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Are mandatory salt reduction policies and universal salt iodisation programmes at loggerheads? A cross-sectional analysis from the WHO-SAGE South Africa cohort

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Are mandatory salt reduction policies and universal salt iodisation programmes at loggerheads? A cross-sectional analysis from the WHO-SAGE South Africa cohort

Short title: Salt reduction and universal salt iodisation

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Abstract

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Objective: The World Health Organization's (WHO) global targets for non-communicable disease (NCD) reduction recommend consumption of <5g salt/day. In 2016, South Africa was the first country to legislate maximum salt levels in processed foods. South Africa's universal salt iodization (USI) fortification programme has successfully eradicated iodine deficiency. Simultaneous monitoring of sodium reduction and iodine status is required to ensure compatibility of the two public health interventions.

Design/setting/participants: A nested cohort design within WHO's 2015 Study on global AGEing and adult health (SAGE, n=2887) including individuals from households across South Africa. Randomly selected adults (n=875) provided 24-hour and spot urine samples for sodium and iodine concentration (UIC) analysis (the primary and secondary outcome measures respectively). Median 24-hour and spot UIC were compared by salt intakes <5g/day, 5 – 9 g/day and ≥9g/day.

Results: Median daily salt excretion was 6.3g salt/day (range 1-43 g/day); 35% had urinary sodium excretion values within the desirable range (< 5g salt/day), 37% had high values (5 – 9 g salt/day) and 28% had very high values (≥ 9g salt/day). Median UIC was 130 µg/L (IQR=58-202), indicating population iodine sufficiency (≥100 µg/L). Both spot and 24hr iodine excretion differed across urinary sodium categories ($p<0.001$) and were positively correlated with 24h urinary sodium ($r= 0.170$ and 0.528 respectively; both $p<0.001$).

Conclusions: 24hr urinary sodium and iodine within a nationally representative cohort study allows simultaneous assessment of the compatibility of both salt reduction strategies and USI. Iodine status of populations undergoing salt reduction strategies needs to be closely monitored to prevent re-emergence of iodine deficiency.

Strengths and limitations of this study

- The study uses the current gold standard of 24-hour urine to assess sodium intake
- The large sample size includes coastal and inland populations from across the country
- Lack of dietary data precludes assessment of sources of iodine or sodium
- The data is only for adults and not children
- The sample includes 14% women of approximate child bearing age (18-49y; n=121)

Keywords: iodine; sodium, dietary; policy; nutritional requirements; legislation, food

Introduction

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Iodine deficiency remains the largest preventable cause of brain damage and mental impairment worldwide. Thyroid hormone production requires an adequate supply of iodine from the diet, and is essential to metabolism and growth across the lifecycle. As well as cretinism in its most severe form, iodine deficiency can also result in miscarriages, stillbirths, and impaired psychomotor development and behavioural problems in children born to iodine deficient mothers[1]. To prevent iodine deficiency disorders, the World Health Organization (WHO) has endorsed universal salt iodization (USI), where all salt for human and animal consumption is iodized[2]. USI is hailed as a public health success story, as 70% of the world's population is estimated to use iodized salt in a total of 130 countries[3]. However, 2 billion individuals worldwide still have insufficient iodine intake, with many in south Asia and sub-Saharan Africa particularly affected[4].

In South Africa, mandatory iodization of table salt, at a level of 40 to 60 ppm, replaced voluntary iodization in December 1995, using potassium iodate as the fortificant[5] because of its stability in warm climates[6], rather than potassium iodide that is used in North America and Europe. The level of fortification was subsequently revised in 2007 to allow a wider range, namely 35 to 65 ppm[2]. The iodization program has effectively eliminated iodine deficiency in the country, but there are some loopholes in the program, such as the domestic use of non-iodized agricultural salt in the northern provinces[7]. Under the legislation, salt used in the manufacturing of processed foods and salt packaged in bags of at least 20 kg are also exempted from mandatory iodization[5]. In 2005, 77% of households in the country used adequately iodized salt, described as salt containing more than 15 ppm of iodine[8]. However, data on the iodine status of the South African population is outdated and a national survey was last conducted in 2005[7]. At that time, South African women and children aged 6 to 9 y old were found to have an optimal iodine status (i.e., MUIC 100–199 mg/L, <20% with UIC levels <50 mg/L)[9] which indicated a well-functioning salt iodization program[10].

At the same time as salt iodization efforts around the world are being celebrated, there is a global focus on salt reduction efforts to lower population level blood pressure. The World Health Organization (WHO) and World Health Assembly targets to reduce non communicable diseases (NCDs) include a 30% reduction in population salt intake by 2025[11] [12]. South Africa was the first country to implement mandatory legislation in July 2016 for maximum salt levels permitted in a wide range of processed foods[13] that are significant contributors to the sodium intake of the population[14-17]. The legislation is predicted to decrease population-level salt intake by 0.85 grams per day[18] and reduce annual deaths from

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cardiovascular diseases by 11%. This public health strategy is estimated to save the government US$51.25 million/year in health care costs; and save households more than US$4 million/year in out-of-pocket medical expenses[19].

Since salt is the vehicle for iodine fortification, successful campaigns to reduce salt intake would also likely result in reduced iodine intake[20]. Dietary modelling conducted in the Netherlands estimated the effect of 12%, 25%, and 50% decreases in salt from processed foods and table salt[20]. Only at a 50% salt decrease would iodine intake become inadequate for a small percentage of the population which, at that time, confirmed a lack of conflict between population-wide strategies of decreasing salt while ensuring adequate consumption of iodized salt to prevent iodine deficiency. We have previously reported no difference in median UIC across categories of sodium excretion equivalent to salt intakes lower than 5g/day, 5 - 9 g/day, and greater than or equal to 9 g/d in a convenience sample of 262 adult men and women in Cape Town in 2004[21]. It was concluded that this was because much of the dietary salt consumed was provided from non-iodinated sources, presumably in salt added to processed foods. Given the introduction of the salt reduction legislation, it is timeous to assess the iodine status of the South African population, according to salt intakes.

The aim of the current study was to simultaneously measure sodium (Na) and iodine in 24hr and spot urinary collections in an adult cohort cohort to determine whether lower salt intakes are associated with a suboptimal iodine status.

Methods

A nested observational study was conducted as part of Wave 2 of the World Health Organization Study on global AGEing and adult health (WHO SAGE). WHO-SAGE is a multinational cohort study examining the health and wellbeing of adult populations and the ageing process. Two waves of this longitudinal study have been completed in China, Ghana, India, Mexico, Russia and South Africa[22]. In total, 42,464 respondents were recruited across the six countries for Wave 1 (2007-2010), including 4223 respondents in South Africa (9% 18-49 years; 40% 50-59 years; 51% 60+ years). Respondents were recruited from selected probability sampled enumeration areas (EAs) using a multi-stage cluster sampling strategy, with stratification by province, residence and race. Urine capture was included as part of SAGE South Africa Wave 2 data collection. The sampling strategy was designed to account for attrition, where households were classified into the following mutually exclusive categories: 1) SAGE Wave 1 follow-up households with one or more members aged 50 years

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or more targeted for selection; 2) new households with one or more members aged 50 years or more; 3) SAGE Wave 1 follow-up households which include residents aged 18-49 targeted for selection; or, 4) new households which include residents aged 18-49. Further detail on the sampling and recruitment strategy can be found in the study protocol paper[23].

For Wave 2 data collection in 2015, twenty survey teams (one nurse and three interviewers per team) simultaneously collected data and samples from respondents across all provinces in the country over a five-month period. Respondents that were recruited to provide urine samples (n=1200) were sampled from among the first households visited within each EA, as a means to simplify logistics and reduce sample transit time to the central Durban laboratory.

Inclusion criteria for urine collection were: respondent must be part of the WHO SAGE cohort, with no indication of urinary incontinence or other condition that could impede 24-hour urine collection; and if female, not menstruating, pregnant, or breastfeeding on the day of collection.

Study Measures

All survey teams were trained with support from WHO Geneva. As part of the larger survey, anthropometry, household and individual questionnaires, blood sampling, blood pressure (BP) and physical function tests were completed as described previously in SAGE Wave 1[22]. Interviewers spoke the respondents' home languages with consent forms available in the most widely spoken languages for each area. All respondents gave free and informed consent prior to taking part. The study complied with ethical principles[24] and all procedures involving human subjects were approved by the WHO Ethics Review Committee [RPC149], and North-West University and University of Witwatersrand research ethics committees in South Africa.

Urine collection

The protocol used for collection of 24-hour urine samples followed the WHO/PAHO guidelines[25]. Respondents were requested to collect all urine produced for 24 hours, excluding the first pass urine on day 1, but including the first urine of the following morning (day 2) in a 5-litre plastic container containing 1g thymol as preservative in South Africa. The spot sample was collected without preservative from the second urine passed on day 1 (marking the start of the 24-hour collection) and decanted into three 15 ml Porvair tubes (Porvair Sciences, Leatherhead, UK) then kept in a cool box powered by the fieldwork

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vehicles. The next morning, the 24-hour sample volumes were recorded and aliquots (4 x Porvair tubes) generated with all samples then shipped to the laboratory, maintaining the cold chain. Thymol, a crystalline natural derivative of the Thyme plant, was used as a preservative. Thymol has been shown to prevent changes in urinary creatinine, sodium and potassium concentrations for up to five days[26]. Incomplete 24-hour urine collections were assumed if: total volume ≤300ml; or creatinine excretion ≤4 mmol/day (women) or ≤6 mmol/day (men)[27].

Urine analysis

Sodium and potassium were determined using the indirect Ion Selective Electrode method and creatinine analysed using the standardised urinary Jaffe kinetic method (Beckman Coulter Synchron DXC600/800 System). The WHO population target for salt intake is 5g salt (NaCl) per day, equivalent to urinary sodium excretion 85 mmol/24hr. With the exception of iodine, all South African samples were analysed at a single laboratory in Durban, South Africa (Global Clinical and Viral Laboratories). Urine samples for iodine analysis were stored at -20° C and batch analysed using the Sandell-Kolthoff method with ammonium persulfate digestion and microplate reading[28] at the North-West University Centre of Excellence for Nutrition. The laboratory participates successfully in the Program to Ensure the Quality of Urinary Iodine Procedures (EQUIP, U.S. Centres for Disease Control and Prevention, Atlanta GA, USA)[29]. A median of <100µg iodine/L indicates population-level deficiency (there are no reference ranges for individuals)[30].

Data capture, analysis and statistical power

All data was captured using an electronic data capture system and uploaded to a secure central server for data cleaning and analysis. The nested cohort sample size for the primary outcome measure of 24-hour urine sodium was calculated as previously described.[23] Allowing for error in 24-hour sample collection (incomplete or missing samples) in this complex field study, a target sub-sample size of 1200 was randomly selected from the main SAGE-Wave 2 cohort, and those with incomplete or missing samples excluded from the analysis. The sample size used for this analysis was deemed adequate based on recommendations of WHO (2007) that states a sample size between 600 and 900 is sufficient to have a reasonable confidence interval around the coverage estimate for urinary iodine concentration[2].

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Both spot urinary iodine analyses (UIC) and 24hr urinary iodine excretion (UIE) were compared across three categories of 24hr urinary Na excretion intake, equivalent to salt intakes <5g/day, 5 – 9 g/day and ≥9g/day. Normality of data was assessed by visual inspection of histograms and the Kolmogorov-Smirnov test. All non-parametric data were reported as median and interquartile range (IQR; 25th, 75th percentile) and continuous variables compared using independent Samples Mann-Whitney U test or Independent Samples Kruskal-Wallis test. Categorical variables were compared across groups using Pearson Chi-Square and Fisher's Exact Test. Data were also analysed according to urinary Na excretion values and by iodine category (sub-optimal: UIC <100 ug/L; iodine replete: 100 – 299 ug/L; and excessive: >300ug/L). To assess the association between salt intake, body size, UIC and UIE, Spearman's rank order and partial correlations were conducted.

Results

Complete urinary Na and iodine data were available in n = 874 participants. Sociodemographic characteristics and health indicators of the sub-sample are compared to the total SAGE-Wave 2 cohort (n = 2887) in Table 1. The sub-sample had a higher proportion of women and more black/coloured respondents than the main cohort, which may explain differences in smoking, education and BP.

Median 24hr Na excretion (n=874) was equivalent to a median salt intake of 6.3gsalt/day (range 1-43 g/day); 35% had values within the desirable range (< 5g salt/day), 37% had high values (5 – 9 g salt/day) and 28% had very high values (≥ 9g salt/day) (Table 2). MUIC (n=875) was 130 µg/L (IQR=58-202), indicating iodine sufficiency (≥100 µg/L) while median 24hr UIE (n=866) was 117 ug/day (IQR 138).

Both UIC and 24hr iodine excretion differed across urinary Na categories and were positively correlated with urinary Na (r= 0.172 and 0.533; both P<0.001) (Table 2). In the lowest salt category of <5g/d, median UIC indicated borderline deficiency of 102 µg/L. Based on 24hr UIE, participants with a salt intake of <5g/day would be considered to be iodine deficient (<100 ug/day).

When the data was analysed according to urinary Na excretion values by iodine category, those in the sub-optimal category (<100 ug/day) had significantly lower salt equivalent excretion values compared to those that were classified as being iodine replete (median (IQR) = 5.4 (2.9; 7.9) vs 6.9 (4.0; 9.9) g/day) (Table 3). Those in the category considered to be

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excessive (>300ug/L) had similar urinary Na excretion values to those in the sufficient category (100 – 299 ug/L), namely 6.9 (4.0, 9.9) and 7.3 (4.7, 10.0) g salt/day, respectively (P = 0.854). Similarly, the median UIC of those with the highest salt excretion (>9g/day) was within the normal range (ie.149 (78, 220) ug/L).

Responses to questions on salt behaviours did not differ between participants across median UIC categories (data not shown), nor according to UIE (Figure 1).

Discussion

Our study found that, although the population are on the whole iodine sufficient, iodine intake is associated with salt intake. With two thirds of the population consuming more than the recommended daily salt intake, and the low salt intake group already exhibiting borderline iodine status, there is a risk that sodium reduction strategies may also impact iodine intake.

Concerted efforts are being made in many countries to lower salt consumption[12]. Because the primary food vehicle for iodine fortification is salt, there is concern that decreasing salt consumption will increase the risk of iodine deficiency. Our study findings indicate that this is a potential public health problem. The findings of the current study are in contrast to previous findings from a sample of adult men and women surveyed in Cape Town in 2004, when UIC did not differ across categories of salt intake[(21)]. This discrepancy may be explained by an increasing number of food manufacturers that have knowingly or unknowingly included iodized salt for food processing over the past decade, or alternatively by an increased consumption of salt provided from processed foods, relative to discretionary salt intake.

The South African strategic plan to reduce cardiovascular disease includes the target to reduce the population intake of salt to less than 5 grams/day. At present the salt intake is higher than this level with an estimated 40% coming from discretionary salt intake[16]. Our study was conducted immediately prior to introduction of the mandatory salt targets in processed foods. Despite iodised salt not being required by law to be used as an ingredient in the manufacturing of processed foods, a study[31] that investigated the iodine content of salt used in bread, margarine, and salty snack flavourings in 2002 provided surprising results. Even though 11 of the 12 manufacturers surveyed at that time reported that they used non-

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iodized salt in their products, substantial amounts of iodine were found in the salt used by a third of these manufacturers' products, with a mean content of 39 to 69 ppm, and these were the items that were mostly distributed countrywide. An appreciable percentage of the food companies used iodized salt unknowingly in the manufacturing of frequently consumed processed foods, and this may have had a considerable impact on the daily iodine intake of consumers. To our knowledge, there is no updated information on the use of iodised salt by food manufacturers. The salt intake estimations in the current study include both added (discretionary) and non-discretionary salt intakes but the lack of data on dietary intakes of the participants prevents further investigation of the source of the salt.

We hypothesize that food manufacturers may have already reduced salt content in processed foods at the time of the study (2015), and that some of these products may have been produced with iodized salt. If this is the case, this would result in lowered iodine intake at the same time as lowered salt intake, as would any reduction in discretionary salt use. Considering the latter, there have been many accompanying health education strategies that target salt reduction behaviours, alongside the salt legislation in processed foods[32]. In 2015, a mass media campaign (Saltwatch), using television, radio advertisement and other platforms for information dissemination was undertaken to increase public awareness related to the association between a high salt intake, blood pressure and cardiovascular disease in South Africa. The campaign, conducted by the Heart and Stroke Foundation of South Africa with funding from the Department of Health, focused on the need to reduce discretionary salt intake. Evaluation of the programme undertaken in 550 black women, aged 18-55 years in three provinces identified that there was an increase in most of the indicators of knowledge, attitudes and behaviour change towards considering and initiating reduced salt consumption following the campaign[33]. Significant increases were found for knowledge items related to high salt intake and its health outcomes. Participants also reported that they added less salt while cooking and at the table. In the current study, responses to questions on salt behaviours did not differ between participants across median UIC categories, nor according to 24-hr UIE. This could mean that the questions are not sufficiently sensitive to discern between salt intake behaviours, or that the contribution of discretionary salt to total iodine intake is influenced by other food sources of iodised salt.

A strength of the study was use of the gold standard method for assessment of salt intake, namely 24hr urinary collections. Limitations relate to the high number of respondents with missing or incomplete urine samples. The difficulty in obtaining complete 24-hour urine

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samples is well-known, and the comparison between the main study cohort and those providing complete samples shows that men, and those with higher education less frequently provided complete 24-hour urine. This may also reflect the nature of the survey as fieldworkers visited the respondent's homes and those that were away with work were less likely to have taken part or would have potentially had more difficulty with the urine collection, creating a selection bias in the data towards the population with lower employment levels. Future research may consider work-based data collection. A further limitation is the lack of dietary data on sources of iodine provided by foods other than iodised salt. Iodine-rich dietary sources include fish and seafood, and dairy products and it is possible that some of these foods may also be high in salt, as in the case of salted dried fish commonly consumed by the coloured population (known as "*bokkems*"). However, generally these foods are not major contributors to sodium in the South African diet[16]. Interestingly, in women, both UIC and UIE correlated positively with body mass index, independently of salt intake. Looking at changes in food consumption patterns in South Africa over time, it seems that there is not only an increase in processed foods but also other foods that may contribute to iodine intake independently of iodized salt such as fish, eggs, seafood, and dairy foods[34]. The contribution of food sources, other than iodized salt, to total iodine intake warrants further investigation in the context of evaluating the universal salt iodization programme in South Africa. Furthermore, this study presents limited data for women of child bearing age and no data for children. Further work is needed to determine if there is an impact of the sodium reduction legislation in these particularly iodine-sensitive groups.

Conclusion

This study highlights the need to closely monitor the iodine status of populations as they undergo population-level reductions in salt intake, in countries where universal salt iodisation is implemented. If salt intake levels drop to the WHO target of <5g/day, there may be a need to increase the level of iodine in fortified table salt. Alternatively, compulsory iodisation of salt used in the production of some staple foods such as bread may be considered. In a country where some sectors of the population may be over-iodised, this strategy would require careful dietary modelling before being pursued. It is recommended that surveys that measure urinary Na excretion also simultaneously measure urinary iodine concentration.

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Authorship: Authors' contributions were as follows – KC, PK, NN designed research; LJW implemented research; JB analysed iodine samples; MC, LJW, KC analysed data; KC, LJW, JB, AES, MC, PK, wrote the paper; KC takes responsibility for the contents of this article. All authors read and approved the final manuscript.

Data sharing statement: The dataset is available on request and will form part of the data catalogue of the World Health Organization Study on Global AGEing and Adult Health (SAGE) (http://apps.who.int/healthinfo/systems/surveydata/index.php/catalog/sage/about)

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Table 1. Characteristics of the main (SAGE South Africa Wave 2, 2015) and subsample study cohort.

	Main SAGE cohort n=2887		Subsample[a] n=875		p value
	median	IQR	median	IQR	
Female, n (%)	1939	67	671	77	<0.001
Age years	57	46, 69	55	44, 67	0.468
Aged over 50 years, n (%)	1979	69	567	65	0.171
Ethnicity, n (%)					
Black	1988	69	410	74	<0.001
Coloured, mixed race	465	16	96	17	
Indian	306	11	41	7	
White	128	1	11	2	
Rural, n (%)	792	28	163	29	0.418
Education years	10	7, 13	9	6, 12	0.028
Never been to school, n (%)	495	18	109	20	0.180
Never had paid employment, n (%)	1101	55	238	56	0.403
BMI, kg/m^2	28.8	23.9, 33.7	29.1	24.0, 34.2	0.540
Waist to height ratio	0.59	0.52, 0.67	0.58	0.50, 0.66	0.070
Never used alcohol, n (%)	1576	80	353	83	0.052
Never used tobacco, n (%)	1635	83	367	86	0.023
Systolic BP mmHg	131	118, 144	128	116, 141	0.073
Diastolic BP mmHg	81	73, 89	79	71, 87	0.029
Hypertension, n (%)	1233	45	232	43	0.239
Diabetes, n (%)	248	13	46	11	0.355

BMI, body mass index. [a]Subsample: all respondents with spot UIC, valid 24-hour urine, sex and age recorded. Some variables may contain missing data as indicated by percentages. Data shown as median and interquartile range (IQR; 25th, 75th percentile) unless otherwise indicated. Hypertensive by measured BP≥140 and/or 90mmHg or previous diagnosis. Education, tobacco/alcohol use, ethnicity, employment and diabetes prevalence by self-report. Continuous variables compared using Independent Samples Mann-Whitney U test, categorical variables compared using Pearson Chi-Square and Fisher's Exact Test.

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Table 2. Spearman's rank order and partial correlations between salt, body size and urine iodine concentration (UIC), SAGE South Africa Wave 2 (2015).

		All	Men	Women
Correlations with spot UIC µg/l				
Salt intake g/day	*rho*	0.172(***)	0.201(**)	0.156(***)
	p	0.000	0.002	0.000
	n	879	203	671
24-hr iodine µg/day	*rho*	0.469(***)	0.510(***)	0.456(***)
	p	0.000	0.000	0.000
	n	871	203	663
BMI kg/m^2	*r*	0.038	0.004	0.097(*)
	p	0.207	0.484	0.034
	n	461	109	350
Weight kg	*r*	0.041	0.016	0.058
	p	0.184	0.433	0.133
	n	482	112	368
Waist circumference cm	*r*	0.019	0.032	0.034
	p	0.339	0.369	0.260
	n	477	111	364
Hip circumference cm	*r*	0.065	0.203(*)	0.046
	p	0.078	0.015	0.187
	n	481	112	367
Correlations with 24-hr UIE µg/d				
Salt intake g/day	*rho*	0.533(***)	0.467(***)	0.546(***)
	p	0.000	0.000	0.000
	n	872	202	665
BMI kg/m^2	*r*	0.079(*)	0.051	0.137(**)
	p	0.046	0.299	0.005
	n	460	109	349
Weight kg	*r*	0.090(*)	-0.015	0.132(**)
	p	0.024	0.436	0.006
	n	481	112	367
Waist circumference cm	*r*	0.035	-0.004	0.064
	p	0.226	0.484	0.111
	n	476	111	363
Hip circumference cm	*r*	0.070	0.083	0.097(*)
	p	0.062	0.191	0.031
	n	479	112	365

BMI, body mass index; UIC, spot urine iodine concentration; UIE, 24-hour urine iodine excretion. Correlations between iodine and body size controlled for salt intake. Correlation is significant at the 0.05 level (*); at the 0.01 level (**); or at the 0.001 level (***).

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Table 3. Urinary iodine and sodium excretion by salt and iodine categories

	24-hour urinary sodium excretion								
	All n=874[a]		Salt <5g/d n=307		Salt 5-9g/d n=322		Salt >9g/d n=245		p value
	median	IQR	median	IQR	median	IQR	median	IQR	
Sodium mg/day	2471	1434, 3506	1393	1068, 1719	2638	2219, 3057	4799	3607, 5993	<0.001
Salt g/day	6.3	3.7, 9.0	3.6	2.8, 4.5	6.8	5.7, 7.9	12.3	9.3, 15.4	<0.001
UIC µg/l	130	58, 202	102	32, 172	131	56, 206	149	78, 220	<0.001
UIC µg/g creatinine	102	48, 157	95	41, 150	105	48, 163	109	58, 161	0.076
24hr UIE µg/day	117	48, 186	74	37, 111	119	57, 181	195	117, 273	<0.001
	Spot urine iodine concentration (UIC)								
	All n=874[a]		UIC <100 µg/l n=343		UIC 100-299 µg/l n=408		UIC >300 µg/l n=107		p value
	median	IQR	median	IQR	median	IQR	median	IQR	
Sodium mg/day	2471	1434, 3506	2102	1144, 3061	2703	1547, 3860	2855	1811, 3899	<0.001
Salt g/day	6.3	3.7, 9.0	5.4	2.9, 7.9	6.9	4.0, 9.9	7.3	4.7, 10.0	<0.001
UIC µg/l	130	58, 202	55	37, 73	169	132, 206	400	332, 469	<0.001
UIC µg/g creatinine	102	48, 157	63	37, 89	119	72, 166	247	169, 325	<0.001
24hr UIE µg/day	117	48, 186	78	38, 119	134	69, 199	240	148, 332	<0.001

UIC, spot urine iodine concentration; UIE, 24-hour urine iodine excretion. [a]One individual in subsample with missing 24-hour sodium analysis. Data shown as median and interquartile range (IQR; 25th, 75th percentile). Continuous variables compared using Independent Samples Kruskal-Wallis test.

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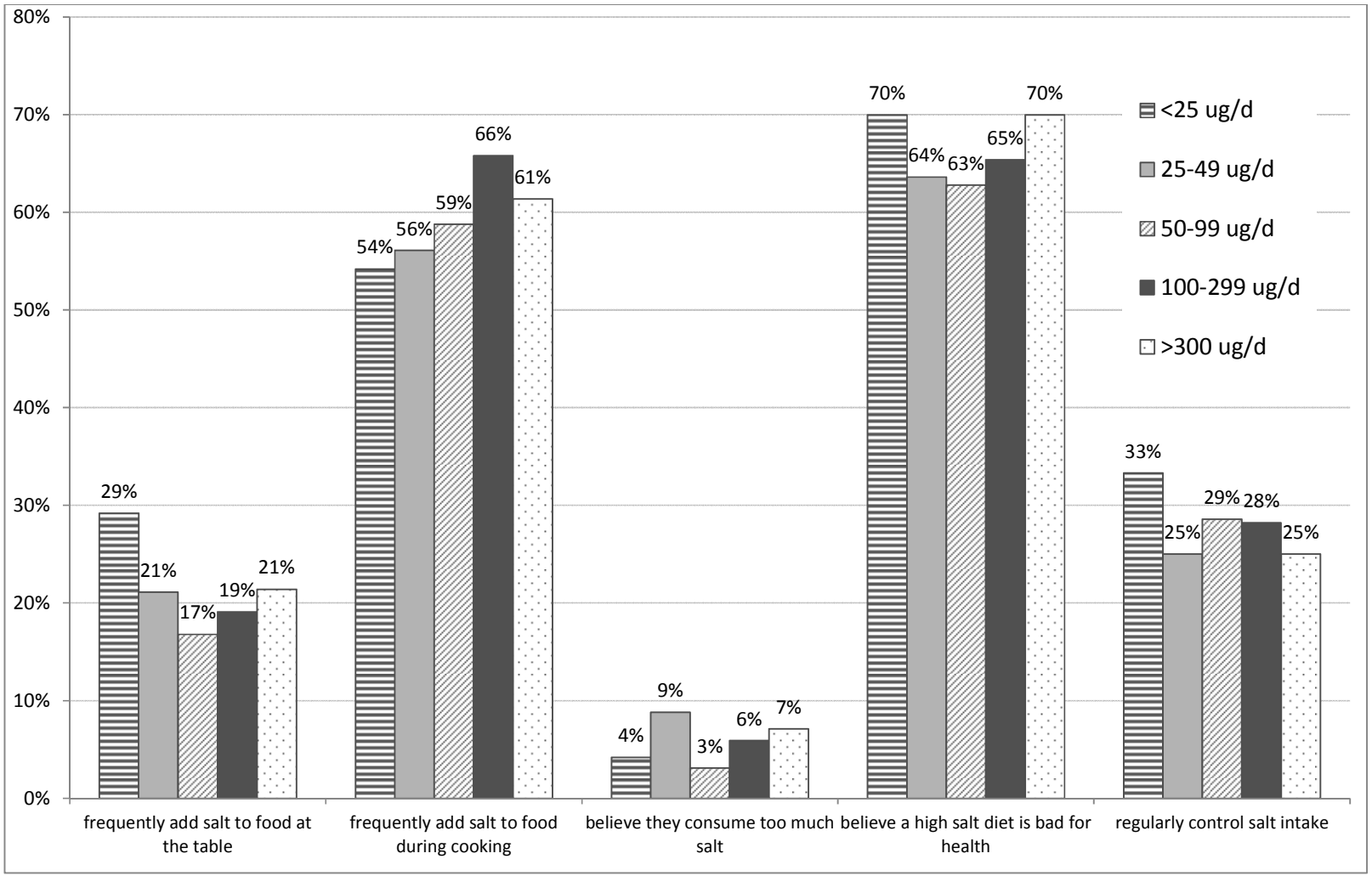
Figure 1. Self-reported salt knowledge, attitudes and behaviour by 24-hour urinary iodine excretion (UIE; n=539)



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	none
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7
		(b) Give reasons for non-participation at each stage	6-7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, p 14
		(b) Indicate number of participants with missing data for each variable of interest	Table 1, p 14
Outcome data	15*	Report numbers of outcome events or summary measures	Table 3, p 16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	none
		(*b*) Report category boundaries when continuous variables were categorized	7-8; Table 3, p 16; Figure 1, p 17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	none
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10; Table 1, p 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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How will South Africa's mandatory salt reduction policy affect its salt iodisation programme? A cross-sectional analysis from the WHO-SAGE Wave 2 Salt & Tobacco study

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How will South Africa's mandatory salt reduction policy affect its salt iodisation programme? A cross-sectional analysis from WHO-SAGE Wave 2 Salt & Tobacco study

Short title: Salt reduction and table salt iodisation

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Abstract

Objective: The World Health Organization's (WHO) global targets for non-communicable disease (NCD) reduction recommend consumption of <5g salt/day. In 2016, South Africa was the first country to legislate maximum salt levels in processed foods. South Africa's salt iodization fortification programme has successfully eradicated iodine deficiency. Simultaneous monitoring of sodium reduction and iodine status is required to ensure compatibility of the two public health interventions.

Design/setting/participants: A nested cohort design within WHO's 2015 Study on global AGEing and adult health (SAGE, n=2887) including individuals from households across South Africa. Randomly selected adults (n=875) provided 24-hour and spot urine samples for sodium and iodine concentration analysis (the primary and secondary outcome measures respectively). Median 24-hour iodine excretion (UIE) and spot urinary iodine concentrations (UIC) were compared by salt intakes <5g/day, 5 – 9 g/day and ≥9g/day.

Results: Median daily sodium excretion was equivalent to 6.3g salt/day (range 1-43 g/day); 35% had urinary sodium excretion values within the desirable range (< 5g salt/day), 37% had high values (5 – 9 g salt/day) and 28% had very high values (≥ 9g salt/day). Median UIC was 130 µg/L (IQR=58-202), indicating population iodine sufficiency (≥100 µg/L). Both UIC and UIE differed across salt intake categories ($p<0.001$) and were positively correlated with 24h urinary sodium ($r= 0.170$ and 0.528 respectively; both $p<0.001$). Participants with salt intakes <5g/day were not meeting the EAR for iodine intake (95 µg/day).

Conclusions: In a nationally representative sample of South African adults, the association between indicators of population iodine status (UIC and UIE) and urinary sodium excretion indicate that low salt intakes may compromise adequacy of iodine intakes in a country with mandatory iodisation of table salt. The iodine status of populations undergoing salt reduction strategies need to be closely monitored to prevent re-emergence of iodine deficiency.

Strengths and limitations of this study

- The study uses the current gold standard of 24-hour urine to assess sodium intake
- Timing of the study was immediately prior to legislation of maximum permitted salt levels in processed foods
- The large sample size includes coastal and inland populations from across the country
- Lack of dietary data precludes assessment of sources of iodine or sodium
- The data is only for adults and not children

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Keywords: iodine; sodium, dietary; policy; nutritional requirements; legislation, food

Introduction

Iodine deficiency remains the largest preventable cause of brain damage and mental impairment worldwide. Thyroid hormone production requires an adequate supply of iodine from the diet, and is essential to metabolism and growth across the lifecycle. As well as cretinism in its most severe form, iodine deficiency can also result in miscarriages, stillbirths, and impaired psychomotor development and behavioural problems in children born to iodine deficient mothers[1]. To prevent iodine deficiency disorders, the World Health Organization (WHO) has endorsed universal salt iodization (USI), where all salt for human and animal consumption is iodized[2,3]. USI is hailed as a public health success story, as 75% of the world's population was estimated in 2016 to use iodized salt in a total of 130 countries[4,5]. The 2016 global estimate of iodine nutrition, based on surveys of school-age children conducted between 2002 and 2016, shows that the iodine intake is insufficient in 15 countries, sufficient in 102, and excessive in 10 countries [6,7]. Among the 15 countries with insufficient intake, only two are classified as moderately deficient and 13 as mildly deficient. This represents a reduction in the number of countries with insufficient iodine intake, from 32 in 2011[8], to 25 countries in 2015[9], to 15 countries in 2016[6] which reflects continuing progress to improved coverage of iodized salt at the national level.[10]

In South Africa, mandatory iodization of table salt, at a level of 40 to 60 ppm, replaced voluntary iodization in December 1995, using potassium iodate as the fortificant[11] because of its stability in warm climates[12], rather than potassium iodide that is used in North America and Europe. The level of fortification was subsequently revised in 2007 to allow a wider range, namely 35 to 65 ppm[13]. The iodization program has effectively addressed iodine deficiency in the country, but there are some loopholes in the program, such as the domestic use of non-iodized agricultural salt in some regions[14,13]. In 2005, 78% of households nationwide purchased salt for household uses from typical food stores. At the same time, 8-37% of households across all the provinces of South Africa obtained salt for household use from "unconventional" channels such as agricultural and other sources of non-iodized salt. Under the legislation, salt used in the manufacturing of processed foods and salt packaged in bags of at least 20 kg are also exempted from mandatory iodization[11]. In 2005, 77% of households in the country used adequately iodized salt, described as salt containing more than

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15 ppm of iodine[13]. However, data on the iodine status of the South African population is outdated and a national survey was last conducted in 2005[14]. At that time, South African women and children aged 6 to 9 y old were found to have an optimal iodine status (i.e., MUIC 100–199 mg/L, <20% with UIC levels <50 mg/L)[15] which indicated a well-functioning salt iodization program[6,16].

At the same time as salt iodization efforts around the world are being celebrated, there is a global focus on salt reduction efforts to lower population level blood pressure. The World Health Organization (WHO) and World Health Assembly targets to reduce non communicable diseases (NCDs) include a 30% reduction in population salt intake by 2025[17] [18]. South Africa was the first country to implement mandatory legislation in July 2016 for maximum salt levels permitted in a wide range of processed foods[19] that are significant contributors to the sodium intake of the population[20-23]. The legislation is predicted to decrease population-level salt intake by 0.85 grams per day[24] and reduce annual deaths from cardiovascular diseases by 11%. This public health strategy is estimated to save the government US$51.25 million/year in health care costs; and save households more than US$4 million/year in out-of-pocket medical expenses[25].

Since salt is the vehicle for iodine fortification, successful campaigns to reduce salt intake would also likely result in reduced iodine intake[26]. Dietary modelling conducted in the Netherlands estimated the effect of 12%, 25%, and 50% decreases in salt from processed foods and table salt[26]. Only at a 50% salt decrease would iodine intake become inadequate for a small percentage of the population which, at that time, confirmed a lack of conflict between population-wide strategies of decreasing salt while ensuring adequate consumption of iodized salt to prevent iodine deficiency. We have previously reported no difference in median UIC across categories of sodium excretion equivalent to salt intakes lower than 5g/day, 5 - 9 g/day, and greater than or equal to 9 g/d in a convenience sample of 262 adult men and women in Cape Town in 2004[27]. It was concluded that this was because much of the dietary salt consumed was provided from non-iodinated sources, presumably in salt added to processed foods. Given the introduction of the salt reduction legislation, it is timeous to assess the iodine status of the South African population, according to salt intakes.

The aim of the current study was to simultaneously measure sodium (Na) and iodine in 24hr and spot urinary collections in an adult cohort to determine whether lower salt intakes are associated with a suboptimal iodine status.

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Methods

A nested observational study was conducted as part of Wave 2 of the World Health Organization Study on global AGEing and adult health (WHO SAGE). WHO-SAGE is a multinational cohort study examining the health and wellbeing of adult populations and the ageing process. Two waves of this longitudinal study have been completed in China, Ghana, India, Mexico, Russia and South Africa[28]. In total, 42,464 respondents were recruited across the six countries for Wave 1 (2007-2010), including 4223 respondents in South Africa (9% 18-49 years; 40% 50-59 years; 51% 60+ years). Respondents were recruited from selected probability sampled enumeration areas (EAs) using a multi-stage cluster sampling strategy, with stratification by province, residence and race. Urine capture was included as part of SAGE South Africa Wave 2 data collection. The sampling strategy was designed to account for attrition, where households were classified into the following mutually exclusive categories: 1) SAGE Wave 1 follow-up households with one or more members aged 50 years or more targeted for selection; 2) new households with one or more members aged 50 years or more; 3) SAGE Wave 1 follow-up households which include residents aged 18-49 targeted for selection; or, 4) new households which include residents aged 18-49. Further detail on the sampling and recruitment strategy can be found in the study protocol paper[29].

For Wave 2 data collection in 2015, twenty survey teams (one nurse and three interviewers per team) simultaneously collected data and samples from respondents across all provinces in the country over a five-month period. Respondents that were recruited to provide urine collections (n=1200) were sampled from among the first households visited within each EA, as a means to simplify logistics and reduce sample transit time to the central Durban laboratory.

Inclusion criteria for urine collection were: respondent must be part of the WHO SAGE cohort, with no indication of urinary incontinence or other condition that could impede 24-hour urine collection; and if female, not menstruating, pregnant, or breastfeeding on the day of collection.

Study Measures

All survey teams were trained with support from WHO Geneva. As part of the larger survey, anthropometry, household and individual questionnaires, blood sampling, blood pressure (BP) and physical function tests were completed as described previously in SAGE Wave 1[28].

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Interviewers spoke the respondents' home languages with consent forms available in the most widely spoken languages for each area. All respondents gave free and informed consent prior to taking part. The study complied with ethical principles[30] and all procedures involving human subjects were approved by the WHO Ethics Review Committee [RPC149], and North-West University and University of Witwatersrand research ethics committees in South Africa.

Urine collection

The protocol used for collection of 24-hour urine samples followed the WHO/PAHO guidelines[31]. Respondents were requested to collect all urine produced for 24 hours, excluding the first pass urine on day 1, but including the first urine of the following morning (day 2) in a 5-litre plastic container containing 1g thymol as preservative in South Africa. The spot sample was collected without preservative from the second urine passed on day 1 (marking the start of the 24-hour collection) and decanted into three 15 ml Porvair tubes (Porvair Sciences, Leatherhead, UK) then kept in a cool box powered by the fieldwork vehicles. The next morning, the 24-hour sample volumes were recorded and aliquots (4 x Porvair tubes) generated with all samples then shipped to the laboratory, maintaining the cold chain. Thymol, a crystalline natural derivative of the Thyme plant, was used as a preservative. Thymol has been shown to prevent changes in urinary creatinine, sodium and potassium concentrations for up to five days[32]. Incomplete 24-hour urine collections were assumed if: total volume ≤300ml; or creatinine excretion ≤4 mmol/day (women) or ≤6 mmol/day (men)[33].

Urine analysis

Sodium was determined using the indirect Ion Selective Electrode method and creatinine analysed using the standardised urinary Jaffe kinetic method (Beckman Coulter Synchron DXC600/800 System). The WHO population target for salt intake is 5g salt (NaCl) per day, equivalent to urinary sodium excretion 1950mg (or 85mmol)/24hr. Sodium (mmol/l) in the 24 h urine sample was converted to salt (g/d) using the formula: Na mmol/l * 24 h volume (litres) * 23.1 (molecular weight of sodium)/390 (390 mg sodium per 1 g sodium chloride (salt)).With the exception of iodine, all South African samples were analysed at a single laboratory in Durban, South Africa (Global Clinical and Viral Laboratories). Urine samples for iodine analysis were stored at -20° C and batch analysed using the Sandell-Kolthoff method with ammonium persulfate digestion and microplate reading[34] at the North-West

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University Centre of Excellence for Nutrition. The laboratory participates successfully in the Program to Ensure the Quality of Urinary Iodine Procedures (EQUIP, U.S. Centres for Disease Control and Prevention, Atlanta GA, USA)[35]. To convert urinary excretion values to estimated daily iodine intake (ug/day), UIE (ug/24hr) values were divided by 0.92 to account for the 92% bioavailability (approximately 8% of consumed dietary iodine consumption is absorbed). A median of <100µg iodine/L indicates population-level deficiency (there are no reference ranges for individuals)[36].

Data capture, analysis and statistical power

All data was captured using an electronic data capture system and uploaded to a secure central server for data cleaning and analysis. The nested cohort sample size for the primary outcome measure of 24-hour urine sodium was calculated as previously described.[29] Allowing for error in 24-hour sample collection (incomplete or missing samples) in this complex field study, a target sub-sample size of 1200 was randomly selected from the main SAGE-Wave 2 cohort, and those with incomplete or missing samples excluded from the analysis. The sample size used for this analysis was deemed adequate based on recommendations of WHO (2007) that states a sample size between 600 and 900 is sufficient to have a reasonable confidence interval around the coverage estimate for urinary iodine concentration[2]. More recently, Karmisholt (2014) recommends that 400 urine samples are required to determine the median UIC of a group with 5% precision[37].

Both spot urinary iodine analyses (UIC) and 24hr urinary iodine excretion (UIE) were compared across three categories of 24hr urinary Na values, equivalent to salt intakes <5g/day, 5 – 9 g/day and ≥9g/day. Normality of data was assessed by visual inspection of histograms and the Kolmogorov-Smirnov test. All non-parametric data were reported as median and interquartile range (IQR; 25th, 75th percentile) and continuous variables compared using independent Samples Mann-Whitney U test or Independent Samples Kruskal-Wallis test. Categorical variables were compared across groups using Pearson Chi-Square and Fisher's Exact Test. Data were also analysed according to urinary Na excretion values and by iodine category (sub-optimal: UIC <100 ug/L; iodine replete: 100 – 299 ug/L; and excessive: >300ug/L). To assess the association between salt intake, body size, UIC and UIE, Spearman's rank order and partial correlations were conducted.

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Results

Complete urinary Na and iodine data were available in n = 874 participants. Sociodemographic characteristics and health indicators of the sub-sample are compared to the total SAGE-Wave 2 cohort (n = 2887) in Table 1. The sub-sample had a higher proportion of women and more black/coloured respondents than the main cohort, which may explain differences in smoking, education and BP.

Median 24hr Na excretion (n=874) was equivalent to a median salt intake of 6.3gsalt/day (range 1-43 g/day); 35% had values within the desirable range (< 5g salt/day), 37% had high values (5 – 9 g salt/day) and 28% had very high values (≥ 9g salt/day). We have previously reported that median salt intakes are higher in younger than older (50+ y) adults in this cohort (8.6 g vs 6.1 g/day; p < 0.001), and in urban compared to rural dwellers (7.0 g vs 6.0 gday; p=0.033)[38] but further analysis of Na vs iodine excretion, by demographic breakdown is outside the scope of the current analysis. No significant difference in median UIE was found according to age category (18-49y; 50+y) or sex, however median UIE was significantly higher in urban compared to rural dwellers (128 (IQR147) vs 115 (IQR 119); p=0.041). No demographic differences were found for median UIC. In the total sample, median UIC (n=875) was 130 µg/L (IQR=58-202), indicating iodine sufficiency (≥100 µg/L) while median 24hr UIE (n=866) was 117 ug/day (IQR 138).

Both UIC and 24hr iodine excretion differed across urinary salt categories and were positively correlated with urinary Na (r= 0.172 and 0.533; both P<0.001) (Table 2). In the lowest salt category of <5g/d, median UIC indicated borderline deficiency of 102 µg/L (Table 3). According to median 24hr UIE values, the group of participants with a salt intake of <5g/day are not meeting their dietary n Estimated Average Requirement (EAR) of 95µg/day (IOM 2003).[39], with 58.4% having intakes below this value (Table 3). Responses to questions on salt behaviours did not differ between participants across median UIC categories (data not shown), nor according to UIE (Figure 1).

Discussion

Our study found that in a sample of South African adults, those with a salt intake within the WHO recommended range of less than 5g/day had urinary iodine excretion values indicative

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of suboptimal iodine intakes, whereas those with higher salt intakes were shown to have adequate intakes using 24hour urinary iodine excretion as a biomarker of intake. . Thus, there is a risk that sodium reduction strategies may impact adversely on iodine intakes and result in populations being at risk of inadequate iodine intakes unless fortificant levels of iodine in salt are revised accordingly.

This data was collected immediately prior to introduction of South Africa's mandatory salt reduction legislation, that requires food manufacturers to comply with maximum salt targets across a wide range of processed foods. The impact of the salt reduction policy on iodised salt intake is unknown. South Africa has had a well functioning table salt iodisation programme since 2005, but salt used in food processing is exempt from mandatory iodisation. Despite iodised salt not being required by law to be used as an ingredient in the manufacturing of processed foods, a study[40] that investigated the iodine content of salt used in bread, margarine, and salty snack flavourings in 2002 provided surprising results. Even though 11 of the 12 manufacturers surveyed at that time reported that they used non-iodized salt in their products, substantial amounts of iodine were found in the salt used by a third of these manufacturers' products, with a mean content of 39 to 69 ppm, and these were the items that were mostly distributed countrywide. An appreciable percentage of the food companies used iodized salt unknowingly in the manufacturing of frequently consumed processed foods, and this may have had a considerable impact on the daily iodine intake of consumers. To our knowledge, there is no updated information on the use of iodised salt by food manufacturers. Thus, it is feasible that the salt reduction legislation may also impact on contribution of iodine intake from iodised salt.

As well as changes to the food supply, nutrition education activities undertaken by the Department of Health and non-governmental organizations in South Africa aim to change consumer behaviour related to table salt use[41 42]. The timing of the WHO SAGE Salt & Tobacco sub-study in South Africa was planned to provide a baseline population salt intake[38] one year before mandatory salt legislation, in order for comparison in the same cohort one year after introduction of the legislation[29] in SAGE Wave 3.The data reported in this paper relate to the pre-salt reduction legislation baseline timepoint. Inclusion of iodine analyses in Wave 3 in 2018 will further allow evaluation of the compatibility of iodine fortification and salt reduction policies.

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Concerted efforts are being made in many countries to lower salt consumption[18]. Because the primary food vehicle for iodine fortification is salt, there is concern that decreasing salt consumption will increase the risk of iodine deficiency. Our study findings indicate that this is a potential public health problem. The findings of the current study are in contrast to previous findings from a sample of adult men and women surveyed in Cape Town in 2004, when UIC did not differ across categories of salt intake[21]. Reasons for this are unclear but may reflect an increased consumption of salt provided from non-iodised sources in processed foods, accompanied by a reduction in discretionary iodised salt intake, since 2004. However, data is not available to further postulate in this regard.

The South African strategic plan to reduce cardiovascular disease includes the target to reduce the population intake of salt to less than 5 grams/day. At present the salt intake is higher than this level, with older reports from the early 2000s estimating that 40% salt was provided from discretionary salt intake[22]. Our study was conducted immediately prior to introduction of the mandatory salt targets in processed foods. The salt intake estimations in the current study include both added (discretionary) and non-discretionary salt intakes but the lack of data on dietary intakes of the participants prevents further investigation of the source of the salt.

We hypothesize that food manufacturers may have already reduced salt content in processed foods at the time of the study (2015), and that some of these products may have been produced with iodized salt. If this is the case, this would result in lowered iodine intake at the same time as lowered salt intake, as would any reduction in discretionary salt use. Considering the latter, there have been many accompanying health education strategies that target salt reduction behaviours, alongside the salt legislation in processed foods[42]. In 2015, a mass media campaign (Saltwatch), using television, radio advertisement and other platforms for information dissemination was undertaken to increase public awareness related to the association between a high salt intake, blood pressure and cardiovascular disease in South Africa. The campaign, conducted by the Heart and Stroke Foundation of South Africa with funding from the Department of Health, focused on the need to reduce discretionary salt intake. Evaluation of the programme undertaken in 550 black women, aged 18-55 years in three provinces identified that there was an increase in most of the indicators of knowledge, attitudes and behaviour change towards considering and initiating reduced salt consumption following the campaign. Significant increases were found for knowledge items related to high salt intake and its health outcomes. Participants also reported that they added less salt while

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cooking and at the table. In the current study, responses to questions on salt behaviours did not differ between participants across median UIC categories, nor according to 24-hr UIE. This could mean that the questions are not sufficiently sensitive to discern between salt intake behaviours, or that the contribution of discretionary salt to total iodine intake is influenced by other food sources of iodised salt.

A strength of the current study was use of the gold standard method for assessment of salt intake, namely 24hr urinary collections. Limitations relate to the high number of respondents with missing or incomplete urine samples. The difficulty in obtaining complete 24-hour urine samples is well-known, and the comparison between the main study cohort and those providing complete samples shows that men, and those with higher education less frequently provided complete 24-hour urine. This may also reflect the nature of the survey as fieldworkers visited the respondent's homes and those that were away with work were less likely to have taken part or would have potentially had more difficulty with the urine collection, creating a selection bias in the data towards the population with lower employment levels. Future research may consider workplace-based data collection. An assumption was made regarding cut-off values for completeness of 24hr urine collection whereby urinary volume < 300ml/day or creatinine excretion ≤4 mmol/day (women) or ≤6 mmol/day (men)[33] were the criteria used for exclusion purposes. In populations with low protein intakes, daily creatinine excretion is more variable than in well nourished populations, and often lower than 1 g (8.84 mmol)per day.[43] A limitation of the study is that neither dietary protein intake, nor lean body mass was assessed which makes it difficult to account for these two confounding variables when deciding on how to interpret low urinary creatinine concentrations.

A further limitation is the lack of dietary data on sources of iodine provided by foods other than iodised salt. Iodine-rich dietary sources include fish and seafood, and dairy products and it is possible that some of these foods may also be high in salt, as in the case of salted dried fish commonly consumed by the coloured population (known as "*bokkems*"). However, generally these foods are not major contributors to sodium in the South African diet[22]. Interestingly, in women, both UIC and UIE correlated positively with body mass index, independently of salt intake. Looking at changes in food consumption patterns in South Africa over time, it seems that there is not only an increase in processed foods but also other foods that may contribute to iodine intake independently of iodized salt such as fish, eggs,

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seafood, and dairy foods[44]. The contribution of food sources, other than iodized salt, to total iodine intake warrants further investigation in the context of evaluating the mandatory salt iodization programme in South Africa. Furthermore, this study presents limited data for women of child bearing age and no data for children. Further work is needed to determine if there is an impact of the sodium reduction legislation in these particularly iodine-sensitive groups.

Conclusion

This study highlights the need to closely monitor the iodine status of populations as they undergo population-level reductions in salt intake, in countries where mandatory salt iodisation is implemented. If salt intake levels drop to the WHO target of <5g/day, there may be a need to increase the level of iodine in fortified table salt. Alternatively, compulsory iodisation of salt used in the production of some staple foods such as bread may be considered. In a country where some sectors of the population may be exposed to excessive iodine intakes, this strategy would require careful dietary modelling before being pursued. It is recommended that surveys that measure urinary Na excretion also simultaneously measure urinary iodine concentration and determine the iodine content in table salt collected from households.

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Data sharing statement: The dataset is available on request and will form part of the data catalogue of the World Health Organization Study on Global AGEing and Adult Health (SAGE) (http://apps.who.int/healthinfo/systems/surveydata/index.php/catalog/sage/about)

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Table 1. Characteristics of the main (SAGE South Africa Wave 2, 2015) and subsample study cohort.

	Main SAGE cohort n=2887		Subsample[a] n=875		p value
	median	IQR	median	IQR	
Female, n (%)	1939	67	671	77	<0.001
Age years	57	46, 69	55	44, 67	0.468
Aged over 50 years, n (%)	1979	69	567	65	0.171
Ethnicity, n (%)					
Black	1988	69	410	74	<0.001
Coloured, mixed race	465	16	96	17	
Indian	306	11	41	7	
White	128	4	11	2	
Rural, n (%)	792	28	163	29	0.418
Education years	10	7, 13	9	6, 12	0.028
Never been to school, n (%)	495	18	109	20	0.180
Never had paid employment, n (%)	1101	55	238	56	0.403
BMI, kg/m^2	28.8	23.9, 33.7	29.1	24.0, 34.2	0.540
Waist to height ratio	0.59	0.52, 0.67	0.58	0.50, 0.66	0.070
Never used alcohol, n (%)	1576	80	353	83	0.052
Never used tobacco, n (%)	1635	83	367	86	0.023
Systolic BP mmHg	131	118, 144	128	116, 141	0.073
Diastolic BP mmHg	81	73, 89	79	71, 87	0.029
Hypertension, n (%)	1233	45	232	43	0.239
Diabetes, n (%)	248	13	46	11	0.355

BMI, body mass index. [a]Subsample: all respondents with spot UIC, valid 24-hour urine, sex and age recorded. Some variables may contain missing data as indicated by percentages. Data shown as median and interquartile range (IQR; 25th, 75th percentile) unless otherwise indicated. Hypertensive by measured BP≥140 and/or 90mmHg or previous diagnosis. Education, tobacco/alcohol use, ethnicity, employment and diabetes prevalence by self-report. Continuous variables compared using Independent Samples Mann-Whitney U test, categorical variables compared using Pearson Chi-Square and Fisher's Exact Test.

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Table 2. Spearman's rank order and partial correlations between urine iodine concentration, salt, and body size SAGE South Africa Wave 2 (2015).

		All n=456	Men n=110	Women n=346
Correlations with spot UIC µg/l				
Salt intake g/day	*rho*	0.166(***)	0.164	0.153(**)
	p	0.000	0.088	0.004
24-hr iodine µg/day	*rho*	0.423(***)	0.483(***)	0.392(***)
	p	0.000	0.000	0.000
BMI kg/m^2	*r*	0.036	0.001	0.096
	p	0.448	0.988	0.076
Weight kg	*r*	0.043	0.035	0.056
	p	0.365	0.716	0.299
Waist circumference cm	*r*	0.001	0.027	0.008
	p	0.991	0.784	0.878
Hip circumference cm	*r*	0.040	0.213(*)	0.008
	p	0.389	0.026	0.883
Correlations with 24-hr UIE µg/d				
Salt intake g/day	*rho*	0.552(***)	0.504(***)	0.561(***)
	p	0.000	0.000	0.000
BMI kg/m^2	*r*	0.092	0.030	0.168(**)
	p	0.051	0.758	0.002
Weight kg	*r*	0.130(**)	-0.023	0.193(***)
	p	0.005	0.814	0.000
Waist circumference cm	*r*	0.032	-0.011	0.069
	p	0.491	0.911	0.200
Hip circumference cm	*r*	0.052	0.056	0.094
	p	0.269	0.563	0.080

BMI, body mass index; UIC, spot urine iodine concentration; UIE, 24-hour urine iodine excretion. Correlations between iodine and body size controlled for salt intake. Correlation is significant at the 0.05 level (*); at the 0.01 level (**); or at the 0.001 level (***).

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Table 3. Urinary iodine, estimated iodine intake and sodium excretion values by salt intake equivalent categories

	24-hour urinary sodium excretion								
	All n=874[a]		Salt <5g/d n=307		Salt 5-9g/d n=322		Salt >9g/d n=245		p value
	median	IQR	median	IQR	median	IQR	median	IQR	
Sodium mg/day	2471	1434, 3506	1393	1068, 1719	2638	2219, 3057	4799	3607, 5993	<0.001
Salt g/day	6.3	3.7, 9.0	3.6	2.8, 4.5	6.8	5.7, 7.9	12.3	9.3, 15.4	<0.001
UIC µg/l	130	58, 202	102	32, 172	131	56, 206	149	78, 220	<0.001
24hr UIE µg/day	117	48, 186	74	37, 111	119	57, 181	195	117, 273	<0.001
Estimated iodine intake µg/day	127	52, 202	80	40, 120	130	63, 197	212	127, 297	<0.001
% with daily iodine intake below EAR for iodine (95 µg/day)†	37.1%		58.4%		34.7%		13.5%		

UIC, spot urine iodine concentration; UIE, 24-hour urine iodine excretion. [a]One individual in subsample with missing 24-hour sodium analysis. Data shown as median and interquartile range (IQR; 25th, 75th percentile). Continuous variables compared using Independent Samples Kruskal-Wallis test.

† Daily iodine intake assumed as 24hr UIE (µg/day)/0.92 to account for bioavailability

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Figure Legend: Self-reported salt knowledge, attitudes and behaviour by 24-hour urinary iodine excretion (UIE; n=539)

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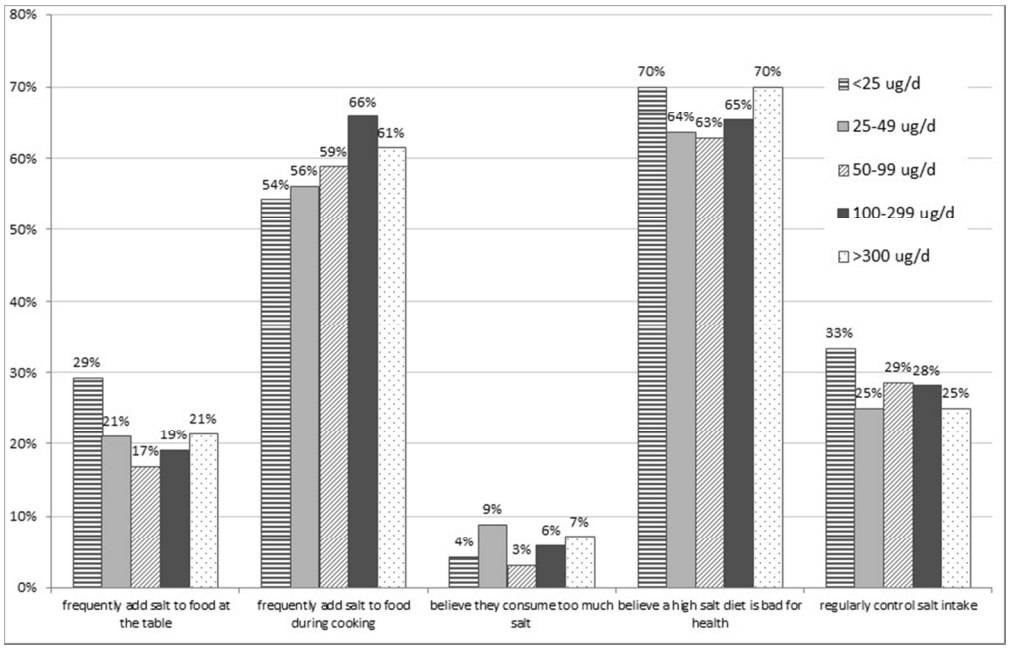

Figure 1. Self-reported salt knowledge, attitudes and behaviour by 24-hour urinary iodine excretion (UIE; n=539)

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	none
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7
		(b) Give reasons for non-participation at each stage	6-7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, p 14
		(b) Indicate number of participants with missing data for each variable of interest	Table 1, p 14
Outcome data	15*	Report numbers of outcome events or summary measures	Table 3, p 16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	none
		(*b*) Report category boundaries when continuous variables were categorized	7-8; Table 3, p 16; Figure 1, p 17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	none
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10; Table 1, p 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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How will South Africa's mandatory salt reduction policy affect its salt iodisation programme? A cross-sectional analysis from the WHO-SAGE Wave 2 Salt & Tobacco study

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How will South Africa's mandatory salt reduction policy affect its salt iodisation programme? A cross-sectional analysis from the WHO-SAGE Wave 2 Salt & Tobacco study

Short title: Salt reduction and table salt iodisation

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Abstract

Objective: The World Health Organization's (WHO) global targets for non-communicable disease (NCD) reduction recommend consumption of <5g salt/day. In 2016, South Africa was the first country to legislate maximum salt levels in processed foods. South Africa's salt iodization fortification programme has successfully addressed iodine deficiency but information is dated.. Simultaneous monitoring of sodium reduction and iodine status is required to ensure compatibility of the two public health interventions.

Design/setting/participants: A nested cohort design within WHO's 2015 Study on global AGEing and adult health (SAGE, n=2887) including individuals from households across South Africa. Randomly selected adults (n=875) provided 24-hour and spot urine samples for sodium and iodine concentration analysis (the primary and secondary outcome measures respectively). Median 24-hour iodine excretion (UIE) and spot urinary iodine concentrations (UIC) were compared by salt intakes <5g/day, 5 – 9 g/day and ≥9g/day.

Results: Median daily sodium excretion was equivalent to 6.3g salt/day (range 1-43 g/day); 35% had urinary sodium excretion values within the desirable range (< 5g salt/day), 37% had high values (5 – 9 g salt/day) and 28% had very high values (≥ 9g salt/day). Median UIC was 130 µg/L (IQR=58-202), indicating population iodine sufficiency (≥100 µg/L). Both UIC and UIE differed across salt intake categories ($p<0.001$) and were positively correlated with estimated salt intake ($r= 0.166$ and 0.552 respectively; both $p<0.001$). Participants with salt intakes <5g/day were not meeting the EAR for iodine intake (95 µg/day).

Conclusions: In a nationally representative sample of South African adults, the association between indicators of population iodine status (UIC and UIE) and salt intake, estimated using 24hr urinary sodium excretion, indicate that low salt intakes may compromise adequacy of iodine intakes in a country with mandatory iodisation of table salt. The iodine status of populations undergoing salt reduction strategies need to be closely monitored to prevent re-emergence of iodine deficiency.

Strengths and limitations of this study

- The study uses the current gold standard of 24-hour urine to assess sodium intake
- Timing of the study was immediately prior to legislation of maximum permitted salt levels in processed foods

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- The large sample size includes coastal and inland populations from across the country
- Lack of dietary data precludes assessment of sources of iodine or sodium
- The data is only for adults and not children

Keywords: iodine; sodium, dietary; policy; nutritional requirements; legislation, food

Introduction

Iodine deficiency remains the largest preventable cause of brain damage and mental impairment worldwide. Thyroid hormone production requires an adequate supply of iodine from the diet, and is essential to metabolism and growth across the lifecycle. As well as cretinism in its most severe form, iodine deficiency can also result in miscarriages, stillbirths, and impaired psychomotor development and behavioural problems in children born to iodine deficient mothers[1]. To prevent iodine deficiency disorders, the World Health Organization (WHO) has endorsed universal salt iodization (USI), where all salt for human and animal consumption is iodized[2,3]. USI is hailed as a public health success story, as 75% of the world's population was estimated in 2016 to use iodized salt in a total of 130 countries[4,5]. The 2016 global estimate of iodine nutrition, based on surveys of school-age children conducted between 2002 and 2016, shows that the iodine intake is insufficient in 15 countries, sufficient in 102, and excessive in 10 countries [6,7]. Among the 15 countries with insufficient intake, only two are classified as moderately deficient and 13 as mildly deficient. This represents a reduction in the number of countries with insufficient iodine intake, from 32 in 2011[8], to 25 countries in 2015[9], to 15 countries in 2016[6] which reflects continuing progress to improved coverage of iodized salt at the national level.[10]

In South Africa, mandatory iodization of table salt, at a level of 40 to 60 ppm, replaced voluntary iodization in December 1995, using potassium iodate as the fortificant[11] because of its stability in warm climates[12], rather than potassium iodide that is used in North America and Europe. The level of fortification was subsequently revised in 2007 to allow a wider range, namely 35 to 65 ppm[13]. The iodization program has effectively addressed iodine deficiency in the country, but there are some loopholes in the program, such as the domestic use of non-iodized agricultural salt in some regions[14,13]. In 2005, 78% of households nationwide purchased salt for household uses from typical food stores. At the same time, 8-37% of households across all the provinces of South Africa obtained salt for household use

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from "unconventional" channels such as agricultural and other sources of non-iodized salt. Under the legislation, salt used in the manufacturing of processed foods and salt packaged in bags of at least 20 kg are also exempted from mandatory iodization[11]. In 2005, 77% of households in the country used adequately iodized salt, described as salt containing more than 15 ppm of iodine[13]. However, data on the iodine status of the South African population is outdated and a national survey was last conducted in 2005[14]. At that time, South African women and children aged 6 to 9 y old were found to have an optimal iodine status (i.e., MUIC 100–199 mg/L, <20% with UIC levels <50 mg/L)[15] which indicated a well-functioning salt iodization program[6,16].

At the same time as salt iodization efforts around the world are being celebrated, there is a global focus on salt reduction efforts to lower population level blood pressure. The World Health Organization (WHO) and World Health Assembly targets to reduce non communicable diseases (NCDs) include a 30% reduction in population salt intake by 2025[17] [18]. South Africa was the first country to implement mandatory legislation in July 2016 for maximum salt levels permitted in a wide range of processed foods[19] that are significant contributors to the sodium intake of the population[20-23]. The legislation is predicted to decrease population-level salt intake by 0.85 grams per day[24] and reduce annual deaths from cardiovascular diseases by 11%. This public health strategy is estimated to save the government US$51.25 million/year in health care costs; and save households more than US$4 million/year in out-of-pocket medical expenses[25].

Since salt is the vehicle for iodine fortification, successful campaigns to reduce salt intake would also likely result in reduced iodine intake[26]. Dietary modelling conducted in the Netherlands estimated the effect of 12%, 25%, and 50% decreases in salt from processed foods and table salt[26]. Only at a 50% salt decrease would iodine intake become inadequate for a small percentage of the population which, at that time, confirmed a lack of conflict between population-wide strategies of decreasing salt while ensuring adequate consumption of iodized salt to prevent iodine deficiency. We have previously reported no difference in median UIC across categories of sodium excretion equivalent to salt intakes lower than 5g/day, 5 - 9 g/day, and greater than or equal to 9 g/d in a convenience sample of 262 adult men and women in Cape Town in 2004[27]. It was concluded that this was because much of the dietary salt consumed was provided from non-iodinated sources, presumably in salt added to processed foods. Given the introduction of the salt reduction legislation, it is timeous to assess the iodine status of the South African population, according to salt intakes.

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The aim of the current study was to simultaneously measure sodium (Na) and iodine in 24hr and spot urinary collections in an adult cohort to determine whether lower salt intakes are associated with a suboptimal iodine status.

Methods

A nested observational study was conducted as part of Wave 2 of the World Health Organization Study on global AGEing and adult health (WHO SAGE). WHO-SAGE is a multinational cohort study examining the health and wellbeing of adult populations and the ageing process. Two waves of this longitudinal study have been completed in China, Ghana, India, Mexico, Russia and South Africa[28]. In total, 42,464 respondents were recruited across the six countries for Wave 1 (2007-2010), including 4223 respondents in South Africa (9% 18-49 years; 40% 50-59 years; 51% 60+ years). Respondents were recruited from selected probability sampled enumeration areas (EAs) using a multi-stage cluster sampling strategy, with stratification by province, residence and race. Urine capture was included as part of SAGE South Africa Wave 2 data collection. The sampling strategy was designed to account for attrition, where households were classified into the following mutually exclusive categories: 1) SAGE Wave 1 follow-up households with one or more members aged 50 years or more targeted for selection; 2) new households with one or more members aged 50 years or more; 3) SAGE Wave 1 follow-up households which include residents aged 18-49 targeted for selection; or, 4) new households which include residents aged 18-49. Further detail on the sampling and recruitment strategy can be found in the study protocol paper[29].

For Wave 2 data collection in 2015, twenty survey teams (one nurse and three interviewers per team) simultaneously collected data and samples from respondents across all provinces in the country over a five-month period. Respondents that were recruited to provide urine collections (n=1200) were sampled from among the first households visited within each EA, as a means to simplify logistics and reduce sample transit time to the central Durban laboratory.

Inclusion criteria for urine collection were: respondent must be part of the WHO SAGE cohort, with no indication of urinary incontinence or other condition that could impede 24-hour urine collection; and if female, not menstruating, pregnant, or breastfeeding on the day of collection.

Study Measures

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All survey teams were trained with support from WHO Geneva. As part of the larger survey, anthropometry, household and individual questionnaires, blood sampling, blood pressure (BP) and physical function tests were completed as described previously in SAGE Wave 1[28]. Interviewers spoke the respondents' home languages with consent forms available in the most widely spoken languages for each area. All respondents gave free and informed consent prior to taking part. The study complied with ethical principles[30] and all procedures involving human subjects were approved by the WHO Ethics Review Committee [RPC149], and North-West University and University of Witwatersrand research ethics committees in South Africa.

Urine collection

The protocol used for collection of 24-hour urine samples followed the WHO/PAHO guidelines[31]. Respondents were requested to collect all urine produced for 24 hours, excluding the first pass urine on day 1, but including the first urine of the following morning (day 2) in a 5-litre plastic container containing 1g thymol as preservative in South Africa. The spot sample was collected without preservative from the second urine passed on day 1 (marking the start of the 24-hour collection) and decanted into three 15 ml Porvair tubes (Porvair Sciences, Leatherhead, UK) then kept in a cool box powered by the fieldwork vehicles. The next morning, the 24-hour sample volumes were recorded and aliquots (4 x Porvair tubes) generated with all samples then shipped to the laboratory, maintaining the cold chain. Thymol, a crystalline natural derivative of the Thyme plant, was used as a preservative. Thymol has been shown to prevent changes in urinary creatinine, sodium and potassium concentrations for up to five days[32]. Incomplete 24-hour urine collections were assumed if: total volume ≤300ml; or creatinine excretion ≤4 mmol/day (women) or ≤6 mmol/day (men)[33].

Urine analysis

Sodium was determined using the indirect Ion Selective Electrode method and creatinine analysed using the standardised urinary Jaffe kinetic method (Beckman Coulter Synchron DXC600/800 System). The WHO population target for salt intake is 5g salt (NaCl) per day, equivalent to urinary sodium excretion 1950mg (or 85mmol)/24hr. Sodium (mmol/l) in the 24 h urine sample was converted to salt (g/d) using the formula: Na mmol/l * 24 h volume (litres) * 23.1 (molecular weight of sodium)/390 (390 mg sodium per 1 g sodium chloride (salt)).With the exception of iodine, all South African samples were analysed at a single

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laboratory in Durban, South Africa (Global Clinical and Viral Laboratories). Urine samples for iodine analysis were stored at -20° C and batch analysed using the Sandell-Kolthoff method with ammonium persulfate digestion and microplate reading[34] at the North-West University Centre of Excellence for Nutrition. The laboratory participates successfully in the Program to Ensure the Quality of Urinary Iodine Procedures (EQUIP, U.S. Centres for Disease Control and Prevention, Atlanta GA, USA)[35]. To convert urinary excretion values to estimated daily iodine intake (ug/day), UIE (ug/24hr) values were divided by 0.92, based on the assumption that approximately 92% of dietary iodine is excreted in urine. A median of <100µg iodine/L indicates population-level deficiency (there are no reference ranges for individuals)[36].

Data capture, analysis and statistical power

All data was captured using an electronic data capture system and uploaded to a secure central server for data cleaning and analysis. The nested cohort sample size for the primary outcome measure of 24-hour urine sodium was calculated as previously described.[29] Allowing for error in 24-hour sample collection (incomplete or missing samples) in this complex field study, a target sub-sample size of 1200 was randomly selected from the main SAGE-Wave 2 cohort, and those with incomplete or missing samples excluded from the analysis. The sample size used for this analysis was deemed adequate based on recommendations of WHO (2007) that states a sample size between 600 and 900 is sufficient to have a reasonable confidence interval around the coverage estimate for urinary iodine concentration[2]. More recently, Karmisholt (2014) recommends that 400 urine samples are required to determine the median UIC of a group with 5% precision[37].

Both spot urinary iodine analyses (UIC) and 24hr urinary iodine excretion (UIE) were compared across three categories of 24hr urinary Na values, equivalent to salt intakes <5g/day, 5 – 9 g/day and ≥9g/day. Normality of data was assessed by visual inspection of histograms and the Kolmogorov-Smirnov test. All non-parametric data were reported as median and interquartile range (IQR; 25th, 75th percentile) and continuous variables compared using independent Samples Mann-Whitney U test or Independent Samples Kruskal-Wallis test. Categorical variables were compared across groups using Pearson Chi-Square and Fisher's Exact Test. Data were also analysed according to urinary Na excretion values and by iodine category (sub-optimal: UIC <100 ug/L; iodine replete: 100 – 299 ug/L; and excessive:

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>300ug/L). To assess the association between salt intake, body size, UIC and UIE, Spearman's rank order and partial correlations were conducted.

Results

Complete urinary Na and iodine data were available in n = 874 participants. Sociodemographic characteristics and health indicators of the sub-sample are compared to the total SAGE-Wave 2 cohort (n = 2887) in Table 1 which included participants aged between 18 and 102y with a BMI of 13.5-69.9. The sub-sample had a higher proportion of women and more black/coloured respondents than the main cohort, which may explain differences in smoking, education and BP.

In the subsample that provided urine collections, median 24hr urine volume was 1385 (IQR 900, 2278) ml/day, with a range from 500 – 4900ml/day. Median urinary creatinine excretion was 1097 (IQR 790, 1682) mg/24hr, with a range from 460 – 6441 mg/24hr. Median 24hr Na excretion (n=874) was equivalent to a median salt intake of 6.3gsalt/day (range 1-43 g/day); 35% had values within the desirable range (< 5g salt/day), 37% had high values (5 – 9 g salt/day) and 28% had very high values (≥ 9g salt/day). We have previously reported that median salt intakes are higher in younger than older (50+ y) adults in this cohort (8.6 g vs 6.1 g/day; p < 0.001), and in urban compared to rural dwellers (7.0 g vs 6.0 gday; p=0.033)[38] but further analysis of Na vs iodine excretion, by demographic breakdown is outside the scope of the current analysis. No significant difference in median UIE was found according to age category (18-49y; 50+y) or sex, however median UIE was significantly higher in urban compared to rural dwellers (128 (IQR147) vs 115 (IQR 119); p=0.041). No demographic differences were found for median UIC. In the total sample, median UIC (n=875) was 130 µg/L (IQR=58-202), indicating iodine sufficiency (≥100 µg/L) while median 24hr UIE (n=866) was 117 ug/day (IQR 138).

Both UIC and 24hr iodine excretion differed across salt intake categories and were positively correlated with 24hr salt intake, estimated from urinary Na excretion (r= 0.166 and 0.552; both P<0.001) (Table 2). In the lowest salt category of <5g/d, median UIC indicated borderline deficiency of 102 µg/L (Table 3). According to median 24hr UIE values, the group of participants with a salt intake of <5g/day are not meeting their dietary Estimated Average Requirement (EAR) of 95µg/day (IOM 2003).[39], with 58.4% having intakes below

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this value (Table 3). Even in those with salt intakes in the moderately raised category of 5 – 9g/day, a considerable proportion (34.7%) had intakes below the EAR. Responses to questions on salt behaviours did not differ between participants across median UIC categories (data not shown), nor according to UIE (Figure 1).

Discussion

Our study found that in a sample of South African adults, those with a salt intake within the WHO recommended range of less than 5g/day had urinary iodine excretion values indicative of suboptimal iodine intakes, whereas those with higher salt intakes were shown to have adequate intakes using 24hour urinary iodine excretion as a biomarker of intake. . Thus, there is a risk that sodium reduction strategies may impact adversely on iodine intakes and result in populations being at risk of inadequate iodine intakes unless fortificant levels of iodine in salt are revised accordingly.

This data was collected immediately prior to introduction of South Africa's mandatory salt reduction legislation, that requires food manufacturers to comply with maximum salt targets across a wide range of processed foods. The impact of the salt reduction policy on iodised salt intake is unknown. South Africa has had a well functioning table salt iodisation programme since 2005, but salt used in food processing is exempt from mandatory iodisation. Despite iodised salt not being required by law to be used as an ingredient in the manufacturing of processed foods, a study[40] that investigated the iodine content of salt used in bread, margarine, and salty snack flavourings in 2002 provided surprising results. Even though 11 of the 12 manufacturers surveyed at that time reported that they used non-iodized salt in their processed foods, substantial amounts of iodine were found in the salt used by a third of these manufacturers' products, with a mean content of 39 to 69 ppm, and these were the items that were mostly distributed countrywide. An appreciable percentage of the food companies used iodized salt unknowingly in the manufacturing of frequently consumed processed foods, and this may have had a considerable impact on the daily iodine intake of consumers. To our knowledge, there is no updated information on the use of iodised salt in food processing by food manufacturers. Thus, it is feasible that the salt reduction legislation may also impact on contribution of iodine intake from iodised salt.

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As well as changes to the food supply, nutrition education activities undertaken by the Department of Health and non-governmental organizations in South Africa aim to change consumer behaviour related to table salt use[41 42]. The timing of the WHO SAGE Salt & Tobacco sub-study in South Africa was planned to provide a baseline population salt intake[38] one year before mandatory salt legislation, in order for comparison in the same cohort one year after introduction of the legislation[29] in SAGE Wave 3.The data reported in this paper relate to the pre-salt reduction legislation baseline timepoint. Inclusion of iodine analyses in Wave 3 in 2018 will further allow evaluation of the compatibility of iodine fortification and salt reduction policies.

Concerted efforts are being made in many countries to lower salt consumption[18]. Because the primary food vehicle for iodine fortification is salt, there is concern that decreasing salt consumption will increase the risk of iodine deficiency. Our study findings indicate that this is a potential public health problem. The findings of the current study are in contrast to previous findings from a sample of adult men and women surveyed in Cape Town in 2004, when UIC did not differ across categories of salt intake[21]. Reasons for this are unclear but may reflect an increased consumption of salt provided from non-iodised sources in processed foods, accompanied by a reduction in discretionary iodised salt intake, since 2004. However, data is not available to further postulate in this regard.

The South African strategic plan to reduce cardiovascular disease includes the target to reduce the population intake of salt to less than 5 grams/day. At present the salt intake is higher than this level, with older reports from the early 2000s estimating that 40% salt was provided from discretionary salt intake[22]. Our study was conducted immediately prior to introduction of the mandatory salt targets in processed foods. The salt intake estimations in the current study include both added (discretionary) and non-discretionary salt intakes but the lack of data on dietary intakes of the participants prevents further investigation of the source of the salt.

We hypothesize that food manufacturers may have already reduced salt content in processed foods at the time of the study (2015), and that some of these products may have been produced with iodized salt. If this is the case, this would result in lowered iodine intake at the same time as lowered salt intake, as would any reduction in discretionary salt use. Considering the latter, there have been many accompanying health education strategies that

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target salt reduction behaviours, alongside the salt legislation in processed foods[42]. In 2015, a mass media campaign (Saltwatch), using television, radio advertisement and other platforms for information dissemination was undertaken to increase public awareness related to the association between a high salt intake, blood pressure and cardiovascular disease in South Africa. The campaign, conducted by the Heart and Stroke Foundation of South Africa with funding from the Department of Health, focused on the need to reduce discretionary salt intake. Evaluation of the programme undertaken in 550 black women, aged 18-55 years in three provinces identified that there was an increase in most of the indicators of knowledge, attitudes and behaviour change towards considering and initiating reduced salt consumption following the campaign. Significant increases were found for knowledge items related to high salt intake and its health outcomes. Participants also reported that they added less salt while cooking and at the table. In the current study, responses to questions on salt behaviours did not differ between participants across median UIC categories, nor according to 24-hr UIE. This could mean that the questions are not sufficiently sensitive to discern between salt intake behaviours, or that the contribution of discretionary salt to total iodine intake is influenced by other food sources of iodised salt.

A strength of the current study was use of the gold standard method for assessment of salt intake, namely 24hr urinary collections. Limitations relate to the high number of respondents with missing or incomplete urine samples. The difficulty in obtaining complete 24-hour urine samples is well-known, and the comparison between the main study cohort and those providing complete samples shows that men, and those with higher education less frequently provided complete 24-hour urine. This may also reflect the nature of the survey as fieldworkers visited the respondent's homes and those that were away with work were less likely to have taken part or would have potentially had more difficulty with the urine collection, creating a selection bias in the data towards the population with lower employment levels. Future research may consider workplace-based data collection. An assumption was made regarding cut-off values for completeness of 24hr urine collection whereby urinary volume < 300ml/day or creatinine excretion ≤4 mmol/day (women) or ≤6 mmol/day (men)[33] were the criteria used for exclusion purposes. In populations with low protein intakes, daily creatinine excretion is more variable than in well nourished populations, and often lower than 1 g (8.84 mmol)per day.[43] A limitation of the study is that neither dietary protein intake, nor lean body mass was assessed which makes it difficult to account for these two confounding variables when deciding on how to interpret low urinary creatinine

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concentrations. It is possible that the use of higher creatinine excretion cut-off reference values as a measure of completeness of urine collection may have resulted in a somewhat lower number of subjects considered to be at risk of inadequate iodine nutrition, as well as a higher estimated salt intake.

A further limitation is the lack of dietary data on sources of iodine provided by foods other than iodised salt. Iodine-rich dietary sources include fish and seafood, and dairy products and it is possible that some of these foods may also be high in salt, as in the case of salted dried fish commonly consumed by the coloured population (known as "*bokkems*"). However, generally these foods are not major contributors to sodium in the South African diet[22]. Interestingly, in women, both UIC and UIE correlated positively with body mass index, independently of salt intake. Looking at changes in food consumption patterns in South Africa over time, it seems that there is not only an increase in processed foods but also other foods that may contribute to iodine intake independently of iodized salt such as fish, eggs, seafood, and dairy foods[44]. The contribution of food sources, other than iodized salt, to total iodine intake warrants further investigation in the context of evaluating the mandatory salt iodization programme in South Africa. Furthermore, this study presents limited data for women of child bearing age and no data for children. Further work is needed to determine if there is an impact of the sodium reduction legislation in these particularly iodine-sensitive groups.

Conclusion

This study highlights the need to closely monitor the iodine status of populations as they undergo population-level reductions in salt intake, in countries where mandatory salt iodisation is implemented. Even at salt intake levels currently above the WHO target of 5g/day, there was a considerable proportion with iodine intakes below the EAR. This indicates there may be a need to increase the level of iodine in fortified table salt. Alternatively, compulsory iodisation of salt used in the production of some staple foods such as bread may be considered. In a country where some sectors of the population may be exposed to excessive iodine intakes, this strategy would require careful dietary modelling before being pursued. It is recommended that surveys that measure urinary Na excretion also simultaneously measure urinary iodine concentration and determine the iodine content in table salt collected from households.

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Data sharing statement: The dataset is available on request and will form part of the data catalogue of the World Health Organization Study on Global AGEing and Adult Health (SAGE) (http://apps.who.int/healthinfo/systems/surveydata/index.php/catalog/sage/about)

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Table 1. Characteristics of the main (SAGE South Africa Wave 2, 2015) and subsample study cohort.

	Main SAGE cohort n=2887		Subsample[a] n=875		p value
	median	IQR	median	IQR	
Female, n (%)	1939	67	671	77	<0.001
Age years	57	46, 69	55	44, 67	0.468
Aged over 50 years, n (%)	1979	69	567	65	0.171
Ethnicity, n (%)					
Black	1988	69	410	74	<0.001
Coloured, mixed race	465	16	96	17	
Indian	306	11	41	7	
White	128	4	11	2	
Rural, n (%)	792	28	163	29	0.418
Education years	10	7, 13	9	6, 12	0.028
Never been to school, n (%)	495	18	109	20	0.180
Never had paid employment, n (%)	1101	55	238	56	0.403
BMI, kg/m^2	28.8	23.9, 33.7	29.1	24.0, 34.2	0.540
Waist to height ratio	0.59	0.52, 0.67	0.58	0.50, 0.66	0.070
Never used alcohol, n (%)	1576	80	353	83	0.052
Never used tobacco, n (%)	1635	83	367	86	0.023
Systolic BP mmHg	131	118, 144	128	116, 141	0.073
Diastolic BP mmHg	81	73, 89	79	71, 87	0.029
Hypertension, n (%)	1233	45	232	43	0.239
Diabetes, n (%)	248	13	46	11	0.355

BMI, body mass index. [a]Subsample: all respondents with spot UIC, valid 24-hour urine, sex and age recorded. Some variables may contain missing data as indicated by percentages. Data shown as median and interquartile range (IQR; 25th, 75th percentile) unless otherwise indicated. Hypertensive by measured BP≥140 and/or 90mmHg or previous diagnosis. Education, tobacco/alcohol use, ethnicity, employment and diabetes prevalence by self-

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report. Continuous variables compared using Independent Samples Mann-Whitney U test, categorical variables compared using Pearson Chi-Square and Fisher's Exact Test.

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Table 2. Spearman's rank order and partial correlations between urine iodine concentration, estimated salt intake, and body size SAGE South Africa Wave 2 (2015).

		All n=456	Men n=110	Women n=346
Correlations with spot UIC µg/l				
Salt intake g/day	*rho*	0.166(***)	0.164	0.153(**)
	p	0.000	0.088	0.004
24-hr iodine µg/day	*rho*	0.423(***)	0.483(***)	0.392(***)
	p	0.000	0.000	0.000
BMI kg/m^2	*r*	0.036	0.001	0.096
	p	0.448	0.988	0.076
Weight kg	*r*	0.043	0.035	0.056
	p	0.365	0.716	0.299
Waist circumference cm	*r*	0.001	0.027	0.008
	p	0.991	0.784	0.878
Hip circumference cm	*r*	0.040	0.213(*)	0.008
	p	0.389	0.026	0.883
Correlations with 24-hr UIE µg/d				
Salt intake g/day	*rho*	0.552(***)	0.504(***)	0.561(***)
	p	0.000	0.000	0.000
BMI kg/m^2	*r*	0.092	0.030	0.168(**)
	p	0.051	0.758	0.002
Weight kg	*r*	0.130(**)	-0.023	0.193(***)
	p	0.005	0.814	0.000
Waist circumference cm	*r*	0.032	-0.011	0.069
	p	0.491	0.911	0.200
Hip circumference cm	*r*	0.052	0.056	0.094
	p	0.269	0.563	0.080

BMI, body mass index; UIC, spot urine iodine concentration; UIE, 24-hour urine iodine excretion. Correlations between iodine and body size controlled for salt intake. Correlation is significant at the 0.05 level (*); at the 0.01 level (**); or at the 0.001 level (***).

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Table 3. Urinary iodine, estimated iodine intake and sodium excretion values by salt intake equivalent categories

	24-hour urinary sodium excretion								
	All n=874[a]		Salt <5g/d n=307		Salt 5-9g/d n=322		Salt >9g/d n=245		p value
	median	IQR	median	IQR	median	IQR	median	IQR	
Sodium mg/day	2471	1434, 3506	1393	1068, 1719	2638	2219, 3057	4799	3607, 5993	<0.001
Salt g/day	6.3	3.7, 9.0	3.6	2.8, 4.5	6.8	5.7, 7.9	12.3	9.3, 15.4	<0.001
UIC µg/l	130	58, 202	102	32, 172	131	56, 206	149	78, 220	<0.001
24hr UIE µg/day	117	48, 186	74	37, 111	119	57, 181	195	117, 273	<0.001
Estimated iodine intake µg/day	127	52, 202	80	40, 120	130	63, 197	212	127, 297	<0.001
% with daily iodine intake below EAR for iodine (95 µg/day)†	37.1%		58.4%		34.7%		13.5%		

UIC, spot urine iodine concentration; UIE, 24-hour urine iodine excretion. [a]One individual in subsample with missing 24-hour sodium analysis. Data shown as median and interquartile range (IQR; 25th, 75th percentile). Continuous variables compared using Independent Samples Kruskal-Wallis test.

† Daily iodine intake assumed as 24hr UIE (µg/day)/0.92 to account for bioavailability

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Figure Legend: Self-reported salt knowledge, attitudes and behaviour by 24-hour urinary iodine excretion (UIE; n=539)

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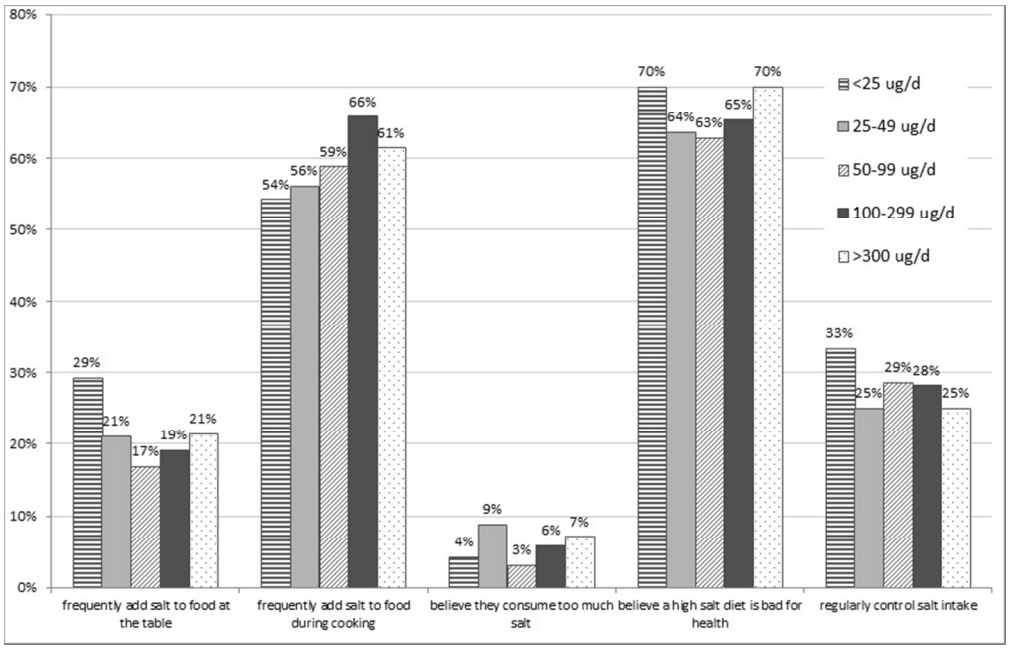

Figure 1. Self-reported salt knowledge, attitudes and behaviour by 24-hour urinary iodine excretion (UIE; n=539)

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	none
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7
		(b) Give reasons for non-participation at each stage	6-7
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, p 14
		(b) Indicate number of participants with missing data for each variable of interest	Table 1, p 14
Outcome data	15*	Report numbers of outcome events or summary measures	Table 3, p 16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	none
		(*b*) Report category boundaries when continuous variables were categorized	7-8; Table 3, p 16; Figure 1, p 17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	none
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10; Table 1, p 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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