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Estimation of the salt intake distribution of Dutch kidney transplant recipients using 24-h urinary sodium excretion: the potential of external within-person variance

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ABSTRACT

Background: There is growing interest in assessing a population's prevalence of inadequate nutrient intake using biomarkers. However, within-person variation is generally ignored because repeated data collections are considered costly and burdensome.

Objectives: The study aimed to show the importance of estimating, from repeated 24-h urine collections, a population's habitual salt intake and to explore the potential of using the ratio of within-person variance to total variance from an external source (W:T variance) with single 24-h urine collection.

Methods: Salt intake was predicted from data for 24-h urinary sodium excretion in adult kidney transplant recipients in 1992–1997 ($n = 432$) and 2006–2011 ($n = 1159$). The salt intake distribution of single-day measurements was compared with estimates from multiple 24-h urine collections, which were statistically corrected for within-person variance. Habitual salt intake was also estimated using single-day measurements and external variance estimates. From each distribution, the proportion below specified cut-off values was estimated.

Results: In 2006–2011 the average habitual salt intake was 10.6 g/d (men) and 8.5 g/d (women); in 1992–1997 these values were 8.6 g/d and 7.5 g/d, respectively. The proportion with salt intake <6 g/d was 5% and 13% in 2006–2011 and 22% and 28% in 1992–1997, respectively, for men and women. Correction for within-person variance significantly narrowed the salt intake distribution—the proportion with salt intake <6 g/d was overestimated by 3–13 percentage points using single-day data. Sensitivity analyses showed the importance of a sufficient sample size for estimating variance components. Variation of the W:T variance showed up to 40 percentage points deviation in the proportion with intakes below a specified cut-off value.

Conclusions: To estimate a population's salt intake distribution, it is important to correct 24-h urinary sodium excretion for within-person variance. Predicting habitual salt intake distribution using single-day measurements with external variances is promising; a sensitivity analysis is recommended to show the effect of different external variances. *Am J Clin Nutr* 2019;00:1–11.

Keywords: salt intake, within-person variance, kidney transplant recipient, 24-h urine, sodium, external variance, habitual intake

Introduction

For public health policy, it is important to estimate the population's prevalence of nutrient inadequacy, because this guides action to maintain or create dietary patterns aimed to provide adequate amounts of nutrients, and as such improve the health of the population. Besides using a valid statistical method to compare the nutrient intake with dietary reference values (1, 2), it is also important to accurately estimate the population's nutrient intake distribution. In this context, it is generally the habitual intake (i.e., the long-run average intake), that is of interest rather than the daily nutrient intake, because dietary reference values are often based on chronic rather than acute health effects. In food consumption surveys detailed data are collected over a limited number of days per participant. To account for within-person variation (also referred to as intraindividual, or day-to-day variation) (3), a statistical correction is applied (4–7). This results in a narrower habitual intake distribution and affects the proportion of inadequate intakes (8).

There is growing interest in using biomarkers to assess the prevalence of inadequate nutrient intake or status, because these are considered more objective than self-reported dietary intake (9, 10). However, the concentration of biomarkers can also vary from day to day within individuals (1, 11).

It is difficult to estimate salt intake using food consumption surveys, whereas the collection of 24-h urinary excretion of sodium is regarded as the gold standard (12, 13). However,
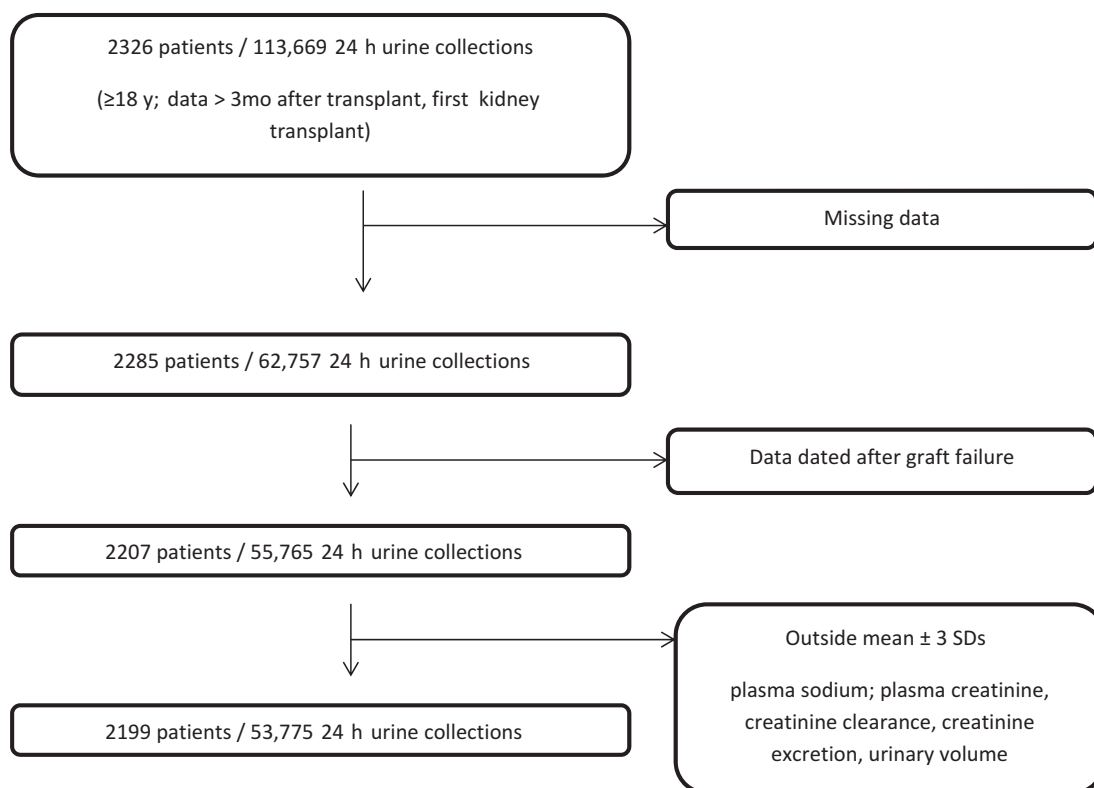
FIGURE 1 Schematic overview of the number of subjects and total number of 24-h urine collections included in our study using data from kidney transplant recipients in northern Netherlands (1990–2015).

24-h urinary sodium excretion shows within-person variation (14–16). Therefore, although single 24-h urine collections can provide a valid estimate of the average population's sodium intake (17), the sodium intake distribution is too wide because it contains between-subject variation as well as within-person variation. As a result, the calculated proportion of excessive intakes (e.g., above a cut-off value) is biased. Averaging repeated measurements per subject will reduce the within-person variation; however, for sodium it is expected that ∼10 replicates of 24-h urine collections are required to estimate the individual's habitual sodium intake precisely (18, 19). To limit the study participant's burden of multiple 24-h urine collections, statistical correction for within-person variation is used together with a few repeated 24-h urine collections per subject. Nevertheless, in many studies results are not adjusted for within-person variation (12, 20–22).

Jahns et al. (23) explored the use of external estimates of within-person variance to estimate the nutrient intake distribution based on single-day data collection. For biomarkers, we are not aware of similar studies. Our study aimed to confirm the importance of adjusting 24-h urinary sodium excretion, as a proxy for salt intake, for within-person variance. A second aim was to explore the application of external within-person variation in studies with single 24-h urine collection. We addressed the aforementioned methodological aims in a large outpatient cohort of kidney transplant recipients (KTRs), who are especially susceptible to adverse effects of high salt intake (24, 25), and from whom 24-h urine was collected at every regular outpatient clinic visit.

Methods

Study population

Data from a large, single-center (University Medical Center Groningen, Netherlands) KTR cohort were used (Transplant-Lines). No specific dietary counseling was included in the routine outpatient visits, except for discouraging excess sodium intake and encouraging weight loss in overweight individuals. For our study, data from patients (aged ≥18 y) with a first kidney transplant between 1 January 1990 and 31 December 2015 (excluding simultaneous transplants) were used. To prevent effects of instability shortly after transplantation, results from urinary collections within the first 3 mo after transplantation were excluded. For subjects with multiple kidney transplants, data until the first graft failure were included. After exclusions due to missing data and potential outliers, data were available from 2199 patients resulting in 53,775 data points (**Figure 1**).

The TransplantLines study protocol was approved by the University Medical Center Groningen Institutional Research Board (METc 2014/077: TransplantLines) and adhered to the Declaration of Helsinki. This research, with data collected historically, did not require informed patient consent.

Data collection

Prior to outpatient clinic visits, patients were requested to collect a 24-h urine sample. Patients were instructed to discard their morning urine specimen and to collect all subsequent

urine through the next 24 h, including the next morning's first specimen. In addition, during the visit to the outpatient clinic blood was drawn after an 8–12-h overnight fasting period, in the morning after completion of the 24-h urine collection. Height and body weight were measured prior to the first kidney transplant, from which BMI was calculated (kg/m^2). To assess renal functioning, the 24-h urinary excretion of urea, sodium, and creatinine was routinely measured. Further, plasma sodium and creatinine concentrations were measured in the blood sample.

Serum creatinine concentrations were determined with a modified version of the Jaffé method (MEGA AU 510; Merck Diagnostica). Plasma and urinary concentration of sodium were routinely determined. Prior to March 2006, these were performed on the Merck Mega Analyzer (Merck). Subsequently, these biochemical analyses were performed on the Roche Modular (Roche Ltd). To correct for differences in results due to the change of methodology in 2006, some biochemical data before 2006 were converted using the following conversion equations: sodium excretion/0.918, (plasma creatinine − 8)/1.07 ([26]). Creatinine clearance (mL/min) was calculated as:

$$\text{urinary creatinine (mmol/L)} \div (\text{serum creatinine } (\mu\text{mol/L})$$
$$\times (24\text{-h urine volume (mL)} \div 1440)) \qquad (1)$$

All laboratory analyses were part of the routine patient care and adhered to the guidelines and accreditation of the coordinating committee to improve quality control of laboratory research in health care.

For individuals with multiple data for specific variables on the same date, the average value for each variable on that day was included in the analyses.

Salt intake

Salt intake (g/d) was calculated from 24-h sodium excretion using the following formula:

$$\text{sodium in urine (mmol/24 h)} \times 23/1000 \times 100/95 \times 2.5 \quad (2)$$

where 23/1000 refers to the conversion of sodium in millimoles to grams, 100/95 refers to the assumption that 95% of the consumed sodium is excreted via urine ([20]), and 2.5 refers to the conversion of sodium to salt intake.

Statistical analyses

Van den Berg et al. ([24]) showed that the value of several biomarkers (e.g., urinary creatinine excretion, serum creatinine) is different for healthy individuals compared with KTRs. Therefore, outlying data points that might indicate renal dysfunction or inaccurate 24-h urine collection were not based on normal biochemical values for healthy subjects. However, for the biomarkers plasma sodium, plasma creatinine, creatinine clearance, creatinine excretion, and urinary volume, values outside the range of mean ± 3 SDs were excluded. The mean and SD were calculated for each of these biomarkers for the total KTR population (1990–2015), after excluding missing data and data dated after graft failure (Figure 1). Data lines with a value outside the mean ± 3 SD (**Supplemental Table 1**) range for at least

1 biomarker were excluded for data analyses. For biomarkers with a difference in mean and SD between men and women, mean and SD were estimated separately (i.e., plasma creatinine, creatinine excretion).

The years refer to the year of observation of sodium excretion. Subjects can have multiple 24-h urine collections within a specified year, and have 24-h urine collections in multiple years, depending on the frequency of outpatient clinic visits. The population's average salt intake (estimated from 24-h urinary sodium excretion) varied in the period 1990–2015 between 7.5 and 10.8 g/d for men, and between 7.0 and 8.7 g/d for women (**Supplemental Table 2**). To limit the effect of a potential time trend in salt intake on the estimated within-person variation, smaller periods were selected to estimate the habitual salt intake. Therefore, the variation in average salt intake in these periods was intended to be smaller than the variation over the whole period 1990–2015 and more or less constant (i.e., maximum to minimum ≤0.5 g salt). In addition, these periods should be large enough to contain multiple 24-h urine collections of many subjects. Although many periods could have been selected, 2 periods of 6 y were selected arbitrarily: 1992–1997 and 2006–2011. Because some of the subjects ($n = 160$) were present in both periods, the data in both periods were not completely independent. This meant that ∼10% of the subjects in the period 2006–2011 were also present in the period 1992–1997. In addition, because the periods were ≥9 y apart, we considered the consumption data for each period to be independent.

To perform a statistical correction for within-person variation at least 2 repeated measurements per subject were required. To show the variation in single-day measurements, as well as the effect of inclusion of more than 2 repeated measurements on the salt intake distribution (see below) within each period, subjects having at least 4 data points were selected and the first 4 data points were included in the analyses.

For each period, the population's salt intake distribution was estimated in 2 different ways:

A. Based on single 24-h urine collections, using the data point with the same ranking in time for all subjects, resulting in 4 possible distributions.
B. Based on statistical correction for within-person variation using two, three, or four 24-h urine collections per subject.

For all ways of analyzing the data, the proportion with an intake below specified values [i.e., 3, 6, 9, and 12 g salt/d; 6 g/d is the maximum daily salt intake proposed by the Dutch Health Council ([27])] was estimated using a cut-off point approach. For the single 24-h urine collections (A), no additional calculations were required. The statistical correction for within-person variation (B) was performed with the US National Cancer Institute (NCI; currently the National Institutes of Health) method (mixtran macro version 2.2 and distrib macro version 2.1) ([6]). As salt (sodium) is consumed and excreted in urine daily by all subjects, the habitual salt intake distribution was calculated with the NCI amount-only model. Because the frequency of consumption is daily for each subject, there was no need to model this. The salt intakes on single days (calculated as described in the above formula) were transformed to an approximately normal distribution. Next, the within- and between-person variances

were estimated for the transformed intake and used to shrink the distribution on the transformed scale. Thereafter, the data were back-transformed to the original scale to obtain the habitual intake distribution, in which the within-person variance was eliminated.

With single-day data it is possible to correct a distribution for within-person variance with the NCI method using the ratio of within-person variance to total variance from another data source (W:T variance). At first the λ for the single-day data was determined with a Box–Cox transformation (with SAS proc transreg procedure). Thereafter the salt intake was calculated on the transformed scale [salt intake$^{(\lambda - 1)/\lambda}$] and with a regression analysis the intercept and total variance were estimated. In addition, using single-day data on the original scale, the minimum salt intake of the population was calculated. The external W:T variance was applied to the estimated total variance of the single-day data, to predict the within- and between-person variance. These variables were used in the NCI distrib macro to predict the habitual intake using external variance. These analyses were performed for several scenarios using single-day data of men in the period 2006–2011. To quantify the uncertainty, a bootstrap ($n = 200$) was performed for all these analyses and expressed as 95% CIs.

To study the effect of variation in the W:T variance on the predicted habitual intake distribution, sensitivity analyses were performed. The habitual intake distribution, as well as the proportions below specified values, were predicted using different values of W:T variance, namely, 0.01, 0.1, 0.2, 0.3, 0.4, 0.45, 0.50, 0.60, 0.70, 0.8, 0.9, and 0.99.

To study the effect of the study sample and sample size on the estimated W:T variance, random samples were repeatedly (50 times) drawn. These new samples were smaller than the original data set of 660 subjects, namely 330, 165, 80, 50, and 25 subjects. Of these samples the habitual intake distribution was estimated using the NCI method, and with the results the W:T variance was calculated. The variation in this ratio was studied.

Median (IQR) or n (proportion of subgroup) were presented for general characteristics of the subgroups 1992–1997 and 2006–2011. Differences between men and women were tested for with a nonparametric Wilcoxon 2-sample test for continuous variables, and with a chi-square test for the proportions. All statistical analyses were performed with SAS 9.4 (SAS Institute Inc.). To compare the results of the different methodological approaches, differences in habitual intake distribution and proportions below cut-off values were evaluated based on 95% CIs, taking nonoverlapping 95% CIs as statistically significant. For the differences in habitual intake distribution and proportions below cut-off values between 1992–1997 and 2006–2011 a more formal test for difference was performed by calculating the difference for each percentile and cut-off value and the 95% CI of this difference based on 200 bootstrap iterations, similar to Dekkers and Slob (28). If 0 was not included in the 95% CI of the difference, the estimates were considered statistically significantly different.

Results

In total 1159 subjects were included for the period 2006–2011 and 432 subjects for the period 1992–1997. General characteristics related to the kidney transplant were similar for men and women, except for body weight and height at the time of transplantation, and BMI at time of transplantation in 2006–2011. At the median, women were shorter and lighter than men (**Table 1**); however, BMI was similar for men and women. In addition, the samples contained significantly more men than women. The plasma sodium concentration was similar for men and women. However, men had a higher median urinary sodium and creatinine excretion per 24 h, higher creatinine clearance, and a higher plasma creatinine concentration compared with women. In 2006–2011, the 24-h urinary volume was similar for men and women; however, in the period 1992–1997 men had a significantly lower urinary volume than women did. Some other characteristics also differed between 1992–1997 and 2006–2011. However, several of these differences could be related to the difference in periods. For instance, the proportion of subjects still alive in 2015 was smaller for the 1992–1997 subgroup than for 2006–2011.

The median observed urinary sodium excretion for men was 28% higher in 2006–2011 compared with 1992–1997, and for women this was 10% higher. However, the median plasma sodium concentration was similar in both periods.

Salt intake distribution

As anticipated, the mean intake based on single-day measurements or habitual intake was similar for all groups; however, most percentiles of the distribution based on single-day measurement deviated from the habitual intake distribution (**Table 2**). In other words, the habitual intake distribution was narrower. These differences were only statistically significant in the period 2006–2011, and not in 1992–1997 due to a larger 95% CI because of a smaller n. Consequently, there was also a difference in the proportion with intakes below specified cut-off values between both statistical methods. The proportions of male KTRs (2006–2011) with an intake <3, <6, or <9 g/d, at the left side of the distribution, were overestimated when using single-day data compared with the habitual intake based on 2 d of measurements. For male KTRs in the period 2006–2011 the differences were 2–8 percentage points. The proportion with salt intakes <12 g/d, at the right side of the distribution, was similar in both periods. For female KTRs in the periods 1992–1997 and 2006–2011 as well as male KTRs in 1992–1997, such under- and overestimations of the proportions below a specific cut-off value were also observed (Table 2 and **Figure 2**). However, the under- or overestimation of the proportion below a specific cut-off value was not equal for all groups (i.e., men/women and 1992–1997/2006–2011): this depended partly on where, on the specific salt intake distribution, the cut-off value was placed.

Inclusion of 2, 3, or 4 d in the estimation of the habitual intake distribution did not greatly affect the point estimates of the percentiles nor the proportions with intakes below the cut-off values (Table 2 and Figure 2). Results were similar for female and male KTRs, as well as for both periods.

In addition, for both male and female KTRs, the average habitual salt intake was significantly higher in 2006–2011 compared with 1992–1997 (Table 2 and **Figure 3**). Male KTRs in 2006–2011 consumed on average 10.6 g salt/d compared with 8.6 g/d in 1992–1997 (habitual intake based on 2 d). For female KTRs these values were 8.5 g/d in 2006–2011 and 7.5 g/d

TABLE 1 General characteristics of kidney transplant recipients in northern Netherlands in the periods 1992–1997 and 2006–2011[1]

Characteristics	Subgroup 2006–2011			Subgroup 1992–1997		
	Men	Women	P	Men	Women	P
n (%)[2]	660 (57)	499 (43)	<0.0001	246 (57)	186 (43)	0.004
Alive (functioning first kidney transplant) at 31 December 2015,[3] n (%)	429 (65)	329 (66)	0.741	60 (24)	56 (30)	0.184
Deaths prior to 31 December 2015,[3] n (%)	156 (24)	109 (22)	0.472	119 (48)	85 (46)	0.581
Graft failure first kidney transplant,[3] n (%)	75 (11)	61 (12)	0.652	67 (27)	45 (24)	0.475
Age at first kidney transplant,[4] y	49 (38, 59)	50 (39, 59)	0.457	46 (36, 54)	48 (34, 57)	0.504
Age at 31 December 2015 (alive),[4] y	58 (48, 67)	60 (52, 67)	0.013	59 (51, 70)	63 (50, 70)	0.681
Age at death,[4] y	67 (61, 73)	67 (59, 72)	0.383	64 (58, 70)	66 (60, 73)	0.354
Number of days between first and second urine collections[4]	42 (21, 304)	42 (21, 343)	0.873	21 (13, 35)	23 (13, 35)	0.400
Number of days between second and third urine collections[4]	44 (21, 274)	49 (21, 336)	0.484	28 (14, 42)	28 (14, 42)	0.286
Number of days between third and fourth urine collections[4]	49 (23, 308)	51 (23, 350)	0.898	30 (20, 50)	29 (18, 57)	0.715
Weight at first kidney transplant,[4] kg	78 (70, 89)	68 (59, 77)	<0.0001	72 (66, 81)	64 (58, 71)	<0.0001
Height at first kidney transplant,[4] cm	180 (175, 185)	168 (163, 172)	<0.0001	177 (173, 183)	167 (163, 171)	<0.0001
BMI at first kidney transplant,[4] kg/m^2	25 (22, 27)	24 (21, 27)	0.047	23 (21, 25)	23 (21, 25)	0.792
24-h urinary volume,[4] mL	2328 (1936, 2724)	2302 (1918, 2755)	0.824	2125 (1863, 2475)	2350 (2075, 2675)	<0.0001
Urinary sodium excretion,[4] mmol/24 h	172.6 (136.1, 210.5)	136.0 (111.0, 170.5)	<0.0001	134.9 (104.6, 180.8)	123.2 (94.0, 155.2)	0.0007
Plasma sodium,[4] mmol/L	141.0 (139.5, 142.3)	140.8 (139.3, 142.3)	0.168	140.5 (137.8, 142.3)	140 (137.5, 141.8)	0.246
Urinary creatinine excretion,[4] mmol/24 h	12.8 (10.9, 15.0)	9.2 (7.7, 10.8)	<0.0001	134.4 (11.8, 15.2)	10.2 (8.8, 11.9)	<0.0001
Plasma creatinine,[4] μmol/L	140.0 (113.0, 173.5)	109 (91, 141)	<0.0001	134.2 (116.4, 165.9)	109.0 (93.2, 137.6)	<0.0001
Creatinine clearance,[4] mL/min	65 (50, 81)	59 (43, 76)	<0.0001	69 (54, 83)	65 (49, 78)	0.07

[1] All values are absolute values. Differences between men and women within a period were tested with the nonparametric Wilcoxon 2-sample test for continuous variables and chi-square test for proportions, $P < 0.05$ is considered statistically significant. Subjects with at least 4 observation days were included and only data of those 4 observation days were included in the analyses; only the first 4 observations (i.e., visits to outpatient clinic) were included, after exclusion of observations with missing data. Subjects were selected from a cohort of kidney transplant recipients from the period 1990–2015.

[2] Proportion of total n (both men and women) in the specific period.

[3] n within gender; proportion in parentheses.

[4] Median; IQR in parentheses.

in 1992–1997. For most percentiles of the habitual salt intake distribution presented, the differences between the 2 periods were statistically significant, except for the 95th percentile of women. In addition, the proportions with intake below the specified cut-off values were significantly different between the 2 periods, except for the cut-off values of 3 and 12 g/d for women. In 1992–1997, 22% of male KTRs and 28% of female KTRs had habitual salt intakes <6 g/d, and in 2006–2011 these proportions decreased to 5% and 13%, respectively (Table 2 and Figure 2).

External variance

The habitual intake distribution of men in the period 2006–2011 was predicted by combining single-day 24-h urine excretion data with external variances. External variances were adopted from the habitual intake calculation based on 2 d for men in the period 2006–2011, women in the period 2006–2011, men in 1992–1997, and women in 1992–1997, and based on 3 and 4 d of men in the period 2006–2011 (i.e., scenarios A–F in **Table 3**). The W:T variance varied from 0.42 to 0.64. In scenario C, the W:T ratio applied (i.e., 0.63 from men 1992–1997) had the largest deviation from the original W:T ratio from men 2006–2100 (i.e., 0.49). However, the differences in the predicted habitual intake distribution were relatively small and not statistically significant (Tables 2 and 3). The same holds for the proportion below the specified cut-off values.

For the remaining scenarios also no statistically significant differences were found when comparing the predicted values with the habitual intake distribution of men in the period 2006–2011 based on 2 measurements. Consequently the predicted values

using external variance performed better than using single-day measurements (Tables 2 and 3).

Sensitivity analyses

As the W:T variance in the above described scenarios and in the original data were relatively similar, a sensitivity analysis was performed with ratios ranging from 0 to 1. The choice of the W:T variance did affect the habitual intake distribution, as well as the estimated proportion below a specified cut-off value. The effect not only depended on the chosen ratio, but also on the chosen cut-off value (**Figure 4**). Both under- and overestimation of the W:T variance biased the results. For the cut-offs of 6 and 9 g salt/d an underestimation of the W:T variance resulted in an underestimation of the proportion with an intake below these cut-off values, and an overestimation of the ratio resulted in an overestimation of this proportion. For the cut-off of 6 g salt/d, the predicted proportion with a lower intake varied from 0% to 13% depending on the ratio, for the cut-off of 9 g salt/d this ranged from 0% to 37%.

The cut-offs in the extremes of the habitual intake distribution were to some extent less affected by the choice of the ratio (Figure 4). However, the effect was not similar at the lower and upper extremes of the distribution. At the lower extreme, using the cut-off of 3 g salt/d, an underestimation of the W:T variance did not greatly affect the proportion below this cut-off value. However, an overestimation of this ratio showed an overestimation of the proportion. The predicted proportion ranged from 0% to almost 2%. Using the cut-off of 12 g salt/d (i.e., at the upper extreme) showed the opposite result. An overestimate of the W:T variance resulted in a prediction of the proportion that did not vary

TABLE 2   Salt intake distribution (g/d) from 4 single-day measurements and habitual salt intake distribution based on 2, 3, and 4 replicate measurements per subject, presented as 5th, 25th, 50th, 75th, and 95th percentiles (denoted P5–P95), for male and female kidney transplant recipients from northern Netherlands in the periods 2006–2011 and 1992–1997[1]

	Salt intake,[2] g/d					
	Mean	P5	P25	P50	P75	P95
Men 2006–2011						
Day 1	10.7 (10.4, 11.0)	4.2 (3.8, 4.5)	7.8 (7.3, 8.1)	10.4 (9.9, 10.8)	13.4 (12.8, 13.9)	18.9 (17.9, 20.2)
Day 2	10.5 (10.2, 10.8)	4.0 (3.2, 4.4)	7.6 (7.2, 7.9)	10.1 (9.6, 10.4)	13.0 (12.5, 13.5)	18.8 (17.5, 19.4)
Day 3	10.8 (10.5, 11.2)	4.4 (4.0, 4.8)	7.6 (7.3, 8.0)	10.1 (9.7, 10.6)	13.5 (13.0, 14.0)	19.3 (18.1, 21.2)
Day 4	10.8 (10.5, 11.1)	4.3 (3.7, 4.8)	7.8 (7.5, 8.1)	10.4 (10.0, 10.6)	13.5 (13.0, 13.9)	19.0 (17.7, 20.0)
Habitual day 1, 2	10.6 (10.3, 10.8)	5.9 (5.5, 6.3)	8.5 (8.2, 8.8)	10.5 (10.2, 10.7)	12.6 (12.2, 13.0)	15.9 (15.2, 16.6)
Habitual day 1, 2, 3	10.7 (10.5, 10.9)	5.7 (5.4, 5.9)	8.5 (8.2, 8.6)	10.5 (10.3, 10.7)	12.7 (12.5, 13.0)	16.0 (15.8, 16.8)
Habitual day 1, 2, 3, 4	10.7 (10.5, 10.9)	5.9 (5.6, 6.1)	8.6 (8.3, 8.7)	10.6 (10.4, 10.7)	12.6 (12.4, 13.0)	15.9 (15.6, 16.6)
Women 2006–2011						
Day 1	8.4 (8.1, 8.8)	3.4 (2.8, 3.9)	6.1 (5.8, 6.4)	8.1 (7.7, 8.5)	10.7 (10.2, 11.3)	14.3 (13.8, 15.0)
Day 2	8.5 (8.1, 8.8)	3.4 (2.9, 3.8)	6.1 (5.7, 6.4)	8.1 (7.7, 8.5)	10.7 (10.1, 11.0)	14.8 (14.0, 15.8)
Day 3	8.6 (8.3, 8.9)	3.8 (3.5, 4.2)	6.1 (5.8, 6.6)	8.1 (7.7, 8.5)	10.6 (10.1, 11.1)	14.6 (13.9, 15.7)
Day 4	8.8 (8.4, 9.2)	3.6 (3.1, 4.1)	6.3 (5.8, 6.7)	8.3 (7.9, 8.8)	10.7 (10.2, 11.1)	16.0 (14.9, 17.1)
Habitual day 1, 2	8.5 (8.2, 8.7)	4.9 (4.6, 5.4)	6.9 (6.6, 7.2)	8.4 (8.1, 8.7)	9.9 (9.6, 10.3)	12.3 (11.7, 12.9)
Habitual day 1, 2, 3	8.5 (8.3, 8.7)	4.7 (4.5, 5.0)	6.9 (6.6, 7.0)	8.4 (8.2, 8.6)	10.0 (9.8, 10.3)	12.4 (12.3, 13.0)
Habitual day 1, 2, 3, 4	8.6 (8.4, 8.8)	4.8 (4.6, 5.1)	6.9 (6.6, 7.0)	8.4 (8.2, 8.6)	10.1 (9.9, 10.3)	12.6 (12.4, 13.1)
Men 1992–1997						
Day 1	8.4 (8.0, 8.8)	2.8 (1.6, 3.8)	5.5 (4.6, 5.9)	7.8 (7.1, 8.6)	11.1 (10.1, 11.5)	16.5 (14.6, 18.3)
Day 2	8.9 (8.3, 9.5)	3.2 (2.7, 4.0)	5.9 (5.5, 6.5)	8.1 (7.5, 8.8)	11.7 (10.0, 12.3)	17.3 (15.3, 18.3)
Day 3	8.9 (8.3, 9.5)	3.2 (2.8, 3.8)	6.1 (5.3, 6.4)	8.2 (7.6, 9.0)	11.6 (10.5, 12.5)	16.5 (14.6, 19.1)
Day 4	8.9 (8.4, 9.5)	4.0 (3.2, 4.5)	6.0 (5.7, 6.5)	8.0 (7.4, 8.8)	11.2 (10.3, 11.9)	16.5 (14.1, 19.1)
Habitual day 1, 2	8.6 (8.2, 9.1)	3.9 (3.4, 4.5)	6.3 (5.8, 6.7)	8.3 (7.9, 8.7)	10.6 (10.0, 11.2)	14.4 (13.4, 15.4)
Habitual day 1, 2, 3	8.7 (8.3, 9.2)	4.1 (3.5, 4.4)	6.4 (5.9, 6.8)	8.4 (8.0, 8.9)	10.7 (10.2, 11.4)	14.5 (13.8, 15.9)
Habitual day 1, 2, 3, 4	8.8 (8.4, 9.3)	4.3 (3.7, 4.6)	6.5 (6.1, 6.9)	8.4 (8.1, 8.9)	10.7 (10.2, 11.3)	14.4 (13.3, 15.6)
Women 1992–1997						
Day 1	7.6 (7.1, 8.1)	2.7 (2.4, 3.5)	4.9 (4.5, 5.6)	7.1 (6.6, 7.8)	10.0 (9.0, 10.5)	13.1 (12.6, 15.7)
Day 2	7.5 (7.0, 7.9)	3.1 (2.8, 3.2)	4.7 (4.2, 5.2)	6.9 (6.2, 7.5)	9.6 (8.7, 10.1)	13.8 (12.9, 15.5)
Day 3	7.6 (7.1, 8.0)	2.9 (1.8, 3.4)	3.5 (4.5, 5.4)	7.1 (6.6, 7.5)	9.9 (8.9, 10.4)	12.9 (13.3, 15.4)
Day 4	7.9 (7.4, 8.4)	3.3 (2.5, 3.9)	5.3 (4.6, 5.8)	7.9 (6.8, 8.1)	9.9 (9.3, 10.7)	14.1 (12.8, 14.9)
Habitual day 1, 2	7.5 (7.1, 7.9)	4.1 (3.4, 4.9)	5.8 (5.3, 6.4)	7.3 (6.8, 7.7)	8.9 (8.4, 9.4)	11.7 (10.6, 12.8)
Habitual day 1, 2, 3	7.5 (7.1, 7.9)	3.9 (3.3, 4.2)	5.7 (5.3, 6.1)	7.3 (6.8, 7.6)	9.1 (8.6, 9.6)	12.1 (11.3, 13.0)
Habitual day 1, 2, 3, 4	7.6 (7.2, 8.0)	4.0 (3.5, 4.3)	5.8 (5.5, 6.2)	7.4 (7.0, 7.8)	9.1 (8.7, 9.6)	12.0 (11.2, 12.8)

[1]All values are absolute values. Differences between salt intake based on single-day and habitual intake were identified by nonoverlapping 95% CIs. Subjects with at least 4 observation days were included; only the first 4 observations (i.e., visits to outpatient clinic) were included, after exclusion of observations with missing data. Subjects were selected from a cohort of kidney transplant recipients from the period 1990–2015. Habitual intake was estimated with a statistical correction for within-person variance using the National Cancer Institute method (6).

[2]Point estimates (95% CIs) based on bootstrap analyses ($n = 200$).

greatly, namely 64–70%. Underestimation of the ratio resulted in larger differences and the predicted proportion ranged from 70% to 100%.

Effect of sample size on prediction of W:T variance

With a small sample size the W:T variance varies considerably among the replicates (**Figure 5**). At a sample size of 25, for example, this ratio varied from 0.06 to 0.82. Considering the results of the sensitivity analyses, this could result in a large random error. For example, the proportion of the population with a salt intake <6 g/d would vary by ∼10 percentage points (based on sensitivity analyses in Figure 5). With an increasing sample size the variation in W:T variance decreased and was in the same order of magnitude for sample sizes of 165 and 330, namely 0.30–0.63 and 0.33–0.61, respectively. Also, with a sample size of 660, which is equal to the sample size of the original data set, there was variation in the W:T variance of 0.44–0.54. Based

on the sensitivity analyses (Figure 5) the random error in results considering the variation in W:T variance of a sample size of ≥165 would be relatively small, but could still be ∼10 percentage points.

Discussion

The main aims of our study were to show the importance of adjusting 24-h urinary sodium excretion for within-person variance when estimating salt intake distribution and to explore the effect of using external variance components. As expected, ignoring within-person variance in 24-h sodium excretion resulted in a wider salt intake distribution and in considerable bias in the population's proportion having intakes below specific cut-off values. For several decades, studies have shown large within-person variance in the 24-h sodium excretion (19, 29–31). We support the need expressed by authors of several of these studies
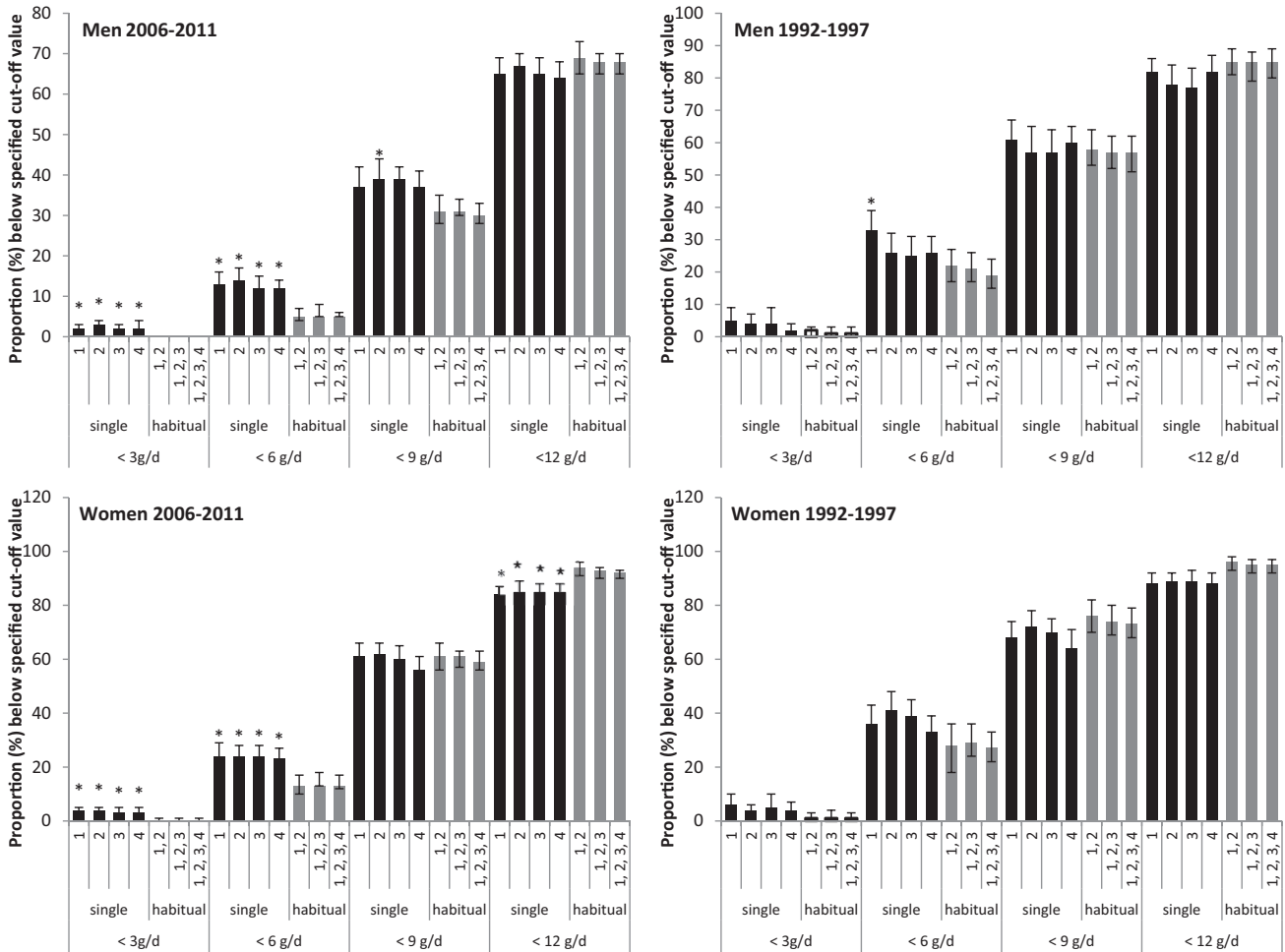
FIGURE 2 Proportion of the population with salt intake (g/d) below a specified cut-off value (3, 6, 9, and 12 g/d) for male and female kidney transplant recipients in the northern Netherlands in 1992–1997 and 2006–2011 based on single-day observations and habitual intake based on 2, 3, or 4 d. Estimates of single-day observations statistically significantly deviating from the habitual estimates based on nonoverlapping 95% CIs are identified with *. Values presented as point estimates with corresponding 95% CI based on bootstrap analyses (n = 200). Subjects with at least 4 observation days were included; only the first 4 observations (i.e., visits to outpatient clinic) were included, after exclusion of observations with missing data. Subjects were selected from a cohort of kidney transplant recipients from the period 1990–2015.

to correct for within-person variation in biomarkers for intake to get better prevalence estimates. Unfortunately, correction for day-to-day variation in biomarkers is still rare. Similar to food consumption surveys (32), for this biomarker of salt intake a limited number of repeated data collections combined with statistical correction for within-person variation yields a more accurate picture of salt intake distribution than single-day data collections.

As far as we know, our study is the first to assess the use of external variances to predict the habitual salt intake distribution and prevalence of intake below cut-off values, using single 24-h urine collections. Applying external variances resulted in a habitual salt intake distribution very similar to the habitual intake distribution estimated with 2 repeated data collections per individual. Some fluctuation in the external W:T variance used did not result in statistically significant differences compared with the habitual intake of the original data with two 24-h urine collections per subject. In the study of Jahns et al. (23) there

was also some variation in the external variances from different studies (within:between person variance of 0.54–0.75); also in that study the effects on the prevalence of inadequate intakes were limited (≤5 percentage points). Our sensitivity analyses showed that besides the value of the external W:T variance the position on the intake distribution is also important for potential bias of results. Because a W:T variance that greatly deviates from the true ratio results in bias, it is important to carefully select an external W:T ratio. However, if only single-day measurements are present the W:T variance is unknown. A solution could be to collect replicate data in a subsample, of sufficient size, of the study population (22, 33). With a limited number of subjects, the W:T variance can be affected by random error. The exact sample size required can vary between populations, as well as between nutrient or biomarker. In our examples, a sample size of 165 could still result in a bias of almost 10 percentage points in the proportion below a specified cut-off value.
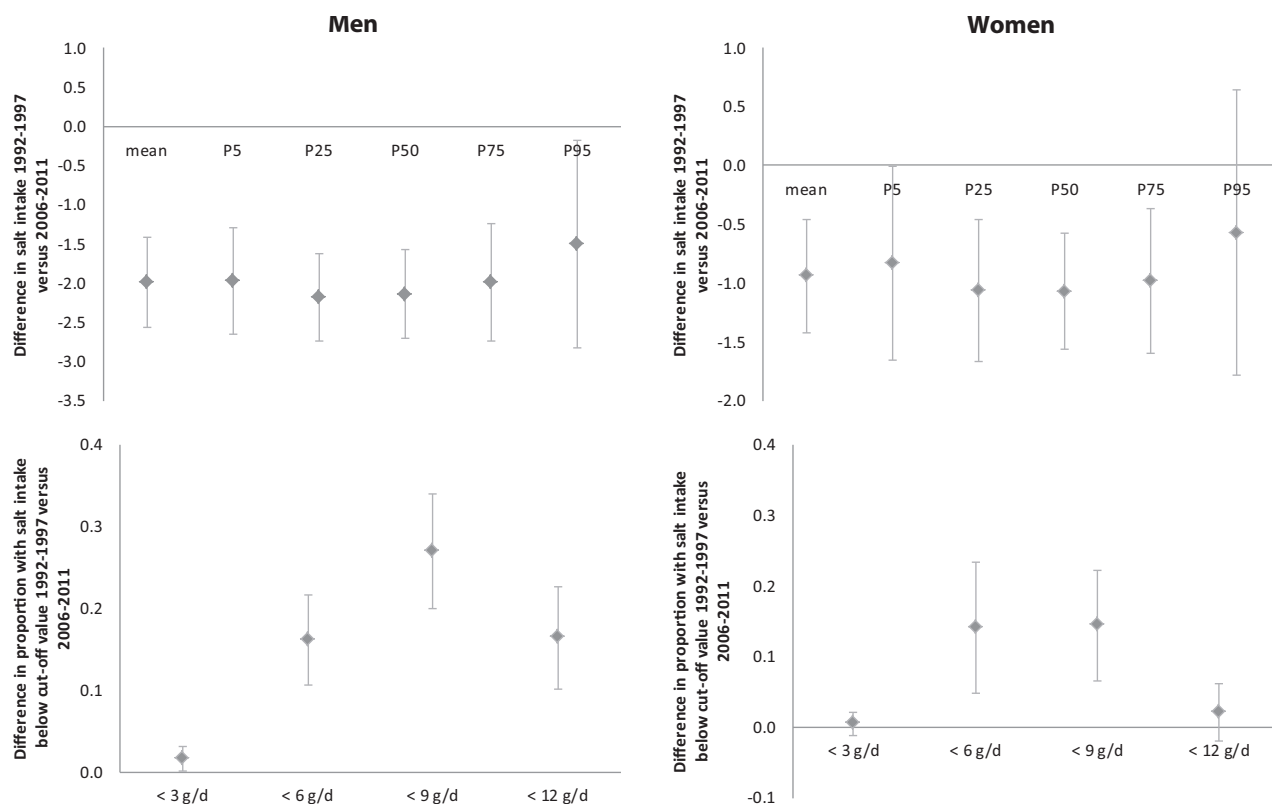
FIGURE 3 Absolute differences (gray diamonds) between mean and percentiles (P5–P95) of the habitual (based on 2 d) sodium intake distribution of 2006–2011 and 1992–2997 (top) and between the proportions (0–1) of the population with habitual sodium intakes below specified cut-off values (bottom) for men (left) and women (right). Error bars represent 95% CIs of differences based on bootstrap with 200 iterations. If 0 is not included in the 95% CI the habitual salt intake at that percentile or the proportion below that specific cut-off value is statistically significantly different between the periods 2006–2011 and 1992–1997.

The W:T variance of 24-h urinary sodium excretion varied between 0.43 and 0.68 in other studies (14, 15, 22). In 2 of these studies, the sample sizes were small ($n < 35$) (14, 15), which might have resulted in random error. However, in a study with a large sample size ($n = 436$), the W:T variance was different for men and women, at 0.43 and 0.67, respectively (22). It is recommended that a sensitivity analysis is done to show the effect of a different W:T variance. For studies with repeated measurements, it is recommended to publish the variance components, so they can be applied as external variances in other studies, as well as to study the variation in the variance components between study populations and over time.

Our study has some limitations, among which is the lack of information on the completeness of the 24-h urine samples of the KTRs. Subar et al. (34) suggested that a check of completeness of urine collection might not be required in large population-based biomarker studies, because attenuation factors based on models of measurement error were similar with and without missed voids. However, it is not clear whether this holds for all population-based studies, as the participants of the Observing Protein and Energy Nutrition (OPEN) study were in general very committed to the study. Another limitation is that the repeated 24-h urine collections were not collected in a similar time frame for all subjects. KTRs with a recent transplant visited the outpatient clinic more frequently than KTRs

with a stable graft. This was also observed as a difference between the periods. In 1992–1997, the median number of days between two 24-h urine collections was smaller compared with 2006–2011. Consequently, the within-person variation could also be (partly) due to a time trend. To reduce this effect, the statistical analyses were limited to 2 periods with similar mean 24-h sodium excretion in each calendar year. To define if the results of different calculation methods deviated, several characteristics (i.e., percentiles and proportions below cut-off values) of the habitual intake distributions were compared based on nonoverlapping 95% CIs. This is a conservative method, representing a significance at an $\alpha < 0.05$. As such, we consider this a surrogate correction for multiple comparisons. Already with this conservative method for testing for differences, the effect of narrowing the distribution with statistical correction for within-person variance was demonstrated. For the comparison between both periods, deviation of the difference between both periods from 0 was tested using the 95% CI of this difference. These results were comparable with the outcomes of comparison of the 95% CIs of the point estimates. In general, the comparison of the 95% CIs of the point estimates was more conservative. Further, the study population of KTRs is not comparable with the general healthy population. Van den Berg et al. (24) showed differences between KTRs and healthy controls. However, the currently used cohort is a unique study population with many repeated 24-h urine collections in which sodium was measured,

TABLE 3 Habitual salt intake distribution (g/d), presented as mean and 5th, 25th, 50th, 75th, and 95th percentiles (denoted P5–P95), and proportion below specified cut-off values of male kidney transplant recipients from northern Netherlands in the period 2006–2011 using single-day measurements (day 1) in combination with external variance estimates of other data sets[1]

	Data about external variance				Habitual salt intake,[2] g/d						Proportion below cut-off value[2]			
Scenario	Period	Gender	Days	Ratio within:total variance	Mean	P5	P25	P50	P75	P95	3 g/d	6 g/d	9 g/d	12 g/d
A	2006–2011	M	1, 2	0.49	10.7 (10.4, 11.2)	6.1 (5.8, 6.5)	8.6 (8.3, 9.1)	10.6 (10.1, 11.0)	12.7 (12.2, 13.1)	16.0 (15.4, 16.4)	0 (0, 0)	5 (3, 6)	30 (24, 35)	68 (63, 73)
B	2006–2011	F	1, 2	0.42	10.7 (10.3, 10.9)	6.4 (6.0, 6.6)	8.8 (8.4, 8.9)	10.6 (10.2, 10.7)	12.6 (12.1, 12.7)	15.6 (15.0, 15.8)	0 (0, 0)	3 (3, 5)	28 (26, 34)	69 (67, 74)
C	1992–1997	M	1, 2	0.63	10.5 (10.3, 10.9)	5.4 (5.0, 5.6)	8.1 (7.8, 8.4)	10.3 (10.0, 10.6)	12.7 (12.4, 13.1)	16.6 (16.2, 17.1)	0 (0, 1)	8 (7, 10)	35 (31, 38)	68 (65, 71)
D	1992–1997	F	1, 2	0.44	10.5 (10.3, 10.9)	6.0 (5.7, 6.3)	8.5 (8.2, 8.7)	10.4 (10.1, 10.7)	12.4 (12.2, 12.8)	15.7 (15.4, 16.2)	0 (0, 0)	5 (4, 6)	32 (28, 35)	70 (66, 73)
E	2006–2011	M	1, 2, 3	0.48	10.5 (10.3, 10.9)	6.0 (5.7, 6.3)	8.5 (8.2, 8.8)	10.4 (10.1, 10.7)	12.4 (12.2, 12.8)	15.7 (15.4, 16.2)	0 (0, 0)	5 (4, 6)	32 (28, 35)	70 (67, 73)
F	2006–2011	M	1, 2, 3, 4	0.45	10.5 (10.3, 10.9)	6.1 (5.8, 6.4)	8.5 (8.2, 8.8)	10.4 (10.1, 10.7)	12.4 (12.1, 12.8)	15.6 (15.2, 16.1)	0 (0, 0)	4 (4, 6)	31 (27, 35)	71 (67, 74)

[1] All values are absolute values. Differences between habitual salt intake estimated with external variance components and habitual intake (men 2006–2011) with internal variance components (Table 2) were identified by nonoverlapping 95% CIs. Subjects with at least 4 observation days were included; only the first 4 observations (i.e., visits to outpatient clinic) were included, after exclusion of observations with missing data. Subjects were selected from a cohort of kidney transplant recipients from the period 1990–2015 (**Supplemental Table 3**). Habitual intake was estimated with a statistical correction for within-person variance using the National Cancer Institute method (6).

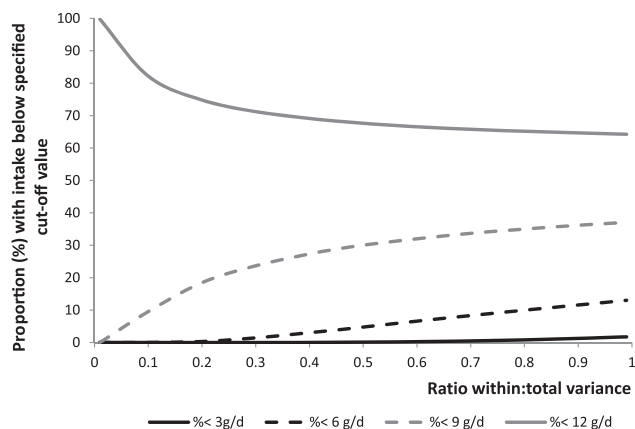[2] Point estimates (95% CIs) based on bootstrap analyses (n = 50).

FIGURE 4 Results of sensitivity analyses, proportion of the population with habitual salt intake below a specified cut-off value (3, 6, 9, and 12 g/d) for male kidney transplant recipients from northern Netherlands (n = 660) in the period 2006–2011 using varying ratios of within-person variance to total variance (0 to 1) as external variance estimates.

making it suitable to study the potential of using external variance to estimate habitual salt intake distribution.

Although our study was designed to study the effect of within-person variance in a biomarker for intake and the potential to use external variances, it also provided some insight in the trend in salt intake in KTRs in the Netherlands from 1990 to 2015. The habitual salt intake was statistically significantly higher in the period 2006–2011 compared with 1992–1997 (median 27% higher for men and 15% higher for women). Also the proportion with a habitual salt intake above the maximum of 6 g/d (27) was ~15% higher in this period. Although there are differences in characteristics in the subjects included for the periods 1992–1997 and 2006–2011, these differences are small and it seems unlikely that these had a large influence on the sodium excretion. In our study, we selected KTRs in two 6-y
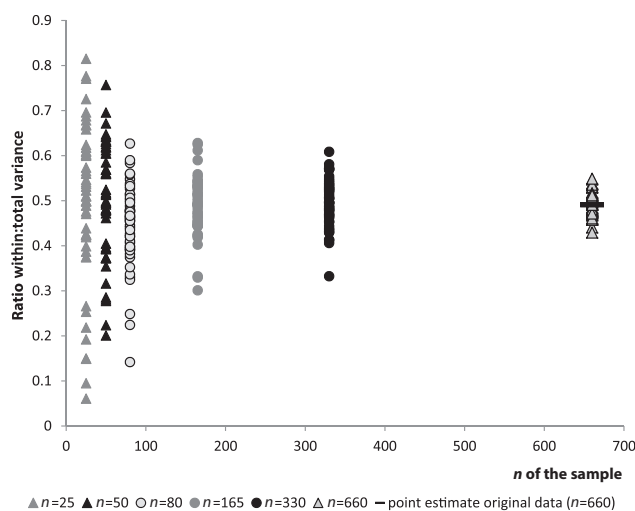

FIGURE 5 Variation in ratio of within-person variance to total variance (W:T variance) by sample size after repeated sampling with several sample sizes from the original data set (male kidney transplant recipients from northern Netherlands, 2 d, 2006–2011, n = 660). Black line at n = 660 is W:T variance of original data set with 2 d of data per subject.

periods with at least 4 urine collections, representing ∼85% of the study population in 2006–2011 and ∼95% in 1992–1997. Subjects with <4 collections were lost to follow-up due to death, graft failure, or other circumstances (e.g., moving out of the region). Therefore, we expect that the salt intake in these periods could be representative for KTRs with a first kidney transplant in northern Netherlands. Our data suggest that salt intake did increase among KTRs in the Netherlands, but because KTRs are a specific patient group, not representative of the general healthy population, it remains unclear what this implies for the general healthy population. Trends in salt intake in the general Dutch population are inconclusive (20, 35, 36). In addition, van den Berg et al. (24) showed a lower creatinine clearance for KTRs compared with healthy adults. This difference in kidney function might have affected urinary sodium excretion and the proportion of sodium intake excreted, but because this is the case for both subgroups in our study, we expect the increasing trend in sodium intake to be valid. Although the absolute estimates of salt intake might be biased, we have no information on the extent of this potential bias.

Although our study focused on 24-h sodium excretion as a biomarker for salt intake, the issue of within-person variance and the potential of using external variances is not unique for this biomarker. However, the within-person variance can vary between biomarkers. The intraindividual variation is, for instance, relatively small for serum 25-hydroxyvitamin D (1). However, for other biomarkers of nutritional status this variation can be bigger (37, 38). Intraindividual variation in dietary intake is not necessarily the only explanation for within-person variance in biomarkers of intake. For example, even with constant salt intake there is fluctuation in urinary sodium excretion (39). Future studies could explore the effects of (external) within-person variance in other populations and for other biomarkers.

In conclusion, it is important to correct salt intake distributions based on 24-h urine excretion of sodium for within-person variance. Two replicates and a statistical correction seem adequate to estimate the habitual intake distribution. Predicting the habitual salt intake distribution using single-day measurements with external variances is promising. It is recommended to collect repeated measurements in a representative subsample of sufficient size rather than using completely external data. In addition, it is recommended to perform sensitivity analyses showing the effect of differently chosen external variances.

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