Sodium and potassium intake as determinants of cardiovascular and renal health

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CHAPTER 8

General Discussion and Conclusions

Hypertension is a major public health issue as it is currently affecting nearly half of all adults worldwide (1) and it is one of the leading risk factors for disease, primarily cardiovascular disease (CVD) (2-4) but also chronic kidney disease (CKD) (5, 6). The prevalence of these diseases, as well as the mortality associated with these chronic diseases, has increased over the past decades and is expected to increase even further if no measures will be taken (7, 8).

Lifestyle is an important modifiable risk factor for the development of hypertension, CVD, and CKD, with diet as an important component. Intake of dietary minerals, in particular sodium and potassium, might play an important role. It is therefore sometimes suggested that public health interventions focused at (decreasing) sodium intake and (stimulating) potassium intake may be be promising approaches for reducing the burden of morbidity and mortality from chronic diseases, including hypertension, CVD, and CKD. However, the evidence on the potential beneficial effects of these dietary interventions is inconsistent. The discrepancies in literature might partly be explained by methodological issues of studies, including varying – and often inaccurate– methods used for the assessment of dietary sodium and potassium intake (9), the fact that sodium and potassium are not always concomitantly considered in the investigation of the association of either of these cations with outcomes, but also the heterogeneity among populations (10, 11).

The aim of this thesis is to investigate the possible roles of sodium and potassium in the development of hypertension, CVD, and renal dysfunction, represented by CKD in the general population and renal graft failure in renal transplant recipients.

SODIUM INTAKE

Over the past century, sodium intake has been the subject of intense scientific research related to blood pressure and CVD. Data derived from observational studies, randomized controlled trials, and meta-analyses have shown that excess sodium intake plays a major role in the pathogenesis of elevated blood pressure and hypertension (12-16). Because hypertension is a strong risk factor for CVD

and CKD, one might expect that a high sodium intake would also increase the risk of these diseases.

Sodium intake and cardiovascular disease

Of all CVDs, stroke is amongst the most disastrous and disabling (17). The evidence for the association between sodium intake and risk of stroke, however, is not consistent, with overall positive associations (18-21), positive associations only in specific subgroups (22, 23), null associations (24-28), and, recently, a large prospective cohort study by O'Donnel et al., reporting a J-shaped association (29). The inconsistency of these data might partly lie in methodological limitations of the studies, i.e. most of the studies relied on dietary questionnaires or spot urine samples, which are less reliable measures of sodium intake compared to measurement of sodium excretion in 24-hour urine collections, which is considered the gold standard (9, 30, 31). In **Chapter 3**, we investigated the association of sodium intake, estimated from multiple 24-hour urine collections, with risk of developing stroke among subjects of the PREVEND study. During a median follow-up of 12.5 years, we observed a 36% increased risk for stroke for every 51 mmol/day decrease in sodium intake (equivalent to 1.2 gram of sodium/day, which corresponds to 3 gram of salt/day). This finding in line with the aforementioned study of O'Donnell et al. (29), which also showed that a low urinary excretion of sodium (<130 mmol/24h, corresponding to <7.6 gram of salt/day) –estimated from spot urine samples– was associated with an increased stroke risk. Interestingly, O'Donnell *et al.* identified a non-linear association, with estimated urinary sodium excretion >304 mmol/24h (corresponding to >18 gram of salt intake per day) also tended to be associated with an increased risk of stroke. The absence of this latter phenomenon in our study might be explained by the relatively low sodium intake of the participants in our study, since <1% of them had a urinary sodium excretion >300 mmol/24h. Therefore, the possibility remains that the association of sodium intake with risk of stroke is J-shaped. However, with our data we could neither confirm nor deny this.

Other than our study, most of the studies which observed a positive association between sodium intake and risk of stroke, assessed intake of sodium via self-reported questionnaires (18, 20-23). These dietary questionnaires,

however, are less objective methods to assess sodium intake compared to 24-hour urine collections (9, 30). Also important to note is that Olde Engberink et al (31) observed that relative to a single baseline 24-hour sodium measurement, the use of subsequent 24-hour urine samples resulted in different estimations of an individual's sodium intake, while population averages remained similar. As a consequence, the observed association between sodium and long-term cardiovascular outcome differed when it was assessed with multiple sodium intake estimates over a longer period of time compared to when its assessment was based on a single baseline measurement. Hazard ratios for cardiovascular outcome changed up to 85% when multiple 24-hour urine collections during follow-up were used compared to a single baseline collection. These differences in how sodium intake is assessed (i.e., dietary questionnaires, spot urine sample, single 24-hour urine collection, or multiple 24-hour urine collections) might explain, at least in part, existing inconsistencies in literature in this field.

Another issue which should be taken into account is that variation in population characteristics can also introduce bias. For example, much of the heterogeneity observed in a meta-analysis investigating the association between sodium intake and stroke appears to be explained by region, with all studies originating from Asia reporting an association between increased intake and risk of stroke, whereas no significant association was found in studies from Europe or North America (11). This was confirmed in a recent published study of Mente et al (10), who observed that increased sodium intake was associated with an increased risk of stroke, but only significantly among communities with the highest sodium intake (>5 g sodium/day, equivalent to 12.5 g salt/day), which were largely confined to China. Furthermore, as dietary patterns differ per region, some diets may be high in sodium content but at the same time be high in so-called cardioprotective factors (e.g. salted fish and vegetables), while other diets may be high in sodium content and low in cardioprotective factors (e.g. fast foods, some processed foods), which might also contribute to between-study differences in findings.

Because robust data from clinical trials are lacking, the results from the various prospective cohort studies that have investigated the association of sodium intake with long-term outcome should be interpreted with caution. Further investigation into the relation of sodium intake with risk of stroke is needed to unravel their

true relation, and in such studies the aforementioned considerations on biasing factors should be taken into account.

Sodium intake and renal outcome in the general population

As discussed earlier, high sodium intake is related to higher blood pressure levels (16). However, whether this relation further translates into subsequent increased risk of renal function decline in the general population is uncertain, as the majority of the previous studies examining the association between sodium intake and risk of CKD included high-risk populations, i.e., subjects with established CKD, vascular disease, or diabetes mellitus (32-34). In previous cross-sectional analyses of the Prevention of Renal and Vascular End-stage Disease (PREVEND) study (35), a Dutch population-based cohort, high sodium intake was found to be associated with increased albuminuria, especially among subjects with a higher BMI. In **Chapter 5** of this thesis, we investigated the prospective association of urinary sodium excretion, assessed in multiple 24-hour urine collections as accurate estimate of intake, with risk of developing CKD in a population-based cohort with a relatively preserved kidney function at baseline. While urinary sodium excretion was associated with albuminuria in cross-sectional analyses (36), we did not observe an association of urinary sodium excretion with risk of developing CKD, based on *de novo* eGFR <60 ml/min/1.73 m^2 or microalbuminuria in these subjects. These findings are in line with data from longitudinal cohort studies examining the association of sodium intake -based on a spot urine or food frequency questionnaire- with risk of renal outcomes among subjects with a relatively preserved kidney function (32-34).

POTASSIUM INTAKE

Potassium is often the 'forgotten electrolyte', overshadowed by sodium in most studies. For example, the causal relationship between high sodium intake and high blood pressure has repeatedly been examined and demonstrated in observational studies, randomized controlled trials, and meta-analyses. In contrast, the role of potassium intake in the development of increased blood pressure is less

frequently studied and results are less clear. Furthermore, whether such a potential association could also further translate into subsequent risk of CVD and renal dysfunction is also not clear.

Potassium intake and hypertension

In **Chapter 2**, we investigated the prospective association of potassium intake, estimated from 24-hour urinary potassium excretion, with risk of developing hypertension in the PREVEND study. We demonstrated that the association of urinary potassium excretion with risk of incident hypertension was nonlinear, in such a way that subjects in the lowest sex-specific tertile of potassium excretion of potassium (men: <68 mmol/24h; women: <58 mmol/24h) had a 20% higher risk of developing hypertension compared to subjects in the upper two tertiles. This association appeared to be independent of conventional risk factors and urinary excretion of various other cations, including sodium. The proportion of hypertension attributable to low potassium excretion was estimated to be 6.2%, suggesting that almost 1 of every 16 incident cases of hypertension might have been prevented if all subjects were in the low-risk group with adequate potassium excretion (>65 mmol/24h). These findings suggest that potassium might be an important factor in the prevention of hypertension.

The World Health Organization (WHO) set the minimal potassium intake for adults at ≥3,500 mg/day (90 mmol/day). Data from around the world show that the average potassium consumption in many countries is well below this recommendation (37-40). This was also confirmed by the data from the PREVEND study presented in **Chapter 2**. We found that 48% of the subjects included in the study would have been classified as having a potassium intake below this recommendation. Importantly, our data indicate that potassium is associated with an increased risk of hypertension when potassium excretion is <65 mmol/24h, which corresponds to a dietary intake of <84 mmol/day when taking an average fractional intestinal absorption of 77% into account (30, 40). Our data therefore support the recommendation of the WHO that individuals who consume less potassium than the recommended value, should increase their potassium intake.

With our data, we could not identify a possible mechanism by which potassium intake lowers blood pressure. The observed association was not affected after

adjustment for plasma aldosterone, suggesting that the mechanism presumably does not involve this hormone. Other mechanisms that have been proposed in literature –but which we could not investigate with our data– include the enhancement of natriuresis (41), vasodilatation by stimulation of the Na^+-K^+-ATPase in vascular smooth muscle cells and adrenergic nerve terminals (42), and inhibition of development of medial hypertrophy of the arterial wall (43-45). Further research on the mechanisms explaining the blood pressure lowering effect of potassium intake will be needed to better understand this relationship.

Potassium intake and cardiovascular disease

Since low potassium intake was shown to be associated with increased risk of hypertension in the PREVEND study as shown in **Chapter 2**, as well as in other studies (46), we hypothesized that increased potassium intake would reduce subsequent risk of CVD. The prospective association of urinary potassium excretion, measured in multiple 24-hour urine collections as accurate estimate of potassium intake, with risk of developing CVD in a population-based cohort was studied in **Chapter 4**. In this chapter, we observed an inverse association between urinary potassium excretion and risk of CVD, and more specifically with risk of ischemic heart disease, independent of age and sex. However, significance was lost after further adjustment for important lifestyle and dietary factors, including urinary sodium excretion. No significant associations were found between urinary potassium excretion and risk of stroke and heart failure.

Only a few observational cohort studies have previously examined the association of potassium intake with risk of CVD, ischemic heart disease, and stroke, and provided inconsistent results (10, 37, 46-48). This might again be a consequence of methodological limitations of studies, i.e., the majority of the studies relied on dietary questionnaires or spot or single 24-hour urine samples, which are less reliable methods for the assessment of potassium intake compared to measurement of potassium in multiple 24-hour urine collections (9, 30, 49). When comparing our results to literature, so far only one observational study (50) has used multiple 24-hour urine collections, which is considered the gold standard (30, 51, 52) to assess potassium intake with risk of CVD. Similar to our findings, this study found a nonsignificant inverse trend between urinary potassium

excretion and risk of CVD among 2,974 pre-hypertensive subjects of the Trials of Hypertension Prevention study after adjusting for important cardiovascular risk factors (50). Moreover, our results of nonsignificant inverse associations between potassium and risk of CVD and ischemic heart disease are also consistent with the results from two meta-analyses (37, 46).

It can be hypothesized that the differences in the association between potassium intake and CVD may be partly due to differences in level of potassium intake between studies. For instance, the median urinary potassium excretion in our study was 70 mmol/24h, which corresponds to an intake of ~90 mmol/d when accounting for a gastrointestinal potassium absorption of 77% (30, 40). This is higher than the intake in eight out of nine studies based on dietary recall methods (37) wherein average potassium intake mostly varied between 45 and 85 mmol per day (24).

Despite its acknowledged effect on blood pressure, it remains therefore to be established whether potassium intake may reduce the risk of cardiovascular events.

Potassium intake and renal outcome: the general population

When examining the association of potassium intake with risk of developing CKD in **Chapter 5** of this thesis, we observed that every 21 mmol/24h decrease in urinary potassium excretion was independently associated with a 16% higher risk of developing CKD (multivariable adjusted HR, 1.16; 95% CI, 1.06-1.28). Although blood pressure was not mediating the association between low potassium excretion and risk of CKD, the observed association was more pronounced in hypertensive subjects (HR, 1.25; 95% CI, 1.09-1.43). Additional adjustment for plasma potassium did not materially change the association. Mechanisms other than by influencing plasma potassium should therefore explain the beneficial effects of potassium intake on development of CKD, for instance induction of tubulointerstitial injury by ammoniagenesis, which has been observed in animal experimental models caused by potassium deficiency (53, 54), or the renoprotective of potassium itself by upregulating renal kinins, such as kallikrein (55). In our study we could not investigate these possible mechanisms because these data were not available.

Our findings confirm and extend previous data of the few prospective cohort studies on potassium intake, since these studies were based on a single (estimated) 24-hour urine or an food frequency questionnaire (32-34), or included high risk populations, i.e. subjects with either established CKD, vascular diseases and/or diabetes mellitus (32-34, 56), instead of a more population-based cohort. Taken together, these studies indicate that a higher consumption of potassium may be a promising approach for the primary prevention of CKD in subjects with normal kidney function. Despite its effect on blood pressure, our data do not provide evidence that lowering sodium intake may decrease the risk of developing CKD.

Potassium intake and renal outcome: renal transplant recipients

Renal impairment may prelude to the development of end-stage renal disease, the stage where renal replacement therapy is needed, of which transplantation is the preferred option compared to dialysis. Prior to transplantation, patients with advanced renal failure and patients on dialysis are generally advised to limit their potassium intake because of the risk of hyperkalemia and associated risk of cardiac arrhythmias and sudden death (57). After transplantation, however, there is usually no incentive to increase potassium intake again and it is therefore likely that renal transplant recipients maintain their habitual potassium restriction, despite that low potassium intake is associated with poor outcomes in population-based studies, including increased risk of hypertension and CKD as discussed in **Chapter 2** and **Chapter 5** of this thesis. In **Chapter 6**, we therefore assessed the dietary intake of potassium, using a single 24-hour urine collection, in a large cohort of stable renal transplant recipients and compared this intake to healthy controls. Our results showed that renal transplant recipients have a significantly lower potassium intake compared to healthy kidney donors (urinary excretions of 73 mmol/24h versus 85 mmol/24h, respectively). The difference in potassium intake was found to be independent of age, sex, and renal function. This might suggest that renal transplant recipients still adhere to the potassium restriction imposed during renal insufficiency or dialysis.

We furthermore investigated the association between potassium intake and long-term outcomes in renal transplant recipients in **Chapter 6.** In this chapter, we showed that low urinary potassium excretion, as measure of intake, was

strongly and independently associated with an increased risk of graft failure and all-cause mortality among renal transplant recipients. This was in such a way that renal transplant recipients in the lowest sex-specific tertile of urinary potassium excretion (women <55 mmol/24h; men <65 mmol/24h) had a 3.7 times higher risk of developing graft failure, and a 2.7 times higher risk of mortality than did renal transplant recipients with a higher urinary potassium excretion.

When looking into potential mechanisms by which low potassium intake could increase risk of poor long-term outcomes in renal transplant recipients, we found that plasma potassium was significantly mediating the association of urinary potassium excretion with all-cause mortality. However, the magnitude of mediation was small, because plasma potassium explained only 4.7% of this association. Of note, we did not find evidence for mediation by urinary ammonia excretion or systolic blood pressure of the associations of urinary potassium excretion with risk of graft failure and all-cause mortality. Our findings should therefore stimulate further research on mechanisms underlying the association of low urinary potassium excretion with higher risk of graft failure and mortality.

Although we cannot draw definitive conclusions regarding the association of potassium intake on long-term renal outcome in the general population as well as renal transplant recipients, given the observational design of the studies described in **Chapter 5** and **Chapter 6**, our findings –in combination with the available literature– strongly suggest that, a sufficient potassium intake is warranted to prevent renal dysfunction.

Plasma potassium and renal function decline: the general population

Although the kidney has a remarkable ability to maintain homeostasis with advancing CKD, disturbances in potassium homeostasis (hypo- and hyperkalemia) are more common in CKD patients compared to the general population (58, 59). Whereas both hypo- and hyperkalemia are associated with disease progression in CKD patients (60-63), the association with risk of developing *de novo* CKD is not well established. In **Chapter 7**, we found hypokalemia (plasma potassium <3.5 mmol/L) to be associated with an increased risk of developing CKD among 5,130 subjects free of CKD at baseline of the PREVEND study, independent of potassium intake, with hypokalemic subjects having a 3.65 times higher risk to develop CKD

compared to subjects with plasma potassium concentrations between 4.0-4.4 mmol/L.

A similar conclusion was reached by Fukui et al. (64), who observed that potassium concentrations <4.0 mmol/L were associated with an increased risk of developing CKD in a cohort of 1,001 healthy Japanese participants not taking any medications, including diuretics. When we explored the role of diuretics in this association –as potassium levels are heavily influenced by those medications–, we found that hypokalemia was associated with an increased risk of CKD, irrespective of diuretic use. This was in contrast to the findings of Chen et al. (65), who showed that hypokalemic subjects not using potassium-wasting diuretics had an increased risk of CKD, whereas a decreased CKD risk was observed in hypokalemic subjects using potassium-wasting diuretics. In **Chapter 7** we similarly found that, in the absence of hypokalemia, higher levels of plasma potassium were associated with an increased risk of CKD in subjects using diuretics, but not in subjects not using diuretics. Of note, these associations might reflect confounding by indication (i.e., diuretic use is known as risk factor for hypokalemia due to increased renal potassium loss (59-61, 66)) or might imply an adverse effect of diuretics. However, if abnormal potassium concentration itself causes adverse outcomes, then clinical treatment may be beneficial. Unfortunately, due to the observational design of our study, no firm conclusions about causal relationship between hypo- and hyperkalemia and risk of developing CKD can be drawn. The potential interaction between plasma potassium concentrations and diuretic use with respect to renal function decline deserves therefore further prospective investigation, preferably in a randomized setting.

INTERACTION BETWEEN SODIUM AND POTASSIUM INTAKE

An interaction between sodium and potassium intake on health outcomes has been observed in several studies; e.g., raising potassium intake blunts the effects of high sodium intake on blood pressure levels (67), and the effect of increased potassium intake on blood pressure levels is more pronounced at higher levels of sodium intake and in salt sensitive individuals (46, 68-70). It has been suggested

that these observations are the consequence of a blood pressure lowering effect of potassium-induced natriuresis, with potassium acting as a diuretic agent (41).

Only few epidemiologic studies have examined the joint association of sodium and potassium intake with subsequent risk of outcomes. Although some studies suggested that the sodium to potassium ratio is a stronger predictor of outcomes than sodium or potassium intake alone (50, 71), we and others (25, 72) did not observe independent associations of the sodium to potassium ratio with risk of hypertension, CVD, or CKD. Mente and colleagues (10) found significant positive associations of the sodium-to-potassium ratio with risk of CVD, including stroke. However, they found significant heterogeneity by region for associations with stroke, with only communities in China, with a high intake of sodium (>5 g sodium/day, equivalent to 12.5 g salt/day), having a significant increased risk of stroke.

CONCLUSIONS

The global burden of hypertension, cardiovascular and renal disease is increasing and is expected to increase even further if no measures will be taken. It is therefore important to explore modifiable risk factors underlying these chronic diseases, including the role of diet. Public health interventions aimed at decreasing sodium intake and increasing potassium intake are suggested to be potential cost-effective measures for reducing the burden of morbidity and mortality from non-communicable diseases. However, the evidence on the potential beneficial effects of a decreased intake sodium and an increased intake of potassium is not consistent, which might be caused by methodological issues of these studies. Therefore, we investigated in this thesis the possible roles of urinary sodium and potassium intake, assessed from 24-hour urine collections as accurate estimate of intake, in cardiovascular and renal health in various populations.

Sodium intake: an overall assessment

The results of this thesis suggest that a low sodium intake is associated with an increased risk of stroke in the general population. This result, together with the considerable body of evidence which supports the link between high sodium

intake and increased risk of CVD (including stroke), makes it plausible that there might be a J-shaped association, which can be an important explanation for differences in findings between studies. We could not detect this phenomenon in our study, which might be due to the fact that subjects included in our study had a relatively low sodium consumption compared to other studies. Furthermore, in this thesis we could not identify an association between sodium intake and risk of developing CKD, which seems to correspond with the available literature in subjects with a relatively preserved kidney function. This finding, however, does not deny a possible role of sodium intake in renal disease progression in subjects with established CKD. These discrepant findings may be due to power issues, i.e. negative effects of risk factors can be found more easily in high-risk subjects. It could also be that in subjects with established CKD, sodium intake leads to other pathophysiological mechanisms.

The average daily salt consumption in the Netherlands is estimated at 8.7 grams per day (3.5 grams of sodium per day) (39), whereas the current guidelines on sodium intake recommend a maximum sodium intake of 5-6 grams per day (2.0-2.4 grams of sodium) (73-75). These recommendations, however, are largely based on evidence coming from short-term clinical trials showing that reducing sodium intake from a moderate to a low level leads to reduction in blood pressure. Implicitly, these guidelines assume that there is no unsafe lower limit of sodium intake. However, these trials could not assess the potential consequences of lower sodium on long-term cardiovascular morbidity and mortality. The benefits of low sodium intake with respect to CVD are extrapolated from models assuming a linear relationship between sodium intake and blood pressure and between blood pressure and CVD (76, 77). It is, however, uncertain whether blood pressure is an appropriate surrogate outcome on which to base the recommendation for sodium intake on.

Based on the available literature, including the results of this thesis, we conclude that the optimal range of sodium intake for cardiovascular health is still controversial. A targeted approach of intervening in countries and communities with a high sodium intake (e.g., >5 g sodium/day, equivalent to 12.5 g salt/day) to reduce the high intake of sodium to moderate levels, might improve reduction of CVD, including stroke. If there is indeed an inverse association between sodium

intake and risk of cardiovascular morbidity and mortality, such a strategy would minimize the potential for harm by sodium reductions in populations with average sodium intake. Future long-term intervention studies are needed to investigate the optimal range of sodium intake regarding cardiovascular and renal health in the general population as well as in specific high risk populations, such as subjects with established CKD.

Potassium intake: an overall assessment

Our results suggest an important role of sufficient potassium intake in the prevention of diseases, as we found low potassium intake to be associated with an increased risk of developing hypertension and CKD in a population-based cohort, and also with poor long-term outcome in renal transplant recipients, including renal graft failure and all-cause mortality. Moreover, hypokalemia was also found to be associated with an increased risk of CKD in subjects with a preserved renal function at baseline, independent of potassium intake. Interestingly, contrary to our hypotheses, none of the associations of low potassium intake with increased risk of renal dysfunction were mediated by blood pressure, indicating that mechanisms other than blood pressure are responsible for –at least the largest part of– the observed associations.

Although potassium intake itself may be an important factor, diets high in potassium often reflect also a high intake of fruits, vegetables, legumes, whole grains, and dairy products (78), which are also high in other nutrients that may have beneficial effects (79). That raises the question whether potassium intake measured in an observational study is just a marker of healthy dietary patterns, rather than the actual mediator of the benefit observed. It is therefore of importance that our results are confirmed by future intervention studies that specifically interfere on one factor.

Strategies for optimizing diets

Results of this thesis, in combination with the available literature, suggest that an increase in potassium intake in persons not meeting the recommendation is desirable, whereas sodium reduction to more healthful levels seems advocated among specific populations, e.g., hypertensives and subjects with a high salt

intake, especially due to its impact on blood pressure. Some strategies to increase potassium intake and lower sodium intake include 1) stimulating consumers to select unprocessed, fresh foods containing potassium (e.g., fruit, vegetables, dairy products) and to avoid processed foods high in sodium, 2) use of less table salt in cooking and at the table, 3) lowering the sodium content by reformulation of industrially produced foods, and 4) taxation of highly processed foods containing high amounts of sodium and/or subsidies on fruit and vegetables.

Because in Western societies, salt added during the processing of foods accounts for the vast majority of salt intake (80%), and consumers may not be able to easily change their dietary behavior by themselves, reformulation of foods may be the most cost-effective approach to lower sodium intake. In the Netherlands, the food industry already has taken several initiatives to improve food composition. In 2014, the Dutch Ministry of Health, Welfare and Sport initiated the 'Agreement for the Improvement of Food Composition 2014-2020' to reduce the levels of sodium, added sugar, saturated fatty acids and the energy density of food products, which aims to improve product composition, including reductions in salt, unsaturated fat, and caloric content. A scenario analysis indicated that if the manufacturers comply with reduction of salt content of the foods according to this agreement, the average daily intake of salt is estimated to be reduced by 0.4 g/day (the average will drop from 8.7 g salt/day to 8.3 g salt/day) (80).

A lack of knowledge and awareness on diet composition and its role in health might hamper the consumer making healthier food choices. Nutrition education might positively influence consumer awareness, attitudes, skills, and behavior around food, diet, and nutrition. Moreover, awareness can also be created by clear labeling of foods, on which the consumer can rely in choosing food with less salt. Despite the improvement in quality of food labels introduced in the Netherlands in 2016 (which requires to state the salt content rather than the sodium content of food), reading and comparing labels is still difficult, because of differences in format between labels. Furthermore, costs are an issue as well in making healthier food choices. In the span of a decade, healthier food products, including fresh fruits and milk products–both important sources of potassium intake in the Netherlands (39)– have become more expensive than unhealthier

processed foods (22% versus 13%, respectively) (81). Taxation of highly processed foods containing high amounts of sodium and/or subsidies on fruit and vegetables might act as effective strategies for decreasing sodium intake and increasing potassium intake. Since in the Netherlands men and women with a low socio-economic status consume less fruit and vegetables compared to men and women with a high socio-economic status (39), taxation might especially be an effective measure to influence their food choices.

OVERALL CONCLUSIONS

In this thesis, we examined the role of sodium and potassium intake in the context of cardiovascular and renal health. The results of this thesis suggest that low sodium intake might be harmful, as we found it to be associated with an increased risk of stroke in the general population. Moreover, we found that a sufficient intake of potassium may play an important role in the prevention of developing hypertension and renal dysfunction in the general population as well as in renal transplant recipients.

Since all of our results are based on observational data, we cannot draw definitive conclusions. Because it is crucial that we better understand the roles and interplay of sodium and potassium intake in health and disease, it is important to further investigate these associations in future preferably long-term randomized controlled trials with accurate assessment of sodium and potassium intake. If our findings are confirmed by such studies, this will render pivotal knowledge for the recommendations for sodium and potassium intake. Importantly, because of multiple underlying pathophysiological mechanisms for renal and cardiovascular disease, it is likely that an integrated approach that tries to influence multiple aspects of diet and lifestyle is more effective than a strategy focused solely on sodium and potassium intake.

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