

## **Serum potassium is associated with prediabetes and newly diagnosed diabetes in hypertensive adults from the general population: the KORA F4-Study**

**Christa Meisinger, D. Stöckl, I. M. Rückert, A. Döring, B. Thorand, M. Heier, C. Huth, P. Belcredi, B. Kowall, W. Rathmann**

### **Angaben zur Veröffentlichung / Publication details:**

Meisinger, Christa, D. Stöckl, I. M. Rückert, A. Döring, B. Thorand, M. Heier, C. Huth, P. Belcredi, B. Kowall, and W. Rathmann. 2013. "Serum potassium is associated with prediabetes and newly diagnosed diabetes in hypertensive adults from the general population: the KORA F4-Study." *Diabetologia* 56 (3): 484–91. <https://doi.org/10.1007/s00125-012-2786-8>.

### **Nutzungsbedingungen / Terms of use:**

**licgercopyright**

Dieses Dokument wird unter folgenden Bedingungen zur Verfügung gestellt: / This document is made available under these conditions:

**Deutsches Urheberrecht**

Weitere Informationen finden Sie unter: / For more information see:

<https://www.uni-augsburg.de/de/organisation/bibliothek/publizieren-zitieren-archivieren/publiz/>



# Serum potassium is associated with prediabetes and newly diagnosed diabetes in hypertensive adults from the general population: The KORA F4-Study

C. Meisinger · D. Stöckl · I. M. Rückert · A. Döring ·  
B. Thorand · M. Heier · C. Huth · P. Belcredi ·  
B. Kowall · W. Rathmann

## Abstract

**Aims/hypothesis** Evidence suggests that low serum potassium concentrations or hypokalaemia induced by the intake of diuretics are associated with incident diabetes and increased risk for diabetes in persons with hypertension. We examined a possible association between serum potassium and prediabetes (defined as isolated impaired fasting glucose [i-IFG], isolated impaired glucose tolerance [i-IGT] or combined IFG/IGT), as well as known and newly diagnosed diabetes (NDD), in 32- to 81-year-old men and women with and without hypertension. **Methods** This cross-sectional analysis was based on 2,948 participants in the Cooperative Health Research in the

Region of Augsburg (KORA) F4 study conducted in 2006–2008 in southern Germany. Serum concentrations of potassium were measured by indirect potentiometry.

**Results** In the total sample there was no association between serum potassium concentrations and prediabetes. In hypertensive persons however serum potassium levels in the first and second quartile compared with the highest quartile were independently significantly associated with prediabetes after multivariable adjustment (OR for prediabetes, 2.02 [95% CI 1.27, 3.21] for quartile 2 and 2.00 [95% CI 1.27, 3.15] for quartile 1), while in persons without hypertension no association was found. In multinomial logistic regression analysis these findings could be confirmed. In hypertensive participants after multivariable adjustment the associations were statistically significant for i-IGT and NDD (i-IGT OR 1.23; NDD OR 1.41). However, in non-hypertensive persons, all associations between serum potassium levels and each of the categories of impaired glucose regulation were non-significant.

**Conclusions/interpretation** Serum potassium levels were independently associated with prediabetes and NDD in hypertensive adults from the general population.

C. Meisinger · D. Stöckl · I. M. Rückert · B. Thorand · M. Heier ·  
C. Huth · P. Belcredi  
Helmholtz Zentrum München,  
German Research Center for Environmental Health (GmbH),  
Institute of Epidemiology II, Neuherberg, Germany

C. Meisinger (✉) · M. Heier · P. Belcredi  
Central Hospital of Augsburg, MONICA/KORA  
Myocardial Infarction Registry, Stenglinstrasse 2,  
86156 Augsburg, Germany  
e-mail: christa.meisinger@helmholtz-muenchen.de

A. Döring  
Helmholtz Zentrum München,  
German Research Center for Environmental Health (GmbH),  
Institute of Epidemiology I, Neuherberg, Germany

B. Thorand · C. Huth  
German Center for Diabetes Research (DZD e.V.),  
Neuherberg, Germany

B. Kowall · W. Rathmann  
Institute of Biometrics and Epidemiology, German Diabetes  
Center, Leibniz Center for Diabetes Research at Heinrich  
Heine University, Düsseldorf, Germany

**Keywords** Hypertension · Population-based study ·  
Prediabetes · Risk factor · Serum potassium

## Abbreviations

|       |                                                       |
|-------|-------------------------------------------------------|
| ARIC  | Atherosclerosis Risk in Communities                   |
| i-IFG | Isolated impaired fasting glucose                     |
| i-IGT | Isolated impaired glucose tolerance                   |
| KORA  | Cooperative Health Research in the Region of Augsburg |
| NDD   | Newly detected diabetes                               |
| NGT   | Normal glucose tolerance                              |

## Introduction

The incidence and prevalence of type 2 diabetes are increasing worldwide, thus the identification of the determinants of this epidemic and the identification of improved measures to prevent and treat this condition is extremely important. While obesity and physical inactivity are recognised as the main risk factors associated with the increase in diabetes, the role of other determinants that could potentially be corrected more easily is often a subject of current research [1, 2].

There is evidence that decreased serum potassium is associated with glucose intolerance [3, 4]. In some earlier studies it was shown that changes in serum potassium levels partially mediate the manifestation of thiazide-induced type 2 diabetes [5, 6]. Moreover, recent observational studies reported a significant association between serum potassium and risk of diabetes independent of diuretic use [7–9]. So far, there is no population-based study that has investigated whether serum potassium levels are associated with prediabetes. Therefore, in the present study the possible association between serum potassium concentrations and prediabetes, defined as isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT) or combined IFG/IGT, was assessed in a population of 32- to 81-year-old men and women in southern Germany. Furthermore, we investigated the association between serum potassium and newly diagnosed, as well as known, diabetes mellitus. Impaired glucose regulation and high blood pressure are closely associated and one common disturbance in both disorders is insulin resistance [10]. Thus, it is thinkable that the effect of serum potassium is only significant among hypertensive persons with diabetes due to the insulin-resistant state. Therefore, we examined whether there are different results in hypertensive and non-hypertensive persons.

## Methods

**Participants** Data are based on the Cooperative Health Research in the Region of Augsburg (KORA) F4 study (2006–2008), a follow-up of the KORA S4 study, a population-based health survey conducted in 1999–2001. For S4 a total sample of 6,640 individuals aged 25–74 years was drawn from the target population consisting of all German residents of the region. Of all 4,261 participants in the S4 baseline study, 3,080 also participated in the 7-year follow-up F4 study. Persons were considered to be ineligible for inclusion in F4 if they lived outside the study region or were completely lost to follow-up ( $n=206$ , 5%) or had demanded deletion of their address data ( $n=12$ , 0.2%). Furthermore, 176 persons (4%) had died during the follow-up time. Of the remaining 3,867 eligible persons,

174 could not be contacted, 218 were unable to come because they were too ill or had no time and 395 were not willing to participate in this follow-up. Altogether 3,080 persons aged 32–81 years participated in the F4 study (response 79.6%) [11]. The current study was restricted to 2,948 participants (1,533 women and 1,415 men) without serum creatinine values  $>150.3 \mu\text{mol/l}$  ( $n=21$ ) or missing values on any of the analytical variables ( $n=111$ ). The investigations were carried out in accordance with the Declaration of Helsinki, including obtaining written informed consent from all participants. All study methods were approved by the Ethics committee of the Bavarian Chamber of Physicians, Munich.

After an overnight fast of at least 10 h, all non-diabetic participants underwent a standard 75-g OGTT [12]. In persons with physician-diagnosed known diabetes no OGTT was carried out. Newly diagnosed diabetes (NDD;  $\geq 7.0 \text{ mmol/l}$  fasting plasma glucose or  $\geq 11.1 \text{ mmol/l}$  2-h post glucose load), i-IFG (fasting plasma glucose  $\geq 6.1 \text{ mmol/l}$ , but  $< 7.0 \text{ mmol/l}$  and 2-h post glucose load  $< 7.8 \text{ mmol/l}$ ), i-IGT (fasting plasma glucose  $< 6.1 \text{ mmol/l}$  and 2-h post glucose load  $\geq 7.8 \text{ mmol/l}$ , but  $< 11.1 \text{ mmol/l}$ ), IFG/IGT and normal glucose tolerance (NGT; fasting plasma glucose  $< 6.1 \text{ mmol/l}$  and 2-h post glucose load  $< 7.8 \text{ mmol/l}$ ) were defined according to the 1999 WHO diagnostic criteria as described elsewhere [11].

Information on sociodemographic variables, lifestyle and risk factors was gathered during a standardised interview. All participants underwent an extensive standardised medical examination as described in more detail elsewhere [13]. BMI was calculated as weight in kilograms divided by the square of height in meters. Systolic and diastolic BP was measured three times using the right arm of seated participants, after at least 5 min at rest, and by use of an oscillometric digital BP monitor (HEM-705CP; Omron Corporation, Tokyo, Japan). The pause between readings was 3 min. The mean of the second and third measurement was calculated and used for the present analyses. Hypertension was defined as blood pressure values (systolic/diastolic)  $\geq 140/90 \text{ mmHg}$  and/or use of antihypertensive medication, given that the individuals were aware of being hypertensive. Individuals who participated in leisure-time physical training during summer and winter and were active for at least 1 h per week in either season were classified as being physically active. A regular smoker was defined as a participant who smoked at least one cigarette per day. Alcohol intake was categorised into three categories: 0, 0.1–39.9 or  $\geq 40 \text{ g/day}$  for men; 0, 0.1–19.9 or  $\geq 20 \text{ g/day}$  for women.

**Clinical chemical measurements** A fasting venous blood sample was obtained from all study participants while sitting. All variables were measured immediately. Blood glucose was analysed using a hexokinase method (GLU Flex;

Dade Behring, Deerfield, IL, USA). The CV for glucose was 1.5% at 15.3 mmol/l and 1.8% at 5.6 and 6.2 mmol/l. Total serum cholesterol, HDL-cholesterol and LDL-cholesterol analyses were carried out using a CHOD-PAP method (Dade Behring). Triacylglycerol was measured with the GPO-PAP-method (TGL Flex; Dade Behring). Serum creatinine was measured using a modified kinetic Jaffé reaction [11]. HbA<sub>1c</sub> was measured with a reverse-phase cation-exchange high-pressure liquid chromatography (HPLC) method (Analyzer HA 8160; Menarini, Florence, Italy). Serum concentrations of potassium were measured by indirect potentiometry (QuikLYTE; Dade Behring). The CV for potassium was 1.7% at 4.5 and 5.0 mmol/l and 1.9% at 5.7 mmol/l.

**Statistical analyses** The  $\chi^2$  test was used to test differences in prevalence. A general linear model was used to compare means (*F* test). The study population was stratified into quartiles of serum potassium concentrations using cut-points of 4.01, 4.18 and 4.35 mmol/l (25th, 50th and 75th percentiles), respectively. In logistic regression analysis the association between serum potassium and prediabetes as the outcome was investigated. In this analysis, study participants with i-IFG, i-IGT and IFG/IGT were regarded as persons with prediabetes and persons with NGT built the reference group. For this analysis, persons with NDD and known diabetes were excluded and three models were fitted: model 1 included serum potassium, age (continuous) and sex; model 2 included all previous factors plus BMI (continuous), systolic BP (continuous), physical activity (active/inactive), regular smoking (yes/no), alcohol intake (sex-specific categories), total cholesterol (continuous) and serum creatinine (continuous); model 3 included, in addition to the previous factors, use of beta blockers (yes/no), diuretics (yes/no) and ACE inhibitors (yes/no). The ORs and 95% CIs were computed for the first, second and third quartiles as compared with the highest quartile. The analyses were repeated by including serum potassium as a continuous variable. The same stepwise modelling strategy (models 1–3) as described above was used in these analyses and ORs were computed for a decrease of 1 SD of serum potassium. Linearity was checked by including a quadratic term of the variable serum potassium in the model. Because the *p* value of the quadratic term was not significant, linearity could be assumed. Additionally, based on the total F4 sample we performed multinomial logistic regression analyses using the SAS procedure PROC LOGISTIC (SAS Institute, Cary, NC, USA) to study the association of serum potassium (per 1 SD decrease) with different categories of impaired glucose regulation. In these analyses the categorical dependent outcome had six groups (NGT, i-IFG, i-IGT, IFG/IGT, NDD and known diabetes) and the reference group for comparison was NGT. In these analyses three

models were fitted as described above. Finally, in a sensitivity analysis, the association between serum potassium levels and HbA<sub>1c</sub> was examined. For this analysis, the persons with known diabetes were excluded. Multinomial logistic regression analyses (three models as described above) with HbA<sub>1c</sub> as the outcome variable (categorised into the following groups: <6.0% (<42 mmol/mol) [reference group], 6.0–6.4% (42–<48 mmol/mol) and  $\geq 6.5\%$  ( $\geq 48$  mmol/mol) as recommended by an International Expert Committee [14]) and serum potassium as continuous variable (OR per 1 SD decrease) were performed. Tests for linear trends across increasing categories of serum potassium levels treated categories as continuous variables in the model. We tested for interaction between serum potassium level and sex as well as hypertension on risk of prediabetes. A *p* value of <0.05 was considered statistically significant. All analyses were performed with SAS software version 9.2. (SAS Institute, Cary, NC, USA).

## Results

Higher serum potassium levels were associated with a lower proportion of participants with prediabetes, NDD and hypertension and a higher proportion of regular smokers. Furthermore, higher serum potassium levels were associated with a more advanced age, a higher BMI and higher total cholesterol, LDL-cholesterol, triacylglycerol, creatinine and HbA<sub>1c</sub> values. Persons with higher serum potassium levels more frequently consumed a high amount of alcohol and were less frequently treated with diuretics and beta blockers (Table 1).

In the analysis regarding the association between serum potassium level and prediabetes (i-IFG, i-IGT and IFG/IGT groups combined) as the outcome, it could be shown that in the total sample the association was not significant after adjustment for age, sex, BMI, regular smoking, alcohol intake, physical activity, systolic BP, total cholesterol, creatinine values and use of beta blockers, diuretics and ACE inhibitors; comparing the lowest vs the highest quartile of serum potassium levels, the OR for prediabetes was 1.32 (model 3: 95% CI 0.96, 1.84) (Table 2). There was no significant interaction between serum potassium and sex on the risk of prediabetes (*p*=0.6880), but a significant interaction between serum potassium and hypertension (*p*=0.0533). Therefore, the analysis was stratified by hypertension status.

As shown in Table 2, in persons with hypertension serum potassium levels in the first and second quartile were significantly associated with prediabetes independent of age, sex, BMI, regular smoking, alcohol intake, physical activity, systolic BP, total cholesterol and creatinine values (model 2: first quartile, OR 2.01, 95% CI 1.30, 3.10; second quartile, OR 2.01, 95% CI 1.28, 3.17). Further adjustment for the use of beta blockers, ACE inhibitors and diuretics (model 3) had

**Table 1** Mean and prevalence of baseline variables according to quartiles of serum potassium levels in persons ( $n=2,948$ ) aged 32–81 years

| Characteristic                                             | Serum potassium                                |                                                        |                                                        |                                                    | <i>p</i> value |
|------------------------------------------------------------|------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------|----------------|
|                                                            | Quartile 1<br>( $<4.01$ mmol/l)<br>( $n=700$ ) | Quartile 2<br>( $4.01$ – $4.17$ mmol/l)<br>( $n=755$ ) | Quartile 3<br>( $4.18$ – $4.34$ mmol/l)<br>( $n=734$ ) | Quartile 4<br>( $\geq 4.35$ mmol/l)<br>( $n=759$ ) |                |
| Serum potassium (mmol/l)                                   | 3.8 (0.16)                                     | 4.1 (0.05)                                             | 4.3 (0.05)                                             | 4.5 (0.17)                                         | $<0.0001$      |
| Measures of glycaemia                                      |                                                |                                                        |                                                        |                                                    |                |
| NGT (%)                                                    | 70.6                                           | 72.1                                                   | 75.5                                                   | 70.6                                               | 0.0453         |
| Prediabetes (%) <sup>a</sup>                               | 17.3                                           | 17.8                                                   | 15.6                                                   | 15.9                                               |                |
| NDD (%)                                                    | 5.1                                            | 3.3                                                    | 2.6                                                    | 3.4                                                |                |
| Known diabetes (%)                                         | 7.0                                            | 6.9                                                    | 6.4                                                    | 10.0                                               |                |
| Fasting glucose (mmol/l) <sup>b</sup>                      | 5.4 (1.2)                                      | 5.3 (1.2)                                              | 5.4 (1.2)                                              | 5.5 (1.2)                                          | 0.0315         |
| 2 h-glucose (mmol/l) <sup>b</sup>                          | 6.0 (1.4)                                      | 6.0 (1.4)                                              | 5.8 (1.3)                                              | 5.8 (1.4)                                          | 0.1405         |
| HbA <sub>1c</sub> value (mmol/mol)                         | 36.6 (6.2)                                     | 37.0 (7.5)                                             | 36.8 (5.8)                                             | 38.1 (6.8)                                         | $<0.0001$      |
| HbA <sub>1c</sub> value (%)                                | 5.5 (0.6)                                      | 5.5 (0.7)                                              | 5.5 (0.5)                                              | 5.6 (0.6)                                          | $<0.0001$      |
| Sociodemographic characteristics                           |                                                |                                                        |                                                        |                                                    |                |
| Age (years)                                                | 55.7 (13.5)                                    | 54.9 (12.9)                                            | 55.9 (13.1)                                            | 57.6 (12.9)                                        | 0.0011         |
| Male sex (%)                                               | 42.4                                           | 46.4                                                   | 48.5                                                   | 54.3                                               | $<0.0001$      |
| Education ( $<12$ years, %)                                | 57.0                                           | 57.4                                                   | 60.5                                                   | 60.1                                               | 0.3970         |
| Clinical characteristics                                   |                                                |                                                        |                                                        |                                                    |                |
| BMI ( $\text{kg}/\text{m}^2$ )                             | 27.0 (4.7)                                     | 27.5 (4.8)                                             | 27.8 (4.9)                                             | 28.1 (4.7)                                         | 0.0001         |
| Obesity (BMI $\geq 30$ $\text{kg}/\text{m}^2$ , %)         | 24.3                                           | 26.0                                                   | 26.3                                                   | 29.1                                               | 0.2068         |
| Actual hypertension (%)                                    | 45.4                                           | 33.6                                                   | 33.5                                                   | 39.8                                               | $<0.0001$      |
| Systolic BP (mmHg)                                         | 122.5 (19.1)                                   | 121.8 (18.4)                                           | 121.4 (18.4)                                           | 122.9 (18.2)                                       | 0.4166         |
| Diastolic BP (mmHg)                                        | 75.0 (10.3)                                    | 75.4 (9.8)                                             | 74.9 (9.8)                                             | 75.4 (10.0)                                        | 0.7310         |
| Regular smoking (%)                                        | 9.3                                            | 12.2                                                   | 16.9                                                   | 22.3                                               | $<0.0001$      |
| Alcohol intake (%)                                         |                                                |                                                        |                                                        |                                                    |                |
| 0 g/day                                                    | 31.9                                           | 31.1                                                   | 27.8                                                   | 30.0                                               | 0.0148         |
| Men, 0.1–39.9 g/day; women,<br>0.1–19.9 g/day              | 52.1                                           | 54.4                                                   | 53.7                                                   | 48.9                                               |                |
| Men, $\geq 40.0$ g/day; women,<br>$\geq 20.0$ g/day        | 16.0                                           | 14.4                                                   | 18.5                                                   | 21.1                                               |                |
| Physically active (%)                                      | 54.0                                           | 56.2                                                   | 55.7                                                   | 53.1                                               | 0.5973         |
| Total cholesterol (mmol/l)                                 | 5.4 (1.0)                                      | 5.6 (1.0)                                              | 5.6 (1.0)                                              | 5.7 (1.0)                                          | $<0.0001$      |
| HDL-cholesterol (mmol/l)                                   | 1.5 (0.4)                                      | 1.4 (0.4)                                              | 1.5 (0.4)                                              | 1.4 (0.4)                                          | 0.3419         |
| LDL-cholesterol (mmol/l)                                   | 3.4 (0.9)                                      | 3.5 (0.9)                                              | 3.5 (0.9)                                              | 3.6 (0.9)                                          | $<0.0001$      |
| Triacylglycerol (mmol/l) <sup>b</sup>                      | 1.2 (1.8)                                      | 1.2 (1.7)                                              | 1.2 (1.7)                                              | 1.3 (1.7)                                          | 0.0173         |
| Serum creatinine ( $\mu\text{mol}/\text{l}$ ) <sup>b</sup> | 76.5 (1.2)                                     | 76.2 (1.2)                                             | 77.3 (1.2)                                             | 81.6 (1.2)                                         | $<0.0001$      |
| Medication use (%)                                         |                                                |                                                        |                                                        |                                                    |                |
| Diuretics                                                  | 28.6                                           | 15.8                                                   | 13.2                                                   | 12.9                                               | $<0.0001$      |
| Beta blockers                                              | 23.1                                           | 15.4                                                   | 16.6                                                   | 18.6                                               | 0.0008         |
| ACE inhibitors                                             | 14.4                                           | 13.4                                                   | 11.0                                                   | 13.2                                               | 0.2741         |

Data are percentages or means (SD)

<sup>a</sup>i-IFG, i-IGT, and IFG/IGT combined<sup>b</sup>Geometric mean (geometric SD)

almost no impact on the strength of the observed associations. In persons without hypertension, a significant association between serum potassium levels and prediabetes could be demonstrated neither in the age- and sex-adjusted nor in the multivariable-adjusted models (Table 2).

When serum potassium was included as a continuous variable in the models, it was also significantly associated with prediabetes after multivariable adjustment in hypertensive but not in non-hypertensive persons (model 3: OR per 1 SD decrease 1.24, 95% CI 1.06, 1.44 in hypertensive

**Table 2** Association between serum potassium levels and prediabetes (combination of i-IFG, i-IGT and IFG/IGT)

| Analysis                                        | Per 1 SD decrease | Serum potassium              |                                  |                                  |                              | <i>p</i> value for trend |
|-------------------------------------------------|-------------------|------------------------------|----------------------------------|----------------------------------|------------------------------|--------------------------|
|                                                 |                   | Quartile 1<br>(<4.01 mmol/l) | Quartile 2<br>(4.01–4.17 mmol/l) | Quartile 3<br>(4.18–4.34 mmol/l) | Quartile 4<br>(≥4.35 mmol/l) |                          |
| Total sample ( <i>n</i> =2,618)                 |                   | <i>n</i> =615                | <i>n</i> =678                    | <i>n</i> =668                    | <i>n</i> =657                |                          |
| Prediabetic cases ( <i>n</i> =490)              |                   | <i>n</i> =121                | <i>n</i> =134                    | <i>n</i> =114                    | <i>n</i> =121                |                          |
| Model 1 <sup>a</sup>                            | 1.11 (1.00, 1.24) | 1.26 (0.93, 1.70)            | 1.29 (0.97, 1.73)                | 0.97 (0.72, 1.31)                | 1.0                          | 0.0414                   |
| Model 2 <sup>b</sup>                            | 1.14 (1.02, 1.27) | 1.41 (1.02, 1.93)            | 1.36 (1.00, 1.84)                | 1.00 (0.73, 1.36)                | 1.0                          | 0.0092                   |
| Model 3 <sup>c</sup>                            | 1.12 (1.00, 1.25) | 1.32 (0.96, 1.84)            | 1.34 (0.98, 1.83)                | 0.98 (0.72, 1.34)                | 1.0                          | 0.0252                   |
| Persons with hypertension ( <i>n</i> =859)      |                   | <i>n</i> =243                | <i>n</i> =201                    | <i>n</i> =196                    | <i>n</i> =219                |                          |
| Prediabetic cases ( <i>n</i> =277)              |                   | <i>n</i> =89                 | <i>n</i> =76                     | <i>n</i> =54                     | <i>n</i> =58                 |                          |
| Model 1 <sup>a</sup>                            | 1.18 (1.03, 1.35) | 1.71 (1.14, 2.58)            | 1.87 (1.22, 2.86)                | 1.06 (0.68, 1.65)                | 1.0                          | 0.0015                   |
| Model 2 <sup>b</sup>                            | 1.24 (1.07, 1.43) | 2.01 (1.30, 3.10)            | 2.01 (1.28, 3.17)                | 1.02 (0.64, 1.62)                | 1.0                          | 0.0001                   |
| Model 3 <sup>c</sup>                            | 1.24 (1.06, 1.44) | 2.00 (1.27, 3.15)            | 2.02 (1.27, 3.21)                | 0.98 (0.61, 1.57)                | 1.0                          | 0.0002                   |
| Persons without hypertension ( <i>n</i> =1,759) |                   | <i>n</i> =372                | <i>n</i> =477                    | <i>n</i> =472                    | <i>n</i> =438                |                          |
| Prediabetic cases ( <i>n</i> =213)              |                   | <i>n</i> =32                 | <i>n</i> =58                     | <i>n</i> =60                     | <i>n</i> =63                 |                          |
| Model 1 <sup>a</sup>                            | 0.94 (0.80, 1.11) | 0.72 (0.45, 1.15)            | 0.91 (0.61, 1.35)                | 0.91 (0.61, 1.36)                | 1.0                          | 0.2071                   |
| Model 2 <sup>b</sup>                            | 0.97 (0.81, 1.16) | 0.83 (0.50, 1.36)            | 0.94 (0.62, 1.44)                | 0.97 (0.64, 1.47)                | 1.0                          | 0.4813                   |
| Model 3 <sup>c</sup>                            | 0.95 (0.80, 1.14) | 0.79 (0.48, 1.31)            | 0.92 (0.60, 1.41)                | 0.96 (0.63, 1.45)                | 1.0                          | 0.3802                   |

Data are shown as ORs (95% CIs)

Reference group: NGT. KORA F4 participants aged 32–81 years

<sup>a</sup>Model 1: adjusted for age and sex

<sup>b</sup>Model 2: adjusted for age, sex, BMI, regular smoking, systolic BP, physical activity, alcohol intake (sex-specific categories), total cholesterol, creatinine

<sup>c</sup>Model 3: adjusted for age, sex, BMI, regular smoking, systolic BP, physical activity, alcohol intake (sex-specific categories), total cholesterol, creatinine, use of beta blockers, diuretics and ACE inhibitors

participants and OR 0.95, 95% CI 0.80, 1.14 in persons without hypertension) (Table 2).

The results of the multinomial logistic regression analysis are given in Table 3. In the total sample, serum potassium concentration was only significantly associated with NDD. In the multivariable-adjusted model, the OR per 1 SD decrease in serum potassium was 1.40 (95% CI 1.16, 1.69) for NDD. After stratification, serum potassium levels were more strongly associated with the different glucose tolerance categories in hypertensive compared with non-hypertensive persons. In hypertensive participants after multivariable adjustment the associations were statistically significant for i-IGT and NDD (model 3: i-IGT OR 1.23; NDD OR 1.41). However, in non-hypertensive persons, all associations between serum potassium levels and each of the categories of impaired glucose regulation were not significant (Table 3).

**Sensitivity analyses** Similar results were found when restricting the analysis to hypertensive participants who were not using diuretics. In these analyses serum potassium levels in the first and second quartile were significantly associated with prediabetes after multivariable adjustment

(first quartile, OR 2.09, 95% CI 1.14, 3.83; second quartile, OR 1.97, 95% CI 1.11, 3.51).

In a further sensitivity analysis examining the association between serum potassium levels and HbA<sub>1c</sub> values, an association was found neither in the total sample nor in the subgroups. In the multivariable-adjusted multinomial logistic regression model in the total sample the OR per 1 SD decrease in serum potassium was 0.95 (95% CI 0.81, 1.11) for the HbA<sub>1c</sub> category 6.0–6.4% (42–<48 mmol/mol) and 1.09 (95% CI 0.80, 1.50) for the HbA<sub>1c</sub> category ≥6.5% (≥48 mmol/mol) in comparison with the HbA<sub>1c</sub> category <6.0% (<42 mmol/mol); for hypertensive participants the corresponding ORs were 1.01 (95% CI 0.84, 1.22) and 1.09 (95% CI 0.78, 1.50) and for non-hypertensive persons 0.76 (95% CI 0.57, 1.03) and 1.16 (95% CI 0.29, 4.63).

## Discussion

In the present population-based study, serum potassium concentrations were not significantly associated with prediabetes in the total sample after multivariable adjustment.

**Table 3** Association of serum potassium values (per 1 SD decrease) with i-IFG, i-IGT, IFG/IGT, NDD and known diabetes

| Analysis                         | i-IFG             | i-IGT             | IFG/IGT           | NDD               | Known diabetes    |
|----------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Total sample                     | <i>n</i> =112     | <i>n</i> =310     | <i>n</i> =68      | <i>n</i> =106     | <i>n</i> =224     |
| Hypertensive persons             | <i>n</i> =60      | <i>n</i> =169     | <i>n</i> =48      | <i>n</i> =83      | <i>n</i> =178     |
| Non-hypertensive persons         | <i>n</i> =52      | <i>n</i> =141     | <i>n</i> =20      | <i>n</i> =23      | <i>n</i> =46      |
| Model 1 <sup>a</sup> OR (95% CI) |                   |                   |                   |                   |                   |
| Total sample                     | 0.99 (0.82, 1.19) | 1.12 (0.99, 1.26) | 1.20 (0.96, 1.50) | 1.36 (1.14, 1.63) | 1.03 (0.90, 1.18) |
| Hypertensive persons             | 1.05 (0.84, 1.33) | 1.19 (1.02, 1.38) | 1.14 (0.89, 1.48) | 1.31 (1.08, 1.59) | 0.99 (0.85, 1.14) |
| Non-hypertensive persons         | 0.85 (0.63, 1.15) | 0.94 (0.78, 1.15) | 1.22 (0.76, 1.97) | 1.15 (0.73, 1.81) | 1.06 (0.76, 1.46) |
| Model 2 <sup>b</sup> OR (95% CI) |                   |                   |                   |                   |                   |
| Total sample                     | 0.99 (0.82, 1.21) | 1.14 (1.00, 1.29) | 1.25 (0.99, 1.58) | 1.40 (1.17, 1.68) | 1.05 (0.92, 1.21) |
| Hypertensive persons             | 1.08 (0.84, 1.38) | 1.22 (1.04, 1.42) | 1.21 (0.93, 1.58) | 1.36 (1.12, 1.66) | 1.01 (0.87, 1.18) |
| Non-hypertensive persons         | 0.87 (0.63, 1.20) | 0.97 (0.79, 1.20) | 1.25 (0.76, 2.05) | 1.28 (0.79, 2.06) | 1.17 (0.84, 1.63) |
| Model 3 <sup>c</sup> OR (95% CI) |                   |                   |                   |                   |                   |
| Total sample                     | 0.97 (0.80, 1.19) | 1.12 (0.99, 1.28) | 1.25 (0.98, 1.59) | 1.40 (1.16, 1.69) | 1.00 (0.87, 1.16) |
| Hypertensive persons             | 1.06 (0.82, 1.37) | 1.23 (1.04, 1.45) | 1.23 (0.92, 1.63) | 1.41 (1.14, 1.73) | 0.98 (0.83, 1.15) |
| Non-hypertensive persons         | 0.88 (0.64, 1.21) | 0.95 (0.77, 1.17) | 1.21 (0.73, 2.00) | 1.39 (0.85, 2.26) | 1.25 (0.88, 1.77) |

Data show OR (95% CI) expressed per 1 SD decrease in serum potassium concentration

Reference group: NGT, KORA F4 study

<sup>a</sup>Model 1: adjusted for age and sex

<sup>b</sup>Model 2: adjusted for age, sex, BMI, regular smoking, systolic BP, physical activity, alcohol intake (sex-specific categories), total cholesterol, creatinine

<sup>c</sup>Model 3: adjusted for age, sex, BMI, regular smoking, systolic BP, physical activity, alcohol intake (sex-specific categories), total cholesterol, creatinine, use of beta blockers, diuretics and ACE inhibitors

However, in stratified analyses, serum potassium values were associated with prediabetes (particularly i-IGT), independent of known metabolic risk factors, lifestyle variables and antihypertensive medication, in hypertensive persons only, while in persons without hypertension no significant association was found. In addition, while we observed no significant association between serum potassium values and known diabetes, there was a significant relationship with NDD in the total sample and in hypertensive persons.

There was no association between serum potassium levels and HbA<sub>1c</sub> in the present study, but this is not astonishing, because from earlier analyses of the KORA study it is known that the groups of prediabetic or diabetic persons differ depending on the applied diagnostic criteria [11].

So far, to the best of our knowledge, there are no studies on the association between serum potassium levels and prediabetes. Hence, our findings extend the current knowledge. Additionally, our results confirm those of earlier studies reporting an association between serum potassium levels and diabetes, but in this cross-sectional investigation an association was seen only with NDD. Persons with known diabetes are usually treated with a number of drugs and suffer from metabolic disorders, which influence serum potassium homeostasis and other electrolytes [15, 16], possibly explaining the lack of association with known diabetes in our analysis. Several recent studies investigated the

association between serum potassium levels and the incidence of type 2 diabetes [7–9]. In the Atherosclerosis Risk in Communities (ARIC) study serum potassium levels were an independent predictor of type 2 diabetes [7]. Compared with persons with a serum potassium level of 5.0–5.5 mmol/l, individuals with serum potassium levels lower than 4.0 mmol/l had a relative risk of incident diabetes of 1.64 (95% CI 1.29, 2.08) after multivariable adjustment including the use of beta blockers, diuretics and ACE inhibitors [7]. Further findings from the ARIC study showed that low serum potassium levels in African-Americans contributed to their excess risk of diabetes relative to Europeans [8]. Another study conducted in Japanese men not using antihypertensive medication reported that every 0.5 mmol/l lower increment in the baseline serum potassium level was associated with a 45% increased risk of diabetes [9]. In that study however, the association only became statistically significant after adjustment for HbA<sub>1c</sub> in addition to the traditional predictors of diabetes. It was further demonstrated that hypokalaemia could be a possible factor involved in the progression from a prediabetic state to type 2 diabetes. A very recent prospective study conducted in a cohort of young adults found that a lower dietary intake of potassium, measured both by urinary potassium and diet history, was also significantly associated with a risk of incident diabetes after multivariable adjustment [17].

In the present study in multivariable logistic regression analysis we could show that among hypertensive individuals low serum potassium levels were associated with prediabetes. However, this was not the case in persons without hypertension. These findings underscore a possible role of serum potassium in the early pathogenesis of type 2 diabetes, particularly in hypertensive persons. Earlier studies showed that decreased serum potassium caused by the use of diuretics is associated with impaired glucose tolerance and increased risk of diabetes in persons with hypertension [5, 6]. In the present study, in hypertensive persons we also found an association between lower serum potassium levels and higher prevalence of prediabetes when participants using diuretics were excluded from analysis, suggesting that in this group serum potassium is related to glucose tolerance independent of the use of thiazides.

A meta-analysis including 59 studies suggested that there was a significant inverse association between changes in serum potassium levels and serum glucose levels in persons using thiazide diuretics [6]. However, other studies have not found such a correlation [18, 19].

It could be hypothesised that the effect of serum potassium is only significant among hypertensive persons with prediabetes or newly detected diabetes due to the insulin-resistant state, which is one shared defect in type 2 diabetes/prediabetes and essential hypertension [10]. A number of pathophysiological mechanisms seem to be credible candidates for a role in the development of hypertension and type 2 diabetes [10]. Insulin resistance is typically associated with hyperinsulinaemia, which can stimulate smooth muscle growth, enhance renal sodium retention and stimulate activity of the sympathetic nervous system. Additionally, there is an excitatory effect of hyperglycaemia on the renin–angiotensin–aldosterone system.

Obesity is closely related to, and a strong risk factor for, both type 2 diabetes and hypertension [10]. Furthermore, there is also an association between BMI and total body potassium [20, 21]. Total body potassium is an index of fat-free mass and is usually inversely associated with BMI [21]. Potassium, the most abundant cation in the body, is important for maintaining the resting membrane potential of cells and plays a key role in human metabolism in both health and disease [22]. About 98% of the total body potassium is found in the intracellular compartment. Although only 2% of the total body potassium remains outside cells, fairly small changes can have marked effects on organ function. Because only a small amount of potassium is located extracellularly, the value of serum (extracellular) potassium concentration as an index of total body potassium stores is limited [23, 24]. Serum potassium is strongly regulated and affected by potassium intake and excretion and also by factors that

influence potassium excretion and distribution between intracellular and extracellular spaces [25]. In the present study, serum potassium levels increased with increasing BMI. The underlying reasons for this finding are not clear. Possibly, the more obese persons in our study had a higher potassium supplementation, from either dietary or pharmacological sources.

The mechanisms by which serum potassium can effect changes in glucose homeostasis are not entirely clear. Earlier studies have investigated the effect of experimentally induced hypokalaemia on glucose homeostasis [3, 4, 26]. It could be shown that hypokalaemia was associated with hyperglycaemia due to decreased insulin secretion [3, 26] and that persons with hypokalaemia have a higher ratio of proinsulin to insulin secretion [6]. Due to the lower biological activity of proinsulin in comparison with insulin, higher serum glucose concentrations could be observed [6].

Further studies are needed to establish the underlying biological mechanisms regarding the role of serum potassium in the development of prediabetes, and subsequently type 2 diabetes, particularly in hypertensive persons.

The cross-sectional design of this study represents a limitation, implying that cause and effect relationships cannot be discerned. We cannot exclude the possibility that unknown risk factors may have biased or confounded the present analysis. Furthermore, no information on potassium supplementation or dietary intake was available in our study. Because the analyses were based on a follow-up examination of the population-based KORA S4 study, it could be argued whether or not the responders are representative of the initial population-based sample. The non-responders in the KORA F4 study were, for example, younger, had lower total cholesterol values, were more often smokers and were more physically inactive than the participants. However, with respect to other important risk factors for diabetes, such as BMI and hypertension, there were no differences between the two groups [27]. The strength of this study is the inclusion of a large number of individuals randomly drawn from the general population, and the availability of data on lifestyle, multiple metabolic risk factors and medication use.

In conclusion, serum concentrations of potassium were independently inversely associated with prediabetes and NDD in hypertensive individuals from the general population. Because the association between serum potassium and prediabetes in hypertensive participants was independent of diuretic use, it could be hypothesised that serum potassium concentration may partially account for the risk of prediabetes and diabetes in hypertensive individuals. In further studies the contribution of serum potassium to the pathogenesis of prediabetic states, and finally to the manifestation of type 2 diabetes, should be investigated.

**Acknowledgements** We thank all members of the Helmholtz Zentrum München and the field staff in Augsburg who were involved in carrying out the study.

**Funding** The KORA research platform is financed by the Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria. The Diabetes Study was funded by a German Diabetes Foundation project grant (201/05/07). This study was supported in part by a grant from the German Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD e.V.).

**Duality of interest** The authors declare that there is no duality of interest associated with this manuscript.

**Contribution statement** CM conducted the analysis, wrote the manuscript and researched data. WR and BK reviewed and edited the manuscript and contributed to the interpretation of the data and its discussion. AD, BT and MH researched data and reviewed and edited the manuscript. DS, IMR, PB and CH contributed to the interpretation of the data and reviewed and edited the manuscript. All authors finally approved the manuscript version to be published.

## References

1. Herman WH, Zimmet P (2012) Type 2 diabetes: an epidemic requiring global attention and urgent action. *Diabetes Care* 35:943–944
2. Lee DC, Park I, Jun TW et al (2012) Physical activity and body mass index and their associations with the development of type 2 diabetes in Korean men. *Am J Epidemiol* 176:43–51
3. Rowe JW, Tobin JD, Rosa RM, Andres R (1980) Effect of experimental potassium deficiency on glucose and insulin metabolism. *Metabolism* 29:498–502
4. Gorden P (1973) Glucose intolerance with hypokalemia. Failure of short-term potassium depletion in normal subjects to reproduce the glucose and insulin abnormalities of clinical hypokalemia. *Diabetes* 22:544–551
5. Shafi T, Appel LJ, Miller ER, Klag MJ, Parekh RS (2008) Changes in serum potassium mediate thiazide-induced diabetes. *Hypertension* 52:1022–1029
6. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL (2006) Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 48:219–224
7. Chatterjee R, Yeh HC, Shafi T et al (2010) Serum and dietary potassium and risk of incident type 2 diabetes mellitus. *Arch Intern Med* 170(19):1745–1751
8. Chatterjee R, Yeh HC, Shafi T et al (2011) Serum potassium and the racial disparity in diabetes risk: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr* 93:1087–1091
9. Heianza Y, Hara S, Arase Y et al (2011) Low serum potassium levels and risk of type 2 diabetes: the Toranomon Hospital Health Management Center Study 1 (TOPICS 1). *Diabetologia* 54:762–766
10. Ferrannini E, Cushman WC (2012) Diabetes and hypertension: the bad companions. *Lancet* 380:601–610
11. Rathmann W, Kowall B, Tamayo T et al (2010) Hemoglobin A1c and glucose criteria identify different subjects as having type 2 diabetes in middle-aged and older populations: The KORA S4/F4 Study. *Ann Med* 44:170–177
12. Rathmann W, Haastert B, Icks A et al (2003) High prevalence of undiagnosed diabetes mellitus in Southern Germany: target populations for efficient screening. The KORA survey 2000. *Diabetologia* 46:182–189
13. Meisinger C, Thorand B, Schneider A, Stieber J, Döring A, Löwel H (2002) Sex differences in risk factors for incident type 2 diabetes mellitus. The MONICA Augsburg Cohort Study. *Arch Intern Med* 162:82–89
14. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes (2009). *Diabetes Care* 32:1327–1334
15. Pun KK, Ho PW (1989) Subclinical hyponatremia, hyperkalemia and hypomagnesemia in patients with poorly controlled diabetes mellitus. *Diabetes Res Clin Pract* 7:163–167
16. McNair P, Madsbad S, Christiansen C, Christensen MS, Transbol I (1982) Hyponatremia and hyperkalemia in relation to hyperglycemia in insulin-treated diabetic out-patients. *Clin Chim Acta* 120:243–250
17. Chatterjee R, Colangelo LA, Yeh HC et al (2012) Potassium intake and risk of incident type 2 diabetes mellitus: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Diabetologia* 55:1295–1303
18. Langford HG, Cutter G, Oberman A, Kansal P, Russell G (1990) The effect of thiazide therapy on glucose, insulin and cholesterol metabolism and of glucose on potassium: results of a cross-sectional study in patients from the hypertension detection and followup program. *J Hum Hypertens* 4:491–500
19. Plavinik FL, Rodrigues CI, Zanella MT, Ribeiro AB (1992) Hypokalemia, glucose intolerance, and hyperinsulinemia during diuretic therapy. *Hypertension* 19(suppl II):II26–II29
20. Kehayias JJ, Fiatarone MA, Zhuang H, Roubenoff R (1997) Total body potassium and body fat: relevance to aging. *Am J Clin Nutr* 66:904–910
21. He Q, Heo M, Heshka S et al (2003) Total body potassium differs by sex and race across the adult age span. *Am J Clin Nutr* 78:72–77
22. Linshaw MA (1987) Potassium homeostasis and hypokalemia. *Pediatr Clin North Am* 34:649–681
23. Mandal AK (1997) Hypokalemia and hyperkalemia. *Med Clin North Am* 81:611–639
24. Halperin ML, Kamel KS (1998) Potassium. *Lancet* 352:135–140
25. Evans KJ, Greenberg A (2005) Hyperkalemia: a review. *J Intensive Care Med* 20:272–290
26. Sagild U, Andersen V, Andreassen PB (1961) Glucose tolerance and insulin responsiveness in experimental potassium depletion. *Acta Med Scand* 169:243–251
27. Meisinger C, Strassburger K, Heier M et al (2010) Prevalence of undiagnosed diabetes and impaired glucose regulation in 35–59-year-old individuals in Southern Germany: the KORA F4 Study. *Diabet Med* 27:360–362