-
groups. In the JHS sub-group, we adjusted for relatedness using generalized estimating equa-
tions in SAS 9.3 (284 out of 862 JHS participants in our analysis related to another included
participant through a known pedigree, maximum family size 13). We found that this analysis
| Serum K (mmol/L) | Minimally Adjusted, Model 1 | Overall | P-value | Whites | P-value | Blacks | P-value |
|-----------------|----------------------------|---------|---------|--------|---------|--------|---------|
| 2.5 ≤ K < 4.1   | 1.39 (1.23, 1.57)          | 0.000   | 1.36 (1.17, 1.58) | 0.000 | 1.37 (1.08, 1.75) | 0.010 |
| 4.1 ≤ K < 4.4   | 1.18 (1.06, 1.32)          | 0.004   | 1.18 (1.04, 1.34) | 0.012 | 1.17 (0.91, 1.49) | 0.217 |
| 4.4 ≤ K < 4.7   | 1.12 (1, 1.25)             | 0.059   | 1.16 (1.02, 1.32) | 0.021 | 0.97 (0.74, 1.27) | 0.827 |
| 4.7 ≤ K ≤ 5.5   | 1 (ref)                   | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| rs5215          | 0.98 (0.92, 1.05)          | 0.563   | 0.99 (0.92, 1.06) | 0.794 | 0.92 (0.76, 1.11) | 0.386 |
| rs5219          | 0.99 (0.92, 1.06)          | 0.732   | 0.99 (0.92, 1.06) | 0.702 | 1.02 (0.82, 1.25) | 0.887 |

| Serum K (mmol/L) | Minimally Adjusted, Model 2 with both K and SNP | Overall | P-value | Whites | P-value | Blacks | P-value |
|-----------------|------------------------------------------------|---------|---------|--------|---------|--------|---------|
| 2.5 ≤ K < 4.1   | 1.39 (1.23, 1.57)          | 0.000   | 1.36 (1.17, 1.58) | 0.000 | 1.37 (1.08, 1.75) | 0.010 |
| 4.1 ≤ K < 4.4   | 1.18 (1.06, 1.32)          | 0.004   | 1.18 (1.04, 1.34) | 0.012 | 1.17 (0.91, 1.49) | 0.216 |
| 4.4 ≤ K < 4.7   | 1.12 (1, 1.25)             | 0.060   | 1.16 (1.02, 1.32) | 0.022 | 0.97 (0.74, 1.27) | 0.823 |
| 4.7 ≤ K ≤ 5.5   | 1 (ref)                   | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| rs5215          | 0.98 (0.92, 1.05)          | 0.569   | 0.99 (0.92, 1.06) | 0.810 | 0.92 (0.76, 1.11) | 0.382 |
| rs5219          | 0.99 (0.93, 1.06)          | 0.751   | 0.99 (0.92, 1.06) | 0.715 | 1.02 (0.83, 1.26) | 0.828 |

| Serum K (mmol/L) | Fully Adjusted, Model 3 | Overall | P-value | Whites | P-value | Blacks | P-value |
|-----------------|-------------------------|---------|---------|--------|---------|--------|---------|
| 2.5 ≤ K < 4.1   | 1.21 (1.05, 1.4)         | 0.008   | 1.18 (0.99, 1.41) | 0.062 | 1.2 (0.92, 1.58) | 0.187 |
| 4.1 ≤ K < 4.4   | 1.3 (1.15, 1.47)         | 0.000   | 1.25 (1.08, 1.45) | 0.002 | 1.29 (0.99, 1.68) | 0.063 |
| 4.4 ≤ K < 4.7   | 1.14 (1.01, 1.3)         | 0.033   | 1.15 (1, 1.32)   | 0.046 | 1 (0.75, 1.34)   | 0.997 |
| 4.7 ≤ K ≤ 5.5   | 1 (ref)                 | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| rs5215          | 1.01 (0.94, 1.08)         | 0.843   | 1.02 (0.94, 1.1)  | 0.663 | 0.93 (0.76, 1.15) | 0.511 |
| rs5219          | 1.02 (0.95, 1.1)          | 0.590   | 1.01 (0.94, 1.09) | 0.741 | 1.08 (0.86, 1.36) | 0.520 |

| Serum K (mmol/L) | Fully Adjusted, Model 4 with both K and SNP | Overall | P-value | Whites | P-value | Blacks | P-value |
|-----------------|---------------------------------------------|---------|---------|--------|---------|--------|---------|
| 2.5 ≤ K < 4.1   | 1.21 (1.05, 1.4)         | 0.008   | 1.18 (0.99, 1.41) | 0.062 | 1.2 (0.92, 1.57) | 0.187 |
| 4.1 ≤ K < 4.4   | 1.3 (1.15, 1.47)         | 0.000   | 1.25 (1.09, 1.45) | 0.002 | 1.29 (0.99, 1.68) | 0.063 |
| 4.4 ≤ K < 4.7   | 1.14 (1.01, 1.3)         | 0.033   | 1.15 (1, 1.32)   | 0.045 | 1 (0.75, 1.34)   | 1.000 |
| 4.7 ≤ K ≤ 5.5   | 1 (ref)                | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| rs5215          | 1.01 (0.94, 1.08)         | 0.819   | 1.02 (0.94, 1.1)  | 0.638 | 0.93 (0.76, 1.14) | 0.505 |
| rs5219          | 1.02 (0.95, 1.1)          | 0.571   | 1.01 (0.94, 1.1)  | 0.717 | 1.08 (0.86, 1.36) | 0.509 |

Model 1- adjusted for age, sex, race (overall only), SNPs and serum K analyzed in separate models
Model 2- adjusted for age, sex, race (overall only), SNP (rs5215 or rs5219), K
Model 3- adjusted for age, sex, race (overall only), BMI, systolic blood pressure, presence of hypertension, use of ABD medications, serum creatinine, serum sodium, fasting glucose, fasting insulin, parental history of diabetes mellitus, physical activity, income, SNPs and serum K analyzed in separate models
Model 4- adjusted for age, sex, race (overall only), BMI, systolic blood pressure, presence of hypertension, use of ABD medications, serum creatinine, serum sodium, fasting glucose, fasting insulin, parental history of diabetes mellitus, physical activity, income, SNP (rs5215 or rs5219), K

https://doi.org/10.1371/journal.pone.0203213.t003
framework did not substantively change the association between serum K and diabetes risk; the SNP of interest and diabetes risk; or the significance of the interaction between serum K X SNP versus a simple logistic regression model. In each of the sub-groups, we additionally adjusted for ten ancestry principal component variables, and we found no significant change in the association between serum K and diabetes risk; the SNP of interest and diabetes risk; or the significance of the interaction between serum K X SNP.

We conducted a post-hoc power calculation to help determine what sample size would be needed to detect a significant association and interaction effects. We assumed a diabetes incidence of 0.27 with 3 controls to each case. We assumed allele frequencies from 0.15 to 0.60 to cover the allele frequencies in both Caucasians and African Americans. Additionally, we assumed a main effects odds ratio for each variant of 1.1, consistent with published data, and a main effects odds ratio of about 1.3 for a standard deviation of 0.5 (from Tables 1 and 2). With these assumptions and with our sample size, we would have had good power to detect a serum K X SNP interaction effect as low as 1.15 in the full data set. However, we likely did not have adequate power to detect the interaction within race strata, especially among African Americans.

**Discussion**

In these analyses of pooled data from ARIC and JHS, we confirmed that serum K is a predictor of incident diabetes, independent of traditional diabetes risk factors and independent of genetic variants of the KCNJ11 gene. We found similar associations among Caucasians and African Americans, although, in stratified models, results were statistically significant only for whites. Additionally, in this combined cohort, we found that genetic variants of the KCNJ11 gene are not significant predictors of diabetes risk for either race; and, these genetic variants are not effect modifiers of the association between serum K and incident diabetes for either race.

| Table 4. Associations of serum K (scaled/continuous), rs5215, and rs5219 with incident diabetes in 11,812 ARIC-JHS participants, overall and by race. |
|---|---|---|---|---|---|
| Minimally Adjusted, Model 1 | Overall (n = 11,812) | P | Caucasians (n = 8653) | P | African Americans (n = 3159) | P |
| Serum K (mmol/L) (scaled) | OR (95% CI) | 0.86 (0.82, 0.89) | 0.00 | 0.88 (0.83, 0.92) | 0.00 | 0.82 (0.76, 0.88) | 0.00 |
| Fully Adjusted, Model 2 rs5215 | Serum K (mmol/L) (scaled) | 0.88 (0.83, 0.94) | 0.00 | 0.87 (0.8, 0.95) | 0.00 | 0.9 (0.82, 0.99) | 0.03 |
| rs5215 | 0.67 (0.35, 1.3) | 0.24 | 0.55 (0.25, 1.22) | 0.14 | 0.49 (0.07, 3.2) | 0.45 |
| Interaction (serum K X rs5215) | 1.04 (0.97, 1.11) | 0.23 | 1.06 (0.98, 1.15) | 0.13 | 1.07 (0.88, 1.31) | 0.50 |
| Fully-adjusted, Model 2 rs5219 | Serum K (mmol/L) (scaled) | 0.89 (0.84, 0.95) | 0.00 | 0.88 (0.81, 0.95) | 0.00 | 0.9 (0.82, 0.99) | 0.02 |
| rs5219 | 0.79 (0.4, 1.54) | 0.49 | 0.6 (0.27, 1.32) | 0.20 | 0.38 (0.04, 3.54) | 0.40 |
| Interaction (serum K X rs5219) | 1.03 (0.96, 1.1) | 0.45 | 1.05 (0.97, 1.14) | 0.19 | 1.12 (0.88, 1.41) | 0.35 |

Model 1: adjusted for age, sex, race (Overall only)
Model 2: adjusted for age, sex, race (Overall only), BMI, systolic blood pressure, presence of hypertension, use of ABD medications, serum creatinine, serum sodium, fasting glucose, fasting insulin, parental history of diabetes mellitus, physical activity, income, serum K (quartiles), SNP (rs5215 or rs5219), and interaction terms (SNP X K)

https://doi.org/10.1371/journal.pone.0203213.t004
Serum K is an independent predictor of diabetes in ARIC, JHS, as well as in other cohorts, but not in all cohorts that have studied this association [1, 2, 19–21]. The potential biological mechanism explaining this association has not been definitively determined on a population level. However, the biological mechanism behind such an association can be hypothesized based on small clinical trials which have revealed that experimentally-induced hypokalemia (low serum K state) causes impairments in insulin secretion by pancreatic β-cells [5–7]. Similarly, the KCNJ11 gene codes for ATP-sensitive K channels, which are instrumental in insulin secretion [8, 9]. These channels rely on a gradient of potassium across cellular membranes to allow entry of extracellular/serum K into cells, a high-K environment, which leads to channel closure, subsequent depolarization of the cell membrane, and stimulation of insulin secretion [9]. A higher serum K level, would allow for easier entry of K into the cells via these channels. Lower serum K would be less favorable for K entry into a high intracellular K environment, and thus may prevent adequate insulin secretion. One in vitro study has demonstrated the impact of different levels of extracellular K levels (equivalent to serum K) on the function of similar voltage-gated K channels [22]. Genetic variants of the ATP-sensitive K channels could, in theory, prevent entry of K into cells and be more sensitive to decreased K gradients across the cellular membranes. However, the function of these ATP-sensitive K channels is complex and could be affected by other factors as well. Another in vitro study found that KCNJ11 variants led to decreased binding of ATP which led to impaired channel closure, thereby impairing insulin secretion [23]. This type of functional change would likely not result in sensitivity of the channel to K gradients.

While the association between serum K and diabetes risk was not found to be modified by the presence of the KCNJ11 variants, the risk of diabetes in certain sub-populations may be more influenced by serum K levels than others. Prior analyses of the ARIC cohort found that the association between serum K and diabetes risk was stronger among African Americans compared to Caucasians and that serum K was a significant mediator of the association between race and diabetes risk [3, 4].

However, in this analysis of a combined ARIC and JHS cohort, while we did find significant associations between serum K and diabetes risk among both Caucasians and African Americans, the associations in this current analysis were not stronger among African Americans. The cohort created for these analyses was different from the cohort created for prior analyses; participants were excluded for missing data of different covariates (particularly genetic data). Additionally, the prior analyses of the ARIC cohort utilized Cox models, while these analyses use logistic regression, which can also account for some of the differences in effect sizes. Therefore, further study is needed to determine whether or not the influence of serum K on risk of diabetes is stronger in African Americans compared to whites.

Other cohorts have identified other sub-populations whose risk of diabetes may be more influenced by serum K than others. A retrospective cohort study of patients followed in an Israeli health care system found a significant inverse association between serum K and diabetes risk; but this study found that age modified the association between serum K and dysglycemia, with a significant inverse association only among patients ≤ 41 years old [21]. A cross-sectional study of a German cohort evaluated the association between serum K and new-onset diabetes as well as with prediabetes [24]. There was a significant inverse association between serum K and risk of new-onset diabetes; however, this inverse association was modified by the presence of hypertension and was significant only among those with hypertension [24]. In this study, the multivariable models did include adjustment for use of blood pressure medications, including diuretics; however, there was no further detailed analysis of the influence of use of diuretics on this association of serum K and prediabetes among the participants with hypertension. Past studies have evaluated the association between antihypertensive
medications and diabetes risk, and several studies, but not all, have found that use of thiazide diuretics is associated with increased glucose levels and diabetes risk [25–28]. Further study of clinical trials evaluating thiazide use has revealed that serum K, which decreases with use of thiazides, may mediate the association between thiazide use and diabetes risk [29, 30]. Based on the studies above, it is clear that further investigation is needed to determine the characteristics of people, whether demographic, anthropometric, clinical, or even genetic factors other than KCNJ11 variants, whose diabetes risk could most be affected by low-normal serum K.

The finding that the presence of KCNJ11 variants was not a significant predictor of diabetes risk in this cohort was not completely unexpected. The significance of KCNJ11 variants on diabetes risk in other cohorts has been evaluated, but these cohorts have primarily been Caucasian or Asian. A meta-analysis of the effects of KCNJ11 on diabetes risk, combing results from 48 studies of Caucasian, East Asians and Indians, found that the adjusted odds of incident diabetes OR (95% CI) per risk allele was 1.12 (1.09, 1.16) [31]. Similar results were observed in a meta-analysis of only Caucasian cohorts [32]. One meta-analysis assessed the significance of the presence of KCNJ11 rs5215 among African Americans with similar results [adjusted OR (95% CI) of incident diabetes of 1.16 (1.09, 1.23)]. However, not all studies have found KCNJ11 to be associated with increased diabetes risk. In the Diabetes Prevention Program (DPP), a cohort of US participants (n = 3,534) with impaired glucose tolerance at baseline and followed for incident diabetes, presence of KCNJ11 variants was associated with decreased insulin secretion at baseline; but, over the initial 3 years of follow-up, the presence of these variants was not associated with an increased risk of diabetes [33]. Effect size heterogeneity or lack of power may contribute to null associations with incident diabetes risk, particularly in smaller cohorts.

In general, genetic studies have found that the presence of individual genetic risk variants may not confer a risk of diabetes that is significant, especially compared to clinical characteristics. However, several gene variants taken together may explain a higher proportion of diabetes risk; and in aggregate, may help identify patients that would benefit from a greater emphasis on prevention efforts.

While this study has several strengths, including a multi-ethnic population with data on multiple covariates, several limitations of these analyses should be mentioned, particularly with relation to the size of our combined cohort. Generalizability of this study may be limited by the following: a significant portion of the cohort (11%) did not have genetic data available; others were excluded due to missing information on variables; and these results are from two US community-based studies, with most of the African Americans primarily from one site, Mississippi, which is an area with characteristics and disease risks which are different than other areas in the US. Finally, we selected the ARIC and JHS cohorts for these analyses because of our past studies, which showed a significant association between serum K and diabetes risk. However, this sample size of this combined cohort is likely under-powered, particularly based on our post-hoc power calculation described in the results section, to detect significant associations between KCNJ11 variants and diabetes risk and to detect potential interactions of serum K with the KCNJ11 variants. Also, we did not adjust our analysis for ancestry principal components derived in a combined JHS and ARIC cohort, though sub-group analyses with adjustment for JHS and ARIC specific ancestry principal components showed no impact on the observed associations. In future studies, evaluating these associations in a larger cohort with standardized principal component variables and adjusting for racial admixture may help to make estimates of associations more reliable, particularly for associations by race.

While this study of the combined ARIC-JHS cohorts found that KCNJ11 variants are not significant risk factors for diabetes, our findings confirm the previously noted association between serum K and diabetes risk, independent of the presence of the KCNJ11 variants. This
study also found that this association is not modified by the presence of either of the two KCNJ11 variants analyzed. Further study is needed to determine the characteristics, both clinical and genetic, of patients that may be at highest risk of diabetes due to a low-normal serum K; and to determine if serum K might be a modifiable risk factor for those high-risk populations.

Acknowledgments

The authors thank the staff and participants of the ARIC study for their important contributions. The authors thank the participants and data collection staff of the Jackson Heart Study. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services. The authors also thank Ethan Lange, PhD, University of Colorado, Denver for his assistance with review of the manuscript.

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References

1. Chatterjee R, Yeh HC, Shafi T, Selvin E, Anderson C, Pankow JS, et al. Serum and dietary potassium and risk of incident type 2 diabetes mellitus: The Atherosclerosis Risk in Communities (ARIC) study. Arch Intern Med. 2010; 170(19):1745–51. https://doi.org/10.1001/archinternmed.2010.362 PMID: 20975023

2. Chatterjee R, Davenport CA, Svetkey LP, Batch BC, Lin PH, Ramachandran VS, et al. Serum potassium is a predictor of incident diabetes in African Americans with normal aldosterone: the Jackson Heart Study (JHS). Am J Clin Nutr. 2017; Feb; 105(2):442–449. https://doi.org/10.3945/ajcn.116.143255 PMID: 27974310

3. Chatterjee R, Brancati FL, Shafi T, Edelman D, Pankow JS, Mosley TH, et al. Non-Traditional Risk Factors are Important Contributors to the Racial Disparity in Diabetes Risk: The Atherosclerosis Risk in Communities Study. J Gen Intern Med. 2014; Feb; 29(2):290–7. https://doi.org/10.1007/s11606-013-2569-z PMID: 23943422

4. Chatterjee R, Yeh HC, Shafi T, Anderson C, Pankow JS, Miller ER, et al. Serum potassium and the racial disparity in diabetes risk: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr. 2011; 93(5):1087–91. https://doi.org/10.3945/ajcn.110.007286 PMID: 21967942

5. Rowe JW, Tobin JD, Rosa RM, Andres R. Effect of experimental potassium deficiency on glucose and insulin metabolism. Metabolism. 1980; 29(6):498–502. PMID: 6991855

6. Helderman JH, Elahi D, Andersen DK, Raizes GS, Tobin JD, Schocken D, et al. Prevention of the glucose intolerance of thiazide diuretics by maintenance of body potassium. Diabetes 1983;Feb; 32 (2):106–11. PMID: 6337892
7. Gorden P. Glucose intolerance with hypokalemia. Failure of short-term potassium depletion in normal subjects to reproduce the glucose and insulin abnormalities of clinical hypokalemia. Diabetes. 1973; 22 (7):544–51. PMID: 4719191

8. Brunetti A, Chieffi E, Foti D. Recent advances in the molecular genetics of type 2 diabetes mellitus. World journal of diabetes. 2014; 5(2):128–40. https://doi.org/10.4239/wjd.v5.i2.128 PMID: 24748926

9. Ashcroft FM, Rorsman P. K(ATP) channels and islet hormone secretion: new insights and controversies. Nature reviews Endocrinology. 2013; 9(11):660–9. https://doi.org/10.1038/nrendo.2013.166 PMID: 24042324

10. Gong B, Yu J, Li H, Li W, Tong X. The effect of KCNJ11 polymorphism on the risk of type 2 diabetes: a global meta-analysis based on 49 case-control studies. DNA and cell biology. 2012; 31(5):801–10. https://doi.org/10.1089/dna.2011.1445 PMID: 22082043

11. Ng MC, Shriner D, Chen BH, Li J, Chen WM, Guo X, et al. Meta-analysis of genome-wide association studies in African Americans provides insights into the genetic architecture of type 2 diabetes. PLoS Genet. 2014; 10(8):e1004517. https://doi.org/10.1371/journal.pgen.1004517 PMID: 25102180

12. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC Investigators. Am J Epidemiol. 1989; 129(4):687–702. PMID: 2646917

13. Fuqua SR, Wyatt SB, Andrew ME, Sarpong DF, Henderson FR, Cunningham MF, et al. Recruiting African-American research participation in the Jackson Heart Study: methods, response rates, and sample description. Ethn Dis. 2005; 15(4 Suppl 6):S6-18-29.

14. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, et al. Genome-wide association study of coronary heart disease and its risk factors in 8,090 African Americans: the NHLBI CARe Project. PLoS Genet. 2011; 7(2):e1001300. https://doi.org/10.1371/journal.pgen.1001300 PMID: 21347282

15. Doenyas-Barak K, Beberashvili I, Vinker S. Serum potassium is an age-dependent risk factor for pre-diabetes and diabetes in the Israeli population. Diab Vasc Dis Res. 2014; 11(2):103–9. https://doi.org/10.1089/dna.2011.1445 PMID: 22082043

16. Lettre G, Palmer CD, Young T, Ejeabe KG, Allayee H, Benjamin EJ, et al. Genome-wide association study of coronary heart disease and its risk factors in 8,090 African Americans: the NHLBI CARe Project. PLoS Genet. 2011; 7(2):e1001300. https://doi.org/10.1371/journal.pgen.1001300 PMID: 21347282

17. Carpenter MA, Crow R, Steffes M, Rock W, Heilbraun J, Evans G, et al. Laboratory, reading center, and coordinating center data management methods in the Jackson Heart Study. Am J Med Sci. 2004; 328 (3):131–44. PMID: 15367870

18. Afkarian M, Katz R, Bansal N, Correa A, Kestenbaum B, Himmelfarb J, et al. Diabetes, Kidney Disease, and Cardiovascular Outcomes in the Jackson Heart Study. Clin J Am Soc Nephrol. 2016; 11(8):1384–91. https://doi.org/10.2215/CJN.13111215 PMID: 27340284

19. Heianza Y, Hara S, Arase Y, Saito K, Totsuka K, Tsuji H, 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):762–7. https://doi.org/10.1007/s00125-010-1984-4 PMID: 21212932

20. Chatterjee R, Zelnick L, Mukamal KJ, Nettleton JA, Kestenbaum BR, Siscovick DS, et al. Potassium measures and their associations with glucose and diabetes risk: The Multi-Ethnic Study of Atherosclerosis (MESA). PLoS One. 2016; 11(6):e0157252. https://doi.org/10.1371/journal.pone.0157252 PMID: 27280455

21. Doenyas-Barak K, Beberashvili I, Vinker S. Serum potassium is an age-dependent risk factor for diabetes and diabetes in the Israeli population. Diab Vasc Dis Res. 2014; 11(2):103–9. https://doi.org/10.1177/147916414521227 PMID: 24464151

22. Babenko AP, Gonzalez G, Aguilar-Bryan L, Bryan J. Reconstituted human cardiac KATP channels: functional identity with the native channels from the sarcolemma of human ventricular cells. Circ Res. 1998; 83(11):1132–43. PMID: 9831708

23. Schnaasstecher C, Neugebauer B, Schulz M, Schwanstecher M. The common single nucleotide polymorphism rs23K in K(IR)6.2 sensitizes pancreatic beta-cell ATP-sensitive potassium channels toward activation through nucleoside diphosphates. Diabetes. 2002; 51 Suppl 3:S363–7.

24. Meisinger C, Stockl D, Ruckert IM, Doring A, Thorand B, Heier M, et al. Serum potassium is associated with prediabetes and newly diagnosed diabetes in hypertensive adults from the general population: The KORA F4-Study. Diabetologia. 2013; Mar; 56(3):484–91. https://doi.org/10.1007/s00125-012-2786-8 PMID: 23183943

25. Burke TA, Strunkboom MC, Ohman-Strickland PA, Wentworth CE, Rhoads GG. The effect of antihypertensive drugs and drug combinations on the incidence of new-onset type-2 diabetes mellitus. Pharmacopidemiol Drug Saf. 2007; 16(9):979–87. https://doi.org/10.1002/pds.1444 PMID: 17605137
26. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. N Engl J Med. 2000 Mar 30; 342(13):905–12. https://doi.org/10.1056/NEJM200003303421301 PMID: 10738048

27. Taylor EN, Hu FB, Curhan GC. Antihypertensive medications and the risk of incident type 2 diabetes. Diabetes Care. 2006; 29(5):1065–70. https://doi.org/10.2337/diacare.2951065 PMID: 16644638

28. Barzilay JI, Davis BR, Cutler JA, Pressel SL, Whelton PK, Basile J, et al. Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive treatment: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med. 2006; 166(20):2191–201. https://doi.org/10.1001/archinte.166.20.2191 PMID: 17101936

29. Shafi T, Appel LJ, Miller ER, Klag MJ, Parekh RS. Changes in Serum Potassium Mediate Thiazide-Induced Diabetes. Hypertension. 2008; 52:1022–9. https://doi.org/10.1161/HYPERTENSIONAHA.108.119438 PMID: 18981326

30. 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. https://doi.org/10.1161/101.HYP.000023152.10054.aa PMID: 16801488

31. Qiu L, Na R, Xu R, Wang S, Sheng H, Wu W, et al. Quantitative assessment of the effect of KCNJ1 gene polymorphism on the risk of type 2 diabetes. PLoS One. 2014; 9(4):e93961. https://doi.org/10.1371/journal.pone.0093961 PMID: 24710510

32. van Dam RM, Hoebee B, Seidell JC, Schaap MM, de Bruin TW, Feskens EJ. Common variants in the ATP-sensitive K+ channel genes KCNJ11 (Kir6.2) and ABCC8 (SUR1) in relation to glucose intolerance: population-based studies and meta-analyses. Diabet Med. 2005; 22(5):590–8. https://doi.org/10.1111/j.1464-5491.2005.01465.x PMID: 15842514

33. Florez JC, Jablonski KA, Kahn SE, Franks PW, Dabelea D, Hamman RF, et al. Type 2 diabetes-associated missense polymorphisms KCNJ11 E23K and ABCC8 A1369S influence progression to diabetes and response to interventions in the Diabetes Prevention Program. Diabetes. 2007; 56(2):531–6. https://doi.org/10.2337/db06-0966 PMID: 17298403