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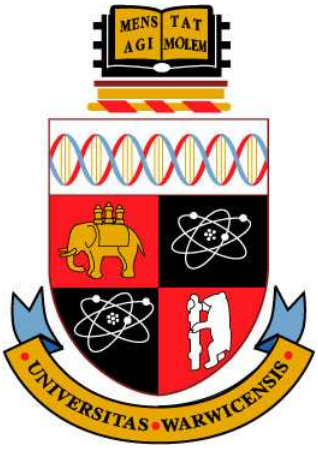

Salt Intake and Iodine Status around the World

by

Chen Ji

A thesis submitted in partial fulfilment of the requirements for the degree of
Doctor of Philosophy in Medicine

THE UNIVERSITY OF WARWICK

Warwick Medical School, February 2013

TABLE OF CONTENTS

List of Tables

List of Figures

Declaration

This thesis is submitted for the University of Warwick in support of my application for the degree of Doctor of Philosophy. I hereby declare that this thesis has not been submitted anywhere for any award and that it is my own work and effort unless otherwise stated. All the sources of information that have been used have been acknowledged by means of references.

In Chapter 3, Section 3.2 is the basis for the publication "Systematic Review of Studies Comparing 24-hour versus Spot Urine Collections for Estimating Population Salt Intake", which was published in the journal of Rev Panam Salud Publica. It was joint work with Lindsay Sykes, Christina Paul, Omar Dary, Branka Legetic, Norm R. C. Campbell, and Francesco P. Cappuccio. Data extraction was conducted jointly by me and Lindsay Sykes. I supported the analysis and drafted the manuscript. Section 3.3 is the basis for the paper "Comparisons of spot vs 24h urine samples for estimating salt intake: validation study in two independent population samples in Britain and Italy" (to be published). It was joint work with Michelle A. Miller, Antonella Venezia, Pasquale Strazzullo and Francesco P. Cappuccio. I carried out the analysis and drafted the manuscript. Section 3.4 is joint work with Lindsay Sykes, Christina Paul, Omar Dary, Branka Legetic, Norm R. C. Campbell, and Francesco P. Cappuccio. Data extraction was conducted jointly by me and Lindsay Sykes. I supported the analysis and drafted the manuscript.

Contents in Chapter 5, Section 5.4, were the basis for the publication "Spatial variation of salt intake in Britain and association with socio-economic status", which was published in the BMJ Open. This is joint work with Francesco P. Cappuccio and

Ngianga-Bakwin Kandala. The modelling, results, tables, and figures were all my work.

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Abbreviations

AHA	American Heart Association
AIC	Akaike information criterion
AMA	American Medical Association
ANOVA	Analysis of variance
BMI	Body mass index
BP	Blood pressure
CVD	Cardiovascular disease
CDC	Centers for Disease Control and Prevention
CI	Confidence intervals
CHD	Coronary heart disease
DIC	Deviance information criterion
DBP	Diastolic blood pressure
DBS	Dried whole blood spots
FDA	Food and Drug Administration
FSA	Food Standards Agency
GCE	General Certificate of Education
GCSE	General Certificate of Secondary Education
GP	General Practitioner
GAM	Generalised additive models
GLM	Generalised linear models
GOR	Government office region

g	gram
g/day	gram per day
GDP	Gross domestic product
GNI	Gross national income
GRF	Gaussian random fields
HCIS	Household coverage of iodised salt
HRP	Household reference person
IG	Inverse Gamma distribution
IoM	Institute of Medicine
ICCIDD	International Council for the Control of Iodine Deficiency Disorders
IQR	Interquartile range
IDD	Iodine deficiency disorders
JHS	Japanese Hypertension Society
µIU/mL	micro international units per millilitre
µg	microgram
µg/day	microgram per day
µg/L	microgram per litre
mg	milligram
mg/day	milligram per daymmol/day millimole per day
MAFF	Ministry of Agriculture Fisheries and Food
MEC	Mobile examination centers
MCMC	Monte Carlo Markov Chain
MRF	Markov random fields
NCHS	National Center for Health Statistics
NHLBI	National Heart, Lung, and Blood Institute

PAHO	Pan America Health Organization
PABA	Para-aminobenzoic acid
ppm	part per million
KIO_3	Potassium iodate
KI	Potassium iodide
PIR	Poverty income ratio
QALY	Quality-adjusted life years
ROC	Receiver operating characteristic
SAC	School-aged children
SES	Socioeconomic status
SSR	Standard statistical region
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
Tg	Thyroglobulin
TSH	Thyroid-stimulating hormone
TGR	Total goitre rate
UK	United Kingdom
UNICEF	United Nations Children's Fund
US	United States
USDA	United States Department of Agriculture
USI	Universal salt iodisation
UIC	Urinary iodine concentration
WASH	World Action on Salt and Health
WHA	World Health Assembly

WHO	World Health Organization

Abstract

Background: Salt reduction and universal salt iodisation programmes are implemented worldwide to prevent cardiovascular disease and iodine deficiency disorders, respectively. Concerns have been raised regarding the potential policy conflicts, and a programme coalition is proposed by the World Health Organization to optimise salt and iodine intakes at population level. This study aimed 1) to estimate population salt intake and iodine status in index countries; 2) to investigate the association between salt and iodine intakes; 3) to assess the impact of salt intake modification on iodine status; 4) to estimate the determinants of and potential geographical variation in salt and iodine intakes where data are available; and 5) to provide suggestions to policy makers.

Data and Methods: In the ecological analysis, national estimations of salt and iodine intakes were extracted from international organisation databases and published papers. Three case studies used population level data obtained from the Kumasi Salt Reduction Study in Ghana, the Third United States National Health and Nutrition Examination Survey (NHANES III) and the 2000-01 UK National Diet and Nutrition Survey 19-64 years (NDNS). Linear regression was used in the Kumasi analysis, and Bayesian geo-additive models were used in the other two analyses by accounting for the spatial effect and important linear and nonlinear risk factors.

Results: Salt intake varied between countries, with Kumasi lower than the western countries. Iodine status also varied by country, but with no consistent association with salt intake. A moderate salt reduction programme is unlikely to have a major

impact on iodine status in countries committed to universal salt iodisation, provided that iodine concentration is titrated to actual salt intake, maximum coverage is achieved as in China and iodised salt becomes part of food processing. At least in Britain, high salt intake is associated with low socioeconomic status, irrespective of geographic location.

Conclusions: Policy-makers may therefore need to adjust iodine content in salt in accordance with each country's context. The Bayesian geo-additive models are useful for monitoring and evaluating salt reduction and iodine supplementation.

Chapter 1 Introduction and Objectives

1.1 Introduction

Salt is commonly consumed worldwide. The biological need for salt is about 1.2 g per day (equivalent to 500 mg sodium per day). However, almost everyone eats more salt than needed (1). High level of salt intake is associated with raised BP, or hypertension (2-6), which is a major risk factor of non-communicable diseases, such as heart disease, stroke, and kidney disease. In particular, about 62% and 49% of stroke and coronary heart disease (CHD) deaths are attributable to raised BP (4). Hypertension is the leading cause of mortality and health burden worldwide (7;8). It is estimated that one in four adults will be hypertensive by 2025 (9). Globally, an estimated 7 million deaths are attributable to hypertension every year (10). In addition, high salt intake is associated with increasing risk of cardiovascular disease (CVD) (11-13). A higher daily salt intake by 5 grams (g) in populations is associated with a significant 17% increase in CVD risk (14).

Therefore, reducing salt intake in the general population has become the primary strategy for the prevention of hypertension and CVD. The World Health Organization (WHO) recommends a daily salt intake of less than 5 g per day (g/day) in the general population (4). Different targets are set for different countries (15). For example, Singapore aims to reduce population salt intake to 5 g/day, France and Switzerland set target at 8 g/day, and in Belgium and Argentina, 6 g/day of salt intake is recommended. Although the United States recommended a salt intake of

5.75 g/day, the American Heart Association (AHA) suggests a greater reduction to 3.8 g/day (16).

Salt is also used as a major vehicle for the fortification of iodine. Iodine is an essential trace element for brain development. Iodine deficiency is the single most common cause of preventable cognitive impairment worldwide. There are nearly 2 billion people from 148 countries at risk of iodine deficiency, including 241 million school-aged children (17). Insufficient iodine intake causes a wide range of serious consequences including endemic goitre, hypothyroidism, cretinism and congenital anomalies, known as iodine deficiency disorders (IDD).

Increasing iodine intake can effectively prevent the risk of IDD in the general population. Salt is the most cost-effective vehicle of the available iodine fortification options (18). It only costs a person US$0.02-0.09 a year to obtain sufficient iodine (19). Universal salt iodisation (USI) has been adopted by many WHO Member States and 71% of the world's population is now covered by iodised salt (20). The USI programme requires all food-grade salt to be adequately iodised (≥15 parts per million, or ppm). The median urinary iodine concentration (UIC) of the general population in the range of 100-199 micrograms per litre (µg/L) is considered to be the optimal iodine status. Thus the WHO recommends an iodine level of 20-40 ppm in salt at production stage to provide 150 micrograms per day (µg/day) of iodine in the diet (21;22). This recommendation is made upon the assumptions of an average salt intake of 10 g/day in adults and 40% loss of iodine during production, transportation and cooking. Since the establishment of the programme worldwide, the household coverage of iodised salt (HCIS) has increased more than 3 fold in 10 years (23) and billions of people are now protected against the risk of IDD.

However, salt reduction and salt iodisation programmes may conflict with each other. On the one hand, salt reduction benefits the prevention of hypertension and CVD but may jeopardise the iodine supplementation in the general population due to the potential restriction on the availability of iodine. On the other hand, it is possible for people to increase iodine intake by increasing salt intake. Thus any salt reduction programme could be compromised. Concerns regarding the conflicts between two health programmes have been raised recently (24;25) and there are suggestions for the coordination of programmes (25-27) by policy adaptation to avoid conflicts and confusions and to keep the sustainability of the programmes to improve the public health.

Gaps of knowledge in the programme coalition have been identified (25;26). The recommendation that current iodine fortification level needs to be reviewed and possibly adjusted is given to all health authorities and policy-makers. However, the existing scientific evidence is not sufficient to answer how much the impact of salt intake modification is, although some studies have demonstrated that reduction in salt intake to some extent can affect the population iodine status (28;29).

In addition, the assumption of 10 g/day salt intake in adults may not be tenable due to the variation of salt intake. Salt intake varies considerably across populations and geographical locations worldwide (21;22). Elliot and colleagues (30) reported an obvious heterogeneity of salt intake in the world: <0.1-12 g/day in 52 populations from 32 countries. Different levels of salt intake were observed even in different regions within the same country (30).

Furthermore, individuals and households usually obtain foods and salt from the stores and markets around them. They who live close to each other tend to have high similarity in dietary habit. These geographical characteristics could be summarised as a geographical network of salt intake. The network, as well as other factors, may lead to a within-country spatial variation of the salt and iodine intakes. Therefore, investigation into the possible variation of salt intake may help policy-makers to adapt their health strategies in the programme coalition.

What is more, the monitoring on both iodine status and salt reduction needs to be enhanced and regulations should be carried out strictly in the coalition. For instance, the non-iodised black market salt in some areas reduces coverage of adequately iodised salt, increasing the geographical disparity of the iodine consumption and further devitalising the effectiveness of the USI programme. Therefore more efforts into the monitoring of the current salt iodisation strategy are needed.

This study is expected to assist policy-makers in the coordination of salt reduction and salt iodisation programmes and help all stakeholders bridge the knowledge gap of optimising the population iodine and salt intakes. Accordingly, policy-makers can adjust their health intervention strategies, if necessary, to improve the coordination and effectiveness of two health programmes in order to protect the general population against risks of IDD and CVD.

As iodine and salt intakes are largely determined by dietary habit, it is reasonable to consider the effects of some known socioeconomic, lifestyle and demographic risk factors. However, some unobserved risk factors may also be associated with iodine status and salt intake. As there is no evidence to identify these risk factors, their

effects are hidden and only reflected in residual variance. Moreover, these unobserved factors may be geographically correlated (i.e. spatially dependent). Neglecting the potential spatial dependence may result in biased estimation and misleading conclusions. The effect of geographical location can be regarded as a surrogate of these factors. Therefore, it should be investigated in order to account for the hidden effects.

The effects of geographical location and several socioeconomic and demographic risk factors will be modelled in a Bayesian geo-additive models framework where data allow. Compared to the conventional regression models, this recently developed class of models is more flexible in estimating spatial effect as well as accounting for both linear and nonlinear effects.

1.2 Definitions

This thesis refers to salt as sodium chloride (1 g sodium chloride=17.1 millimolar (mmol) sodium or 393.4 milligrams (mg) of sodium) (4;30).

In addition, this thesis refers to iodine intake as mass amount of iodine. The unit is microgram (µg).

1.3 Objectives

The objectives of this study are

1) to estimate population salt intake and iodine status in three different countries and use the estimations to examine the validity of the assumed average population salt intake;

2) to investigate the association between salt and iodine intakes in different countries and compare the associations in countries with different settings and policies on salt reduction and salt iodisation;

3) to assess the impact of salt intake modification on iodine status under different circumstances of salt reduction and salt iodisation policies;

4) to estimate the determinants of and potential geographical variation in salt and iodine intakes where data are available; and

5) to provide suggestions to stakeholders, particularly policy-makers, to help the programme coordination of salt reduction and iodine supplementation in each country and improve WHO policy adaptation.

1.3.1 Outline of Thesis

This thesis is arranged in the following structure: **Chapter 2** provides a literature review of elimination of iodine deficiency and salt reduction in the world. Chapter 3 further discusses the reliability and accuracy of nutrient intake measurements, through reviews that compare population salt and iodine intakes estimated by 24-hour urine collection and spot urine sample methods. Salt intakes estimated by two popular spot urine methods and 24-hour urine collection were compared to examine the reliability and reproducibility of the spot urine methods. **Chapter 4** explains the

Bayesian geo-additive models in details. **Chapter 5** has four sections. The first section presents the results of an ecological correlation analysis of salt intake and iodine status worldwide. The following three sections present results of the analyses based on one population data and two population-wide surveys: the Kumasi Salt Reduction Study, the Third United States National Health and Nutrition Examination Survey (NHANES III) and the 2000-01 UK National Diet and Nutrition Survey 19-64 years (NDNS). The survey data from the US and the UK are nationally representative while the Kumasi study is a regional sample (Ashanti Region) of Ghanaian population. Results of the Kumasi and the US analyses are used to answer the questions of interest as both countries have implemented salt iodisation programmes, although salt iodisation in the US is on a voluntary basis. The UK data is used as a reference to illustrate the effect of iodine supplementation through other dietary vehicles. This may encourage governments and international organisations to invest more scientific and political efforts in integrating different iodine fortification approaches to optimise both salt reduction and USI programmes. **Chapter 6** discusses the association between iodine intake and salt intake on the basis of results obtained in Chapter 5, estimates the impact of salt reduction on current iodine fortification worldwide and gives an overall discussion on other major findings of this study. Suggestions are expected to be derived from these findings for the current WHO iodine supplementation and salt reduction policies to improve the coalition of the salt reduction and USI programmes and reduce the health threat imposed by iodine deficiency disorders and the diseases associated with high salt intake. This thesis then ends with brief conclusions in **Chapter 7**.

1.4 Summary of Chapter 1

Chapter 1 briefly introduces the background and motivations of this study. This thesis aims to provide evidence and support to the optimisation of population iodine and salt intakes by assessing salt intake and iodine status in different populations, estimating their determinants, investigating their association, and evaluating the effect of salt intake modification on iodine status. The structure of this thesis was also illustrated in this chapter.

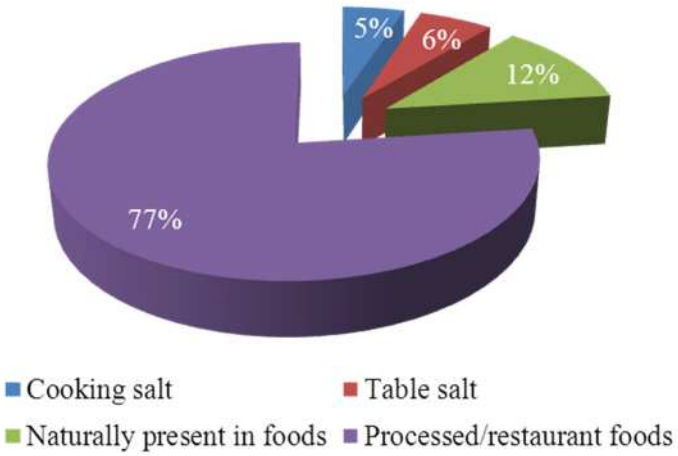
Chapter 2 Literature Review

2.1 Salt Intake: An Introduction

Dietary salt is commonly consumed in almost every household throughout the year. It contains approximately 40% sodium and 60% chloride. That is, 1 g salt≈400 mg or 17.1 mmol sodium. Our body's physiological need for sodium is 0.6-1.2 g/day salt (equivalent to 10-20 mmol/day or 240-480 mg/day sodium). Most people eat salt well above the physiological need and the average daily consumption of salt varies hugely from location to location (e.g. 9-12 g/day in the UK, 7.5-12 g/day in the US, 15 g/day in Tianjin, China (30)), with some exceptions (e.g. <0.1 g/day in the Yanomamo Indians in Brazil (30)).

Different sources of salt are available in our daily diet. In many industrialised countries, processed foods are the major salt contributor. For example, in the United States, 77% of the consumed salt is hidden in processed and restaurant foods while only 11% is added in cooking and on the table (Figure 2.1) (31). However, in other countries, the major contributor of salt is cooking salt and seasonings (4). In China and Brazil, at least 70% of dietary salt is added in home cooking or at the table (30;32;33). In Japan, the largest salt contributor is soy source (20% of total salt intake) (32).

Figure 2.1 *Salt sources in the United States*



Note: Percentages were quoted from Mattes and Donnelly (31).

2.2 Salt, Blood Pressure, and Cardiovascular Disease

Sodium is essential to cell function and the maintenance of fluid and electrolyte balance in the body. However, high level of sodium consumption contributes to raised BP, defined as systolic/diastolic blood pressure (SBP/DBP) ≥140/90 millimetres of mercury (mmHg). Increased level of sodium causes the body to retain water. This imposes more pressure on the blood vessel walls, which constricts increasing pressure and flow, leaving the vessel smaller and at the same time compressing the space for blood. A direct consequence is the elevation of arterial BP.

Salt and blood pressure

The scientific evidence that supports the association between salt intake and BP is compelling. A wide range of scientific studies provide conclusive evidence of the association between levels of sodium consumption and levels of BP (11-13;34), including animal studies, randomised clinical trials, and population studies.

Animal studies

Animal studies suggested that high salt intake is a causal factor of raised BP in humans. Denton *et al.* (35) examined the effect of salt on BP in chimpanzees (sharing 99% of DNA with human beings) for three years. Twenty six chimpanzees were included in the study. Half of them were randomly allocated into an experimental group with a high salt diet. The control and experimental groups were age and sex matched. The salt intake in the experimental group was increased to 5, 10 and 15 g/day progressively in 20 months, while the control group maintained the normal diet with an average salt intake of 0.6 g/day. Consequently, significant increases in SBP and DBP were observed in the experimental group but not in the control group.

Elliot *et al.* (36) further investigated the impacts of more modest modifications of salt intake on BP in two colonies of chimpanzees. In the Gabon colony, 17 chimps were given a diet with changed salt intake from 4.4 g/day to 2 g/day and then to 7 g/day (equivalent to 75, 35 and 120 mmol/day of sodium intake) for 3 years. In the Bastrop colony, 110 chimps were randomly allocated into two groups: 50 in an intervention group and 60 in a control group. Both groups were given a standard diet with a salt intake of 14.6 g/day (250 mmol/day of sodium) for 2 years. In the following 2 years the intervention group was given a diet with halved salt intake, while the control group maintained the standard diet. The results appeared to be different in the two colonies. In Gabon, changes of salt intake were significantly associated with changes in SBP and DBP, with or without adjustment for age, sex, and baseline weight. A reduction in salt intake by 6 g/day (100 mmol/day in sodium)

was significantly associated with a reduction of 12.7/7.5 mmHg in SBP/DBP. In Bastrop, both groups experienced reduced BP. The group differences of reductions in BP were significant without age, sex and weight adjustment. However, after taking into account the effect of age, sex and weight, the differences became non-significant.

Clinical trials

More than 50 clinical trials have been conducted on the role of salt reduction in reducing BP. One large trial was the DASH (Dietary Approaches to Stop Hypertension) Sodium trial. It was a multicentre randomised clinical trial conducted in 412 US participants. They were randomly allocated to either a DASH diet or a control diet. The DASH diet was rich in fruits, vegetables, and low-fat dairy foods. The control diet contained the typical foods that were commonly consumed in the US population. During the trial, high, intermediate and low levels of sodium intake (142, 107 and 65 mmol/day, or approximately 8.3, 6.3 and 3.8 g/day of salt intake, respectively) were randomly assigned to participants in both diets (37). Each lasted 30 days. A sodium reduction from high to low level in the control diet was associated with a reduction in BP by 8.3/4.4 mmHg in hypertensives and 5.6/2.8 mmHg in normotensives. Furthermore, the reduction was increased to 11.5/5.7 mmHg in SBP/DBP in hypertensives and 7.1/3.7 mmHg in normotensives with the combination of the DASH diet (38). This association was consistent across all ethnic and age groups and in both genders (39). However, the question remains regarding the contribution of other dietary nutrients to the decrease in BP. The findings might also be only applicable in the US adult population.

Meta-analyses of randomised clinical trials further suggested the effect of salt reduction on lowering BP (40-43). He and MacGregor (2) evaluated the effect of a modest salt reduction on BP in their recent review of 28 randomised controlled trials, which includes 11 trials in normotensives (n=2,220 subjects) and 17 in hypertensives (n=734). A dose-dependent relationship was identified, suggesting that a reduction in daily sodium intake of 100 mmol (approximately 6 g of salt) results in a significant drop of 7.1/3.9 mmHg in SBP/DBP. Cutler, Follmann and Allender (5) conducted a similar investigation of the effect of moderate salt reduction in 2,635 subjects from 32 trials with salt reduction duration from 2 weeks to 36 months. A dose dependency was also found between sodium intake and BP. A reduction of 100 mmol in sodium intake significantly lowers BP by 5.8/2.5 and 2.3/1.4 mmHg in SBP/DBP in hypertensive and normotensive subjects, respectively. Graudal *et al.* (44) tested the association of short-term salt reduction on BP in 2,161 hypertensive participants from 58 trials and in 2,581 normotensive participants from 56 trials. The salt reduction duration was 28 and 8 days for hyper- and normo-tensives, respectively. In the hypertensives, an unweighted reduction in sodium intake by 129 mmol/day (approximately 7.5 g/day in salt) was associated with a decrease in SBP/DBP by 4.5/2.3 mmHg. In the normotensives, an unweighted reduction in sodium intake by 165 mmol/day (approximately 9.6 g/day in salt) corresponded to a fall in SBP/DBP by 1.6/0.4 mmHg. However, the effect of short-term large salt reduction may not be sufficient to imply the benefit of long-term gradual salt reduction to the public health.

Graudal *et al.* in their updated meta-analysis of 167 studies suggested an inconsistent effect of salt reduction between hypertensive and normotensive participants across ethnic groups (45). The average salt reduction was approximately 7.3 g/day in the

hypertensives for 28 days and 8.8 g/day in the normotensives for 7 days. The reductions were associated with a significant fall in SBP/DBP in the white, black and Asian hypertensives, but the changes of BP of the black and Asian normotensives were not consistent. The findings arguably suggested that the short-term reduction in salt intake might have deleterious effects on health. However, the analysis was widely criticised for the small number of studies in the blacks and Asians and the large salt reduction in a short duration (46).

In contrast, the findings of the trials of hypertension prevention phase I (TOHP I) and phase II (TOHP II) supported the long term effect of salt reduction on BP. Respectively, 744 and 2,382 normotensive participants aged 30-54 were randomised to a low salt intake group or a control group. TOHP I lasted 18 months and TOHP II lasted 36 to 48 months. In TOHP I, a reduction of sodium intake by 44 mmol/day (approximately 2.6 g salt per day) was associated with a significant fall of 1.7/0.9 mmHg in SBP/DBP (47). In TOHP II, sodium intake was reduced by 50 and 40 mmo/day (approximately 2.9 and 2.3 g salt per day, respectively) at 6 and 36 months, respectively (48). Correspondently, BP was lowered by 2.9/1.6 and 1.2/0.7 mmHg at 6 and 3 months, respectively. The studies also suggested that a diet with higher potassium and lower sodium intake would be more effective in reducing BP.

He and MacGregor (49) conducted another meta-analysis in the children and adolescents population by including 10 trials with 966 subjects aged 8-16 years. A pooled analysis of 9 trials with urinary sodium measurement (biomarker of sodium consumption) indicated that a median of 42% reduction in salt intake significantly

reduces SBP/DBP by 1.2/1.3 mmHg. In the same study, a median of 54% reduction in salt intake in infants contributes to a 2.5 mmHg drop in SBP.

Finally, a recent systematic review and multiple meta-analyses of all randomised clinical trials of moderate salt reduction in adults and children has unequivocally confirmed the consistent, significant and dose-dependent beneficial effects on BP without evidence of harm in relation to cardiovascular biomarkers (43)

Population studies

Population based studies suggest positive associations between salt intake and BP. The INTERSALT study was conducted using data collected from 10,079 subjects aged 20-59 years coming from 52 populations around the world (50). The within- and cross-centre associations between salt intake (measured by 24-hour urinary sodium excretion) and BP were both examined. The within-centre association was significant and positive, while the cross-centre association appeared to be non-significant after excluding 4 populations with low sodium intakes.

In a revisit analysis of the INTERSALT study, Elliot and co-workers (6) suggested that an increase of 100 mmol/day urinary sodium excretion (approximately 6 g of salt per day) was associated with a median of 5-7/2-4 mmHg higher SBP/DBP, with greater association in older populations.

Another study conducted in two matched villages (intervention and control) in Portugal further suggested the effect of salt reduction on population BP (51). Both villages had about 800 adult residents and the mean salt intake was around 21 g/day (360 mmol sodium per day) before the intervention. The intervention village had half

the level of salt intake than the control group during the two years of the study. Mean BP in the intervention village fell significantly by 3.6/5.0 mmHg after one year and by 5.0/5.1 mmHg after two years, while in the control village DBP remained unchanged and SBP increased.

Takahashi and co-workers (52) assessed the effect of salt reduction on BP in a study in north-eastern Japan. The study was carried out to compare the BP between two villages (n=550, aged 40-69 years) after a one-year dietary education programme in the intervention village. The intervention village achieved a reduction of 15 mmol/day in sodium intake after the education. Meanwhile the control village had 11 mmol/day higher sodium intake. Correspondingly, SBP was significantly reduced by 2.7 mmHg in the intervention village, and remained at the same level in the control village. Another study in the Ashanti region of Ghana, also achieved a similar conclusion by means of a 6-month health education programme (53).

Salt and cardiovascular disease

Hypertension is the leading global risk factor of mortality and burden of disease (8), accounting for more than 7 million deaths every year (10). Prolonged raised BP causes damage to heart, brain, kidney and other organs, giving rise to increased risk of chronic diseases, such as CVD, stroke, and kidney stones, at population level. It is suggested that suboptimal BP (SBP >115 mmHg) contributes to 62% of stroke and 49% of CHD worldwide (54). A high level of salt intake is associated with increased risk of chronic diseases (4). Strazzullo *et al*. (14) included 17 studies with 19 cohort samples (n=177,836, aged 25-79 years) in a systematic review. High salt intake was significantly related to an increased risk of stroke. A revised pooled estimate implied

that the risk of CVD is more likely to be higher in populations with a high salt intake (relative risk: 1.17 with 95% confidence intervals: (1.02, 1.34), p=0.02). Evidence from cohort studies is however considered a lower quality evidence due to several methodological issues, like risk of reverse causality, systematic error in the assessment of sodium intake with current methods, residual confounding, loss to follow up, high random error in sodium intake and inadequate statistical power (43). Therefore, their findings should be carefully reviewed when guiding policy.

Reducing salt intake lowers BP, reduces risk of CVD and eventually alleviates the health burden in the world. Cook *et al.* (13) examined the association between long-term salt reduction and risk of CVD using TOHP 10-15 years follow-up data obtained from more than 2,000 participants. The participants with reduced sodium intake had up to 30% lower risk of CVD than those in the control group. It is estimated that a population-wide reduction of 3 g/day in salt intake would lead to a drop of 2.5/1.4 mmHg in SBP/DBP, in which could lead to a fall of 12-14% in stroke and 9-10% in CHD (55). Accordingly, in the United Kingdom (UK), for example, 6,500-8,000 stroke deaths and 7,500-12,000 CHD deaths could be prevented annually, based on the total number of 43,539 deaths in stroke and 74,185 deaths in CHD every year (15;56).

Nationwide campaigns of salt reduction have achieved great success in terms of lowering BP and reducing CVD risk. In 1957 in Japan, stroke mortality was among the highest in the world (57). A national salt reduction campaign led by the Japanese government was implemented in the 1950s. Population salt intake was reduced 1.4 g/day (from 13.5 to 12.1 g/day) on average in 10 years (58). The northern regions

achieved a larger reduction (4 g/day). During the same period, BP levels in the population were also lowered and the stroke mortality fell by 80% (58). In Finland, the SBP/DBP level of the general population was successfully lowered by more than 10 mmHg through a one-third reduction in salt intake from the 1970s, leading to a fall of 75% to 80% in both stroke and CHD mortality and an increase in life expectancy of 5-6 years (59).

2.3 Salt Reduction in the World

The WHO recommends that the average population salt intake be <5 g/day (4). The High Level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases in 2011 endorsed the implementation of salt reduction in foods to treat and prevent non-communicable diseases (60). In the 65th World Health Assembly (WHA) in 2012 all WHO Member States continued to support the adoption of the WHO recommendation of salt reduction, setting a target of a 30% reduction in salt intake by 2025 as a contribution of the overall target of a 25% reduction in NCD by 2025 (“25 by 25”) (61). Cappuccio and colleagues (62) reported that 41 countries worldwide had established initiatives for salt reduction, with the majority in Europe (66%) and the rest in the Americas (17%) and the West Pacific region (17%).

In Europe, a framework for national salt initiatives was developed in 2008, which was endorsed by many member states. By 2012, 11 countries had a target of a reduction at least 16% in salt intake in 4 years compared to the 2008 levels (63). Actions will be taken to reduce salt content in at least 5 of 12 food categories.

Particularly, more efforts have been made on salt reduction in the UK. In 2003, the Food Standards Agency (FSA) has set an overall target for the UK population to reduce salt intake to 6 g/day by 2012, with various lower limits for children. The government has also set voluntary salt reduction targets in 80 categories of foods, and are in close partnership with the food industry to reformulate food products to reduce salt content. On-going public awareness campaigns enhance salt reduction in the general population. Together, these efforts have reduced the salt intake of the UK population by 0.9 g salt to 8.6 g/day from 2001 to 2008 (64), and further to 8.1 g/day in 2011 in England (65).

Finland started their salt reduction programme in the late 1970s. Health education of salt reduction was promoted through mass media campaigns. Collaboration with the food industry improved the effectiveness of voluntary salt reduction and clear labelling in processed foods. Regular monitoring also ensured sustained success in this programme (62). The average population salt intake was accordingly reduced by 25% (from 12 g/day to 9 g/day) (66).

In 2009 the Pan American Health Organization (PAHO) embraced the WHO salt reduction target (67). A regional task force will be established and efforts will be made on seeking scientific support and enhancing collaboration between governments. Many PAHO Member States have taken actions on salt reduction. For example, Canada has set a target of reducing average population salt intake to 5.75 g/day (2,300 mg of sodium per day) by 2016 and to 3.8 g/day (1,500 mg of sodium per day) in the long-term (68). Argentina and Brazil have also set a target of 6 and 5 g/day, respectively (62). In the United States, current guidelines recommend the

general population an intake of salt less than 5.75 g/day (2,300 mg sodium per day) (69). The American Heart Association (AHA) suggested an ambitious target in 2006 to restrict the sodium in processed and restaurant foods by 50% and cut the sodium intake to 1,500 mg/day (about 3.8 g salt per day) in next 10 years (16).

In Asia and Australasia, some countries have identified the need for salt reduction (4;70), but few countries have set up population salt reduction targets (15). However, the awareness of salt reduction is rising. Consultations on salt reduction are to be held to develop salt reduction strategies in the region (71).

The Japanese government started salt reduction in the 1950s by means of long-term nationwide health education programmes. The Japanese Hypertension Society (JHS) recently revised recommendation of salt intake from 7 g/day to 6 g/day. As a result of the long-term nationwide efforts, the average salt intake in the Japan population was continuously reduced from 14.5 g/day in 1973 (72) to 11.1 g/day in 2007 (73).

In Africa, however, only Nigeria and South Africa have guidelines for salt intake (70). Reliable data are needed for baseline measurement.

2.4 Economic Imperative of Salt Reduction

Population-wide salt reduction is cost-effective to reduce BP and prevent chronic diseases (4). A voluntary reduction in salt intake by 15% is estimated to have averted 8.5 million deaths over 10 years and only cost less than US$0.1 per person per year (74). It is estimated, by means of a computer-simulation model based on the U.S. population aged 35 years and over, that a reduction of 3 g per day in salt intake leads

to a potential annual saving of 194,000 to 392,000 quality-adjusted life years (QALY) and $10 billion to $24 billion in healthcare costs (75). What is more, the effect of this amount of salt reduction is equivalent to those of halving tobacco use, reducing BMI in obese adults by 5%, or using statins in the population with low or intermediate CHD risk (75). Given the same reduction level, 14,000 to 20,000 CVD deaths can be averted annually in the UK (76), which translates into a gaining of 130,000 QALYs and a saving of £350 million in healthcare costs (56). Even a small cut of 1 g/day in salt intake (approximately 400 mg/day in sodium intake) in the uncontrolled hypertensive U.S. population would save $2.3 billion in medical costs (77) and achieve a potential gain of productivity by $2.5 billion (78). These findings corroborate the results of the studies in Norway (79), Canada (80) and Denmark (81).

2.5 Policy Options for Population Salt Reduction

Several population-based policy options are available for countries to carry out salt reduction at population level (Table 2.1).

Table 2.1 *Policy options for population salt reduction*

Policy options	Evidence Base	Synergies	Likely salt reduction (per person per day)
Professional education and health promotion	Primary care in the UK	-	Negligible
Social marketing	UK, New York City	Politically popular	0.1 g*
Labelling	Finland, European Community	Will also benefit fat and sugar	0.5 g†
Product reformulation	Finland, UK	Will also benefit fat and sugar	1 g‡
Substitution	China	-	Not available
Taxation	Finland, New York City	Consistent with fat and sugar tax	2 g†
Regulation and marketing control	Finland, Belgium and Italy (bread), New York City	Greatest benefit in deprived groups - reduce inequalities	3 g†

Note: Reproduced from Cappuccio et al. (15) with permission.
**: Estimated, no data available.*
†: Data from Finland.
‡: Data from Finland and Food Standards Agency of England and Wales.

Among these options, regulation and marketing control is the most effective option according to the estimated salt reduction in the general population. It forces the food industry legally to be compliant with salt reduction requirements so that salt hidden in processed foods can be substantially and quickly reduced.

Social marketing uses commercial marketing strategies to influence social behaviours so that consumers' dietary habit and lifestyle can be improved. For example, the UK targeted the public and different specific groups to raise consumer awareness by TV campaigns and partner campaigns (82).

Salt tax is also proposed in some countries. For instance, in Belgium, a certain amount of taxes is charged to food producers in order to suppress the use of salt in food processing. Unpublished results of a recent study in 19 developing countries suggests that a 40% increase in salt tax can reduce population salt intake by 6% (83).

Product reformulation requires the direct engagement of government and health authority with the food industry and food distributors. The UK FSA has set up different voluntary targets of salt reduction for a range of processed foods. The progress and achievements were reviewed recently and more challenging targets were published in 2011 (84).

Mandatory labelling helps consumers to recognise the “healthy” foods. For example, Finland implemented different salt content limits for food producers (e.g. 1.4% in sausages and 1.3% in bread) and required that low or high salt content warnings be labelled (85).

In China, more than 80% of salt intake is attributable to discretionary salt and soy source that is used in home-made foods (30). Product reformulation and other intervention approaches may be not suitable for the population to reduce their salt intake. Therefore, sodium substitution is now being assessed in China. Briefly, it replaces two thirds of the sodium in salt with potassium to reduce the intake of sodium but increase the intake of potassium. Although the flavour difference is slight (86), more data are needed to assess the acceptability of the substituted salt and the salt reduction effect in the general population.

Each policy option requires the government to engage with different stakeholders. Hence different policy options have different advantages and disadvantages. Therefore, each country may select a single or a combined option to implement the salt reduction programme according to its context.

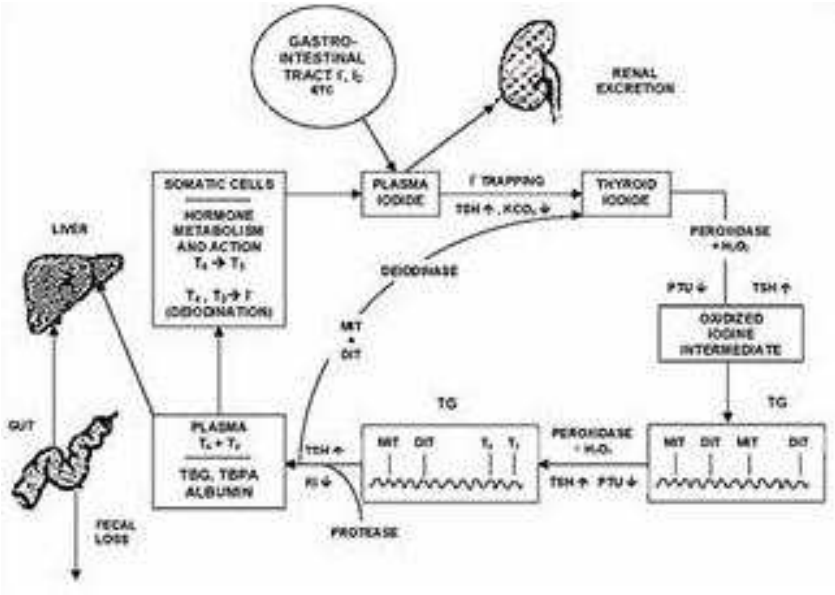
2.6 Iodine Deficiency: An Introduction

Millions of people have been adversely affected by iodine deficiency, suffering from a wide range of devastating health consequences, collectively known as iodine deficiency disorders (IDD). People over 12 years of age need a daily iodine intake of at least 150 microgram (µg) to maintain good health. An estimated 1.9 billion people, including 241 million school-aged children, are currently at risk of IDD. In the 148 countries with available iodine data, 32 are still deficient in iodine (17). Eliminating iodine deficiency has been a long term commitment of World Health Organization (WHO) Member States.

Our body does not produce iodine. Most iodine exists in seawater and marine organisms. The water cycling brings small amounts of iodine to soils through precipitation with iodine concentration ranging from 1.8-8.5 µg/L (87). Iodine content in soils is determined by geographical locations. Inland regions, particularly mountainous areas, are commonly deficient in iodine. In areas affected by floods, erosion and melting glaciers, soils often have a low level of Iodine content. The Himalayas, Papua New Guinea, the European Alps, and the Andes are historically iodine deficient regions. Foodstuffs, such as crops and grains, contain as low as 10 micrograms per kilogram (µg/kg) iodine in dry weight in iodine deficient regions and as high as 1 milligram per kilogram (mg/kg) in iodine sufficient areas (87). Accordingly, human beings may have varying levels of iodine intake depending on the dietary foods made from these foodstuffs and animal products.

Iodine enters the thyroid gland by ingestion to synthesise thyroid hormone, thyroxine (T4) and triiodothyronine (T3). The thyroid hormone has been recognised as one of the most important factors for the growth of the nervous system (88). Most ingested iodine reduces to iodide (I^-) before entering the blood circulation. The thyroid gland selectively absorbs a small amount of iodide from the plasma, while more than 90% of the iodide is excreted in urine (89;90). The absorbed iodide is then oxidised and incorporated into thyroglobulin[1] (Tg) to generate T3 and T4. As shown in Figure 2.2, thyroid gland breaks down Tg to release thyroid hormone. Meanwhile a little amount of iodine is deiodinated and reused in the thyroid. The secreted T3 and T4 enter blood circulation and act on controlling metabolic rate. The hormone is deiodinated. The iodide is partly absorbed again by thyroid gland to start a second cycle and the rest is excreted by the kidney.

Figure 2.2 *The iodide cycle*



Note: Reprinted from Rousset and Dunn (91) with permission.

[1] Thyroglobulin (Tg) is the most abundant protein carrying thyroid hormone in the thyroid gland.

2.7 Consequences of Iodine Deficiency

Inadequate iodine intake results in less production of T3 and T4, forcing the thyroid gland becoming “underactive” (hypothyroidism). Since thyroid hormones are critical for regulating body metabolism, neurological development and numerous other body functions, a reduction of the hormone decreases the speed of several body functions, such as energy burning and body reactions, causing depression, weight gain, and heart failure. When iodine intake is reduced to less than 150 micrograms per day (μg/day), the risks of serious health problems emerge. Increasing iodine intake can reduce the risks effectively. However, too much iodine is also prejudicial to health. The upper limit for optimal daily iodine intake is 299 μg. Iodine intake over 449 μg/day is defined as excessive iodine intake. Excessive iodine intake forces the thyroid gland to be “overactive”, causing weight loss, anxiety and diarrhoea. Iodine excess leads to increased risks of iodine-induced hyperthyroidism (IIH) and autoimmune thyroid disease. Extremely high iodine may lead to severe health outcomes, such as thyroid papillary cancer and iodermia (92).

Inadequate iodine intake can lead to various clinical manifestations of IDD. On the other hand, excessive iodine intake can also result in several diseases. Some of them have similar clinical presentations to those of the disorders caused by iodine deficiency (93). However, these presentations can disappear within a few years with proper iodine intake. Different manifestations of iodine deficiency in different life stages are presented in Table 2.2.

Table 2.2 *The manifestations of IDD at different stages of life*

Stage	Manifestations
Foetus	Abortions Congenital anomalies Increased perinatal mortality Neurological cretinism: *mental deficiency, deaf mutism, spastic Diplegia squint* Myxoedematous cretinism: *mental deficiency, dwarfism, hypothyroidism* Psychomotor defects Stillbirths
Neonate	Endemic mental retardation Increased susceptibility of the thyroid gland to nuclear radiation Neonatal goitre Neonatal hypothyroidism
Child and adolescent	Delayed physical development Goitre Impaired mental development Impaired intellectual performance Increased susceptibility of the thyroid gland to nuclear radiation
Adult	Goitre Hypothyroidism Impaired mental function Increased susceptibility of the thyroid gland to nuclear radiation Iodine-induced hyperthyroidism Spontaneous hyperthyroidism in the elderly

Note: Modified from de Benoist et al.(94).

To most people, endemic goitre has historically been the most common manifestation of iodine deficiency, presented with a swollen neck. Goitre occurs in all life stages and is mostly seen in mountainous regions such as the Himalayas, the European Alps, and the Andes. Estimated in 2003 from school-aged children, Africa has the highest goitre prevalence (26.8%), and Latin America and the Caribbean have the lowest (4.7%) (94). Endemic goitre is curable using iodine and thyroxine preparations.

Pregnant women and foetuses are the most vulnerable populations at risk of iodine deficiency. During pregnancy, the level of thyroid hormone increases by up to 50%. Normal daily diets may not provide adequate iodine intake to cover the needs of both mothers and foetuses. Hence mothers and foetuses are subject to risks of various disorders depending on the severity of iodine deficiency. More importantly, many IDD in adults can be treated by iodine fortification, but the damage caused by iodine deficiency to the development of foetuses is irreversible. Among various degree of neurological deficit, endemic cretinism is the most extreme form, stunting up to 10% of the population's physical and mental development in areas severely deficient in iodine (87).

However, cretinism and other severe health outcomes are only the tip of the iceberg. More people suffer from subtle neurological and mental impairments. These mild impairments bring damage to brain development, resulting in a lower intellectual capacity which is reflected in a loss of Intelligence Quotient (IQ) (95-98). Two meta-analysis studies reported that iodine deficient children have 12-13.5 lower IQ points than those normal children (97;98). Lower IQ leads to poor school performance, reduced intellectual ability and impaired work capacity. Consequently entire populations may suffer considerable social and economic loss.

Maintaining sufficient maternal iodine supplement is of great importance to mothers and foetuses (95;99;100), particularly from the second trimester of pregnancy when the most critical period of foetal brain development starts (101). Recent studies suggest the necessity of a high amount of iodine intake in pregnant and lactating women (102;103). The WHO recommends an iodine intake of 150-249 μg/day for

mothers during pregnancy and lactation. Long-term consumption of iodised salt is linked to better maternal thyroid function (18).

Excessive iodine intake also causes adverse health problems. Recently there has been growing awareness of side effects of high dose iodine intake. It is reported that sudden increase in iodine intake leads to IIH in early stage of iodine fortification, particularly in elderly populations who were previously of mild to moderate deficiency in iodine (94). Liu *et al.* find drinking water with high iodine content significantly reduces primary school students' IQ by 9 points in Tianjin, China (104).

However, IIH is transient and it disappears in 1-10 years. Hence, the priority of iodine correction is to eliminate iodine deficiency since its risks are far more devastating than those of iodine excess (105).

2.8 Assessment of Iodine Status

There are four commonly used indicators to assess the severity of IDD: total goitre rate (TGR), urinary iodine concentration (UIC), serum thyroid stimulating hormone (TSH), and serum thyroglobulin (Tg).

Total goitre rate reflects goitre prevalence in a region. There are two approaches to diagnose goitre at individual level: neck palpation and thyroid ultrasonography. In 1994 a simplified 3-grade classification system was introduced by the WHO for palpation diagnosis: grade 0, no palpable or visible goitre presence; grade 1, a goitre is palpable but not visible in normal position of the neck, and nodular thyroid is in this grade if an enlarged thyroid is invisible; and grade 2, a visibly swollen neck in a

normal position is presented and is consistent with an enlarged thyroid when the neck is palpated.

Total goitre rate is defined as the rate of grade 1 and 2 goitre in percentage in the general population. The WHO recommends the following criteria to determine a population's iodine status: ≥30%, severe deficiency; 20.0-29.9%, moderate deficiency; 5.0-19.9%, mild deficiency; <5.0%, iodine sufficiency.

In endemic areas, thyroid size may not return to normal for months, sometimes even years, after supplemental iodine fortification (90;106). Therefore TGR is useful to assess the history of the severity of IDD, but is not a good indicator of the present iodine status in a population.

Urinary iodine concentration is so far the most widely used indicator recommended by the WHO. It is more sensitive than TGR to recent change (i.e. days) of iodine intake in a population. School-aged children (6-12 years) are the ideal age group for the assessment of the iodine intake status in the general population.

Two approaches are used to assess UIC: 24-hour urinary sample test and spot urinary sample test. It is better to use 24-hour sample to estimate accurately urinary iodine status, but the spot approach is more practical and commonly used, in spite of day-to-day variations in the spot samples at individual level (107;108).

The iodine status indicator is usually expressed as median level of UIC in microgram per litre. Table 2.3 shows cut-off values of iodine status for different populations.

Iodine status can also be assessed by testing thyroid stimulating hormone levels in newborns. Thyroid stimulating hormone determines serum concentration of thyroid hormone. It is a more sensitive indicator of iodine deficiency in neonates rather than in older children and adults. A population which has <3% newborns with TSH >5 micro International Units per millilitre (μIU/mL) is defined as iodine sufficiency; 3-20% as mild deficiency; 20-40% as moderate deficiency; and >40% as severe deficiency.

Table 2.3 *Cut-off values for epidemiological classification of population iodine nutrition status based on median urinary iodine concentration*

Population group	Median UIC (μg/L)	Iodine intake	Iodine status
Children less than 2 years old	<100	Insufficient	
	≥100	Adequate	
Pregnant women	<150	Insufficient	
	150-249	Adequate	
	250-499	More than adequate	
	≥500	Excessive	
Lactating women	<100	Insufficient	
	≥100	Adequate	
School-aged children (6-12 years) and other adults	<20	Insufficient	Severe iodine deficiency
	20-49	Insufficient	Moderate iodine deficiency
	50-99	Insufficient	Mild iodine deficiency
	100-199	Adequate	Optimal iodine nutrition
	200-299	More than adequate	Risk of iodine-induced hyperthyroidism within 5-10 years following introduction of iodised salt in susceptible groups
	≥300	Excessive	Risk of adverse health consequences (iodine induced hyperthyroidism, auto-immune thyroid diseases)

Note: Reproduced from Andersson et al. (109).

Recently thyroglobulin has been regarded as a promising IDD indicator (107;110). Other than TSH, Tg level can be assessed in school-aged children so that it has wider application than TSH. Serum Tg level can be tested using dried whole blood spots (DBS) (107). The WHO describes the reference interval for DBS Tg in iodine sufficient school-aged children as 4-40 μg/L.

2.9 Correcting Iodine Deficiency

Correcting iodine deficiency has been a long term commitment of the World Health Organization, with the goal of eliminating iodine deficiency by 2000 set in the 1990 World Summit for Children[2]. Iodine repletion in the general population is such that the median urinary iodine concentration is higher than 100 μg/L, with no more than 20% of the population being below 50 μg/L.

Diverse vehicles for iodine supplementations are available, including water, milk, dairy products, flour, oil, salt, etc. Iodination of water can be an effective way to increase iodine levels in humans, crops and animals. Iodised irrigation water has been successful in reducing iodine deficiency in China (111). Similarly, fortified animal feeds can also raise the iodine concentration in animal products. Accordingly daily iodine supplementation can be obtained through food products like bread, milk and infant formula (112). Another approach is to add iodine into foods, such as flour. However, little research has been conducted and the effect of this approach is still unclear. Further assessments are needed, particularly on the iodisation technology,

[2] In 2002, the target was later extended to 2005 at the Special Session on Children of the United Nations General Assembly (94).

optimal iodine fortification levels and its potential coverage. Iodised oil is usually distributed in populations in remote areas where other iodine supplementation vehicles are difficult to reach. It is prepared by adding iodine to seed or vegetable oil. It contains about 40% organically combined iodine. Iodised oil can be administered orally or given by intramuscular injection once or twice a year (113;114).

Compared to the previous vehicles, salt is the major vehicle for iodine supplementation worldwide. It is mainly because of the following advantages (32;57):

- Salt is commonly and stably consumed by people throughout the year;
- Salt production is limited to a few geographical areas;
- The quality of iodised salt is easily monitored;
- The addition of iodine to salt does not affect its taste, odour and colour;
- Salt iodisation programmes are easy to implement.

Salt iodisation is the most cost-effective way to improve the population iodine intake. It costs only US$0.02-0.09 per person per year to obtain sufficient iodine. The implementation of salt iodisation in children can avert $1,000 per child death and save $34-36 per disability-adjusted life years (DALYs) (115).

Universal salt iodisation (USI) was adopted in the 54th World Health Assembly in 1994 to promote the use of iodised salt in the general population and eliminate IDD in the world. The WHO, United Nations Children's Fund (UNICEF) and International Council for Control of Iodine Deficiency Disorders (ICCIDD) have been recommending salt iodisation as the primary strategy for controlling iodine

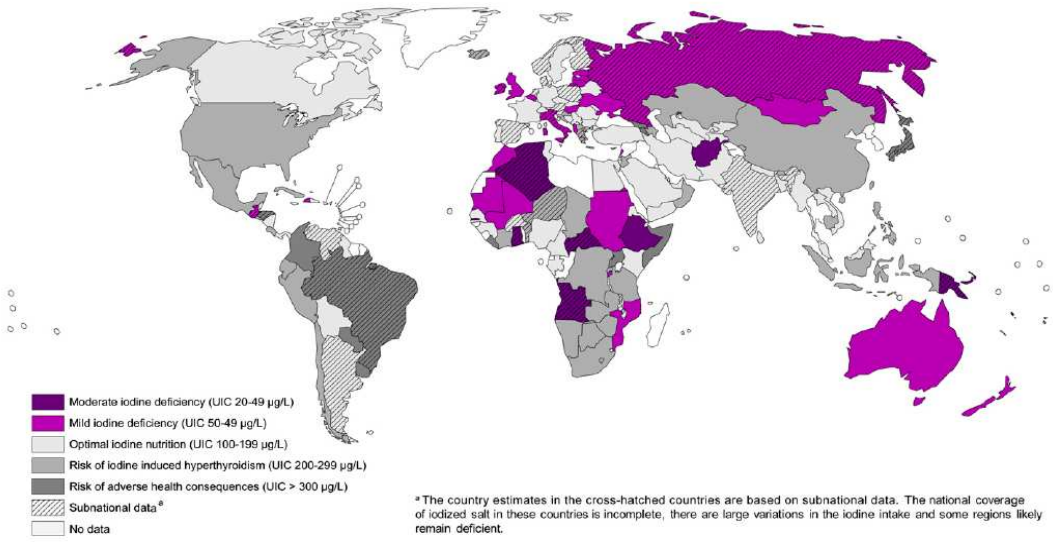
deficiency since then. USI requires all food grade salt be iodised. Several countries in Europe and North America, such as Sweden, Austria and the United States, add potassium iodide (KIO_3) to salt. Other countries usually add potassium iodate (KI) because it is more stable and less soluble than KIO_3, especially in hot and humid conditions (e.g. tropical regions). Assuming average daily salt intake of 10 grams per capita and 40% iodine loss from salt during delivery and cooking (107), the salt industry is advised to add 20-40 mg iodine in each kg of salt during production. Therefore individuals can consume 150 μg/day iodine, as recommended by the WHO.

To achieve the goal of sustainable elimination of IDD, two indicators are used: 1) at least 90% of households should be covered by adequately iodised salt (≥15 ppm); and 2) median UI should be 100-199 μg/L in the general population and 150-249 μg/L in pregnant women (107).

Remarkable achievements have been obtained since the introduction of USI worldwide. More than 170 countries have adopted the USI programme for controlling iodine deficiency by 1998 (116). Of the 130 countries affected by IDD, 110 have established legislations on salt iodisation (117). The overall coverage of iodised salt is steadily improving: an estimated 69% of households worldwide are using iodised salt, compared to less than 20% in 1990s (23), although populations in Central Eastern Europe, Commonwealth of Independent States and South Asia have much lower coverage of iodised salt. The number of countries at risk of iodine deficiency reduced from 110 in 1993 to 47 in 2007 (118), and further down to 32 in

2011 (17). Over 90 million newborns every year are now protected from learning disabilities caused by IDD.

Figure 2.3 *Iodine status based on national median UIC data*



Note: Reprinted from Andersson et al. (17) with permission.

However, the progress of the USI programme differs from one region to another. Wide geographical variations are observed in the availability and consumption of iodised salt (119) in different parts of the world. For instance, East Asia has an 86% coverage of iodised salt, whereas 49% South Asian households are still not protected by iodised salt. More disparities are found from country to country (90). In South Asia, Sri Lanka and Bhutan have met the USI 90% target line, while the coverage in Pakistan and Afghanistan is less than 30% (119). In Africa, the goitre prevalence rate dropped considerably after introduction of iodised salt: 20%, 60%, 50% and 38% reduction in goitre rates were achieved in Kenya, Cameroon, Zambia and Zimbabwe respectively (120). In Lesotho, iodine deficiency is no longer a public health problem after legislation on USI was established in 2000 (121). Access to iodised salt can

vary even within a country. For example, with 30% households covered by iodised salt in Russia, the coverage in 7 out of 17 surveyed regions is lower than 10% (122).

Additionally, there are diverse geographical patterns of iodine status at national and sub-national level. In Sub-Saharan Africa, several countries (e.g. Chad and the Central African Republic) are severely iodine deficient, whereas their neighbouring countries, such as Nigeria and the Democratic Republic of Congo, are at risk of IIH (Figure 2.3). Valeix *et al.* (123) reveal a west-east pattern with regard to median UIC concentration in France. In a study in Albania, significant geographical variations of median UIC (3.52-1,079 μg/L) are found among four regions (124). In Russia, while iodine deficiency has been reduced in certain Russian regions (e.g. Moscow and Tartarstan) in accordance with increased urinary iodine concentration, it remains unchanged in others (122).

2.10 Economic Impact of Iodine Deficiency

Little research has been carried out on the economic impact of iodine deficiency. Muir and Zegarac (125) reviewed the economic costs due to IQ loss. It was estimated that in 1999, a loss of 5 IQ points cost US$301 billion in the US and Canadian $30 billion in Canada annually and the projected social cost would be up to $92 billion for the US and Canada combined.

Thus the elimination of iodine deficiency would be economically beneficial to society. It is estimated that every US$1 spent on the iodine fortification returns a per capita productivity gain of US$26-28 (25;119).

2.11 Perceived Conflicts of Policies of Iodine Fortification using Salt and Population Salt Reduction

The WHO recommends a salt intake of <5 g/day in the general population while the USI programme is adopted by many countries to maintain the population iodine intake within the optimal range (150-299 µg/day) with the assumption of 10 g/day salt intake and 20-40 ppm iodine content in salt.

It is conceivable that the health policies have potential conflicts. Salt reduction may result in reduced iodine availability, particularly in many low- and middle-income countries that heavily rely on dietary salt for iodine supplementation. This could jeopardise salt iodisation programmes and expose more people to the risk of IDD. On the other hand, people may inadvertently increase salt intake in the hope of increasing iodine intake. Although there is no population level study reporting such a scenario, such behaviour may compromise the efforts towards salt reduction and put people at risk of hypertension and CVD.

Another issue related to the USI policy is the average salt intake assumption. The assumption is the basis of salt iodisation policy. However, it may not be applicable worldwide. Evidence shows considerable variation of population salt intake across the world (126). For those countries committed to salt reduction, the population salt intake is likely to change over time. Varied salt intake may influence the iodine intake in the general population and therefore jeopardise USI programmes.

2.12 Summary of Chapter 2

Chapter 2 reviewed the literature related to the effects of salt and iodine intakes in two separate sections.

For salt, the association between its intake and BP and cardiovascular disease was reviewed. The association is well supported by overwhelming scientific evidence from animal studies, randomised clinical trials and observational population studies. Many countries have established different goals or guidelines for population salt reduction, following the WHO recommendation of 5 g salt per day, mainly because it is the most cost-effective strategy to reduce BP and prevent chronic diseases. However, the progress of salt reduction programmes differs across the world. The salt review ended with a summary of several available population-based policy options for the programme.

For iodine, the review began with a brief introduction on the effects of iodine deficiency, particularly from a physiological perspective. Insufficient iodine intake leads to iodine deficiency disorders (IDD), causing irreversible brain and physical damage and other consequences. Iodine status is best assessed by urinary iodine concentration (UIC) and the optimal UIC is set in the range of 100-199 μg/L for adults with different ranges for different population. Correcting iodine deficiency is cost saving and beneficial to the society. In order to supplement iodine at a population level, salt is used as the most cost-effective vehicle across the world since the 1990s, compared to other vehicles such as water, flour, dairy products and livestock feeds.

Thus, two health programmes, salt reduction and salt iodisation, overlap when salt iodisation is the chosen policy to supplement populations with iodine. The potential conflicts between the programmes are that salt reduction may jeopardise salt iodisation and salt iodisation may unintentionally lead to an increase in salt consumption.

Chapter 3 Salt Intake and Iodine Status: An Assessment

3.1 Objectives of this Chapter

This Chapter was added to address the complexities in the nutritional assessments of both salt and iodine intakes and of the need for the use of valid urinary biomarkers. Salt and iodine intake measurements were systematically reviewed. In addition, two common methods of estimating salt intake using spot urine samples were validated by comparison with 24-hour urinary sodium in two populations.

3.2 Systematic Review of Studies Comparing 24-hour versus Spot Urine Collections for Estimating Population Salt Intake

3.2.1 Introduction

In steady state conditions, the kidneys handle most of the sodium eaten in a day. The majority (up to 95%) is eventually excreted in the urine in the subsequent 24-hour. The remaining is excreted in sweat, saliva and gastro-intestinal secretions. The daily renal excretion rate of sodium is not constant throughout the 24-hour, depending on sodium consumption pattern, such as time of day, individual's posture, and neuro-hormonal influences.

Twenty-four-hour urine collection is the gold standard for assessing salt intake through urinary sodium excretion both in individuals and in populations (127). However, it is often deemed inconvenient for repeated use in large population studies. There are concerns that high participation burden, lack of completeness and high cost will impact on response rate and feasibility. Over the years, alternative methods have been implemented to try and overcome this concern, such as spot and timed urine samples.

The assessment of population salt intake and its changes over time underpins salt reduction policies and represent one of the major pillars of such programmes globally (4;12;15;128). And yet intake is not known for many countries.

Several questions need answering: can average population salt intake be assessed with methods other than 24-hour urine collections? Can we predict daily intake from spot urines? Can we estimate daily intake from spot urines? Is the validation for groups the same as for individuals? Can we use alternative methods to 24-hour urinary sodium for a reliable monitoring of population changes? Are these methods valid in different population subgroups according to gender, age and ethnicity?

The aim of the present section was systematically to review all studies comparing 24-hour urine collections with alternative methods (spot, overnight, daily, timed) for the assessment of salt intake in both adults and children.

3.2.2 Methods

Literature search

We developed a search strategy to identify studies that reported the association between sodium excretions obtained with 24-hour urine collection compared to spot urine samples. We searched the electronic databases MEDLINE (from 1950 to April week 4, 2010) and EMBASE (from 1980 to week 18, 2010), as well as the Cochrane Library using the terms “sodium [dietary, chloride, intake, excretion]” “salt [intake]” and “urine [timed, spot, random, 24-hour].” Furthermore, we reviewed reference lists of original and review articles to search for more studies. Only full-length articles were considered. No language restriction was applied. Only studies in humans were included.

Inclusion and Exclusion Criteria

Studies had to fulfil the following criteria: (a) full paper, (b) human study, (c) population study or those in large groups ($n \geq 30$), (d) availability of both 24-hour urine and one of alternative methods (spot, overnight, timed), (e) availability of urinary analytes. Studies were excluded if: (a) not in the English language, (b) abstract form, (c) sample size <30, (d) studies in special patients’ groups (e.g. renal or heart failure, CHD, diabetes, or treated patients’ groups). If multiple published reports from the same study were available, we included only the one with the most detailed information for both exposure and outcome.

Data extraction

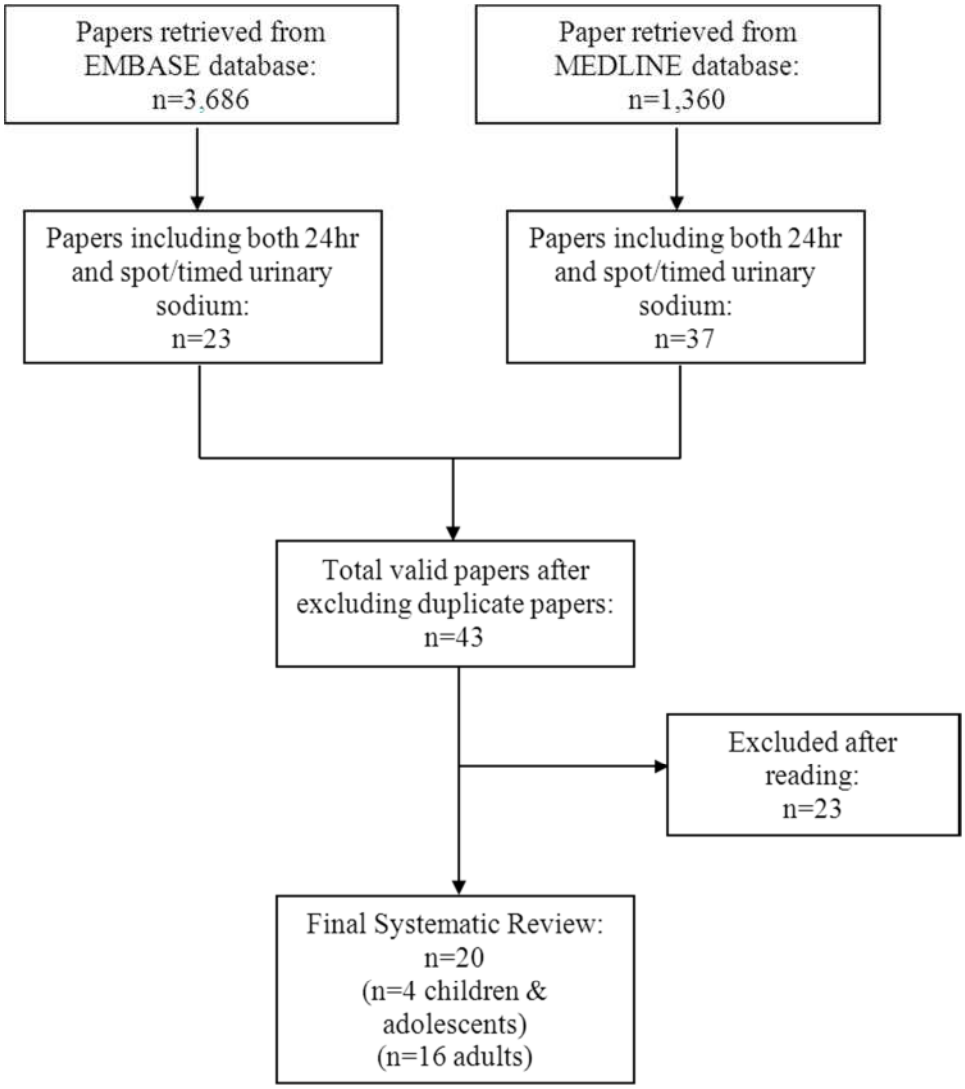
Three investigators (CJ, LS and CP) extracted data independently and differences were resolved by discussion and consensus. Relevant data included the first author's surname, year of publication, country of origin of the population studied, population type, sample size, age, duration, description of urine sampling, mean sodium for 24-hour and for alternative samples, outcome measures (correlations, ratios).

3.2.3 Results

Characteristics of studies

Forty-three papers met the inclusion criteria. Of these 23 were excluded due to lack of data and 20 were suitable for final review, 16 in adults (129-144) and 4 in children (145-148) (Figure 3.2.1). Where results were reported separately for independent groups, they were entered into the tabulation as separate studies (132-134;145;149). Overall, the review included 1,380,130 participants from 7 different countries (5 from the USA, 6 from Japan, 3 from China, 2 from Brazil, and 1 each from France, Croatia and the Netherlands). Fourteen studies recruited both men and women, while 2 studies recruited only women. Four studies in 5 samples were carried out in children and adolescents.

Figure 3.2.1 *Flow chart of systematic review of salt intake*



Studies comparing 24-hour with overnight samples in adults

Table 3.2.1 summarises studies in adults. Nine studies tested the correlation between 24-hour and overnight urinary sodium (132;135-137;144;149-152). Ten used flame photometry for the analysis of sodium concentrations (133-136;140;144;150;151;153), while one (152) used ion-selective electrode method and one (149) a new salt monitor. One study (135) analysed the correlation coefficient of the true mean 24-hour urine sodium and the true mean overnight urine sodium in order to eliminate the influence of intra-individual variation. It suggested that at least a week of overnight samples would be required to reduce the intra-individual variation.

Luft *et al*. (137) studied the sodium intake by placing participants on a fixed diet and monitoring their urinary output. They found that the mean sodium intake showed a greater correlation with the 24-hour (r=0.75) than the overnight sodium (r=0.55). They recognized that daily variation in salt intake is a limitation, and concluded that overnight urinary collections do not appear promising in estimating mean sodium intake.

Another study (136) found a correlation of 0.94 between the true mean 24-hour and overnight sodium excretion. The urine samples were not collected on consecutive days. They also completed another study (151) where six 24-hour urine samples were collected within ten days. They reported a high correlation between the true mean overnight and 24-hour urinary sodium (r=0.92). There was a greater degree of intra- and inter-individual variation with the overnight urine sodium collections than

the 24-hour excretions and thus a greater number of samples would be needed to measure accurately sodium intake in populations.

He *et al*. (150) found a correlation coefficient of 0.843 between the 24-hour and overnight true mean values when pooling data from rural and urban residents. Despite a strong correlation, double the amount of samples would be needed to limit the diminution of correlation coefficient to less than 5%. The strength of this study was the inclusion of rural population samples in contrast with previous studies of predominantly urban populations with a high salt intake.

In relation to time of day, one study (152) found that the correlation between 24-hour urinary electrolytes and half-day (12-hour duration) urine contents were better than correlations with overnight (8-hour duration) urine contents. This was probably due to the longer time period involved with the half-day collections. This study did not find a strong correlation between the 24-hour and overnight urinary sodium, and cautioned the use of a partial sample as substitute for 24-hour urinary sodium analysis.

A few studies piloted the use of purpose-built devices to facilitate partial urine collections. Kamata & Tochikubo (132) devised a urine-sampling pipe with a two-way stopcock that could trap overnight urine proportionally, to estimate the volume of overnight urine and to estimate the 24-hour urinary sodium. They accounted for the lean body mass of individuals to estimate the 24-hour urinary sodium levels. Using an electrical device to monitor daily salt intake at home, another study (149) found a significant correlation between 24-hour urinary sodium excretion and overnight values. The correlation between 24-hour urinary sodium with ion electrode

method and the measured value with a new salt monitor using overnight urine was significant (r=0.72). The self-monitoring method suggested overnight sampling as an adequate substitute for 24-hour urine.

Studies comparing 24-hour with spot sampling in adults

Eight studies included in our review made a comparison between 24-hour urinary sodium contents and single spot urinary sodium (133;134;139;140;144;153-155).

Kawasaki *et al*. (133) showed in 242 participants that a single 24-hour urine specimen does not represent the individual average of daily sodium excretions. The correlation coefficient between spot and 24-hour urine was 0.467. When they took the average of 3 daily collections from 117 participants, the correlation coefficient was 0.624. They also compared urine samples from 59 persons with an intra-individual standard deviation of spot urine specimen for excretion of creatinine within 20%. The correlation coefficient was 0.725.

Wolf *et al*. (153) looked at using a spot urine sample instead of the usual 24-hour sample to measure urinary sodium. There was an overestimation of both the excretion rate and sodium/creatinine ratio when the spot urine was compared to the 24-hour sample. The spot sample, carried out in the morning after overnight fasting, was closely related to the 24-hour sample.

Kawasaki *et al*. (134) found that spot samples of second morning voided urine, collected over 3 days, gave a more reliable and accurate estimation of 24-hour urinary sodium than a one day collection. They found a highly significant correlation

(r=0.774). They also found that there was a stronger correlation when using morning spot samples in comparison to those at night.

Costa *et al*. (155) analyzed the relationship between systolic pressure and sodium excretion at different levels of diastolic pressure. They used a single casual spot sample instead of 24-hour urine to estimate sodium excretion. They found that spot samples showed significantly higher estimates of sodium excretion in comparison to 24-hour collections, with a weak positive correlation coefficient (r=0.28). They concluded that this weak but significant correlation suggests that an even larger sample of spot urine collections would be needed in comparison to 24-hour urines to detect an association with BP and sodium excretion.

Tanaka *et al*. (140) found that the correlation between the 24-hour and the spot urinary sodium was 0.65. They concluded that the method would be a convenient and accurate way to estimate population sodium intake. They discussed that individual monitoring should still use 24-hour samples, but spot samples is a good alternative to monitor and evaluate population mean sodium intake.

In another study (154), the ratio between 24-hour and spot samples was 2.0. It also reported a correlation of 0.45 between spot and 24-hour urinary sodium. This study concluded that spot urine could be used instead of "tedious and impractical 24-hour urine collection". They did note that spot sampling is not sufficient in all cases, but is a reliable alternative.

Mann & Gerber (139), more recently, looked at 3 different spot samples – random, AM and PM - in comparison to the 24-hour sample. When sodium/creatinine ratios were adjusted for 24-hour creatinine excretion, all correlations were strengthened.

The correlations between the 24-hour sodium excretions were 0.17, 0.31, and 0.86 for random, AM and PM, respectively. The value for the random sample was not significantly correlated and therefore would not be a good alternative to 24-hour urinary sodium collections. However, a spot sample collected in the late afternoon or early evening before dinner (PM sample), adjusted for 24-hour creatinine excretion, predicts 24-hour sodium excretion accurately. They concluded that the use of spot urine is convenient and cost-effective in assessing sodium excretion in clinical practice and epidemiological studies.

All but one (133) studies that made a comparison between spot and 24-hour urine collections advocated using the spot sampling method. There was a significant consensus that a greater number of collections would be necessary using spot urine samples, but regardless this would be more convenient and feasible for general populations that require monitoring.

Studies comparing 24-hour with multiple other sampling techniques in adults

Yamori *et al*. (144) looked at 24-hour urine samples split in three parts, and found that the highest correlation of sodium in the urine samples occurred in the daytime voided urine and the second in the overnight voided urine. The correlation was low. Despite the higher correlation of daytime voided urine with 24-hour collection, practicality favours evening and overnight collection as these can be completed at home for most individuals. They suggest the use of partial urine samples to analyse sodium intake, and even the use of single spot urine samples for large population surveys.

Studies comparing 24-hour with other sampling techniques in children

The studies in children and adolescents are summarised in Table 3.2.2. The studies have included ages from 3 to 19 years and have all compared overnight urines with 24-hour samples. In all studies, multiple collections were used (from a minimum of two (148) to a maximum of seven days (145;146)). Most studies used correlation coefficients to assess concordance, reliability and reproducibility, with values varying from 0.62 (147) to 0.95 (146).

Table 3.2.1 *Systematic review of studies in adults*

Author (year)	Country	Population	Sample (n)	Age (yrs)	Duration	Urine samples	Mean (24h)	Mean (spot)	Ind. samples	Correlation	Notes
Liu *et al.* (1979)	USA	Business and administrative volunteers	116 men	30-44	4d	24h v day-time v overnight	165-183	116-138 d 45-57 ov	No	0.722 versus ov	Flame photometry. Conditional probability of 24h Na in V Q to III T ranges from 0.58 to 0.77, given night Na in V Q. If overnight used, at least a week collection.
Yamori *et al.* (1982)	Japan	Healthy volunteers	Farming & fishing villagers 39 men & 44 women	30-50	1d	24h v day-time v evening v overnight v spot	202 farming 198 fishing		No	Na/Cr 0.717 d 0.559 e 0.419 ov 0.463 spot	Flame photometry. Day-time best substitute
Luft *et al.* (1982)	USA	University Students or employees	12 white men, 10 white women, 14 black men, 7 black women	19-54	15 consecutive days	24h versus 16h diurnal versus 8h nocturnal for 10 days	139	28 (night)	No	0.22	Nocturnal urines are not useful to estimate mean Na intake
Kawasaki *et al.* (1982)	Japan	Healthy volunteers	91 men, 151 women	20-63	3d	24h versus spot (within 4h after first morning void)	218		No	0.467 versus spot 0.624 versus 3-day average	Flame photometry with Li as internal standard.
Wolf *et al.* (1984)	France	Healthy volunteers	Supine (s): 61 men, 30 women Upright (u): 30 men, 30 women	20-68		24h versus spot	6.15[a] s 5.91[a] u	13.3[b] s 7.85[b] u	Yes		Flame photometry. Spot urine overestimates urinary Na excretion rate

Table 3.2.1 *cont'd*

Author (year)	Country	Population	Sample (n)	Age (yrs)	Duration	Urine samples	Mean (24h)	Mean (spot)	Ind. samples	Correlation	Notes
Liu *et al*. (1986)	China	Healthy doctors and technicians	49	30-50	6 samples over 3 months	24h versus day-time versus overnight for 6 days	231 d 262 ov	94 110	No	0.94	Flame photometry. Overnight urine sample could be used but 6 specimens needed
Liu *et al*. (1987)	China	Normotensive health professionals	50 men	27-50	10 d	24h versus day-time (12h) versus night-time (12h) 6 d	235 d 260 n	122-142 d 109-122 n	No	0.92	Flame photometry. Conditional probability of 24h Na in V Q to III T ranges from 0.774 to 0.950, given night-time Na in V Q
Kawasaki et *al*. (1993)	Japan	Healthy free-living individuals	Group 1: 91 men & women Group 2: 15 men & women	20-79 40-67	1 d 2 d	24h versus spot	233 men 185 women	n/a	Yes	0.728 0.531 (external gp)	Flame photometry.
He *et al*. (1993)	China	Normotensive Chinese men	30 farmers, 33 urban dwellers	19-55	3 d	24h versus overnight (8h)	147 d 1 155 d 2 165 d 3	38 in 8h 41 in 8h 43 in 8h	No	0.843	Flame photometry. Overnight collections underestimated 24h Na by -1.99 mmol/h (~48 mmol/24h)
Costa *et al*. (1994)	Brazil	Healthy individuals	611	20-74	single	24h versus spot	220	n/a	Yes	0.28	Flame photometry. Spot urine overestimates Na excretion

Table 3.2.1 *cont'd*

Author (year)	Country	Population	Sample (n)	Age (yrs)	Duration	Urine samples	Mean (24h)	Mean (spot)	Ind. samples	Correlation	Notes
Pan *et al*. (1994)	China	Research staff	21 men & 19 women	24	1 mo	24h versus half-day (hd) versus overnight	151	69 hd 31 ov	No	0.83 versus same day 0.41 versus adjacent day 0.41 versus 1 mo apart using hd urine 0.60 versus same day 0.28 versus adjacent day 0.28 versus 1 mo apart using ov urine	Ion-selective electrode method.
Tanaka *et al*. (2002)	Japan	Group 1: INTERSALT participants, Group 2: manual workers	295 men & 296 women	20-59	n/a	24h versus spot	187	179 (estimated)	Yes	0.54	Emission flame photometry. (a) Estimated means lost accuracy on lower salt intakes. (b) Spot urines underestimated true excretion. (c) needs population-specific validation with age, wt, ht and 24h
Kamata & Tochikubo (2002)	Japan	Healthy individuals	Study 1: 126 men Study 1: 225 women Study 2: 71 men Study 2: 78 women	38 50 35 49	n/a	24h versus predicted by Cr and lean mass 24h v overnight with sampling pipe	n/a	n/a	No	0.73 0.78 0.59 0.67	Automated ion-electrode method. Population-specific, needs validation. Overnight urine underestimates the true value with gender differences and risk of bias

Table 3.2.1 *cont'd*

Author (year)	Country	Population	Sample (n)	Age (yrs)	Duration	Urine samples	Mean (24h)	Mean (spot)	Ind. samples	Correlation	Notes
Yamasue *et al.* (2006)	Japan	Healthy adults	Study 1: 62 men & 188 women	54	n/a	24h versus overnight	n/a	n/a	No	n/a	Comparing two different methods
			Study 2: 70 men & 154 women	53	21-66 d	24h with IEM versus overnight with NSM				0.72	
Ilich *et al.* (2009)	Croatia	Healthy participants	143 women	30-79	n/a	24h versus fasting spot	16.6[b]	12.9[b]	Yes	0.452	Flame AA/emission spectrometry
Mann & Gerber (2010)	USA	Unselected volunteers	81	21-82	n/a	24h versus spot, AM & PM	181 spot 188 AM 164 PM	160 176 158	No	0.17 Spot 0.31 AM 0.86 PM	Treated individuals

Note: Ind.: independent, Na: sodium, Cr: creatinine, n/a: not available, IEM: ion-electrode method, NSM: new salt monitor;
a: Na (mmol/h);
b: Na/Cr ratio (mmol/h).

Table 3.2.2 *Systematic review of studies in children and adolescents*

Author (year)	Country	Population	Sample (n)	Age (yrs)	Urine Samples	Duration	Mean (24h)	Mean (spot)	Independent sample	Correlation	Notes
Liu *et al.* (1979)	USA	6^{th}-8^{th} grade	31 boys 42 girls	11 to 14	24h versus overnight	7 days	123 150	49 69	No	0.73	Automated methods. Conditional probability of 24h in V Q to III T ranges from 0.59 to 0.78, given night-time Na in V Q
Micheli & Rosa (1982)	Brazil	Children & Tees	31	6 to 17	24h versus overnight v food record	2days	146 162	137	No	0.71	Ion selective electrode method. 24h urine still the most reliable method to determine UNa
Luft *et al.* (1984)	USA	Twins	52 boys 43 girls	3 to 18	24h versus overnight	5d over 1mo	115	37 (night)	No	0.62	Flame photometry
Knuiman *et al.* (1988)	Netherlands	Boys	28	8 to 9	24h versus overnight	7 days	101	34 (night)	No	0.95	Flame AAS. Overnight may replace 24h in young boys, but more overnight than 24h specimens are required to achieve similar precision

Note: Na: sodium.

3.2.4 Discussion

This is the first systematic review of studies comparing simple measures of urinary sodium excretion with 24-hour urinary sodium excretion. The studies are heterogeneous in objectives, protocols, types of urine collections, number of repeated measures, populations studied, measures taken for validation, and analytical approaches. It does not provide, therefore, a uniform pool of data to assess the evidence with consistency. This is reflected in the contrasting conclusions that the authors have reached over the years either in favour of or against the suitability of alternative methods for the assessment of urinary sodium excretion (a proxy for salt intake) instead of 24-hour urinary sodium excretion.

Advantages and disadvantages

There are advantages and disadvantages of the different options (4;156). Twenty-four-hour urine collection is the gold standard for assessing daily salt intake. It will capture over 90% of the sodium ingested around the time of the collection. When applying it to population samples, however, it may pose a high burden on the participants with the risk of low participation rates.

The inaccuracy of completeness (both under- and over-collections) is also of concern. The biochemical method of using para-amino-benzoic acid (PABA) administration for three days preceding the urine collection would overcome this problem (157-159). PABA is a substance not metabolised by the body and, once absorbed in the bloodstream, is flushed through the kidneys with excretion being 100% of the ingested load. A direct measurement of PABA in the urine would allow a direct

measure of completeness. This method does not provide a feasible alternative for population monitoring though, especially in low- and middle-income countries. It reduces response rate as participants will have to plan in advance and take three pills on the days preceding the collection. Non-responders (hence defaulters) will only be identified once PABA has been measured (and undetected) in the urine, with resource implications in terms of additional laboratory costs, pill costs and unnecessary screenings.

A less precise but more feasible alternative is the measurement of urinary creatinine excretion, constant within an individual at rest, and is dependent mainly on lean body mass and age.

Finally, one advantage of 24-hour urine collection is that it could be used at the same time for monitoring total iodine intake and therefore complements population programmes of universal iodization for the prevention of iodine deficiency (25).

Feasibility and usefulness

24-hour urine collections have been employed in population studies for over four decades. The most compelling evidence of feasibility and usefulness derives from the INTERSALT study, an international study of the relationships between salt intake and BP (126). INTERSALT was carried out in 52 population samples around the world, in all continents, and included samples from remote populations in the Amazon jungle, Africa, Australasia and rural China. Practicalities were addressed with local training that allowed the quality of 24-hour urine collections to be preserved.

In addition, community-based studies in rural Africa have been able to perform 24-hour urine collections following the training of health care assistants at low cost (53;160-162).

Alternative methods

There are several methods of partial urine collections (spot, timed, daytime, evening-time, overnight) in alternative to 24-hour urine. They are less onerous for participants, can allow faster screening time and fewer training needs for staff. They are highly variable at the individual level but can give reasonable estimates of group means, an aspect that makes them of interest for long-term monitoring and population surveillance. These methods are highly dependent on hydration, duration and volume of collection, and high proportional residual bladder volume. They are expressed as sodium concentration per litre (rather than total daily excretion) and converted into an estimated 24-hour sodium excretion. No validation is available to establish the precision, validity and reliability of these conversions.

The method by Tanaka *et al*. (140), for example, is population-specific; requires internal calibration with age, weight and creatinine; overestimates low intakes and underestimates high intakes; and it has very low specificity for identifying lower salt intake (163). Moreover, the relationship between urinary concentrations and total excretions does not give information on population distributions (164).

Spot urines are currently used for monitoring iodine status in global iodization programmes around the world, mainly in children and women of childbearing age (25). These methods are less desirable for the initiation of monitoring programs of

population salt reduction because they cannot provide an absolute measure of salt intake at baseline. However, they may prove useful in repeated assessments over the course of the programmes to assess relative 'changes from a known baseline' (156).

Implications for future research and policy

The assessment of population salt intake underpins the implementation of salt reduction policies (4;15). This can be achieved by measurements and estimates of 'average' population levels and 'average' changes over time in the population as a whole and in subgroups, and the population distributions (164). This objective differs from the need to measure an individual's salt intake. The present systematic review indicates that most studies were aimed at answering the latter question, and almost every study relied on correlation analyses and the strength of the correlation coefficients to draw conclusions. The majority of studies have compared 24-hour urine data with data derived from partial collections that were part of the 24-hour collection (i.e. dependent collections) rather than independent of it. This is an important point recently highlighted by Mann & Gerber (139). The appropriate validation test would be between a 24-hour sample and an alternative sample which would be independent of the 24-hour collection (as it would be when reassessing salt intake in different population samples over time, to avoid spurious inter-correlations).

Correlation may not be the best measure to assess the question in the current context of monitoring and evaluating public health programs of population salt reduction in which 'average' values are estimated and followed up over time. Very few studies have used this approach. In Scotland, for example, in the 2006 Health Survey, 24-hour urinary sodium was weakly correlated with urinary sodium/creatinine ratio

obtained from spot urine collections (165). There was poor reproducibility of three consecutive spot urines (worse in women), and poor discrimination between groups in the second, third and fourth quintile of 24-hour urinary sodium distribution.

A comprehensive validation analysis was carried out in Section 3.3 in which the reliability and reproducibility of salt intake measured from 'timed' and 'independent' urine collections were examined in a British multi-ethnic population of men and women and were independently validated in another population sample of Italian men (163). The analysis compared different methods to estimate 24-hour sodium output from 'timed' collections and used not only correlations but Bland-Altman plots, prediction of quintile position and sensitivity and specificity of detecting a reduction of sodium excretion below 100 mmol/day (about 6 g salt per day) using Receiver Operating Characteristic (ROC) areas under the curve. In short, the analysis showed consistent bias, moderate sensitivity and low specificity using time urines.

Finally, a national survey of salt intake in Ireland used spot urine collections to estimate population levels of salt intake and 24-hour collections in an independent sub-sample of the population (166). The average values were close to each other (10.3 v 10.4 g of salt/day in men and 7.4 v 7.4 g of salt/day in women). The study did not present breakdown data by age or by quintiles of salt intake to determine whether biases across ages and levels of intake were present.

3.2.5 Conclusion

The present systematic review, whilst inconclusive in providing an answer to modify current recommendations, highlights the inadequacies of current evidence and the

need for validation studies pertinent to the context of population monitoring of salt intake and of evaluation and surveillance of salt reduction programmes. At the same time it suggests that 24-hour urine collections in small surveys are viable and reliable. In the absence of more definitive evidence, we endorse the recommendations of the PAHO/WHO Regional Expert Group in that *"until more studies are carried out to assess simpler but reliable methods of urine collection for the purpose of estimating daily excretions of [sodium], 24 hour urine collections are recommended"* (156).

3.3 Comparisons of Spot vs 24-hour Urine Samples for Estimating Salt Intake: validation study

3.3.1 Introduction

A twenty-four hour urinary collection is the gold standard for assessing salt intake through 24-hour urinary sodium excretion both in individuals and in populations (167). This method has been used for a long time in physiological, metabolic and epidemiological research. However, particularly for repeated use in large population studies, 24-hour urine collections are often deemed inconvenient and alternative methods have been derived (168-170). Spot and timed urine samples have been suggested as an alternative and several methods have been devised and tested to calculate the daily excretion from partial urine collections (171).

The aim of the present study was to investigate if spot urine can be an acceptable substitute for 24-hour urine to estimate 24-hour sodium in men and women from different ethnic groups (discovery study). The study tested the validity of spot urines

applying different methods used in the literature and replicated the analysis in an independent population of white men (validation study).

3.3.2 Data and Methods

Study 1 (discovery study)

Participants were selected from general practitioners' registers in the South-West London area, as described in detail elsewhere (172;173). In brief, the study was a population-based cross-sectional survey of men and women between 40 and 59 years old of three different ethnic groups: northern European origin (whites); West African or Caribbean origin (blacks) and South Asian Indian origin (S Asians). The study was designed so that there were approximately 250 people in each gender and ethnic group stratum. In all 1,577 participants were studied between 1994 and 1996. The present analysis includes 915 participants (297 white [131 men], 326 of black African origin [125 men] and 292 South Asian [154 men]) who were untreated and who provided both 24-hour urine collections and timed urine samples. The study had ethical approval (EG/CL/92.5.17 and 10/H1211/29) and participants gave their informed consent. The participants were asked to attend a screening unit between 08.00 am and 12.00 noon. They were requested to fast for the 12 h prior to the visit. All attendees were administered a questionnaire, which was used to determine age, ethnic origin, history of migration, socioeconomic and lifestyle characteristics. Height and weight were measured and used to calculate body mass index (BMI) (weight/(height)^2). Supine BP was measured with standardised procedure using an automatic machine as previously described. After the interview participants were asked to collect 24-hour urine sample within a few days. They were given written

detailed instructions on how to collect complete 24-hour urine sample. Complete urine collections were either returned by the participants or were collected at the participant's address. Time and volume of collections were immediately recorded, aliquots taken and stored at -20°C until assayed. A timed urine collection after an overnight fast was also obtained on the morning of the investigation after the participants had drunk one-to-two glasses of tap water in the morning. Volume (in ml) and duration (in min) of the collection were recorded and specimens were aliquoted and stored at -20°C until assayed. Urinary sodium and creatinine (Cr) concentrations were measured using an automated analyser.

Study 2 (validation study)

The study started in 1975 with periodical follow-up for 30 years and involved the Olivetti factories male workforce in southern Italy (www.olivettiheartstudy.org). Data presented in this study were collected during the 2002–2004 follow-up examination; a total of 148 healthy men, aged 32 to 75 years were examined, as described elsewhere (174). The local ethics committee approved the study protocol, and participants gave their informed consent. Body weight and height were measured on a standard beam balance scale. Body weight was measured to the nearest 0.1kg and height was measured to the nearest centimeter. The BMI was calculated as in Study 1. BP was taken after the subject had been sitting upright for at least 10 min. Systolic and diastolic (phase V) BP were measured with a random zero sphygmomanometer (Gelman Hawksley Ltd., Sussex, UK) three times, 2 min apart. The first reading was discarded, and the average of the last two readings was recorded. A 24-hour urine collection was obtained from each participant for the

measurement of sodium excretion to estimate daily dietary sodium intake. On the day before the visit, participants were instructed to discard the first urine of the morning of the collection and to save all urines voided for the following 24hour. Urine was collected in polypropylene bottles, and delivered to the laboratory for immediate storage of the samples at -80°C. Urinary sodium concentration was measured by flame photometry. The 24-hour urinary creatinine excretion was used as an estimate of the completeness of the collection: the participants whose urinary creatinine felt below the 5th percentile of the distribution (0.6 g creatinine/24 h) were excluded from the analysis. Urinary creatinine was determined by picric acid colorimetric method (Jaffe`) using Cobas-Mira analyzer.

Statistical analyses

Estimation methods

Two methods are used to estimate 24-hour urinary sodium from timed urinary sodium: Tanaka's prediction and arithmetic extrapolation.

Tanaka's prediction is completed in the following three equations:

$$\textbf{24-hour Ur Cr} \approx \textbf{Predicted 24-hour Ur Cr} \tag{1}$$

$$\frac{\textbf{24-hour Ur Na}}{\textbf{24-hour Ur Cr}} \propto \frac{\textbf{timed Ur Na}}{\textbf{timed Ur Cr}} \tag{2}$$

$$\textbf{24-hour Ur Na} \propto \frac{\textbf{timed Ur Na}}{\textbf{timed Ur Cr}} \times \textbf{Predicted 24-hour Ur Cr} \tag{3}$$

where Na is sodium and Cr is creatinine. Equation (1) assumes that 24-hour urinary creatinine excretion at population level can be approximately estimated on the basis of age, weight and height. Equation (2) assumes that 24-hour urinary sodium to

creatinine ratio is proportional to timed urinary sodium to creatinine ratio. Equation (3) is simply obtained by transforming equation (2) and replacing the measured 24-hour urinary creatinine with the predicted values. More details of Tanaka's prediction can be found elsewhere (175-177).

The *arithmetic extrapolation* is shown in equation (4). The estimated 24-hour urinary sodium is obtained by simply extrapolating the timed 24-hour urinary sodium excretion level from timed duration to 24-hour scale:

$$\begin{aligned}\textbf{Estimated 24-hour Ur Na} &= (\textbf{timed Ur Na concentration} \times \textbf{timed Ur vol}) \\ &\times (\textbf{24-hour/Ur collection time})\end{aligned} \quad (4)$$

Statistical methods

In Study 1 the analyses were stratified by gender since men and women differ significantly in weight and height, and therefore have different level in urinary creatinine and sodium. Stepwise regression was used to predict 24-hour urinary creatinine, as stated by Tanaka *et al.* (175). Correlation coefficients were examined to compare the estimated and measured 24-hour sodium. Bland-Altman plot is generally used to compare agreement of measurements in a graphical way. We used it to validate the agreement between the estimated and measured 24-hour values (178). The agreement was also examined by area under the curve (AUC) of Receiver Operating Characteristic (ROC) curve and sensitivity and specificity with a cut-off of <100 mmol/day (6 g salt per day) of urinary sodium (179). In addition, timed urinary sodium was compared by quintiles of 24-hour urinary sodium. A p-value

<0.05 was considered statistically significant. All analyses were conducted using SPSS v17.

3.3.3 Results

Study 1 (discovery study)

The characteristics of the participants in Study 1 are shown in Table 3.3.1. Men were heavier and taller than women. Daily urinary sodium and creatinine excretions were significantly higher in men, whilst daily sodium to creatinine ratio was higher in women (all p-values ≤ 0.001). Similar differences were seen in timed sodium and creatinine concentrations. Timed sodium to creatinine ratio was significantly higher in women across all ethnic groups (all p<0.001). Timed urine volume was greater in women than men, irrespective of ethnicity, while only white women had lower 24-hour urinary volume than white men (2,173 v 2,724 ml/day, p<0.001). The average sodium (salt) intakes estimated with the Tanaka methods were not surprisingly comparable to the measured ones, since they were used to develop coefficients for the Tanaka equations. However, the arithmetic method consistently underestimated the intake.

Table 3.3.1 *Age adjusted characteristics of population in Study 1 (discovery study) by gender and ethnic group*

	Whites (n=297)		p value	African origins (n=326)		p value	South Asians (n=292)		p value
	Female (n=166)	Male (n=131)		Female (n=201)	Male (n=125)		Female (n=138)	Male (n=154)	
Age (year)	50.3 (49.4, 51.2)	51.3 (50.4, 52.3)	0.117	51.1 (50.3, 51.9)	52.5 (51.5, 53.6)	0.025	49.6 (48.6, 50.6)	49.5 (48.6, 50.5)	0.926
Height (cm)	160.9 (159.8, 161.9)	174.7 (173.5, 175.8)	<0.001	160.9 (160.0, 161.7)	172.7 (171.5, 173.8)	<0.001	155.1 (154.1, 156.1)	170.3 (169.3, 171.2)	<0.001
Weight (kg)	67.1 (65.2, 69.0)	77.2 (75.1, 79.3)	<0.001	76.1 (74.2, 77.9)	79.3 (77.0, 81.7)	0.036	65.5 (63.4, 67.5)	71.4 (69.4, 73.3)	<0.001
BMI (kg/m^2)	26 (25.3, 26.6)	25.3 (24.5, 26.0)	0.161	29.4 (28.8, 30.0)	26.5 (25.7, 27.3)	<0.001	27.2 (26.5, 27.9)	24.6 (23.9, 25.3)	<0.001
Waist to hip ratio	0.804 (0.794, 0.814)	0.916 (0.904, 0.927)	<0.001	0.836 (0.827, 0.846)	0.92 (0.908, 0.932)	<0.001	0.849 (0.836, 0.861)	0.937 (0.925, 0.949)	<0.001
Systolic B.P. (mmHg)	123.1 (120.5, 125.7)	125.6 (122.6, 128.5)	0.226	135.6 (132.8, 138.4)	135.6 (132.1, 139.1)	0.999	128.8 (126, 131.6)	129 (126.3, 131.6)	0.945
Diastolic B. P. (mmHg)	77.2 (75.8, 78.7)	81.2 (79.6, 82.8)	<0.001	85.2 (83.8, 86.7)	88.7 (86.9, 90.5)	0.004	80.4 (78.8, 81.9)	85.3 (83.9, 86.8)	<0.001

Table 3.3.1 *cont'd*

	Whites (n=297)		p value	African origins (n=326)		p value	South Asians (n=292)		p value
	Female (n=166)	Male (n=131)		Female (n=201)	Male (n=125)		Female (n=138)	Male (n=154)	
24-hour Urine volume (mL)*	2,173 (2,034, 2,324)	2,724 (2,528, 2,936)	<0.001	2,271 (2,141, 2,409)	2,180 (2,023, 2,350)	0.407	2,165 (1,998, 2,346)	2,298 (2,131, 2,480)	0.287
24-hour Urinary Na (mmol/day)*	129.9 (121.9, 138.5)	174.9 (162.8, 187.8)	<0.001	145.9 (137.9, 154.5)	170.9 (159, 183.6)	0.001	129.8 (121.2, 139.0)	161.4 (151.3, 172.2)	<0.001
24-hour Urinary Cr (mmol/day)*	9.5 (9.1, 9.9)	13.9 (13.2, 14.5)	<0.001	12.2 (11.7, 12.7)	17.2 (16.4, 18.1)	<0.001	7.6 (7.2, 8.0)	12 (11.4, 12.6)	<0.001
24-hour Urinary Na/Cr	13.7 (13, 14.4)	12.6 (11.9, 13.4)	0.043	12 (11.4, 12.6)	9.9 (9.3, 10.6)	<0.001	17 (16.0, 18.1)	13.5 (12.8, 14.3)	<0.001
timed Urine volume (mL)*	246 (218, 278)	200 (174, 230)	0.028	233 (211, 258)	151 (133, 172)	<0.001	223 (193, 256)	183 (160, 209)	0.048
timed Urine collection time (min)*	148 (141, 155)	137 (130, 144)	0.038	152 (145, 159)	145 (137, 154)	0.269	139 (130, 149)	141 (132, 150)	0.772
timed Urinary Na concentration (mmol/L)*	47.4 (43.6, 51.4)	61.9 (56.4, 67.8)	<0.001	54.8 (50.6, 59.4)	89.6 (80.9, 99.2)	<0.001	49.4 (44.5, 54.7)	64.5 (58.5, 71.1)	<0.001
timed Urinary Cr concentration (mmol/L)*	3.4 (3.0, 3.8)	6 (5.3, 6.9)	<0.001	4.4 (4.0, 4.9)	9.8 (8.5, 11.2)	<0.001	3 (2.6, 3.5)	5.2 (4.5, 5.9)	<0.001
timed Urinary Na/Cr*	13.9 (12.7, 15.2)	10.3 (9.3, 11.3)	<0.001	12.4 (11.5, 13.4)	9.1 (8.3, 10.0)	<0.001	16.3 (14.8, 18.0)	12.5 (11.4, 13.7)	<0.001

*Note: Values are shown as Mean (95% CI) unless stated; Na: sodium, Cr: creatinine; *: Geometric means.*

Tanaka's prediction

Estimates of daily urinary sodium using the Tanaka method were derived for men and women in each ethnic group. Correlations between measured and estimated 24-hour urinary sodium were weak, although significant in Whites ($r_{Spearman}$=0.251; p=0.004 in men and 0.330; p<0.001 in women) and South Asians (0.187; p=0.02 and 0.310; p<0.001 in men and women respectively) (Table 3.3.2). Low grade and non-significant correlations were seen in men and women of African origin (0.166; p=0.065 and 0.055; p=0.436, respectively).

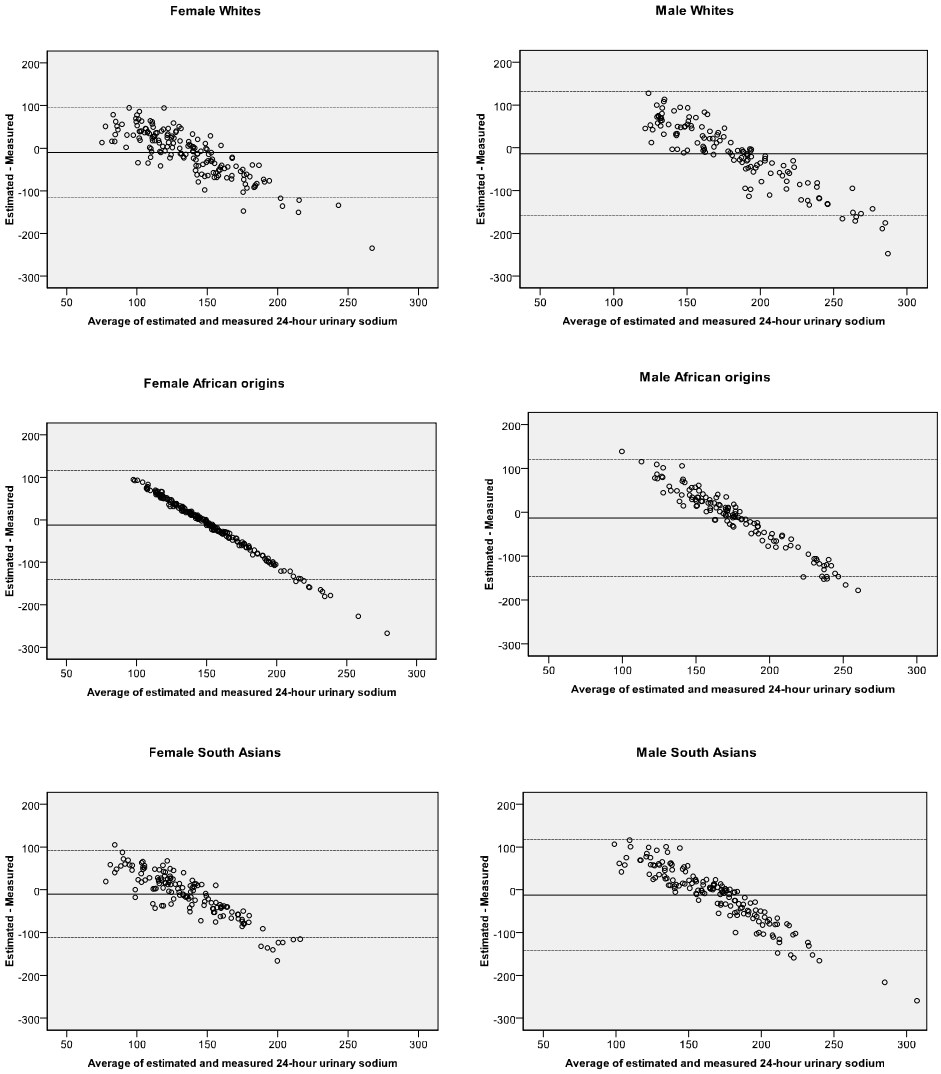
Table 3.3.2 *Correlations between estimated 24-hour urinary sodium by Tanaka method and by Arithmetic method, and measured 24-hour urinary sodium*

	Tanaka's method			Arithmetic method		
	Whites	African origins	South Asians	Whites	African origins	South Asians
Women	0.330 (<0.001)	0.055 (0.436)	0.310 (<0.001)	0.367 (<0.001)	0.116 (0.102)	0.264 (0.002)
Men	0.251 (0.004)	0.166 (0.065)	0.187 (0.020)	0.282 (0.001)	0.221 (0.013)	0.170 (0.035)

Note: Values are expressed as coefficient (p-value).

The Tanaka's prediction produced overestimated values in the low 24-hour urinary sodium levels and underestimated values in the high 24-hour urinary sodium levels across genders and ethnic groups indicating consistent bias (Figure 3.3.1). The bias was mainly due to the inaccuracy of age, weight and height to predict 24-hour creatinine excretion in the three ethnic groups, particularly in those of African origin (data not shown).

Figure 3.3.1 *Study 1: Bland-Altman plot comparing estimated 24-hour urinary sodium by Tanaka method and measured 24-hour urinary sodium*



Note: Solid and dashed lines are mean and 95% confidence interval of the difference between estimated and measured 24-hour urinary sodium.

Using Receiver Operating Characteristic (ROC) Areas Under the Curve (AUC) estimated 24-hour urinary sodium values were poor (all <0.750) using measured 24-hour urinary sodium as gold standard. Using a measured 24-hour urinary sodium >100 mmol/day as positive test, estimated values had moderate sensitivity and poor specificity in both genders and all ethnic groups (Table 3.3.3).

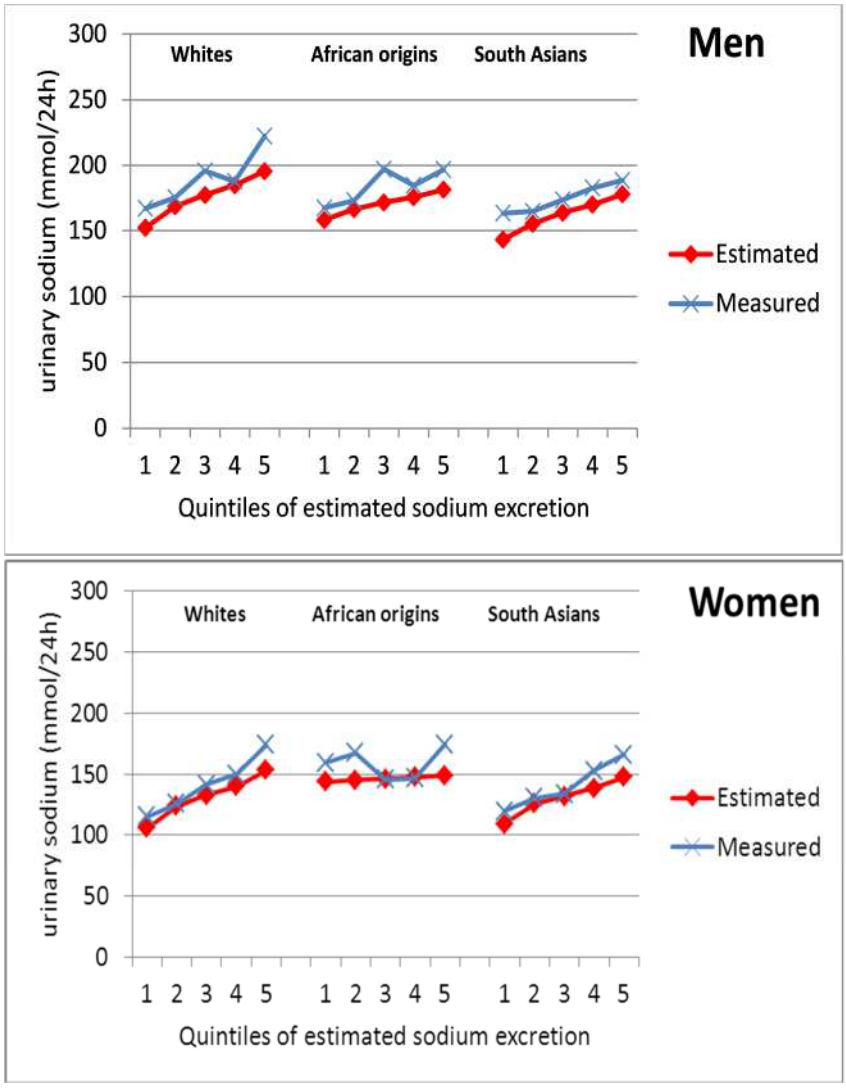
Table 3.3.3 *ROC, sensitivity and specificity of two methods of estimation*

	Tanaka's method			Arithmetic method		
	Whites	African origins	South Asians	Whites	African origins	South Asians
Women	0.652 (95.8/8.5)	0.550 (100/0)	0.631 (95.3/6.3)	0.640 (68.1/51.1)	0.533 (64.4/42.1)	0.603 (68.9/53.1)
Men	0.538 (100/0)	0.521 (100/0)	0.582 (100/0)	0.514 (69.0/33.3)	0.575 (70.4/20.0)	0.624 (68.9/45.5)

Note: Measured 24-hour urinary sodium 100 mmol/day is defined as positive; results are expressed as Area Under Curve (sensitivity %/specificity %).

Figure 3.3.2 shows both estimated and measured 24-hour urinary sodium plotted against quintiles of estimated 24-hour sodium. Poor discrimination of measured sodium was found between Q3 and Q4 in white men and Q1, Q2 and Q3 in South Asians. The worst estimation of group means was in those of African origin.

Figure 3.3.2 *Study 1: Measured 24-hour urinary sodium by quintiles of estimated 24-hour urinary sodium using Tanaka's method*

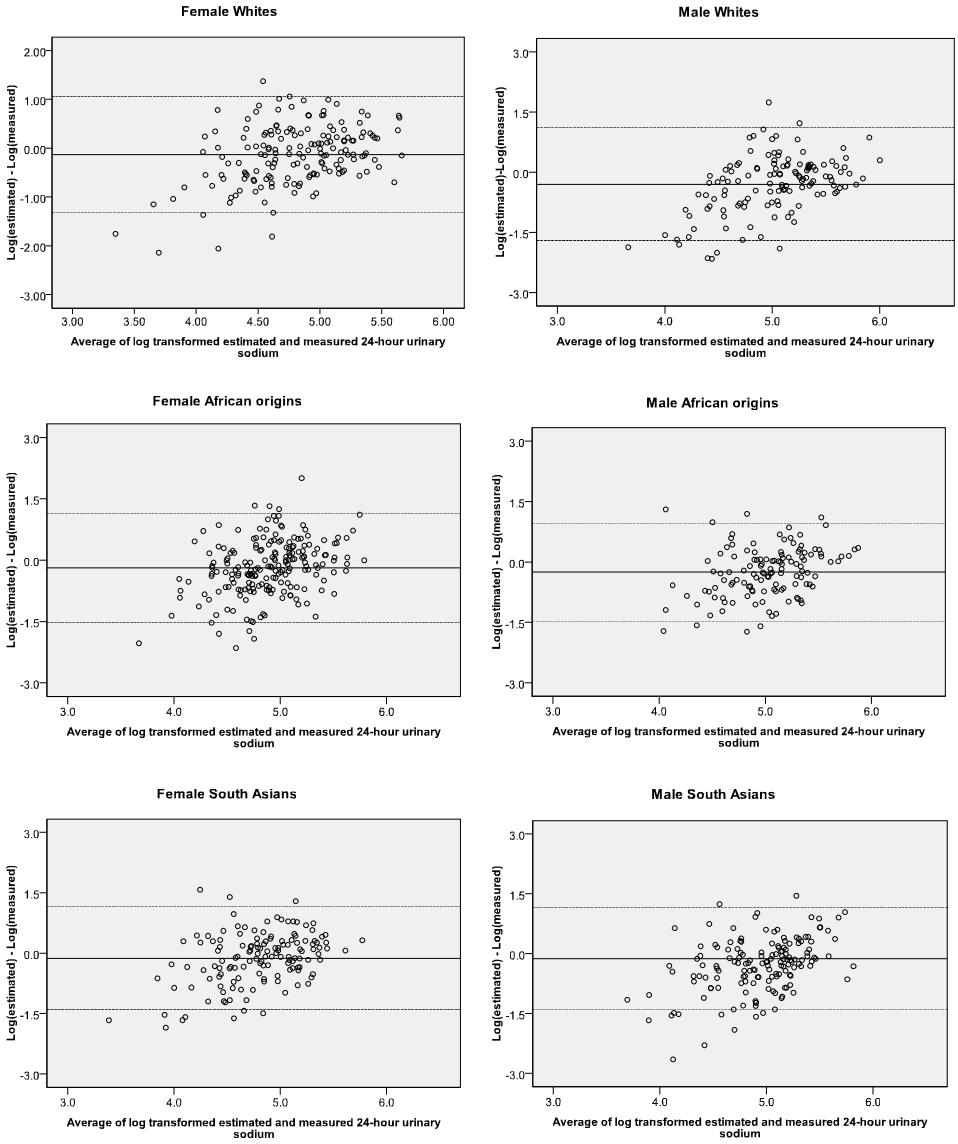


Arithmetic extrapolation

Similar to the Tanaka's method, correlations between measured and estimated 24-hour urinary sodium were weak, although significant in Whites ($r_{Spearman}$=0.282; p=0.001 in men and 0.367; p<0.001 in women) and South Asians (0.170; p=0.035 and 0.264; p=0.002 in men and women respectively). In people of African origin the correlation was significant in men (0.221; p=0.013) but not in women (0.116; p=0.102).

The Arithmetic extrapolation produced underestimated values in the low 24-hour urinary sodium levels and overestimated values in the high 24-hour urinary sodium levels across genders and ethnic groups indicating consistent bias (Figure 3.3.3). The bias was in the opposite direction as that described using the Tanaka's method.

Figure 3.3.3 *Study 1: Bland-Altman plot comparing estimated 24-hour urinary sodium by Arithmetic method and measured 24-hour urinary sodium*



Note: Solid and dashed lines are mean and 95% confidence interval of the difference between estimated and measured log transformed 24-hour urinary sodium.

Using Receiver Operating Characteristic (ROC) Areas Under the Curve (AUC), again, estimated 24-hour urinary sodium values were poor (all <0.750) using measured 24-hour urinary sodium as gold standard. Using a measured 24-hour urinary sodium >100 mmol/day as positive test, estimated values had moderate sensitivity and poor specificity in both genders and all ethnic groups (Table 3.3.3).

Figure 3.3.4 *Study 1: Measured 24-hour urinary sodium by quintiles of estimated 24-hour urinary sodium using the Arithmetic method*

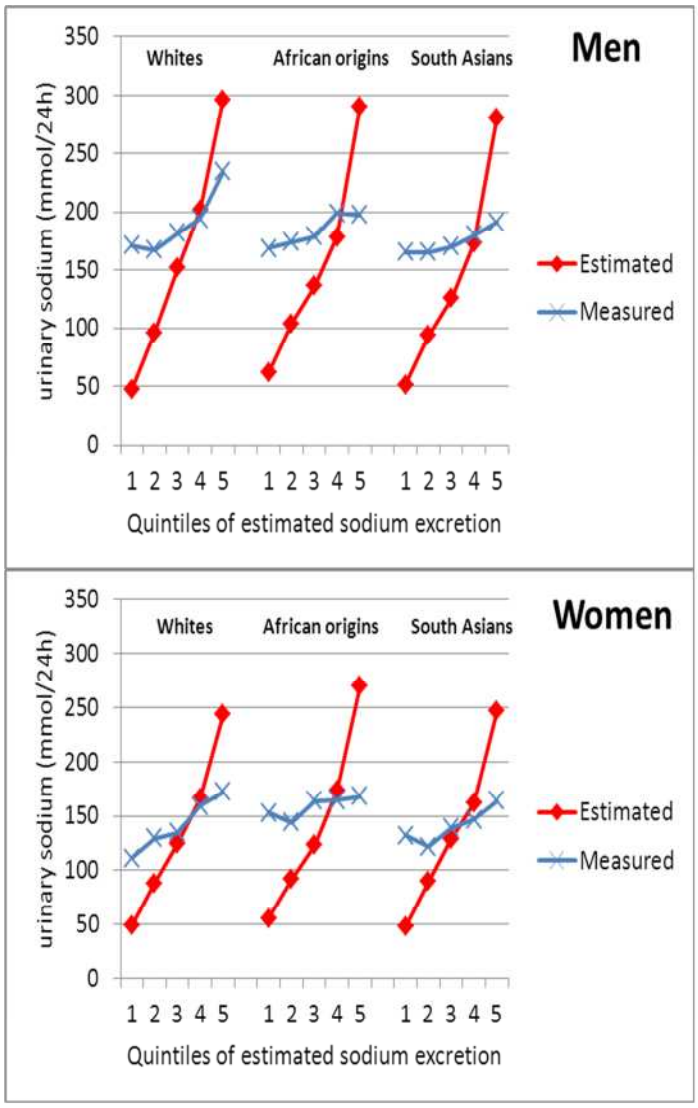


Figure 3.3.4 shows both estimated and measured 24-hour urinary sodium plotted against quintiles of estimated 24-hour sodium. There is a very poor discrimination of measured sodium. Furthermore, a bias is clearly detected with gross underestimate at low intakes and gross overestimates at high intakes across genders and ethnic groups.

Note that natural logarithm transformation was applied in this case on the estimated and measured sodium values in order to remove the dependence of variation on the magnitude of urinary sodium level.

Study 2 (validation study)

We carried out a validation analysis in an independent population sample of white men, whose characteristics are shown in Table 3.3.4.

Table 3.3.4 *Age adjusted characteristics of population in Study 2 (validation study) (n=148)*

Variables	Mean (95% CI)
Age (year)	58.3 (57.1, 59.4)
Height (cm)	166.9 (166.0, 167.9)
Weight (kg)	75.8 (74.0, 77.6)
BMI (kg/m^2)	27.2 (26.6, 27.7)
Waist to hip ratio	0.985 (0.974, 0.995)
Systolic BP (mmHg)	138.1 (135.4, 140.8)
Diastolic BP (mmHg)	89.8 (88.3, 91.3)
24-hour Urinary Na (mmol/day)*	193.3 (181.1, 206.4)
24-hour Urinary Cr (mmol/day)*	12.6 (12.0, 13.3)
24-hour Urinary Na/Cr	15.3 (14.4, 16.3)
timed Urine volume (mL)*	275 (250, 303)
timed Urine collection time (min)*	119 (117, 121)
timed Urinary Na concentration (mmol/L)*	54.7 (48.9, 61.1)
timed Urinary Cr concentration (mmol/L)*	3.5 (3.1, 4.0)
timed Urinary Na/Cr*	15.5 (14.3, 16.9)

Note: Na: sodium, Cr: creatinine: Geometric means.*

Tanaka's prediction

As the participants were all whites, the formulas for white men obtained in Study 1 were used. The pattern of correlation between measured and estimated 24-hour urinary sodium was similar to the one obtained in white men in Study 1, although the correlation coefficient was stronger ($r_{Spearman} = 0.499$; $p<0.001$). Like in Study 1, the Bland-Altman plot indicated overestimated values in the low 24-hour urinary sodium levels and underestimated values in the high 24-hour urinary sodium levels indicating consistent bias (Figure 3.3.5a). Although the Area Under the Curve (AUC) of ROC was higher than white men in Study 1 (0.649), it was still below 0.750 with specificity of 100% (sensitivity 0%) for the detection of values <100 mmol/day. Figure 3.3.5c shows the comparison between estimated and measured 24-hour urinary sodium in Study 2 by quintile. Again the quintile was created on the basis of estimated urinary sodium values. The estimated values show significant underestimation in the Q3-Q5.

Arithmetic extrapolation.

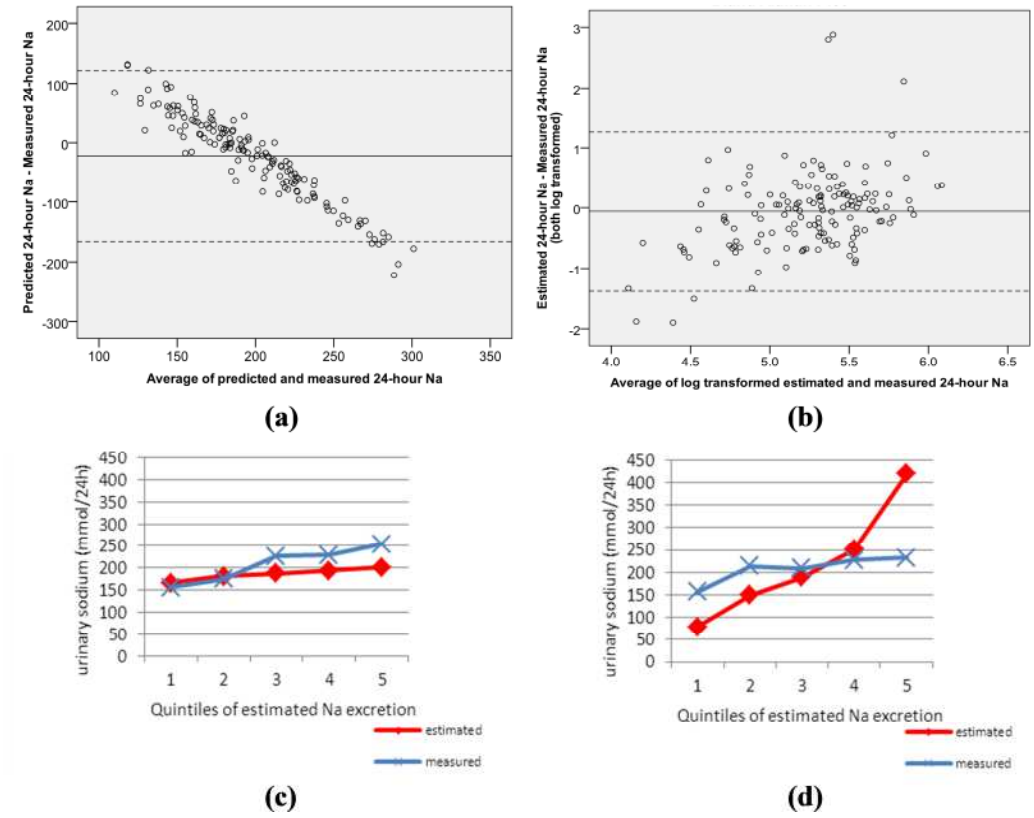
Similar to the Tanaka's method, correlations between measured and estimated 24-hour urinary sodium were weak, although significant ($r_{Spearman}=0.329$; $p<0.001$).

The Arithmetic extrapolation produced underestimated values in the low 24-hour urinary sodium levels and overestimated values in the high 24-hour urinary sodium levels indicating consistent bias (Figure 3.3.5b). The bias was in the opposite direction as that described using the Tanaka's method, consistent with the results of Study 1.

Using Receiver Operating Characteristic (ROC) Areas Under the Curve (AUC), like in Study 1, estimated 24-hour urinary sodium values were poor (0.576) using measured 24-hour urinary sodium as gold standard. Using a measured 24-hour urinary sodium >100 mmol/day as positive test, estimated values had moderate sensitivity (85.5%) and poor specificity (20.0%).

Figure 3.3.5d shows both estimated and measured 24-hour urinary sodium plotted against quintiles of estimated 24-hour sodium. Using this method, there is poor discrimination of measured sodium. Furthermore, a bias is clearly detected with underestimate at low intakes and overestimates at high intakes. Note that, as in Study 1, natural logarithm transformation was applied in this case on the estimated and measured sodium values in order to remove the dependence of variation on the magnitude of urinary sodium level.

Figure 3.3.5 *Study 2. Comparison of 24-hour urinary sodium measured by Tanaka's method (a) and arithmetic method (b) and 24-hour urine sample (solid line - mean of difference, dash lines - mean±2SD). Comparison between estimated and measured 24-hour urinary sodium by quintiles of sodium with the Tanaka method (c) and the arithmetic methods (d)*



Note: Na: sodium.

3.3.4 Discussion

This study investigated the reliability and reproducibility of two methods of assessing daily sodium excretion (hence salt intake) alternative to 24-hour urinary sodium, based on spot timed urine collections, using two independent population samples. The results show that simple and less expensive alternative methods using spot and timed urine samples produce biased estimations and have low-grade agreement with 24-hour urine collections in both populations. This is in spite of the average value in sex and ethnic groups were highly comparable with one method.

The methods show different performance in male and female white, black and South Asian groups, with the worst estimation in people of black African origin. The results suggest that whilst alternative methods using spot and timed urine samples may be able to approximate average true levels in population samples, they are unreliable and not reproducible for estimating salt intake between groups within the same population and they are therefore unsuitable for monitoring group changes over time. Our conclusions are in keeping with those of a recent systematic review of the world literature carried out in over 1.3M participants in adults and children (171). The present study adds to the previous evidence in that it provides a systematic validation study repeated in an independent population sample to show the presence of bias. This is a great importance since the assessment of population's salt intake and its changes over time underpin current policies for population salt reduction and it is a major pillar of such programs globally (180).

The estimations by the two methods across all ethnic groups show consistently low-grade correlation with measured 24-hour urinary sodium. The weak correlations of the estimation by the Tanaka's method are different from other studies. Tanaka *et al.* (181) reported a correlation coefficient of 0.54 in a Japanese population sample but a coefficient of 0.32 in a validation Japanese sample, both using random spot urines. Kawasaki *et al.* (182) adopted a similar estimation method. They produced a correlation coefficient of 0.73 with measured values in a Japanese sample using second morning voiding urines. In the United States, Mann also employed this method and used measured 24-hour urinary creatinine in a group of patients with unstated illness. Correlation coefficients were 0.17, 0.31 and 0.86 in random spot,

morning and evening urines. The variation of reported coefficients indicates that Tanaka's method perform inconsistently in different populations.

Although the alternative methods can provide a convenient and less expensive way to estimate 24-hour urinary sodium, the estimations are dependent on the variability of urinary sodium concentration. Sodium concentration in spot and timed urines has high inter-individual and intra-individual variability, which are caused by various factors, including time of collection (e.g. morning vs afternoon), dietary consumption (e.g. high-salt-content meal vs low-salt-content meal), hydration and residual bladder volume (171). Using quintile analysis and Bland-Altman plots, the estimation by the Arithmetic method has also shown large discrepancy with measured 24-hour sodium in both samples. It is mainly caused by the sodium variability. If sodium concentration in the timed urine is close to 0, the estimated 24-hour urinary sodium will also be close to 0. Therefore, the Arithmetic method is very likely to produce extreme estimates. Compared to the Arithmetic method, Tanaka's method estimates 24-hour urinary sodium with adjustment for 24-hour urinary creatinine. Although the adjustment somewhat reduces the variability of sodium concentration, its 24-hour sodium estimation is still constrained by the accuracy in prediction of 24-hour urinary creatinine excretion. The prediction assumes that participants' age, weight and height can approximately produce accurate 24-hour creatinine excretion. Our results, however, indicate that this assumption is population-specific. The correlation between predicted and measured 24-hour urinary creatinine is weak (results not shown). Although the quintile comparison shows underestimation across all ethnic groups, which is consistent with Tanaka and colleagues' results (181), poor discrimination is presented in some ethnic groups, e.g.

African men and women and White women. Consistent bias is shown in Bland-Altman plots with poor diagnostic performance presented in sensitivity and specificity test. Tanaka's method produced underestimations at high levels of salt intake and overestimations at low levels.

Strengths and limitations

Timed urine samples were used in our analysis instead of spot urine samples. It is known that sodium concentration varies considerably in spot urines. The variability in timed urine samples may be stabilised by the collection time. In addition, our analysis was conducted in participants from populations rather than from patients' groups. Different ethnic representation enabled us to investigate the reproducibility and reliability in different groups. Moreover, our analysis used not only correlation coefficient and quintile comparison, but Bland-Altman plot, Receiver Operating Characteristic curve and sensitivity/specificity test for comparing agreement and diagnostic performance.

Our analysis has limitations. The validation sample only includes Italian White men. This may limit our validation in both genders and people of African origin and South Asian groups. We relied on a single 2h-h urine collection for each participant. This may not be adequate for accurate measurement as salt intake differs largely from day to day (183). Our analysis tested two methods. Other forms of estimation, such as sodium to potassium ratio, are not analysed and discussed here. The inaccuracy of completeness (both under- and over-collections) is also a limitation. We did not use the para-aminobenzoic acid method (184;185) as it would not be feasible for

population studies, especially in low- and middle-income countries, would reduce response rate, and would increase resources needed for surveillance programs (171).

Implications

The use of alternative methods based on spot and timed urines have become increasingly popular as they are less onerous for participants, allow faster screening time and require less training of staff. Although they are convenient, the methods are likely to produce biased estimations of salt intake in populations. Moreover, these methods are not reproducible. The estimated coefficients for equations used in both Tanaka's methods and the Arithmetic method are different across ethnic groups. This indicates that for each specific population, the sodium to creatinine ratio, sodium concentration, and anthropometric information have to be collected each time in order to obtain the estimation equations for the population.

3.3.5 Conclusions

Urinary sodium concentration in spot and timed urines does not provide reliable and reproducible estimates of 24-hour urinary sodium excretion. 24-hour urinary collection for measurement of sodium excretion remains the preferred tool for assessing salt intake in populations.

3.4 Systematic Review of Studies Comparing 24-hour versus Spot Urine Collections for Estimating Population Iodine Intake

3.4.1 Introduction

Urinary iodine is widely used to measure iodine intake. Two approaches are used to assess urinary iodine: 24-hour urinary collection and spot urinary samples. Twenty-four-hour collection is the gold standard to estimate urinary iodine status (186). At least 90% of iodine intake is excreted in the urine within the next 24 hours. The remaining iodine in the body is utilised by the thyroid gland, as shown in Figure 2.2. The spot samples approach is more practical and easy to use, in spite of day-to-day variations in the spot samples at individual level (107;108). However, the reliability and reproducibility of the spot urine approach are not always satisfactory.

The present section aimed to systematically review all studies comparing iodine intake measured by both 24-hour urine collections and alternative methods (spot and timed) in both adults and children.

3.4.2 Methods

Literature search

Similar to the salt intake review, a search strategy was developed to identify studies that reported the association between iodine excretions measured by 24-hour urine collection and spot urine samples. We searched the electronic databases MEDLINE

(from 1950 to May week14, 2010) and EMBASE (from 1980 to week 18, 2010), as well as the Cochrane Library using the terms “sodium [dietary, chloride, intake, excretion]” “salt [intake]” and “urine [timed, spot, random, 24-hour]”. In addition, we reviewed reference lists of original and review articles to search for more studies. Only full-length articles were considered. No language restriction was applied. Only studies in humans were included.

Inclusion and Exclusion Criteria

Studies were included if they meet the criteria as set out below: (a) full paper, (b) human study, (c) population study or those based on large groups, and (d) availability of both 24-hour and ‘spot’, ‘overnight’ or ‘timed’ urinary iodine. Studies were excluded if the following criteria were met: (a) not in the English language, (b) abstract only, (c) sample size <40, (d) studies in special patients group (e.g. renal or heart failure, CHD, diabetes, etc.), and (e) studies not reporting either 24-hour urinary iodine or one of alternative methods (spot, overnight, timed urinary iodine). If multiple published reports from the same study were available, only the one with the most detailed information for both exposure and outcome was included.

Data extraction

Three investigators (CJ, LS and CP) extracted data independently and differences were resolved by discussion and consensus. Relevant data included the first author’s surname, year of publication, country of origin of the population studied, population type, sample size, age, description of urine sampling, mean or median iodine for 24-hour and for alternative samples, outcome measures (correlations, regression coefficients, Bland-Altman plots).

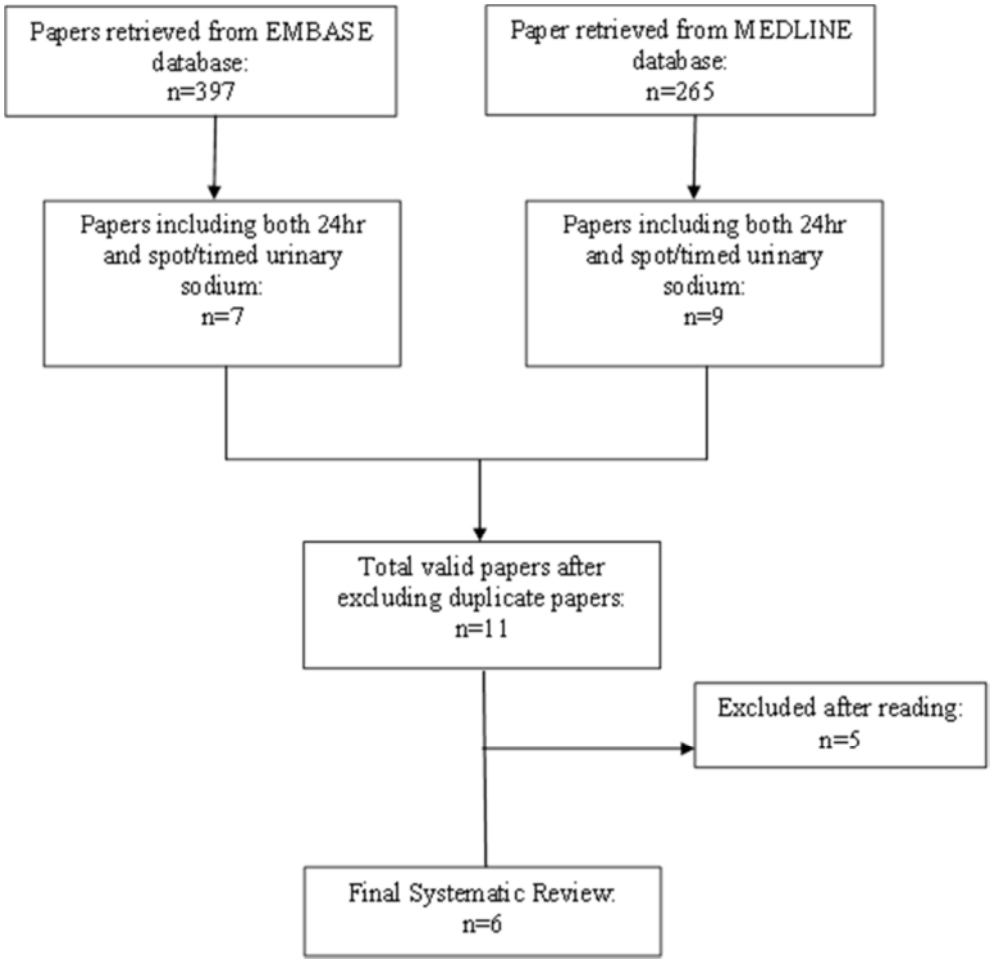
3.4.3 Results

Characteristics of studies

Eleven papers met the inclusion criteria. Five papers were excluded after reading the full papers due to lack of data. The actual sample size of participants providing both 24-hour and spot urinary iodine measurements in 2 papers was less than 40 (187;188). The other 3 papers only reported either 24-hour urinary iodine excretion or spot urinary iodine concentration (189-191). Of these three, 2 papers used the same population (189;190). Only 6 papers were finally included for this review (Figure 3.4.1). Four papers were conducted in the adult population, 1 in adolescents and 1 in both adults and children.

Overall, there were 1,434 participants from 5 countries (1 from Brazil, 2 from New Zealand, 1 from Norway, 1 from China and 1 from Ivory Coast). All studies recruited both male and female participants.

Figure 3.4.1 *Flow chart of systematic review of iodine intake*



Summary of studies

Details of these papers were listed in Table 3.4.1. One study (192) used an auto-Analyzer technique for iodine measurement, while the other three (193-195) used the Sandell-Kolthoff reaction method.

Two studies reported 24-hour urinary iodine excretion (UIE) and spot urinary iodine concentration (UIC) (196;197). However, no comparison (correlation, Bland-Altman plot, etc.) was made between the two measurements.

Frey *et al.* (192) conducted the study in a group of healthy Norwegian physicians and nurses. The urine samples were collected on an ordinary working day. The authors regressed the urinary iodine to creatinine ratio (I/Cr) estimated from the afternoon urine samples on the 24-hour UIE for men and women. Both relationships were significant (regression coefficient=0.5 for men and 0.76 for women). The coefficients were then applied in a population group to estimate the population iodine intake. The authors recommended using the spot urinary I/Cr for the estimation of 24-hour UIE, rather than using a theoretical value which ignored circadian variation in iodine excretion.

Thomson *et al.* (193) compared the association of urinary iodine levels measured from spot urine samples and 24-hour urine collection in a group of volunteers in New Zealand. Two types of spot urine samples were obtained: 1) a fasting urine sample collected one day prior to the 24-hour urine collection, and 2) a random sample obtained from the 24-hour urine collection. The authors reported a higher association between 24-hour UIE and the random UIC (r=0.58) and a lower association between 24-hour UIE and the fasting UIC (r=0.34). Although both correlations were significant, they concluded that a 24-hour urine collection was necessary for diagnosing iodine deficiency in individuals. They also suggested the use of fasting urines to estimate the iodine deficiency in the populations.

In another study in New Zealand, two groups of people were recruited from two blood transfusion centres. Thomson *et al.* (194) compared the 24-hour UIE with the UICs measured from overnight fasting urine samples and double voided fasting morning samples. Both concentrations showed comparable correlations with the 24-hour UIE (r=0.492 for overnight fasting and 0.475 for double voided) using the

pooled sample. The authors confirmed the necessity of using 24-hour urine collection to determine iodine status in individuals.

Vanacor *et al.* (195) conducted a study in a group of Brazilian men and women. Twenty-four-hour urine collection was obtained from four continuously collected samples: morning, afternoon, evening and overnight. The afternoon sample had a higher correlation with 24-hour UIE, compared to the other three timed urine samples (r=0.78 for afternoon, r=0.54 for morning, r=0.37 for evening and r=0.77 for overnight). The Bland-Altman plot suggested the afternoon sample was the best in estimating 24-hour UIE. The other three samples had increased level of over- and under-estimation. In particular, both evening and overnight samples had a trend of underestimated values in the low 24-hour urinary iodine levels and overestimated values in the high 24-hour urinary iodine levels. It was suggested that the afternoon sample was the best among the four spot urine samples to estimate the iodine status.

Table 3.4.1 *Systematic review of studies in adults*

Author (year)	Country	Population	Sample (n)	Age (yrs)	Urine samples	Urinary Iodine[a]	Ind.	Measure[b]	Notes
Frey *et al.* (1973)	Norway	Physicians Nurses	33 men 29 women	22-64 20-57	24h v spot (PM)	24h mean: 216 µg/d spot I/Cr: 114 µg/g 24h mean: 165 µg/d spot I/Cr: 125 µg/g	No	Regression: spot I/Cr=0.5*24h UIE Regression: spot I/Cr=0.76*24h UIE	Auto-Analyzer technique
Thomson *et al.* (1996)	New Zealand	Volunteers	31 men 31 women	18-56 18-58	24h v fasting spot v random spot	24h mean: 0.45 mmol/d 0.34 mmol/L F mean: 0.34 mmol/L R mean: 0.34 mmol/L	24h & random are dependent	F v 24h UIE: r=0.34 F v 24h UIC: r=0.39 R v 24h UIE: r=0.58 R v 24h UIC: r=0.56	Sandell-Kolthoff reaction method. 24h urines are necessary for diagnosis of iodine deficiency in individuals
Thomson *et al.* (1997)	New Zealand	Otago Blood Transfusion Centre Waikato Blood Transfusion Centre	102 men, 86 women 67 men, 77 women	18-68 19-72	24h v overnight fasting v double voided fasting morning	24h: 60 µg/d 42 µg/L ov: 43 µg/L DV: 43 µg/L 24h: 76 µg/d 53 µg/L ov: 50 µg/L DV: 45 µg/L	No	24h UIC v UIE: r=0.697 ov_fasting v 24h UIE: r=0.492 DV v 24h UIE: r=0.475 24h I/Cr v 24h UIE: r=0.833 ov_fasting I/Cr v 24h UIE: r=0.587 DV I/Cr v 24h UIE: r=0.597	Sandell-Kolthoff reaction method. UI concentrations comparable in threes samples. However, spot UIC poorly associated with 24h UIE, Bland-Altman plot indicated unsatisfactory agreement
Vanacor *et al.* (2008)	Brazil	Volunteers	17 men, 43 women	33.7	24h v AM, PM, eve, overninght	24h mean: 292 µg/d AM: 182 µg/L PM: 201 µg/L eve: 238.4 µg/L ov: 253.1 µg/L	No	AM v 24h UIE: r=0.544 PM v 24h UIE: r=0.778 eve v 24h UIE: r=0.366 ov v 24h UIE: r=0.771 Bland-Altman: PM estimates were closer to 24h, overestimation in eve and overnight samples	Sandell-Kolthoff reaction method. UI concentration in afternoon sample better reflected 24h UI concentration

Table 3.4.1 *cont'd*

Author (year)	Country	Population	Sample (n)	Age (yrs)	Urine samples	Urinary Iodine[a]	Ind.	Measure[b]		Notes
Hess *et al.* (1999)	Ivory Coast	Adults urban	30 men, 22 women	30.6	24h	443 µg/d	Yes	n/a		Sandell-Kolthoff reaction method. No comparison
		Adults rural	28 men, 21 women	29		166 µg/d				
		Children urban	110	10	spot (AM)	488 µg/L				
		Children rural	103	9.3		263 µg/L				
		Pregnant women urban	72	25.9		351 µg/L				
		Pregnant women rural	66	23		136 µg/L				
Wong *et al.* (1998)	China	Student	476 spot, 80 of them 24h	15.3 spot 15.1 24h	24h v spot (AM)	24h: 189 µg/d 170 µg/L spot: 190 µg/L	Yes	n/a		Ceric ion-arsenious acid reaction. No comparison

Note: Ind.: independent, UIE: urinary iodine excretion, UIC: urinary iodine concentration, I/Cr: urinary iodine/Creatinine ratio (ug/g), n/a: not available;
a: median values unless specified;
b: r: correlation coefficient; Regression: regression coefficient; Bland-Altman: Bland-Altman plot.

3.4.4 Discussion

This is the first systematic review of studies comparing urinary iodine levels estimated in spot urines and measured in 24-hour urine collection. Compared to the salt intake review (Section 3.2), very few studies have conducted such comparison in iodine. However, the included studies are still different in objectives, urinary iodine determination methods, types of urine collection, study populations, measures for comparison and protocols. The studies cannot provide convincing evidence on whether the gold standard can be replaced with any of the proposed methods or which urine sample is the best for estimating 24-hour urinary iodine excretion or concentration.

Advantages and disadvantages

Urinary iodine is a sensitive indicator of iodine intake and commonly used by the WHO and many Member States for measuring population and individual iodine status. More than 90% of the iodide is excreted in urine in the next 24 hours (89;90). Twenty-four-hour urine collection is the gold standard for iodine measurement.

However, this method has three major issues, including high participation burden, high cost and lack of completeness. In particular, a quality assurance tool was not widely used in the iodine measurement. In the four studies, only one study (195) reported that they used 75% of 24-hour urinary creatinine as a validation of urine collection completeness. Frey *et al.* (192) only asked participants to confirm the completeness. The other two studies did not report any method of such validation. The lack of quality assurance indicates the potential inaccuracy in 24-hour urinary

iodine measurement. In the salt intake review (Section 3.2), two possible methods were discussed: para-amino-benzoic acid (PABA) and urinary creatinine. The use of such methods needs to be included in the protocols for high quality urinary iodine measurement.

Alternative methods

Three studies used spot UIC to estimate 24-hour urinary iodine excretion. The UIC values were estimated from spot, morning, afternoon, evening, overnight and timed samples. Spot urinary iodine to creatinine ratio (I/Cr) was also used in one paper (192).

Correlation coefficient is commonly used for comparisons between spot UIC and 24-hour UIE. The results varied in different types of samples. Vanacor *et al.* (195) found the afternoon sample had the strongest correlation with 24-hour urine collection. Two New Zealand studies led by Christine Thomson both reported weak correlations between the overnight and double voided fasting samples and 24-hour collection.

Two of the 4 included studies (194;195) used Bland-Altman plot to examine the agreement of urinary iodine in spot samples and 24-hour urine collection. Bland-Altman plot perform better than correlation in terms of accuracy. Both studies produced unsatisfactory results according to the plots. In one study, the plots showed under- or over-estimation in all (morning, afternoon, evening and overnight) urine samples. In particular, these overestimated values may misclassify individual and

population iodine status, exposing more individuals than expected to the risk of iodine deficiency.

One study used urinary I/Cr to estimate 24-hour UIE. However, spot urinary creatinine varies considerably across populations, ethnic and age groups and by gender (198;199). Thus, creatinine correction may not properly adjust iodine for demographic differences.

Therefore, although median spot UIC may be used to monitor population iodine status, these alternative methods would not perform as well as the gold standard to make accurate classification of those at risk of mild, moderate and severe iodine deficiency.

Implications

The number of valid papers is far from sufficient to provide conclusive comparisons in urinary iodine between spot urine samples and 24-hour collection. However, the included papers highlighted methodological challenges in the comparison.

Firstly, spot urine samples were part of the 24-hour urine collection. The dependence inevitably increases the resulting correlation strength. Ideally, the comparison should be carried out using a spot or timed sample independent of the 24-hour collection.

Secondly, validation of 24-hour urine completeness did not appear to be a common practice in the studies. Any inaccurate collection could lead to biased estimation of the urinary iodine. Future studies could include one of the effective methods (e.g. PABA or urinary creatinine) for such validation.

In addition, there are concerns about the reliability and reproducibility of the spot urine methods in the adult population and the generalisability of the results for policy decisions. Four included papers were carried out in an adult population. No valid comparison was made in the most vulnerable populations (i.e. newborns, children, and women of pregnant age) to iodine deficiency and the main target of population iodisation programmes. Their dietary patterns and iodine status classification are different from the adults. Therefore, the findings in the included papers may not be applicable in these vulnerable populations. Studies specifically designed for these populations are needed to answer the question of this review.

When using spot urine samples to estimate urinary iodine excretion in a 24-hour span, people may encounter another issue related to total iodine intake. Studies often report UIC, UIE or both. There seems to be no consensus on which indicators should be consistently used. The WHO defines the optimal iodine status as 100-199 μg/L, which corresponds to the optimal average iodine intake of 150-300 μg/day. Even if UIC in spot urine samples has a high correlation with that in 24-hour urine collection, a high UIC is not necessarily associated with a high level of daily iodine intake. This is partly due to the circadian rhythm of urinary iodine excretion (191). In the same 24-hour span, spot UIC could be high at one time and low at another, while 24-hour UIE is constant. In addition, UIC (μg/L) is a measure that does not allow for the amount of urinary volume produced and hydration status. Further comparison of the association between UIC and UIE in both timed urine samples and 24-hour urine collection is desirable to provide better understanding of this issue and improve the report quality of iodine intake and iodine status.

Conclusions

The present systematic review suggests that simple methods using spot urine samples may not be as reliable and accurate as the gold standard for iodine intake measurement and it highlights the need for further methodological investigations. Given the limited evidence, 24-hour urine collection should still be the method for iodine intake measurement.

3.5 Summary of Chapter 3

Chapter 3 systematically reviewed the measurements of population salt and iodine intake since the reliability and reproducibility of such intakes are important to monitoring and evaluation of salt reduction and salt iodisation programmes. Twenty-four-hour urine collection is the gold standard for both salt and iodine intakes measurements, but it is also subject to high cost, lack of completeness and high participation burden. However, current evidence is not adequate and consistent, indicating that simple methods using spot urine samples are not as reliable and accurate as the gold standard for both salt and iodine intake measurements.

In particular, two popular measurements of salt intake based on spot urine samples were examined for their reliability and reproducibility in two independent populations using correlation, Bland-Altman plot, Receiver operating characteristics curve and quintile analysis. The resulting biases in the estimated 24-hour urinary sodium excretion suggested that 24-hour urine collection remains the preferred tool for assessing salt intake in populations.

Chapter 4 Research Methodology

4.1 Introduction

Before the introduction of universal salt iodisation (USI), iodine status varied geographically due to its natural distribution. There was higher prevalence of iodine deficiency in inland and mountainous areas than coastal areas. For example, the "goiter belt" in the United States (see Section 4.3 in Chapter 4) and the Alps and Pyrenees of Europe. After years of implementation of USI programmes worldwide, the geographical inequality is still reported at national (17;118) and sub-national levels (200-202). Likewise, data showed the levels of salt intake varied across (32;126) and within countries (203;204).

In many population studies, geographical information is collected but its usage is usually limited for descriptive purposes only. The exploration of the geographical structure of the data in the stage of data modelling is even rare. However, geographical information can be useful in that the effect of geographical location, known as spatial effect, can be regarded as a surrogate of many risk factors in that people clustered in the same area are usually exposed to similar risk factors, e.g. weather, food sources, education, and access to medical services, etc. Therefore, the inclusion of the spatial effect in the models is helpful to improve the estimation and understanding of the interested health outcomes.

A class of Bayesian geo-additive models will be used to estimate the spatial effect and the effects of other risk factors. Compared to conventional statistical models, such as general or generalised linear models, this innovative method has a few

advantages. Firstly, geographical locations are more or less inter-related in some way. Locations close to each other may exhibit a higher degree of correlation than those far apart (205). Therefore, many variables, particularly in national survey data, may have an unobserved spatial structure. Linear regression models may be able to estimate uncorrelated spatial patterns, but are incompetent to deal with the structure because the assumption of independence of model residuals is violated (206). Neglecting the spatial correlation may result in underestimation of standard errors of risk factors.

Secondly, health data, particularly national health survey data, are usually collected using complex sampling designs, such as stratification and multistage sampling. Although efficient and cost-saving, the sampling faces two issues. One is that some low level geographical locations (i.e. community or county) may be subjected to small sample size due to the design and response rate. The estimated spatial effect of these locations may be biased. The other is caused by clustered data. Some surveys often recruit two or more participants within one household. These participants are highly unlikely to be independent of each other, particularly in terms of dietary intakes and socioeconomic status. Appling sampling weight in the classic regression models would not correct the dependence issue. Accordingly, the resulting estimations of risk factors are possibly biased. Bayesian geo-additive models can take into account these issues by using a hierarchical model structure and spatial smoothing techniques to borrow strength from neighbouring locations to reduce posterior uncertainty.

Moreover, Bayesian geo-additive models can overcome the difficulty in dealing with the geographical variable. To incorporate a geographical variable in a regression

model, a common practice is to use dummy variables (207), i.e. one variable represents one specific geographical location. However, some health data were collected at the region or county level. Therefore the analysis probably has to handle a large number of dummy variables (e.g., US national surveys can generate 50 and more than 3,000 dummy variables for state and county information respectively), as well as other continuous and categorical covariates. The high-dimension of variables could be problematic and leads to great mathematical difficulty in parameter estimation.

In addition, some risk factors may have nonlinear associations with the interested health outcomes, e.g. age and income with mortality risk (208-210): here a simple linear assumption becomes inappropriate. Using a flexible nonlinear function could improve the reliability and accuracy of the estimations.

In short, Bayesian geo-additive models provide a unified framework for modelling linear and non-linear covariate effects and estimating the spatial effect simultaneously. This class of models can also produce visualised maps and graphs for better interpretation and presentation of the results.

Therefore, in this study, linear regression models will be used in data that do not contain sufficient geographical information (i.e. the Kumasi data), while a class of Bayesian geo-additive models will be used where data allow (i.e. the UK and US data). The following sections of this chapter give a detailed introduction of the Bayesian geo-additive models.

4.2 Model Construction

The Bayesian geo-additive models are developed by extending the generalised linear models (GLM) within the Bayesian framework. Consider n observations with a dependent variable y_i, and a vector of r covariates z_i, $i = 1, \ldots, r$, which contain either continuous or categorical variables, or both. The GLM assumes that the dependent variable belongs to an exponential family. The effects of the covariates are related to the expected mean (μ_i) of the dependent variable through a known link function $g(\eta_i)$, and η_i is a linear predictor that can be modelled by $z_i'\beta$, i.e.,

$$\boldsymbol{\mu_i = g(\eta_i) + \varepsilon_i, \eta_i = z_i{}' \beta, i = 1, \cdots, n} \tag{5}$$

Hastie and Tibshirani (211) extended the GLM to the GAM by replacing the single linear predictor with an additive semi-parametric predictor. Hence we have

$$\boldsymbol{\eta_i = f_1(x_{i1}) + \cdots + f_p(x_{ip}) + w_i{}' \delta} \tag{6}$$

where $f_1, \cdots, f_p$ are unknown smooth functions of continuous covariates $x_1, \cdots, x_p$, and $w_i'\delta$ are the strictly linear effects of covariates $w_1, \cdots, w_q$ which are categorical in most cases. Note that the original covariates vector z_i is divided into two sub sets: p dimensional set of x_{ip}, and q dimensional set of w_{iq}, where $p + q = r$. By adding a spatial effect $f_{spatial}$, the model is able to estimate the spatial effect on the dependent variable:

$$\boldsymbol{\eta_i = f_1(x_{i1}) + \cdots + f_p(x_{ip}) + f_{spatial}(s_i) + w_i{}' \delta} \tag{7}$$

where $s_i \in (1, \cdots, S)$ is the region index and $f_{spatial}(s_i)$ represents the spatial effect of the region s to which observation i belongs. The spatial effect is usually a

surrogate of many unobserved risk factors: some of them may follow certain spatial structures, while others may be only presented locally. Accordingly we can further divide this single spatial effect into two independent components: one is a correlated (structured) effect, f_{corr}, and the other is an uncorrelated (unstructured) effect, f_{uncorr}. Therefore the model finally becomes

$$\boldsymbol{\eta_i = f_1(x_{i1}) + \cdots + f_p(x_{ip}) + f_{corr}(s_i) + f_{uncorr}(s_i) + w_i' \delta} \quad (8)$$

4.3 Prior Construction

The estimation of the parameters in the Bayesian approach requires priors assigned to the unknown parameters. All these unknown parameters are regarded as random variables. Since there is no prior knowledge of the linear coefficient parameters δ, independent diffuse priors are assigned to the parameter, i.e., $\delta \in const$.

For the unknown smooth functions, a few smoothness prior choices have been proposed, including Bayesian smoothing splines (212), random walk priors (213) and Bayesian penalised splines (P-splines) (214). However, the Bayesian P-splines approach leads to more parsimonious and yet flexible modelling (215). Hence, it will be used in the following analyses. The Bayesian P-splines approach is a Bayesian analogue of the P-splines introduced by Eilers and Marx (216). They suggest that a smooth function can be approximated by a polynomial regression spline using a large number (k+1), usually 20 to 40, of equally spaced knots over domain of $x_j, j = 1, \cdots, p$. Therefore, for each covariate x_j, an l degree P-spline is a linear combination of $K_j = k + l$ basis function B_j. That is,

$$\boldsymbol{f_j(x_j) = \sum_{\lambda=1}^{K_j} \alpha_{j\lambda} B_{j\lambda}(x_j)} \quad (9)$$

where $\alpha_{j\lambda}$ is the unknown regression coefficient of B_j. Eilers and Marx use squared b^{th} order (usually 1st or 2nd) penalty to prevent overfitting and ensure the smoothness of smooth functions. The Bayesian P-splines substitute the penalty term with a b^{th} (correspondently first or second) order random walk, i.e. $\alpha_{j,t} = \alpha_{j,t-1} + \varepsilon_t, t \in (2, \cdots, p)$ or $\alpha_{j,t} = 2\alpha_{j,t-1} - \alpha_{j,t-2} + \varepsilon_t$, $t \in (3, \cdots, p)$ with Gaussian errors $\varepsilon_t \in N(0, \sigma^2_{smooth})$ and diffuse priors $f_1 \in const$ or $f_1 \; and \; f_2 \in const$. Therefore, the estimation of the smooth functions is reduced to the estimation of those unknown coefficients.

The correlated and uncorrelated spatial effects are assigned with different priors. For the correlated spatial effects, common choices are stationary Gaussian random fields (GRF) priors, two dimensional P-splines and Markov random fields (MRF) priors (217;218). However, GRF and two dimensional P-splines are commonly used for point-level geographical data (i.e. longitude and latitude), while MRF is used for aggregated geographical data (i.e. county and districts) (217). Hence, MRF is used to construct the priors of correlated spatial effects in this study. The MRF approach is based on the assumption that the spatial effect in region s depends on its neighbouring regions. In spatial statistics, two regions are defined as neighbours if they share a common boundary. Hence, the distribution of the spatial effect in region s is conditional on its neighbouring regions:

$$\boldsymbol{f_{corr}(s_i) = f_{corr}(s_i)|f_{corr}\left(s_i^{'}\right) \sim N\left(\sum \frac{1}{N_{s_i^{'}}} f_{corr}\left(s_i^{'}\right), \frac{\sigma_{cor}^2}{N_{s_i^{'}}}\right)} \quad (10)$$

where $f_{corr}(s_i')$ is the effect of each neighbouring region of region s_i and $N_{s_i'}$ is the total number of all neighbours of region s_i. Note that the mean of the spatial effect of a specific region is the average of its neighbours' spatial effects.

For the uncorrelated spatial effects, we assume them as normally distributed random variables with mean 0, i.e., $f_{uncorr}(s_i) \sim N(0, \sigma_{uncorr}^2)$.

The variance terms σ^2 (e.g. σ_{smooth}^2, σ_{corr}^2, and σ_{uncorr}^2) are assumed as random variables so that they can be simultaneously estimated with the smooth functions and spatial effects. In addition, since there is no prior knowledge of these variances, highly dispersed inverse Gamma (IG) distributions are assigned to these variances as the conjugate priors. By introducing hyperparameters a and b, we have $\sigma^2|a, b \sim IG(a, b)$. Values of a and b are usually small and choices of the values vary. A common choice proposed in Brezger and Lang's work (219) is $a = b = 0.001$. Alternative values, such as $a = 1$, $b = 0.005$ or 0.0005, and $a = b = 0.01$, can be used in the sensitivity analysis to detect a possible dependent relationship between the simulation results and the choices of the hyperparameters' values.

4.4 Posterior Updating

The full Bayesian inference is made upon the posterior distribution of the data. Generally computation of the posterior distribution is mathematically intractable. An efficient attempt to tackle this problem is to use the Markov chain Monte Carlo

(MCMC) algorithm. MCMC is a computer-intensive statistical tool providing us an alternative to handle complicated calculations. Suppose f is the vector of all functions of effects (e.g. $f_1, \cdots, f_p, f_{corr}, f_{uncorr}$), the variances term σ^2 and fixed effects parameter δ. We have the full posterior as

$$\boldsymbol{p(f, \sigma^2, \delta|y) \propto \prod_{i=1}^{n} L(y_i; \eta_i) \prod \{p(f|\sigma^2)p(\sigma^2)\} \prod_{m=1}^{q} p(\delta_m)} \quad (1$$

$$\propto \prod_{i=1}^{n} \boldsymbol{L(y_i; \eta_i) \prod \{p(\alpha_j|\sigma^2_{smooth})p(\sigma^2_{smooth})\}}$$

$$\boldsymbol{p(f_{corr}|\sigma^2_{corr})p(\sigma^2_{corr})p\left(f_{uncor} \;\middle|\sigma^2_{uncorr}\right)p(\sigma^2_{uncorr}) \prod_{m=1}^{q} p(\delta_m)}$$

where $L(\cdot)$ is the likelihood function. Note that the posterior distribution is proportional to the product of the likelihood function and prior distributions. Since the full conditional distributions for the unknown functions, spatial effects and fixed effects are multivariate Gaussian and for the variance terms are diffuse inverse gamma, we use Gibbs sampler to achieve MCMC simulation and obtain the posterior distribution. Gibbs sampler is an example of MCMC which uses full conditional distribution as proposal distribution. It sequentially draws from the full conditional distribution for blocks of parameters $(\alpha_j, f_{corr}, f_{uncorr}, \delta_m)$. The statistical characteristics of the posterior distribution, such as mean and precision, are obtained by drawing samples from the posterior distribution.

4.5 Model Selection

As there are usually a number of risk factors available in a dataset, a few models can be constructed using different combinations of these risk factors. Thus, model selection is needed to find the one that fits the data most efficiently. A common approach is to compare the goodness of fit of the models. The goodness of model fit usually increases as more parameters included in the model. However, too many parameters lead to overfit and increased estimated variance (i.e. larger standard errors) of parameters. On the contrary, too few parameters reduce the model fit and result in high bias in parameters. Therefore an efficient model selection method has to trade off model fit and variance of parameters.

A recently popular method is the deviance information criterion (DIC) (220). It is a Bayesian generalisation of the Akaike Information Criterion (AIC). The standardised deviance, $D(\theta)$, is defined as

$$\boldsymbol{D(\theta) = -2log\big(p(y|\theta)\big) + 2log\big(h(y)\big)} \quad (12)$$

where θ represents the set of parameters in the model, $p(y|\theta)$ is the likelihood function and $h(y)$ is a standardising term that is the function of data alone.

The effective number of parameters, pD, measures the complexity of model. It is defined as

$$\boldsymbol{pD = \overline{D(\theta)} - D(\bar{\theta})} \quad (13)$$

Where $\overline{D(\theta)}$ is the posterior mean of the deviance, measuring the goodness of fit, $\bar{\theta}$ is the expectation of θ and $D(\bar{\theta})$ is the point estimate of the deviance of posterior mean.

According to Spiegelhalter *et al.* (220), the deviance information criterion is thus constructed by the sum of posterior estimate of the deviance and effective number of parameters,

$$\boldsymbol{DIC = \overline{D(\theta)} + pD} \tag{14}$$

According to equation (13), DIC also can be written as

$$\boldsymbol{DIC = D(\bar{\theta}) + 2pD} \tag{15}$$

As the number of parameters increase, $\overline{D(\theta)}$decreases and pD increases. Therefore the value of $\overline{D(\theta)}$ is penalised by pD, reflecting the trade-off between model fit and complexity. To choose the best model, the lowest DIC is preferred.

4.6 Summary of Chapter 4

In Chapter 4, a methodology, Bayesian geo-additive models, was illustrated. Bayesian geo-additive models are developed from generalised additive models (GAM), an advanced form of generalised linear model (GLM), within the Bayesian framework. In GAM, smooth functions are employed to estimate possible nonlinear effects of continuous risk factors. By adding a spatial effect term, Bayesian geo-additive models provide a unified framework for modelling linear and non-linear covariate effects and estimating the spatial effect simultaneously. Different priors are assigned to different types of risk factors: Markov random fields (MRF) priors to

spatial effects and Bayesian P-splines to continuous factors. In addition, inverse Gamma (IG) distribution is assigned to the hyperparameters of the variance terms. Posterior means of the effects of risk factors can be obtained by updating the priors using Markov Chain Monte Carlo methods. Deviance Information Criterion (DIC) can be used to select the best model with lowest DIC value.

The Bayesian models are advantageous over the classic linear regression models in that they can properly account for spatial effect, particularly spatial dependence, they are competent to deal with a large number of risk factors and complex sampling designs without being affected by clustered data, and they can simultaneously estimate possible nonlinear effects to improve the reliability and accuracy of the estimations.

Chapter 5 Salt Intake and Iodine Status in the World

5.1 Salt Intake and Iodine Status – An Ecological Analysis

5.1.1 Introduction

Concerns of potential conflicts between salt reduction programmes and universal salt iodisation programmes have been raised recently (24;25). For the majority of the world, salt is the most cost-effective vehicle for iodine supplementation in the general population. Many countries have improved population-wide iodine status after implementing salt iodisation programmes (118). The current recommended addition of iodine in salt ranges from 20-40 ppm at salt production stage, based on the assumption of 10 g/day salt consumption in the adult population. This assumption is close to the average salt intake in western countries (10-12 g/day), and is lower than the levels in rice-eating populations (221). However, the goal of the salt reduction programme is to reduce salt intake to <5 g/day, removing more than half of current salt intake in populations. It is believed that the widely accepted reduction will inevitably curtail iodine intake (28) and expose populations to higher risk of IDD.

From the perspective of salt reduction, another concern is that people may voluntarily eat more salt to increase iodine intake, although this is rarely documented. This could happen when confusions and anxieties rise from unclear health information on salt reduction and iodine supplementation given to the public. In his

comments (24) on Asaria *et al.*'s salt reduction paper (74), Beard mentioned the case of the Australian public being told to reduce discretionary use of salt, but at the same time being told that "certain kind of salt is essential, especially for children" (222). Additionally, in some extreme scenarios, consumption of iodised salt may increase unexpectedly due to the increasing demand for iodine. For instance, people increased purchase and consumption of iodised salt in fear of radiation exposure during the Japan Tohoku earthquake (223).

Although the World Health Organization (WHO) states that both policies of salt iodisation and salt reduction can be compatible (4), adjustment in levels of iodine fortification is probably needed, as well as coordination of both programmes among governments, global organisations, scientists, media, industry, the public and other interested stakeholders.

In order to adapt accurately the current policies at national level, the relationship between iodine status and salt intake and the potential impact of salt reduction on iodine supplementation should be quantitatively scrutinised. The results can improve the interaction and congruence among all stakeholders, and can act as a benchmark for health policy-makers in the long term monitoring and evaluation of both programmes.

However, countries are generally different to each other in respect to the development of policies and the implementation of health programmes. Different approaches may be required to support the policy-makers towards potential adaptation in salt reduction and salt iodisation programmes and to meet the interests of other stakeholders. Therefore, each country may need unique and dedicated

analyses to coordinate the two health programmes. Before analysing specific cases, it will be pragmatically useful to summarise iodine status and salt intake and estimate the cross-country salt and iodine intake association using an ecological analysis. Ecological analysis is usually used to analyse aggregate data (i.e. population characteristics) rather than individual data. Hence the results of this analysis may contribute to better understanding of the positions of both programmes and provide us a good basis to further investigate specific cases. Thus the aims of this section are

1) to describe and understand the diversity of population salt intake and iodine status in different countries; and

2) to evaluate the cross-country associations between salt and iodine intakes and between household coverage of iodised salt and iodine intake, and derive a hypothesis of the within-country association between salt and iodine intakes from a global perspective based on the evaluation.

5.1.2 Data and Methods

Data on national iodine nutrition level and salt intake were extracted from several online databases of international organisations and published reports.

National iodine nutrition level

Population iodine status can be assessed by various indicators (94;224;225). The most commonly used indicator is the median urinary iodine concentration (UIC), which reflects the recent change of iodine intake. It is usually surveyed among school-aged children (6-12 years) as they are easily accessible and their status is then

generalised to the general population (94). The WHO 2004 iodine status report (94) provides a list of national median urinary iodine concentrations surveyed in school-aged children (SAC) and adults at national and sub-national levels. Only countries with SAC data were extracted. The Iodine Network database[3] was also used as a supplementary source of national iodine status.

Household coverage of iodised salt (HCIS)

Household coverage of iodised salt is an indicator used mainly by UNICEF to measure the iodine status of the general population. It is defined as the percentage of households using or covered by salt containing adequate iodine (≥15 ppm). This indicator is thought to be related to the median UIC since high coverage of iodised salt would result in higher overall consumption of iodine in the populations.

The national coverage data were obtained from the selected countries with extracted valid iodine status. The sources include the WHO online database[4], UNICEF online databases[5], Salt Institute[6] and Iodine Network and International Council for the Control of Iodine Deficiency Disorders (ICCIDD) newsletters[7] and other published reports (119;226).

Salt intake

Several methods can be commonly used to measure salt intake in the general population: food frequency questionnaire, food diary, 24-hour urine collection and

[3] http://www.iodinenetwork.net
[4] http://who.int/countries/en
[5] http://www.unicef.org/infobycountry/index.html and http://www.childinfo.org/idd_profiles.php
[6] http://www.saltinstitute.org
[7] http://www.iccidd.org/pages/idd-newsletter.php

spot urine samples. The estimate made from the 24-hour urinary collection is considered the most reliable and accurate. However, national levels of salt intake were extracted from reports using any one of the above methods due to the difficulties in 24-hour urine collection. Cappuccio *et al.*'s paper e was used as the source for salt intake data extraction. The intake was presented as g/day of sodium chloride. For those countries only reporting salt intake by gender, an unweighted mean was taken by dividing the sum of men's salt intake and women's salt intake by 2.

Universal salt iodisation programme

USI implementation has substantial effect on improving iodine status across the world. This indicator was created for discussion purpose.

National economic status

The economic status of countries is used in this analysis. Similar to individual's socioeconomic status, it can be a surrogate of a country's national characteristics and permit the grouping countries with similar contexts in salt iodisation and salt reduction. The World Bank sets the criteria based on each country's gross national income (GNI) per capita (227). All countries are classified as low income ($1,005 or less), lower middle income ($1,006-$3,975), upper middle income ($3,976-$12,275) and high income ($12,276 or more).

Statistical analysis

To estimate the relationship between iodine intake, household coverage of iodised salt and salt intake, Spearman's rank correlation coefficient was calculated in all

countries and later by countries' economic status. It was used because Spearman's rank correlation is not restricted by the normal distribution assumption and is less sensitive to outliers when compared to Pearson correlation. Note that although the World Bank's definition of income economy has 4 groups, there were only 2 countries classified as low- and middle-income economies. Hence they were merged with the upper-middle income economies (n=6) as middle-income economy group, which would be compared with high income economy group (n=13). As the sample size was small, Fisher's exact test was used to compare the iodine status distribution between high-income and low- and middle-income countries. The significance level was defined as 0.05.

5.1.3 Results

Data of median UIC, HCIS and salt intake were extracted from 41, 34 and 34 countries, respectively. In total, a database was constructed including 22 countries with complete data of national iodine nutritional level, salt intake and household coverage of iodised salt. Chile reported a very high level of UIC (984 µg/L), suggesting that at least 50% of the population consumes more than 1,000 µg iodine per day (assuming an average daily urine excretion of 1.2-1.5 L). The US Institute of Medicine (IoM) sets 1,100 µg/day as the upper intake level of iodine for adults (228). Hence the reported iodine status indicated an extremely high health risk in the population. It was considered not realistic and it was excluded from the analysis. Finally 21 countries were included: 12 are in Europe, 5 in South and North America, 3 in Australasia and 1 in Asia (see Table 5.1.1).

Table 5.1.1 *Constructed database for countries with reported national iodine status and salt intake and their data sources by country's economic status (n=21)*

Low- and middle-income	Salt iodisation legislation	Median UIC (µg/L)[a]	Year of report (UIC)	HCIS (%)[b]	Year of report (HCIS)	Salt Intake (mg/day)
Fiji	Yes	34	1994	31	1994	5.3†
Guatemala	Yes	222	1995	76	2007	19.0†
Lithuania	No	75	1995	6	2000	11.0†
Brazil	Yes	360	2000	96	2006	9.6†
Bulgaria	Yes	111	1996	100	2006	12.0†
China	Yes	241	2002	96	2009	12.0†
Costa Rica	Yes	233	1996	92	1996	7.0†
Ecuador	Yes	420	1999	99	1999	10.0†
High-income	**Salt iodisation legislation**	**Median UIC (µg/L)[a]**	**Year of report (UIC)**	**HCIS (%)[b]**	**Year of report (HCIS)**	**Salt Intake (mg/day)**
Australia	No	77	2001	10	2006	9.2‡
Hungary	No	80	1994-97	27	1995	17.0†
Italy	No	94	1992-99	3	2002§	10.8†
Netherlands	Yes	154	1995-96	40	1998	8.6‡
New Zealand	No	66	1999	83	1996-99	6.5†
Spain	No	109	1995-2002	27	1982	9.8‡
United States	No	237	1988-94	70	2000	8.6†
Belgium	Yes	80	1998	10	2002§	11.0‡
Czech Republic	Yes	119	2000	90	2002§	11.5†
Denmark	Yes	61	1997-98	100	2002§	8.7‡
Finland	Yes	164	1997	90	2002§	8.8‡
France	Yes	85	1996	55	2002§	8.4†
Switzerland	Yes	115	1999	94	1999	9.5‡

Note: UIC: urinary iodine concentration; HCIS: household coverage of iodised salt.
a: Median UIC was extracted from de Benoist et al. (94).
b: Data of HCIS were extracted from different sources for the following countries: Australia (229), Hungary (230), Netherlands, Spain, Switzerland (226); HCIS of Fiji, Guatemala, Bulgaria, China, Costa Rica, Ecuador, New Zealand were extracted from the WHO country profile (231); HCIS of Brazil, Lithuania and United States were extracted from UNICEF country statistics (232), Iodinenetwork country profiles (233), and Salt institute (234), respectively; HCIS of Denmark, Finland, France, Belgium, Italy and Czech Republic were extracted from ICCIDD Newsletter (235).
†: Salt intake was estimated using dietary survey.
‡: Salt intake was measured from 24-hour urine collection.
§: Data were reported in ICCIDD 2002 newsletter. No exact date of survey was mentioned. Hence the year of HCIS for each country may be earlier than 2002.

Summary of the data

The UIC ranged from 34 µg/L in Fiji to 420 µg/L in Ecuador. The mean UIC was 149.4 µg/L (Standard Deviation: 22.2). Italy had the lowest HCIS (3%) while 100% coverage was found in both Bulgaria and Denmark. The mean HCIS is 61.7% (36.6%). In the 21 countries, mean salt intake was 10.2 (3.1) g/day. Fijians had the lowest level of salt consumption (5.3 g/day) and Guatemalans had the highest level (19.0 g/day) (see Table 5.1.2).

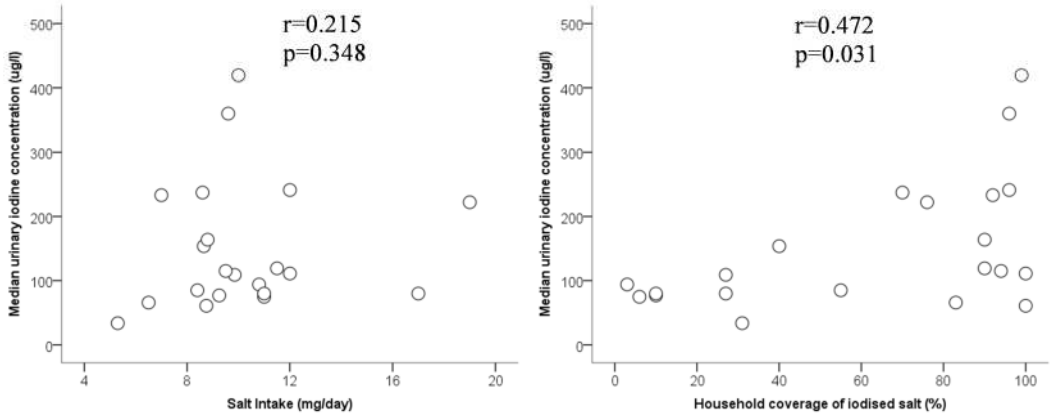
Table 5.1.2 *Summary of the iodine status and salt intake in 21 countries*

	Mean (Standard Deviation)	**Range**
Median Urinary Iodine Concentration (µg/L)	149.4 (101.8)	34-420
Household Coverage of Iodised Salt (%)	61.7 (36.6)	3-100
Salt Intake (mg/day)	10.2 (3.1)	5.3-19

Overall, UIC and salt intake are not significantly correlated. The correlation strength is also weak (r=0.215). HCIS had significant and strong correlation with iodised salt (r=0.472, p=0.031) (see Figure 5.1.1).

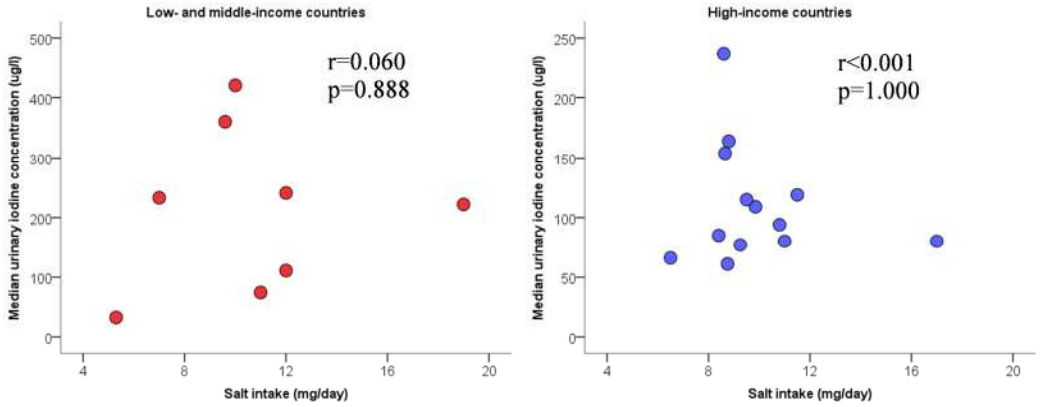
A further comparison was made by country's economic status. In the stratified analysis, the correlations between UIC and salt intake remain weak and not statistically significant (Figure 5.1.2). However, the relationship between HCIS and UIC is not statistically significant (Figure 5.1.3). In the high-income countries, the correlation is weak and in the low and middle-income countries, the correlation appears to be stronger but remain not statistically significant (r=0.611, p=0.108).

Figure 5.1.1 *Scatterplot between national urinary iodine concentration, salt intake and household coverage of iodised salt*



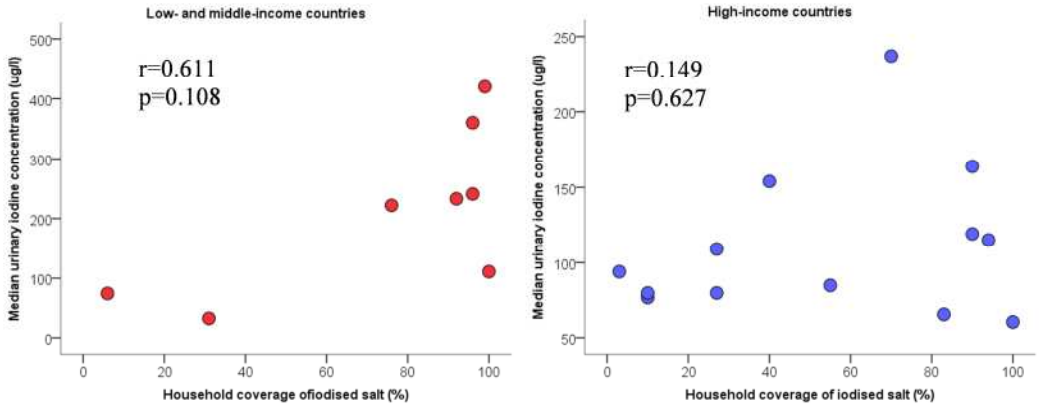
Note: Spearman's correlation coefficients were calculated and shown with corresponding p *value in each plot.*

Figure 5.1.2 *Scatterplot between national urinary iodine concentration and salt intake by country's economic status*



Note: Spearman's correlation coefficients were calculated and shown with corresponding p value in each plot.

Figure 5.1.3 *Scatterplot between national urinary iodine concentration and household coverage of iodised salt by country's economic status*



Note: Spearman's correlation coefficients were calculated and shown with corresponding p value in each plot.

Table 5.1.3 shows the distribution of countries' iodine status by economic status. The results suggest that mild iodine deficiency is more common in high-income countries while in low and middle-income countries excessive iodine intake is common (p=0.019).

Table 5.1.3 *Distributions of iodine deficiency in countries by median urinary iodine concentration*

		Country's economic status*	
		Low- and middle-income (n=8)	High-income (n=13)
Iodine Status	moderate iodine deficiency	1 (12.5)	0 (0.0)
	mild iodine deficiency	1 (12.5)	7 (53.8)
	optimal iodine status	1 (12.5)	5 (38.5)
	more than adequate iodine intake	3 (37.5)	1 (7.7)
	excessive iodine intake	2 (25.0)	0 (0.0)

Note: Values were expressed as count (percentage).
**: Comparison was made using Fisher's exact test. P value=0.019.*

Impact of high salt intake on the associations

The left panel of Figure 5.1.1 showed that two countries had higher salt intakes which might bias the correlations. Therefore, a further estimation was made by excluding the two countries, Guatemala and Hungary. Spearman's correlation coefficients were shown in Table 5.1.4. The correlation strength increased in the correllation between salt intake and UIC in all countries and by economic status. On the contrary, the strength decreased in the correlation between HCIS and UIC in all countries and by economic status. However, the statistical significance was not changed. Therefore the relationship between salt intake and UIC and the relationship between HCIS and UIC remained unchanged and the results before the exclusion will be discussed later.

Table 5.1.4 *Correlations between urinary iodine concentration and salt intake, and between urinary iodine concentration and household coverage of iodised salt in all countries and by economic status, after excluding two countries with high salt intake*

	Urinary iodine concentration		
	Overall	**Low- and middle-income country**	**High income country**
Salt intake	0.250 (0.302)	0.180 (0.699)	0.084 (0.795)
Household coverage of iodised salt	0.460 (0.047)	0.595 (0.159)	0.102 (0.753)

Note: Spearman's correlation coefficients were calculated. Values were expressed as correlation r (p value).

5.1.4 Discussion

Key findings

This analysis is the first attempt to explore the relationship between iodine levels and salt intake from a global perspective. One of the main findings is that there was no substantial association between urinary iodine concentration and salt intake across the world, which echoes the WHO statement of the compatibility of two programmes. Based on these findings, a hypothesis can be made: that a moderate reduction in salt intake would not affect the iodine status of the general population, which will be compared and tested in the following case studies (see Section 5.2-5.4). The findings were mainly for description purpose only. Nonetheless, the results helped us understand the various levels of population salt and iodine intakes in different countries. In the specific case we were able to stratify by socioeconomic status but were unable to allow for differences in age distributions, gender distributions, anthropometric indices and other behavioural and social factors.

Notwithstanding, various reasons could be considered to either independently or interactively lead to these findings. A large proportion of consumed salt is non-iodised. In the countries examined, 6 out of 7 (86%) low- and middle-income countries have implemented the USI programme, whereas only 7 out of 13 (54%) high-income countries have enacted regulations on compulsory salt iodisation. Moreover, although there are calls to iodise all food grade salt (221), some countries only require mandatory fortification on discretionary salt (i.e. table and cooking salt) (236-238). Nonetheless, around 75% of salt intake in the general population in industrialised countries is derived from processed foods (33;239;240) which are

mostly “energy-dense but micronutrient-poor foods” (241). Only 10-12% is added at table or during cooking. The rest is present naturally in foods or from other supplementations. Therefore in an industrialised population with average salt intake of 10 g/day, the estimated amount of iodised salt is only 1-1.2 g/day, which translates to an iodine intake of 15-18 μg/day.

Iodine intake from alternative sources may also weaken the link between salt intake and UIC. There are many iodine-rich foods available to the general population, including milk and dairy products, meat, seafood, egg, etc. In some countries, such as the UK and Norway, milk and dairy products have historically been the major determinants of iodine intake (242;243), despite the recent decreasing trend of iodine content in milk (244).

In addition, poor quality of salt iodisation may also contribute to the lack of association between UIC and salt intake. The techniques of salt iodisation are simple and low-cost – an extra expenditure of 2-9 US cents a year can ensure sufficient iodine intake for each person (19). Most countries require 20-40 ppm addition of iodine during salt production (25). However, reports have revealed that inadequately iodised salt is still available to the general population across iodine sufficient and iodine deficient countries (245;246). The inadequacy of iodine content in salt could be caused by various factors. For instance, some countries in Europe and North America use potassium iodide (KI) for fortification while others use potassium iodate (KIO_3). The former compound is less stable and more soluble than the latter and is more likely to be affected by heat and humidity. The salt fortified with KI may lose more iodine during packaging, transportation and storage. Experience in

Indonesia (247) also reveals that a limited supply of iodine compound can result in less than adequate iodine in salt. Furthermore, ineffective monitoring and evaluation may be responsible for inadequately iodised and non-iodised salt on the market. For instance, black market salt is still prevalent in some areas. The considerably lower cost of non-iodised salt (usually 2-3 times lower than iodised salt) makes it more attractive in rural and border areas, and consequently more people are exposed to the risk of iodine deficiency.

After almost 20 years of promotion of salt iodisation, USI has become a popular and effective public health intervention to combat iodine deficiency in many countries. However, one should be vigilant about the alleged re-emergence of iodine deficiency, particularly in high-income countries. In this analysis, more than half of the high income countries (53.8%) were classified as having mild deficiency when assessed through UIC. If these figures were consistent in all age and gender groups, the results would suggest that a high proportion of children and women of reproductive age may still be at risk of stunted growth, low educational attainment and other iodine deficiency diseases. In countries not fully dependent on USI, some studies suggest that the re-emergence of iodine deficiency is attributable to the reduction in milk and dairy consumption (248), exacerbated by reduced iodine concentration due to limited use of iodophor in foodstuffs (249) and consumption of goitrogenic foods in animals (250).

In contrast, some populations have been consuming too much iodine (251-255). Excessive iodine intake has adverse effects on human health, causing increased events of iodine-induced hyperthyroidism, goitre (93;256-258) and thyroid papillary

cancer (92). For this reason, the Ministry of Health in China has adapted the standard of salt iodisation from 20-60 ppm to 20-30 ppm in 2011 (259). Hence prompt actions should be taken to prevent the adverse health outcomes.

Strengths and limitations

The ecological approach is a convenient way to investigate the global association of salt intake and iodine status. In addition, this analysis provided an opportunity to propose a hypothesis of the salt and iodine association, which could be used as a benchmark for the following case studies for comparison. Thirdly, most data were obtained from the online databases or reports of the authoritative international organisations..

This analysis is also subject to several limitations. Firstly, the analysis used national estimates of median urinary iodine concentration, household coverage of iodised salt and mean salt intake. Some data may not reflect up-to-date nutritional intake related information. For example, Italy did not adopt a salt iodisation programme at the time of UIC measurement (260) until 2005 (261), and the WHO did not record any UIC measurement in or after 2005 in Italy. Therefore Italy was still classified as non-USI country in this analysis, in order to make it consistent with the UIC data. As population salt and iodine intakes vary over time, the quality of this constructed database was less desirable and the estimation of the cross-country salt and iodine association could be potentially biased. However, it is not possible to infer whether new data can enhance or weaken the association. Furthermore, updating the data from recently published individual studies may need more time than the present study allowed. In short, the limited data sources restricted the extent of this analysis.

The WHO now urges Member States to monitor iodine status every three years (262) and salt intake every five years (263). Better monitoring and evaluation is promising.

Another limitation is that no matched data were used since there were no health surveys or studies in the sources reporting iodine and salt intake and use of iodised salt at the same time. This caused a wide span of more than 30 years in the constructed database, making the validity of these health indicators questionable. What is more, the urinary iodine concentration is used to reflect the recent change of iodine level. The data may become more unreliable when considering the great achievements of elimination of iodine deficiency obtained in the past decades.

Additionally, salt intake was estimated using a 24-hour urine collection and food questionnaire. Twenty-four-hour urine collection provides the most reliable and accurate measurement of salt intake. Food questionnaire, however, underestimates the salt intake at individual level, as it usually does not measure discretionary use of salt. Hence these national estimates of salt intake do not fully reflect their true levels.

Moreover, some countries reported salt intake by sex. The national average was then estimated by simply averaging two salt intakes. Such estimation might lead to some bias as no adjustment for sex and age was made. However, it would be also difficult to make the adjustment due to the lack of the detailed age and sex data.

Implications

This ecological analysis is merely a description of recent positions of global iodine status and salt intake and their relationship. Although subject to the above limitations, this analysis helps develop a hypothesis on the association of salt iodisation and salt

reduction, which can be tested and compared in case studies at country level (see Section 5.2 in this Chapter).

Analyses within each national framework may offer more insights into how to improve the coherence of both programmes and give instructive support and rational suggestions to health policy-makers. Meanwhile, the following work will take the opportunity to quantify the impact of possible salt reduction on iodine supplementation (and vice versa) according to each country's context (see the following sections in this Chapter). Moreover, as the aggregate data often conceal significant geographical variations, the impact of the geographical locations and other determinants can be specifically investigated using more consistent and representative national data (see Section 5.3 and 5.4 in this Chapter). It will also be important to concentrate the attention on the socially disadvantaged and vulnerable groups in order to maximise the effects of health intervention programmes (see Section 5.2-5.4).

5.2 Salt Intake and Iodine Status in Ghana

5.2.1 Introduction

Salt is commonly used in the African diet. Discretionary use of salt (i.e. table and cooking salt) is the major source of salt intake in African populations. However, substantial scientific evidence has supported the fact that increased salt intake is associated with raised BP (11;13;34;264). High BP, or hypertension, is the leading modifiable cause of death in the world (8), and is among the leading causes of death in the low- and middle-income countries (7). In West Africa, 15.6% of the

population is hypertensive (265). The prevalence is gradually increasing in many African countries (266) along with economic development, urbanisation and changes in diet (162). Urban populations usually have higher prevalence of hypertension (267).

The health care burden attributable to non-optimal BP in Sub-Saharan Africa is US$2 billion (268) and there are growing concerns regarding the increasing prevalence of hypertension (267;269;270). Prevention, management and control of hypertension are sub-optimal in Africa. Most of the African countries have not established strategies to reduce salt intake in the general population except Nigeria and South Africa (4;15). The limited resources and health budget also restrict governments' ability to tackle this health issue.

Population-wide salt reduction is recommended by the WHO as a cost-effective way to reduce population BP and, therefore, cardiovascular disease (CVD). This strategy is effective in both sexes and in all age and ethnic groups (15) and is also cost saving (75;271;272).

On the other hand, salt is a major vehicle for iodine supplementation in Africa. Iodine is an essential nutrient for human beings. Iodine deficiency was first recognised as a major public health threat in Africa in 1987 (120). At the time of the 54th World Health Assembly (WHA), there were about 181 million African people (32.8%) at risk of iodine deficiency disorders (273). Although severe iodine deficiency leads to devastating consequences for the affected individuals, moderate to mild deficiency can cause 10% loss in GDP due to considerable economic and productivity losses (274). The elimination of iodine deficiency could be integrated in

the Millennium Development Goals set in 2000 by United Nations and support the achievement of at least six of those goals.

Universal salt iodisation (USI) was introduced in Africa in the 1990s, though Kenya and Zambia have had legislation on salt iodisation much earlier than the introduction (120). Many countries have adopted the USI programme with different regulations on the addition level of iodine in salt. Some require the iodine content in salt to be up to 100 ppm (245). Remarkable progress has been achieved. An estimated 55% of households in Africa are now covered by iodised salt, although the average coverage hides a significant geographical variation at national and community levels. For instance, the household coverage of iodised salt ranges from 2% in Mauritania to 98% in Nigeria (275). The number of iodine deficient countries has reduced from 17 in 2003 to 10 in 2011 (17). Children are also better protected. The proportion of school-aged children at risk of iodine deficiency has reduced from 42.3% to 39.3% during the same time.

The prevention, management and control of hypertension and iodine deficiency are both a high priority in Africa. Although population salt reduction and universal salt iodisation programmes are perhaps intrinsically compatible (26), reduced salt intake may, in principle, curtail iodine intake while increasing iodine intake may result in an unintended increase in salt intake if current iodisation practices and salt reduction targets remain unchanged. Thus, adaptation of current policies is required and they are critical to improve the coordination between both programmes (33).

A number of studies assessed iodine intake, household coverage of iodised salt, and/or salt intake in African populations. However, the investigation of the

relationship between salt and iodine intakes is scarce (197). Hence these studies are not able to provide the solution to the potential conflict between the two programmes to international organisations, policy-makers and other stakeholders for policy harmonization. Therefore, this analysis has the following objectives by using the data extracted from a community based study in Kumasi in the Ashanti region of Ghana:

1) to estimate salt intake and iodine status in a non-industrialised African population;

2) to assess the association of salt intake and iodine intake in this population which is mainly dependent on iodised salt for iodine supplementation;

3) to investigate the impact of modifications of salt intake on iodine status in similar countries; and

4) to provide suggestions to policy-makers.

5.2.2 Data and Methods

Country profile

Ghana is a West African country bordered by Togo, Burkina Faso, and Ivory Coast and facing the Gulf of Guinea in the south (Figure 5.2.1(a)). From the south to the north, Ghana has five distinct geographical regions: low plains, Ashanti uplands, the Volta Basin, the Akwapim-Togo Ranges and high plains. The country has 10 administrative regions: Ashanti, Brong Ahafo, Central, Eastern, Greater Accra, Northern, Upper West, Upper East, Volta, and Western (Figure 5.2.1(b)).

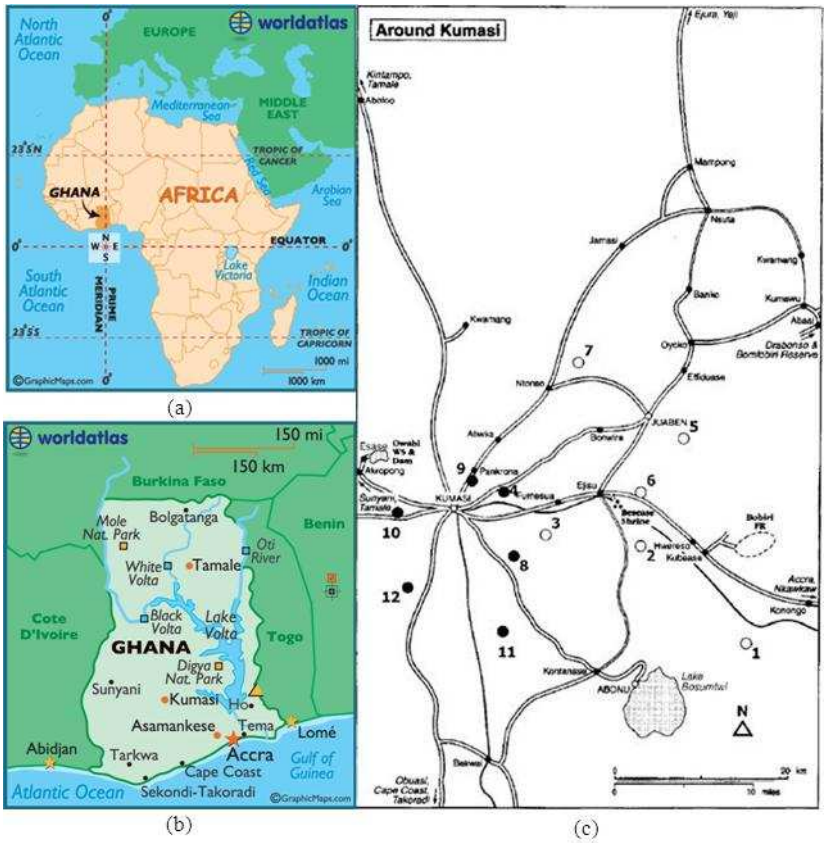
In 2010, the total Ghanaian population was 24.2 million. Ghana is a low-middle income country with an estimated $1,230 gross national income (GNI) per capita. It is one of the two largest salt producing countries in West Africa with an annual output of 250,000 metric tonnes.

Study area

The data used in this analysis were obtained from a community-based study at Kumasi in the Ashanti region of Ghana. The study was designed to investigate the prevention of hypertension and stroke in the region through a modification of salt intake with health promotion (276;277).

Prior to the study, a census was conducted during January and March 2001 in 12 villages with rare day-to-day contact in the Ejisu-Juabeng and Kumasi Districts of the Ashanti region. The villages are Pemenase, Edwenase, Domeabra, Tikrom, Ofoase, Atia, Dumakwai, Appeadu, Duase, Apatrapa, Feyiase and Nwamase (Figure 5.2.1(c)). Six of them were defined as rural villages because they are distant from Kumasi city and lack piped water and electricity. The rest of the villages were defined as semi-urban villages because they are closer to the city and have piped water and electricity. The total number of the local population was 16,965 at the time of the census. The adult populations in the rural and semi-urban areas were 50% and 57%, respectively. Two thousand seven hundred and forty three villagers were in the range of 40-75 years. The population structure was approximately equivalent to the national counterpart. Details of the census have been described elsewhere (276).

Figure 5.2.1 *Map of Africa (a), Ghana (b) and the Ashanti region with the locations of 12 villages (c)*



Note: The left panel was adapted from http://www.worldatlas.com*, and the right panel was reprinteded from Plange-Rhule et al. (276). White circles are rural villages: 1. Pemenase; 2. Edwenase; 3. Domeabra; 5. Ofoase; 6. Atia; 7. Dumakwai. Black spots are semi-urban villages: 4. Tikrom; 8. Appeadu; 9. Duase; 10. Apatrapa; 11. Feyiase; 12. Nwamase.*

One thousand eight hundred and ninety six villagers were randomly selected from the 40-75 age-group (n=2,743) between June 2001 and June 2002 using an age and sex stratification that is identical to the structure in the census population. Pregnant and lactating women and individuals with mental or physical illness were excluded. Higher proportions of villagers were invited from villages with small populations. About 53% (n=1,013) of the selected individuals took part in the community-based study. The study team including doctors, nurses and clerks collected individuals' information from the 12 villages. In the census, it was found that the self-reported age might not be reliable as many villagers did not have birth certificates or other

forms of birth identification. Therefore, the villagers were shown with a list of important dates and events in Ghana history to improve the accuracy of the age information (276). The study protocol was approved by institutional ethics committees in Ghana and in the UK, and by the Chief and the Council of Elders in each participating village. More details of the study design and participant recruitment have been described elsewhere (53).

Baseline measurement

Each study individual was asked to complete a detailed questionnaire gathering demographic, socioeconomic, personal and family medical history and dietary information. The whole procedure was administered by fieldworkers in English, and in Twi, a local language, if necessary.

Height was measured barefoot (no shoes) to the nearest 0.5 cm. Weight was measured barefoot and with light clothing to the nearest 0.5 kg. Body mass index (BMI) was calculated using weight divided by squared height (kg/m^2).

Sitting BP readings were taken three times at one minute intervals following at least 5 minutes rest with a semi-automated device (277). The first reading was discarded and the average of the other two readings was used for the analysis.

Participants also provided information on socioeconomic status, lifestyle and medical history, such as education, main job, smoking and drinking habits. Extra dietary information was also collected, such as the use of salty foods, including salted pigs' feet, salted beef, kako, koobi, momoni, and the use of salt at table or during cooking (278).

Approximately 90% of the daily consumption of iodine and salt is excreted in a 24-hour urine sample. Thus 24-hour urinary sodium and iodine excretions were used to estimate the daily salt and iodine intakes. Two consecutive 24-hour urine samples were collected at the baseline. 24-hour urinary biomarkers, including 24-hour urinary sodium excretion and 24-hour urinary iodine excretion, were then measured using AutoAnalyzer 3 based on the Sandell-Kolthoff reaction (201).

Iodine status was determined by median urinary iodine concentration at population level. There are 5 categories of the status according to epidemiological criteria: <20 μg/L, severe iodine deficiency; 20-49 μg/L, moderate iodine deficiency; 50-99 μg/L, mild iodine deficiency; 100-199 μg/L, optimal iodine status; 200-299 μg/L, more than adequate iodine intake; ≥300 μg/L, excessive iodine intake.

Intervention programme

In the design of this community-based study, the major objective was to investigate the prevalence of hypertension and the potential for prevention through dietary salt modification in an African population. The villages were randomly assigned to intervention and control groups. Each group had six villages, which was a mixture of rural and semi-urban villages. The locality stratification and the matching of villages in clusters were made by an independent statistician (279). The random allocation was carried out in two stages. The power calculation of 4.8 mmHg in SBP with a power of 90% and a significance level of 5% gave an estimated number of 70 villagers per village. However, the first stage of 95 villagers from each village was not satisfactory due to a larger refusal rate than the assumed 25%. Therefore, an increased refusal rate was set to include more participants in each village (53). In all

villages, community health workers gave villagers intensive health education on a range of public health issues, such as diabetes and hypertension. For the intervention group, a health promotion package on how to reduce salt intake was added. Villagers were told to reduce their salt intake in several ways, such as removing salt from salted fish and meat before its consumption, and not to add salt at the table or in cooking (for instance by avoiding the use of 'Maggi' cubes, common practice in the area).

Follow-ups

Follow-up measurements were conducted after six months. There were 801 individuals remaining in the study at 6 months. Weight, height, BP and 24-hour urinary biomarkers were measured in the same way.

Main results

The main results of the programme have been reported previously (53;277). In brief, (a) there was a significant positive relationship between salt intake and both systolic and diastolic blood pressure at baseline; (b) at six months the intervention group showed a reduction in systolic and diastolic blood pressure when compared to control; (c) there was no significant change in urinary sodium excretion between groups; (d) smaller villages showed greater reductions in urinary sodium than larger villages; (e) irrespective of randomization there was a consistent and significant relationship between change in urinary sodium and change in systolic blood pressure, when adjusted for confounders.

Rationale for the present analyses

Because the aim of salt iodisation is to promote the supplementation of iodine via dietary salt, reduction in salt will only affect the iodine intake in those consuming iodised salt. This implies that the impact of salt reduction on iodine status can be assessed in the villages, which were covered by iodised salt.

A criterion to determine whether villages were using iodised salt was to determine the correlation (both at baseline and at 6 months) between urinary sodium and iodine excretions. A strong correlation would indicate use of iodised salt as the main source of salt in that village.

Therefore, the associations in each village were tested. If the association was significant, the village was then assigned to the “concordant” group. The villages with lack of correlation between iodine and sodium were assigned to the “discordant” group. Furthermore, differences in sodium excretion between baseline and 6 months were correlated with the changes in iodine excretion over the same period to estimate the likely effect of variations in salt intake on iodine status.

Statistical analysis

For the cross-sectional analysis at baseline and 6 months follow-up, t-test and chi-square test were used to examine the sex and locality differences of continuous risk factors and categorical risk factors, respectively. Pearson’s correlation coefficient was used to test the correlation of the changes of iodine and sodium excretion in each village as both changes are approximately normally distributed. For the analysis of changes during the study period, chi-square test was used to compare categorical

variables (i.e. iodine status distribution). The overall change of iodine status during 6 months in two groups was tested using the test of marginal homogeneity. This test is suitable for testing the repeated measures of ordinal data.

The impact of the change of sodium intake on the change of iodine intake in discordant and concordant villages was estimated using three linear regression models. No adjustment was made for Model I. Model II was adjusted for age and sex. Model III was adjusted for age, sex and locality.

The significance level for all tests was set as 0.05. All analyses were performed with SPSS V19.0 (IBM Corp. Armonk, NY, USA).

5.2.3 Results

Population characteristics

Table 5.2.1 summarises the characteristics of the Kumasi population. Of the 1,013 participants, 38% (n=385) were men and 47.5% (n=481) were living in rural villages. The mean age was 54.7 years (Standard Deviation: 11.3). Participants had a mean body weight of 54.3 kg (11.2) and a mean height of 160.4 (8.5) cm. The average BMI was 21.1 (4.2) kg/m^2.

The population BP had a normal distribution with mean systolic and diastolic blood pressures of 125.5 (26.1) mmHg and 74.4 (13.6) mmHg, respectively.

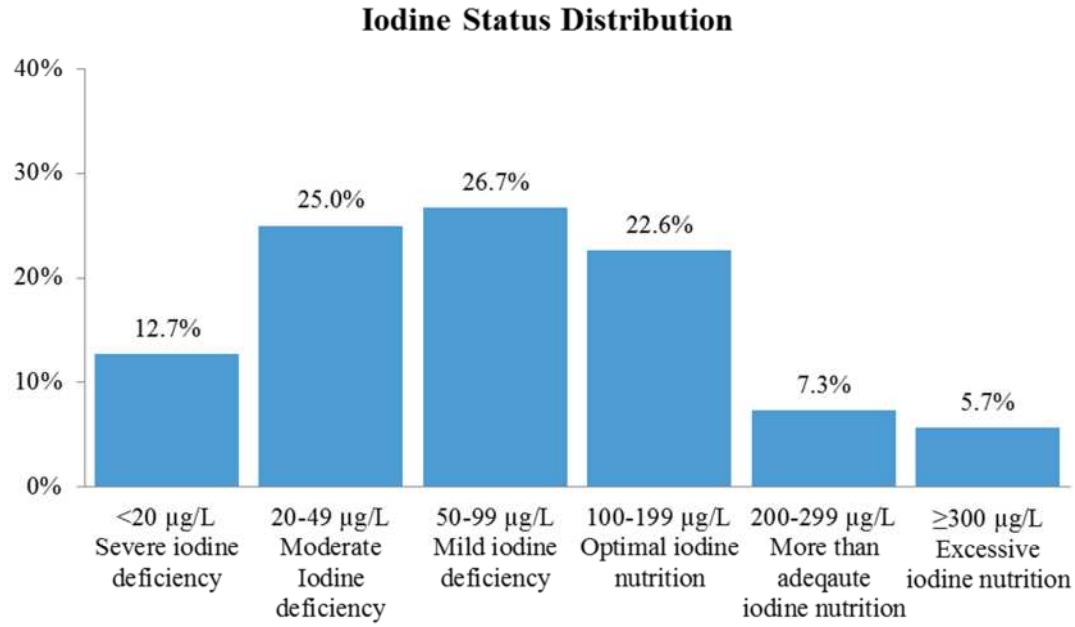
Twenty-four-hour urinary sodium excretion was 101.2 (45.0) mmol/day and 24-hour urinary iodine excretion was 70.6 (95% confidence intervals: 66.8, 74.7) µg/day. The median urinary iodine concentration was 68.9 (IQR: 100.2) µg/L.

Table 5.2.1 *Characteristics of the study population at baseline (n=1,013)*

Study population (n=1,013)	Mean(Standard Deviation)
Age (year)	54.7 (11.3)
Sex (%)-Male	38
Female	62
Weight (kg)	54.3 (11.2)
Height (cm)	160.4 (8.5)
BMI (kg/m^2)	21.1 (4.2)
Systolic blood pressure (mmHg)	125.5 (26.1)
Diastolic blood pressure (mmHg)	74.4 (13.6)
Locality (%)-Rural	47.5
Semi-urban	52.5
24-hour urinary sodium (mmol/day)	101.2 (45.0)
24-hour urinary iodine (μg/day)*	70.6 (66.8, 74.7)
Urinary iodine concentration (μg/L)†	68.9 (100.2)

Note: Results are mean and standard deviation unless specified.
**: Geometric mean with 95% confidence intervals.*
†: Median (IQR).

Figure 5.2.2 *Iodine status distribution of the study population*



The median urinary iodine concentration was 68.9 μg/L, indicating that, on average, the study population was at risk of mild iodine deficiency. 64.4% of the population

had a urinary iodine concentration of less than 100 μg/L; 12.7% had a concentration of less than 20 μg/L (Figure 5.2.2).

Baseline characteristics

Extreme values of sodium or iodine excretions may influence the mean estimates of salt and iodine intakes substantially, and lead to biased estimation and interpretation. Therefore, the dataset was checked for outliers. Of the 1,013 study participants at baseline, 1,004 were included with complete and valid urinary measurements. A further check of baseline 24-hour urinary iodine and 24-hour urinary sodium indicated 7 outliers in the data. They were excluded from this analysis. Hence 997 participants with complete data contributed to the final analysis at baseline. Their characteristics did not differ from the whole study population (data not shown).

Table 5.2.2 shows that the mean age was comparable between men and women. Men were significantly heavier and taller but women had significantly higher BMI.

Men and women had comparable levels of daily salt and iodine intakes but men had significantly higher urinary iodine concentration (86.5 vs 74.0 μg/L, p=0.024), although both groups were mildly iodine deficient.

Compared to semi-urban participants, rural participants had significantly lower weight, BMI, and both systolic and diastolic blood pressures.

Twenty-four-hour urinary sodium excretion was not significantly different between rural and semi-urban participants (p=0.228) but 24-hour urinary iodine excretion was significantly higher in semi-urban participants. Urinary iodine concentration was

also higher in semi-urban participants. The median urinary iodine concentration indicated optimal iodine status in semi-urban area and mild iodine deficiency status in rural area.

Follow-up characteristics

Five more outliers were excluded at 6 months follow-up, leaving 780 participants with full sets of data at baseline and 6 months for the follow-up analysis 38.6% of them (n=302) were men and 49.9% (n=390) were rural residents.

As for the baseline, there were no sex differences in 24-hour urinary sodium and iodine excretions. The rural and semi-urban differences remained significant for 24-hour urinary iodine excretion. Iodine status was comparable to that at baseline. 24-hour urinary sodium excretion between rural and semi-urban areas became significantly different (p=0.001) with higher level in participants living in semi-urban villages (94.8 (SD: 43.8) vs 85.8 (SD: 36.2) mmol/day).

Table 5.2.2 *Characteristics of the study population at baseline and at 6 months follow-up*

Baseline	All (n=997)	Men (n=378)	Women (n=619)	p value	Rural (n=475)	Semi-urban (n=522)	p value
Age (year)	54.7 (11.3)	54.5 (10.9)	54.8 (11.5)	0.706	54.4 (11.2)	54.9 (11.4)	0.468
Weight (kg)	54.2 (11.3)	56.3 (9.7)	53.0 (11.9)	<0.001	51.0 (9.5)	57.1 (11.9)	<0.001
Height (cm)	160.4 (8.5)	166.7 (6.9)	156.5 (7.0)	<0.001	160.5 (8.6)	160.2 (8.5)	0.635
BMI (kg/m^2)	21.1 (4.2)	20.2 (3.1)	21.6 (4.6)	<0.001	19.8 (3.1)	22.3 (4.6)	<0.001
Systolic blood pressure (mmHg)	125.5 (26.1)	126.3 (24.4)	124.9 (27.1)	0.417	121.4 (25.1)	129.2 (26.5)	<0.001
Diastolic blood pressure (mmHg)	74.3 (13.6)	75.8 (13.7)	73.4 (13.6)	0.008	72.3 (13.1)	76.2 (13.8)	<0.001
24-hour urinary sodium (mmol/day)	101.0 (44.9)	99.5 (45.7)	101.9 (44.5)	0.405	99.2 (45.1)	102.7 (44.8)	0.228
24-hour urinary iodine (μg/day)*	69.5 (8.3)	74.0 (12.5)	66.8 (9.6)	0.078	52.7 (7.6)	89.4 (13.7)	<0.001
Urinary iodine concentration (μg/L)†	78.2 (124.9)	86.5 (127.9)	74.0 (121.3)	0.024	60.2 (70.6)	111.4 (178.5)	<0.001
6 Months follow-up	**All (n=780)**	**Men (n=302)**	**Women (n=478)**	**p value**	**Rural (n=388)**	**Semi-urban (n=392)**	**p value**
Weight (kg)	55.0 (11.3)	56.8 (9.7)	53.9 (12.0)	<0.001	52.1 (9.7)	57.9 (11.9)	<0.001
BMI (kg/m^2)	21.4 (4.2)	20.4 (3.2)	22.0 (4.6)	<0.001	20.2 (3.3)	22.6 (4.7)	<0.001
Systolic blood pressure (mmHg)	128.2 (27.0)	129.9 (25.8)	127.2 (27.7)	0.172	123.9 (25.5)	132.5 (27.7)	<0.001
Diastolic blood pressure (mmHg)	77.9 (14.3)	79.5 (15.0)	76.9 (13.8)	0.015	75.8 (13.9)	80.0 (14.4)	<0.001
24-hour urinary sodium (mmol/day)	90.3 (40.4)	89.4 (41.9)	90.8 (39.5)	0.635	85.6 (36.2)	94.8 (43.8)	0.001
24-hour urinary iodine (μg/day)*	67.2 (7.5)	72.7 (14.0)	64.0 (10.7)	0.053	48.8 (7.7)	92.3 (16.4)	<0.001
Urinary iodine concentration (μg/L)†	77.8 (123.4)	86.3 (126.7)	72.3 (115.8)	0.009	60.1 (68.9)	110.2 (170.6)	<0.001

Note: Results are mean and standard deviation, unless specified.
**: Geometric mean with standard error.*
†: Median (IQR).

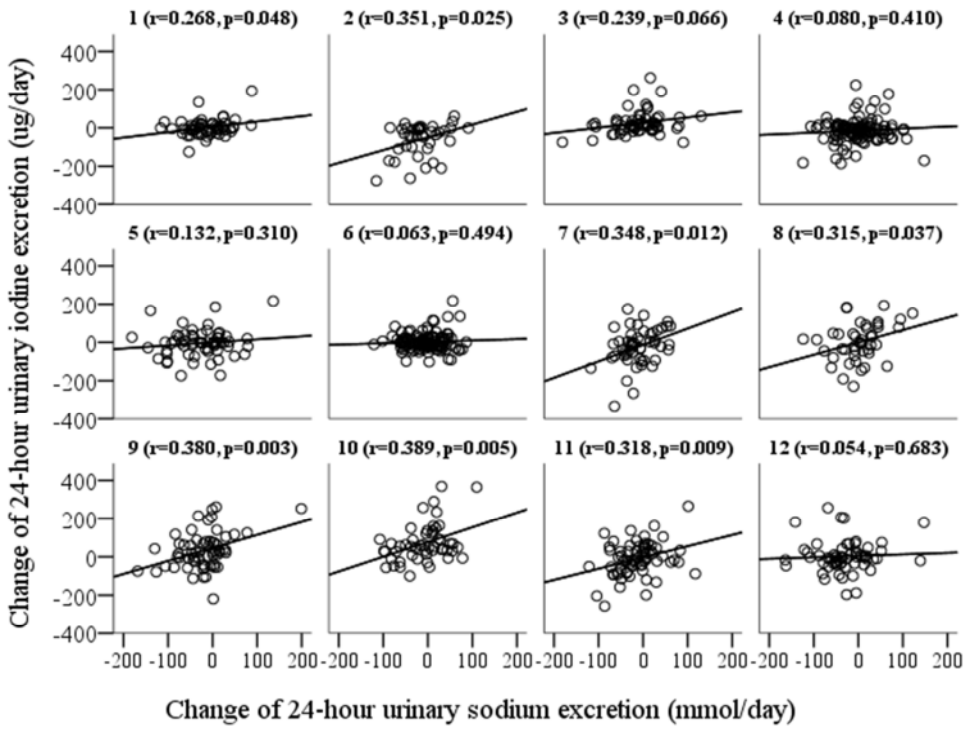
Concordant and discordant groups

The changes of urinary sodium and iodine excretions in each village were plotted in Figure 5.2.3. The correlation between iodine and salt intake was positive in all villages; however the strength varied substantially. The correlation strength was

medium in villages 2, 7, 8, 9, 10, 11, small in villages 1, 3, 5, and negligible in villages 4 and 12.

Based on the p values of the correlation coefficients, iodine and salt intake were significantly correlated in villages 1, 2, 7, 8, 9, 10 and 11. Therefore these villages were defined as concordant village group; villages 3, 4, 5, 6 and 12 were defined as discordant village group thereafter.

Figure 5.2.3 *Scatterplot of the change in urinary iodine excretion against the change of urinary sodium excretion in the eligible participants (n=780) in 12 villages after 6 months of follow-up*



Note: The title for each sub-plot shows the village identification number with Pearson's correlation coefficient and p value in brackets. Each plot is fitted with a linear regression line.

Changes of salt and iodine intakes in 6 months

Table 5.2.3 shows the test results of the changes of salt and iodine intakes by correlation group during the study period. Salt intake was significantly reduced in

both concordant and discordant groups (p<0.001 for both). The means were -12.0 (46.7) mmol/day and -11.3 (51.2) mmol/day, respectively. The change of iodine intake was, however, not significant. Larger variation was seen in the concordant group. On average, iodine intake increased by 3.5 (94.2) μg/day in the concordant group and was reduced by 0.1 (63.4) μg/day in the discordant group.

Table 5.2.3 *Test of the changes of 24-hour urinary sodium and iodine excretion during 6 months follow-up*

	Concordant group		Discordant group	
	Mean (Standard Deviation)	p value	Mean (Standard Deviation)	p value
Change of urinary sodium excretion	-12.0 (46.7)	<0.001	-11.3 (51.2)	<0.001
Change of urinary iodine excretion	3.5 (94.2)	0.475	-0.1 (63.4)	0.978

Note: The hypothesis of mean of change=0 was tested. If p value <0.05, the change could be considered significant.

Association between iodine intake and salt intake

Three linear regression models were created to estimate the impact of the change of sodium intake on the change of iodine intake in discordant and concordant villages. Results are shown in Table 5.2.4. Model I was not adjusted for covariates. Model II was adjusted for age and sex. Model III was adjusted for age, sex and locality. Locality was used here to account for possible geographical variation and socioeconomic differences. All coefficients of the sodium change in the concordant group were significant, while all coefficients in the discordant group were not significant, whether or not adjustments were considered.

Table 5.2.4 *Linear regression models of the change of iodine intake in relation to the change of sodium excretion in concordant and discordant village groups, with adjustment for age, sex, residential locality*

	Village group	Change of urinary sodium excretion†		
		Model I	Model II	Model III
Change of urinary iodine excretion	Discordant	0.115 (-0.005, 0.235)	0.111 (-0.010, 0.232)	0.111 (-0.010, 0.232)
	Concordant*	0.628 (0.432, 0.824)	0.628 (0.431, 0.824)	0.620 (0.429, 0.811)

Note: Results are presented as coefficient (95% confidence intervals).
**: All models of the concordant group are significant. P values for model I, II and III are all <0.001.*
†: No adjustment was made for Model I; Model II was adjusted for age and sex; Model III was adjusted for age, sex and locality.

The coefficient of sodium change in Model III was 0.62, indicating that 10 mmol/day change of sodium was associated with a change of 6.2 μg/day iodine.

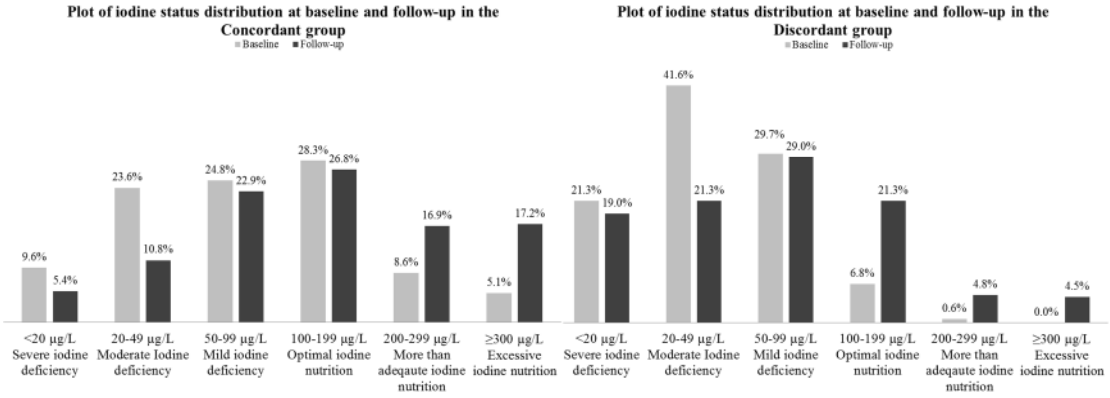
Change of iodine status distribution

The distributions of iodine status in concordant and discordant groups are shown in Figure 5.2.4. Distribution at baseline and at follow-up was plotted together to compare the change during 6 months.

Iodine status improved significantly in both groups over 6 months ($p<0.001$ for both). The graph shows that the overall distributions of iodine concentration shifted to the right. The proportion of iodine deficiency (including severe, moderate and mild deficiency) was reduced. The reduction in moderate iodine deficiency was the most obvious: an absolute reduction of 12.8% and 20.3% lower in concordant and discordant group, respectively – approximately 50% reduction throughout the study period. On the other hand, the proportion of people with excessive iodine intake increased significantly in both village groups. In the concordant group, the number of participants at risk of iodine-induced hyperthyroidism (IIH) was almost doubled

(from 8.6% to 16.9%) while the number of participants at risk of adverse health issues was more than tripled (5.1% to 17.2%). The absolute change was not large in the discordant group. However, the increase in the population with excessive iodine intake was still evident, particularly in the concentration of more than 300 µg/L level (from 0% to 4.5%).

Figure 5.2.4 *Comparison of the iodine status change in the participants of the concordant village group (left panel) and the discordant village group (right panel) after the 6 months health promotion of salt reduction*



Note: For both groups, $p<0.001$ using the test of marginal homogeneity.

5.2.4 Discussion

Key findings

This analysis was set out to assess the salt intake and iodine status in an African population, and also to investigate the association between salt and iodine intakes in the population by modelling the changes of urinary sodium and iodine excretions between baseline and follow-up, using data directly obtained from a community-based study.

As one would have expected, urinary sodium excretion (used as a proxy for salt intake) had a strong association with urinary iodine excretion (used as a proxy of iodine status) in some but not all villages. The analysis suggests that the effect is predominantly explained by the use of iodised salt in some villages but not in others. The relationship suggests that a population-wide variation in salt intake by an average of 1 gram of salt per day (or 17.1 mmol/day of sodium) will lead to a parallel change in iodine intake of 10.6 μg/day. This assumes widespread use of iodised salt in the community and a constant iodine level in salt. This is likely not to be the case in real life scenarios as indicated by the fact that half the recruited villages did not appear to have iodised salt as the main source of salt in their community.

The study population had relatively low salt intake compared to average worldwide population intakes (15). The average salt intake was about 6 g/day (equivalent to 101.0 mmol/day, 1 g salt=17.1 mmol sodium). The estimated level of urinary iodine concentration indicated that the population was at risk of mild iodine deficiency. Significant rural and semi-urban differences in iodine status were seen, as the semi-urban participants had a higher proportion of participants with optimal iodine status compared to the rural participants.

Furthermore, the proportion of iodine deficient people was surprisingly reduced in both concordant and discordant groups, although overall status was almost unchanged and salt intake was reduced in both groups after 6 months of promoting salt reduction in some villages.

The distribution of iodine status changed during the study period. The comparison of urinary iodine concentration between baseline and follow-up showed an overall improvement of iodine status, with less risk of iodine deficiency and increased risk of IIH and other adverse health circumstances, although there was only little change in the concentration of urinary iodine.

Finally, the present analysis also revealed significant geographical variation of iodine intake in the Kumasi area. Semi-urban residents consumed more iodine than rural residents.

Discussion of findings

This is the first analysis to quantify the association between salt intake and iodine intake in an African population. The need for the investigation of this association is obvious. Dietary salt intake is assumed to be 10 g per day worldwide. The amount of iodine added to salt is usually in the range of 20-40 ppm to guarantee an iodine intake of 150 µg per day for an adult, considering the 40% loss of iodine during production, transportation, storage and cooking. Although the salt reduction programme and the USI programme are deemed to be compatible (26), a reduction in salt intake may cause lower iodine intake and lead to worse iodine status in the general population. Thus, for a population at optimal iodine status, the reduction may put the population at risk of iodine deficiency. For a population already deficient in iodine, the reduction could make things worse. On the contrary, people may increase their salt intake in an attempt to increase iodine intake, given that iodine supplementation in Ghana is exclusively delivered through iodised salt used in the households.

Theoretically, if a population reduces its salt intake from 10 g per day to 5 g per day (the WHO target), iodine intake would be reduced by 53 μg/day in the general population. However, this reduction is untenable for policy adaptation. On the other hand, an increase in iodine content of salt calculated to deliver the extra 53 μg/day necessary to offset the impact of a reduction in salt intake on iodine status would make the two policies compatible. Precise and consistent scientific evidence is urgently needed to provide more practical support for international organisations (e.g. WHO, UNICEF), governments, policy-makers, salt industry, media and other stakeholders in order to improve the coalition of both programmes.

The results of the present analysis provide the evidence that reduced salt intake would lower iodine intake in the general population covered by iodised salt. The estimated effect, however, is weaker than the theoretical relationship.

The mixed coverage of iodised and non-iodised salt in the concordant group might be a major cause. Ghana is a major salt producing country in West Africa. The annual output of salt reaches 250,000 metric tonnes. Only small amounts are imported from the UK, Germany and China. However, major salt plants only produce 58% of the salt needed. The rest is produced and sold by many small-scale salt plants, mostly without iodisation. Although sale of non-iodised salt is illegal, these salts are still popular on the market. An important reason is the price. The cost of iodised salt is higher than non-iodised salt. Households of low socioeconomic status are usually more sensitive to prices. Hence they are inclined to buy cheaper salt. Moreover, in some areas with poor road links, difficulties in transportation either increase the total cost of salt or make the delivery of iodised salt impossible,

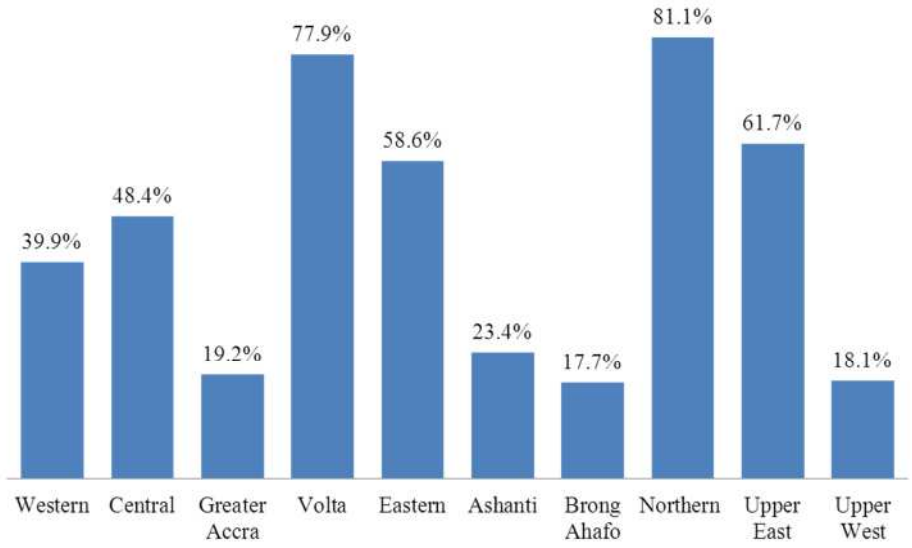
resulting in even lower coverage of iodised salt. According to the 2006 micronutrient survey in Ghana, only one third of the households consumed iodised salt adequately, and 20% consumed salt with less than 15 ppm iodine, whereas 45% of salt was non-iodised (280). In the present analysis, the insignificant weak correlation between salt intake and iodine intake in 5 villages also suggested the lack of adequate iodised salt consumption, which is in agreement with the survey findings.

The other possible explanation might be that the loss of iodine was more than expected before salt consumption. In Ghana, law and regulation on salt iodisation was enacted in 1995 by parliament (281). Potassium iodate (KI) is added to salt in the range of 25-45 ppm. Although this compound is more stable and less soluble than potassium iodide (KIO_3), there is still loss of iodine in the stages of packaging, transportation, storage and cooking. The tropical weather with excessive heat and humidity can also increase the loss.

Significant rural and semi-urban differences in iodine intake and iodine status were detected. This geographical variation reflected the historical inequality between rural and urban areas. In Africa, rural residents are more disadvantaged with poorer socioeconomic status, less access to medical facilities and less food availability. The household coverage of iodised salt in rural areas is only half of that in urban areas (281). The on-going globalisation and urbanisation continue to aggravate the inequality gap. Urban residents have access to more iodine-rich foods and have higher iodine intake due to the increasing food diversity, whereas rural residents have limited food sources and are more vulnerable to food shortage.

In fact, the household coverage of iodised salt also has considerable geographical variation in the country (Figure 5.2.5). In the 2006 Ghana Multiple Indicator Cluster Study (MICS) (280), it was revealed that a few regions had very low coverage of iodised salt, including the Ashanti region in which only 23.1% of households reported the regular use of iodised salt. The lowest household coverage of iodised salt was in Brong Ahafo (17.7%) while Volta had the highest household coverage of iodised salt (82.9%).

Figure 5.2.5 *Household coverage of iodised salt in Ghana*



Note: Modified from the 2006 Ghana Multiple Indicator Cluster Study report (280).

The ineffective monitoring and weak enforcement of salt iodisation (282) contributes to the geographical variation. It also slows the progress of the USI programme. Although salt iodisation was made mandatory in the 1990s, the production and sale of non-iodised salt is still persistent, resulting in the recurrence of declining iodised salt coverage. National health surveys and micronutrient surveys in the past 15 years showed that the coverage increased dramatically from 0.7% in 1997 to 49.1% in 2002 (283) and then declined to 41.5% (284). Although strict monitoring put in place

in 2005 pushed the coverage back to 74.1%, recent reports revealed that only 32% is covered by iodised salt (285). The coverage of adequately iodised salt is even lower (280). Consequently, population iodine status varied over time. The median urinary iodine concentration was 77 μg/L in a 1993 national survey and later increased dramatically to 196 μg/L in the ThyroMobil visit in 2001 (280;286). A recent study recruiting 112 randomly selected school-aged children in Greater Accra showed the median urinary iodine concentration was only 68 μg/L (287).Salt intake in the Kumasi area was lower than the estimated national average according to UNICEF (10 g/day). The difference is hardly sufficient to prove the geographical variation within Ghana due to lack of more evidence. However, a few studies in different African countries and populations indicate that the salt intake is different from country to country. Hess *et al.* (197) evaluated the salt intake of 188 adults and children living in coastal and inland areas in Ivory Coast by means of 3-day weighed food records and 24-hour urine collections. The average dietary salt intake was 6.8 g/day in adults and 5.7 g/day in the whole study sample. The 24-hour urinary sodium was 7.4 g/day, with little difference between north and south. Maseko *et al.* (288) reported a salt intake of 6.8 g/day and 6.5 g/day in normotensive and on-treatment hypertensive urban South Africans, respectively. In their review of global salt intake, Elliot and Brown (30) listed studies on different African populations in the last two decades. For example, Pavan reported 4 g/day (equivalent to 1,575 mg sodium per day) in Uganda and Tanzania (289), and Charlton and his colleagues estimated that black, mixed ancestry and white urban South Africans consume 7.9-9.6 g/day (135.3-164.8 mmol/day) (290). In the INTERSALT study (126), it was showed that

Zimbabweans consume about 8.2 g/day salt. The salt intake is 5.4 g/day in rural Nigerians and 8.7 g/day in urban Jamaicans, estimated in a randomised trial (291).

Despite the low salt intake revealed in this analysis, the prevalence of hypertension in Ghana was comparable to that of industrial countries (292) and continue to increase rapidly. Before the 1990s, only 8-13% of the urban population and 4.5% of the rural population were hypertensive (293). The prevalence was 28.3% in 2003 (294) and increased to 29.4% in 2004 (295). Moreover, the number of hypertensives increased almost five-fold from 1988 to an estimated 249,342 in 2005, and then doubled to 505,180 in 2007.

In fact, not only Ghana, but also other low- and middle-income countries are facing an increasing threat from hypertension and CVD. The CVD mortality in low- and middle-income countries accounts for almost 90% CVD deaths in the world (296). By 2020, the number of coronary heart disease (CHD) events could increase by more than 120% in both sexes (297).

Additionally, the ageing population (≥60 years), which has a higher risk of CVD, is expanding in low- and middle-income countries. In Sub-Saharan Africa, the number will double by 2030 (298). Considering the limited resources available, the accessibility and affordability of the same treatments as industrialised countries remain a big question to the governments and health officers in those less developed countries.

Therefore, precautions should be taken by means of salt reduction to prevent higher prevalence of hypertension and increasing CVD risk. Consumer awareness campaign

and population-wide health intervention should be emphasised, particularly in urban areas where the consumption of processed foods is increasing due to urbanisation and globalisation (299). The information in campaigns or health promotions should be simple and clear. This is to avoid misunderstanding among individuals, e.g. some people may increase salt consumption to increase iodine intake.

The present analysis did not show a significant rural-urban difference in salt intake. One possible explanation is that the dietary habits of semi-urban residents were similar to those of rural residents. However, rural-urban disparity in salt intake is common in low- and middle-income countries (300;301). Urban residents usually have more choice of food and have growing preference in processed foods. Therefore, it is not surprising to see a higher prevalence of hypertension in the urban areas. Mbanya (302) reported that the age-adjusted prevalence was 16.4% and 12.1% in urban men and women, compared to 5.4% and 5.9% in their rural counterparts. In the International Collaborative Study of Hypertension in Blacks (ICSHIB) study, higher prevalence in urban areas was also revealed in Nigeria and Cameroon (265).

The iodine status distribution was improved for both groups after 6 months, while the overall iodine change was small and non-significant in both groups. One possible explanation is that the iodine intake in many participants was increased so that their individual iodine status was improved. But some participants might have much lower levels of urinary iodine measured at the follow-up. That is, the many small increases were neutralised by the few large decreases. The large standard deviation of the iodine changes may provide the evidence (Table 5.2.3). In addition, urinary iodine varies not only between individuals, but within individuals. Like other urinary

biomarkers, the iodine variation can be day-to-day and have circadian rhythm (303). Different food intakes could lead to large day-to-day difference in urinary iodine levels. Therefore, one simple collection may not fully reflect the true level of iodine intake in individuals.

Strengths and Limitations

The data contains a baseline measurement and a follow-up measurement. This enables us to investigate the impact of the change of salt intake on the iodine intake and iodine status. Moreover, the comparison of the nutritional intake changes provided an opportunity to identify the varied use of iodised salt in the villages while this problem would be disguised if we only use a cross-sectional data set (i.e. the baseline measurement) and the association between salt intake and iodine status would have been distorted.

This analysis has several limitations. Firstly, the lack of sufficient geographical information limited the assessment of spatial effect on the intakes and their association. Although there was residential locality information, it was not an ideal surrogate of many latent risk factors. Therefore, the investigation and discussion related to the geographical variation of salt and iodine intakes are far from complete. Secondly, the study period lasted for 6 months. There was possible seasonal impact on individuals, particularly in dietary sources and habits, as food diversity changes according to the harvest season. However, this analysis does not include these changes and was not able to provide much insight into the temporal variation in salt intake and iodine status. Additionally, as the community-based study was designed to examine the effect of salt reduction in population, there were no pre-defined

protocols to assess iodine status independently. It was not possible to do a retrospective data collection. Therefore, although the criterion used to determine the concordant and discordant groups may not be the most reliable, it was the best option to assess the salt and iodine association in the data. Moreover, the original data were collected from a single homogeneous community in Ghana (>90% of the Ashanti tribe). Although some suggestions and interpretations were made based on the results, they might be not applicable to other countries. For example, some Asian countries with low- and middle-income status have different cultures and dietary patterns. The association between salt and iodine should be re-estimated in those settings. Therefore the generalisability should be made with caution.

Implications

Many countries are facing the dilemma that the implementation of both health programmes may jeopardise each other. This present analysis indicates that a reduction in population salt intake by 1 g per day could reduce the iodine intake of 10.6 μg per day in the general population. The association is expected to increase if the household coverage of iodised salt is improved. In order to achieve success in both programmes, in low- and middle-income countries where the majority of iodine comes from table and cooking salt, the best solution would be to increase the iodine content in salt.

In addition, the USI programme should be improved, with special emphasis on the monitoring and enforcement of the use of iodised salt. In Ghana, the lack of such strictness has led to a stagnant status of the programme, leaving tens of thousands of people, especially children and pregnant women, at risk of iodine deficiency. For

countries that produce salt locally, the governments should extend their close partnership with all producers and encourage the local small-scale producers to add sufficient iodine during production. Essential political advocacy is needed to achieve the elimination of iodine deficiency.

Meanwhile, attention should be paid to the monitoring and control of salt intake. The trend of increasing salt intake has been seen during the economic development of many industrialised countries. With the on-going epidemiological transition in many low- and middle-income countries such as Ghana, the trend is expected to repeat. Additionally, the less developed countries, unlike their industrialised counterparts, usually have fewer budgets allocated to health care, and struggle to compete with some more urgent diseases such as malaria and HIV/AIDS. They are likely to underperform in the prevention, management and control of hypertension.

Several approaches are used to enhance the salt reduction programme, including social marketing, labelling, public awareness campaigns, product reformulation, regulation and taxation (15). The use of “salt substitutes”, i.e. potassium chloride instead of sodium chloride, is also being examined in China. However, the effect is unclear. Regulation, taxation and product reformulation are the most effective approaches in most developed countries. The estimated total reduction could reach up to 6 g per person per day (15). One recent example of an adoption of such a policy is the Foodstuffs, Cosmetics and Disinfectants Act draft published in South Africa in July 2012, to regulate the food industry and food distribution to achieve a reduction in the salt content of the main food categories by 2016 (304). These policies, by incorporating the need to use iodised salt in food manufacturing, would

address the harmonisation of the two public health policies without the involvement of individuals in the responsibility of delivering a public health service. However, for many low- and middle-income countries, the majority of salt intake still comes from salt added to food and in the cooking process. For these countries, also relying on table salt as the main vehicle for iodine supplementation, close partnership with food manufacturers and effective health awareness campaigns may be more appropriate and practically cost-saving to enhance the salt reduction programme and improve the coalition with the salt iodisation programme. At the same time, it is imperative that the fortification of salt be reviewed and that the population coverage be increased.

During the implementation of both programmes, attentions should be paid to the socioeconomic inequality. The socioeconomically disadvantaged groups, such as rural residents, women and household at low income, usually have lower iodine intake and higher salt intake. Governments and health policy-makers should adhere to the population-wide approaches to reduce the inequality. Experience in the industrialised countries indicates the individual based approaches expand the socioeconomic inequality (305). However, both types of approaches can be combined to reduce the health burden substantially in short- to medium-term (306). For instance, in the framework of the USI programme, iodised oil could be distributed to remote areas where iodised salt is not available.

As our case study is based on the Ghana data, the association between iodine and salt intakes may be changed according to the context of each country. Therefore, it is recommended that every country should conduct a detailed investigation regarding this association to make a tailored adaptation to their own policy.

5.3 Salt Intake and Iodine Status in the United States

5.3.1 Introduction

High salt intake has become the 7th leading risk factor for premature death in the United States (US) (307). The causal effect of high salt intake as a determinant of high BP is supported by a large body of scientific evidence (15). High salt intake is responsible for 30% of hypertensive events in the United States (308). The link between high salt intake and cardiovascular disease (CVD) is also established (4). Salt reduction programmes to lower BP and to prevent the risk of CVD and other chronic diseases are adopted widely in the general population. The WHO calls for a reduction of salt intake to less than 5 g per day for all countries (4). In the United States, the target is set to reduce sodium intake to 2,300 mg/day (equivalent to 5.75 g/day salt) (69). The American Heart Association recommends an even greater reduction to <1,500 mg/day (about 3.8 g/day salt) (16). New York City initiated a programme to reduce salt in foods by 25% in order to achieve a 20% reduction in the population as a whole (1).

Many high-income countries have established legislations or regulations on salt iodisation (309). The United States Food and Drug Administration (FDA) began salt iodisation in early 1920s (310) after David Cowie's successful experiments of treating goitre using iodine supplementation in Michigan (311). Although the salt iodisation is on a voluntary basis and so far only discretionary salt, i.e. table and cooking salt, is widely iodised, iodine deficiency is rare in the country.

However, some concerns have been raised recently regarding the compatibility of population salt reduction and universal salt iodisation (USI) programmes (25;33). Reducing salt intake may restrict the availability of iodine and jeopardise the salt iodisation programme. As discovered in the previous section, salt and iodine intakes have a strong association in a Ghanaian urban-rural mixed community when iodised salt is commonly used. However, due to methodological differences in the assessment of biomarkers to monitor these programmes and to the historic lack of links between the two programmes, little is known of the reciprocal effects of these programmes in high-income countries. The existing studies (28;29) may be useful in answering the question "whether salt reduction will impact on salt iodisation programme?" but are unable to provide the answer to "what is the extent of the impact?".

Misunderstanding, waste of health investment and potentially conflicting values can all jeopardise the progress of both health programmes in all high-, middle-and low-income countries. The need to assess the impact of salt reduction on iodine supplementation is thus apparent and urgent to promote the coordination of both programmes and improve the public health.

This analysis will use the United States as an example

1) to estimate salt intake and iodine status in an industrialised population in which processed foods dominate their diets;

2) to assess the association between salt and iodine intakes in high-income countries that implement salt iodisation programmes;

3) to investigate the impact of modifications of salt intake, mainly from processed foods, on iodine status in the population;

4) to investigate the potential geographical variation and determinants of the iodine intake and salt intake in the US population;

5) to provide suggestions to policy-makers.

5.3.2 Data and Methods

Country profile

The United States of America is a confederation of states located in North America, neighbouring Canada in the north and Mexico in the south. The nation consists of 50 states and one federal district. Forty-eight are contiguous while Alaska and Hawaii are separated from the majority of the country. The total population in the United States is about 314 million people. The country is composed of diverse racial and ethnical groups. White American is the major group, comprising more than 70% of the US population. The remaining groups include African American (or Black American), Asian, American Indian, Hispanic American, etc.

As the wealthiest country by GDP and the second largest economy in the world, the US also has the largest health expenditure per capita ($8,362) in 2010 (312). Similar to other high-income countries, CVD is the major cause of death in the United States (313).

Introduction of NHANES III

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative (excluding institutional population) population health surveillance programme administered by the Centers for Disease Control and Prevention (CDC). It contains a series of surveys with a complex, multistage, stratified probability design. The aim of the programme is to assess the health and nutrition status of the US population and to develop health promotions and improve disease prevention in the country.

The first survey was carried out in the 1960s and the third, NHANES III, was conducted during 1988-1994. The survey has been conducted every two years since 1999. Several sub-populations are over-sampled to improve the reliability of the analyses. These sub-populations include African Americans, Mexican-Americans, people aged 60 and over and children. Oversampling in low-income White Americans started in 2000.

The NHANES III was carried out in two phases and data are kept in the National Center for Health Statistics (NCHS). The first phase was carried out between 18th October 1988 to 24th October 1991, and the second from 20th September 1991 to 15th October 1994. Participants and their households were randomly selected to complete the home interview and examination procedures in the survey. A total of 85.6% (n=33,994) of the 39,695 selected individuals aged 2 months and over attended the interview. In the NHANES III, the interview was conducted at the participant's home by means of household questionnaires with computer assistance. The questionnaires, administered by trained personnel, included a Household

Screener Questionnaire, a Family Questionnaire, a Household Adult Questionnaire, and a Household Youth Questionnaire. Participants provided demographic, socioeconomic, and dietary information, as well as answering health related questions.

All of the interviewed participants were then invited to the mobile examination centers (MEC) for physical and physiological examination and laboratory testing. About 90% (30,818) of the interviewed participants attended the MEC examination. Blood and spot urine samples were collected. In addition, five automated questionnaires were also carried out at the MEC: a MEC Adult Questionnaire, a MEC Youth Questionnaire, a MEC Proxy Questionnaire, a 24-hour Dietary Recall, and a Dietary Food Frequency Questionnaire. Some participants were not able to attend the MEC examination. They included infants aged 2-11 months and adults aged 20 years and over who had difficulty coming to the MEC. Home examination was then conducted instead in 493 participants. However, these participants were not included in this analysis as they were not involved in the 24-hour dietary recall and urine test.

Anthropometric measurement

The adult population included participants aged 17 years and over, and the youth population included participants aged 2 months to 16 years. To keep the confidentiality of those aged 90 years and over, their age was recoded into a single age category, “90+”. All participants were defined as one of the following race-ethnicity groups: Non-Hispanic White, Non-Hispanic Black, Mexican-American, and other.

Standing height was measured to the nearest 0.1 cm and weight was measured to the nearest 10 g. Body mass index was calculated by weight over height squared (kg/m^2).

Multiple BP readings were taken by trained doctors at the MEC using sphygmomanometry recording Korotkoff sounds. Three measurements were obtained and the average systolic and diastolic blood pressure records were based on all readings.

Each participant's marital status was recorded. The status included married (spouse in household), married (spouse not in household), living as married, widowed, divorced, separated, and never married. According to the living status, those who were living with partners were grouped as "living together" and the rest, including married (spouse not in household), were grouped as "living alone".

Participants provided their education background by answering "what is the highest grade or year of regular school?" The majority was in the category of 12 grade/years education (equivalent to high school qualification). According to the analytical recommendation in the NHANES III documents, three levels were used to categorise the education background: below high school, high school (12 grade/years), and above high school.

Smoking habit was determined on the basis of two questions: "Have you smoked at least 100 cigarettes during your entire life?" and "Do you smoke cigarettes now?" Non-smoker was defined as the person not smoking now who might have smoked less than 100 cigarettes in the past. Former smoker was defined as the person who

smoked at least 100 cigarettes but not smoking now. Current smoker was defined as the person still smoking.

Participants were asked about their employment status in the past two weeks at the time of interview. However, this information could not provide long-term reflection of the participants' socioeconomic status. Therefore, poverty income ratio (PIR) was included in this analysis to describe the family income as well as their socioeconomic status. PIR reflected the position of the midpoint of the observed family income category in the poverty threshold. As indicated in the NHANES III Examination Data File, PIR "allows income data to be analysed in a comparable manner across the six years of the survey".

Urine test

Urine test was based on spot urine samples. No volume information was available, although the fasting time was recorded. Twenty-four-hour urine collection was not carried out because it was deemed unfeasible (314). Details of the test have been described in the Laboratory Procedures Used for NHANES III. Briefly, urinary iodine concentration (UIC) was measured by the Iodine Research Laboratory, University of Massachusetts Medical Center using Sandell-Kolthoff spectrophotometric method. The limit of detection of the UIC is 0.2 µg/dL. Values lower than 0.5 µg/dL were defined as "below level of detection" in the NHANES III. Hence the values were recoded to be "missing" in the analysis. In the analysis, the valid UIC was converted to µg/L by using the conversion equation: µg/L=µg/dL*10. The WHO uses the median UIC as the indicator of iodine status at a population level.

The measured UIC was used in this analysis as an indicator of iodine nutrition and to assess the iodine status in the US adult population.

Urinary creatinine concentration was measured by the Jaffé alkaline picrate method. The concentration levels lower than 10 mg/dL were “statistically suspect” and were defined as “below level of detection”. Hence these values were also recoded to missing values. The concentration levels were recorded as mg/dL in the raw data set. The unit was converted to mmol/L by using the conversion equation: mmol/L=mg/dL*0.0884.

24-hour dietary recall

The NHANES III adopted a 24-hour dietary recall (midnight to midnight) to assess participants’ dietary pattern and nutrition intakes. The information was obtained via a computer-aided dietary interview at the MEC. Nutrient intakes were measured on the reported foods and beverages. The nutrient intakes from other sources, such as nutrient supplements, medications, table and cooking salt and drinking water, were not recorded nor measured. The amount of nutrient intakes was assessed based on two US Department of Agriculture (USDA) food composition databases that were updated in 1993 and 1995, respectively.

In the NHANES III, salt intake was measured by dietary sodium intake calculated from the dietary recall. The final dietary recall dataset provided data of the dietary sodium and energy intakes as well as the consumption of alcohol. The dietary iodine intake was not calculated. The dietary sodium intake was recorded in mg/day and the dietary energy intake was recorded in kcal/day. Alcohol consumption was recorded

in g/day. However, the majority of the participants reported a 0 g/day intake of alcohol. Hence alcohol consumption was dichotomised. Those who answered no consumption were grouped as “non-drinker” and those who had some consumption (>0 g/day) were grouped as “drinker”.

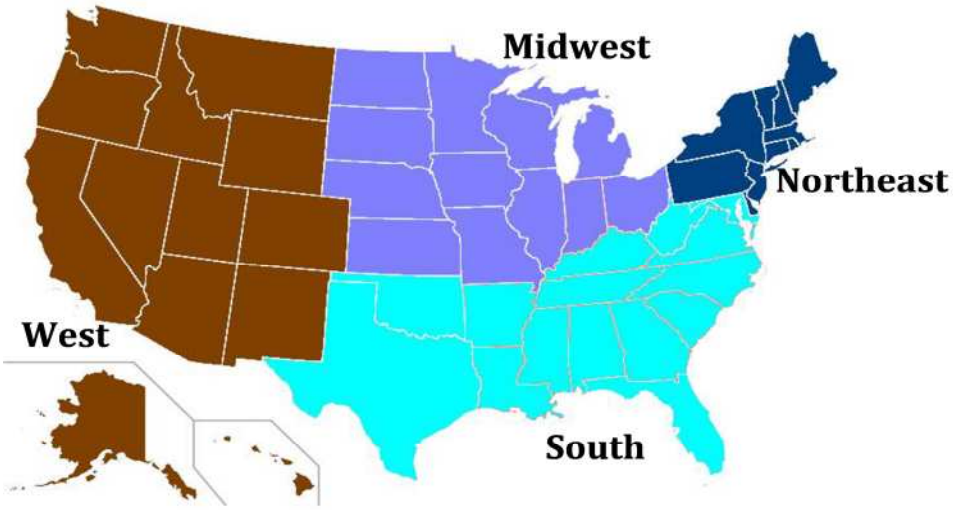
Geographical location

The survey was conducted in 4 census regions (see Figure 5.3.1), including 50 states and 760 counties. However, the released data only contain geographical information of the census region. More detailed geo-information, such as county and state information, is not publicly available[8]. Hence the investigation of geographical variation effect was limited at census region level.

In addition, residential location was classified as rural or urban. In the NHANES III, the residential location within a metropolitan statistical area (counties with populations more than 100,000) was defined as urban and the residential location out of a metropolitan statistical area was defined as rural.

[8] The CDC restricts the use of more detailed geo-information and requires researchers use these confidential data at their Hyattsville (at Washington DC) or Atlanta centre. The cost also prohibited me from accessing these data. CDC requires $750 for set-up fees and $300/day for on-site access. As there was no extra funding in this project to cover the cost, the analysis has to be limited to the census region level.

Figure 5.3.1 The United States census regions used in the NHANES III survey



Sampling weight

Several sampling weights were calculated and used for the adjustments for non-response, oversampling of selected sub-populations and non-coverage. There were a number of sampling weights available for different analytic purposes, e.g. by survey year. However, in this analysis, two sampling weights were used for national estimate: interview weight for home interview variables and MEC examination weight for examination and blood and urine test variables. Details of the sampling weights have been discussed in the survey documents and elsewhere (315). At the modelling stage, no sampling weight was used. Some participants in the NHANES III were from the same household. Bayesian geo-additive models were used to take into account the potential within-household dependence.

Statistical analysis

The means and standard errors were reported for the continuous variables. For the categorical variables, the medians and interquartile ranges (IQR) were calculated. These analyses were weighted for sampling weights using SAS SURVEYMEANS and SAS SURVEYFREQ procedures.

Comparisons by sex and region were also made. However, the SAS survey procedures are unable to produce weighted p values for the comparisons. Hence unweighted methods were used. One way Analysis of Variance (ANOVA) was used to compare age, weight, height and BMI. Dietary indicators were compared using the Kruskal Wallis test as normality assumption might not be suitable for them. For instance, extreme values were found in UIC. For the categorical variables, Pearson's chi-squared test was used to test the difference.

Bayesian geo-additive models were used to investigate the association between iodine intake and sodium intake and to assess the effects of risk factors on both intakes. The details of model construction are illustrated in Chapter 3.

Four models were created to test the different combinations of risk factors, the nonlinearity of the continuous risk factors and the regional effect (see Table 5.3.1). However, the software is unable to estimate spatial effects (correlated and uncorrelated effects) at this level due to limited geographical information. Therefore, the census region was included in the models as a fixed-effect risk factor.

For UIC, Model 1 estimates the effect of sodium intake and regional impact. Model 2 expands Model 1 by adjusting for age, sex, BMI and urinary creatinine

concentration. Model 3 develops Model 2 by adjusting for demographic, lifestyle and socioeconomic risk factors (race-ethnicity group, marital status, education, smoking and drinking habit, and household location and economic status). Model 4 attempts to explore the nonlinear effects of the continuous risk factors. The model structures for dietary sodium intake are almost identical to those of UIC.

Table 5.3.1 *List of Bayesian models*

Dependent variable	Model	Risk factor
Urinary iodine concentration	Model 1	Region + Sodium intake
	Model 2	Region + Sodium intake + Age + Sex + BMI + Urinary creatinine concentration
	Model 3	Region + Sodium intake + Age + Sex + BMI + Race-ethnicity + Marital status + Education + Smoking + Drinking + PIR + Location + Urinary creatinine concentration
	Model 4	Region + Sodium intake (nonlinear) + Age (nonlinear) + Sex + BMI (nonlinear) + Race-ethnicity + Marital status + Education + Smoking + Drinking + PIR + Location + Urinary creatinine concentration (nonlinear)
Dietary sodium intake	Model 1	Region
	Model 2	Region + Age + Sex + BMI + Dietary energy intake
	Model 3	Region + Age + Sex + BMI + Race-ethnicity + Marital status + Education + Smoking + Drinking + PIR + Location + Dietary energy intake
	Model 4	Region + Age (nonlinear) + Sex + BMI (nonlinear) + Race-ethnicity + Marital status + Education + Smoking + Drinking + PIR + Location + Dietary energy intake (nonlinear)

Note: Nonlinear: the effect was assumed to be nonlinear.

As there were some extremely high levels of urinary iodine concentration, a direct modelling of this variable may produce biased results and lead to incorrect interpretation. These values were difficult to normalise, even after attempts at different mathematical transformations (e.g. log transformation, square root, and Box-Cox transformation). High iodine intake leads to hyperthyroidism, thyroid papillary cancer and iodermia (92). The US Institute of Medicine (IoM) instructs that

no more than 1,100 µg/day iodine should be consumed in adult population. Therefore, this upper limit was used as a reference to exclude these extreme values in the modelling. By using a conservative estimate of 1.2 L/day urine output, the cut-off value was defined as 916.7 µg/L. There were 263 out of 17,043 (1.6%) participants who had valid urinary iodine measurement beyond this value. They were not included in the following modelling. An exponential transformation was applied to the concentration variable to normalise the data: transformed UIC=UIC^0.1. Log transformation was also used for comparison. As the models of both transformations produced similar results, the log transformed UIC was finally chosen as the dependent variable.

For the categorical risk factors, dummy variables were generated using dummy coding (1 vs 0). One level of each risk factors was defined as the reference level (value=0). The designated reference level was indicated in Table 5.3.2.

Different transformation methods were used to normalise the dietary sodium variable. Exponential transformation was also applied. The equation is: transformed sodium=sodium^0.3. Log transformation was compared with this transformation. However, the performance of the exponential transformation was better. Hence the models of the non-transformed sodium intake were finally chosen.

Deviance information criterion (DIC) (220) was used for model selection. It is a tool to measure the model performance by trading off model complexity and fit. The model with the smallest DIC value was regarded as the best model.

Table 5.3.2 *List of categorical variables with defined reference level*

Variable	Category	Indicator
Region	Northeast	reference level
	Midwest	
	South	
	West	
Race-ethnicity	Non-Hispanic White	reference level
	Non-Hispanic Black	
	Mexican-American	
	Others	
Sex	Female	reference level
	Male	
Smoking	Non-smoker	reference level
	Former smoker	
	Current smoker	
Marital status	Living together	reference level
	Living alone	
Education	Above high school	reference level
	High school	
	Below high school	
Drinking	Non-drinker	reference level
	Drinker	
Poverty Income Ratio	At or above poverty	reference level
	Below poverty	
Location	Urban	reference level
	Rural	

For the preliminary analysis, all p values <0.05 are regarded as significant. For the Bayesian modelling results, 90% credible intervals were computed. If both the lower and upper limits were either negative or positive, the effect of the corresponding risk factor was regarded as significant. The preliminary analysis was conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA). The Bayesian models were constructed and estimated using BayesX version 2.0.0 (06.05.2009).

5.3.3 Results

Population characteristics

The population characteristics are summarised in Table 5.3.3. The total number of included participants was 20,050, representing a population of 187,647,206 US adults aged 17 and older. Home interview weight was applied in the analysis. The South region had the largest adult population (34.3%), followed by the Midwest (24.1%), the West (20.9%) and the Northwest (20.8%). There were fewer participants involved in the MEC examination and blood and urine measurements. The total numbers of participants provided valid examination and urine measurements were 18,106 and 17,107, respectively. The MEC measured variables include height, weight, BMI, SBP, DBP, and all dietary and urine variables. A separate MEC examination weight was applied to these variables.

The mean age of the US adult population was 43.3 (Standard Error**:** 0.4) years. Men were younger than women (42.3 (0.4) vs 44.2 (0.4)). The population was divided into four race-ethnic groups. The non-Hispanic Whites were the major group (76.0%), almost 7 times larger than the non-Hispanic Blacks (11.2%). Mexican-Americans and other minor race-ethnic groups consisted of 12.8% of the population. The mean height and weight were 168.4 (0.1) cm and 75.0 (0.3) kg. The computed BMI was 26.3 (0.1), kg/m^2, indicating overweight in the population. The average systolic and diastolic blood pressures were 121.8 (0.4) and 73.7 (0.2) mmHg.

The majority of participants were cohabiting. Single, widowed, or living separately (including married couples) comprised 39.1% of the adult population.

Nearly half (47.2%) were non-smokers while there were 24.5% and 28.2% former and current smokers. Less than one quarter (23.6%) of the population reported alcohol consumption in the dietary interview. The majority (76.4%) had no beverages or foods containing alcohol.

The educational attainment in the population had an inverse pyramid structure. More people had higher educational attainment. Almost a quarter of the population (73.2%) had at least high school qualification, while 39.4% had studied for more than 12 years. One third (33.0%) of the participants had no job or had run no business in the two weeks preceding the time of the interview. Nonetheless, the family economic status seemed unrelated to the short-term employment stats. There were only 12.8% of the households below the poverty threshold.

The total daily dietary energy intake was 2,000 (IQR: 1,291) kcal. The dietary sodium intake was 3,133 (IQR: 2,356) mg/day.

Table 5.3.3 Characteristics for NHANE III participants

Variable	Total (n=20,050)‡
Age (year)	43.3 (0.4)
Sex (%)-Male	47.8
Female	52.2
Race-Ethnicity (%)-Non-Hispanic White	76.0
Non-Hispanic Black	11.2
Mexican-American	5.2
Other	7.6
Height (cm)	168.4 (0.1)
Weight (kg)	75.0 (0.3)
BMI (kg/m^2)	26.3 (0.1)
SBP (mmHg)	121.8 (0.4)
DBP (mmHg)	73.7 (0.2)
Education (%)-Above high school	39.4
High School	33.8
Below high School	26.8
Marital status (%)-Living together	60.9
Living alone	39.1
Smoking (%)-Non-smoker	47.2
Former	24.5
Current	28.2
Employment in last 2 weeks (%)-Jobless	33.0
Have a job/business	67.0
Poverty Income Ratio (%)-Below poverty	12.8
At or above poverty	87.2
Location (%)-Urban	49.7
Rural	50.3
Census region (%)-Northeast	20.8
Midwest	24.1
South	34.3
West	20.9
Alcohol drinking (%)-Non-drinker	76.4
Drinker	23.6
Food energy (kcal/day)†	2,000 (1,291)
Dietary sodium intake (mg/day)†	3,133 (2,356)
Urinary iodine concentration (μg/L)†	133.3 (142.6)
Urinary creatinine concentration (mmol/L)†	10.6 (10.3)

Note: Results are mean and standard deviation unless specified. Sampling weights were applied. The examination weight was applied to the MEC variables and the home interview weight was applied to the rest variables for mean, median and percentage estimation.
†: Median (Interquartile range).

Table 5.3.4 Characteristics for NHANE III participants by sex and region

	Sex		p value‡	Region				p value‡
	Male (n=9,401)	Female (n=10,649)		Northeast (n=2,931)	Midwest (n=3,854)	South (n=8,558)	West (n=4,707)	
Age (year)	42.3 (0.4)	44.2 (0.4)	0.501	44.1 (0.8)	43.7 (0.7)	42.4 (0.6)	43.3 (1.0)	<0.001
Race-Ethnicity (%)-Non-Hispanic White	76.3	75.8	<.0001	81.3	85.4	71.6	67.1	<.0001
Non-Hispanic Black	10.4	11.9		8.8	9.3	17.7	5.0	
Mexican-American	5.7	4.8		0.3	2.3	4.2	15.1	
Other	7.6	7.6		9.6	3.0	6.4	12.7	
Height (cm)	175.6 (0.1)	161.9 (0.1)	<0.001	167.7 (0.2)	169.3 (0.3)	168.7 (0.2)	167.8 (0.4)	<0.001
Weight (kg)	81.6 (0.4)	68.9 (0.4)	<0.001	74.3 (0.7)	75.8 (0.6)	75.3 (0.4)	74.1 (0.8)	<0.001
BMI (kg/m^2)	26.4 (0.1)	26.3 (0.1)	<0.001	26.3 (0.3)	26.4 (0.3)	26.4 (0.1)	26.2 (0.2)	0.003
SBP (mmHg)	124.2 (0.4)	119.6 (0.5)	<0.001	121.8 (0.8)	120.9 (0.9)	122.5 (0.5)	121.8 (0.7)	<0.001
DBP (mmHg)	76.1 (0.2)	71.4 (0.2)	<0.001	72.6 (0.6)	73.3 (0.2)	74.6 (0.3)	73.7 (0.2)	<0.001
Education (%)-Above high school	41.6	37.4	<0.001	41.8	40.0	33.5	46.0	<0.001
High School	30.7	36.5		32.3	37.0	34.6	30.0	
Education (%)-Below high School	27.6	26.1		25.9	23.0	31.9	24.0	
Marital status (%)-Living together	65.0	57.2	<0.001	58.2	62.1	61.7	61.1	<0.001
Living alone	35.0	42.8		41.8	37.9	38.3	38.9	
Smoking (%)-Non-smoker	38.4	55.2	<0.001	46.4	46.6	46.8	49.4	<0.001
Former	29.9	19.7		26.5	23.5	23.0	26.4	
Current	31.7	25.1		27.1	30.0	30.2	24.2	
Employment in last 2 weeks (%)-Jobless	23.9	41.4	<0.001	35.1	31.2	31.7	35.3	<0.001
Have a job/business	76.1	58.6		64.9	68.8	68.3	64.7	
Poverty Income Ratio (%)-Below poverty	10.8	14.7	<0.001	12.8	10.7	15.4	11.2	<0.001
At or above poverty	89.2	85.3		87.2	89.3	84.6	88.8	
Location (%)-Urban	50.4	49.1	0.223	56.9	47.1	36.1	67.9	<0.001
Rural	49.6	50.9		43.1	52.9	63.9	32.1	
Census region (%)-Northeast	69.2	82.8	<0.001	74.0	76.0	80.5	72.3	<0.001
Midwest	30.8	17.2		26.0	24.0	19.5	27.7	
Food energy (kcal/day)†	2489 (1398)	1668 (909)	<0.001	1958 (1305)	2031 (1342)	2028 (1258)	1986 (1287)	0.014
Dietary sodium intake (mg/day)†	3836 (2690)	2644 (1797)	<0.001	3044 (2439)	3186 (2291)	3223 (2357)	3022 (2257)	0.046
Urinary iodine concentration (µg/L)†	148.3 (144.7)	119.7 (134.7)	<0.001	124.3 (141.5)	124.7 (127.0)	142.0 (149.6)	137.9 (151.7)	<0.001
Urinary creatinine concentration (mmol/L)†	12.6 (9.8)	8.6 (9.7)	<0.001	10.8 (9.8)	10.7 (10.3)	10.7 (10.1)	10.1 (10.8)	<0.001

Note: Results are mean and standard deviation unless specified. Sampling weights were applied. The examination weight was applied to the MEC variables and the home interview weight was applied to the rest variables for mean, median and percentage estimation.

†: Median (Interquartile range).

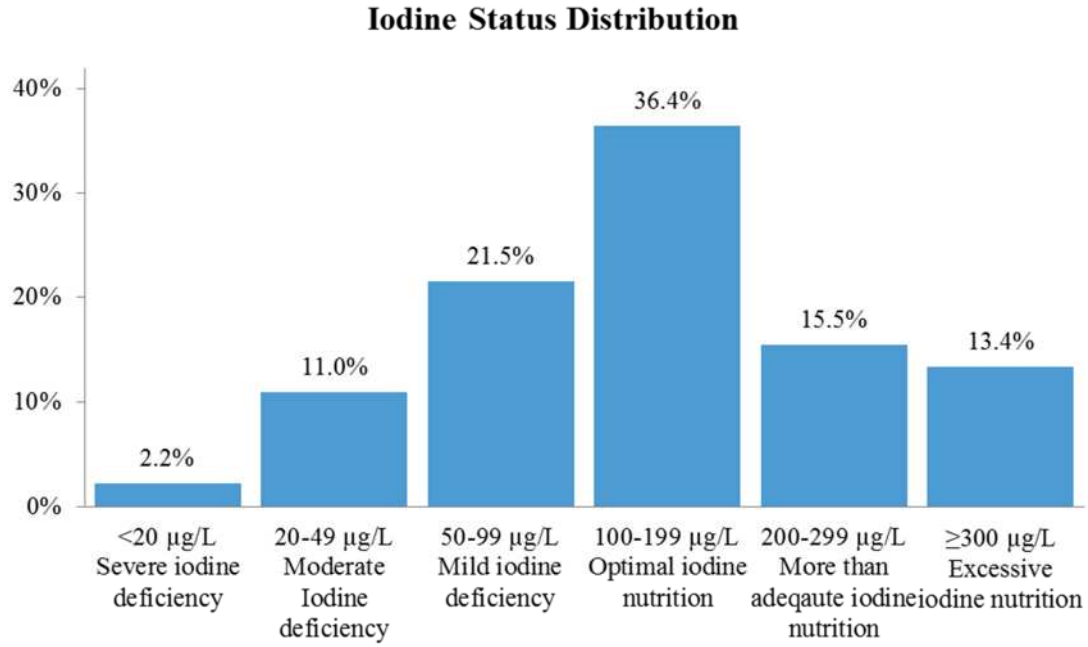
‡: Tests were not weighed for sampling weights.

The characteristics were compared by sex and census region. As indicated previously, no sampling weight was applied for calculating the p values. The results were shown in Table 5.3.4. Almost all variables differed significantly between men and women and across regions. Most p values were less than 0.001. Dietary sodium intake and UIC differed significantly across the regions ($p<0.001$ and $p=0.046$, respectively).

Iodine status and distribution

The median UIC of the population was 133.3 (IQR: 142.6) µg/L (see Table 5.3.3), indicating the population was of optimal iodine status. Men had significantly higher urinary iodine concentration than women (148.3 µg/L vs 119.7 µg/L). People living in the South and West regions had higher UIC levels, but none of the regions showed risk of iodine deficiency.

Figure 5.3.2 *Distribution of iodine status in the US adult population. Weighted by the examination sampling weight*



As shown in the Figure 5.3.2, 36.4% of the participants had optimal iodine intake, whilst 34.7% of the participants had some degree of iodine deficiency. However, the proportion of severe iodine deficiency was very low (2.2%). Some participants were at risk of iodine-induced hyperthyroidism (IIH) due to excessive iodine intake. In particular, a few participants had extremely high urinary iodine concentration levels. The highest iodine concentration was 110,000 µg/L. Using the 916.7 µg/L cut-off value, 267 participants had unacceptable levels of iodine intakes.

DIC results

The DIC values of two pairs of models are shown in Table 5.3.5. Model 3 produced the lowest DIC for both UIC and dietary sodium intake. The inclusion of nonlinearity effect increased the complexity of the model (shown as the increased pD, effective number of parameters). Hence only the results of Model 3 are presented below and the discussion is mainly based on these results.

Table 5.3.5 *DIC results calculated from the models of urinary iodine concentration and dietary sodium intake*

	Urinary iodine concentration			Dietary sodium intake		
	Deviance	**pD**	**DIC**	**Deviance**	**pD**	**DIC**
Model 1	16228.7	7.3	16243.2	17073.5	5.8	17085.0
Model 2	16648.7	10.0	16668.6	17041.4	9.8	17061.0
Model 3	14482.9	21.9	14526.7	15274.8	20.9	15316.6
Model 4	14459.7	46.1	14551.8	15259.3	40.2	15339.7

Urinary iodine concentration

The estimated fixed effects of the continuous and categorical risk factors are shown in Table 5.3.6. The effects are shown as means with standard deviation and 90% credible intervals. The significance of the effects was determined by the position of

the credible intervals. If both the upper and lower limits were either positive or negative, the effect was considered significant.

Table 5.3.6 *Estimated fixed effects of urinary iodine concentration (Model 3)*

	Mean effect	Standard Deviation	5% quantile	95% quantile
Age (year)	0.0052	0.0003	0.0047	0.0058
Sex-Female	0			
Male	-0.0046	0.0061	-0.0149	0.0050
Body Mass Index (kg/m^2)	-0.0005	0.0010	-0.0021	0.0010
Race-ethnicity-Non-Hispanic White	0			
Non-Hispanic Black	-0.1938	0.0117	-0.2136	-0.1750
Mexican Americans	0.1653	0.0126	0.1441	0.1857
Other	-0.0070	0.0214	-0.0412	0.0282
Education (%)-Above high school	0			
High school	-0.0180	0.0080	-0.0308	-0.0044
Below high school	0.0557	0.0085	0.0418	0.0700
Marital status-Living together	0			
Living alone	0.0112	0.0057	0.0018	0.0205
Smoking habit-Non-smoker	0			
Former	-0.0015	0.0091	-0.0162	0.0136
Current	-0.0336	0.0092	-0.0487	-0.0191
Alcohol drinking-Non-drinker	0			
Drinker	-0.0097	0.0071	-0.0212	0.0021
Dietary sodium intake (mg/day)	2.18×10^{-5}	2.83×10^{-6}	1.70×10^{-5}	2.67×10^{-5}
Urinary creatinine concentration (mmol/L)	0.0591	0.0008	0.0577	0.0603
Poverty income ratio-At or above poverty	0			
Below poverty	0.0289	0.0072	0.0169	0.0407
Location-Urban	0			
Rural	0.0158	0.0061	0.0060	0.0261
Region-Northeast	0			
Midwest	-0.0865	0.0108	-0.1045	-0.0681
West	0.0324	0.0114	0.0141	0.0517
South	0.1273	0.0090	0.1123	0.1419

Older people were associated with higher UIC. Significantly higher UIC was also found in participants with the following characteristics: Mexican Americans, having lower educational attainment (below high school), living alone in rural areas, and poorer family economic status. On the contrary, black participants who were current

smokers/drinkers and attained only high school qualification had significantly lower levels of iodine concentration. Overall, participants of lower socioeconomic status appeared to have higher iodine concentration.

Although the model was not able to capture the spatial correlation, the regional variation was still significant. People living in the South and the West regions were more likely to have higher UIC, while those in the Midwest region were more likely to have lower UIC, compared to those in the Northeast region.

Association between urinary iodine concentration and dietary sodium intake

Higher dietary sodium intake was significantly associated with higher UIC. However, the effect of dietary sodium was comparatively small (2.18×10^{-5}) in the model.

Dietary sodium intake

The estimated fixed effects of the included risk factors on the exponentially transformed dietary sodium intake are shown in Table 5.3.7.

Older people appeared to eat less sodium, probably because they tend to consume less food. In fact, higher sodium intake was significantly associated with higher BMI and more energy intake. This was true particularly for those overweight or obese people who tend to eat more energy-dense foods.

Significantly higher sodium intake was also found in the male participants who were living in rural areas, had quit smoking, had only high school qualification and were in “Other” race-ethnic group. Compared to white Americans, significantly lower dietary sodium intake was found in blacks and Mexican Americans who were current

smokers/drinkers with below high school qualification, living alone and having poorer family economic status.

The geographical effect was still significant for dietary sodium intake. The effect varied across the census regions. The levels of sodium intake were significantly higher in the South region, compared to the Northeast region.

Table 5.3.7 *Estimated fixed effects of dietary sodium intake (Model 3)*

	Mean effect	Standard Deviation	5% quantile	95% quantile
Age (year)	-0.0014	0.0006	-0.0024	-0.0005
Sex-Female	0			
Male	0.0814	0.0221	0.0467	0.1186
Body Mass Index (kg/m^2)	0.0036	0.0018	0.0008	0.0064
Race-ethnicity-Non-Hispanic White	0			
Non-Hispanic Black	-0.0746	0.0283	-0.1212	-0.0274
Mexican Americans	-0.1838	0.0304	-0.2324	-0.1335
Other	0.2210	0.0573	0.1253	0.3130
Education (%)-Above high school	0			
High school	-0.1121	0.0271	-0.1576	-0.0677
Below high school	-0.0140	0.0274	-0.0580	0.0312
Marital status-Living together	0			
Living alone	-0.0485	0.0214	-0.0827	-0.0141
Smoking habit-Non-smoker	0			
Former	0.0935	0.0262	0.0525	0.1360
Current	-0.0371	0.0251	-0.0766	0.0071
Alcohol drinking-Non-drinker	0			
Drinker	-0.2676	0.0257	-0.3089	-0.2247
Dietary energy intake (kcal/day)	0.0014	1.08×10^{-5}	0.0014	0.0014
Poverty income ratio-At or above poverty	0			
Below poverty	-0.0966	0.0255	-0.1378	-0.0557
Location-Urban	0			
Rural	0.0444	0.0225	0.0086	0.0822
Region-Northeast	0			
Midwest	0.0253	0.0362	-0.0340	0.0855
West	0.0135	0.0367	-0.0473	0.0734
South	0.1030	0.0334	0.0503	0.1600

5.3.4 Discussion

Key findings

This analysis sought to assess the association between salt intake and iodine intake and to estimate both intakes and possible risk factors in the United States using the third National Health and Nutrition Examination Survey. An important finding is the weak association between dietary sodium intake and urinary iodine concentration. In addition, the US adult population consumed 3,133 mg of sodium per day during the survey time (1988-1994), which was approximately a consumption of 7.8 g salt (sodium chloride) per day. The UIC of the population was 133.3 µg/L, indicating an optimal iodine status of the population. The risk of severe iodine deficiency was also small in the population. Less than 3% of people had a UIC of less than 20 µg/L.

Discussion of findings

Salt intake in the United States

In the NHANES III dietary assessment of sodium intake accounts only for sodium present in food, without the assessment of discretionary sources. Therefore, the estimation was lower than the real salt consumption. In the US, salt hidden in processed and restaurant foods contributes to approximately 75% of total salt intake (31;316). Discretionary salt contributes about 10-12% and the salt naturally presented in foods makes up the rest. Therefore, the total salt intake in the population can be estimated by adding a 25%. So the average consumption would be about 10.4 g/day (or 4,177 mg sodium per day). This estimate would be slightly higher than the salt intake reported in the INTERSALT study (30;126) but would be

comparable to that reported in the INTERMAP study (317). Both studies used 24-hour urine collection to measure salt intake.

The causal effect of high salt intake on raised BP, or hypertension, is well established (2;6;39;126). An estimated 30% hypertension prevalence is attributable to high salt intake in the United States (308). In the US, one in three adults aged 18 and over is hypertensive (318) which translates into an estimated 76 million hypertensives in 2012 (319). According to CDC estimates, age-adjusted hypertension prevalence remained unchanged in the last 10 years (320). This may be largely attributable to the constant increase in the awareness, treatment and control of hypertension in the public (321). However, mortality caused by high BP still increased 20.2% in the same period (319).

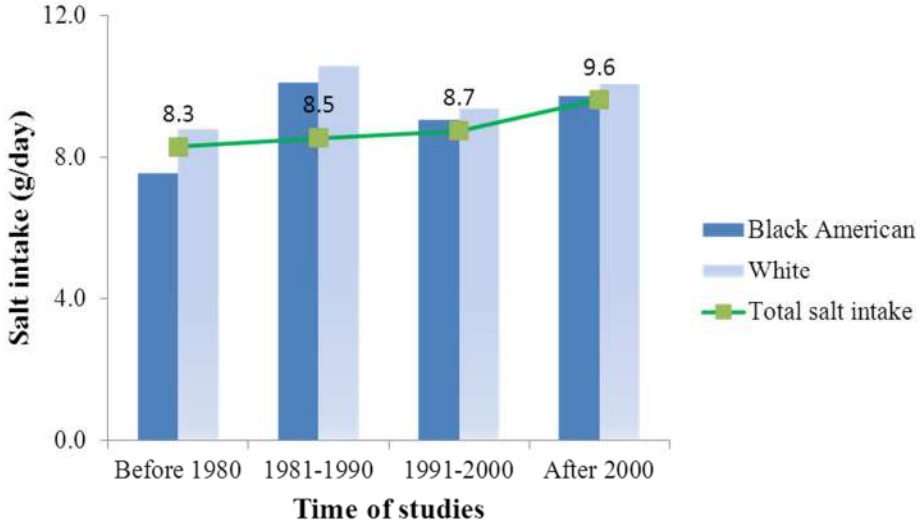
High salt intake is also associated with higher risk of CVD (14;322;323). An increased salt intake by 5 g/day is associated with a significant 17% increase in CVD risk (14).

Population-wide salt reduction is the most cost-effective approach to lower BP and the second most cost-effective to prevent CVD (15;74;272). The cost of hypertension is huge. It is estimated that the total cost of high BP is $50.6 billion (319). Bibbins-Domingo and her colleagues (75) estimated that a reduction of 3 g per day in salt intake could save 194,000 to 392,000 quality-adjusted life years (QALY) and $10 billion to $24 billion in healthcare costs.

A population-wide dietary salt reduction is recommended by the WHO and by many national and regional health organisations as the primary strategy to reduce hypertension and to prevent, treat and manage cardiovascular disease. In the US, salt

reduction was firstly proposed in 1969 (324). Nonetheless, the average salt intake has remained unchanged in recent decades. Bernstein and Willett (325) reviewed 38 studies that reported 24-hour urinary sodium excretion in the US population between 1957 and 2003. It is clear that salt intake before 2000 varied by a very small range (8.3-8.7 g/day) and surprisingly increased after 2000 (see Figure 5.3.3). Although the changes are not significant, the trend indicates that the surveillance efforts on salt reduction are far from sufficient. In addition, the salt intake in Black Americans is always lower than that in Whites, which is consistent with the findings in both preliminary and modelling results.

Figure 5.3.3 Change of salt intake during 1953 and 2003 in the United States



Note: Modified from Bernstein and Willett (325).

Therefore, the American Medical Association (AMA) recently urged the FDA and called on the public to reduce salt intake by 50% (16). In 2008, New York City also initiated a programme, aiming at a 20% reduction of population salt intake by reducing sodium content in foods by 25% in 5 years (1).

Iodine intake in the United States

Salt iodisation in the US can be dated back to the early 20th century when David Cowie started his experiment in Michigan about treating goitre patients with iodine supplementation (311). The US FDA later began a salt iodisation programme following David Cowie's success (310). The effect of the programme was evident. Before the implementation of salt iodisation, high prevalence of goitre was present in the Northwestern, Great Lakes, and Appalachian regions (the so called "goiter belt"). The prevalence in children varied from 26% to 70% (326) in this belt. After the use of iodised salt, the country experienced significant improvement in iodine status and the "goiter belt" disappeared (327).

Despite the early start, only table and cooking salt is iodised on a voluntary basis in the US. Potassium iodide (KI) is added to salt at a recommended level of 60-100 ppm (equivalent to 46-77 mg iodine per 1 kg salt). However, potassium iodide is less stable and more soluble than potassium iodate (KIO_3). The loss of iodine during production, transportation, storage and cooking may be more than expected. In a study by Dasgupta and colleagues (310), 88 table salt samples were collected from different locations in the US, and the content of iodine was measured at different environmental conditions (different humidity, heat and light). The iodine content was in the range of 12.7 to 129 ppm, with a median of 44.1 ppm. Only 41% of the samples contained iodine within the FDA recommended range, while 52% was below the range. The study also revealed that the magnitude of iodine loss increased rapidly as the humidity increased in a 40-day observation. High heat can cause up to 25% loss of iodine depending on the salt brands. The study also found that not all household iodised salt was consumed by household members. For instance, salt used

in boiling water for cooking pasta is wasted after use, while the salt in home-baked cakes is shared by people out of the household. In addition, only half of the salt products on the market are iodised (328). Hence, the iodine obtained from discretionary salt may be even less than expected.

In fact, iodine supplementation of the US population relies on many other dietary and nutritional sources. In the US, as well as other high-income countries, a diverse selection of foods is available to the public. Some foods are rich in iodine, including seafood, milk and dairy products, and bread. For example, the iodine content in one gram of kelp can reach 8,165 μg (329). The iodine content ranges from 352-464 μg per litre in the milk sold in the US, while bread contains iodine from 10.1 μg to more than 300 μg per slice (112).

With the long-term commitment to salt iodisation and diverse iodine rich food supply, the US is believed to have eliminated iodine deficiency. This analysis showed that the iodine status in the adult US population was optimal during 1988-1994. However, Hollowell *et al.* described a declining iodine intake in the population after comparing the urinary iodine concentration in the NHANES I and NHANES III (314). Nonetheless, the declining trend ceased as the data in the NHANES 2001-02 and NHANES 2005-08 showed higher median UIC in the population (330;331).

Although iodine deficiency would raise more attention, the US government and health authorities should be alerted to those with extremely high iodine concentrations. Albeit a small number in the NHANES III data, people may suffer from a variety of severe health issues induced by extreme iodine intake. The high iodine concentration was likely to be caused by the consumption of iodine-rich foods,

nutrient supplements or medications. In particular, Americans have a high preference for supplementing micronutrients by consuming nutrient supplements. It is reported that more than 50% of the general population are consuming vitamin and micronutrient supplements (332). As this survey did not measure the use of supplements, it was not possible to estimate and validate the impact of nutrient supplements that contains iodine.

Unfortunately, the 24-hour dietary recall did not calculate the amount of iodine in the self-reported foods. Hence, the contribution of the iodine-rich foods is still inconclusive in this case.

The compatibility of salt reduction and salt iodisation programmes

A significant association between urinary iodine concentration and dietary sodium intake was obtained in the analysis. However, the US does not require the use of iodised salt in food manufacturing. Hence, no contribution of iodine from the salt used in food industry is expected. The association was probably caused by the foods that contain both iodine and non-iodised salt, e.g. cheese and meat. High consumption of these foods led to higher intake of both iodine and salt, while reducing salt during food manufacturing would not affect iodine availability.

Few studies investigated the impact of salt reduction on iodine status in high-income countries. Tayie and Jourdan (28) estimated the relationship between salt restriction and iodine status using the data of NHANES 2001-2004. However, they dichotomised the sodium intake by a cut-off value of 2,400 mg/day and grouped the urinary iodine concentration into 3 levels. Although they concluded that salt restriction is associated with iodine deficiency in women, the analytical method lost

much useful information of sodium intake and urinary iodine concentration and was not able to produce a numerical estimate of the association. Verkaik-Kloosterman *et al.* (29) used a simulation model to assess the impact of salt reduction on iodine deficiency in the Netherlands. They simulated 3 levels of salt reduction in processed foods: 12%, 25% and 50%. All reductions would reduce some iodine intake but would not affect current iodine status in the population. Only when there is a 50% salt reduction in processed foods, at the table and in cooking, would the general population be affected, with about 10% of the population possibly being exposed to iodine deficiency. However, cooking salt are iodised compulsorily and iodised baker salt is used on a voluntary basis in the Netherlands. Hence, the contribution of iodised salt to the population iodine intake would be much larger than that in the US. This also indicated that the extended use of iodised salt in the food industry might offset any predicted fall in the US population iodine status.

The salt and iodine intake measurements in the NHANES III were subjected to inaccuracy and might lead to misleading calculations. Therefore, the assessed association should be interpreted with caution and further analysis using accurate sodium and iodine intake measurements is needed.

The effects of risk factors

Some sub-populations had lower sodium intake but higher iodine concentration. They included Mexican Americans, those with lower educational attainment, poorer family economic status, and those living alone. A possible explanation is that these sub-populations, particularly those in low SES, might consume more iodine-rich foods. The higher urinary iodine concentration could also be the result of a greater

use of discretionary salt not detected by the dietary assessment of salt intake used in the NHANES III. Recent data in the UK shows a SES gradient in salt intake (333) but not in iodine intake (see Section 5.4 in this Chapter). In the US, however, low SES has been linked with poor diet quality (334;335). People with low SES have a higher preference for buying fast foods (336) and other processed foods (337). Higher awareness of salt reduction is also found in higher SES (337).

Rural participants had higher UIC and sodium intake. The rural-urban difference suggested a consumption of high sodium-density and iodine-rich foods in rural participants. This may be partly explained by the cultural diet in rural areas that consists of energy dense foods. However these foods are usually less nutritional. Hence, this can hardly explain the association with high UIC. Moreover, the definition of rural/urban areas was based on the population density (metropolitan statistics area), which is different from traditional governmental definition. This led to a different rural/urban population, which might cause the significant rural effect in this analysis.

In addition, Black Americans had significantly higher negative association with both UIC and sodium intake. People of African descent usually have a higher preference in using table and cooking salt. However, discretionary salt is not likely to contribute sufficient iodine to the blacks. It is possible that Black Americans opted in for a comparatively low iodine diet.

It should be noted that these contradictory results might be due to the data collection methods. The urinary iodine concentration was measured from spot urine samples. This method usually produces less reliable and less accurate estimates compared

with 24-hour urine collection. Results are also often affected by the food consumed during the day preceding the urine collection. Some measurements may be extremely low or high. For the dietary sodium intake, the estimates were calculated from the 24-hour dietary recall. The food consumption was self-reported. Although the data collection was computer aided, the data quality was largely affected by memory and misreporting (338). For example, people may exaggerate the consumption of healthy foods, such as fruits and vegetables, and under-report the consumption of unhealthy foods, such as high energy and high fat foods. As there is no validation data to prove the discovered association in the present analysis, this finding remains inconclusive.

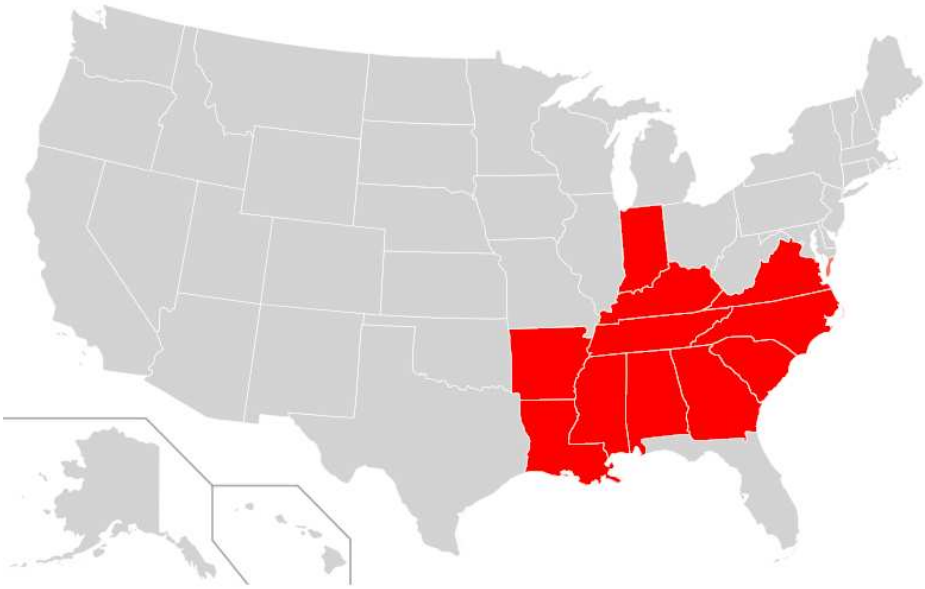
Geographical variation

Although this analysis was limited to the census region level, the results still indicate significant geographical variations in iodine concentration and sodium intake. After adjustment for the selected covariates, the South and the West regions were associated with a higher level of iodine concentration, and the South region alone was associated with a higher dietary sodium intake. These findings coincide with the well-known “goiter belt” and “stroke belt”. Before the implementation of salt iodisation, high prevalence of goitre was presented in the Northwestern, Great Lakes, and Appalachian regions, and the water and soil in these regions were both deficient in iodine. The iodine status was improved after the implementation of salt iodisation. The present finding indicates that the traditional geographical heterogeneity of the iodine intake still exists. It might still be caused by the soil and water being deficient in iodine. However, the iodine status in the West region was better than that in the Midwest and Northeast regions. Therefore, more emphasis on the iodine

supplementation should be placed in these two regions, particularly in those disadvantaged and vulnerable subpopulations.

The “stroke belt” (see Figure 5.3.4) was discovered in the 1980s. The National Heart, Lung, and Blood Institute (NHLBI) compared the age-adjusted stroke mortality at state level and discovered higher than average stroke mortality in 11 adjacent states. These states are mostly in the South region. Various reasons are suggested to explain the high mortality, such as genes, lifestyle, dietary habit and CVD risk factors (339). The coincidence between the high sodium intake and high stroke mortality in the South indicated that high salt intake, particularly the salt hidden in processed foods, could be a critical risk factor of the high stroke mortality in the region. Therefore, emphasis on reducing salt intake can help the public lower the risk of stroke and reduce the large healthcare cost.

Figure 5.3.4 *The “stroke belt” in the United States*



Strengths and limitations

My analysis used a large national representative data set to describe the iodine status and salt intake in the US population. The availability of both iodine and sodium information enabled me to assess the association between salt intake (in the form of dietary sodium intake) and iodine status (in the form of urinary iodine concentration). However, the analysis and measurements had their limitations. Firstly, the SAS survey procedures are not able to produce weighted p values for group comparisons. Therefore, the unweighted p values in Table 5.3.4 may be biased. The spot urinary iodine concentration is also of high variability. It is subject to a few limiting factors, including collection time, temperature, urine volume, and food consumption before the collection. Although some efforts were made to extrapolate mathematically the spot urinary electrolyte estimates to the 24-hour scale (134;139;140), the reliability and accuracy are still uncertain compared to the measurements based on 24-hour urine collections. Moreover, dietary content varies over time. The 24-hour dietary recall is not able to describe a representative food consumption pattern. In addition, the 24-hour dietary recall only recorded the sodium in dietary foods. The consumption of discretionary salt was not measured. As the US policy only requires the iodisation of discretionary salt on a voluntary basis, the association between sodium and iodine might have been stronger if the sodium intake at the table and cooking had been accounted for. However, the increase in the strength of the association cannot be estimated in this analysis, particularly when the use of iodised salt is largely affected by customer preference and market coverage (for detailed discussion, see Section 6.3 in Chapter 6). Due to the limited availability of geographical information, this analysis was only carried out at regional level. No

spatial correlation was taken into account in the models. Hence, the precisions of the estimated effects may be over-estimated. Furthermore, the classification of the SES variables may not be precise enough to represent the entire population. Therefore, the confounding effect of SES was probably not fully controlled for. Another limitation lies in the study population. This analysis was carried out in the adult population. Although the youth data are available, they were not used as other analyses in this thesis would use adult population only. Hence the study population may limit the generalisation of the findings to the whole population. Additional studies are recommended in children and adolescents since food consumption and other risk factors may differ in young people.

The extent of the present analysis is limited by the lack of detailed geographical information. The accuracy of geographical effect could be improved if there is detailed geographical information available. The latent correlated and uncorrelated spatial pattern can be captured and the map can be used for virtual illustration and monitoring.

Implications

In most high-income countries, salt iodisation and salt reduction programmes are carried out simultaneously. These countries are characterised by a high consumption of processed and restaurant foods and some have similar SES structure to the US. Hence the association between dietary sodium intake and UIC in the US can be generalised to these countries. In addition, high availability of iodine-rich foods is attributable to the majority of individuals' iodine intake in many high-income countries. Thus iodised salt becomes a complementary tool for iodine

supplementation. Therefore the salt reduction programme may be also compatible with salt iodisation programme in these countries.

As the change of dietary sodium intake has little impact on UIC, increasing iodine content in salt seems not to be the best option for improving iodine intake in high-income countries. A better solution would be to increase the consumption of iodine-rich foods and to increase the iodine content in the daily diet, e.g. flour and bread.

It should be noted that the re-emergence of iodine deficiency is reported in several high-income countries (244;340;341). The replacement of iodophor in milk and dairy products (249), reduced consumption of iodine-rich foods (248) and consumption of goitrogenic foods in animals (250) are largely to blame for the declining iodine intake. Although these countries do not rely on salt iodisation for iodine supplementation, other countries that have voluntary or mandatory salt iodisation programmes should be alerted about the trend. In the coordination of salt reduction and salt iodisation programmes in high-income countries, the monitoring procedure would be ideally extended to the iodine content of the iodine-rich foods and their consumption, as these foods contribute more iodine than the iodised salt.

However, iodine intake should also be kept within a healthy range. The extremely high iodine concentrations discovered in the NHANES III indicates that the knowledge of iodine intake in the general population might be insufficient. Therefore, the need for improvement in public awareness and knowledge of iodine supplementation and salt reduction simultaneously is apparent and also important in the joint coordination of both programmes.

Again, for all countries that adopt both health programmes, the collection of reliable data on both iodine and salt intakes is critical in estimating the salt and iodine association in their own country context. Without the available iodine and salt measurements, it is difficult to quantify the association and to make policy adjustments. Additionally, the use of 24-hour urine collection is recommended to obtain the most reliable and accurate measurements. The use of 24-hour urine collection can also make the comparison consistent and comparable either along with time or by country, which will improve the monitoring quality of the programmes. Given the possible methodology bias in this analysis, further studies on the impact of salt reduction on salt iodisation are needed to validate the present findings.

Last but not least, the efforts with salt reduction and salt iodisation programmes have to be consistent to keep the quality of both programmes. In particular, sufficient and coherent political support should be guaranteed. However, the absence of a specified salt reduction target (342) in a recent UN High-Level Meeting on non-communicable diseases (60) indicates that political consensus on salt reduction has not yet been reached. Therefore, the coordination between governments, global health organisations, health authorities, media, health researchers and industry should be more effective and partnership between the government and industry needs improvement to avoid misunderstanding of the policies and mistrust between both sides.

5.4 Salt Intake and Iodine Status in Britain

5.4.1 Introduction

Raised BP is the major risk factor of cardiovascular disease (CVD) in the United Kingdom (UK). Nearly 20% of the UK population is hypertensive (56). About half of coronary heart disease (CHD) deaths are attributable to high BP (343). It is estimated that every increase of 2 mmHg in systolic blood pressure results in 7% more CHD deaths and 10% more stroke deaths (344). The burden of CVD is considerable. It cost the UK healthcare £14.3 billion in 2006 for treating CVD and the consequent productivity loss, and informal care cost due to CVD is worth more than £16 billion (345).

Association between high salt intake and raised BP has been demonstrated consistently in many studies (2;39-42). It is estimated that if the general population reduced salt intake by 3 g/day, the mean systolic and diastolic blood pressure (SBP and DBP) in the population would fall by 2.5/1.4 mmHg (55). Accordingly stroke mortality would reduce by 12 to 14% and CHD mortality by 9-10% (55). Hence, in the UK, about 6,500-8,000 stroke deaths and 7,500-12,000 CHD deaths would be averted annually. The WHO recommends less than 5 g/day salt intake in the general population. In the UK, the Food Standards Agency (FSA) has set a target of reducing daily salt intake to 6 g/day, with various targets for children in different age groups. The National Institute for Health and Clinical Excellence (NICE) also suggests a target of 3 g salt per day by 2025 (56).

In contrast, iodine deficiency has not been considered as a significant public health threat for decades in the UK. However, recent data arguably suggested the re-emergence of iodine deficiency in the UK population:. Vanderpump *et al.* (244) reported a median urinary iodine concentration of 80.1 μg/L in school girls aged 14-15 years based on spot urine samples. Historically, the elimination of iodine deficiency was coincidental (346) as there was no programme specifically developed for iodine supplementation in the country. Dietary salt is not required to be iodised in the UK. The major dietary source of iodine is milk and dairy foods. Iodine was initially added in feeding stuffs in the 1920s to increase the level of animal reproduction. Consequently it is presented in milk and dairy products and consumed by individuals. In 1946, the UK parliament passed the School Milk Act which provided children under 18 with free milk (1/3 pint). With the increasing consumption of milk, iodine intake in children and adults progressively increases. Measured in the 1980s, milk alone has already provides 150 μg/day iodine (347). A recent retail survey held by the FSA reported mean iodine concentration ranges from 0.30 to 3.10 mg/kg in cow, goat and sheep's milk, and 0.60 to 0.99 mg/kg in cheese, egg and yoghurt (348).

Globally, it is critical to coordinate and integrate the salt reduction and the USI programmes to avoid conflict and to achieve success for both WHO policies. For countries implementing both salt iodisation and salt reduction programmes, the UK provides a good example of alternative strategies to adapt the policies and to coordinate the health programmes. However, although the positive effect of milk and dairy foods on iodine status has been acknowledged, there is a large gap in knowledge for this effect and the association between salt intake and iodine status in

a country that does not rely on salt iodisation for iodine supplementation. Moreover, it is also important to know if there are any geographical and socioeconomic inequalities of iodine and salt intakes in the UK and what determinants are likely to affect the distribution of iodine and salt consumption.

Therefore, the objectives of this analysis are

1) to estimate salt intake and iodine status in white British adults;

2) to assess the association of salt intake and iodine intake in dietary foods in the adult population with high percentage of processed foods consumption but without established salt iodisation programme;

3) to investigate the impact of modifications of salt intake on iodine status and determine the effect of milk and dairy consumption on iodine intake;

4) to investigate the potential geographical variation and determinants in iodine intake and salt intake; and

5) to provide suggestions to policy-makers, particularly on the use of alternative iodine fortification vehicles to improve iodine supplementation and offset potential impact of salt reduction on salt iodisation programmes.

5.4.2 Data and Methods

Country profile

Britain, or Great Britain, is the largest of island of the United Kingdom, situated at North-West Europe. It is a union of England, Scotland and Wales. The island is

geographically divided by the Tees-Exe line. Lowlands dominate the east and south Britain and highlands dominate the north and west Britain.

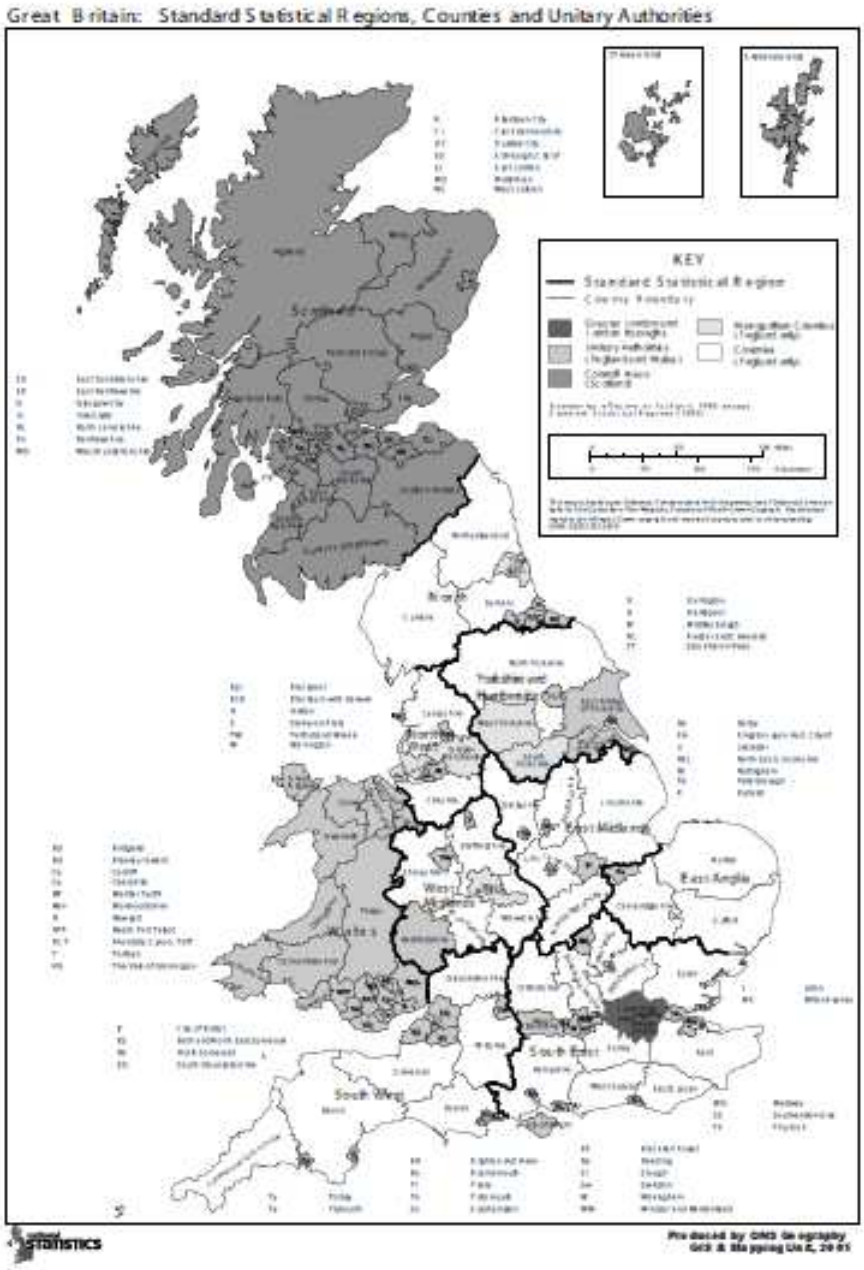
The population in Britain was estimated to be around 62 million in 2010. The majority ethnic group is White British, followed by other White, Indian, Pakistani, Black Caribbean and African, and other minority groups.

The United Kingdom has the sixth largest economy in the world and the third largest in Europe. The health expenditure per capita in the United Kingdom is US$3,503 (312), ranking the 20th in the world.

Data

This analysis was conducted using the 2000-01 National Diet and Nutrition Survey (NDNS). The NDNS contains a series of cross-sectional surveys of different population age-groups. The 2000-01 survey is a nationally representative survey covering the adults aged 19 to 64 years living in private households in Britain. It was carried out by 12 Government Office Regions (GORs). However, to maintain consistency with previous surveys, the regional information in this 2000-01 survey has been recoded according to the classification of Standard Statistical Regions (SSRs). A map with 11 regions is shown in Figure 5.4.1: Scotland, North, Yorkshire and Humberside, North West, East Midlands, West Midlands, Wales, East Anglia, London, South East and South West. Field work was undertaken between July 2000 and June 2001. Dietary and nutritional information of the British population was collected to provide evidence for government to improve people's nutritional status and health.

Figure 5.4.1 *Standard Statistical Regions of Great Britain (Adapted from the website of the Food Standards Agency)*



The survey was composed of the following components: 1) an interview covering socio-demographic and lifestyle information; 2) a 7-day record of bowel movements; 3) a 7-day record of physical activity; 4) a weighed 7-day record of dietary consumption; 5) blood test and 24-hour urine sample; 6) physical and blood pressure measurements; and 7) a self-count of the number of teeth and amalgam fillings.

Five thousand six hundred and seventy three households were selected randomly and 3,704 (65.3%) were eligible for the survey interview. After excluding the refusals and non-contacts, a total of 2,251 participants from 11 regions completed an interview. Of those who responded, 76.6% (n=1,724) completed a 7-day dietary record and 64.8% (n=1,459) provided completed 24-hour urine collection. Participants came from different ethnic groups, such as White, Caribbean, African, Indian, Bangladeshi, and Chinese, etc. White participants were the major group (93.6%, n=2,108). Since estimation based on few participants may not be representative for minority ethnic groups, especially when compared by region, only White participants were included in this analysis.

Height was measured to the nearest 0.1 cm using the Leicester Height Measure and a Frankfort Plane card. Weight was measured to the nearest 0.1 kg using digital personal weighing scales. Body mass index (BMI) was calculated using weight over height squared (kg/m^2).

For the participants who consented to the BP measurement procedure, three sitting BP readings were taken at one minute intervals using the Dinamap 8100 oscillometric monitor, and were later scrutinised by the survey doctor or a general practitioner (GP). Mean BP was calculated on the basis of the second and third readings.

Daily iodine and sodium intakes were obtained from the 7-day dietary record, calculated from all foods and supplements. Participants were required to keep a diary of all food they consumed in the 7-day period. They were encouraged to record and weigh all home-made and take-away food (including supplements, water and

medicines), or give description of food consumed outside of home and food that cannot be weighed as far as possible. The use of table and cooking salt was not recorded. Only questions regarding the frequency of the use of discretionary salt were asked at the interview. Dietary sodium intake was calculated in milligram per day (mg/day). Daily iodine intake was also obtained from the 7-day dietary record, calculated in microgram per day (μg/day) from all foods and supplements. Additionally, energy intake, milk and dairy consumption and alcohol consumption were also recorded and calculated. Daily energy intake was calculated in kilocalorie per day (kcal/day) on the basis of all dietary foods and supplements consumed over the 7-day period. Milk and dairy products included all cow, sheep and goat milk, cheese, and yogurt. It was calculated in grams per day (g/day). Alcohol consumption was calculated based on the total amount of alcohol consumption from drinks and foods. The units were also recorded in g/day.

Educational attainment was recorded in 7 groups: degree or equivalent; higher education below degree level; GCE A level or equivalent; GCSE grades A-C or equivalent; GCSE grades D-E or equivalent; other qualifications; no qualifications. In this analysis, the educational attainment was simplified and re-categorised into 4 groups: degree or equivalent; below degree level, GCE A level or equivalent; GCSE, other qualification or equivalent; no qualification.

There were 7 types of marital status in the NDNS questionnaire: married; cohabiting; single; widowed; divorced; separated; same sex couple. The marital status was then simplified in this analysis according to whether the participant was living alone (including single, widowed, divorced, and separated) or living with someone else (married, cohabiting and same sex couple). In the following analysis, “living

together" represents the status of cohabiting with someone else, and "living alone" represents the status of living alone.

Social class was originally recorded according to the social class of the household reference person (HRP). HRP was used because of "the availability of the large number of cases and less dependent on age and sex differences in participants". The standard 6 categories listed in the NDNS User Guide were recoded into 3 groups in the survey as follows: non-manual (including social classes I, II and III skilled non-manual); manual (including social class III manual, IV and V); unclassified (those not assigned with a social class due to various reasons). However, as there were only 3 persons in the unclassified category, social class was further simplified by removing this category in the present analysis. Hence, non-manual can be regarded as high social class and manual can be regarded as low social class.

Smoking habit was recorded in 3 groups: non-smoker; former smoker; current smoker Based on two questions: "Have you ever smoked a cigarette, a cigar or a pipe" and "Do you smoke cigarettes at all nowadays".

Twenty-four-hour urine collection was tested and 24-hour urinary sodium and creatinine excretion level was used in this analysis. The marker substance para-aminobenzoic acid (PABA) was used to test the completeness of the collection. 1,495 participants provided a 24-hour urine collection and 1,458 (91.1%) collections were finally included.

The geographical boundaries of 11 British regions were obtained in order to estimate the spatial effect. According to the SSRs classification, the UK digitalized boundary data, in shapefile format, and map information were downloaded from the

UKBORDERS[9]. Then the boundary files were converted to the specific format that can be recognised in the Bayesian software.

Statistical analysis

The means and standard errors were reported for the continuous demographic variables. For the urinary and dietary variables, medians and interquartile ranges were presented. For the categorical variables, percentages were presented. One way ANOAVA was used to compare the means of demographic variables by sex and region with adjustment for age and sex when appropriate. The Mann-Whitney test was used to compare the medians of dietary and urinary variables between men and women. The Kruskal-Wallis test was used to test the difference in dietary and urinary variables across the regions. The non-parametric test ws used as the variables did not appear to be approximately normal distributed. Percentages were compared using Pearson's chi-squared test. No sampling weight was used because only White participants were included in the analysis. Bayesian geo-additive models were used to investigate the association between dietary iodine and sodium intakes and to assess the effects of other risk factors on dietary iodine intake, dietary sodium intake and 24-hour urinary sodium excretion.

Four Bayesian geo-additive models were constructed and fitted for dietary iodine intake, dietary sodium intake and 24-hour urinary sodium excretion to assess the association between iodine intake and sodium intake, as well as the linear and nonlinear effects of other risk factors. The dietary iodine intake, dietary sodium

[9] http://edina.ac.uk/ukborders/

intake and 24-hour urinary sodium excretion are all continuous variables. Thus the normal distribution was assumed in the model construction. Cube root transformation was used for all dependent variables as it performed better than log and square root transformations, suggested by the Box-Cox transformation.

The models are shown in Table 5.4.1. For dietary iodine intake, Model 1 assessed the effect of dietary sodium intake and regional impact. Model 2 was adjusted for age, sex, BMI and dietary energy intake on the basis of Model 1. Model 3 extended Model 2 by adjusting for socioeconomic, lifestyle and dietary risk factors. Milk and dairy consumption was also included in the model to estimate the contribution of milk and dairy products to the iodine intake. Model 4 explored the nonlinear effects of the continuous risk factors. For dietary sodium intake, the models were similar to the iodine models. The difference was the exclusion of the dietary sodium intake and milk and dairy consumption. The models of 24-hour urinary sodium excretion were also similar to those of the dietary sodium intake. A minor change was the replacement of the dietary energy intake with the 24-hour urinary creatinine excretion.

Table 5.4.1 *List of Bayesian geo-additive models*

Dependent variable	Model	
Dietary iodine intake	Model 1	Region + Dietary sodium intake
	Model 2	Region + Dietary sodium intake + Age + Sex + BMI + Dietary energy intake
	Model 3	Region + Dietary sodium intake + Age + Sex + BMI + Race-ethnicity + Marital status + Education + Smoking + Alcohol consumption + Social class + Dietary energy intake + Milk and dairy consumption
	Model 4	Region + Dietary sodium intake (nonlinear) + Age (nonlinear) + Sex + BMI (nonlinear) + Race-ethnicity + Marital status + Education + Smoking + Alcohol consumption + Social class+ Dietary energy intake (nonlinear) + Milk and dairy consumption (nonlinear)
Dietary sodium intake	Model 1	Region
	Model 2	Region + Age + Sex + BMI + Dietary energy intake
	Model 3	Region + Age + Sex + BMI + Race-ethnicity + Marital status + Education + Smoking + Alcohol consumption + Social class+ Dietary energy intake
	Model 4	Region + Age (nonlinear) + Sex + BMI (nonlinear) + Race-ethnicity + Marital status + Education + Smoking +Alcohol consumption + Social class + Dietary energy intake (nonlinear)
24-hour urinary sodium excretion	Model 1	Region
	Model 2	Region + Age + Sex + BMI + 24-hour urinary creatinine excretion
	Model 3	Region + Age + Sex + BMI + Race-ethnicity + Marital status + Education + Smoking + Alcohol consumption + Social class + 24-hour urinary creatinine excretion
	Model 4	Region + Age (nonlinear) + Sex + BMI (nonlinear) + Race-ethnicity + Marital status + Education + Smoking + Alcohol consumption + Social class + 24-hour urinary creatinine excretion (nonlinear)

Note: Nonlinear: the effect was assumed to be nonlinear.

Dummy coding (1 vs 0) was used to create dummy variables for all categorical variables. The effect of each category on dependent variables was assessed by comparison to a predefined reference category (value set as 0). Details of the coding are listed in the Table 5.4.2.

Table 5.4.2 List of categorical variables with defined reference level

Variable	Category	Indicator
Sex	Female	reference level
	Male	
Smoking habit	Non-smoker	reference level
	Former smoker	
	Current smoker	
Social class	Non-manual work	reference level
	Manual work	
Marital status	Living together	reference level
	Living alone	
Education	Higher education	reference level
	A level or equivalent qualifications	
	GCSE or equivalent qualifications	
	No qualification	

Model choice was determined by deviance information criterion (DIC). The model with the lowest DIC value was regarded as the best model.

The preliminary analysis of the NDNS data were conducted in SPSS v17.0 (IBM, New York, USA) and Bayesian modelling and estimated graph plotting were conducted in BayesX version 2.0.0 (06.05.2009). The statistical significance level in the descriptive analysis was set as $\alpha=0.05$ and the level in the Bayesian analysis was set as $\alpha=0.1$.

5.4.3 Results

Characteristics by sex

A total of 2,105 participants' records were obtained. Results are shown in Table 5.4.3. The overall mean age was 42 years. Men were heavier and taller than women (84.7 vs 69.5 kg and 176.3 vs 161.9 cm, $p<0.001$ for both). Men had significantly higher body mass index than women (27.3 vs 26.5 kg/m^2, $p=0.004$),

which indicates overweight in both sexes in the study population. Women had significantly lower systolic and diastolic blood pressure than men (122.6 vs 130.5 mmHg and 68.9 vs 74.3 mmHg, $p<0.001$ respectively).

Educational attainment differed significantly between men and women. More men had higher educational qualifications (A level and above qualifications), while more than two thirds of women obtained lower qualifications (GCSE and lower qualifications).

More than half of the households (58.8%) were classified as a non-manual social class. Men and women were found to be at similar marital status, with around two thirds of men and women (63.7% and 59.6%, respectively) living together with their partner. Women had almost even distribution in the smoking status (32.2%, 32.4% and 35.4% in non-, former, current smoker category). More men (41.7%) quit smoking before the survey started. There were only 6.9% participants on antihypertensive medications.

The median energy intake was 1,745 (Interquartile Range: 726) kcal/day. The median dietary iodine intake was 181 (107) µg/day. The median dietary sodium intake was 2,611 (1,243) mg/day, which is equivalent to an estimated salt intake of 6.5 g/day. Men appeared to have significantly higher sodium and iodine intake (3,226 (1,257) mg/day and 215 (111) µg/day) than women (2,263 (846) mg/day and 157 (89) µg/day). These differences reflected the higher food intake of men compared to that of women. After the adjustment of dietary energy intake, the difference between men and women remained in the dietary sodium to energy ratio

but disappeared in the dietary iodine to energy ratio. In other words, men ate more high-sodium dense food than women.

The median alcohol consumption was 8.6 (22.0) g/day in the British White population. The median alcohol consumption was almost 3-fold higher in men than in women. Likewise, the consumption of milk and dairy foods of women (222.1 (196.7) g/day) were significantly lower than that of men (248.2 (226.8) g/day).

The median 24-hour urinary sodium was 140.6 (99.4) mmol/day, or approximately an estimated salt intake of 8.2 g/day. Men had significant higher levels of 24-hour urinary sodium, potassium and creatinine. However, the median 24-hour urinary sodium to creatinine ratio was higher in women than men (11.7 (6.3) vs 10.0 (4.9)).

The difference between the salt intakes measured by dietary record and 24-hour urine collection was approximately 1.7 g/day (or about 21% of the total salt intake). This can be deemed as an estimation of the use of discretionary salt and natural sources. Allowing for inaccuracies in the estimations of salt intake with either method, these figures are in line with those of 23% reported elsewhere (31).

Table 5.4.3 *Basic characteristics of the 2000-01 National Diet and Nutrition Survey (19-64 years) with adjustment for age and sex when appropriate*

Variable	Total (n=2,105)	Sex		p value
		Male (n=938)	Female (n=1,167)	
Age (year)	42.0 (0.3)	42.1 (0.4)	41.9 (0.4)	0.609
Weight (kg)	77.1 (0.4)	84.7 (0.5)	69.5 (0.5)	<0.001
Height (cm)	169.1 (0.2)	176.3 (0.2)	161.9 (0.2)	<0.001
BMI (kg/m^2)	26.9 (0.1)	27.3 (0.2)	26.5 (0.2)	0.004
Systolic blood pressure (mmHg)	126.5 (0.4)	130.5 (0.5)	122.6 (0.5)	<0.001
Diastolic blood pressure (mmHg)	71.6 (0.3)	74.3 (0.4)	68.9 (0.3)	<0.001
Education (%)-HE	17.2	20.6	13.8	<0.001
AE	24.9	28.2	21.6	
GE	39.4	35.2	43.5	
No	18.5	15.9	21.1	
Marital status (%)-LA	38.4	36.3	40.4	0.049
LT	61.6	63.7	59.6	
Smoking habit (%)-NO	29.1	26.0	32.2	<0.001
FM	37.0	41.7	32.4	
CR	33.8	32.3	35.4	
Social class (%)-NM	58.8	51.3	66.2	<0.001
MN	41.2	48.7	33.8	
Sodium intake (mg/day)†	2,611 (1,243)	3,226 (1,257)	2,263 (846)	<0.001
Iodine intake (µg/day)†	181 (107)	215 (111)	157 (89)	<0.001
Energy intake (kcal)†	1,745 (726)	2,077 (703)	1,547 (532)	<0.001
Alcohol consumption (g/day)†	8.6 (22.0)	14.8 (31.1)	5.3 (15.6)	<0.001
Milk and dairy consumption (g/day)†	235.6 (210.8)	248.2 (226.8)	222.1 (196.7)	0.006
Dietary sodium to energy ratio†	1.5 (0.4)	1.6 (0.4)	1.5 (0.4)	<0.001
Dietary iodine to energy ratio†	0.104 (0.050)	0.104 (0.051)	0.104 (0.050)	0.840
24hr urine volume (L)†	1.8 (1.1)	1.9 (1.2)	1.7 (1.0)	<0.001
24hr urinary sodium (mmol/day)†	140.6 (99.4)	167.0 (120.9)	123.4 (73.5)	<0.001
24hr urinary creatinine (mmol/day)†	12.9 (7.1)	17.0 (7.1)	10.9 (4.2)	<0.001
24hr urinary sodium to creatinine ratio†	10.9 (5.7)	10.0 (4.9)	11.7 (6.3)	<0.001

Note: Results are mean and standard deviation unless specified. Education: HE=Higher education, AE=A level or equivalent qualifications, GE=GCSE or equivalent qualifications, No=No qualifications; Marital status: LA=Living alone, LT=Living together; Smoking habit: NO=Non-smoker, FM=Former smoker, CR=Current smoker; Social class: NM=Non-manual work, MN=Manual work.
†: Median (IQR).

Characteristics by region

Of the 11 regions, the South East had the largest group of participants (n=430) and Wales had the smallest group (n=102). As shown in Table 5.4.4, no significant age and weight difference was found across regions. The mean BMI varied across Britain with overall overweight found in all regions. Participants residing in the North had the highest BMI (28.2 kg/m^2) and participants residing in London had the lowest (26.0 kg/m^2). BP also showed some geographical difference, systolic blood pressure ranging from 123.6 mmHg in London to 129.7 mmHg in Yorkshire and Humberside and diastolic blood pressure from 70.1 mmHg in London to 73.8 mmHg in Wales.

The proportion of former smokers ranged from 47.0% in East Anglia to 18.0% in Wales while no region had less than 30% current smokers in the NDNS sample. No significant difference was found for either marital status levels across regions, although the East Midlands has the highest proportion of couples living together.

Significant geographical variation in educational attainment was observed across Britain. Among the regions, London had the highest proportion (36.8%) of participants with a degree and the lowest proportion (11.0%) in the no qualification level. On the contrary, the North had the lowest (5.5%) and highest proportion (32.0%) in the highest and lowest education levels, respectively. It seemed that GCSE or other equivalent qualifications was the most common educational attainment in Britain.

A high proportion of participants in southern England was classified as being of non-manual class, with London having the highest proportion (77.8%). In the North and

in Wales, fewer than half the participants were in this class (45.6% and 48.0% respectively). Overall geographical variation was significant ($p<0.001$).

Dietary energy intake varied significantly across the 11 regions ($p=0.039$). Participants living in London had the lowest intake of energy and those in the South East and South West had the highest intake. No significant geographical difference was observed in daily dietary iodine and sodium intake. The dietary sodium to energy ratio, calculated to adjust sodium for daily energy intake, however, appeared to be significantly different among the British regions ($p<0.001$), i.e. participants living in Scotland and the North consumed a higher amount of sodium and iodine for every calorie they ate. Participants in London consumed the lowest amount of milk and dairy foods (178.0 g/day).

A significant geographical difference was observed in the 24-hour urinary sodium excretion across the regions ($p=0.035$). The 24-hour urinary creatinine excretion and the 24-hour urinary sodium to creatinine ratio, however, did not vary significantly.

Maps of dietary iodine, sodium intake and 24-hour urinary sodium are presented in Figure 5.4.2. The horizontal colour band at the bottom of the maps shows the range of observed values. The colour in each region was determined on the basis of the average of iodine and sodium levels. Little change in the colour was spotted in iodine map, while sodium maps showed slight variation in colours.

Table 5.4.4 *Characteristics of the 2000-01 UK National Diet and Nutrition Survey (19-64 years) by region with adjustment for age and sex when appropriate*

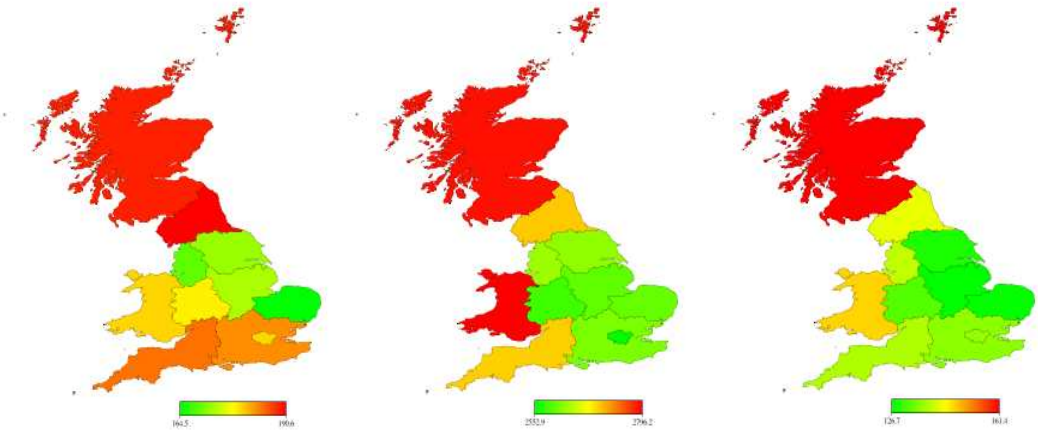
Variable	Region											p value
	North (n=128)	York & Humberside (n=198)	North West (n=270)	East Midlands (n=119)	West Midlands (n=200)	East Anglia (n=124)	London (n=156)	South East (n=430)	South West (n=191)	Wales (n=102)	Scotland (n=187)	
Age (year)	42.9 (1.1)	42.0 (0.9)	42.0 (0.7)	42.3 (1.1)	40.4 (0.9)	40.6 (1.1)	42.5 (1.0)	41.9 (0.6)	43.5 (0.9)	43.3 (1.2)	41.3 (0.9)	0.377
Weight (kg)	79.9 (1.4)	76.6 (1.2)	75.8 (1.0)	78.3 (1.5)	75.9 (1.2)	78.5 (1.4)	76.0 (1.3)	76.7 (0.8)	78.7 (1.2)	78.4 (1.8)	75.7 (1.3)	0.223
Height (cm)	168.3 (0.6)	169.2 (0.5)	169.0 (0.4)	169.0 (0.6)	169.2 (0.5)	168.3 (0.6)	170.5 (0.5)	169.9 (0.3)	168.9 (0.5)	167.6 (0.7)	167.9 (0.6)	0.006
BMI (kg/m^2)	28.2 (0.5)	26.7 (0.4)	26.5 (0.4)	27.3 (0.5)	26.4 (0.4)	27.7 (0.5)	26.0 (0.4)	26.5 (0.3)	27.6 (0.4)	27.9 (0.6)	26.7 (0.5)	0.004
Systolic blood pressure (mmHg)	125.8 (1.4)	129.7 (1.2)	126.3 (1.0)	124.8 (1.4)	128.1 (1.1)	129.0 (1.4)	123.6 (1.3)	126 (0.8)	126.4 (1.1)	127.5 (1.8)	124.4 (1.3)	0.017
Diastolic blood pressure (mmHg)	71.3 (1.0)	73.4 (0.8)	71.7 (0.7)	71.0 (1.0)	72.5 (0.8)	72.1 (1.0)	70.1 (1.0)	71.1 (0.6)	70.8 (0.8)	73.8 (1.3)	71.1 (0.9)	0.189
Education (%)-HE	5.5	10.6	14.4	15.1	18	13.7	36.8	17.8	14.1	11.8	23.5	
AE	21.9	25.8	25.9	23.5	29	16.9	24.5	25	23	27.5	23	<0.001
GE	40.6	43.4	36.7	39.5	35.5	46.8	27.7	44.4	43.5	40.2	35.8	
No	32	20.2	23	21.8	17.5	22.6	11	12.9	19.4	20.6	17.6	
Marital status (%)-LA	39.8	38.9	39.6	26.1	35	38.7	44.9	39.5	33	40.2	44.9	0.059
LT	60.2	61.1	60.4	73.9	65	61.3	55.1	60.5	67	59.8	55.1	
Smoking habit (%)-NO	32.8	31.3	25.2	35.3	28	23.4	32.1	24.7	34.6	38.2	32.1	
FM	33.6	32.3	35.6	32.8	40.5	45.2	34.6	43.7	35.6	17.6	33.2	0.001
CR	33.6	36.4	39.3	31.9	31.5	31.5	33.3	31.6	29.8	44.1	34.8	
Social class (%)-NM	45.6	56.5	59.7	57.9	54.1	51.6	77.8	67	61.6	48	55.5	<0.001
MN	54.4	43.5	40.3	42.1	45.9	48.4	22.2	33	38.4	52	44.5	

Table 5.4.4 *cont'd*

Variable	Region											p value
	North (n=128)	York & Humberside (n=198)	North West (n=270)	East Midlands (n=119)	West Midlands (n=200)	East Anglia (n=124)	London (n=156)	South East (n=430)	South West (n=191)	Wales (n=102)	Scotland (n=187)	
Sodium intake (mg/day)†	2,644 (1,598)	2,519 (1,250)	2,711 (1,325)	2,485 (1,487)	2,636 (1,369)	2,498 (1,110)	2,547 (1,180)	2,622 (1,097)	2,717 (1,104)	2,523 (1,671)	2,609 (1,186)	0.623
Iodine intake (µg/day)†	195 (134)	175 (818)	172 (120)	176 (100)	187 (106)	167 (107)	176 (95)	188 (119)	182 (103)	173 (104)	188 (114)	0.060
Energy intake (kcal)†	1,742 (654)	1,703 (698)	1,657 (809)	1,694 (811)	1,778 (749)	1,734 (639)	1,610 (724)	1,790 (679)	1,790 (736)	1,774 (852)	1,775 (809)	0.039
Alcohol consumption (g/day)†	8.3 (24.9)	7.1 (20.3)	9.7 (26.8)	8.5 (18.7)	8.6 (21.1)	5.0 (17.4)	12.0 (23.7)	9.2 (20.5)	8.2 (17.6)	7.9 (23.1)	8.7 (21.2)	0.342
Milk and dairy consumption (g/day)†	259.3 (216.5)	248.0 (216.0)	242.4 (217.1)	249.6 (232.3)	239.0 (189.7)	190.3 (195.4)	178.0 (205.8)	232.4 (215.0)	253.4 (188.6)	250.1 (213.7)	243.4 (206.1)	0.007
Dietary sodium to energy ratio†	1.5 (0.5)	1.6 (0.4)	1.6 (0.5)	1.6 (0.5)	1.5 (0.4)	1.5 (0.3)	1.5 (0.4)	1.5 (0.4)	1.5 (0.4)	1.5 (0.3)	1.6 (0.4)	<0.001
Dietary iodine to energy ratio†	0.107 (0.066)	0.103 (0.044)	0.107 (0.052)	0.106 (0.045)	0.102 (0.050)	0.096 (0.039)	0.102 (0.042)	0.105 (0.051)	0.101 (0.054)	0.095 (0.044)	0.110 (0.061)	0.054
24hr urine volume (L)†	1.8 (1.2)	1.7 (1.0)	1.8 (0.9)	1.7 (1.1)	1.7 (1.1)	1.6 (1.2)	1.8 (1.1)	1.9 (1.1)	1.8 (1.1)	1.9 (1.1)	1.7 (1.0)	0.378
24hr urinary sodium (mmol/day)†	147.0 (96.6)	138.6 (87.2)	148.7 (92.8)	130.7 (92.7)	149.1 (113.1)	124.2 (71.3)	143.2 (93.8)	139.8 (96.5)	134.6 (104.3)	155.7 (113.8)	162.4 (135.7)	0.035
24hr urinary creatinine (mmol/day)†	12.8 (6.8)	12.4 (8.1)	12.9 (6.8)	13.9 (8.4)	13.1 (9.2)	12.0 (6.4)	12.6 (8.0)	13.2 (7.1)	12.9 (6.1)	13.4 (5.8)	14.0 (7.2)	0.256
24hr urinary sodium to creatinine ratio†	11.4 (6.2)	10.9 (5.4)	11.4 (5.5)	10.1 (5.2)	10.8 (5.5)	10.1 (6.8)	10.3 (6.3)	10.6 (5.9)	10.8 (5.1)	11.9 (6.2)	12.4 (6.0)	0.061

Note: Results are mean and standard deviation unless specified. York & Humberside= Yorkshire & Humberside; Education: HE=Higher education, AE=A level or equivalent qualifications, GE=GCSE or equivalent qualifications, No=No qualifications; Marital status: LA=Living alone, LT=Living together; Smoking habit: NO=Non-smoker, FM=Former smoker, CR=Current smoker; Social class: NM=Non-manual work, MN=Manual work.
†: Median (IQR).

Figure 5.4.2 *Observed dietary iodine intake (left panel), dietary sodium intake (centre panel) and 24-hour urinary sodium (right panel) across Britain*



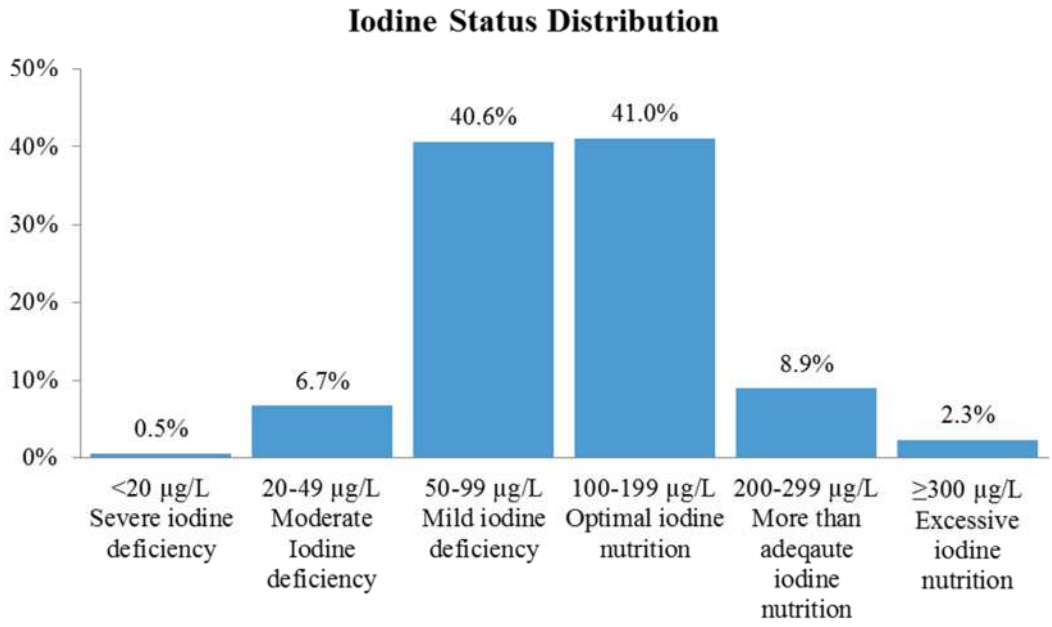
Note: red/green indicates high/low level of dietary intake or urinary sodium level.

Iodine status distribution

The median dietary iodine intake in the 2000-01 NDNS White population was 181.3 (IQR: 106.7) µg/day with no significant geographical variation. However dietary iodine intake is not a commonly used indicator of iodine status in the general population. The WHO recommends using median urinary iodine concentration (UIC) to determine the population iodine status. Nonetheless, the urinary iodine concentration or excretion was not measured in the NDNS. In the UK, there is no USI programme or other voluntary salt iodisation programme. The iodine content in salt is estimated to be low (260). Thus the majority iodine should be obtained from dietary foods and supplements. The UIC of each participant was then approximately estimated using the dietary iodine intake divided by the 24-hour urine volume in this analysis. However, it should be noted that this method slightly underestimates the true urinary iodine concentration at both individual and population levels.

The estimated median UIC was 103.4 µg/L, with just under 50% of participants having urinary iodine levels below 100 µg/L and less than 10% below 20 µg/L (see Figure 5.4.3). The majority of participants had mild iodine deficiency and optimal iodine status. The result indicated overall optimal iodine status in the White population in Britain, but with risk of re-emergence of iodine deficiency.

Figure 5.4.3 *Distribution of iodine status in the 2000-01 National Diet and Nutrition Survey (19-64 years) white population*



DIC results

Table 5.4.5 listed computed DIC values of all constructed models of dietary iodine intake, dietary sodium intake and 24-hour urinary sodium excretion. Model 3 of dietary and urinary sodium had the lowest DIC value while Model 2 of dietary iodine intake had the lowest DIC value. Therefore these models were considered the best models and only the results of these models were presented below. The assumption

of the nonlinear effect, whilst improving the fitness, increased the complexity of the model. Therefore this assumption was not likely to improve the statistical estimation.

Table 5.4.5 *DIC results calculated from the models of dietary iodine and sodium intakes and 24-hour urinary sodium excretion*

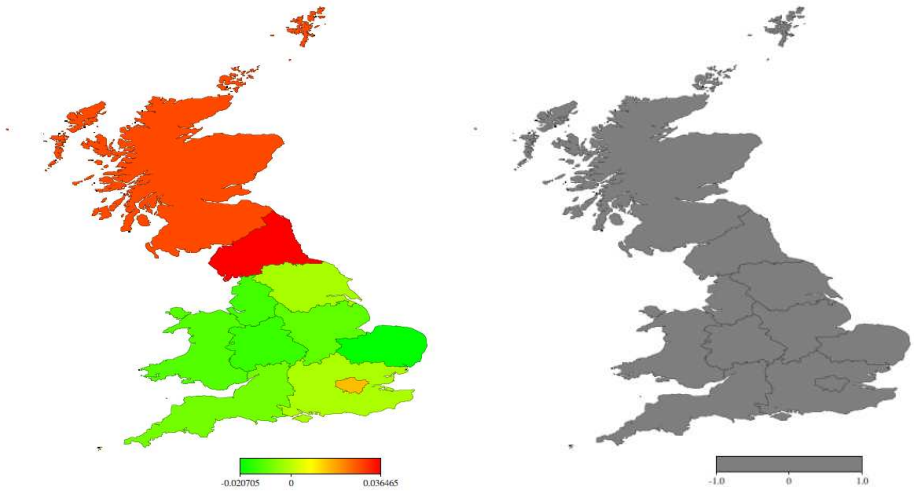
	Dietary iodine intake			Dietary sodium intake			24-hour urinary sodium excretion		
	Deviance	pD	DIC	Deviance	pD	DIC	Deviance	pD	DIC
Model 1	1616.1	9.5	1635.0	1618.1	7.6	1633.4	1355.2	8.7	1372.7
Model 2	1516.9	12.9	1542.8	1517.4	13.9	1545.1	1329.1	13.3	1355.7
Model 3	1492.6	23.3	1539.2	1490.8	21.7	1534.3	1259.4	21.0	1301.4
Model 4	1470.3	43.6	1557.4	1477.4	36.1	1549.6	1245.2	33.8	1312.9

Dietary iodine intake

Spatial effect

The estimated spatial distribution of dietary sodium intake was drawn in Figure 5.4.5. The left panel of the graph is the estimated residual spatial regional effects on dietary iodine intake. The colour band represents the range of daily dietary iodine intake in each region. Shaded areas in red/green indicate high/low level of iodine consumption. The 90% posterior probability map on the right of the graph further showed the statistical significance of the spatial variation of sodium consumption. This probability graph usually employs simple colour indications: white (value=1.0) indicates regions with significantly positive spatial effect, grey (value=0) indicates regions with non-significant effect, and black (value=-1.0) indicates regions with significantly negative effect. In Figure 5.4.4, although the mean effect was higher in Scotland and lower in English regions and Wales, the spatial effect was not significantly different, which indicated that dietary iodine intake had no particular spatial pattern in Britain.

Figure 5.4.4 *Estimated posterior mean residual spatial regional effects (left) and 90% posterior probability map (right) of dietary iodine intake*



Note: Left panel: red/green indicates high/low level of dietary iodine intake; Right panel: white (value=1.0) indicates significantly positive spatial effect, grey (value=0) indicates non-significant effect, and black (value=-1.0) indicates significantly negative effect.

Fixed effects

Estimated fixed effects of continuous and categorical risk factors were shown in Table 5.4.6. The fixed effects can be interpreted as linear association. Although BayesX cannot produce the exact p value for each estimation, significance at specific credible level, α=0.1 in this analysis, can be decided by the credible intervals. If overall credible intervals are under or above 0, the effect of the risk factor can be regarded as significant. Therefore, the participant's age, daily energy and sodium intake, daily alcohol and dairy consumption had a significantly positive effect on iodine intake. In particular, the effect of dietary sodium intake was smaller than that of milk and dairy consumption. Current smokers who attained low or no educational qualification, however, were more likely to consume less iodine. The effect of education also tended to decrease as the educational attainment level decreases.

Table 5.4.6 *Estimated fixed effects of dietary iodine intake (Model3)*

	Mean effect	Standard Deviation	5% quantile	95% quantile
Constant	3.76	0.11	3.59	3.94
Age†	0.0091	0.0013	0.0069	0.0112
Sex-Female	0			
Male	-0.0004	0.0350	-0.0564	0.0567
BMI (kg/m^2)	-0.0020	0.0028	-0.0065	0.0027
Education-Higher education	0			
A level or equivalent qualifications	-0.0717	0.0435	-0.1402	0.0007
GCSE or equivalent qualifications†	-0.1545	0.0436	-0.2287	-0.0847
No qualification†	-0.1716	0.0548	-0.2571	-0.0781
Marital status-Living together	0			
Living alone	0.0168	0.0285	-0.0324	0.0630
Smoking habit-Non-smoker	0			
Former	0.0034	0.0344	-0.0513	0.0576
Current†	-0.0641	0.0370	-0.1267	-0.0036
Social Class-Non-manual work	0			
Manual work	-0.0282	0.0321	-0.0808	0.0234
Alcohol consumption (g/day)†	0.0134	0.0008	0.0121	0.0147
Dietary sodium intake (mg/day)†	7.34×10^{-5}	2.60×10^{-5}	3.06×10^{-5}	1.15×10^{-4}
Energy intake (kcal/day)†	0.0004	4.46×10^{-5}	0.0003	0.0005
Milk and dairy consumption (g/day)†	0.0023	0.0001	0.0021	0.0024

†: Significant at α=0.1 level.

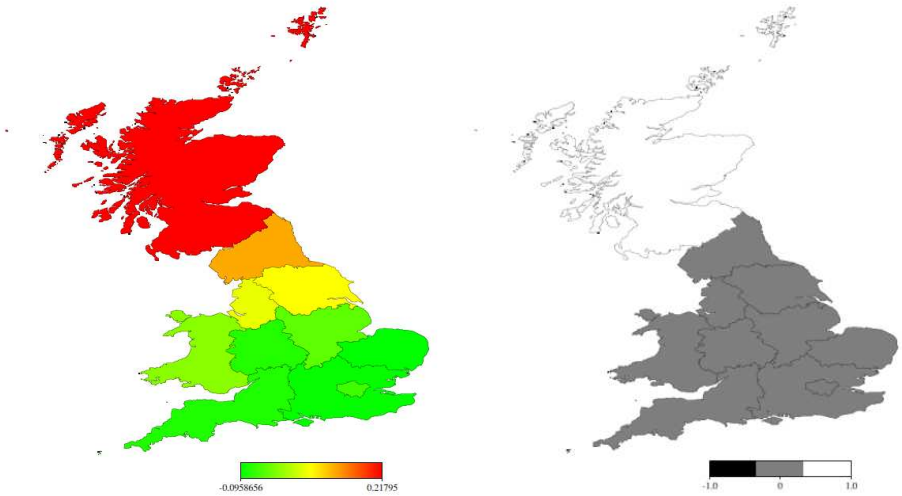
Dietary sodium intake

Spatial effect

Estimated mean spatial effect of dietary sodium intake was shown in the left of Figure 5.4.5. It was obvious that participants living in Scotland had a higher level of sodium intake than the rest of Britain. A decreasing trend was also shown as the latitude lowers. Participants in southern England appeared to consume the lowest level of salt. The 90% posterior probability map on the right of the graph further showed the statistical significance of the spatial variation of sodium consumption. This map confirmed that participants in Scotland were more likely to eat higher level

of dietary sodium, while people from the rest of Britain, including England and Wales, were no different in dietary sodium intake.

Figure 5.4.5 *Estimated posterior mean residual spatial regional effects (left) and 90% posterior probability map (right) of dietary sodium intake*



Note: Left panel: red/green indicates high/low level of dietary sodium intake; Right panel: white (value=1.0) indicates significantly positive spatial effect, grey (value=0) indicates non-significant effect, and black (value=-1.0) indicates significantly negative effect.

Fixed effects

The estimated effects of those controlled risk factors were shown in Table 5.4.7.

Men who had no educational attainment were more likely to consume higher levels of dietary sodium while current smokers who were living alone were more likely to consume lower level of dietary sodium. In particularly, the effect of education decreased as the educational attainment level became lower. The age effect on dietary sodium intake decreased as the age increases. However, other continuous risk factors, including BMI, alcohol consumption and energy intake, had significantly positive effects on dietary sodium.

Table 5.4.7 *Estimated fixed effects of dietary sodium intake (Model 3)*

	Mean effect	Standard Deviation	5% quantile	95% quantile
Constant	9.74	0.19	9.43	10.05
Age†	-0.0117	0.0023	-0.0155	-0.0078
Sex - Female	0			
Male†	0.3243	0.0604	0.2320	0.4289
BMI (kg/m^2)†	0.0154	0.0049	0.0074	0.0232
Education-Higher Education	0			
A level or equivalent qualifications	0.0219	0.0763	-0.1025	0.1456
GCSE or equivalent qualifications	0.0651	0.0770	-0.0566	0.1994
No qualification†	0.1565	0.0983	0.0030	0.3186
Marital status-Living together	0			
Living alone†	-0.1399	0.0522	-0.2280	-0.0549
Smoking habit-Non-smoker	0			
Former	-0.0340	0.0618	-0.1360	0.0713
Current†	-0.1873	0.0654	-0.2919	-0.0778
Social Class-Non-manual work	0			
Manual work	-0.0498	0.0597	-0.1477	0.0538
Alcohol consumption (g/day)†	0.0099	0.0013	0.0077	0.0122
Energy intake (kcal/day)†	0.0021	0.0000	0.0021	0.0022

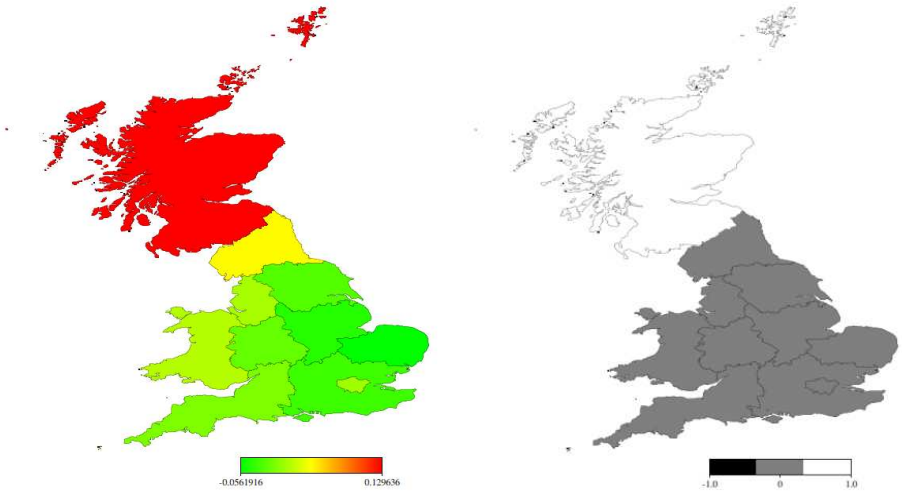
†: Significant at α=0.1 level.

24-hour urinary sodium excretion

Spatial effect

The estimated maps shown in Figure 5.4.6 also revealed a clear spatial pattern of the 24-hour urinary sodium. Participants in Scotland had the highest 24-hour urinary sodium excretion and those living in south-east of England appeared to have low level, with people in the North and Wales had sodium levels in between. The probability map on the right showed that Scotland had significant positive spatial effect on 24-hour urinary sodium excretion. These two maps were similar to those of the dietary sodium, which confirmed the north-south pattern of sodium consumption and excretion in Britain.

Figure 5.4.6 *Estimated posterior mean residual spatial regional effects (left) and 90% posterior probability map (right) of 24-hour urinary sodium excretion*



Note: Left panel: red/green indicates high/low level of 24-hour urinary sodium excretion; Right panel: white (value=1.0) indicates significantly positive spatial effect, grey (value=0) indicates non-significant effect, and black (value=-1.0) indicates significantly negative effect.

Fixed effects

Higher levels of BMI and 24-hour urinary creatinine were significantly associated with higher level of 24-hour urinary sodium (Table 5.4.8). Participants with A level qualification or no educational attainment and from households with lower social class had significantly higher level of 24-hour urinary sodium. Gender had a different effect on urinary sodium compared to the effect on dietary sodium. It was mainly due to the adjustment for 24-hour urinary creatinine. In a further analysis by removing the 24-hour urinary creatinine, the effect of being a male changed to be significantly positive.

Table 5.4.8 *Estimated fixed effects of 24-hour urinary sodium excretion (Model 3)*

	Mean effect	Standard Deviation	5% quantile	95% quantile
Constant	3.51	0.14	3.28	3.73
Age	-0.0011	0.0018	-0.0042	0.0018
Sex - Female	0			
Male	-0.0845	0.0519	-0.1680	-0.0027
BMI (kg/m^2)	0.0136	0.0040	0.0071	0.0201
Education-Higher Education	0			
A level or equivalent qualifications	0.1095	0.0642	0.0019	0.2135
GCSE or equivalent qualifications	0.0674	0.0645	-0.0411	0.1777
No qualification†	0.1488	0.0784	0.0237	0.2813
Marital status-Living together	0			
Living alone	-0.0234	0.0431	-0.0957	0.0439
Smoking habit-Non-smoker	0			
Former	0.0430	0.0513	-0.0412	0.1264
Current	0.0198	0.0541	-0.0694	0.1095
Social Class-Non-manual work	0			
Manual work	0.0826	0.0474	0.0044	0.1598
Alcohol consumption (g/day)	0.0012	0.0010	-0.0004	0.0029
24-hour urinary creatinine excretion (mmol/day)†	0.0926	0.0044	0.0854	0.0997

†: Significant at α=0.1 level.

5.4.4 Discussion

Key findings

In the present study, spatial distribution of dietary iodine, urinary and dietary sodium and their demographic and socioeconomic determinants from 2,105 White participants living in 11 British regions were analysed. One important finding is that there was a clear north-south pattern of dietary and 24-hour urinary sodium in Britain but no significant spatial variation of dietary iodine intake across those regions. In particular, people living in Scotland had a significantly higher salt intake than those living in England and Wales. Moreover, people with lower educational attainment and from a lower social class background had higher salt intake. Different

age effects were also shown by comparing the results of the dietary sodium and urinary sodium models.

The inconsistency between the spatial distributions of iodine intake and salt intake (using sodium intake as the proxy) is not surprising. Although in many countries, particularly in the low- and middle-income countries, iodised salt is the primary strategy for iodine supplementation, salt is not mandatorily required to be iodised in the UK. Only 2.5% salt is iodised on the UK market (260). The spatial patterns of iodine and salt intakes are thus not necessarily matched.

The dietary iodine model results indicated that salt and iodine intake were significantly associated. However, the significance did not necessarily indicate that a change of salt intake would lead to a change of iodine intake. The association was possibly due to confounding since the salt used in food manufacturing and household is not iodised in the UK. Some commonly consumed iodine-rich foods, such as cheese and processed meat, are added high levels of salt during manufacturing. Therefore, higher consumption of these foods could result in a high level of salt and iodine intake. Nevertheless, reducing salt content in these foods would not reduce iodine content at the same time.

Historically, milk and dairy products have been the major iodine supplementation vehicle. Iodine was initially added to feedstuffs to increase animal reproduction. With the implementation of the School Milk Act in 1946, milk and dairy products gradually became a part of people's daily diet and contributed more than 40% of daily iodine intake in the UK adult population in the 1990s (349;350). The average

iodine intake accordingly increased at population level. The 2000-01 NDNS report also estimated that 38% iodine intake was contributed by milk and dairy foods (351).

According to the iodine model results, the milk and dairy products had a much larger effect on iodine status than dietary sodium intake. Unlike salt iodisation, milk and dairy consumption is not likely to be affected by salt reduction. In addition, the technology of iodine addition in feedstuffs is mature. In the UK, adding iodine to feedstuffs has been used since 1920s. In fact moderate to high iodine concentration has been found in milk and dairy products in many European countries, ranging from 45-601 μg/kg (352). In fact, the consumption of milk and dairy products may be beneficial to prevent CVD. Elwood *et al*. (353) in a meta-analysis of 15 studies showed significantly lower risks of stroke (relative risk: 0.79, 95% confidence intervals: (0.75, 0.82) and CHD (0.84(0.76, 0.93)).

The iodine concentration in cow's milk was on the increase during the 1980s and 1990s and was estimated to be more than 300 μg/kg in the 1998/9 UK Ministry of Agriculture Fisheries and Food (MAFF) survey (350). However, Bath *et al*. (250) recently observed lower concentration in organic milk, although the concentration of iodine was at the same level as the previous MAFF surveys. The organic milk, produced by the cows that were fed organic feed, had a median iodine concentration of 145 μg/L, which was less than 60% of that in other conventional milk samples. With the growing popularity of organic milk, the population iodine status might be negatively affected.

In fact, the reduced iodine content in milk has been blame for the re-emergence of iodine deficiency in several countries that did not introduce salt iodisation

programmes, e.g. Australia (248) and New Zealand (354). Vanderpump *et al*. (244) also reported a median UIC of 80.1 µg/L in UK school girls aged 14-15 years in a recent cross-sectional study, indicating a mild iodine deficiency status in the UK population. The reduced iodine concentration in milk is attributable to the following reasons: the replacement of iodophor in milk and dairy products (249), reduced consumption of iodine-rich foods (248) and consumption of goitrogenic foods in animals (250). Therefore, strict surveillance of iodine content in milk and dairy products is necessary to keep the general population at safe.

In this analysis, the estimated median UIC was 103.4 µg/L, indicating a borderline optimal iodine status in the White population. However, the iodine intake was measured from dietary foods and supplements only. This approach underestimated the real habitual intakes because of the under-reporting of the energy intake in this survey (355). Therefore the true population urinary iodine concentration should be higher. A better and accurate measurement should be made by 24-hour urine collection

Although participants with A-level or equivalent educational attainments had significantly higher urinary sodium levels, the results showed consistently that participants with lower educational attainment had lower iodine intake and higher sodium intake, while participants with lower educational attainment and in lower social class had higher 24-hour urinary sodium excretion. Educational attainment and social class are two commonly used indicators of socioeconomic status (SES). The findings are in line with those of the INTERSALT study (356). Therefore those socioeconomically disadvantaged people had increasing risks of both iodine deficiency and hypertension with ensuing cardiovascular disease.

This analysis is the first to present significant spatial variations of dietary and 24-hour urinary sodium in Britain. People living in Scotland were more likely to eat more salt compared to those living in the rest of Britain. The dietary sodium to energy ratio (sodium density) also showed that sodium level in every unit of energy intake was higher in northern Britain, indicating people in these regions, particularly in Scotland, ate more salty foods.

Maintaining a low sodium diet helps control hypertension and reduces the risk of CVD. A high sodium diet usually is associated with low diet quality. In Scotland, the high level of salt intake suggested a high risk of CVD in the country, which echoes the "Scottish effect" – a phenomenon describing high mortality in Scotland. This particular phenomenon has been extensively discussed and explored in recent years (357) and it is associated with a complex combination of diet quality, economic deprivation and other lifestyle and environmental factors (357-361). Recent research suggested that if the Scottish opted for the English diet, 40% of the CHD deaths could be averted (360). The present models were not adjusted for diet quality. The unobserved effect of diet quality was likely to have been accounted for by the spatial effect. However, the specification of diet quality could possibly contribute to a better explanation of the spatial variation of the salt intake in Britain, which will be examined in the future.

The resulting spatial pattern could also be partly attributed to residual confounding. The social class used in this analysis was a crude summary of the study population and may not have been precise enough to describe the social gradient. Therefore, the effects of other social groups that may play an important role in relation to salt intake and diet quality, particularly in Scotland, may not have been adjusted for. Therefore,

it would also be of interest to use a more comprehensive SES variable to avoid this confounding issue.

To reduce salt intake in the general population, the UK government has set targets for the food industry. The visualised spatial maps can be useful for policy-makers, the public and other stakeholders to spot the difference of salt intake across areas and help health officers to review and monitor the progress of salt reduction.

Strengths and limitations

This analysis is the first study that has assessed the association between salt intake and iodine status in the UK. An innovative approach, Bayesian geo-additive models, was used to simultaneously estimate spatial effect and linear and nonlinear effects. The SES gradient was consistent in salt and iodine intakes in this analysis, irrespective the different measurements.

However, there are some limitations of this analysis apart from the residual confounding and diet quality discussed previously. Firstly, this analysis was based on the 2000-01 NDNS data. The UK started a national salt reduction programme in the past decade and the mean salt intake has fallen by 0.9 g/day from 9.5 g/day in 2001 (64). The recent report based on the latest 2011 NDNS (19-64 years) showed that the average salt intake in England is reduced to 8.1 g/day (65). It would be important to repeat this analysis on the latest data to update the progress of salt reduction in Britain and monitor the population iodine status in the context of long term salt reduction in the country. The new data also offer an opportunity to estimate whether the reduction in salt intake has modified the social and spatial inequality over time. In addition, this analysis only included White participants. Hence

generalisation of the results to the whole population should therefore be made with caution. It is possible that the associations may be altered in some areas with larger ethnic presence, such as London. Larger sample size of the minority groups is needed to produce more robust estimations. Another limitation was that this survey did not collect information on pregnant women who are one of the most vulnerable populations to iodine deficiency. Concerns of iodine deficiency in pregnant women and women of child bearing age are raised (362;363). As the iodine deficiency-induced damage to foetuses is severe and irreversible, it is critical to evaluate and monitor the iodine status in these vulnerable subpopulations. Further analysis on the iodine status of pregnant women and women of reproductive age will be of interest when data become available. The level of geographical classification was another limitation. The correlated spatial effects could have been better estimated if more detailed classification (for instance, county) was available. The 11 SSRs might result in over-smoothing the estimates and hiding significant spatial variation at lower geographical levels. Finally, the analysis was also limited by the use of repeated dietary records for estimation of dietary intakes. Dietary records are useful in national survey but lack accuracy (364). Problems like under-reporting have been revealed. Twenty-four-hour urine collection is the gold standard for sodium and iodine estimation. Thus the collection 24-hour urine samples should be used as a standard procedure in the coming national dietary and health surveys.

Implications

The UK NDNS data were used here as an example to show that alternative approaches of iodine fortification, such as milk and dairy consumption, can effectively reduce and eliminate the risk of iodine deficiency at population level.

This approach also provides an economical solution to avoid the potential conflict of salt iodisation against salt reduction as two WHO policies may put each other in jeopardy. Milk and dairy foods are likely to act more effectively as a vehicle for iodine supplementation in the countries that had a tradition of or increasing trend of milk and dairy consumption. As there is no specific programme utilising milk and dairy products for iodine supplementation, it may be appropriate for international organisations to integrate this approach into the coordination of salt reduction and salt iodisation programmes. Like the salt reduction programme, the UK experience may be shared to other countries to improve the iodine status. Policy-makers, industry and other stakeholders should also be aware of the potential limitations, such as dietary habit, political influence and economic restriction.

In addition, the evaluation of spatial variation of iodine and salt intakes could be an innovative and useful monitoring tool for policy-makers and academic researchers. The models and resulting maps provide a visual snapshot of the progress of the health promotions and may help the media campaigns to raise public awareness.

In conclusion, this analysis described a north-south pattern of salt intake across Britain with people living in Scotland having higher salt intake than those in England and Wales. Iodine status is considered optimal in Britain with no significant spatial variation at regional level. Low socioeconomic status is associated with higher levels of salt intake and lower level of iodine intake, indicating higher risk of CVD. Special attention should be given to social and regional differences in salt intake to achieve sustainable success in salt reduction in the UK. Milk and dairy products can be considered as an approach for iodine supplementation and may help to reconcile the

potential conflicts between salt reduction and salt iodisation programmes in the world.

5.5 Summary of Chapter 5

In Chapter 5, the thesis objectives were explored firstly in an ecological analysis from a global perspective. The association between salt and iodine intakes were determined using Spearman's correlation coefficients across the world and by national economic status. The weak and non-significant coefficients suggested that a moderate modification of salt intake would not affect the iodine status of the general population, which was also served as a hypothesis to be further examined in the following three case studies.

In the first case study, data obtained from a 6-month salt reduction study in a Ghanaian community including 6 rural villages and 6 semi-urban villages were used. Linear regression models, instead of Bayesian geo-additive models, were carried out to estimate the association of changes in salt and iodine intake over the study period. Although iodine intake did not change significantly during the study period in the concordant group (villages consuming iodised salt on a regular basis) and discordant group (villages not consuming iodised salt on a regular basis), the salt and iodine association was significant in the concordant group but not in the discordant group. Given the variation in household coverage of iodised salt, the results suggested that a moderate salt reduction in the countries dependent on iodised salt for iodine supplementation is unlikely to have a major impact on the population iodine status.

The second case study used the data of the third United States National Health and Nutrition Survey (NHANES III). Bayesian geo-additive models were constructed to estimate the salt and iodine association in the US population, as well as the determinants of both intakes. The results showed a weak but significant association between salt intake (measured from dietary foods only) and iodine intake (measured by spot urinary iodine concentration). However, the association was possibly caused by the addition of both non-iodised salt and iodine in foods as the US does not conventionally use iodised salt in food processing. Therefore, the results were not sufficient to suggest a substantial effect of salt reduction on iodine intake in the US. The analysis also revealed regional difference of salt and iodine intake, suggesting more variations in the sub-regional levels. However, no spatial dependence could be estimated due to lack of sufficient geographical data. The US data indicated that higher socioeconomic status was associated with higher salt intake and lower iodine intake.

This chapter finished with the third case study on the white participants in the 2000-01 National Diet and Nutrition Survey in Britain. The British population obtains sufficient iodine intake mainly from milk and dairy consumption. The Bayesian geo-additive models showed a weak but significant salt and iodine association based on dietary data. However, the association did not indicate a possible impact of salt reduction on iodine intake as there is no salt iodisation programme in Britain. The study served as an example to demonstrate the possibility of using milk and dairy products as an alternative vehicle to salt in some countries sharing similar dietary pattern with the British population. Milk and dairy products had a strong association with iodine intake. The model results also described a significant north-south spatial

pattern of salt intake at regional level after controlling for a set of socioeconomic and demographic risk factors, suggesting the Scottish were likely to eat more salt than the others living in England and Wales. In addition, low socioeconomic status was associated with high salt intake and low iodine intake, suggesting higher risks of CVD and IDD in the vulnerable subpopulation.

Chapter 6 Discussion

6.1 Summary of the Thesis

Salt plays an important role in regulating BP (4;6). It is also used as the major fortification vehicle to supplement iodine in the general population (94). Salt reduction programmes aim to lower BP and prevent the risk of cardiovascular disease (CVD) by reducing population salt intake, while universal salt iodisation (USI) programmes are adopted to control iodine deficiency disorders (IDD). There have been increasing regional and national initiatives worldwide (17;26;63) for both programmes, and remarkable achievements have been obtained by both programmes (17;58;59;107).

A substantial reduction in salt intake, through a reduction in the use of discretionary salt, may potentially cause a reduction in iodine intake through a reduced delivery of potassium iodide where iodised salt is used, possibly undermining salt iodisation programmes. On the other hand, there is also the potential risk that the implementation of a universal salt iodisation programme might unintentionally lead to an increase in salt intake and ensuing risk of avoidable cardiovascular events. Furthermore, salt iodisation programmes worldwide use rough estimates of average population salt consumption to set the amount of iodisation necessary to deliver the desired amount of iodine. These estimates are often wrong and out of date giving rise to concerns on the appropriateness of the current criteria used for defining iodine content of salt (25).

To reconcile any potential conflicts, a global coordination of programmes has been proposed (25;26;365;366). The World Health Organization (WHO) recommends that health authorities and policy-makers adapt current policies to optimise the population salt and iodine intakes.

Scientific evidence is crucial to inform and adapt policies. However, research on the programme coalition is scarce. In particular, it is accepted that the iodine content in salt should be adjusted according to the country's salt intake. No study is able to verify if the adjustment is universally needed or to provide information of the possible adjustment level to policy-makers, international organisations, salt and food industries, media and civil society.

This study set out with the aims of evaluating the population salt intake and iodine status and assessing the salt-iodine association. A class of Bayesian geo-additive models was also employed to investigate the risk factors and the spatial variations of the salt intake and iodine intake or status, where possible.

6.2 Validity of the Average Salt Intake Assumption

The present study assessed the salt intake in three populations. All estimated intakes were less than the assumed salt intake (10 g/day), although the US data only took into account the salt in dietary foods. The results indicated that the assumption of the average salt intake used for setting up the criteria of salt iodisation needs to be updated, particularly for those countries that have implemented salt reduction programmes or are in economic transition with a changing dietary pattern. The current assumption might cause an over- and under-estimation bias in projected

amount of iodine supplementation, which could perhaps widen the inequality of iodine status across the world and potentially result in more hidden economic burden and loss of health.

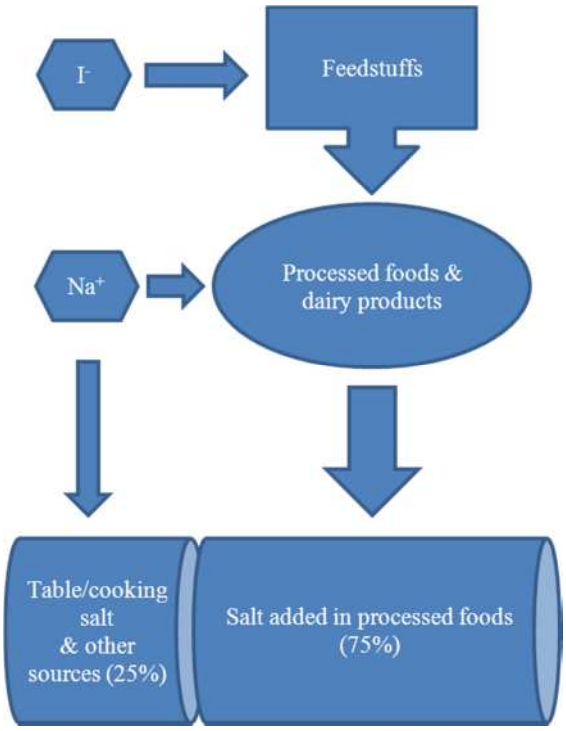
6.3 Impact of Salt Reduction on Iodine Supplementation

Different estimations of the association between salt and iodine intakes were produced in three case analyses. The British analysis was used in this study as an example of alternative approaches of iodine fortification. The UK does not have a salt iodisation programme in place. Hence a non-significant salt and iodine association was expected. However, an opponent result was obtained. The association is possibly due to confounding. Figure 6.1 showed how sodium and iodine are added into foods and contribute to the total salt and iodine intakes in the UK. Iodine is usually added to feedstuffs and subsequently appears in milk and dairy products, while some iodine rich processed foods, such as cheese and processed meat, are blended with high level of non-iodised salt separately during manufacturing. Therefore, when people eat these foods, both iodine and salt intakes increase. If the salt content in processed foods is reduced, the iodine availability could be affected minimally. This possibility was also supported by the inconsistent spatial patterns of dietary iodine intake and dietary sodium intake.

Milk and dairy products have been the major contributors to iodine intake in the UK for a long time. The energy intake adjusted effect of milk and dairy consumption was stronger than that of sodium intake in the model. Salt reduction is not likely to affect the iodine intake via milk and dairy consumption. Therefore, the UK experience can

be shared to other countries with similar dietary habit to use milk and dairy products as an effective alternative to salt for population-wide iodine supplementation.

Figure 6.1 *The addition of iodine (Γ) and sodium (Na^+) in foods in the UK*

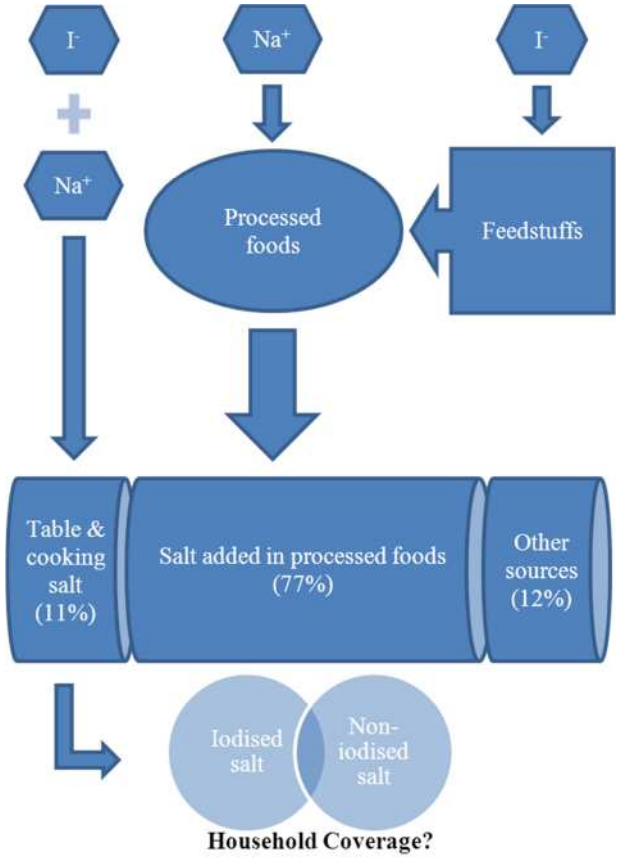


Note: Na^+: sodium; Γ: iodide; Percentages were quoted from James et al. (316).

As a case study of a high-income country that implements salt iodisation, the US analysis showed a significant association between urinary iodine concentration and dietary sodium intake. However, only discretionary salt is iodised on a voluntary basis, while the salt added in food manufacturing is usually not iodised. Thus, this association was possibly caused by the same reason that explained the salt and iodine association in the British analysis, i.e. confounding, possibly via energy intake and a greater use of table salt in those eating more food. If salt were reduced during food manufacturing, the iodine level would not be expected to change accordingly (see Figure 6.2).

Although not assessed in this study, the modification of table and cooking salt consumption might affect the iodine intake in the US population. However, the use of discretionary salt only constitutes approximately 11% of the total salt intake (31). Its contribution to the population iodine intake is also dependent on the household coverage of iodised salt and consumers' preference. Data showed that only half of the table and cooking salt on the market is iodised (328). Thus the supplementation of iodine via discretionary salt is proportionally reduced. As a consequence, the impact of salt reduction on iodine intake in the US could be greatly diluted. Due to the limitation of sodium and iodine measurements, more data are needed to investigate the association by using accurate salt and iodine intake measurements (e.g. 24-hour urine collection).

Figure 6.2 *The addition of iodine (I) and sodium (Na^+) in foods in the United States*

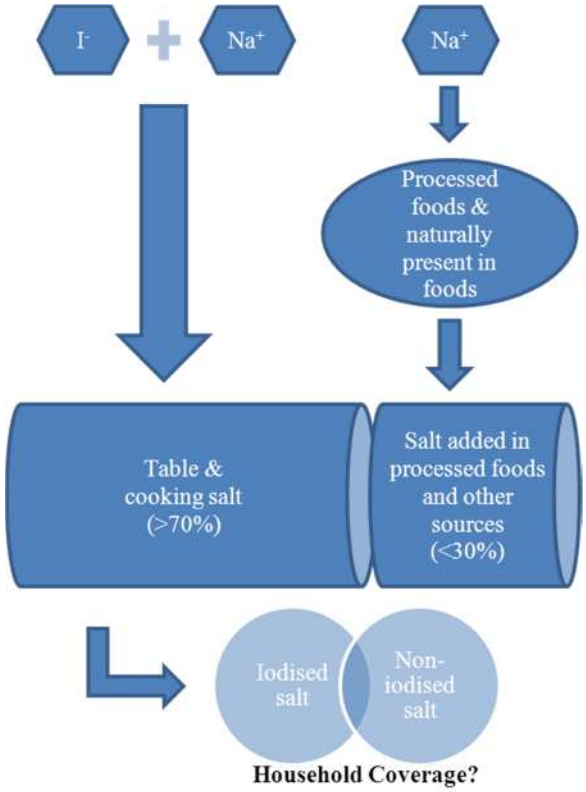


Note: Na^+: sodium; I: iodide; Percentages were quoted from Mattes and Donnelly (31).

In the Kumasi area of Ashanti, Ghana, a significant association between urinary iodine and urinary sodium excretions was found in 50% of participating villages (referred to as 'concordant'). Iodised discretionary salt is the major source of iodine intake in Ghana, as well as many other low- and middle-income countries (see Figure 6.3). The use of discretionary salt is usually dominant in people's daily salt intake (278). More than 70% of the total salt intake is added at the table or during cooking (30;33;367). The association estimated in the 'concordant' group indicated that a change of 1 g in salt intake per day would result in a parallel change of 10.6 µg in iodine intake per day. However, the analysis also revealed a non-significant association in the 'discordant' group. Population household coverage of iodised salt

is likely to be the major reason for inconsistent association between salt and iodine intake in these West African villages in the Kumasi area of Ashanti, Ghana. Half of the study villages did not appear to use iodised salt on a regular basis. Therefore, a population-wide salt reduction would cause less of a reduction in iodine intake that it would be expected from theoretical assumptions based on large population coverage.

Figure 6.3 *The addition of iodine (I⁻) and sodium (Na^+) in foods in Ghana*



Note: Na^+: sodium; I⁻: iodide; Percentages were estimated from the studies in Nigeria, Brazil and China (30;33;367).

6.4 Impact of Iodine Supplementation on Salt Reduction

Although lacking substantial evidence, universal salt iodisation programmes may inadvertently increase salt intake. It is conceivable that people could intentionally eat more iodised salt to improve iodine status. An Australian study showed that increasing purchase of iodised salt was associated with increased media coverage of

the risk of iodine deficiency (229). Nevertheless, no study has confirmed this tendency at population level. The present study was also not able to provide accurate estimation of the impact of iodine supplementation on salt reduction programme.

As explained previously, household coverage of iodised salt is an important determinant of the impact of salt reduction on the population iodine intake. The coverage also plays an important role in determining the impact of iodine supplementation on salt reduction. Logically, by increasing salt intake in areas with mixed coverage, people may end up with having higher salt intake but less than expected iodine intake.

Despite lack of evidence, policy-makers perhaps still need to be prepared for the potential risk of such behaviour, particularly in the disadvantaged and vulnerable populations who have limited iodine sources. Thus, simple and clear health promotion messages should be delivered to the public to increase effectively their awareness and knowledge of current salt reduction and salt iodisation policies. Support is needed in the disadvantaged and vulnerable populations to provide additional protection.

6.5 Socioeconomic Inequality

A finding, perhaps not unexpected, was that socioeconomic status (SES) was inconsistently associated with salt and iodine intakes in the present studies. People from more disadvantaged social groups in a population have increased mortality and morbidity (368;369). However, the association between SES and nutritional intakes is not entirely consistent. Although some studies suggested that high SES is

associated with lower salt intake (337;356;370), others were unable to produce similar results (336;371;372). For iodine, the evidence is more consistent. High SES is associated with better iodine status (measured by goitre rate and thyroid volume) (373) and higher cognitive function (374), while low SES has lower coverage and awareness of the use of adequately iodised salt (245;375). Although some studies reported the lack of such association (376;377), the use of residential and school based SES variables might be attributable to the results.

Aside from the mixed literature, there are several possible explanations for the inconsistent SES effect in this thesis. The methodological difference in the assessment of SES might have contributed to the disparity of the SES effect, particularly between the analyses in the US and Britain. The SES variables in the analyses were defined differently, as presented in Sections 5.2-5.4. In population studies, education, occupation and income are three major indicators of SES and capture different dimensions of people's social environment. Nonetheless, there is no consensus regarding the choice of the indicators. The definitions of these indicators may vary from country to country and from study to study. However, these indicators are not interchangeable (378) and hence may perform differently in relation to nutritional intakes (379).

Secondly, the definitions of the SES variables in both US and British analyses may be inaccurate so that the inconsistency might be partly caused by residual confounding. For example, in the British analysis, social class was defined by only two groups, and in the US analysis, family economic resources was represented by a binary variable (poverty income ratio). Therefore, the confounding effect of SES

could not be completely controlled for in the models due to the lack of detailed SES specification.

Thirdly, differences in the measurements of salt and iodine intake could be another possible explanation. In most population studies, dietary record, spot or timed urine samples and 24-hour urine collections are generally used to measure salt and iodine intakes. As discussed previously, alternative methods to 24-hour urine collection have various flaws in the measurements of nutritional intakes. The inaccuracy and reduced reliability may explain in part the inconsistent effect of SES.

In addition, the possible interference of diverse dietary patterns cannot be ruled out. Different patterns involve different salt and iodine consumption habits. High SES is not always linked with healthier nutritional intakes (380), particularly in countries that are in rapid social and economic transformation (381).

Therefore, the interpretation of the SES effect should be cautious. Comparison might be more meaningful in a longitudinal study design by monitoring the change within the same country.

Finally, geographical variations in nutritional patterns and in the distribution of SES may represent an additional caveat when comparing patterns of association between studies in different localities. In our analysis in Britain we were able to show for the first time that salt intake was higher in low SES once any geographical variation was taken into account (382).

6.6 Spatial Variation and Bayesian Geo-additive Models

The study demonstrated different spatial patterns of salt and iodine intakes in three analyses. In Ghana, a significant rural-urban difference was observed in iodine intake. In the US, the pattern of salt intake corresponded to the well-known stroke belt, while the iodine status had a different geographical distribution. Finally, in Britain, a north-south gradient of salt intake was identified.

The investigation of the spatial variation was conducted differently in the three data sets. In Ghana, the rural-urban difference was compared with adjustment for age and sex. In the US, the geographical variable was treated as a linear and fixed effect. Only in the British analysis was the spatial correlation taken into account. The major reason for the different investigation was the availability of detailed geographical information. The collection of corresponding boundary data is likely to be an important limitation. In this study, only the UK National Diet and Nutrition Survey publicly released the regional level information. However, lower geographical information is still desirable. The currently used regional classification may lead to over-smoothing, which consequently conceals the sub-regional variation. In particular, in the US analysis, I was unable to estimate the spatial correlation due to the small number of regions. Therefore, the estimated standard errors of the included risk factors may be over-estimated and important spatial variation of iodine and salt intakes at lower geographical levels may still be hidden.

Despite the restrictions in model applications, the estimated spatial patterns are potentially helpful for policy-makers to identify the high-risk areas that had high salt intake and low iodine intake and, accordingly, to make decisions on resource

allocations. The results indicated the usefulness of the Bayesian geo-additive models in support of the monitoring and evaluation of a health programme.

6.7 Policy Implications

The coordination of salt reduction and USI programmes can maximise the benefits that the health programmes bring to the general population and minimise the related healthcare cost and the impact of potential conflicts between the two programmes. Based on the findings of the present study, several suggestions are made to help coordinate the salt reduction and USI programmes.

1. Direct knowledge of up-to-date population salt intake level is needed for policy-makers to understand the true iodine availability to the general population. It also serves as an important basis for future policy adaptation and can inform the international organisations, salt and food industries and the public of the need for better understanding and close interaction during the coalition. Based on the present study, each country has its own population salt intake level and trends. Therefore, governments and health authorities are encouraged to measure the population salt intake before any possible policy adaptation.
2. The household coverage of iodised salt needs to be improved. Insufficient coverage jeopardises salt iodisation programmes and may widen the social and geographical health inequality. In addition, iodine content in salt may need to be increased to offset the impact of salt reduction on salt iodisation programmes. This adjustment, however, should be made according to each country's context of salt reduction and iodine status.

3. Alternative vehicles for iodine fortification could be considered where possible. The British analysis suggests the appropriateness of milk and dairy products as a complementary iodine vehicle to salt. Others, such as flour, can also be considered in some countries, since bread is consumed in many countries. Some suggestions are given in Table 6.1. These suggestions are mainly made upon dietary assumptions. That is, high-income populations have a high proportion of processed foods in the diet, while low- and middle-income populations are assumed to largely rely on iodised salt for iodine supplementation with a small proportion of processed foods in their diet. For countries in economic transition, diets evolve over time. The level of iodine-rich foods (e.g. milk and meat) consumption is usually approaching that of high-income countries (383). Therefore, milk, other animal products and bread can be used as alternative vehicles for iodine supplementation in these countries.

Table 6.1 *Possible alternative options for population iodine supplementation*

Country	Options
High-income countries	Milk and other animal products, irrigation or drinking water, flour*
Low- and middle-income countries	Iodised oil, irrigation or drinking water, flour*
Countries in economic transition	Milk and other animal products

**: Further research is needed for assessment of effect.*

4. Encouraging the food industry to use iodised salt in food manufacturing is recommended. In the Netherlands, using iodised salt in the making of bread and other bakery products is required. A 50% reduction of salt in processed foods in the Netherlands could result in an estimated reduction of iodine intake of 19-34 µg/day in children and 21-32 µg/day in adults (29). An extension of the use of

iodised salt in food manufacturing beyond bread and bakery products may offset any predicted fall in iodine status.

5. Joint population monitoring and surveillance of sodium and iodine through 24-hour urine collection should be encouraged. Twenty-four-hour urine collection is the most reliable and accurate measurement of salt and iodine intakes. Using other measurements may lead to over- or under-estimation of the nutritional intakes and their association. In addition, the current recommended reporting frequency for salt and iodine intakes is 3 and 5 years (262;263), respectively. However, a unified framework for jointly reporting these nutritional intakes is recommended. It would not only help policy-makers and other stakeholders of salt reduction and salt iodisation programmes to better understand the population nutritional status and improve the monitoring quality, but it would also reduce the programme cost, especially the human cost.

In addition to the above suggestions, it is important for policy-makers to reduce the social inequality in salt and iodine consumption. SES is a key determinant of health (368;369;384;385). Higher SES is associated with lower hypertension prevalence (386) and CVD risk (387). Reducing the dietary gap across SES levels can potentially lower the risks of CVD and IDD in the general population and may further alleviate the health burden and reduce healthcare cost. Further research is needed to interpret the various salt and iodine gradients over SES levels possibly from a wider scope by considering the impact of, for example, diet quality and dietary habit. Policy-makers are encouraged to provide support to those disadvantaged and vulnerable populations.

The present study also demonstrated the usefulness of the spatial analysis of the dietary intakes. In particular, the Bayesian geo-additive models can be used as an effective monitoring and evaluation tool in a coordinated programme. The models can improve the estimation by accounting for the spatial correlation that is usually overlooked in the analyses using classic regression models. Through the use of posterior maps, policy-makers are able to highlight the high risk areas so that appropriate health programme enforcement can be delivered to the targeted areas. The maps are also helpful to raise the public awareness and increase the understanding of the programme progress among the salt and food industries to enhance their collaboration with governments.

6.8 Future Work

With the analyses in three population data sets in this study, it might be useful to extend such investigation to other countries to produce country-specific estimations and provide suggestions to policy-makers and other stakeholders.

The spatial effect was not fully explored in this study due to the limited geographical information. Not all population surveys record the geographical information sufficiently, mostly on the grounds of confidentiality or study design. However, if the data become available, it would be meaningful to re-run the analyses for a better data interpretation.

Moreover, new data have been continuously collected in recent years, such as the UK 2010-11 National Diet and Nutrition Survey. These data provide up-to-date information of the population dietary intakes, which are essential to the monitoring

the progress of the health programmes. Therefore, updating the analysis using new data and extending the British analysis to minority ethnic groups are recommended if data were available. In addition, it would be of interest to compare the change of dietary intakes in the population over time and investigate if there is any temporal and spatial interaction in the general population.

Recently concerns on the iodine status of women of child-bearing age and children have been raised. They are the most vulnerable groups subjected to the risk of IDD. Their salt and iodine intakes, as well as salt reduction targets and iodine intake requirements, are different compared to those of other adults. Further analysis using the Bayesian geo-additive models in these vulnerable populations is desirable to provide policy-makers and other stakeholders with more population-specific information for the programme coalition.

6.9 Summary of Chapter 6

Chapter 6 began with a brief summary of the background and motivation of the thesis. Based on the results obtained from the three case studies, this chapter went on to discuss the following findings:

1) The assumed average salt intake (10 g/day) is no longer valid across the world. Three case studies indicated different population salt intake in different countries. The current assumption might cause an over- and under-estimation bias in projected amount of iodine supplementation.
2) The possible impact of salt intake modification on iodine status varies in different countries. Three estimated associations in Ghana, the US and

Britain were summarised separately according to the respective country settings. In high-income countries like the US, salt reduction is unlikely to have influential impact on population iodine status in part because of the high proportion of non-iodised salt consumption from processed foods, irrespective of the implementation of USI programme. In particular, the impact in the US is further weakened by the coverage of iodised salt and customer preference. In low- and middle-income countries relying on iodised salt for iodine supplementation like Ghana, salt reduction may have a stronger impact on population iodine status. However, a population-wide salt reduction would cause less of a reduction in iodine intake that it would be expected from theoretical assumptions based on large population coverage, mainly due to the varied coverage and use of iodised salt. The British analysis provided an example for countries with similar dietary habit that use milk and dairy products as an effective alternative to salt for population-wide iodine supplementation.

3) The effect of socioeconomic status (SES) on both salt and iodine intakes is inconclusive. Inconsistent effects were obtained in the case studies. The inconsistency, however, might be caused by the methodological differences in defining SES variables, residual confounding of the SES and spatial variables, different intake measurements, and diverse dietary patterns.
4) Diverse spatial patterns of the nutritional intakes were identified in the case studies. The present study still suffered from insufficient geographical data, particularly in the US analysis. Despite the data restrictions, Bayesian geo-additive models are useful to support policy-makers in the monitoring and evaluation of a health programme.

Several suggestions, particularly on salt iodisation policy, were subsequently made to help coordinate the salt reduction and USI programmes:

1) Direct knowledge of up-to-date population salt intake level is needed for policy-makers to understand the true iodine availability to the general population.
2) The household coverage of iodised salt needs to be improved.
3) Alternative vehicles for iodine fortification could be considered where possible.
4) Iodised salt could be used in food manufacturing to offset any predicted fall in iodine status.
5) Joint population monitoring and surveillance of sodium and iodine through 24-hour urine collection should be encouraged.
6) The Bayesian geo-additive models can be used as an effective monitoring and evaluation tool in a coordinated programme.

This chapter ended with a brief projection of future work in relation to the programme coordination, which will also be useful to policy-makers and other researchers.

Chapter 7 Conclusions

In conclusion, this study shows different population salt and iodine intakes across the world, suggesting the need to revise the assumption of average salt intake in adults in the salt iodisation policy. Moreover, this study suggests that iodine content in salt perhaps needs to be adjusted to optimise population salt and iodine intakes, particularly in countries that rely on discretionary salt for iodine supplementation. Attention needs to be paid and support needs to be given to the disadvantaged and vulnerable subpopulations to reduce health inequalities and maximise the benefit of salt reduction and salt iodisation policies to the population as a whole.

The current findings add substantially to our knowledge of the coordination of salt reduction and salt iodisation programmes. They can serve as a basis for policy adaptation and further research related to the programme coalition.

The Bayesian method used in this study could be applied to both programmes' monitoring and evaluation. The flexible estimations and resultant maps provide all stakeholders with a better understanding and may contribute to the progress of the prevention, management and control of hypertension, CVD and IDD.

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