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Published in:
The Journal of Nutrition

DOI:
10.1093/jn/nxac215

The Journal of Nutrition
Nutritional Epidemiology

Low Urinary Potassium Excretion Is Associated with Higher Risk of All-Cause Mortality in Patients with Type 2 Diabetes: Results of the Dutch Diabetes and Lifestyle Cohort Twente (DIALECT)

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ABSTRACT

Background: Low 24-h urinary potassium excretion, reflecting low potassium intake, is associated with premature mortality in the general population.

Objectives: To determine whether urinary potassium excretion is associated with all-cause mortality in patients with type 2 diabetes.

Methods: We performed a prospective cohort study in 654 patients with type 2 diabetes in the Diabetes and Lifestyle Cohort Twente (DIALECT). Sex-specific tertiles of 24-h urinary potassium excretion were analyzed in a multivariable Cox regression model with all-cause mortality. The outpatient program of the hospital uses a continuous surveillance system by the municipal registry of death to ensure up-to-date information on the patient's status (alive or deceased). FFQs were used to study associations between urinary potassium excretion and food products.

Results: Urinary potassium excretion at baseline was 84 ± 25 mmol/d in males and 65 ± 22 mmol/d in females, corresponding to estimated potassium intakes of 4250 ± 1270 mg/d and 3300 ± 875 mg/d. During a median follow-up of 5.2 (IQR: 2.7–7.9] y, 96 participants died. In a fully adjusted model, patients in the lowest sex-specific tertile had a higher risk of all-cause mortality, compared with patients in the highest sex-specific tertile (HR: 2.09; 95% CI: 1.06, 4.10; $P = 0.03$). Patients in the lowest sex-specific tertile consumed fewer fruits and vegetables, dairy, coffee, and potato products compared with patients in the highest sex-specific tertile (all $P < 0.05$).

Conclusions: Low potassium intake is associated with a higher risk of all-cause mortality in Dutch patients with type 2 diabetes. Intervention studies are needed to determine whether potassium supplementation improves longevity in patients with type 2 diabetes. This trial was registered in the Dutch Trial Register as NTR trial code 5855. *J Nutr* 2022;152:2856–2864.

Keywords: type 2 diabetes, 24-hour urinary potassium excretion, food-frequency questionnaire, all-cause mortality, diet

Introduction

The prevalence of type 2 diabetes (T2D) is rapidly increasing worldwide (1). Patients with T2D have an increased risk for complications such as chronic kidney disease (CKD) and cardiovascular disease (CVD) due to hyperglycemia, hypertension, and dyslipidemia (2). Intensive pharmacological treatment could reduce the risk of these complications (3). Despite these efforts, many patients still have an increased risk of premature mortality (4), underscoring the urgent need to explore other options, such as dietary intervention to reduce complications (5).

The WHO recommends a daily potassium intake of 3500 mg/d (6). Potassium is an essential mineral that is abundantly present in leafy green and root vegetables and fruits, but it is also

Manuscript received May 5, 2022. Initial review completed June 21, 2022. Revision accepted September 9, 2022.
First published online September 20, 2022; doi: https://doi.org/10.1093/jn/nxac215.

present in coffee, dairy, and cereals (7). Dietary potassium intake is often inadequate in individuals consuming a Western diet, which is characterized by high intake of meat, refined grains, and processed food and a low intake of fruit and vegetables (7). In addition, availability and affordability of healthy diet components (e.g., fruit and vegetables) may play a crucial role in maintaining a healthy diet (8).

Multiple observational studies have shown that urinary potassium excretion, a reflection of potassium intake, is inversely associated with the risk of hypertension, CVD, and mortality in the general population (9, 10). One study in patients with T2D found that urinary potassium excretion is inversely associated with a slower decline in kidney function and a lower incidence of cardiovascular complications (11). Moreover, intervention studies showed that an increase in potassium intake lowers blood pressure, which could potentially be promising, particularly in patients with high cardiovascular risk (12). Recent literature indicates that substitution of sodium chloride by potassium chloride lowered rates of major cardiovascular events and all-cause mortality (13).

In the current study, we hypothesized that, in patients with T2D, a low potassium intake is associated with an increased risk of premature mortality. In addition, we hypothesized that lower intakes of specific potassium-rich food products contribute to the excess mortality risk in patients with T2D.

Methods

Study design

This study was conducted with data from the Diabetes and Lifestyle Cohort Twente (DIALECT), an observational cohort study in patients with T2D aged ≥18 y, treated in a secondary health care center. Details of this study are described in detail elsewhere (14). Patients were enrolled between 2009 and 2018. This study was conducted according to the guidelines of Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all participants prior to participation. The study was approved by the local institutional committees (METC registration numbers NL57219.044.16 and 1009.68020) and registered in the Dutch Trial Register (NTR trial code 5855).

Patients

All adult patients with type 2 diabetes, who were treated at the outpatient clinic of Ziekenhuisgroep Twente (ZGT), Almelo and Hengelo, the Netherlands, were eligible for participation ($n = 668$). The diagnosis of T2D was derived from the electronic patient files, as noted by the treating physicians. In case of doubt, additional blood measurements were performed—for example, T2D was diagnosed if anti-glutamic acid decarboxylase concentrations were <10 kU/L. Patients were screened for eligibility in the electronic patient file and subsequently invited for a study visit (14). Exclusion criteria were renal replacement therapy and inability to understand the informed-consent procedure. For the current study, all patients with available baseline urinary potassium excretion data ($n = 654$) and nutritional data ($n = 628$) were included. A patient inclusion flowchart is shown in **Supplemental Figure 1**.

Estimated potassium intake

For proper collection of the 24-h urine samples, patients were instructed to discard the first morning urine and then collect all urine in the provided canister until the first morning urine of the following day. The canisters were stored in a dark and cool place until the next day when patients returned the canister during the baseline visit. The 24-h urinary potassium concentration was measured by an indirect ion-selective electrode method (Cobas 8000 Modular Analyser; Roche Diagnostics). The concentrations from the 24-h urine collections were then multiplied by the volume of the 24-h urine collection to obtain urinary potassium excretion. Estimated potassium intake was calculated by multiplying the net 24-h urinary potassium excretion (mmol/24 h) by the molar weight of potassium (39 g/mol), under the assumption of a renal excretion rate of 77% (9). Estimated sodium intake was calculated by multiplying the net 24-h urinary sodium excretion (mmol/24 h) by the molar weight of sodium (23 g/mol).

Sources of dietary potassium

Dietary potassium sources were assessed with a semi-quantitative FFQ. The FFQ was developed and validated in 2005 at Wageningen University (15). The FFQ asked the patient regarding the intake of 177 dietary items during the past month. The frequency of each item is indicated in times per day, week, or month. The number of servings was expressed in natural units (e.g., sandwich or apple) or household measures (e.g., cup or spoon). The questionnaire was self-administered and completed at home. The filled-in questionnaires were checked for completeness by a trained researcher and inconsistent answers were verified with the patients. Dietary data were converted to daily nutrient intake using the Dutch Food Composition Table 2013 (16). Food groups were created according to the Dutch Healthy Diet Index (17).

Covariates

During the study visit, body weight (kg) and height (cm) were measured. BMI was calculated as weight divided by height squared (kg/m^2). Body surface area (BSA) in meters squared was determined with the DuBois and DuBois formula: [weight (kg)$^{0.425}$ × height (cm)$^{0.725}$] × 0.007184. Information on lifestyle exposure (e.g., smoking) was collected through a self-administered questionnaire. Blood pressure was measured in the supine position by an automated device (Dinamap; GE Medical Systems) for 15 min at 1-min intervals. The mean systolic and diastolic blood pressures from the last 3 measurements were used for analysis. History of CVD was defined as history of unstable angina pectoris, myocardial infarction, peripheral artery disease, transient ischemic attack, and cerebrovascular diseases (cerebral infarction and hemorrhage). Routinely measured variables (e.g., serum creatinine and LDL cholesterol) were determined with the enzymatic colorimetric method with a Clinical Chemistry Analyzer and Immunochemistry Analyzer (COBAS 6000; Roche Diagnostics GmbH). LDL cholesterol was calculated using the Friedewald formula (only if triglycerides <4.5 mmol/L) (18). Estimated glomerular filtration rate (eGFR) was assessed based on serum creatinine concentrations using the Chronic Kidney Disease Epidemiology Collaboration formula: eGFR = 141 × min[serum creatinine (μmol/L)/$_a$]^b × max[serum creatinine (μmol/L)/$_a$]$^{-1.209}$ × 0.993^{Age} (× 1.018 if female), in which $_a$ = 80 μmol/L for males and 62 μmol/L for females and ^{b} = −0.411 for males and −0.329 for females, min is the minimum of serum creatinine (μmol/L)/$_a$ or 1, and max is the maximum of serum creatinine

This project is supported by the Dutch Kidney Foundation (K+onsortium) and a research grant from the Ziekenhuisgroep Twente Hospital.
Author disclosures: GN reports an unpaid fiduciary role from the Health Council of The Netherlands and unpaid advisor to ZorgOnderzoek Nederland-Medische Wetenschappen (ZON-MW) governmental funding body for medical research. MHdB reports consulting fees from AstraZeneca and Vifor Pharma, outside the submitted work. GDL reports grants from Sanofi, grants from Novo Nordisk, personal fees from Lilly, grants and personal fees from AstraZeneca, grants and personal fees from Vifor Pharma, and grants and personal fees from Abbott, outside the submitted work. The other authors report no conflicts of interest. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Supplemental Figures 1–3 and Supplemental Tables 1–7 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.
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Abbreviations used: BSA, body surface area; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DIALECT, Diabetes and Lifestyle Cohort Twente; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; T2D, type 2 diabetes.

(μmol/L/$_a$) or 1 (19). Serum glycated hemoglobin (HbA1c) was measured by the Roche Tina-quant 3rd generation immunoturbidimetric method, standardized according to the International Federation of Clinical Chemistry and Laboratory Medicine. Serum concentration of C-reactive protein (CRP) was measured routinely using immunoassay. Cardiovascular history was derived from the electronic patient files and verified during the baseline visit.

Outcome measurement

The main outcome measurement was all-cause mortality. The outpatient program of the hospital uses a continuous surveillance system by the municipal registry of death to ensure up-to-date information on the patient's status (alive or deceased). Survival time was calculated as the difference in days between baseline visit and date of mortality or censoring date, defined as the date of last check in the surveillance system. Patients who were lost to follow-up were censored at the last date at which the surveillance system ensures information on the patient's status.

With regard to dietary components that contribute to potassium intake, potassium-rich products were adjusted for total energy intake by the residual method. Therefore, we used the mean total caloric intake of our population in the regression equations (20).

Statistical analysis

Normally distributed data are presented as means ± SDs. Skewed variables are presented as medians (IQR), and percentages were used for categorical data. Patients were divided according to sex-specific tertiles of 24-h urinary potassium excretion. Differences in characteristics between these tertiles were tested using the 1-factor ANOVA for normally distributed variables, the Kruskal-Wallis test for skewed variables, and the chi-square test for categorical data. All statistical analyses were performed using IBM SPSS for Windows (version 23.0; IBM Corporation). A 2-sided P value <0.05 was considered statistically significant.

Some participants had missing values for baseline variables. Exclusion of participants with missing values could result in bias, and therefore, we used multiple imputation [fully conditional specification (Markov chain Monte Carlo)] to obtain 5 imputed datasets. Rubin's rules were used to obtain pooled estimates of the regression coefficients and their SEs across imputed datasets.

We subsequently analyzed the association between baseline urinary potassium excretion and all-cause mortality with Cox proportional hazards regression analyses using the highest sex-specific tertile as the reference group. We constructed the following models to account for possible confounding: model 1 is the crude model; model 2 additionally adjusted for age; model 3 additionally adjusted for diabetic and lifestyle factors such as BSA, CVD, eGFR, total urinary protein excretion, LDL cholesterol, serum HbA1c, diabetes duration, smoking status, and alcohol consumption; and model 4 additionally adjusted for urinary sodium excretion, urinary urea excretion, and urinary creatinine excretion as objective measures of sodium intake, protein intake, and muscle mass, respectively. We used restricted cubic spline with 3 knots (5th, 50th, and 95th percentile) to visualize the continuous association between urinary potassium excretion and risk of all-cause mortality by fitting the Cox regression analysis of the final model.

We analyzed potential interaction effects of age, sex, eGFR, and BMI by fitting models containing both main effects and their cross-product terms in the analyses of all-cause mortality risk ($P > 0.10$ for all interaction terms).

Sensitivity analysis

Multiple sensitivity analyses were performed. First, we repeated multivariable Cox regression models with additional adjustment for use of diuretics. Second, we excluded participants with potential under- or over-collection from analysis ($n = 38$). Such samples were identified through assessing the difference between the estimated and measured volume of a participant's 24-h urine sample. The estimated 24-h urine volume was derived from the following formula: Creatinine clearance = (urine creatinine × 24-h urine volume) · serum creatinine^{-1}, where creatinine clearance was estimated using the Cockcroft–Gault formula. If accurately collected, estimated creatinine clearance using 24-h urine specimens and estimated creatinine clearance using a serum-based equation (which is entirely independent of the timed urine) should be similar. Samples with potential under- or over-collection were defined as the upper and lower 2.5% of the difference between the estimated and measured volume of a participant's 24-h urine sample. Third, we excluded participants with possible accidental cause of death ($n = 4$).

In the subgroup of patients with available FFQ data ($n = 627$), we repeated multivariable Cox regression models and we additionally adjusted for caloric intake. Also, we performed sensitivity analysis in which patients with extreme energy intake levels, defined as a deviation of >3 SDs from the mean, were excluded from analysis ($n = 9$).

With regard to food-group analysis, we first show the contribution of each potassium-rich food group to total potassium intake. In addition, we disentangled specific food items within each potassium-rich food group and show each association with 24-h urinary potassium excretion. Also, we performed multivariable linear regression analysis to assess which potassium-rich food groups independently relate to 24-h urinary potassium excretion. Fourth, we performed multiple sensitivity analyses with either energy-adjusted meat intake, energy-adjusted intake of mono- and disaccharides, energy-adjusted intake of fats/oils, or energy-adjusted magnesium intake. Finally, we analyzed whether sex-specific tertiles of potassium-rich products were associated with all-cause mortality.

Results

Baseline characteristics

Baseline characteristics by sex-specific tertiles of 24-h urinary potassium excretion are shown in **Table 1**. The total population ($n = 654$) included 61% male participants, with a mean age of 64 ± 10 y and mean BMI (kg/m^2) of 32.6 ± 5.8; 63% of the patients with T2D used insulin. Mean 24-h urinary potassium excretion was significantly higher in males (84 ± 25 mmol/24 h) than in females (65 ± 22 mmol/24 h), corresponding to an estimated potassium intake of 4250 ± 1270 mg/d for males and 3300 ± 875 mg/d for females. In addition, 38% of the patients did not adhere to the recommended daily potassium intake of >3500 mg/d. Patients in the highest sex-specific tertile of 24-h urinary potassium excretion had a higher eGFR, more commonly used blood glucose–lowering agents, and less frequently used diuretics, whereas patients in the lowest sex-specific tertile of 24-h urinary potassium excretion had a lower diastolic blood pressure. Furthermore, the 24-h urinary potassium excretion was positively associated with urinary sodium excretion, urinary creatinine excretion, and urinary protein excretion, and inversely with CRP. There was no significant association between serum potassium and urinary potassium excretion.

Nutritional correlates of urinary potassium excretion

Subsequently, we analyzed which potassium-rich products contributed to higher urinary potassium excretion. Total energy-adjusted potassium intake as estimated with the FFQ was higher across increasing sex-specific tertiles of 24-h urinary potassium excretion ($P < 0.001$; data not shown). Differences in potassium intake from potassium-rich products across sex-specific tertiles of 24-h urinary potassium excretion are shown in **Figure 1**. Patients in the lowest sex-specific tertile of 24-h urinary potassium excretion consumed less fruits and vegetables compared with patients in the second and highest tertile of 24-h urinary potassium excretion ($P = 0.003$). Moreover, patients in the lowest sex-specific tertile of 24-h

TABLE 1 Baseline characteristics by sex-specific tertiles of 24-h urinary potassium excretion of 654 patients with type 2 diabetes from the DIAbetes and LifEstyle Cohort Twente[1]

Variables	Overall	Tertile 1 (males: <74 mmol/24 h; females: <56 mmol/24 h)	Tertile 2 (males: 74–91 mmol/24 h; females: 56–74 mmol/24 h)	Tertile 3 (males: >91 mmol/24 h; females: >74 mmol/24 h)	*P*-trend
Total participants, *n*	654	219	219	216	
Males	397	134	131	132	
Females	257	85	88	84	
Urinary potassium excretion, mmol/24 h	76 ± 26	51 ± 14	75 ± 10	103 ± 18	
Males	84 ± 25	58 ± 12	82 ± 5	112 ± 17	
Females	65 ± 22	41 ± 10	65 ± 6	90 ± 13	
Age, y	64 ± 10	65 ± 11	64 ± 9	63 ± 9	0.06
Smoking status, *n* (%)					0.25
Current smoker	106 (16)	44 (20)	31 (14)	31 (14)	
Former smoker	337 (52)	102 (47)	122 (56)	113 (52)	
Never smoker	212 (32)	73 (33)	66 (30)	73 (34)	
Alcohol consumption, *n* (%)					0.36
No consumption	238 (38)	89 (42)	78 (37)	71 (35)	
Moderate consumption	225 (36)	71 (34)	72 (34)	82 (40)	
High consumption	164 (26)	52 (25)	62 (29)	50 (25)	
BMI, kg/m^2	32.6 ± 5.8	32.2 ± 6.1	32.6 ± 5.8	33.0 ± 5.4	0.31
Body surface area, m^2	2.09 ± 0.22	2.04 ± 0.22	2.09 ± 0.23	2.14 ± 0.20	<0.001
Diabetes duration, y	12 [7–19]	11 [7–19]	12 [7–19]	12 [7–19]	0.99
CVD at baseline, *n* (%)	242 (37)	88 (40)	84 (38)	70 (32)	0.22
LDL cholesterol, mmol/L	2.0 ± 0.8	2.0 ± 0.8	2.0 ± 0.7	2.1 ± 0.8	0.09
Systolic blood pressure, mmHg	134 ± 16	132 ± 17	135 ± 17	134 ± 14	0.08
Diastolic blood pressure, mmHg	74 ± 10	72 ± 11	75 ± 9	75 ± 9	0.002
eGFR, mL /min/1.73 m^2	76 ± 24	73 ± 27	74 ± 24	80 ± 22	0.005
Blood and urine sampling					
Serum potassium, mmol/L	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	0.34
Serum sodium, mmol/L	139 ± 3	140 ± 3	139 ± 3	139 ± 3	0.005
Serum HbA1c, mmol/mol	58 ± 12	58 ± 13	58 ± 12	59 ± 11	0.57
CRP, mg/L	2 [1–5]	3 [1–6]	2 [1–5]	2 [1–4]	0.04
Total urinary volume, mL/24 h	2000 ± 785	1600 ± 644	2040 ± 657	2360 ± 850	<0.001
Urinary potassium concentration, mmol/L	41.2 ± 15.1	35.9 ± 14.0	40.2 ± 14.1	47.5 ± 14.9	<0.001
Urinary sodium excretion, mmol/24 h	178 ± 77	138 ± 58	183 ± 77	215 ± 75	<0.001
Estimated sodium intake, mg/d	4100 ± 1770	3160 ± 1330	4210 ± 1760	4940 ± 1740	<0.001
Sodium-to-potassium ratio, mmol/mmol	2.4 ± 0.9	2.7 ± 1.0	2.4 ± 0.9	2.1 ± 0.7	<0.001
Urinary creatinine excretion, mmol/24 h	13.5 ± 4.7	10.9 ± 3.6	13.7 ± 4.5	16.1 ± 4.4	<0.001
Urinary protein excretion, g/24 h	0.20 [0.10–0.30]	0.16 [0.10–0.30]	0.20 [0.10–0.30]	0.20 [0.10–0.30]	0.02
Urinary urea excretion, mmol/24 h	409 ± 152	315 ± 123	411 ± 131	503 ± 140	<0.001
Pharmacological management, *n* (%)					
Insulin use	415 (63)	132 (60)	138 (63)	145 (67)	0.36
Blood sugar–lowering agent	528 (81)	168 (77)	172 (79)	188 (87)	0.02
Antihypertensive agents	556 (85)	188 (86)	192 (88)	176 (81)	0.14
RAASi	461 (70)	152 (69)	155 (71)	154 (71)	0.93
Diuretics	346 (53)	117 (53)	130 (59)	99 (46)	0.018
Thiazides and loop diuretics	328 (50)	111 (51)	121 (55)	96 (44)	0.08
Potassium-sparing diuretics	82 (13)	29 (13)	31 (14)	22 (10)	0.41

[1] Continuous variables are reported as means ± SDs or median [IQR], and categorical variables are reported as *n* (%). Missing values for BMI ($n = 1$), LDL cholesterol ($n = 41$), blood pressure ($n = 12$), serum sodium ($n = 1$), serum HbA1c ($n = 1$), CRP ($n = 1$), urinary sodium excretion ($n = 2$), estimated sodium intake ($n = 2$), sodium-to-potassium ratio ($n = 2$), urinary protein excretion ($n = 2$) and urinary urea excretion ($n = 38$). CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; RAASi, renin angiotensin aldosterone system inhibitors.

urinary potassium excretion consumed less dairy ($P = 0.001$) and potato products ($P = 0.030$) compared with patients in the highest tertile of 24-h urinary potassium excretion. In addition, coffee consumption was higher across increasing tertiles of 24-h urinary potassium excretion ($P < 0.001$), ranging from 3 cups/d (375 mL/d) in the lowest tertile of 24-h urinary potassium excretion to 5 cups/d (625 mL/d) in the highest tertile of 24-h urinary potassium excretion.

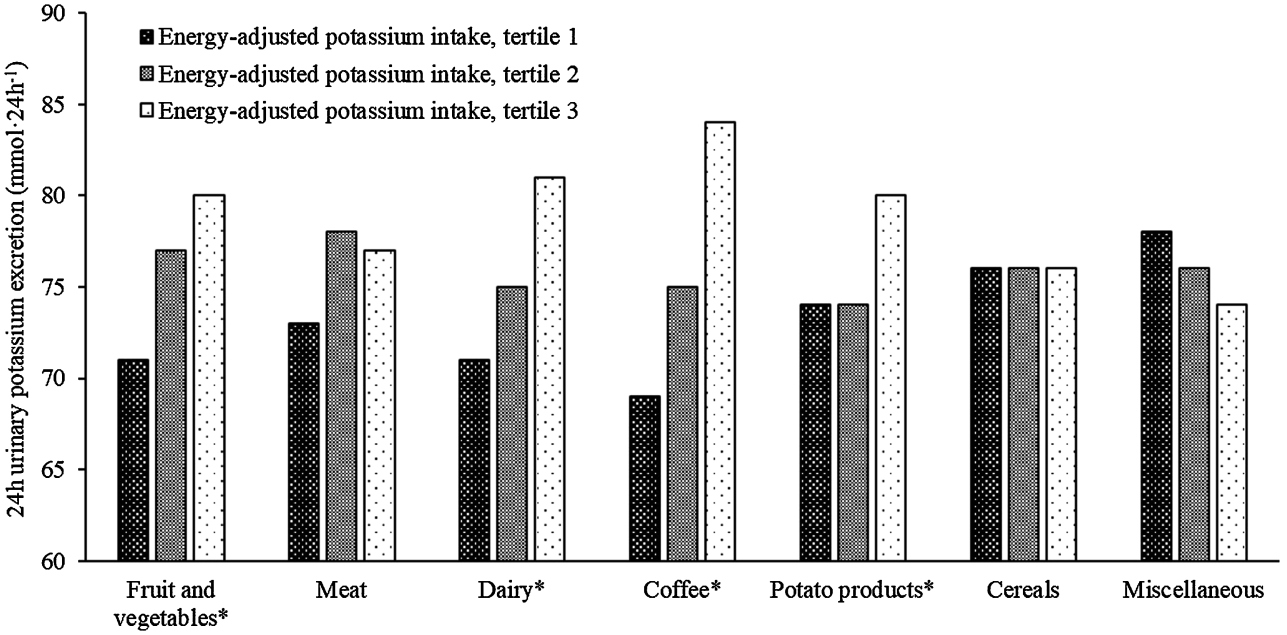

FIGURE 1 Twenty-four-hour urinary potassium excretion by sex-specific tertiles of energy-adjusted potassium intake from potassium-rich products assessed with FFQs in 627 patients with type 2 diabetes from the DIAbetes and LifEstyle Cohort Twente. *Significant difference across sex-specific tertiles of 24-h urinary potassium excretion within each category of potassium-rich products ($P < 0.05$).

Urinary potassium excretion and all-cause mortality

During a median follow-up of 5.2 y (2.7–7.9 y), 96 participants had died and 24 participants were lost to follow-up. Upon Cox proportional hazards regression analyses, in the fully adjusted model, participants in the lowest sex-specific tertile of 24-h urinary potassium excretion had an increased risk for all-cause mortality compared with the highest tertile of 24-h urinary potassium excretion (HR: 2.09; 95% CI: 1.06, 4.10; $P = 0.033$) (Table 2). No significant interaction effects of age, sex, BMI, and eGFR were found. Figure 2 shows the continuous association between urinary potassium excretion and all-cause mortality risk.

Sensitivity analyses

We performed several sensitivity analyses. In the analysis in which we additionally adjusted for use of diuretics, there were no material differences compared with the results of the primary analyses (**Supplemental Table 1**). Also, in the analyses where we excluded 24-h urine samples with possible under- or over-collections ($n = 616$), there were no material differences compared with the results of the primary analyses (**Supplemental Table 2**). In addition, we performed a sensitivity analysis in which we excluded patients with possible accidental deaths and the results did not materially differ from the primary results (**Supplemental Table 3**).

In the subgroup of patients with available FFQ data ($n = 627$), we repeated multivariable Cox proportional hazards regression analyses, with additional adjustment for total caloric intake, which did not significantly change the results (**Supplemental Table 4**). Additionally, we performed sensitivity analysis in which patients with extreme energy intake levels, defined as a deviation of >3 SDs from the mean, were excluded from analysis (**Supplemental Table 5**). The results of this analysis remained unchanged.

With regard to food-group analysis, we first showed that the majority of potassium intake is from fruit and vegetables (17.4%), followed by intake of potato products (16.5%), dairy (16.2%), and coffee (16.1%) (**Supplemental Figure 2**). In addition, we showed that specifically citrus fruit, potatoes, and almost all vegetables except for broccoli and cauliflower are positively associated with urinary potassium excretion, while whole-milk products are inversely associated with urinary potassium excretion (**Supplemental Figure 3**A–D). In a multivariable linear regression analysis, we assessed that intakes of fruit and vegetables, dairy, coffee, and potato products independently positively relate to 24-h urinary potassium excretion (**Supplemental Table 6**). Finally, we performed multiple sensitivity analyses with either energy-adjusted meat intake, energy-adjusted intake of mono- and disaccharides, energy-adjusted intake of fats/oils, or energy-adjusted magnesium intake. The results of these analyses did not materially differ from the primary analyses (**Supplemental Table 7**). None of the potassium-rich products were associated with all-cause mortality.

Discussion

In this prospective cohort of patients with T2D, 24-h urinary potassium excretion, as a reflection of dietary potassium intake, was inversely associated with all-cause mortality. This association remained after adjustment for conventional risk factors and total caloric intake. Moreover, we found that patients in the lowest sex-specific tertile of 24-h urinary potassium excretion consumed less fruits and vegetables, dairy, coffee, and potato products compared with patients in the highest sex-specific tertile of urinary potassium excretion.

The mean estimated potassium intake in our cohort was 3880 ± 1300 mg/d, which is in line with another diabetes cohort (21). Thirty-eight percent of patients did not reach the WHO-recommended intake of 3500 mg/d. The finding that low urinary potassium excretion is associated with a higher all-cause mortality risk is in line with previous studies (10). One study in 1230 patients with diabetes found

TABLE 2 Associations between 24-h urinary potassium excretion and mortality in 654 patients with type 2 diabetes from the DIAbetes and LifEstyle Cohort Twente[1]

	Sex-specific tertiles of 24-h urinary potassium excretion, mmol/24 h		
	Males: <74 mmol/24 h; females: <56 mmol/24 h	Males: 74–91 mmol/24 h; females: 56–74 mmol/24 h	Males: >91 mmol/24 h; females: >74 mmol/24 h
Participant numbers	219	219	216
Events	41	38	17
Models			
1	2.91 (1.65–5.13)***	2.19 (1.24–3.88)**	Reference
2	2.39 (1.35–4.23)**	1.82 (1.03–3.24)*	Reference
3	2.43 (1.34–4.41)**	1.74 (0.97–3.14)	Reference
4	2.09 (1.06–4.10)*	1.67 (0.91–3.05)	Reference

[1]Values are HRs (95% CIs) unless otherwise indicated. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Model 1: crude model. Model 2: as model 1 and additionally adjusted for age. Model 3: as model 2 and additionally adjusted for BSA, eGFR, CVD, LDL cholesterol, smoking status, alcohol consumption, total urinary protein excretion, serum HbA1c, and diabetes duration. Model 4: as model 3 and additionally adjusted for urinary sodium excretion, urinary urea excretion and urinary creatinine excretion. BSA, body surface area; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.

an inverse association between urinary potassium excretion and a composite outcome of kidney function decline and mortality, but only 6 deaths were recorded compared with 124 renal events (22). In addition, a prospective study in patients with T2D and normal renal function (eGFR ≥60 mL/min/1.73 m^2) found an inverse association between urinary potassium excretion and kidney function and cardiovascular complications (11). In patients with CKD, low urinary potassium excretion has been shown to be associated with increased risk of all-cause mortality and progression of CKD (23, 24). These findings suggest that patients with CKD may benefit from a higher intake of potassium, a subject that is currently being investigated in a multicenter, randomized controlled trial in the Netherlands (25). Recently, a trial showed that partial substitution of sodium chloride by potassium chloride lowered rates of major cardiovascular events and all-cause mortality in more than 20,000 individuals (13). Our study population represents a real-life population of patients with T2D with above-average elevated cardiovascular risk, in which renal function

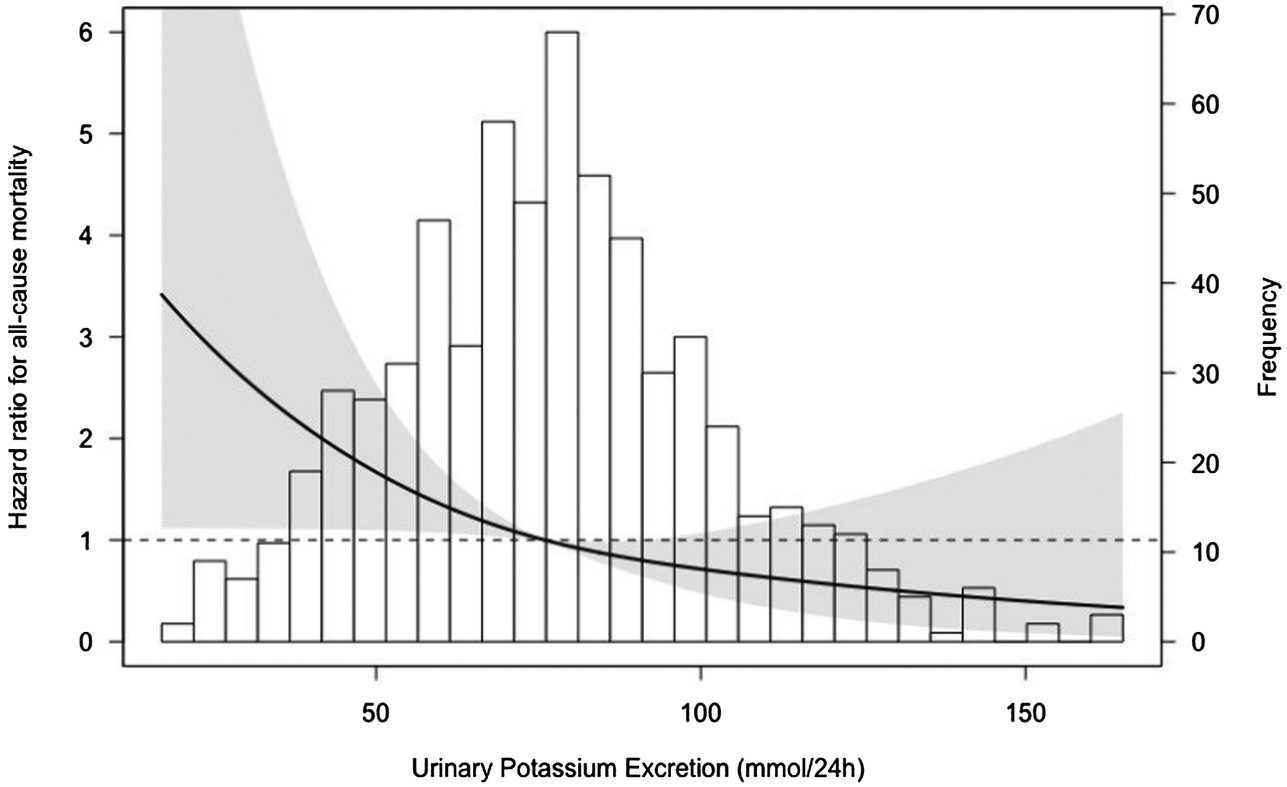

FIGURE 2 Associations between urinary potassium excretion and all-cause mortality in 654 patients with type 2 diabetes. Data were fit by a Cox proportional hazards regression model based on restricted cubic splines (5th, 50th, and 95th percentile knots) and adjusted for age, sex, BSA, eGFR, CVD, LDL cholesterol, smoking status, alcohol consumption, total urinary protein excretion, serum HbA1C, diabetes duration, urinary sodium excretion, urinary urea excretion, and urinary creatinine excretion. The gray shaded area represents the 95% CI. BSA, body surface area; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.

impairment is prevalent in almost 30% of patients. Intervention studies are needed to determine whether potassium supplementation may reduce adverse outcomes in patients with T2D.

Whether potassium in itself, or rather high-potassium products that are rich sources of vitamins, minerals, fibers, and proteins, which all might have a beneficial impact on health, is unknown. Several studies have found that coffee and dairy intakes are inversely associated with CVD and mortality (26, 27), while potato products are nutrient-dense products with potential health-promoting effects (28). However, higher potato intake has been associated with an increased risk of diabetes, and increasing potato intake might therefore not be advisable in the T2D population (29). Some studies in mice and humans with diabetes show that potatoes might lower HbA1c, lipid concentrations, and other metabolic markers (30, 31). Moreover, a recent study showed that, due to the biological rhythm of insulin secretion, consuming potato before noon is associated with long-term survival (32). One might argue that reduced intake of potassium is actually a proxy for reduced intake of healthy products that are rich in potassium, and therefore potassium itself is not causally related to mortality risk but an overall marker of intake of healthy food, without a specific product highlighted. Alternatively, our finding that none of the separate potassium-rich products was associated with all-cause mortality could be consistent with the notion that the association is determined by potassium intake per se. Another potential bias could be that low potassium excretion reflects total low nutritional intake, and therefore is associated with higher mortality. However, on examination, adjusting for total caloric intake and urinary urea excretion, a marker for protein intake, the association between low potassium excretion and higher mortality risk remained intact.

With regard to the underlying mechanism between potassium intake and mortality risk, several intervention studies have shown that potassium supplementation lowers blood pressure (12). Underlying mechanisms might include potassium-induced natriuresis or lower sympathetic activity (12, 33). Furthermore, higher potassium intake may improve endothelial function, and vascular resistance, which may lead to vasodilation or enhanced endothelium-dependent relaxation (34). Other experimental studies have shown that potassium supplementation may reduce vascular calcification (35).

Furthermore, potassium might play an important role in glucose regulation. Previous studies showed that hypokalemia—for example, present in hyperaldosteronism and during use of thiazide diuretics—is associated with increased glucose intolerance (36). Some observational studies found an association between low serum potassium and low dietary potassium intake and the development of T2D (37). Although we did not observe a significant association between potassium intake and serum potassium, it seems that potassium depletion could increase glucose intolerance and insulin insensitivity (38). However, in our study, no association between HbA1c and urinary potassium excretion was observed at baseline. This observation might be confounded by the higher use of blood glucose–lowering agents in patients with high urinary potassium excretion, possibly due to more strict glucose management.

Dietary intervention is a vital part in the prevention and management of diabetes (5). Current dietary guidelines in patients with T2D focus on weight loss by energy intake reduction, dietary consumption with low glycemic loads, and salt and fat intake reduction (5). With regard to dietary potassium intake, diets rich in, among others, fruit and vegetables might contribute to elevated dietary potassium intake in patients with T2D (5). Accumulating data suggest that a plant-based diet and increased potassium intake might be vital additional dietary recommendations in T2D management (39). Although it is not contraindicated as a part of diabetes management, substituting carbohydrates by dietary protein may be another a promising approach (40). Rather than arbitrarily increasing dietary protein intake in patients with T2D, it appears more appropriate to replace animal proteins with vegetable proteins (41).

The current study has several limitations. The sample size of this study is relatively small and the cohort mainly consists of patients of European ancestry. Therefore, on the one hand, we cannot ascertain that the results of our study are generalizable to other populations, while on the other hand, it could well be that the results of our study are generalizable to other populations with a similar range of urinary potassium excretion. Because of the observational nature of our study, cause–effect relations cannot be derived. Our study can move the field forward by providing support for performing and designing an intervention study that can establish cause–effect relations, particularly if studies in other cohorts find similar associations. Although 24-h urinary potassium excretion is a reliable measurement of potassium intake, and is considered the gold standard, single measurement may lead to misclassification. Nevertheless, the strength of this study is that we were able to validate dietary potassium intake with FFQ data, which is suitable to rank individuals according to their intake. In addition, with FFQ data, we were able to estimate relative intake of potassium-rich products in studies of this size.

In conclusion, our main finding is that lower 24-h urinary potassium excretion, reflecting dietary potassium intake, is associated with a higher risk of premature all-cause mortality in patients with high-risk T2D. Intervention studies are needed to determine whether potassium supplementation may reduce adverse outcomes in patients with T2D.

Acknowledgments

The authors' responsibilities were as follows—SMHY, MMO, MP, GDL, MHdB, and SJLB: designed the research; SMHY, MMO, and MP: conducted the research; GDL, MHdB, and SJLB: provided essential materials; SMHY, MMO, and MP: analyzed data or performed statistical analysis; SMHY, MMO, MP, SJLB, MHdB, and GDL: wrote the manuscript; SMHY, MMO, MP, MHdB, and GDL: had primary responsibility for final content; SMHY, MMO, MP, CMG, JIR, EJH, LV, GN, SJLB, MHdB, and GDL: reviewed and edited the manuscript; and all authors: read and approved the final manuscript.

Data Availability

The clinical trial data can be requested by any qualified researcher who engages in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan and execution of a data-sharing agreement by the corresponding author. Data requests can be submitted by e-mail from 12 mo after

publication of this report and data will be made accessible for 12 mo, with possible extensions considered.

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