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Association between urinary potassium excretion and blood pressure: A systematic review and meta-analysis of observational studies

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Abstract 24

Aims and background: The evidence base regarding the association between urinary potassium and blood pressure (BP), or risk of hypertension, is inconsistent. Therefore, we sought to conduct a qualitative and quantitative literature review on the association between potassium excretion and BP. 25
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Methodology: Medline, Scopus, Web of Science, Science Direct, and Google Scholar were searched up to June 2020. All observational studies that reported BP and measured potassium excretion in overnight or 24-hour urine samples were included. Correlation coefficients, mean urinary potassium excretion, and odds ratio (ORs) of hypertension were extracted from the included studies. There were no language or publication date restrictions. 28
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Results: Overall, twelve observational studies, including 16174 subjects, were identified for inclusion in the present meta-analysis, and 21 effect sizes were extracted. Pooled mean potassium excretion was 3.46 mmol/24h higher in normotensive individuals compared with hypertensive subjects (95% CI: 0.61, 6.31). High urinary potassium excretion was not associated with the risk of hypertension (OR: 0.95; 95% CI: 0.79, 1.13). The pooled correlation coefficient between BP and urinary potassium was not significant (ES: 0.01; 95% CI: -0.03, 0.05). However, a subgroup analysis by age indicated a significant positive correlation between urinary potassium and systolic BP in children (ES: 0.12; 95% CI: 0.04, 0.19). 33
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Principal conclusions: 24h urinary potassium excretion was not correlated to BP and risk of hypertension. In contrast, mean urinary potassium excretion was higher in normotensive individuals compared with hypertensive counterparts. Future studies should focus on the association between different sources of dietary potassium and BP. 41
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Keywords: Potassium excretion, urinary potassium, blood pressure 45
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Introduction:

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Hypertension is regarded as one of the leading modifiable causes of morbidity and mortality worldwide, affecting approximately 1.39 billion adults, and the prevalence is predicted to increase by at least 30% by 2025 ^[1]. Nearly 40% of people aged >25 y worldwide are reported to suffer from hypertension ^[2]. Lifestyle determinants, including dietary factors, profoundly impact blood pressure (BP) and the risk of hypertension, ^[3]. Although dietary interventions for the prevention and management of hypertension have predominantly focused on the reduction of sodium intake, many other dietary factors, such as adequate intake of potassium, calcium, and magnesium, should be considered as part of a healthy diet for patients with hypertension ^[4]. Several studies have reported that the effects of non-salt components of a healthy diet, such as adequate potassium, magnesium, and calcium consumption, produced more favorable improvements in BP than reducing salt intake ^[5, 6]. Potassium is an essential mineral in BP regulation, and it can modulate the adverse effects of sodium on BP ^[7]. Several epidemiologic and intervention studies have reported an inverse correlation between potassium intake, BP, and the prevalence of hypertension ^[8-10].

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Accuracy of measuring daily intake of potassium is one of the greatest concerns in epidemiologic studies ^[10, 11]. Although most studies utilize self-reported measurement of dietary intake, such methods are inherently limited by participant ability to recall detailed information on foods, beverages, and portion sizes ^[10]. Serum potassium concentration and 24-hour (24h) urinary potassium excretion are two biomarkers of potassium intake ^[12, 13], and given that serum potassium is strictly controlled by physiological pathways, 24h urine is recommended as the gold standard for measuring potassium intake ^[10, 14].

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Serum potassium level, both below and above the normal range, has been associated with adverse clinical outcomes, including hypertension ^[15]. The association between 24h urinary potassium excretion and blood pressure has been investigated in several epidemiologic studies ^[2, 10, 14], however, results have been inconsistent. Indeed, some studies have shown a negative association

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between potassium excretion and BP [2, 14, 16-18], whilst, in contrast, others have reported a null or a positive relation between urinary potassium and BP [19-22]. To the authors knowledge, there is no comprehensive systematic review and meta-analysis that has explored the relationship between 24h urinary potassium and blood pressure. Thus, the aim of the present study was to conduct a systematic review and meta-analysis based on published observational data regarding the association between urinary potassium excretion and blood pressure or risk of hypertension.

Methods

Search strategy

This study was planned, conducted, and reported according to the Meta-Analysis of Observational Studies in Epidemiology guidelines [23]. Electronic databases, including Medline, Scopus, Web of Science, ScienceDirect, and Google Scholar were searched from inception to June 2030. The following search terms were used: (“potassium excretion” [Title/Abstract] OR “urinary potassium” [Title/Abstract] OR “urine potassium” [Title/Abstract] OR “urinary cations” [Title/Abstract]) OR “potassium intake” [Title/Abstract] OR “potassium status” [Title/Abstract]) AND (“blood pressure” [MeSH] OR “systolic blood pressure” [Title/Abstract] OR “diastolic blood pressure” [Title/Abstract] OR “hypertension” [MeSH] OR “high blood pressure” [Title/Abstract]) OR “Cardiovascular events” [Title/Abstract] OR “chronic disease” [Title/Abstract]). No other restrictions were imposed in the literature search, and the reference lists of all relevant original and review articles were also searched manually.

Study selection

In the first round of screening, the title and abstract of all retrieved articles were independently evaluated by two authors (R.Z and S.F) to identify eligible studies. In the second round of screening, full text of publications identified for further evaluation were reviewed. Any disagreements between authors were discussed and resolved by consensus. All observational studies that reported the association between blood pressure and potassium excretion, in overnight or 24h urine samples, were

included. Duplicate publications, reviews, experimental researches, letters, comments, editorials, 97
case reports, conference reports, and studies that measured urinary potassium excretion in a spot 98
urine samples, respectively, were excluded. 99

Data extraction 100

Characteristics of eligible articles including the first author's last name, publication year, study 101
location, total and gender-specific sample size, mean age, study design, follow-up duration, urine 102
sample collection method, reported statistics, adjusted confounders, and main findings were 103
extracted and tabulated. The correlation coefficient between urinary potassium excretion and systolic 104
(SBP) and diastolic (DBP) blood pressure, mean and standard deviation or standard error of urinary 105
potassium excretion in normotensive and hypertensive individuals, and risks of hypertension in the 106
highest category of urinary potassium excretion were also extracted from eligible articles. 107

Quality assessment 108

The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale. This 109
scale consists of three categories: selection, comparability, and exposure or outcome. Total quality 110
score can range from 0 to 9 for case-control and cohort studies, and from 0 to 10 for cross-sectional 111
studies. In general, studies that were scored ≥ 7 were considered as high quality [24, 25]. 112

Statistical analysis 113

Reported standard errors were converted to standard deviations, and all units for means \pm standard 114
deviations were converted to mmol/day [26]. Log-transformed odds ratios of hypertension across 115
different categories of urinary potassium excretion were used to calculate appropriate effect sizes. 116
The overall risk of hypertension was estimated by pooling the reported and calculated ORs. The 117
analysis was performed separately for means and risk of hypertension. 118

Overall effect sizes were calculated by pooling the effect sizes derived from each study. When the 119
number of effect sizes was less than five, overall effect sizes were estimated using a fixed-effect 120
model [27]. Otherwise, a random-effects model was used to pool effect sizes. Between-study 121

heterogeneity was assessed using the I-squared (I^2) statistic. In the case of significant between-study heterogeneity, subgroup analysis was conducted to investigate the potential sources of heterogeneity. Between-subgroup heterogeneity was evaluated using a fixed-effects model. Sensitivity analysis was carried out to test the robustness of the pooled results, whilst Begg's rank correlation test and Egger's linear regression test, respectively, were used to detect potential publication bias. When publication bias was significant, a trim-and-fill analysis was performed to determine the possible impact of publication bias. All statistical analyses were performed using Stata software (version 11.2, Stata Corporation, College Station, Texas, USA); additionally, analyses were two-tailed, and statistical significance was set at $P < 0.05$, *a priori*.

Results

A flow diagram of the study selection process is shown in **Figure 1**. Finally, 22 articles were included in the present study [10, 14, 17, 19, 20, 22, 28-43].

Characteristics of eligible studies are reported in **Table 1**. Eighteen studies [10, 17, 19, 22, 30-43] used a cross-sectional design, two were case-control studies [28, 29], and two had a cohort design [14, 20]. Cohort studies enrolled healthy subjects, case-control studies used healthy subjects in control groups and hypertensive subjects in case groups, and cross-sectional studies included both healthy and hypertensive participants. All studies enrolled adults, except for two studies which recruited subjects aged <18 years old [33, 38]. Although most studies used 24h urinary collections for potassium excretion measurement [10, 14, 17, 19, 22, 29, 30, 33-35, 37-39, 41-43], 6 studies used an over-night urinary specimen [20, 28, 31, 32, 36, 40]. Study bias assessment showed that most studies were of high quality [8, 10, 14, 17, 20, 22, 30-32, 34, 35, 37-43]. Six studies were conducted using partial adjustment [40, 41, 44-47], fourteen studies with full adjustment [39, 42, 43, 48-58], and in two studies, correlation coefficients were reported without any adjustments [59, 60]. Factors which were adjusted are as follows; age, body mass index, sex, alcohol intake, total energy intake, each of the other dietary electrolytes, smoking status, plasma aldosterone, physical activity, antihypertensive medication use, and waist circumference.

Eight studies reported no significant association between urinary potassium concentrations and BP [22, 36, 38, 40, 41, 43, 45, 59]. Mean 24h urinary potassium was not significantly different between normotensive and hypertensive individuals in 3 studies [28, 29, 42]. Although eight studies reported a significant negative correlation between urinary potassium and BP [10, 14, 17, 30, 31, 34, 35, 37], three studies showed a positive association [39, 48, 60]. Also, the results were inconsistent between men and women in one study [19].

Pooled correlation coefficient:

Sixteen studies were eligible for meta-analysis [10, 14, 17, 19, 20, 22, 28, 32, 33, 36-40, 42, 43, 58] and 22 effect sizes were extracted (n=19261). The correlation coefficient between urinary potassium excretion and SBP or DBP was reported in 10 studies (11 effect sizes) [17, 19, 20, 22, 32, 33, 36, 40, 58]. As shown in **Figure 2**, the pooled correlation coefficient between DBP and urinary potassium excretion was not significant (ES: 0.02; 95% CI: -0.02, 0.05), with no significant heterogeneity ($I^2=33.1\%$; $P=0.134$). Although a comparable result was obtained for SBP (ES: -0.01; 95% CI: -0.06, 0.04), between-study heterogeneity was high in this case ($I^2=73.9\%$; $P<0.001$). Therefore, we ran a subgroup analysis based on gender, region, age, and type of urine sample. Although studies conducted on children (<18 years) showed a significant positive correlation between urinary potassium and SBP (ES: 0.12; 95% CI: 0.04, 0.19), results indicated no significant correlation in adults (ES: -0.03; 95% CI: -0.08, 0.02) (**Figure 3**). Heterogeneity was not significant in the children subgroup ($I^2=0.0\%$; $P=0.84$), however, it was high in the adult subgroup ($I^2=73.9\%$; $P=0.000$). In addition, between-subgroup heterogeneity was high ($P=0.001$). Subgroup analysis based on type of urine sample is shown in **Figure 4**. Accordingly, the overall effect size of studies which used 24h (ES: -0.01; 95% CI: -0.09, 0.07) or overnight urinary samples (ES: 0.01; 95% CI: -0.02, 0.04) reported no correlation between urinary potassium and both SBP and DBP. Although there was no significant heterogeneity in the overnight urine sample subgroup ($I^2=0.0\%$; $P=0.683$), heterogeneity in the 24h urine sample subgroup was

high ($I^2=79.9\%$; $P<0.001$). Further subgroup analysis which did not attenuate heterogeneity is displayed in **Table 2**.

Mean urinary potassium in normotensive vs. hypertensive subjects was reported in 5 studies (n=4030). As shown in **Figure 5**, mean potassium excretion was 3.31 mmol/24h higher in normotensive individuals, compared with hypertensive subjects (95% CI: 1.22, 5.39). We did not observe any significant heterogeneity ($I^2=0.0\%$; $P = 0.944$).

The association between urinary potassium and risk of hypertension was reported in 5 studies (n=11651). There was no association between urinary potassium excretion and risk of hypertension (odds ratio: -0.12; 95% CI: -0.35, 0.10), and between-study heterogeneity was significant ($I^2=64.4\%$; $P=0.024$) (**Figure 6**).

Sensitivity analysis and publication bias

Overall correlation coefficients for both SBP and DBP were not changed after removing each study, individually, and the same results were obtained for risk of hypertension. In contrast, pooled mean urinary potassium was significantly changed after omission of the study by Jackson *et al.* [10].

No publication bias was detected for systolic blood pressure (Begg's: $P=0.721$; Egger's: $P=0.563$), diastolic blood pressure (Begg's: $P=0.581$; Egger's: $P=0.923$), and mean urinary potassium excretion (Begg's: $P=0.142$; Egger's: $P=0.225$). However, there was significant publication bias in studies that reported risk of hypertension (Begg's: $P=0.042$; Egger's: $P=0.06$). Trim-and-fill analysis was conducted and no trimming was performed.

Discussion

The results of this meta-analysis revealed that BP is not significantly correlated with 24h urinary potassium excretion. However, we found a positive correlation between SBP and urinary potassium excretion in children. Mean urinary potassium excretion was significantly higher in normotensive

individuals than hypertensive patients, and the risk of hypertension had no association with potassium excretion. To the authors knowledge, this is the first systematic review and meta-analysis to have assessed the relationship between 24h urinary potassium excretion and BP.

Urinary samples are an important tests utilized to assist in the diagnosis, prognosis, and determination of treatment strategy ^[61]. A 24h urine specimen is regarded as the gold standard for the measurement of dietary potassium intake in a healthy population ¹⁴, in addition to yielding detailed information regarding the circadian variation in the urinary excretion of potassium ^[62].

In the present study, and in contrast to adults, a positive correlation between SBP and potassium excretion was observed in children. Renal ability to excrete potassium is fully developed in early childhood. Therefore, potassium intake is expected to have a comparable relationship with blood pressure in children and adults ^[63]. Indeed, our results must be interpreted with caution due to two reasons. 1) There was a limited number of studies in this field ^[33, 38, 64, 65]; 2) Most included studies reported unadjusted correlation coefficients, and we did not include regression coefficients adjusted for confounders in our analysis. Therefore, it is conceivable that the observed correlation between potassium excretion and SBP in children was confounded by covariates; nevertheless, further studies into the specific relationship in children should be conducted.

Pooled mean urinary potassium was 3.46 mmol/24h higher in normotensive individuals compared with hypertensive subjects. The normal range of urinary potassium concentration is between 25 to 125 mmol/24h (diet dependent) ^[66]., therefore, the observed difference between normotensive subjects and hypertensive patients is less than 4% of variation in normal range of urinary potassium. Although our finding is statistically significant, it seems likely that it has no clinical significance ^[67, 68].

In contrast to our study, which included observational research, meta-analyses of clinical trials have reported that increased potassium intake (dietary + supplement) can yield a beneficial effect on BP

[63, 69-71]. We detected a small difference in potassium excretion between normotensive participants compared with hypertensive counterparts, however, notwithstanding this difference, it was not sufficient to elicit any change in BP. In contrast, however, potassium intake was markedly increased by nutritional intervention. Empirical data suggests that 12 weeks dietary intervention can result in a mean increase in 24h urinary potassium excretion of 45 mmol^[72]. Therefore, a nutritional intervention is capable of eliciting a significant difference in potassium intake, and, consequently, BP.

Although 24h potassium excretion is considered the gold standard for estimating ingested potassium, it has some limitations: 1) It does not and cannot reflect long-term dietary potassium intake^[73], 2) It cannot cover day-to-day variation in potassium intake. Therefore, a single 24h urine sample is prone to random measurement error, which can overestimate or underestimate the actual potassium intake. It has been recommended that using multiple 24h urine samples may provide a more reliable estimate^[14], 3) There are concerns regarding the adequacy of 24h urine sample collection. Indeed, some evidence highlights that under-collection of 24h urine sample is prevalent^[74], 4) Intestinal absorption efficacy of dietary potassium is variable among individuals. For instance, on average, 73.7 to 80.3% of dietary potassium is absorbed^[75], thus, the concentration of potassium in a 24-hour urinary sample may be not equal to ingested potassium. Given the above limitations, it is, therefore, imperative that findings manifest using 24h urinary potassium excretion should be interpreted with caution.

To the best of our knowledge, this was the first systematic review and meta-analysis to have investigated the association between 24h urinary potassium excretion and BP, as well as risk of hypertension, and represents a major strength. Indeed, a further strength of our study was the use of a comprehensive subgroup analysis. Also, according to Egger's test and Begg's test, our findings were not affected by publication bias. Moreover, we tried to analyze all the possible reported data including OR, correlation coefficient and mean difference. despite the aforementioned strengths, there are some limitations that must be considered. A significant heterogeneity was detected in sub-

group analysis, suggesting that some results may not be reliable, and require further investigation. 243

Although we included all reported potential sources of heterogeneity, there are still some factors 244

which should be considered in future studies (e.g., of 24h urinary sodium concentration, the dietary 245

origin of potassium and participants' medication history). The greatest impact of dietary potassium 246

intake on SBP has been reported in individuals with high sodium consumption ^[63], highlighting that 247

it is important to measure both sodium and potassium simultaneously ^[76]. Dietary sources of 248

potassium excreted in urine were not reported in most studies, which could viably have impacted 249

some results. In addition to potassium rich foods, such as fruits and vegetables, there are some 250

potassium-based food additives (e.g., potassium sorbate) found in processed cheese, yogurt, 251

beverage, processed meat, cake, and pastry, which can influence the amount of potassium excreted 252

in the urine ^[77]. The authors advocate that the use of antihypertensive treatments should be carefully 253

considered in future studies. 254

Conclusion 255

In conclusion, the current systematic review and meta-analysis highlighted that 24h urinary 256

potassium excretion was not correlated with SBP, DBP, and risk of hypertension. However, mean 257

urinary potassium excretion was higher in normotensive individuals compared with hypertensive 258

subjects. In order to better understand the relationship between potassium and BP, it is advisable that 259

future studies consider the impact of different sources of dietary potassium. 260

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Table 1. Characteristics of studies included in the systematic review of the relationship between urinary potassium excretion and blood pressure.

First author (publication year)	Country	Sample size (male/female)	Mean age (years)	Study design	Follow-up duration (years)	Method of urine collection	Extracted statistics	Adjustment for potential confounders	Main results	Quality score*
Staessen (1983) (55)	Belgium	688 (355/333)	34.4	Cross-sectional	-	24-hour urine	Correlation coefficient	Partial	No significant association	7/10
Hoosen (1985) (56)	South Africa	583 (320/263)	41.4	Case-control	-	Overnight urine	Mean urinary potassium excretion	Partial	No significant difference	5/9
Bulpitt (1986) (57)	England	618 (459/159)	45.3	Cross-sectional	-	24-hour urine	Correlation coefficient	Partial	Significant negative association in men and significant positive association in women	7/10
Zhu (1987) (58)	China	148 (148/0)	7.5	Cross-sectional	-	24-hour urine	Correlation coefficient	Full	No significant association	8/10
Rose (1988) (59)	International	10079 (5045/5034)	39.5	Cross-sectional	-	24-hour urine	-	Full	Significant negative association	8/10
Liu (1990) (60)	China	3251 (1638/1613)	39.5	Cross-sectional	-	Overnight urine	Correlation coefficient	Full	Significant positive association with SBP in men	7/10
Klag (1995) (61)	China	831 (831/0)	37.6	Cross-sectional	-	Overnight urine	-	Partial	Significant negative association	7/10

Tian (1995) (62)	China	663 (328/335)	43.5	Cross-sectional	-	24-hour urine	-	Full	Significant negative association with SBP	8/10
Nakagawa (1999) (63)	Japan	503 (246/257)	39.5	Cross-sectional	-	24-hour urine	Correlation coefficient	Full	Significant negative association	8/10
Maldonado-Martín (2002) (64)	Spain	553 (274/279)	10.3	Cross-sectional	-	24-hour urine	Correlation coefficient	Unadjusted	Significant positive association with SBP	6/10
Jan (2006) (65)	Kashmir	237 (115/122)	39.4	Case-control	-	24-hour urine	-	Unadjusted	No significant difference	5/9
Chien (2008) (66)	Taiwan	1520 (729/791)	52.0	Cohort	7.9	Overnight urine	Correlation coefficient and risk of hypertension	Full	Significant positive association with DBP	7/9
Yamasue (2008) (67)	Japan	85 (43/42)	63.5	Cross-sectional	-	Overnight urine	Significant negative association with HTN risk	Full	No significant association	5/10
Tayo (2012) (68)	Nigeria, Jamaica, and United States	2704 (1217/1487)	39.9	Cross-sectional	-	24-hour urine	-	Full	Significant negative association	8/10
Kieneker (2014) (69)	Netherlands	5511 (2499/3012)	51.5	Cohort	7.6	24-hour urine	Risk of hypertension	Full	Significant negative association with HTN risk	9/9
Yan (2015) (70)	China	1948 (NR/NR)	41.4	Cross-sectional	-	24-hour urine	Mean urinary potassium excretion and risk of hypertension	Full	Significant negative association with HTN risk	9/10

Jackson (2018) (71)	United States	766 (373/393)	44.5	Cross-sectional	-	24-hour urine	Mean urinary potassium excretion and risk of hypertension	Full	Significant negative association with HTN risk	9/10
Deng (2020)	China	584(278/306)	53.4	Cross-sectional	-	24-hour urine	Mean urinary potassium excretion in hypertensive and non-hypertensive adults	Full	Significantly higher level of urine potassium in hypertensive patients	9/10
Lemogoum (2018)	Cameroon	300 (165/135)	35	Cross-sectional	-	Overnight urine	Correlation coefficient	Partial	Urinary potassium excretion was not related to blood pressure	8/10
Modesti (2018)	Italy	319 (165/154)	49.4	Cross-sectional	-	24-hour urine	Mean urinary potassium excretion and hypertension	Partial	No significant association	7/10
Ge	China	1906 (991/914)	42.9	Cross-sectional	-	24-hour urine	Risk of elevated blood pressure	Full	No significant association	8/10
Moliterno (2018)	Uruguay	149 (60/89)	54.5	Cross-sectional	-	24-hour urine	Mean urinary potassium excretion in hypertensive and normotensive adults	Full	Mean potassium excretion was similar in hypertensive and normotensive individuals	9/10

Abbreviations: DBP, diastolic blood pressure; HTN, hypertension; NR, not reported; SBP, systolic blood pressure.

* Based on the Newcastle-Ottawa Scale.

Table 2: Subgroup analysis to assess the correlation between systolic blood pressure and urinary potassium excretion

Subgroups		Studies (n)	Effect size	I^2	P heterogeneity	P between subgroup heterogeneity
Region	Asian	6	-0.02 (-0.08, 0.04)	68.7%	0.007	0.354
	European	3	0.02 (-0.1, 0.14)	86%	<0.001	
Gender	Male	6	0.02 (-0.11, 0.14)	89.2%	<0.001	0.179
	Female	5	0.04 (-0.02, 0.11)	40.4%	0.152	
	Both	4	-0.06 (-0.15, 0.14)	75.6%	0.006	
Age group	Children	2	0.12 (0.04, 0.19)	0.0%	0.847	0.001
	Adults	8	-0.03 (-0.08, 0.02)	74%	<0.001	
Type of urine sample	Overnight urine sample	3	0.02 (-0.01, 0.05)	0.0%	0.583	0.006
	24-hour urine sample	7	-0.01 (-0.09, 0.07)	79.9%	<0.001	

