Supplementary data from:

**Serum uromodulin is associated with but does not predict type 2 diabetes in elderly KORA F4/FF4 study participants**

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The associated article has been submitted to the *Journal of Clinical Endocrinology and Metabolism* (jc2018-02557).

Please cite the original article when using these data.

**Description**

**Background**: Serum uromodulin (sUmod) is a novel biomarker for kidney function and was suggested to be associated with type 2 diabetes (T2D) in patients admitted for coronary angiography. In the associated article, we show an association of sUmod with T2D in men, but not in women in the population-based KORA F4 study. Here, we analyzed the association of sUmod with parameters of glucose regulation.

**Methods**: In 1119 participants of the KORA F4 study aged 62 - 81 years, sUmod was measured. The association of sUmod with HbA1c values, fasting glucose, fasting insulin, fasting proinsulin and HOMA-IR was assessed using logistic and linear regression models stratified for sex. Correction for confounders was performed in multinomial models as indicated in the tables. Participants with missing covariables were excluded from the respective analyses. The final numbers of participants included in each analysis in the respective fully adjusted model are indicated in the tables or table captions, respectively.

**Results**: SUmod was inversely associated with HbA1c values in the diabetic range (≥ 48 mmol/mol (6.5%)) in the total cohort and in men after adjustment for age, BMI and eGFR. In women, the inverse relation of sUmod and HbA1c values ≥ 48 mmol/mol (6.5%) was no longer significant after adjustment for age and BMI (table 1). The relation of sUmod with moderately elevated HbA1c levels in the prediabetic range (39 – 46 mmol/mol (5.7 - 6.4 %)) was not significant in women and no longer significant in the total study cohort and in men after adjustment for age and BMI. SUmod was associated with a lower fasting glucose and a lower insulin resistance as determined by HOMA-IR. In women, the association with HOMA-IR was attenuated to non-significance after adjustment for age and BMI. After adjustment for age, BMI and eGFR, fasting insulin was weakly, but significantly inversely associated with sUmod in men, but not in women, whereas a relation of proinsulin with sUmod could not be established after correction for age, sex, BMI and eGFR (table 2). Table 3 displays the characteristics of the study participants included in the follow-up analysis of the KORA F4 study (KORA FF4 study with a mean follow-up time of 6.5 ± 0.3 years).

**Table 1** Relation of sUmod and categories of HbA1c. Adjusted ORs (95% CI) for categories of HbA1c (< 39 mmol/mol (5.7 %) as reference, ≥ 39 mmol/mol and < 48 mmol/mol (6.5 %) (prediabetes), ≥ 48 mmol/mol (T2D)) as dependent variable and sUmod as independent variable (per standard deviation): Results of multinomial logistic regression models; n (in the fully adjusted model: total cohort; men; women) = 1004; 500; 504 for the analysis of HbA1c in the prediabetic range (prediabetic range yes: 427; 208; 219); n (in the fully adjusted model: total cohort; men; women) = 684; 357; 327 for the analysis of HbA1c in the diabetic range (diabetic range yes: 109; 66; 43)

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| --- | --- | --- |
|  | **HbA1c ≥ 39 mmol/mol (5.7%),** **< 48 mmol/mol (6.5%)** | **HbA1c ≥ 48 mmol/mol (6.5%)** |
| Without adjustment |
| Total cohort  | 0.83 (0.73 - 0.95) \* | 0.5 (0.39 - 0.65) \*\*\* |
| Men  | 0.73 (0.59 - 0.89) \* | 0.46 (0.32 - 0.65) \*\*\* |
| Women  | 0.9 (0.76 - 1.07) | 0.58 (0.41 - 0.83) \*\*\* |
| Adjustment for age, (sex) and BMI |
| Total cohort  | 0.93 (0.81 - 1.07)  | 0.66 (0.5 - 0.86) \*\* |
| Men  | 0.81 (0.65 - 1.00) | 0.55 (0.38 - 0.80) \*\*  |
| Women  | 1.03 (0.86 - 1.24) | 0.81 (0.54 - 1.19)  |
| Adjustment for age, (sex), BMI and eGFR |
| Total cohort  | 0.94 (0.82 - 1.08) | 0.69 (0.52 - 0.92) \*\* |
| Men  | 0.82 (0.66 - 1.03) | 0.57 (0.38 - 0.85) \*\* |
| Women  | 1.04 (0.86 - 1.25) | 0.86 (0.57 - 1.29) |

\* p < 0.05; \*\* p < 0.01; \*\*\* p < 0.001

**Table 2** Relation of sUmod and parameters of glucose homeostasis. β ± standard deviation for fasting serum glucose, insulin, proinsulin and HOMA-IR as dependent variables and sUmod as independent variable: Results of multinomial linear regression models

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Fasting glucose** | **Fasting insulin a** | **Fasting proinsulin** | **HOMA-IR** |
| Without adjustment |
| Total cohort  | -0.205 ± 0.030 \*\*\* | -0.146 ± 0.033 \*\*\* | -0.160 ± 0.040 \*\*\*  | -0.204 ± 0.031 \*\*\*  |
| Men  | -0.187 ± 0.050 \*\*\*  | -0.168 ± 0.046 \*\*\* | -0.081 ± 0.061 | -0.258 ± 0.048 \*\*\* |
| Women  | -0.183 ± 0.03 \*\*\*  | -0.130 ± 0.049 \* | -0.215 ± 0.052 \*\*\* | -0.143 ± 0.041 \*\*\* |
| Adjustment for age, (sex) and BMI |
| Total cohort | -0.126 ± 0.029 \*\*\* | -0.064 ± 0.031 \* | -0.054 ± 0.040  | -0.100 ± 0.030 \*\*\*  |
| Men  | -0.146 ± 0.052 \*\*  | -0.088 ± 0.041 \* | -0.0140 ± 0.059 | -0.154 ± 0.045 \*\*\* |
| Women  | -0.109 ± 0.031 \*\*\*  | -0.036 ± 0.047 | -0.105 ± 0.05 \* | -0.052 ± 0.039 |
| Adjustment for age, (sex), BMI and eGFR |
| Total cohort | -0.108 ± 0.030 \*\*\* | -0.055 ± 0.032 | -0.032 ± 0.041  | -0.086 ± 0.030 \*\* |
| Men  | -0.136 ± 0.053 \* | -0.088 ± 0.043 \* | 0.026 ± 0.059  | -0.143 ± 0.046 \*\*  |
| Women  | -0.089 ± 0.031 \*\* | -0.026 ± 0.047 | -0.096 ± 0.054 | -0.039 ± 0.040 |
| n b | 1097; 559; 538 | 869; 424; 445 | 618; 326; 292 | 984; 494; 490 |

a excluding subjects with T2D

\* p < 0.05; \*\* p < 0.01; \*\*\* p < 0.001

b numbers of participants included in the fully adjusted models (total cohort; men; women)

**Table 3** Characteristics of participants in the follow-up analysis a

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All subjects** | **Men** | **Women** | **p b**  |
| n | 635 | 334 | 301 |  |
| Age (years) | 75.4 (± 5.0) | 75.5 (± 5.1) | 75.3 (± 4.8) | n.s.# |
| BMI (kg/m2) | 28.3 (± 4.4) | 28.3 (± 3.8) | 28.3 (± 4.9) | n.s.# |
| Waist circumference (cm) | 100.0 (± 12.2) | 104.5 (± 10.3) | 94.8 (± 12.4) | < 0.01# |
| Systolic blood pressure (mmHg) | 123.2 (± 19.3) | 126.0 (± 19.3) | 120.1 (± 18.9) | < 0.01# |
| Diastolic blood pressure (mmHg) | 69.3 (± 9.9) | 70.4 (± 10.2) | 68.1 (± 9.3) | < 0.01# |
| Arterial hypertension (%) | 418 (66) | 230 (69) | 188 (62) | n.s.### |
| Prediabetes (%) | 206 (32) | 115 (34) | 91 (30) | n.s.### |
| Type 2 diabetes (%) | 172 (27) | 105 (31) | 67 (22) | 0.01### |
| HbA1c (mmol/mol) | 38.0 (36.1; 41.0) | 38.0 (35.0; 42.0) | 38.0 (36.1; 41.0) | n.s.## |
| HbA1c (%) | 5.6 (5.4; 5.9) | 5.6 (5.4; 6.0) | 5.6 (5.4; 5.9) | n.s.## |
| eGFR (ml/min/1.73 m2) | 68.6 (58.2; 80.4) | 69.3 (58.7; 81.1) | 67.4 (57.9; 78.8) | n.s.## |

a Means ± standard deviation, median (first quartile; third quartile), or proportion (%);

b The p value is related to the null hypothesis of no sex differences;

# t-Test; ## Mann-Whitney U-test; ### Chi-square test

n.s. not significant