Sodium – dietary intake, awareness and clinical outcomes in treated hypertensive patients

by

Adyani Md Redzuan
M.Pharm (Clinical Pharmacy)

Institute of Cardiovascular and Medical Sciences
University of Glasgow

A thesis submitted for the degree of Doctor of Philosophy in the School of Medicine, College of Medical, Veterinary and Life Sciences of the University of Glasgow

March 2012

Summary

High blood pressure (defined as > 140/90 mmHg) is the biggest contributor to heart disease-related death in the world. According to WHO World Heath Report 2002, globally 62% of cerebrovascular disease and 49% of ischemic heart disease were attributable to elevated blood pressure. A multifaceted strategy to reduce the risks associated with high BP includes healthy lifestyle changes, with reduction in dietary salt intake being the most cost-effective intervention.

Multiple lines of investigation including genetic, epidemiological and interventional studies have demonstrated consistently a positive relationship between salt intake, blood pressure increment and cardiovascular consequences. In addition, it has been documented that excessive salt intake can be attributed to other health complications such as asthma, osteoporosis, obesity and gastric cancer. On the contrary, reduction in salt intake has been shown to reduce blood pressure and improve health outcomes, although the evidence is not completely unequivocal. Despite this discrepancy, low-sodium diet is widely being recommended to all hypertensive patients in particular, as evidence against its efficacy in conjunction with optimum hypertensive treatment is well established.

The work contained in this thesis describes a study which was designated to assess sodium and its clinical outcomes among hypertensive patients. All patients attending follow-up care at Glasgow Blood Pressure Clinic (GBPC), Western Infirmary were invited to participate in the first part of the study by completing two separate questionnaires; first containing food frequency questionnaire (FFQ) to estimate salt intake and the other involves knowledge, attitude and perception (KAP) towards dietary salt consumption. In the second part of the study, data obtained from the FFQ for sodium estimation and spot urine analysis were merged to the corresponding dataset from GBPC database to study blood pressure outcomes, and finally the effects of serum sodium and mortality were investigated in an uncontrolled hypertensive cohort of GBPC.

To determine salt intake status among the patients, a modified FFQ was constructed and validated against corrected spot urine samples and 24-hour

urine collections in sub-samples. On average, FFQ provided higher estimates of sodium consumption compared to estimation based on corrected spot urine sodium. The FFQ demonstrated a strong sensitivity (80.2%), high negative predictive value (61.1%) and significant moderate strength of reproducibility (r = 0.619, k = 0.505). The application of this modified version of sodium FFQ in an out-patient clinic setting is acceptable provided that it is used in conjunction with other monitoring parameter such as serial spot urine measurements.

Assessment on current level of awareness and practise regarding healthy salt intake is important as this will encourage patients to take active control over their own BP management. In this study, patients' knowledge, awareness, attitude and perception (KAP) towards salt intake were examined based on KAP questionnaire. Overall, majority of patients recognized the harmful effects of too much salt in their diet although very few knew that salt can contribute to various health complications other than increased in blood pressure. Knowledge regarding salt intake limit and sodium to salt conversion need to be improved. Further education is suggested to improve patients' attitude regarding food-label utilisation and salt-sensory adaptation.

The association between daily sodium consumption and related clinical outcomes were studied in a cohort of treated hypertensive patients attending the specialist Glasgow Blood Pressure Clinic. Complete data for all covariates were available for 439 patients. Analysing longitudinal SBP and DBP change over time, subjects in the highest tertile of salt intake based on FFQ showed the greatest and sustained drop in SBP in contrast to those in the lowest tertile of salt intake. Whilst this is counter-intuitive, the association can be explained by the higher prevalence of cardiovascular disease and LVH in the highest tertile. It is likely that these individuals were subject of aggressive BP management because of their co-morbidities. This highlights the major drawback of observational studies which is confounding and this can be addressed through randomised control studies.

Serum sodium is homeostatically maintained within a narrow range through multiple mechanisms. Previous studies have shown that hyponatremia is a poor prognostic sign in hospitalised patients, patients with heart failure and liver

disease. In a large cohort of 13380 treated hypertensive patients followed up for 35 years, I have shown that low serum sodium is associated with increased mortality when adjusted for all the conventional covariates. However this relationship disappears when the additional electrolytes are included in the model (chloride, bicarbonate and potassium). This novel finding raises the prospect that other electrolytes may have a bigger impact on blood pressure and cardiovascular risk – not sodium in isolation.

In summary, FFQ can be a useful tool for assessing sodium compliance in hypertensive patients, provided that it's being used in conjunction with other robust dietary measure such as 24-hour urine collection. Health care professionals and public agencies need to contribute actively to improve patients overall knowledge, awareness, attitude and perception towards healthy salt intake. The observational nature of the hypertensive cohort in this study limits the generalisability of the findings to the population though it may be relevant to similar treated hypertensive cohorts. The role of other electrolytes on blood pressure control and cardiovascular outcomes deserve further investigations.

Table of Contents

List of Tables

List of Figures

Presentations of work undertaken in this thesis

Oral presentation

Adyani Md Redzuan, Beverley Beynon-Cobb, Gordon McInnes & Sandosh Padmanabhan. Assessment of dietary salt intake among patients with resistant hypertension. British Pharmacological Society Winter Meeting, London, UK, 2010.

Poster Presentation

A Md Redzuan, S Padmanabhan, G McInnes, B Beynon-Cobb. Knowledge and attitude to dietary sodium intake among hypertensive patients. Scottish Society for Experimental Medicine, Glasgow, UK, 2010.

Published Abstract

Adyani Md Redzuan, Beverley Beynon-Cobb, Gordon McInnes & Sandosh Padmanabhan. Assessment of dietary salt intake among patients with resistant hypertension. (2011), Proceedings of the BPS Clinical Pharmacology Section, 14–16 December 2010, Queen Elizabeth II Conference Centre, London. British Journal of Clinical Pharmacology, 71: 971–994. doi: 10.1111/j.1365-2125.2011.03930.x

Acknowledgement

First and foremost, I wish to express my sincere gratitude to my supervisor, Dr Sandosh Padmanabhan for providing the most valuable guidance throughout my PhD journey. He has kindly offered significant amount of patience, motivation, enthusiasm and generously shared his broad and immense knowledge. This thesis would not have been completed without his consistent effort and constructive comments.

I would also like to thank the Government of Malaysia and Universiti Kebangsaan Malaysia for granting me with the scholarship award and paid study-leave for the duration of the study. Thank you to my academic advisor, Prof. Dr Gordon McInnes for his support and valuable insights throughout this project.

I am truly grateful to all staffs and nurses at the Glasgow Blood Pressure Clinic, Western Infirmary, Glasgow for assisting me with the questionnaires collection and urine sampling. Special thanks to staffs in GCRC who were helping out with the pilot testing of the questionnaires, Miss Beverley Beynon-Cobb for brilliant dietetic consultation and Jeemon George for assisting with the data analysis.

To my dearest friends in the so called 'PhD support-group': Aiste Monkeviciute, Samantha Alvarez, Chiara Taurino and Amanda Sampson, thank you so much for your emotional support and encouragement. I've been told that PhD can be such a boring and lonely adventure, but you guys had proved that this was in fact untrue.

Last but not least, I am forever indebted to my beautiful families: my wonderful parents and sister (especially my mom, a superwoman who embraced through Scotland's toughest winter), my most understanding in-laws, my beloved and angelic husband, Hairul (who quit his job and taken over the challenging domestic role for the last 3 years) and my three precious gems – Afiqah, Harith and baby Ayiesha. I would not be standing where I am today without the loving environment and inseparable support and prayers from all of you, thank you.

Author's Declaration

I declare that the work presented in this thesis is, to the best of my knowledge and belief, original and my own work, unless specified otherwise in the text. All data collection and analysis were carried out by myself with the exception of spot urine and 24-hour urine assay for electrolyte measurements (Biochemistry Department, Gartnavel General Hospital) and Glasgow Blood Pressure Clinic Database extraction (Dr Sandosh Padmanabhan). Generalised estimation equations (GEE) in Chapter 5 Section 5.3.5 was performed by Panniyammakal Jeemon, and cox-regression analysis was done by me with the assistance of Dr Sandosh Padmanabhan and Panniyammakal Jeemon. Ethics approval for works related to Glasgow Blood Pressure Clinic Database has been granted by West of Scotland Research Ethics Services (No: 11/WS/0083). This work has not been submitted previously for a higher degree and was carried out under the supervision of Dr Sandosh Padmanabhan.

Adyani Md Redzuan
March 2012

List of Abbreviations, Acronyms & Symbols

ACE	Angiotensin Converting Enzyme
20-HETE	20-hydroxyeicosatetraenoic acid
24-h	24-hour
ACEI	Angiotensin Converting Enzyme Inhibitor
Ang II	Angiotensin II
ANOVA	Analysis of variance
ANP	Atrial natriuretic peptide
ARB	Angiotensin II Receptor Blocker
AT1	Angiotensin II receptor, type 1
AT2	Angiotensin II receptor, type 2
BMI	Body Mass Index
BP	Blood pressure
cm	Centimeters
CASH	Consensus Action on Salt and Health
CHF	Congestive Heart Failure
CI	Confidence interval
CKD	Chronic Kidney Disease
CoV	Coefficient of variation
COX-2	Cyclooxygenase-2
Cr	Creatinine
CV	Cardiovascular
CVA	Cerebrovascular Accidents
CVD	Cardiovascular Disease
DALY	Disability-adjusted life year
DASH	Dietary Approaches to Stop Hypertension Study
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EDV	End Diastolic Volume
EF	Ejection Fraction
eGFR	Estimated glomerular filtration rate
eNOS	Endothelial nitric oxide synthase
EPIC-Norfolk	Norfolk Cohort of the European Prospective Investigation into Cancer
ESV	End Systolic Volume
FAO	Food and Agriculture Organization
FFQ	Food Frequency Questionnaire
FSA	Food Standards Agency
g	Grams
GBPC	Glasgow Blood Pressure Clinic
GEE	Generalized Estimating Equations
GFR	Glomerular filtration rate
GOF	Goodness-of-fit
Hb	Haemoglobin
HCTZ	Hydrochlorothiazide
HR	Hazard ratio
IHD	Ischaemic Heart Disease
INTERMAP	International study of macro- and micro-nutrients and blood pressure
INTERSALT	International study of electrolyte excretion and blood pressure

kg	Kilograms
K	Potassium
KAP	Knowledge, awareness, attitude and perception
KM	Kaplan-Meir
LDL	Low-density lipoprotein
LV	Left ventricular
LVH	Left Ventricular Hypertrophy
mEq/L	Milliequivalents per litre
mEq/day	Milliequivalents per day
mg	Miligrams
mmHg	Milimeter of mercury
mmol	Millimoles
mmol/L	Millimoles per litre
MDRD	Modification of Diet in Renal Disease Study Group
Na	Sodium
Na/Cr ratio	Sodium to Creatinine ratio
Na/K ratio	Sodium to Potassium ratio
NaCl	Sodium chloride
NHANES	National Health and Nutrition Examination Surveys
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
OR	Odds Ratio
PABA	Para-aminobenzoic acid
PAS	Patient Administration System
PGE2	Prostaglandin E2
PH	Proportional Hazard
QALY	Quality-adjusted life year
r	Pearson correlation
RAAS	Renin-angiotensin-aldosterone system
RRs	Relative risks
SBP	Systolic Blood Pressure
SD	Standard deviation
SIMD	Scottish Index of Multiple Deprivation
SMU	Second morning voiding urine
SPSS	Statistical Package for the Social Sciences
STATA	Data Analysis and Statistical Software
TOHP	Trials of Hypertension Prevention
TONE	The Trial of Nonpharmacologic Interventions in the Elderly
UK	United Kingdom
UL	Tolerable upper intake levels
UN	United Nations
US$	United States Dollars
USA	United States of America
WASH	World Action on Salt and Health
WDR	Weighed dietary records
WHO	World Health Organization

1 Introduction

1.1 History of salt intake

Sodium, the cation of salt was first discovered in 1807 by the English chemist Sir Humphrey Davy through the electrolysis of sodium hydroxide. The symbol of the element is ‘Na’ originating from the Latin name for a common sodium compound known as natrium (from the Greek ‘nitron’ refers to a natural salt) (1;2). Commonly found in foods as sodium chloride, salt is the key ingredient in taste enhancement as well as food preservation. It can also be considered as a major food additive since it contributes to approximately 90% source of sodium in today’s modern diet (3).

Historical evolution proposed that human developed a hedonistic taste for salt and have been adding it to food since 10,000 years ago. Romans in the first century AD consumed large amounts of salt. Gaius Plinus Secundus (Pliny The Elder) estimated that an average of 25 g of salt was ingested daily from food as it was presented at the table. He also believed that salty foods made people slim, whereas sweet foods made them fat (4). Romans used salt as currency (“salary”) and considered it synonymous with health (“salus,” “salubritas”) and more necessary than gold (5) . The habit of adding salt to meals at the table was developed particularly during the Renaissance, when the salt cellar became both common usage and art object. For instance, a salt dispenser was presented to François I as a gift by Benvenuto Cellini in 1543 (Figure 1-1). It was suspected that the French king must have used it excessively because he died of apoplexy 4 years after receiving the present, at the age of 52 years (5).

In ancient medical science, salt is mentioned as an essential ingredient in some of the oldest medical scripts. The ancient Egyptian papyrus Smith, recommends salt for the treatment of an infected chest wound since it was believed that salt would dry out and disinfect the lesion. The healing methods of Hippocrates denote salt as a powerful expectorant ingredient; therefore mixture of water, salt and vinegar has been employed as emetic potion. Hippocrates also mentioned inhalation of steam from salt-water which was claimed to provide relief from respiratory symptoms. In addition, salt-based remedies have been widely prescribed in Greek medicine for various medical conditions such as eczema, psoriasis, mycosis, constipation, fever and even for accelerating childbirth (6).

Figure 1-1. Salt cellar made of gold, enamel, and ebony by Benvenuto Cellini (1500 to 1571)

This was presented in 1543 as a gift to Francois I, King of France (1494 to 1547). From (5).

Other than its therapeutic value, salt has also been extensively used in preservation. It was claimed that the Chinese were the first to discover that salt could be used to preserve foods (7). Preservation was achieved by soaking meat in brine, allowing salt to permeate food making bacterial life impossible. Salt then became the substance of high economic value as it was possible to preserve foods during winter and allowed the development of settled communities.

The economic value of salt is reflected by the fact that a lot of cities are named after salt: Salins in France, Salzburg in Austria, Salzkotten in Prussia, Saltdean in England and Saltcoats in Scotland. The ending of the word 'wich' also denotes that in the past salt had been produced in a saltern in this specific village. The Celtic syllable 'hal' (for salt) can be found in city names such as Hall/Tirol while the German word for salt which is 'salz' can also be found in village names such as Langensalza and Saltcotes (8). One of the oldest roads in Italy is the Via Salaria (Salt Route) over which Roman salt from Ostia was carried into other parts of Italy. In fact, cakes of salt were once deemed as highly valuable and had been used as money in Ethiopia and elsewhere in Africa and in Tibet (9).

During several millions years of evolution, human beings like all other mammals, consumed less than 0.25 g of salt per day (3). This was mainly the amount of salt naturally present in food to provide enough to regulate the amount of fluid in our bodies. Strong mechanisms for conserving salt within our bodies were then developed (7). These involved complex interactions of various systems in the human body with the kidney having a vital role.

Human kidneys are programmed to conserve sodium and excrete potassium. Prehistoric humans, who consumed a sodium-poor and potassium-rich diet, were well served by this mechanism. A typical Palaeolithic diet contains 30 mmol of sodium per day so that human physiology evolved over millions of years in a low-sodium, high potassium environment (Table 1-1). With such a diet, sodium excretion is almost negligible and potassium excretion is high, matching total potassium consumption. In contrast, today's modern diet consists of highly salted processed foods, which makes the salt-conserving mechanism potentially dangerous. Modern humans are ill-equipped to handle the current exposure of high sodium diet. As a result, the kidneys fail to adapt with this new diet revolution leading to an excess of sodium particularly in hypertensive patients (10).

Table 1-1. Estimated diet of late Palaeolithic man compared with that of contemporary Americans.

Nutrient	Late Paleolithic diet (assuming 35% meat)	Current American diet
Protein (% of energy)	30	12
Carbohydrate (% of energy)	45-50	46
Fat (% of energy)	20-25	42
Polyunsaturated-saturated fat ratio	1.41	0.44
Fiber (g/d)	86	10 -20
Sodium (mg)	604	3400
Potassium (mg)	6970	2400
Potassium-sodium ratio	12 : 1	0.7 : 1
Calcium (mg)	1520	740

The essential element of salt as a preservative was no longer relevant with the invention of the refrigerator and the deep freezer. Cooling techniques have made it possible to gradually reduce the addition of salt to foods. This new means of preservation method started in the United States around 1925 and became popular in most European countries only after 1950 (11). Along with a decrease in consumption of potatoes, bread and cereals, salt intake and sales had been declining particularly as observed in Belgium, Switzerland and France. Nevertheless, with recent widespread inexpensive commercial access to salt, its intake is now increasing again. In developed countries, salt intake is usually between 9 to 12 g/day, with many Asian countries having mean intakes over 12 g/day (12). These values are far greater than the current recommended maximum daily intake of salt. The current World Health Organization recommendations for adults are to reduce salt intake to 5 g/day or less, and the UK and US recommendations are 6 g/day or less (13).

1.2 Difference between salt and sodium

The terms salt and sodium are often used synonymously, however, on a weight basis, salt comprises 40% of sodium and 60% chloride. The conversion of different units for sodium and salt is summarized in Table 1-2.

Table 1-2. Equivalent amounts of sodium (in mg and mmol) and salt.

Sodium (mg)	Sodium (mmol)	Salt (g)
1200	51	3
2000	87	5
2400	104	6
4000	174	10

From (14).

1.3 Salt consumption and its sources

In developed countries up to 80% of salt comes from processed foods. Conversely, in Asia and other developing nations, most salt is added during cooking or contained in sauces and seasoning. Sodium is naturally present in small quantities in unprocessed foods, but is also commonly added to foods either during processing, cooking or at the table. The main purpose for addition of salt in food processing are for flavour, texture, preservation and to promote thirst, hence boost up beverages sales.

In industrialized countries, most of the sodium ingested is added (as sodium chloride) during food production and foods eaten away from home. He and MacGregor (3) estimated that approximately 15% of the salt consumed was added either at the table or during cooking , 5% was naturally present in the foods, and the majority 80%, was added by the food industry in processed, canteen, restaurant, and takeaway foods. Table 1-3 lists the differences in salt content between processed and unprocessed varieties for selected common

foods; tinned salmon, for example, contains five times the sodium content of fresh steamed salmon, while smoked salmon contains 16 times as much.

According to UK National Food Survey data collected in 2000 (15), cereal products (including bread, other baked goods and breakfast cereals) accounted for the greatest proportion (38%) of household sodium intake in United Kingdom. The second largest source (21%) was meat products (including processed meats such as ham, bacon, etc.) followed by soups, pickles, sauces, and table spread.

Similar data are available for the USA (16). Bread, ready-to-eat cereal and cakes, dairy products, salad dressings, potato chips, and processed meats are the main contributors to dietary salt intake. With regard to restaurant foods, various dishes on their own contain over 2.3 g (100 mmol) of sodium, which is equivalent to the recommended daily Tolerable Upper Intake Level (UL) for the USA (17).

A different picture with regard to dietary sources of sodium is apparent in some Asian countries. In China and Japan, a large proportion of sodium in the diet comes from sodium added in the cooking and from various sauces (17). Looking at the main sources of sodium in the diets of INTERMAP (18) participants from China and Japan, again the predominant source in China was salt added during cooking (78%). In Japan, the main sources were soy sauce, fish and other seafood, soups and vegetables (66% in total) with a further 10% being contributed by salt added during cooking. Some foods commonly consumed in Malaysia are also very high in sodium; for example a bowl of Mee curry and a bowl of Mee soup available from ‘Hawker’ markets contain about 2.5 g (109 mmol) and 1.7 g (74 mmol) sodium respectively. Additionally, in many sub-Saharan African countries, particularly in less urbanized settings, the main source of dietary sodium is predominantly from salt added to food for preservation, for taste and added in the cooking process (19).

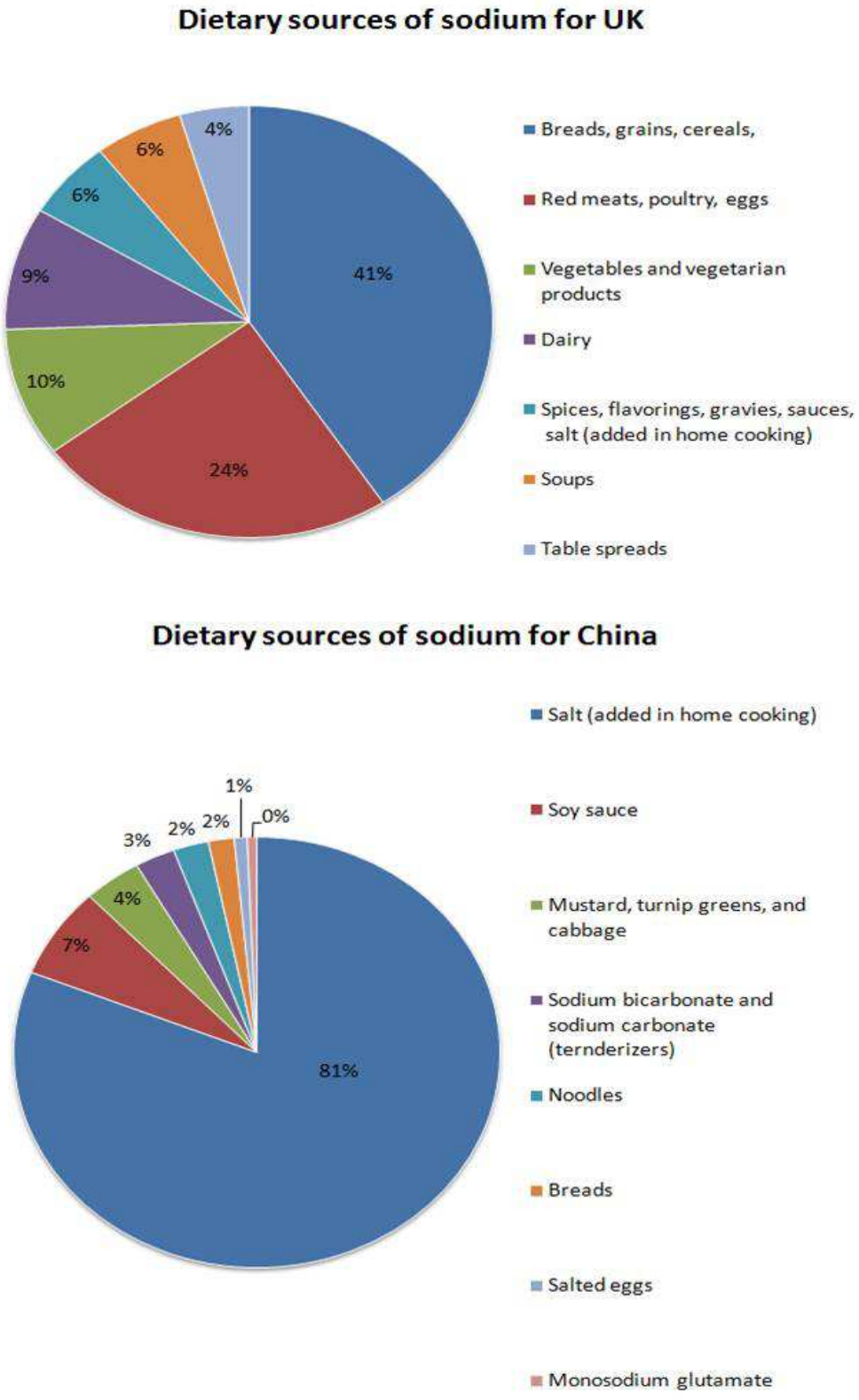
Table 1-3. Comparison of sodium content between processed and unprocessed foods.

Food item	Description	Sodium content (mmol/100 g)
Beef	Topside, roast, lean and fat	2.1
	Corned beef, canned	41.3
Bran	Bran, wheat	1.2
	Bran flakes	43.5
Cheese	Hard cheese, average	27.0
	Processed cheese	57.4
Chick peas	Dried, boiled in unsalted water	0.2
	Canned, re-heated, drained	9.6
Crab	Boiled	16.1
	Canned	23.6
Cod	Cod, in batter, fried in blended oil	4.3
	Fish fingers, fried in blended oil	15.2
New potatoes	Raw, boiled in unsalted water	0.4
	Canned, re-heated, drained	10.9
Peanuts	Plain	0.1
	Dry roasted	34.3
	Roasted and salted	17.4
Peas	Raw, boiled in unsalted water	Trace
	Canned, re-heated, drained	10.9
Potato chips (fries)	Homemade, fried in blended oil	0.5
	Oven chips, frozen, baked	2.3
Salmon	Raw, steamed	4.8
	Canned	24.8
	Smoked	81.7
Sweet corn	On-the-cob, whole, boiled in unsalted water	Trace
	Kernels, canned, re-heated, drained	11.7
Tuna	Raw	2.0
	Canned in oil, drained	12.6
	Canned in brine, drained	13.9

Sodium: 1 mmol = 23 mg.

From (12).

Figure 1-2. Comparison in sodium sources between United Kingdom and China based on INTERMAP data.



1.4 Physiology of sodium

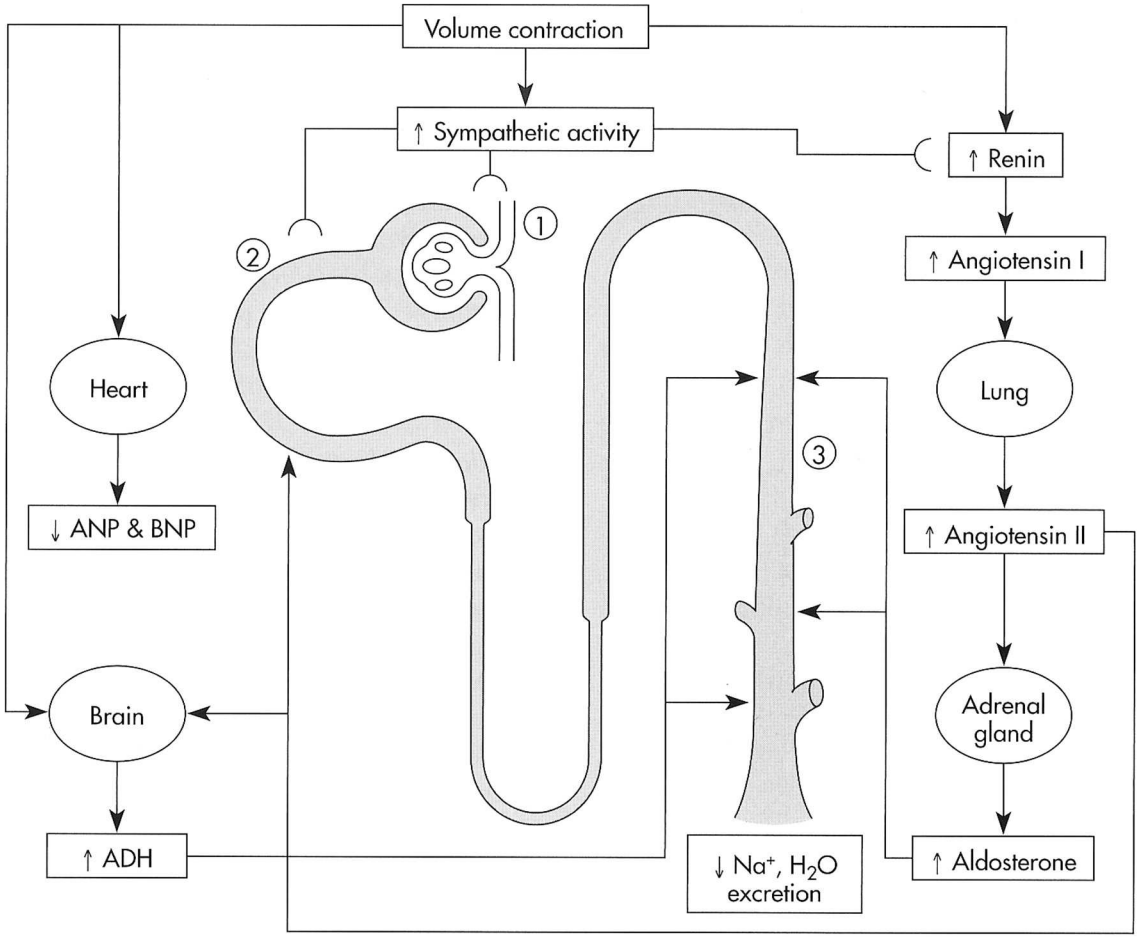
The physiological need for sodium is around 180–230 mg/day (20). A proper balance of sodium levels in every part of human body is of vital importance; the osmotic pressure of the extracellular fluids of our body is dictated for 90% by sodium-ions and their counter-ions, mainly chloride. A tight regulation of the sodium levels in our blood plasma and interstitial fluids is crucial for basic physiological functions of virtually all cells within a human body since a lot of transport processes are dependent on it. Slight deviations from these normal parameters can affect the electrical activity of muscle and nerve cells, renal function, capillary exchange, cardiac output, and therefore impact blood pressure in multiple ways (21).

Neuronal and hormonal systems have therefore evolved to control salt intake behaviour and sodium excretion mechanisms. The hedonic value of salty taste and its regulation are an example of the neuronal, while aldosterone and the renin/angiotensin system are the most important elements of the hormonal mechanisms (Figure 1-3). Hence, it provides the reason why we generally prefer salt solutions resembling the extracellular levels in salt concentration, and that thirst and human appetite for salt are apparently modulated by physiological needs (22). A sodium-deprived state leads to a decreased salty taste response in human beings and a variety of animals (23). It is thought that this drives the behaviour towards preference of salt-containing food on one hand and protects us from ingestion of toxic sodium levels on the other hand. This appears to be controlled by mineralocorticoids (i.e. aldosterone) (24). In addition to this hormonal regulation there is evidence for an additional central nervous regulation (25). Salt craving, a common behaviour of many animals in need of sodium, has only incidentally been observed in humans suffering from extreme sodium loss (26).

While these control mechanisms might have evolved to handle scarce sodium availability in our ancient diet, they are apparently insufficient to limit our salt intake to the physiological needs in today’s modern Western diets. In many industrialized countries sodium intake is between 3600–4800 mg/day (20) indicating that most people consume excess dietary salt than the amount that is required to remain in good physical health (27). Therefore in general the amount

of salt eaten in western countries is not driven by a physiological need, but rather by taste preference.

Figure 1-3. Summary of the renin-angiotensin-aldosterone system



Renin is directly secreted into circulation in response to volume contraction (decreased in renal perfusion). Renin cleaves angiotensinogen to angiotensin I which is converted by angiotensin-converting enzyme in the lungs to angiotensin II. Angiotensin II triggers various cascades leading to: decreased glomerular filtration rate (1), increased NaCl and water reabsorption by the proximal tubule and loop of Henle (2), and increased NaCl and water reabsorption by the distal tubule and collecting duct by aldosterone (3). ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; ADH, antidiuretic hormone. From (28).

1.5 Sodium and blood pressure

There are a lot of observational data which support a strong positive association between sodium intake and blood pressure within and between populations. Epidemiologic studies have shown that dietary sodium intake is directly related to cardiovascular mortality and to the increase in blood pressure with aging. Long term studies regarding salt intake and blood pressure have demonstrated

its adverse prognostic outcome in both hypertensive and normotensive populations.

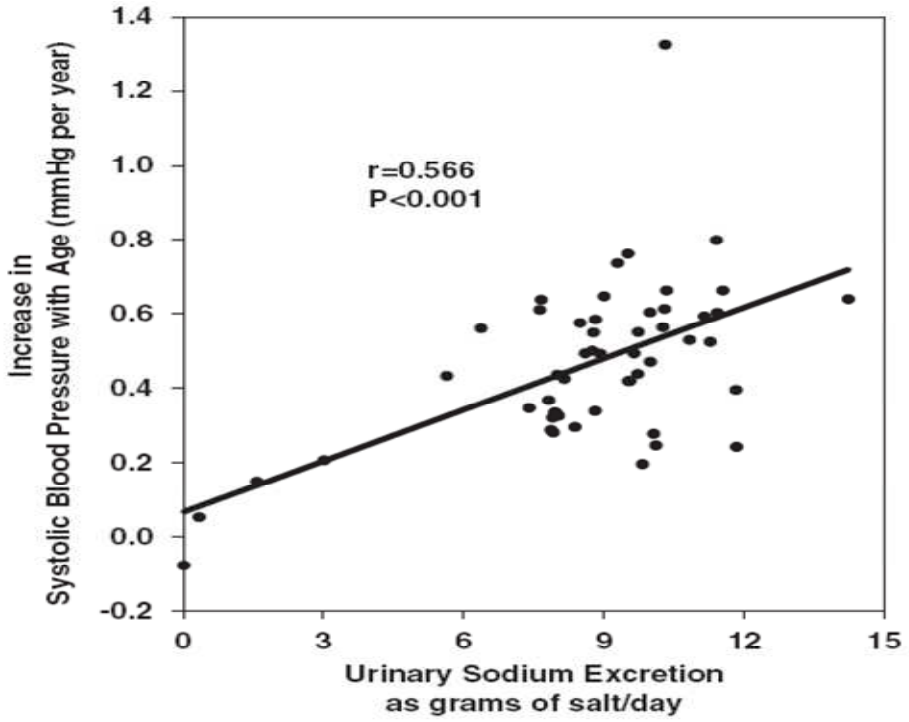
1.5.1 Epidemiological studies

Prehistoric populations consuming a low-sodium diet, such as the Alaskan Eskimo or the Yanomamo Indians from the Amazon, have an almost negligible prevalence of hypertension and their blood pressure does not rise with age compared to all westernized, industrialized populations. The Yanomamo Indians, who excrete ≈ 1 mmol sodium per day, have an average blood pressure of 96/61 mmHg.

The absence of hypertension may be associated with other lifestyle variance, but primitive people living under similar environments who consume large quantities of sodium develop hypertension. Page et al (29) noted that among the prehistoric men of the Qash'qai tribe of Southern Iran, who ingested an average of 180 mmol of sodium per day, 18% were hypertensive.

The INTERSALT study was one of the major global studies on sodium intake using standardized method for measuring blood pressure (BP) and 24-hour urinary sodium (30). It involved 10 079 individuals from 52 centres around the world, with the aim to study communities with a wide range of salt intake from 0.5 to 25 g/day. Among all the communities recruited into the study, only four had a low salt intake (3 g per day or less) whereas the majority lay between 6 and 12 g/day. None had the high salt intake as initially anticipated. The results of the study revealed a significant positive association between 24-hour urinary sodium and BP. Reducing dietary salt intake by 5.8 g was associated with a 3.1 mmHg decrease in systolic blood pressure (31). There was also a highly significant positive relationship between dietary salt intake and the increase in blood pressure with age. The investigators estimated that an increase of 6 g/day in salt intake over 30 years would lead to an increase in systolic blood pressure by 9 mmHg (30).

Figure 1-4. Relationship between salt intake and the slope of increase in systolic blood pressure with age in 52 centres in the INTERSALT study.



From (30).

More recent studies have confirmed these findings and provided more supportive evidence on the important role of dietary salt in determining the levels of blood pressure in the population. The INTERMAP study (International Study of macro and micro-nutrients and blood pressure) showed that a lower dietary salt intake and smaller sodium/potassium ratio resulted in lower population blood pressure (32). This cross-sectional epidemiologic study recruited 4680 men and women aged 40-59 years from 17 diverse population samples from China, Japan, UK and USA with the main objective to confirm influences of multiple nutrients on systolic and diastolic BP. All participants were assessed regarding blood pressure measurement (8 readings), individual intake of 76 nutrients from four 24-hour dietary recalls/person accompanied by 2 sets of 24-hour urine collection. The results revealed a highly significant positive association of sodium with both systolic and diastolic BP measurements. The estimates of association of sodium with systolic BP ranged from 0.8 to 3.0 mmHg/100 mmol, while diastolic BP corresponding estimates were 0.2 to 1.4 mmHg/100 mmol sodium.

Another large study, EPIC-Norfolk (the Norfolk Cohort of the European Prospective Investigation into Cancer) also confirmed sodium to be an important determinant of population blood pressure level (33). This prospective study

included ≈25000 men and women aged 45–79 years, unselectively recruited from general practice age-sex registers in Norfolk, United Kingdom. Sodium intake was assessed based on casual urine specimens (all samples) and in a subset of patients, 7 days food diary and 24-hour urine collection were also requested. The results showed that systolic and diastolic blood pressure increased as the ratio of urinary sodium to creatinine increased, with differences of 7.2 mmHg for systolic blood pressure and 3.0 mmHg for diastolic blood pressure (P<0.0001) between the top and bottom quintiles. This trend was independent of age, body mass index, urinary potassium:creatinine, and smoking and was consistent by sex and history of hypertension.

1.5.2 Migration studies

Several studies have shown that migration from isolated low-salt societies to an urban environment with higher dietary salt intake was associated with an increase in blood pressure. In Kenya, a well-controlled migration study of a rural tribe (Luo migrants) revealed that upon migration to Nairobi, their sodium excretion increased from ≈ 60 to 110 mmol/day , potassium intake reduced, and their blood pressure rose significantly over a few months, compared with those in a similar control group who remained in the rural environment (34). After 2 years of followed-up, mean systolic/diastolic BP of the migrants increased from 117/53 mmHg to 126/66 mmHg in men, and 112/61 mmHg to 119/60 in women. In China, Yi farmers living in remote villages were compared against Yi migrants in the country (35). The Yi migrants consumed more sodium, less potassium and had a higher urinary sodium/potassium ratio. Urinary sodium excretion was found to be greater in Yi migrants than in Yi farmers (159.4 mmol/24 hour vs. 73.9 mmol/24 hour, respectively), reflecting lifestyle changes including dietary alterations, resulting in significantly higher blood pressure among Yi migrants. Results from the multiple regression analysis revealed that an increase in sodium intake of 100 mmol/day corresponded to an increase of 2.3 mmHg systolic blood pressure and 1.8 mmHg diastolic pressure. Notably, there were very little increments of blood pressure with age among Yi farmers, whereas it increased with age in Yi migrants.

1.5.3 Population-based intervention studies

There are a few studies which showed a reduction in population blood pressure following a successful restriction of dietary salt intake in a population. Forte et al (36) conducted an intervention study in two similar villages in Portugal. An intensive health education concerning salt reduction was introduced, emphasizing on avoidance of foods that had previously been identified as the major sources of salt in the intervention village. A very substantial 50% reduction in salt intake was achieved in the intervention community, resulted in a difference of 13/6 mmHg in systolic /diastolic blood pressure after 2 years. A recent randomized community-based intervention trial in 2 rural villages in north-eastern Japan demonstrated that dietary counselling for one year effectively reduced salt intake by 2.3 g/day as measured by 24-hour urinary sodium (37). This reduction was accompanied with a decrease of 3.1 mmHg in systolic blood pressure.

Similar studies from developing countries are few; however, in one of the first salt reduction trials in Africa, a community-based cluster randomized trial in Ghana involving 1013 participants discovered that at 6 months, the intervention group achieved a 2.5/3.9 mmHg reduction in systolic/diastolic blood pressure (38). A recent community based sodium reduction trial in Pakistan revealed a significant 6 mmHg reduction in systolic measurement among participants with high normal blood pressure (39).

1.5.4 Intervention studies

These observational findings were further supported by various trials of sodium reduction in normotensive and hypertensive individuals. Table 1-4 provides a summary of results from meta-analyses regarding sodium restriction and blood pressure reduction. An overview of 40 trials of sodium reduction confirmed a direct relation with BP and found an average decrease in systolic/diastolic pressures of 5.2/3.7mmHg and 1.3/1.1mmHg among hypertensive and normotensives subjects, respectively (40). A Cochrane review then restricted the analysis to studies lasting more than 4 weeks with a modest reduction in urinary sodium of at least 40 mmol. The results revealed blood pressure reductions of 5.0/2.7mmHg (systolic/diastolic) for hypertensives and 2.0/1.0 mmHg among

normotensive participants (41). A dose–response relation was established, with a fall in BP of 7.1/3.9mmHg among hypertensive and 3.6/1.7mmHg among normotensive participants for every 100 mmol reduction in urinary sodium. In another meta-analyses, Hooper et. al. (42) restricted trials which lasted 6 months or longer, including a few trials up to 5 years. In these relatively few trials, the degree of sustained sodium reduction was less, hence leading to a non-significant degree of blood pressure reduction.

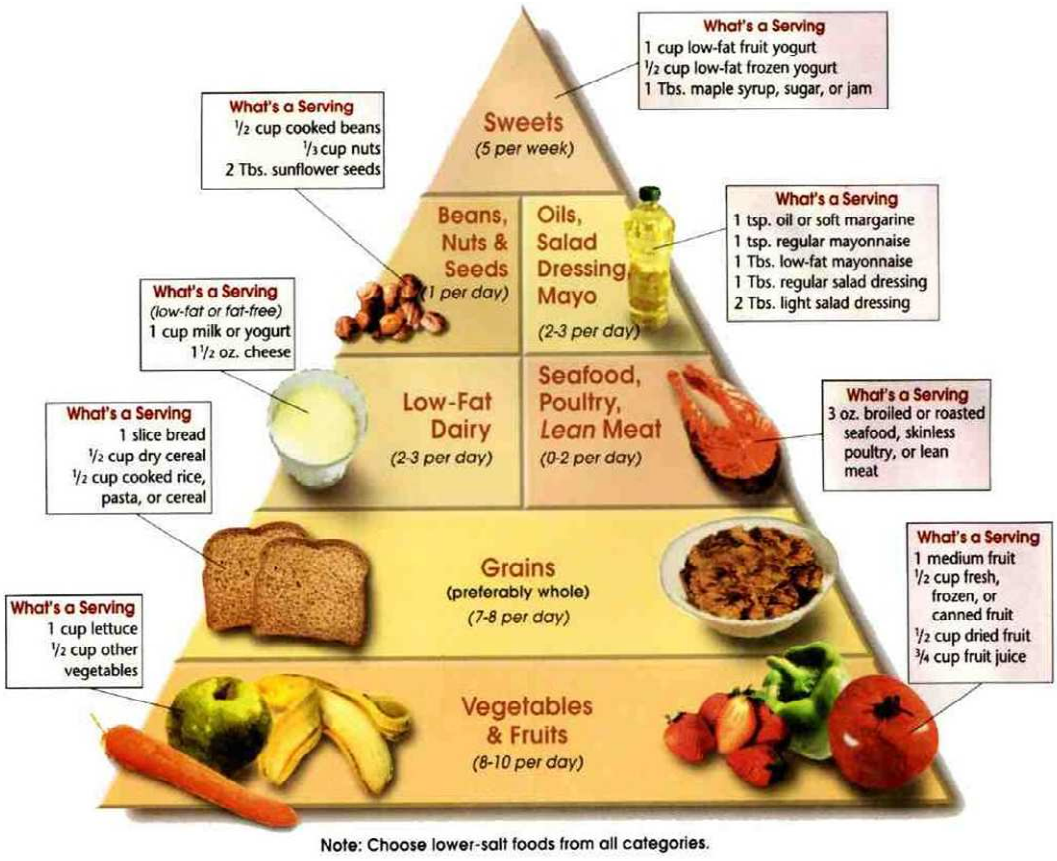
Table 1-4. Meta-analyses of trials of dietary sodium reduction

Reference	No. of trials	Duration	Reduction in 24-hour sodium excretion	Reduction in blood pressure	
				Normotensive SBP/DBP	Hypertensive SBP/DBP
Geleijnse et al., 2003	40	>2 weeks	-77 mmol	-1.3/-1.1	-5.2/-3.7
He & MacGregor, 2003	26	>4 weeks	-78 mmol	-2.0/-1.0	-5.0/-2.7
Hooper et al., 2002	7	6-12 months	-49 mmol	-2.5/-1.2	
	4	13-60 months	-35 mmol	-1.1/-0.6	

SBP = systolic blood pressure, DBP = diastolic

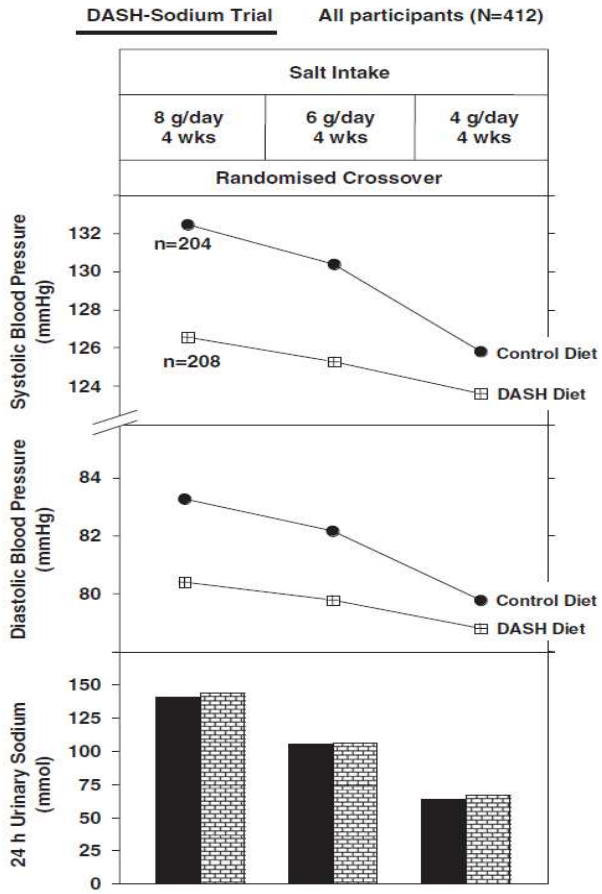
The Dietary Approaches to Stop Hypertension (DASH)-Sodium study provides the most robust evidence of the short term effects on BP of a well maintained low-sodium diet (43). Three different levels of salt intake (8, 6 and 4 g/day) were studied based on two different diets; the normal American diet and the DASH diet, which is rich in fruits, vegetables, and low-fat dairy products (Figure 1-5).

Figure 1-5. Food pyramid representing various food groups and portion sizes included in DASH diet.



Both type of diet and sodium reduction were found to be effective in lowering BP (Figure 1-6). Comparing the high with low sodium groups, the differences in systolic BP were 6.7mmHg among those on the control diet and 3.0mmHg among those on the DASH diet, with stronger effects among hypertensive participants. The corresponding differences in diastolic BP were 3.5 and 1.6 mmHg respectively. Subsequent analyses found that the effect of sodium reduction remained among all subgroups defined by demographic characteristics and baseline measures including age, body mass index (BMI) and urinary sodium excretion (44). Remarkably, sodium reduction was also reported to reduce BP in non-hypertensive on both diets though to a lesser degree compared to the hypertensive subjects.

Figure 1-6. Changes in blood pressure and 24-h urinary sodium excretion with the reduction in salt intake in all participants on the normal American diet vs. DASH diet.



From (45).

There were four long term, well controlled preventive trials which examined the effects of combined lifestyle modifications including sodium reduction in lowering blood pressure. These trials involved subjects with high-normal blood pressure and lasted for at least 1 year of duration. In the Hypertension Prevention Trial which randomized healthy men and women aged 25 to 49 years to one of four lifestyle interventions, the sodium reduction group achieved a 13% decrease in sodium excretion at 6 months and a mean decrease of 1.7mmHg in systolic BP (46;46;47;47). Results, however, were not sustained at 3 years.

Evidence from outcomes trials revealed that a reduction in salt intake results in a decrease in cardiovascular disease. A follow-up study of individuals who took part in two large randomized salt reduction trials, Trial of hypertension prevention (TOHP) I (48)and II (49), has shown a significant effect of dietary salt

reduction in relation to cardiovascular disease. More than 3000 participants with an average baseline blood pressure of 127/85 mmHg were randomized to a reduced-salt group or to a control group.

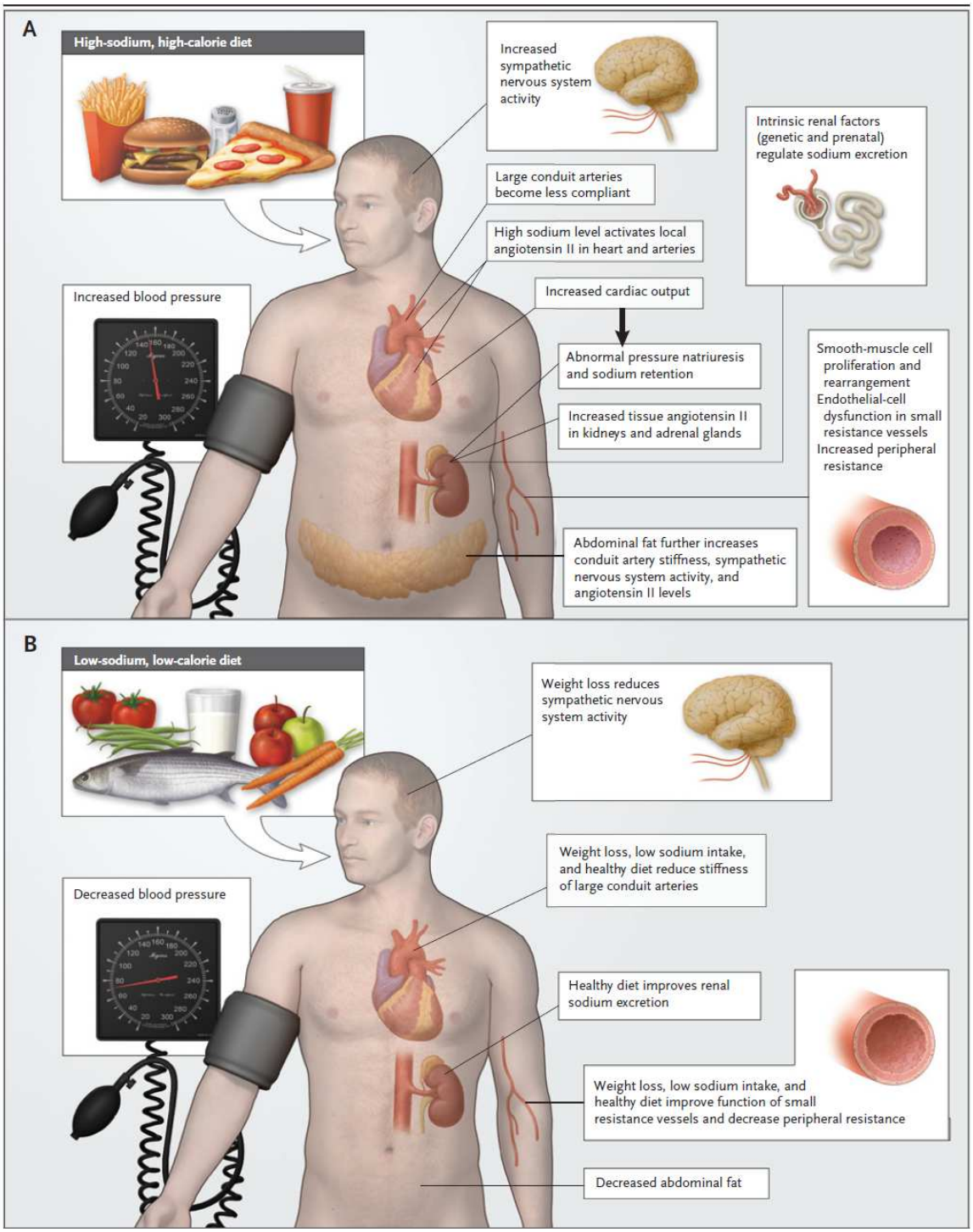
In the Trials of Hypertension Prevention (TOHP) Phase I, those randomized to the sodium reduction group had lowered their average sodium excretion by 44 mmol/day resulting in an average decrease of 1.7/0.9mmHg in systolic/diastolic BP at 18 months. Subsequently in TOHP Phase II, at 36 months the average reduction in sodium was 40 mmol/day, and a significant reduction of 1.2mmHg in systolic BP was maintained, along with an 18% reduction in the incidence of hypertension. No further advice was offered to the participants after the trials were completed. A follow-study at 10-15 years post trial revealed that subjects who were originally allocated to the reduced-salt group had a 25% reduction in the risk of developing cardiovascular events after adjusting for confounding factors.

The Trial of Nonpharmacologic Interventions in the Elderly (TONE) (50) recruited 975 men and women aged 60 to 80 years whose hypertension was controlled with single antihypertensive drug. Subjects were randomized to weight loss, sodium reduction, both interventions or usual care with attempted withdrawal from medication. Over the following 30 months, the proportion of patients who remained normotensive and drug-free was only 16% in the usual-care group, more than 35% in those on one of the two interventions, and 43.6% in those who received both interventions. The primary endpoint of hypertension or cardiovascular event was also reduced by 32% in the sodium reduction group.

1.6 Dietary sodium restriction as adjunctive therapy of hypertension

Idiopathic, or essential hypertension accounts for more than 95% of cases and appears to be caused by a complex interaction between genetic predisposition and environmental factors (51). Its pathophysiology is complex, with much remaining to be discovered (Figure 1-7). Lifestyle changes including dietary modification are recommended by current guidelines as initial treatment for

Figure 1-7. Mechanisms linked to increases in blood pressure and the therapeutic effects of healthy dietary patterns, sodium reduction, and weight loss.



From (52).

most hypertensive patients. The triads of dietary treatment of hypertension – a healthy dietary pattern (by consuming more fresh fruits and vegetables), reduced sodium intake, and reduced body fat – influence the pathophysiology of hypertension at many of its points of control.

Dietary sodium restriction is widely accepted by both the scientific community and the general public as a mode of primary prevention for hypertension and an effective treatment of established hypertension. For example, patients with prehypertension (SBP between 120 and 139 mmHg or DBP between 80 and 89 mmHg) should adopt healthy lifestyle changes (including sodium reduction), given the benefit of dietary therapy at these BP levels (53). Even though drug therapy plays an essential role in treating hypertension, they should not be used as a substitute against dietary management. Rather, the two forms of treatment should be considered complementary (52).

In a meta-analysis of clinical trials Cutler et al (54) reported a dose-response relationship between sodium reduction and BP, such that for every 100 mmol/day decrease in sodium, BP decreased 5.8/2.5 mmHg in hypertensive patients and 2.3/1.4 mmHg in those without hypertension. In the DASH-sodium trial, as discussed in great details in Section 1.5.4, it has been shown that reducing dietary sodium intake resulted in a significant incremental reduction in both systolic and diastolic blood pressure in both groups assigned to either DASH diet or control diet. It is also interesting to note that sodium reduction was also reported to reduce BP in non-hypertensive on both diets though to a lesser degree compared to the hypertensive subjects.

Patients with resistant hypertension in particular might benefit the most from dietary sodium restriction. This is supported by Pimenta et. al. (55) in a study looking at the impact of salt reduction in patients treated for resistant hypertension. The investigators recruited consecutive patients with resistant hypertension where twelve patients with systolic blood pressure (SBP) greater than 140 mmHg or diastolic blood pressure (DBP) greater than 90mmHg despite the use of at least three antihypertensive medications, completed the study. At enrolment, they were receiving an average of 3.4 medications, including at least 25mg of hydrochlorothiazide (HCTZ) (or equivalent diuretic), with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker

(ARB) medication. The average manually recorded office BP was 145.8±10.8 /83.9±11.2 mmHg at baseline. Patients were randomized to 1-week treatment periods of a low Na (50mmol/day) diet formulated and provided by a research kitchen, or the same diet with the addition of 6 g/day NaCl tablets (250mmol/day of Na). Compliance to the diets was assessed using 24 hour urinary Na measurements. All medications were continued throughout the study.

On the high-salt diet, office blood pressure averaged 145.6±15.1/84.0±12.1 mmHg, whereas on the low-salt diet, it was 122.8±14.0/74.9±12.5mmHg, for an average reduction in blood pressure of 22.7/9.1. Consistent results were seen across daytime, night-time, and average ambulatory blood pressure values. The authors claimed that this study was the first to examine the impact of aggressive salt restriction in patients identified as resistant to medication, and highlighted the effectiveness of aggressive salt restriction in these patients' population.

1.7 Factors influencing salt intake

Individual salt intake varies depending on various factors such as inheritance, behaviour and environment (56).

1.7.1 Genetics

Genetic endowment plays an important role in determining salt intake. It is generally accepted that several genes may contribute to the blood pressure levels which reflects a complex network of gene-gene and gene-environment interactions. However, in some individuals defects in a single gene cause marked abnormalities of blood pressure regulation. Genetic studies of these rare Mendelian forms of high and low blood pressure have shown an underlying common pathway: the kidney's ability to excrete or retain sodium (57). The monogenic causes of high blood pressure reduce the kidney's ability to excrete sodium and cause high blood pressure when salt is consumed. The monogenic causes of low blood pressure result in the kidney being unable to retain sodium, thereby causing low blood pressure. In Gitelman's syndrome for example, loss of function mutations of the gene (*SLC12A3* gene) encoding sodium-chloride cotransport results in a defect in the ability to conserve sodium (58). Those whom are affected, either heterozygotes or homozygotes, will have a higher

than normal dietary salt intake without being aware of their heightened salt appetite. Despite this, blood pressure remains low-normal in these individuals.

1.7.2 Environment

Early exposure to sodium intake may have a lasting impact. This is supported in a recent study by Stein et. al. (59) who investigated the relationship between early sodium exposure and the development of salty taste acceptance. In the study, 61 infants were tested at 2 and 6 months old to assess their response to 0.17 and 0.34 mol NaCl/L in water. Acceptance, calculated as solution intake relative to water, was examined as a function of exposure to starchy table food—a significant source of sodium. As a control, similar comparisons were based on exposure to fruit table food. A subset of 26 subjects returned at 36–48 months for assessment of salty taste hedonics and preference. Results from the study showed that dietary experience was related to salt acceptance, with only those infants previously exposed to starchy table foods preferring the salty solutions at 6 months old ($P = 0.007$). Fruit exposure was not associated with sodium chloride acceptance. Infants eating starchy table foods at 6 months old were more likely to lick salt from the surface of foods at preschool age and were more likely to eat plain salt. This study not only suggested an influential role of early dietary experience in shaping salty taste responses of infants and young children, but also demonstrated that a liking for salt is not intrinsic but rather acquired throughout life via exposure to salty foods.

Much of the increased consumption of convenience foods can also be attributed to the ‘de-skilling’ and the ‘de-domestication’ of consumers today. The majority of women nowadays work, whilst maintaining the bulk of responsibilities for home and family life (60). Therefore there is less time for food preparation and family meals. With less time for food preparation, limited cooking skills, and diversity in dietary preferences, control over what one eats is diminished and somewhat manipulated by the growing power of the retailer, irrespective of the high cost of convenience foods. Consequently, home-cooked meals are being substituted with convenience foods, such as ready meals which mostly have high salt content (61).

1.7.3 Behaviour

There appears to be a high correlation between caloric intake and salt intake, mainly due to the fact that most salt is consumed in foods. Thus, people with high-energy consumptions presumably have a higher salt intake. Moreover, since energy intake (and therefore sodium intake) is likely to reflect energy expenditure, individuals who are physically active (e.g. athletes) or those who exercise vigorously tend to consume more salt than their sedentary counterparts.

1.7.4 Cultural and ethnic influences

Due to increased travel and emigration, ethnic influences are now widely reflected in consumer's diet. This is most apparent from the variety of ethnic style ready meals currently available. However, the growth and popularity of ethnic style ready meals is of considerable concern, given that these products are often heavily loaded with salt (62). For example, a recent survey by Consensus Action on Salt and Health (CASH) revealed that a leading supermarket brand of Indian Chicken Tikka Masala and Pilau Rice contained 5.0g salt per portion (63), which is equivalent to the maximum recommended amount of daily salt intake as suggested by WHO.

1.8 Controversies

Controversies exist surrounding the value of such moderate sodium reduction. Advocates insist that the recommendation is justified because sodium reduction has been proven to lower blood pressure, hence preventing stroke and myocardial infarction. Sceptics argue that modification of this surrogate end point does not guarantee a health benefit amid the possibilities of causing harms that outweigh its benefits. The alleged hazards associated with sodium reduction include the following:

1.8.1 An increase in myocardial infarction

Alderman et. al. (64) conducted a cohort investigating the relationship of sodium intake to subsequent cardiovascular disease over an average of 3.8 year follow-up. The 24-hour urinary excretion of electrolytes and plasma renin activity were

measured in 2937 hypertensive subjects. The results revealed a 4-fold increase in myocardial infarctions in treated hypertensive men with the lowest urinary sodium excretion, averaging 65 mmol/day. The investigators however, did not find any association for myocardial infarction in women or for stroke in either sex. These data have been criticized due to the small number of events, only 46 out of 1900 men, 22 of which occurring in the 483 in the lowest quartile of urinary sodium excretion. Blood pressure measurement appeared to be highest in the men in the lowest quintile of sodium intake, possibly reflecting that these population represents patients with difficult to control hypertension. The results were based only on a single 24-h urine sample and no attempt was made to ascertain long term sodium intake. The likely presence of multiple confounding factors such as unreported alcohol use and lack of detail information regarding the smoking status have also been suggested (65).

1.8.2 An increase in mortality

A recent study by Stolarz-Skrzypek et. al (66) claimed that 'lower sodium excretion was associated with higher cardiovascular disease (CVD) mortality'. The study which included 3681 subjects without CVD, was conducted to assess blood pressure and health outcomes (incidence of mortality and morbidity) based on 24-hour urinary sodium excretion. Participants were followed up for an average of 7.9 years. The results showed that systolic blood pressure positively correlated with 24-hour urinary sodium excretion. Conversely, lower sodium excretion predicted higher cardiovascular disease mortality. The investigators concluded that the findings from this study 'did not support the current recommendations of a generalized and indiscriminate reduction of salt intake at the population level'.

This study sparked controversies as some media have misleadingly reported that these results proved low-salt diet to be ineffective. Advocates on salt restriction criticised the study as being small, with low event rates and relatively young participants (mean age was 40 years old) (67). Other criticisms of the study include unreliable measurement of sodium intake, failure to account for key factors that influence sodium intake and heart disease risk (such as differences in height, physical activity, and total calories consumption), and missing or incomplete urine data from large numbers of participants (68).

Taylor et. al. (69) reported a meta-analysis of randomised trials with follow-up for at least 6 months on the effect of reducing dietary salt on total mortality and cardiovascular mortality and events. The authors investigated seven randomized controlled trials, and found that sodium reduction lead to a decrease in urinary salt excretion but no evidence of cardiovascular benefit. The investigators reported that the relative risks (RRs) for all-cause mortality in normotensives (RR: 0.90, 95% confidence interval (CI): 0.58 – 1.40) and hypertensives (RR: 0.96, CI: 0.83 – 1.11) showed no strong evidence of any effect of salt reduction. In addition, they also suggested that salt restriction increased the risk of all-cause mortality in patients with heart failure (RR: 2.59, CI: 1.04 – 6.44). The conclusion of the study in plain language, as being disputed by He et. al. (70), was 'cutting down on the amount of salt has no clear benefits in terms of likelihood of dying or experiencing cardiovascular disease'.

The review has been criticised mainly due to small number of studies were included (7 studies), and none of them were specifically designed to investigate the effects of sodium reduction interventions on cardiovascular events and mortality (71). In addition, one of these trials involved a heart failure study, for which according to He & MacGregor (70), should have been excluded because the participants were severely salt and water depleted due to aggressive diuretics therapy, and that salt restriction in these patients were likely to result in unfavourable outcomes. He et. al. (70) also suggested that the data should be analysed by combining the data for hypertensives and normotensives together (instead of separate analysis done by the investigators). By doing so, a significant reduction in cardiovascular events by 20% ($p<0.05$) and a non-significant reduction in all-cause mortality (5-7%) were demonstrated.

In other studies involving representative sample of 20,729 U.S. adults surveyed in the National Health and Nutrition Examination Surveys (NHANES) I, II and III, the data revealed an increased in all-cause mortality as the level of sodium intake is reduced (72-74). These data, based on a single-day dietary recall, showed increased all-cause mortality in the lower the sodium intake in a representative sample of 20,729 U.S. adults. These data also have been questioned mainly for the weakness of the measure of sodium intake, resulting in a level so low (30 mmol per day) which seemed impossible to achieve in a free living population; the presence of known and (likely) unknown confounding

factors; and the inability to ascertain long-time sodium intake (75;76). Moreover, when these same data were looked at separately for the 6,797 non-obese and the 2,688 obese subjects, highly significant direct association between increased sodium intake and stroke, coronary heart disease, and cardiovascular and all-cause mortality were found among the obese subjects (77).

1.8.3 Potentially harmful disturbances in various hormonal, lipid, and physiologic responses

Graudal and colleagues have performed a study in collaboration with the Nordic Cochrane Centre to estimate the effects of low versus high sodium intake on blood pressure, renin, aldosterone, catecholamines, and lipids (78). One hundred and sixty seven studies were included. The effects on blood pressure on low sodium intake were found to be heterogeneous: in normotensive Caucasians blood pressure fell 1.3/0.05 mmHg, in blacks 4/2 mmHg, and Asians 1.3/1.7 mmHg. The fall in systolic pressure in blacks was significant. In hypertensives, the falls were more impressive: Caucasians 5.5/2.8 mmHg, Blacks 6.4/2.4 mmHg and Asians 10.2/2.6 mmHg. On the contrary, there were predictable rises in plasma renin, aldosterone, catecholamines, and lipids.

This review has been criticised as the investigators failed to highlight the fact that there was no significant increase in cholesterol or LDL cholesterol in those studies which lasted four or more weeks. Studies which showed significant increases in cholesterol were acute and short term studies which are of no relevance to the proposed gradual long term reduction in dietary salt intake. In addition, the review in fact supports the wealth of evidence that reducing dietary salt intake will result in significant reduction in blood pressure across all ethnic groups, which would be greatly beneficial in preventing strokes and other cardiovascular complications (79). In addition Kaplan (80) argued that these kind of disruptions have usually been noted only when sodium intake has been severely restricted (to as low as 10 mmol/day) over short intervals.

1.8.4 Salt restriction and iodine deficiency

Tayie et. al. (81) conducted a study to evaluate the association between dietary salt intake restriction and iodine deficiency among adults in the United States.

The study included 996 men and 960 women from the 2001-2004 waves of the National Health and Nutrition Examination Surveys (NHANES). The study revealed that 24.96% of men and 40.42% of women were iodine deficient. Compared against women who did not restricted salt intake, women who were restricting dietary salt were found to have significantly lower urinary iodine concentration (p=0.01), and were more likely to be iodine deficient (adjusted odds ratio = 1.79, p=0.03).

In a more recent study, Vanderpump et al (82) conducted a cross-sectional survey with the aim of assessing current iodine status in 810 schoolgirls aged 14–15 years attending secondary school in nine UK centres. Urinary iodine concentrations and tap water iodine concentrations were measured in June–July, 2009, and November–December, 2009. Results from the study showed that urinary iodine measurements indicative of mild iodine deficiency were present in 51% (n=379) of participants, moderate deficiency in 16% (n=120), and severe deficiency in 1% (n=8). The investigators concluded that these findings have great public health importance for the UK since the results indicated that a lot of teenage girls in the country were iodine deficient. It was suggested that more iodine should be given to the UK population in the form of iodinised salt.

Although it is undeniable that iodine deficiency is a potentially serious problem, the recommendation to iodinise salt presents a conflict in public health issues, especially when it is in contrary with the UK's salt reduction strategy. MacGregor (83) suggested that alternative options, such as iodinisation of bread, flour or cereals, should be considered as this method has been successfully implemented in other countries such as Australia and New Zealand. If iodine must be added to salt, it was recommended that all sources of salt should be iodinised in a quantity that allows salt intake to be reduced to less than 5-6g per day, as per current recommended guideline by UK Food Standard Agency.

1.9 Proposed mechanisms of salt-induced hypertension

Dietary salt intake is one of the major regulators of blood pressure. The exact mechanisms whereby salt raises blood pressure are not fully understood. The existing concepts focus on the tendency for an increase in extracellular fluid volume (84). Vliet BV and Montani (85) proposed that salt affects blood pressure

in at least two separate ways. One being a relatively acute effect involving days or weeks and the other occurring over a much longer period of time, including decades in humans. Alternatively, Roberts (7) suggested that the rise in pressure in essential hypertension depends on the magnitude of the excess salt intake, the type of severity and combination of intrinsic renal abnormalities which impair the kidney's ability to excrete salt, and the duration of existence of these abnormalities.

1.9.1 Role of the kidneys

The most compelling evidence for the role of the kidney in the pathogenesis of hypertension comes from cross transplantation studies between normotensive and hypertensive strains of rats. Dahl et. al. (86;87) demonstrated that in young bilaterally nephrectomised spontaneously hypertensive rat, a kidney transplant from a normotensive rat resulted in no blood pressure increments of the hypertensive rats. Conversely, when a kidney from a young hypertensive rat (before developing hypertension) was transplanted into a bilaterally nephrectomised normotensive rat, the BP of the normotensive rat rose. In human, the high blood pressure measurements of patients with essential hypertension who developed kidney failure became normal after bilateral nephrectomy and transplantation with a kidney from a normotensive donor (88). Over a mean follow-up of 4.5 years, mean arterial blood pressure readings in these patients were reduced from 168±9 mmHg (before transplant) to 92±1.9 mmHg ($P \leq 0.001$). These findings evidently demonstrate that regardless of any functional abnormalities occurring at different sites, renal dysfunction is the primary disturbance that initiates the rise in blood pressure.

1.9.2 Role of extracellular volume

The traditional concepts regarding the mechanisms for salt-induced hypertension involved the impairment of the kidney's ability to excrete sodium causing sodium and water retention. Having a high salt intake therefore can contribute to volume expansion and stimulation of various compensatory mechanisms. The persistent occurrence of the compensatory mechanisms eventually causes BP to rise which in turn assists the kidneys to overcome the difficulties in excreting sodium. Based on animal studies, Guyton (89) showed that in 70%

nephrectomised dogs given large amounts of saline solution intravenously daily for 2 weeks, volume expansion raises BP by the autoregulatory effect on resistance vessels.

1.9.3 Direct role of plasma sodium

Presently, there is increasing evidence showing dietary salt intake triggers small changes in plasma sodium, hence results in changes of blood pressure. A number of studies have shown that an alteration in salt intake (either increase or decrease) causes parallel changes in plasma sodium in both hypertensive and normotensive individuals. For example, when salt intake was reduced from 20 to 1 g/day for 5 days, plasma sodium decreased by approximately 3 mmol/L ($p < 0.001$). In a well-controlled double-blind trial of 1 month, plasma sodium was reduced by 0.4 mmol/L ($P < 0.05$) when salt intake was decreased from approximately 10 to 5 g/day in 118 hypertensive. The decrease in plasma sodium was weakly but significantly correlated with the fall in systolic BP (84).

Several epidemiological studies have shown a significant positive association between plasma sodium and blood pressure. In a study of 3578 London civil servants, a 1 mmol/L increase in plasma sodium was associated with a 1 mmHg increase in systolic BP after adjusting for confounding factors (90). In another study of a Japanese population (3222 normotensive subjects and 741 patients with essential hypertension), serum sodium distribution was shifted by approximately 2 mmol/L toward higher values in the hypertensive subjects (91). Nevertheless, the Framingham Heart Study showed that serum sodium was not associated with BP, with the development of hypertension during 4 years of follow-up (92).

Plasma sodium is a major determinant of extracellular volume, thereby, influencing BP. At the same time, small changes in plasma sodium may have a direct effect on BP, independent of extracellular volume (93). Using peritoneal dialysis in rats, Friedman et. al. (94) were able to change plasma sodium in an opposite direction to extracellular volume by altering sodium concentration of the dialysis fluid. When plasma sodium was increased by 10 to 15 mmol/L, there was a rapid increase in BP despite a reduction in extracellular volume. When plasma sodium was decreased, there was a fall in BP despite an increase in

extracellular volume. The changes in BP were directly related to the changes of intracellular sodium. Friedman et. al. (94) suggested that increases in intracellular sodium may affect vascular smooth muscle tension and thereby BP. There is also evidence to suggest that small changes in plasma sodium may directly affect the hypothalamus' control of BP through the local renin-angiotensin system (93).

Tissue culture experiments demonstrated that increasing bath sodium concentration within the physiologic range caused marked cellular hypertrophy in both arterial smooth muscle and cardiac myocytes (95). In cultured bovine endothelial cells, when bath sodium concentration was increased from 137 to 142 mmol/L, endothelial nitric oxide synthase (eNOS) activity was reduced by 25%. The decrease in eNOS activity was in a sodium concentration dependent manner within the range studied (137-157 mmol/L) (96). Using cultured human endothelial cells, Oberleithner et. al. (97) demonstrated that an increase in the sodium concentration of the culture medium from 135 to 145 mmol/L stiffened endothelium and reduced nitric oxide release.

Recent studies in humans confirmed that salt intake does affect endothelial function. A randomized trial in 29 overweight and obese normotensive individuals showed that, when salt intake was reduced from 9.2 to 3.8 g/day for 2 weeks, there was a significant improvement in endothelial function as measured by brachial artery flow-mediated dilatation (98). A study in healthy volunteers showed that an increase in salt intake was associated with a blunted endothelial response to acetylcholine (99).

1.10 Salt-sensitivity and salt-resistance

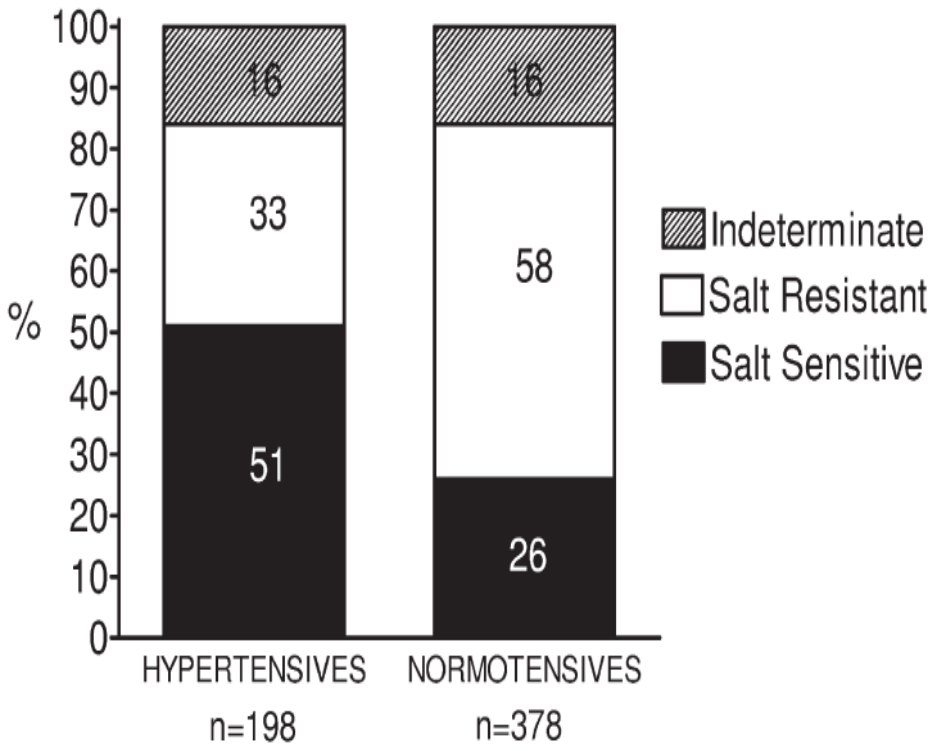
The term salt-sensitivity was used to classify individuals in whom the percentage of change or absolute difference in blood pressures between salt-restricted and salt-loaded states reached an arbitrary high level. In humans, the response of the blood pressure to an acute change in salt intake, or a diuretic, has been used to determine salt-sensitivity. Conversely, individuals in whom a severe abrupt change in salt intake or excretion causes the least change in arterial pressure are termed salt-resistant (100). Salt-sensitivity of blood pressure may

be inherited or acquired – *in utero*, during early postnatal life, or during adult life as a result of a low-potassium diet or uncontrolled hypertension.

The 'developmental origins of adult disease' hypothesis, often called the 'Barker hypothesis' after one of its leading proponents, states that adverse influences early in development, and particularly during intrauterine life, can result in permanent changes in physiology and metabolism, which result in increased disease risk in adulthood (101;102). The majority of the studies in children, adolescents and adults included in a recent, extensive review on this topic reported that blood pressure fell with increasing birth weight, the size of the effect being approximately 2 mm Hg/kg (103). Skeletal and non-skeletal postnatal catch-up growth were positively associated with blood pressure, with the highest blood pressures occurring in individuals of low birth weight but high rates of growth subsequently (103). The underlying mechanisms that lead to these phenomena are still unclear and widely debated. When nutritional deficiency occurs in utero at a critical period of development, the resulting adaptive changes may be permanent and may lead to long-term changes in structure and function (104). Birth weight is also associated with salt sensitivity of blood pressure, and this may play a role in the maintenance of elevated blood pressure in individuals with a low birth weight (105). Simonetti et. al. reported that renal mass is reduced in children born with low birth weight and depends on the degree of in utero growth retardation, which then determines lower glomerular filtration rate, increased salt sensitivity, and elevated blood pressure (106).

Several methods were used to determine salt-sensitivity, including the salt-sensitivity index (the ratio of change in mean blood pressure to change in sodium excretion during a salt load) proposed by Kimura and Brenner (107) and the variability adjusted blood pressure change (difference in blood pressures in study periods divided by intraperson standard deviation (SD) of the average of 3 blood pressure measurements) described by Flack et al (108). The most accepted method to determine salt-sensitivity was introduced by Weinberger et. al.(109) as shown in Figure 1-8.

Figure 1-8. Proportion of salt sensitive and salt-resistant individuals.



Data from Weinberger, who compared blood pressure after infusion of 2L of saline solution over 4 hours with blood pressure after salt depletion induced with a salt-restricted (sodium, 10 mmol/day) diet plus three 40-mg doses of oral furosemide. A difference in mean blood pressure between salt loaded and salt-depleted phases of 10 mmHg or greater is defined as salt-sensitivity. A blood pressure difference of 5 mmHg or less is defined as salt resistance.

Weinberger et al. (109) defined sodium sensitivity as a 10 mmHg, or greater, fall in mean blood pressure from the level recorded after a 4-h infusion of 2 litres saline, compared with the level measured after 1 day on a 10 mmol/day sodium diet, during which three oral doses of furosemide are given. Those with a decrease of 5 mmHg or less (including an increase in pressure) were considered sodium-resistant. Subjects with a decrease in BP between 6 and 9 mmHg were classified as indeterminate. The responses of the BP were heterogeneous and formed a Gaussian distribution in both normotensive and hypertensive groups. It was found that 26% of the normotensive subjects were salt-sensitive and 58% salt-resistant, whereas in the hypertensive group, 51% were sensitive and 33% were resistant. Blacks have been shown consistently to have a greater frequency of salt-sensitivity than whites (110).

Weinberger observed that 73% of black hypertensive patients were salt-sensitive, compared with 56% of a white hypertensive group. However, in the normotensive

population, the frequency of salt-sensitivity among blacks (36%) was similar to that seen among whites (29%). Plasma renin activity (low, normal, high) did not predict the sodium response. In both groups, the sodium-sensitive individuals were significantly older and had lower baselines of renin values than sodium resistant subjects. Subpopulations with increased frequencies of salt-sensitivity have been shown to be associated with high-BP, higher age, and African-American ethnicity.

Familial resemblance to acute and chronic salt challenges has been reported, but the genetic basis of salt-sensitivity, which is likely to be related to the genetics of hypertension, remains poorly known (111). For example, in 44 families of identical twin children who participated in a sodium restriction protocol (less than or equal to 4.3 g/day salt for a period of 12 weeks), mother-offspring resemblance in blood pressure change with sodium restriction was significant both for systolic (r = 0.31, $p < 0.001$) and diastolic (r = 0.20, $p < 0.05$) pressure (112). Sibling-sibling and twin-twin resemblance was also highly significant, thus demonstrating significant familial resemblance in blood pressure change with sodium restriction in normotensive persons.

Multiple mechanisms for sodium sensitivity have been proposed such as a defect in renal sodium excretion manifested by renal vasoconstriction, increased activity of the sodium-hydrogen exchanger in the proximal tubule, impaired natriuretic response to 20-hydroxyeicosatetraeonic acid (20-HETE), a higher level of sympathetic nervous system activity, and endothelial dysfunction related to a decreased nitric oxide response to sodium loads (113). Various numbers of proposed mechanisms for salt-sensitivity highlight the uncertainty regarding which exact mechanisms are involved. Regardless of how it occurs, greater sodium sensitivity is positively associated with a higher incidence of cardiovascular events and mortality (80).

1.11 Importance of Pressure-Natriuresis

The domination of the kidneys in the regulation of blood pressure has been confirmed by the experimental and conceptual work developed by Guyton (89) on the pressure natriuresis and diuresis response. Guyton proposed the phenomenon known as pressure-natriuresis, which suggested that when blood

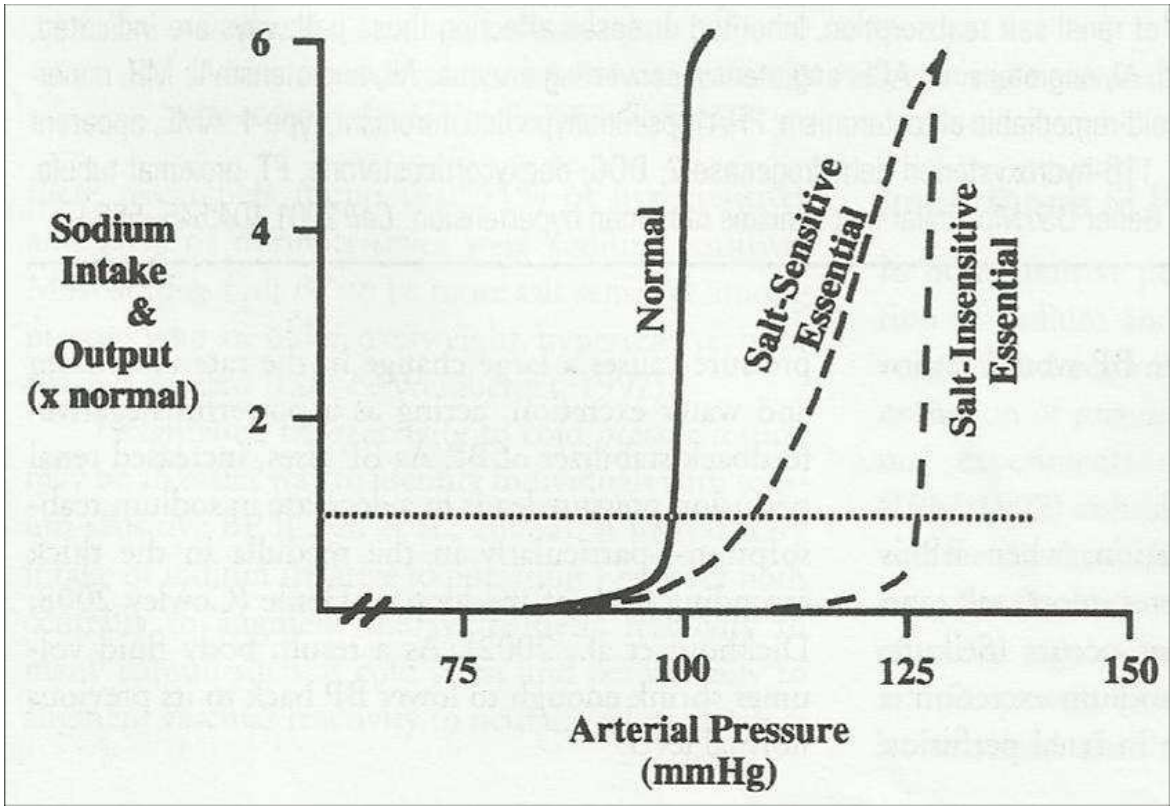
pressure rises, renal excretion of sodium and water increases, reducing fluid volume and returning the blood pressure to normal. Conversely, when the pressure falls below normal, the incoming salt and water overbalance the excreted fluid, and the pressure rises. Several systems have been identified responsible in regulating blood pressure, which largely differ regarding time once the pressure becomes abnormal (80). Some systems based on neural receptors react within seconds while others such as the hormonal systems respond within minutes. Nevertheless, the system which plays a huge and vital role is the kidney-fluid volume system, which reacts within hours or days.

1.11.1 Resetting of Pressure-Natriuresis

In patients with essential hypertension, a resetting of the pressure-sodium excretion curve prevents the return of blood pressure to normal, hence fluid balance is maintained but at the expense of high blood pressure (114). Experimental evidence suggested that the resetting plays a key role in causing hypertension rather than merely an adaptation to increased blood pressure. This resetting mechanism explains why sodium retention occurs when blood pressure is lowered by nondiuretic drugs.

Different types of renal insult are reflected in varying sensitivity to sodium (115). As seen in Figure 1-9, either the entire curve can be shifted to the right or the slope can be depressed. Salt resistant hypertension is characterized by a parallel shift in the pressure-natriuresis curve, whereas salt-sensitive hypertension is accompanied by a change in slope, an exaggerated increase or decrease in blood pressure with increased or decreased sodium intake, respectively.

Figure 1-9. Salt resistant mechanism simplified.



A schematic presentation showing resetting of pressure-natriuresis in hypertension. Steady-state relationships between arterial pressures and sodium excretion (equal to intake) are shown for both salt-sensitive and salt insensitive essential hypertension. As blood pressure increases, natriuresis increases to maintain BP at normal levels. In salt-sensitive hypertensive individuals, natriuresis increases with increasing BP, but BP does not decline to normal levels, while in salt-insensitive individuals, natriuresis does not occur until BP crosses a high threshold. From (113).

1.11.2 Mechanisms of resetting

Pressure-natriuresis, and the resetting that occurs in hypertension, is mediated first and foremost by changes in tubular sodium transport with unchanged glomerular filtration rate. Extensive rat studies of Cowley (116) identify the outer renal medulla as the key site in which pressure-natriuresis occurs.

The renal medulla is uniquely vulnerable to ischemic insult for several reasons. Oxygen extraction is almost near maximal under resting conditions to maintain the basal activity of energy-dependent sodium transporters, which are highly concentrated in this part of the kidney. With a sudden increase in blood pressure, medullary blood flow must increase to match the increased energy demands of these transporters. In other words, blood flow to the renal medulla must be poorly autoregulated if pressure-natriuresis is to occur. Impaired

medullary blood flow regulation impairs pressure-natriuresis and is evident in virtually all rat models of hypertension (113).

1.11.2.1 Intrarenal mechanisms

The best available evidence so far regarding the intrarenal mechanisms, is the presence of imbalance between an overactive Renin-angiotensin-aldosterone system (RAAS), which reduces renal medullary blood flow, and a defective nitric oxide pathway, which normally maintains medullary blood flow and protects against hypertension (117).

The RAAS is a key mechanism regulating renal sodium handling, producing most of its biological effects via AT1 receptors (118). In the kidney, AT1 receptors activation causes renal medullary vasoconstriction and increase sodium reabsorption, whereas in the brain, they regulate salt appetite, thirst, and modulate vasopressin release. In addition, adrenal AT1 receptors enhance secretion of aldosterone, the main mineralocorticoid.

Ang II has been shown repeatedly to cause a rightward shift in the pressure-natriuresis curve (115). The effect is potent since sodium retention is greatly enhanced at the very low Ang II concentrations, even lower than the concentration required to cause vasoconstriction. Ang II normally triggers a coordinated calcium signal to promote vasoconstriction and causing the release of nitric oxide. The latter, is a potent vasodilator which can offset Ang II-dependent vasoconstriction (117). The balance between vasoconstrictor and vasodilator factors is termed “tubulovascular crosstalk”. Other associated vasoconstrictor factors include reactive oxygen species (both superoxide and hydrogen peroxide); associated vasodilator factors include cyclooxygenase (COX-2) and prostaglandins (PGE2) (116). Any imbalance occurring between these factors can lead to medullary ischemia, impaired pressure-natriuresis, and salt-induced hypertension.

Ang II is selectively concentrated in the kidney hence, emphasizes the reason why RAAS is vital in renal sodium handling. Navar et. al. have shown that intrarenal concentrations of Ang II are several fold higher than circulating blood levels because the kidney actively produces and sequesters Ang II (119). In

multiple experimental forms of hypertension, renal Ang II levels are high even when plasma levels are normal or low. Thus, selective over activity of the intrarenal RAAS may drive hypertension even when extrarenal blood tests indicate that systemic RAAS activity is either suppressed or “inappropriately normal”.

While AT1 receptors promote sodium retention, AT2 receptors on the contrary promote natriuresis. This is partly mediated by the release of nitric oxide (120). The angiotensin receptor blockers, which cause selective AT1 receptor blockade, induce natriuresis in rodents by unmasking and activating AT2 receptors in the proximal tubule. Despite abundant experimental support, this theory remains untested in patients as selective AT2 receptor antagonists are not available for use in human subjects.

1.11.2.2 Extrarenal mechanisms

The following systemic mechanisms also have been associated in resetting pressure natriuresis and have been implicated in causing salt-sensitive hypertension:

Table 1-5. A summary of extra renal involvement in resetting pressure natriuresis.

Mechanisms	Summary
Dysfunction of the natriuretic peptides	Studies in humans indicate that secretion of ANP may be blunted in black salt-sensitive hypertensives in response to high salt diets (121). Further, a loss of function polymorphism of the ANP gene has been observed more frequently in black salt-sensitive hypertensives, compared to normotensives or white hypertensives (122).

Insulin	Insulin promotes sodium reabsorption, and hyperinsulinemia, as well as obesity. It was also proposed as a mechanism of sodium retention and hypertension in patients with metabolic syndrome (5)
α-Melanocyte stimulating hormone	This particular hormone can cause or exacerbate salt-sensitive hypertension in rodent models via the central melanocortin system and activation of sympathetic nerve activity (123).
Activation of renal sympathetic nerves	Activation of the renal sympathetic nerves shifts the pressure-natriuresis curve and contributes to salt-sensitive hypertension in rats. Conversely, renal denervation prevents the development, attenuates the magnitude, or delays the onset of hypertension in multiple animal models (124) and may lower blood pressure in hypertensive patients (125).

Modified from (113).

1.11.3 Importance of renal inflammation

Animal studies showed that renal inflammation can act as both the cause and the consequence of renal medullary ischemia (126). Renal inflammation is a hallmark of both the initiation and progression of experimental salt-sensitive hypertension. Eventually, ongoing renal ischemia will kill enough nephrons to decrease GFR.

1.11.4 Nocturia

Abnormal pressure-natriuresis can be clinically presented as nocturia. It also provides a clue to uncontrolled salt-sensitive hypertension related to aging, hypertension, and particularly a blunted or reversed nocturnal dipping pattern in blood pressure (127). Nocturnal urine flow accounts for 53% of urine output in 60- to 80-year-old normotensive individuals compared to 25% in 25- to 35-year-olds (128). Hypertensives however, have even more nocturia, presumably reflecting the resetting of the pressure-natriuresis relationship (129). Fluid retained peripherally during the day leads to central volume expansion at night, with elevated nocturnal blood pressure driving pressure-natriuresis.

1.12 Other effects of dietary salt in addition to hypertension

1.12.1 Left ventricular mass

Left ventricular hypertrophy (LVH) is a frequent and prognostically unfavourable finding in patients with essential hypertension. Evidence from human studies revealed a link between ventricular mass and cardiovascular mortality and morbidity independent of the blood pressure (130;131). In normotensive individuals, left ventricular mass and diastolic filling have been found to be positively correlated with urinary sodium excretion (132). In two normotensive groups followed up for 3 to 8 years the initial left ventricular mass and wall thickness were significantly related to the subsequent development of hypertension (130). Gerdts et. al. (133) in a study looking at the effects of antihypertensives on blood pressure, albuminuria, and left ventricular mass in hypertensive patients with type 1 diabetes, identified dietary sodium intake as an independent predictor of left ventricular mass. The study also found no significant association between left ventricular mass and the blood pressure. Studies in animals revealed almost similar findings. Normotensive rats given 1% saline solution for several weeks develop LVH evident by an increase in heart weight but without an increase in blood pressure (134).

The increase in left ventricular mass associated with essential hypertension has been shown to be reversible by reducing salt intake. This is evident by results from The Treatment of Mild Hypertension Study Research Group (135), which

showed a significant correlation between the reduction in salt intake and left ventricular mass. In the whole study group reducing salt intake was the only factor which was significantly correlated with a reduction in left ventricular mass.

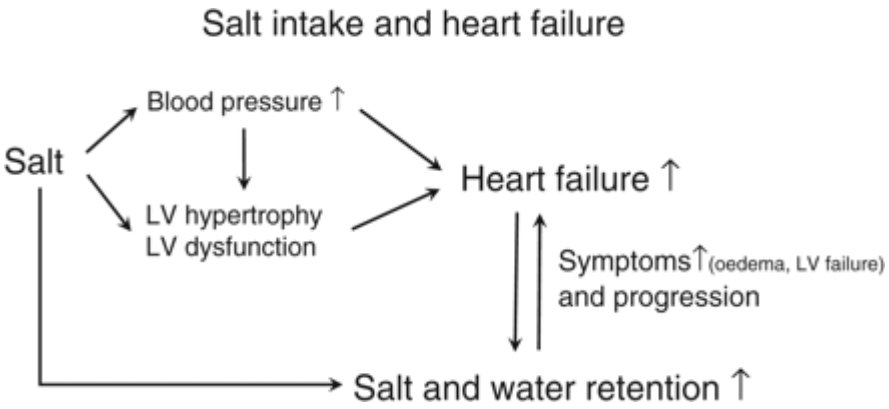
1.12.2 Vessels

Stiffness of conduit arteries, measured as an increase in pulse wave velocity or pulse pressure, is a strong independent predictor of cardiovascular risk (136). Studies in both humans and animals have shown that an increase in salt intake increases the stiffness of conduit arteries and the reactivity of the small resistance vessels and the wall thickness of both (137;138). In a study of two Chinese populations, the age-associated increase in pulse wave velocity was blunted in the population with a lower salt intake (139). Similarly, the pulse wave velocity of a group of normotensive subjects who reduced their salt intake for a mean of about 2 years was significantly lower than that of a control group, independent of the blood pressure (140). He et. al. in a randomized double-blind study shows that a modest reduction in dietary salt intake reduces pulse pressure both in individuals with isolated systolic hypertension and in those with both raised systolic and diastolic blood pressure, suggesting that salt reduction improves arterial distensibility (141). Another recently published paper by Gates et al (142) demonstrates that directly measured large elastic artery compliance is increased by dietary salt restriction in middle-aged and older men and women with stage 1 systolic hypertension.

1.12.3 Cardiac failure

Raised blood pressure is major cause of cardiac failure with hypertension preceding the development of cardiac failure in almost 90% of patients (53). A high dietary salt intake increases blood pressure and the risk of left ventricular hypertrophy and left ventricular dysfunction, thereby increasing the risk of cardiac failure (Figure 1-10).

Figure 1-10. Relationship between salt intake and heart failure.



From He et. al. (143).

Predominantly, there is systolic contractile dysfunction due to the salt induced hypertension (144). Diastolic dysfunction may occur in some elderly patients attributable to impaired ventricular filling, which usually precedes systolic dysfunction. This complication occurs as a consequence of the collagen deposition and fibrosis of the ventricle which are strongly associated with high dietary salt intake. A prospective cohort study which involved 10 352 men and women has shown that a higher dietary salt intake was associated with a higher risk of developing heart failure over a follow-up period of 19 years. This association was found in overweight individuals, but not in those with normal body weight (145). Similarly, the administration of drugs which can promote sodium and fluid retention (e.g. Non-steroidal anti-inflammatory drugs) have been demonstrated to significantly increase the risk of congestive heart failure in susceptible patients (146).

Ahn J et. al. (147) showed that in spontaneously hypertensive rats, dietary salt excess increased arterial pressure more than in rats receiving normal salt diets and promoted diastolic dysfunction manifested by extended isovolumetric relaxation time. These echocardiographically measured ventricular relaxation abnormalities were associated with a further increase in left ventricular mass and hydroxyproline concentration (an index of ventricular collagen content). Moreover, the subgroup of younger salt-loaded spontaneously hypertensive rats developed heart failure with impaired systolic and diastolic function associated with a greater left ventricular mass myocardial fibrosis.

In addition, the salt-induced increase in the size of the cardiac muscle mass and the salt-induced thickening of the coronary arteries, impair coronary perfusion which can be detected as an inadequate reserve of coronary blood flow (148;149). Myocardial function is further impaired by the increase in cardiac output, resulting partly from the increase in right auricular pressure secondary to salt. Weight gain associated with the salt and water retention that accompanies cardiac failure also increases cardiac work load. Hence, the mainstay of non-pharmacological therapy for patients with cardiac failure is a low salt diet, which has been shown to improve symptoms similar to that which occurs with diuretics (150).

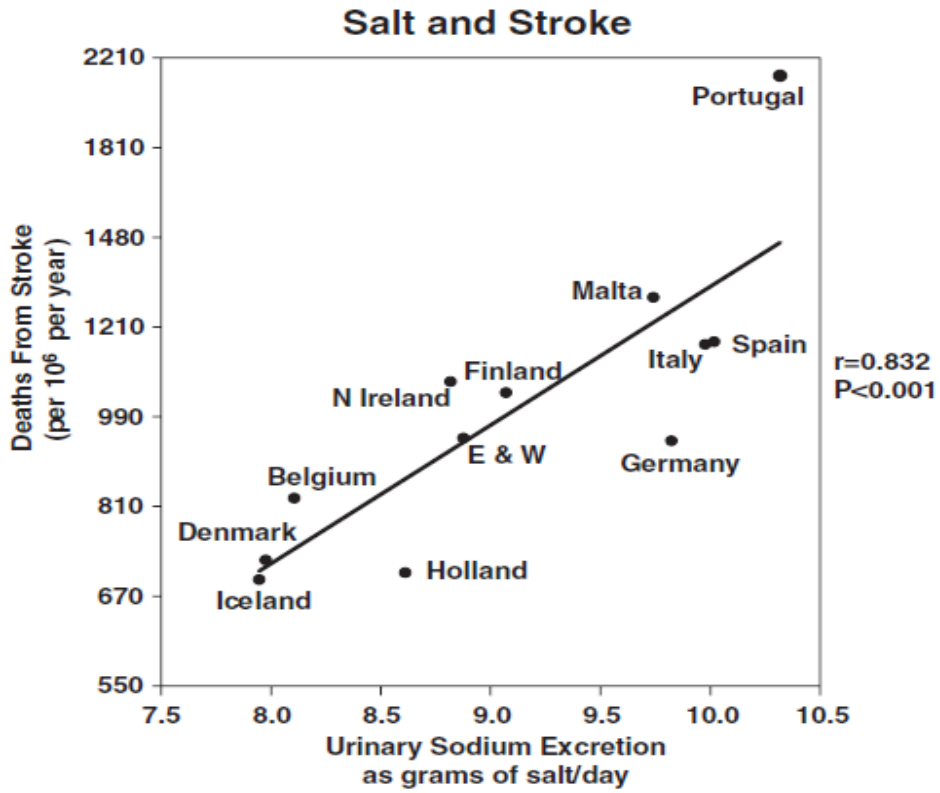
1.12.4 Stroke

Hypertension is the single most important cause of stroke. According to the World Health Organization, 62% of all strokes and 49% of coronary heart disease events are attributable to high blood pressure (151). The direct causal relation between levels of dietary salt intake and blood pressure at the population level has also been recognised. In addition, there is also increasing evidence that salt may have a direct effect on strokes, independent of and in addition to the effect it has on blood pressure (152). Given the graded causal relation between blood pressure and cardiovascular disease, it is reasonable to expect considerable benefit on the rate of cardiovascular disease from a reduction in dietary salt intake.

Data from the INTERSALT study (looking at individuals aged 20 to 40 years) and from the sex-specific stroke mortality data from 25 countries worldwide revealed that there was a significant relationship between stroke mortality and sodium excretion in men, and the Na^+/K^+ ratio in women (153). Strazullo et. al. (151) in a recent meta-analysis of 19 independent cohort samples from 13 studies, with 177,025 participants showed that a high salt intake is associated with significantly increased risk of stroke and total cardiovascular disease. The authors suggested that reducing current salt intake from 10g to 5g per day, would reduce stroke rate by 23% and overall cardiovascular disease by 17%. Such measure could potentially prevent 0.25 million deaths from strokes and almost 3 million deaths from cardiovascular disease each year. In another study, Perry and Beevers (154) performed an ecological analysis of the relationship between

urinary sodium excretion and stroke mortality in Western Europe. The investigators found a significant positive correlation between urinary sodium excretion and stroke mortality and this relationship is much stronger than that found when urinary sodium is plotted against blood pressure.

Figure 1-11. Relationship between salt intake and deaths from strokes in 12 European countries.



From Perry and Beevers (154).

1.12.5 Platelets

In one study by Gow et. al. (155) which involved normotensive male subjects, platelet aggregation induced by adenosine 5´-diphosphate was significantly greater when they were on a high-salt diet. Similarly in normotensive women a change in salt intake from 10 to 200 mmol/day resulted in a significant increase in platelet aggregation (156). In two groups of men with and without a family history of hypertension, a high-salt diet increased the blood pressure measurement in participants with positive family history, whereas platelet aggregation increased in both groups, with more favouring towards those with a family history (157). The effect of salt intake on adrenaline-induced platelet

aggregation and α-2 adrenergic receptors on platelet membrane fraction has been studied in patients with essential hypertension. The response was linked to the associated changes in blood pressure. In those in whom there was a rise in blood pressure, platelet aggregation also increased as well as the number of α-2 adrenergic receptors (158).

1.12.6 Renal function

There is growing evidence in both animal and human studies associated with direct and indirect adverse consequences of high dietary salt on the kidney. Models of indirect mechanisms suggest a complex relationship between increased sodium load, increased blood pressure and proteinuria. Alternatively, direct mechanisms involve elevation of oxidative stress in the mammalian kidney by increasing and decreasing the breakdown of reactive oxygen species (159).

Albuminuria has been well established to be an important and independent risk factor for the development and progression of renal disease and also for cardiovascular disease in individuals with diabetes, chronic kidney disease, hypertension and the general population (3). In addition, the risk appears to increase throughout the range of albumin excretion with no threshold. Several epidemiological studies have demonstrated a direct association between salt intake and urinary albumin excretion, independent of blood pressure. Swift et. al. (160) in randomized double-blind trial which involved 40 black hypertensive patients demonstrated that a reduction in salt intake from approximately 10 to 5 g/day reduced 24-hour urinary protein by 19% ($p< 0.01$). In another more recent double-blind trial, a larger number of individuals including 71 whites, 69 blacks, and 29 Asians with mildly elevated blood pressure showed that even a smaller reduction in dietary salt intake, from an average of 9.7 to 6.5 g/day, significantly reduced 24-hour urinary albumin excretion in all 3 ethnic groups (161).

Other studies in patients with proteinuria or diabetes revealed that the antiproteinuric effect of an angiotensin-converting enzyme (ACE) inhibitor is dependent on salt intake: low salt intake enhances and high salt intake abolishes the antiproteinuric effect of ACE inhibitor. Cianciaruso et. al. (162) who conducted a retrospective analysis of 57 chronic kidney disease patients with an

average observation period of 3 years, showed that a lower salt intake reduced proteinuria and slowed down the progression of renal disease. This observation occurred despite a similar BP control between the 2 groups on a high and low salt intake. Reduction in dietary salt intake would also benefit chronic kidney disease patients who are on dialysis, in whom blood pressure management is rather challenging. By encouraging a low salt diet, the amount of fluid consumed between dialyses will be reduced, resulting in decreased weight gain between dialyses, and improved blood pressure control (45).

1.12.7 Obesity

Obesity is a major public health burden and is strongly associated with health complications such as diabetes, hypertension and cardiovascular disease. According to NHS data (163), male obesity in the UK has increased from 13.2% in 1993 to 23.1% in 2005, while obesity amongst women has increased from 16.4% to 24.8% over the same period. Even though there is no direct causal relationship between obesity and dietary salt intake, the latter plays a major influencing factor through its effect on soft drink consumption.

Furthermore, the appropriate physiological responses to increased plasma sodium levels (i.e., osmolality) are stimulation of vasopressin release and of the thirst mechanism. Thirst-induced increased fluid intake would lead, initially, to an increased blood volume which would persist for only a short time until urine plus sodium excretion returned volume and osmolality to the normal range in response to the reduced release of the hormones vasopressin and aldosterone (164).

In adults, it has been shown that a reduction in salt intake reduces fluid consumption and would lead to a concomitant reduction in soft drink intake. It has been estimated that a reduction in current salt intake from 10 g/day to the WHO recommended level of 5 g/day would reduce fluid consumption by ~350 ml/day (45). A study by Karppanen et. al. (165) which analysed the sales of salt and carbonated beverages in the USA between 1985 and 2005 showed a strong correlation between the two, including a parallel link with obesity. They were also in parallel with the trend of prevalence of obesity.

In children, sugar-sweetened soft drinks are an important component of total fluid intake. A study by James et. al. (166) revealed that 31% of the fluid consumed by 4-18 year olds is sugary soft drinks. Hence, it is a significant source of calories in children and is also claimed not to give rise to any feeling of satiety. He et. al. (167) who analyzed the data from the National Diet and Nutrition Survey for young people in Great Britain in 1997 suggested a reduction of 1 g/day in salt intake would reduce the total fluid by 100 g/day and decrease sugar sweetened soft drink consumption by 27 g/day per child. This demonstrates that a reduction in salt intake might, therefore, be important in reducing sugar-sweetened soft drink consumption and, thus reducing childhood obesity.

1.12.8 Osteoporosis

Osteoporosis affects mainly the older population, with estimated 3 million people are suffering from the condition in the United Kingdom. According to the National Osteoporosis Society, 1 in 2 women and 1 in 3 men over the age of 50 have had a fracture at least once, primarily due to brittle bone condition. Since 1960's there has been a 7 fold increase in the number of osteoporosis cases, costing the NHS approximately 2.3 billion pounds every year (168).

Urinary sodium excretion, hence dietary sodium intake controls calcium excretion in the urine. A high-salt diet therefore contributes to an increase in urinary calcium, which over the long term may lead to calcium mobilisation from bone (169). Itoh and Suyama (170) conducted a study in 410 healthy men and 476 healthy women aged between 20 to 79 years old. They discovered that the higher the sodium intake, the greater the loss of urinary calcium and the excretion of hydroxyproline, which is an indicator of increase in bone resorption. An increase in dietary sodium of 100 mmol/day was associated with an increase in calcium excretion of 0.6 – 1 mmol. In another study which involved post-menopausal women, it has been shown that the loss of hip bone density over 2 years was related to the 24-hour urinary sodium excretion at entry to the study and was as strong as that relating to calcium intake (171). Thiazide diuretics, through a reduction in extracellular volume, reduce calcium excretion leading to a positive calcium balance, increase bone density and reduce bone fractures

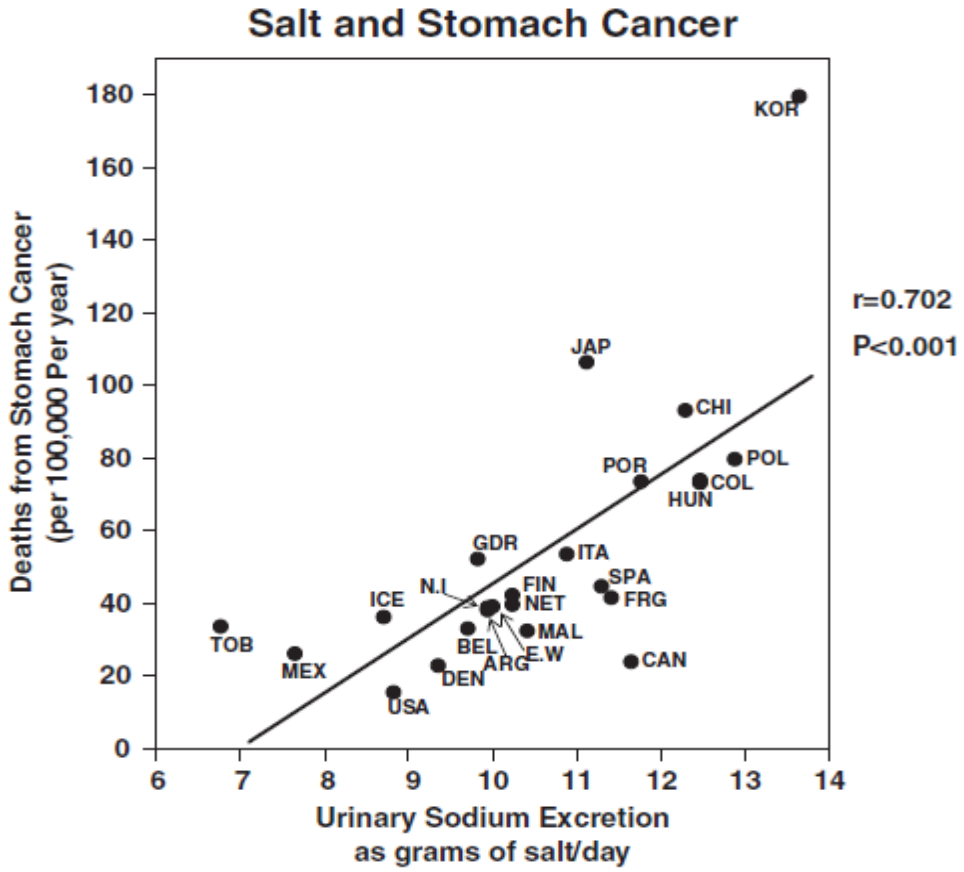
(172). Salt reduction therefore has been postulated to achieve the same positive effects.

1.12.9 Gastric cancer

Gastric cancer is the second most common cancer in the world. Of all the possible causes linking to its occurrence, the relationship to salt is the strongest (173). A high salt diet in both humans and experimental animals has been shown to cause gastritis and when coadministered with known gastric carcinogens, it promotes their carcinogenic effect (152). One such promoter is *Helicobacter pylori*, which has been proven to be associated with progression of gastritis to gastric cancer (174). Prospective studies have shown a positive correlation between *Helicobacter pylori* and gastric cancer amounting to a two-to three-fold increase in risk. In addition, a high salt diet also increases *Helicobacter pylori* colonisation (175).

Joossens et. al. (173) conducted a study looking at mortality associated with gastric cancer among 39 populations from 24 countries based on randomly selected 24-hour urine collections. Median sodium excretion levels were standardised for age and sex between the ages of 20 and 49 years and averaged for each country. Based on correlation-regression analyses, the investigators found a significant and direct association between sodium excretion levels and national gastric cancer mortality rates in both men and women. Countries with high salt intake are more likely to have higher mortality rates due to gastric cancer. In Japan for example, where gastric carcinoma is the most common cancer, a positive correlation between salt intake and gastric cancer incidence in different geographical regions has been found (176). In addition, a higher risk of gastric cancer has been discovered in those who prefer salty food including salt-preserved meat and fish (177;178).

Figure 1-12. Relationship between salt intake and deaths from stomach cancer.



Linear regression between stomach cancer mortality per 100 000/year, age adjusted between 45—74 years and mmol Na/24-hours. ARG = Argentina; BEL = Belgium; CAN = Canada; CHI = P.R. of China; COL = Colombia; DEN = Denmark; E.W = England and Wales; FIN = Finland; FRG = Fed. Rep. of Germany; GDR = German Dem. Rep.; HUN = Hungary; ICE = Iceland; ITA = Italy; JAP = Japan; KOR = South Korea; MAL = Malta; MEX = Mexico; NET = the Netherlands; N.I = Northern Ireland; POL = Poland; POR = Portugal; SPA = Spain; TOB = Trinidad and Tobago; USA = United States. From (173).

1.12.10 Asthma

Regional data from England and Wales have shown that there is a strong correlation between the purchase of table salt and asthma occurrence in men and children (179). Presently, there are two interventional randomised double-blind, placebo controlled, crossover trials in men with mild to moderate asthma, looking at the effect of altering dietary sodium intake for several weeks.

Burney et. al. (179) recruited 27 asthmatic patients and assessed the clinical severity of the condition whereas in the second study, 36 patients were involved whereby the subjects' airway response to histamine was measured. Results from

both of these small trials demonstrated that an increase in dietary sodium, 80 mmol/day and 204 mmol/day respectively, increased both the severity of the asthma and bronchial reactivity. Another observational study on 138 men with mild to moderate asthma confirmed that bronchial reactivity was strongly related to 24-h urinary sodium excretion, allowing for the effect of age, atopy and cigarettes (180). Similarly, a population-based study in children aged 6-7 years demonstrated that adding salt to food was strongly and independently associated with an increased risk of respiratory symptoms which include wheeze and asthma (181). Mickleborough et. al. (182) in a double-blind study illustrates the mechanism of how a higher salt intake may exacerbate asthma. The authors suggested that dietary salt loading enhances airway inflammation, and that small salt-dependent changes in vascular volume and microvascular pressure might have substantial effects on airway function, secondary to mediator-induced (post-exercise) increased in vascular permeability.

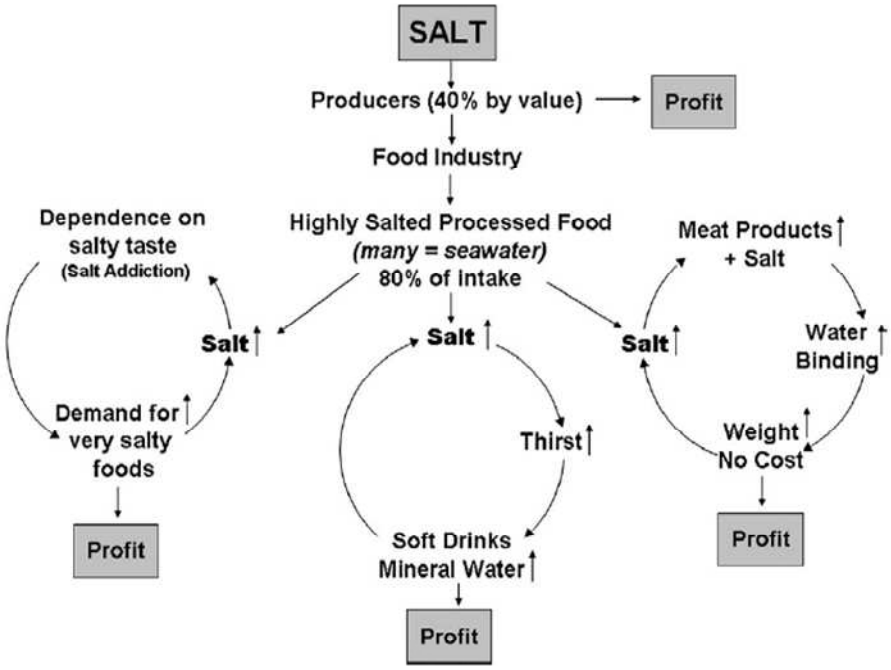
1.13 The role of the food industry in salt reduction

In most developed countries, approximately 80% of salt consumption is from the processed foods rather than discretionary (183). Salt is added to foods at the stage of manufacturing and the consumers have no control over the quantity being used. Therefore, to achieve a reduction in population salt intake, it is imperative that the food industry reduces the total amount of salt added to all foods. In view of the compelling evidence on the benefits of salt reduction, most food companies recognize the importance of initiating a salt reduction programs and start the initiative to reformulate their products (184).

Nevertheless, some members of the food industry are still reluctant to oblige due to commercial reasons (Figure 1-13). Salt makes cheap, unpalatable food edible at no additional cost. With continuous consumption of highly salted foods, the salt taste receptors are suppressed. The habituation to salty foods develops, together with greater demand for profitable highly salted processed foods. In addition, increasing salt concentration in meat products together with other water-binding chemicals results in enhanced water-binding capacity, so the product weight can be increased by up to 20% with water (45). Salt is also a

major determinant of thirst, hence any reduction in salt intake will reduce fluid consumption with a subsequent reduction in soft drink and mineral water sales (167).

Figure 1-13. The commercial importance of salt in processed foods.



From He et. al. (45).

Some of the largest snack companies in the world are linked to companies selling soft drinks. It is therefore not surprising that the salt industry and some members of the food industry are very reluctant to see any reduction in salt intake and have been largely responsible for trying to make salt such a controversial issue relative to other dietary changes (3). The commercial reasons for this opposition need to be acknowledged. Nevertheless, they should not be a hindrance factor to pursue salt reduction as this approach will be of major benefit to the future health of the whole population, particularly if it is combined with other dietary and lifestyle changes such as increasing fruit and vegetable consumption, reducing saturated fat intake, regular exercise and smoking cessation (185).

1.14 Global initiative for salt reduction

The Global Burden of Disease study identified high blood pressure as the leading cause of mortality, attributable to more than 7 million deaths (186). In addition, the WHO World Health Report (187) estimated that globally 62% of cerebrovascular disease and 49% of ischaemic heart disease were attributable to elevated blood pressure (systolic > 115 mmHg). Heart diseases are the leading cause of death for persons over 60 years of age and the second cause of death for persons aged 15–59 years. The report proposed strategies to reduce the risks associated with CVD and emphasized that in all settings population-wide salt reduction strategies were the most cost-effective.

In 2003, a technical report by WHO and the Food and Agriculture Organization (FAO) of the United Nations (UN) recommended a population-wide daily salt intake of no more than 5 g (2,000 mg sodium) in adults (188). Subsequently, in 2007, a report was issued proclaiming the available evidence “conclusive” for excess sodium to cause hypertension (20). This report called for worldwide reformulation of processed and restaurant foods, to achieve the lowest possible sodium content combined with consumer education and creation of an environment facilitating choice of low-sodium foods.

To promote sodium reduction worldwide, World Action on Salt and Health (WASH) was established in 2005. This group of experts in hypertension encourages multi-national food companies to reduce sodium in their products and works with governments in different countries to highlight the need for a sodium reduction strategy (189). The overall aim is to achieve reduction in salt intake throughout the world by reducing the amount of salt in processed foods as well as discretionary.

Many individual countries around the globe have already taken action against reducing population salt intake. Webster et. al. (190) in a recent review identified 32 countries around the world with current national salt reduction initiatives. These strategies were either led by government, nongovernment organizations or industry. Most countries had maximum population salt intake targets, ranging from 5 to 8 g per person per day. The average salt intakes level documented among these countries were 9 g/person per day. Five countries

(United Kingdom, Finland, France, Ireland and Japan) had demonstrated a positive impact, either on population salt consumption, salt levels in foods or consumer awareness.

1.14.1 The UK strategy for salt reduction

The UK is one of the pioneer countries in salt reduction. In 1996, 22 experts on salt and BP set up an action group known as Consensus Action on Salt and Health (191). Since then, CASH has lead a highly successful campaign to persuade food manufacturers and suppliers to universally and gradually reduce the salt content of processed foods. They are also involved in educating the public in becoming more aware regarding the harmful impact of salt on their health, and translate the evidence into public health policy. CASH persuaded the UK Department of Health to change its stance on salt, resulting in the Chief Medical Officer endorsing the recommendations to reduce national salt intake to less than 6 g/day in adults, and also ensured that the UK Food Standards Agency (FSA) took on the task of reducing salt intake (189).

A strategy to reduce population salt intake was developed based on the UK's average salt intake of 9.5 g/day (192) as measured by 24-h urinary sodium (Table 1-6). It was estimated that ≈15% of the salt consumed (i.e., 1.4 g) was added either at the table or during cooking, 5% was naturally present in the foods (0.5 g), and the rest 80% (7.6 g) was added by the food industry in processed, canteen, restaurant, and takeaway foods. To reach the target of 6 g, a total reduction of 3.5 g (i.e., 40%) was needed. Therefore, the food industry would need to reduce the amount of salt added to foods from 7.6 to 4.6 g (40% reduction) and the public would need to reduce the amount of salt they add to foods themselves from 1.4 to 0.9 g (40% reduction).

Table 1-6. UK strategy for reducing salt.

Salt intake			
Source	g/day	Reduction needed	Target intake (g/day)
Table/cooking (15%)	1.4 g	40% reduction	0.9 g
Natural (5%)	0.5 g	No reduction	0.5 g
Food industry (80%)	7.6 g	40% reduction	4.6 g
	Total: 9.5 g		Target: 6.0 g

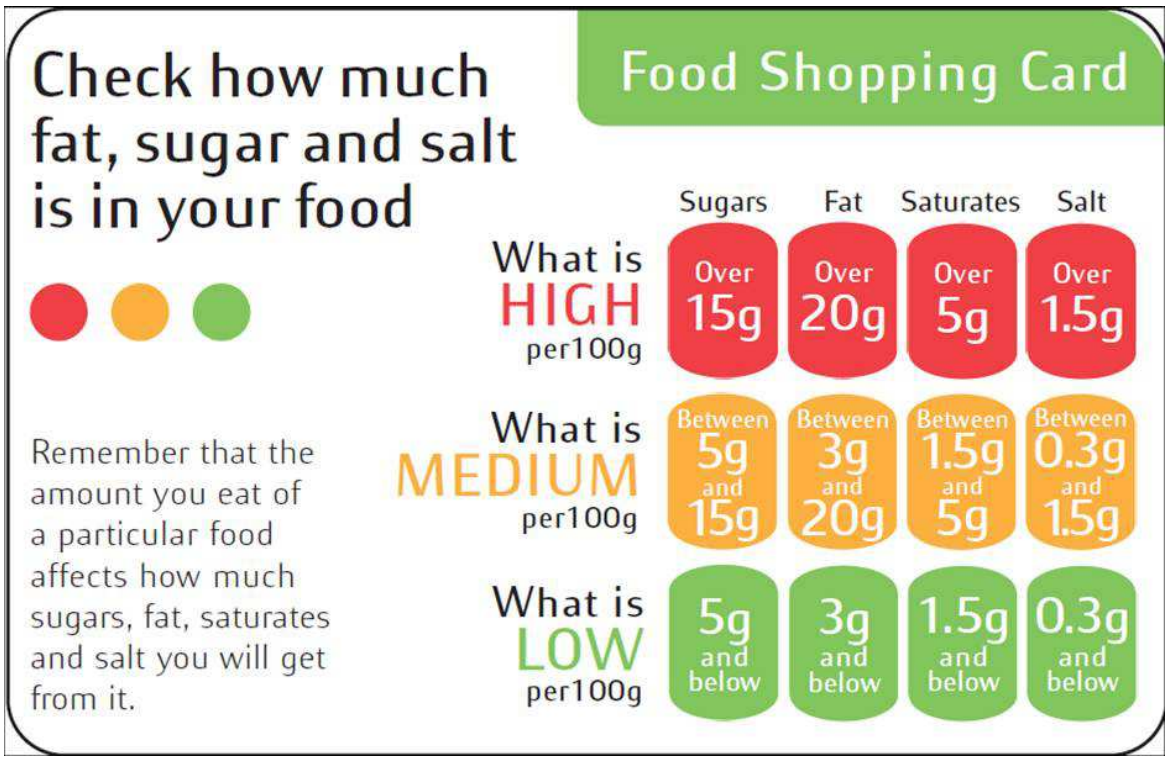
In the UK, it was estimated that only ≈15% of foods were eaten outside the home i.e. restaurant, canteen, etc. Hence, the main target in the initial phase of salt reduction focused on foods that were bought in supermarkets (3). These foods, where salt was added, were split into more than 80 categories. The FSA set target levels of salt for each food category that the food industry required to achieve within a certain time period (193). The aim was to implement a step-wise reduction in salt added to foods, reducing by 10–20% and repeated at 1–2 year intervals. Such gradual reductions are not detectable by human salt taste receptors and pose neither technical nor safety issues to the relevant foods (194). It also poses no risk to manufacturers and is well accepted by the consumers. Recently, the salt targets have been revised to ensure that salt intake will reach the target of 6 g/day by 2012 (195).

The UK salt reduction campaigns started around 2003 and have been successful. Today, the salt content in many food categories has already been reduced. These include a one-third reduction in the average amount of salt in branded, prepacked, sliced bread, and a reduction of over 40% in branded breakfast cereals (193). Table and cooking salt sales have also been reduced by ≈40–50%. The average salt intake, as measured by 24-h urinary sodium, in the general adult population in the UK has fallen from the previous 9.5 to 8.6 g/day by May 2008 (196). This change reverses the previous increasing trend for salt intake and marks the beginning of a substantial reduction in salt intake with the food industry collaboration. The UK salt reduction campaigns, which cost just £15 million, led to almost 6000 fewer CVD deaths per year, saving the UK economy by £1.5 billion per annum. This cost reflects potential savings from expenditure

associated with primary care, outpatient care, Accident and Emergency (A&E) admission, inpatient care, medications and productivity losses (197).

Clear labelling of the salt content of food is essential for assisting consumers to choose products with less salt. A front of pack signpost labelling system has been developed in the UK (Figure 1-14), which uses a combination of the 'traffic light' system, where there is a colour-coding of green, amber, and red for low, medium, and high amounts of salt, fat, saturated fat, and sugar present in the foods (198). The label also contains the Guideline Daily Amount system where the amount of salt per portion is expressed as a percentage of the daily recommended maximum. This type of standardised label is already being implemented by many supermarkets and is much preferred by consumers, as they can see at a glance whether a product has a little or a lot of salt (199).

Figure 1-14. Traffic light system labelling interpretation as suggested by FSA.



1.14.2 Other countries

In Ireland, France, and Canada, a national programme aiming for reduced sodium levels in foods has been developed in order to reduce the average

sodium intake towards the recommended amounts (20). In North America, no concrete action plans have been made yet. However, the US Food and Drug Administration recently agreed to re-examine the regulatory position on the sodium content in foods (21).

In Finland, the government has worked closely with food companies since the late 1970s to decrease the sodium content of products. They also invested in educating the physicians and the public regarding the importance of lowering sodium intake. Since the 1980s, salt-labelling legislation has been introduced in Finland; a mandatory labelling of the salt content and a “highly salted” warning if the amount of salt is higher than the set limit, and a voluntary “low or light salted” label if the salt content is lower than the set limits. These joint efforts between the government, health care sector, media, and industry have led to a reduction in sodium intake of 40% (165).

Following the UK initiatives, the National Heart Foundations of New Zealand and Australia also implemented the labelling system. The programme known as “Pick the Tick” features a logo that identifies foods that are meeting strict nutritional criteria (200).

1.15 Awareness on salt intake

Reducing salt in the diet requires knowledge of current salt intake of the population, foods that are major contributors of salt and individual’s behaviour regarding adding or avoiding salt in their diet. Currently, there are very limited studies that have explored people’s knowledge of salt and health and their current effort to reduce salt intake.

1.15.1 Role of CASH

In United Kingdom, CASH action group is actively involved in raising public awareness regarding the harmful effect of excess salt in the diet. Since 2001, CASH has been organizing a yearly event of ‘Salt Awareness Week’ to educate the public concerning the impact of salt on their health. Each year, a different theme is proposed and as for 2012 the programme focused on ‘Reducing salt ; preventing stroke’(201). During the week, CASH organizes a reception at the

House of Commons. This prestigious event creates the platform to spread the message to MPs, food retailers, food manufacturers and other supporters and stakeholders. In addition, it provides the food companies an opportunity to demonstrate their current efforts in reducing salt in their products. Also as part of the activity for the awareness week, other institutions such as hospitals, GP surgeries, health charities, schools, universities and the food industry participate in supporting events to help raise awareness among the public (201).

To increase public awareness regarding healthy salt intake, CASH took the initiative to conduct surveys among the public from time to time. For example, in a recent public survey by CASH (202), it was revealed that 90% of people in the UK are aware that excessive salt intake is detrimental to health. However, very few realize that it can contribute to other serious complications such as stroke (34%), cardiovascular disease (61%) or osteoporosis (4%). Young adults are even less likely to realize the damaging effect of salt as they possibly perceived it as irrelevant. The survey also indicated that there are differences in knowledge across the UK population. Individuals in Scotland are more likely to be aware that salt can lead to health complications compared to those in Wales (awareness score 70% and 55%, respectively). Social inequalities are also evident; people from lower socio-economic groups are over twice as likely not to know how salt can damage their health as those in higher socio-economic groups (16% vs. 7%).

1.15.2 Role of Food Standards Agency (FSA)

In order to raise awareness of salt as a public health issue and educate consumers how to reduce their intakes, the FSA has been running a public awareness campaign since 2003 with a supporting consumer focused website (190). This initiative forms an important part in making healthy eating an easier option and reducing diet-related diseases. The FSA ran 4 phases of a public awareness campaign to disseminate health issues associated with high salt intakes and highlight actions that can be taken to reduce current salt consumption (203). This supported product reformulation as it made consumers aware of the reason for products content changes and provides an incentive to industry to take action as more consumers will be opting for lower salt products.

The first phase of the campaign was launched in September 2004, with the key aim of ensuring that consumers were aware of why too much salt is bad for their health. This is followed by the second phase which was launched in October 2005, with the main messages focusing on encouraging consumers to check food labels for information on the salt content and to raise awareness of the aim to eat no more than 6g of salt a day. The FSA launched the third phase of its public awareness campaign on March 2007. The theme focused on educating consumers that 75% of the salt eaten is already contained in everyday foods as well as encouraging and enabling them to choose products with lower levels of salt (204).

All three phases of the campaign have focused on women aged 35-65 in social class categories C1 (lower middle class such as supervisory or clerical and junior managerial, administrative or professional), C2 (skilled working class comprises of skilled manual workers who have served apprenticeships e.g. foremen) and D (working class which includes semi-skilled and unskilled manual workers, including labourers and people serving apprenticeships e.g. laboratory assistants). Although men are more likely to suffer from heart disease and stroke, women continue to be the "gatekeepers" with regard to buying and preparing food in family households in the UK, hence the focus on this group. A range of media have been used to deliver the messages, including TV advertising, posters, articles in women's press and national newspapers and news coverage. As well as the salt website, all three phases of the campaign have produced materials for consumers, such as leaflets and credit card sized prompts, to try and help consumers increase their awareness of the issues and the actions they can take. For phases 2 and 3 work was also undertaken by a range of stakeholders, both in the food industry and non-governmental organisations, to try and get the campaign messages across to a wider audience (205).

Each of the strategy phases was evaluated by an independent company using a UK representative survey of 2000 adults. The evaluation of the campaign, which was conducted through monitoring changes in consumers' claimed behaviour, suggests that the number of consumers cutting down on salt has increased by 33%, a 10-fold increase in awareness of the 6g a day message and the number of consumers trying to cut down on salt by checking labels has doubled since the

campaign was introduced. Of the different methods of advertising, television produced the highest awareness level. Internet also plays a vital role as during the campaign, traffic to the FSA's website (www. salt.gov.uk) rose by 44% with over 66,000 daily visits (206).

The fourth phase of consumer awareness programme was launched on 5 October 2009. The campaign highlights the positive changes that can be attempted by consumers to reduce their salt intake. This phase reinforced the previous subjects but also introduced a new key message which emphasizes that most of the salt we eat is contained in everyday foods. Consumers were encouraged to read the foods label, to compare products, and choose foods that are lower in salt. All adults should aim to have no more than 6g of salt per day, and children under 11 should have considerably less (204).

Overall the high visibility of all three phases of the campaign has increased consumer awareness of the health risks associated with a high salt intake and recent consumer research indicates a continued downward trend in the amount of salt consumed by people in the UK. The new findings based on 24-hour urine sodium excretion indicate that the UK's average daily salt consumption has fallen from 9.5g to 8.6g, which reflects an overall drop of 0.9g since the National Nutrition and Diet Survey in 2000/01 (207). The campaigns also raised the profile of salt in the food industry and have encouraged the development of partnerships between industry, retailers and other non government organizations. Many major retailers and manufacturers have now committed themselves to reducing salt in their products and several have already met the initial targets set in 2006 (205).

1.15.3 Role of consumers

Given the considerable efforts by industry to reduce the salt content of manufactured food products for home consumption and initiatives taken by the agencies to boost public awareness, it is also necessary to highlight the importance of consumers' role to actively reduce salt in the diet. Consumers can help lower their salt intakes towards the recommended population average of 6g a day by checking products labels, buying reduced salt products and adding less salt to their food. The following guidelines had been suggested by Mahtani

(208;208) and Gilbert et. al. (184) to help consumers in reducing daily salt intake.

1.15.3.1 Reading food label

Consumers are encouraged to always check the sodium or salt content on nutritional labels upon foods purchasing. Where sodium is listed instead of salt, consumer should be able to convert the amount of sodium to salt equivalence. The use of colour coding in the 'traffic light system' is also beneficial for the consumer to identify foods with low salt content at a glance.

Currently, the practice of reading product nutrition label is still minimal. This is evident through a study conducted by Grunert et. al. (209) which investigates the use of nutrition information on food labels and its understanding among consumers in the UK. Data were collected based on in-store observations in three major UK retailers, in-store interviews and self-administered questionnaire. The study revealed that only 27% of respondents had looked at nutrition information on the package before making a selection.

1.15.3.2 Minimized processed foods intake

In United Kingdom, it is estimated that 80% of sodium intake comes from food processing, 15% is discretionary (half of which is contributed by table salt and half by added salt in cooking), and only 5% is naturally occurring in foods (3).

This so called 'hidden salt' is conveniently available in processed foods and they are often added to please taste buds which grow ever more dependent upon high-salt content foods. For example, a single slice of processed cheese may contain more sodium than an entire bag of crisps. A simple way of achieving a modest reduction therefore, would be to reduce the consumption of processed supermarket, canteen, restaurant, and fast food.

1.15.3.3 Avoid adding salt to foods

The simple measure of removing salt from the table and in cooking could cut salt consumption significantly. The use of alternative methods for food flavouring such as herbs, spices, lemon juice and chillies can be suggested. Seeking low-salt

recipes may be another way and the Food Standards Agency offers links to sites that can provide such information. For those who cannot bear to go without salt, a mineral salt with potassium (e.g. Lo-Salt) could be used. This 'low-sodium' salt however, is not recommended for patients with kidney problems.

1.15.3.4 Eating a balanced diet

As previously discussed, the Dietary Approaches to Stop Hypertension (DASH) study revealed that a diet low in saturated fat and cholesterol but high in protein, carbohydrate, potassium, calcium, and magnesium resulted in reduced blood pressure when compared with a representative average Western diet (210). When the DASH diet was combined with a lower sodium intake, the reduction of blood pressure was even greater (43). As a result the National Institute of Health now recommends the DASH eating plan. This particular diet strategy which consists of potassium-rich foods, such as bananas, avocados, dried fruit, seeds, tomato juice, and salad vegetables, together with magnesium-rich foods, such as leafy green vegetables, nuts, seeds, and oats, may provide additional benefits in reducing blood pressure when combined with a low sodium intake.

1.15.3.5 Take-away and eating outside

Food can be consumed outside the home through a variety of sources and venues – for example restaurants, fast food outlets, coffee shops, in work canteens or in leisure venues such as theme parks, sports venues and cinemas. Sixty one percent of people aged 18-24 eat out at least once a week; and 22% of people in the UK eat a takeaway at least once a week (211).

Foods offered in these venues have frequently been found to be less healthy options (high in fat, saturated fat, salt and sugar). For example, a CASH survey on 50 samples of Chicken Tikka Massala with Pilau Rice and 11 samples of Chinese chicken dishes with fried rice revealed that many contain more than a daily salt limit in a single meal (212). The survey revealed that almost two thirds (64%) of the Chinese meals tested contained more than 6g of salt per serving, which is the maximum recommended daily intake. Over half (52%) of the Indian meal samples contained more than 4g of salt, with one sample containing 7.11g

of salt. In addition, a survey by the Food Commission recently found that portion sizes in fast food restaurants have also been increasing, hence increasing the amount of total salt consumption.

Whilst the UK has now made progress in implementing better nutritional labelling for the food that is bought for consumption at home, consumers purchasing food to eat outside the home often have no way of knowing how healthy their meal is at the point of purchase. In a recent study by Mackinson et. al. (213), over half of the participants (55%) indicated that they would like to see information on salt content of menu items at all catering outlets. This study, which was based on self-administered questionnaire, was conducted to investigate UK consumers' interest for the provision of nutrition (salt, energy and fat) and ingredient information in catering outlets. Out of 786 respondents recruited, almost half of the respondents (42%) reported eating at a catering outlet at least once a week. Take-away and sandwich outlets were the most commonly frequented venues with 17.2% and 16.7%, respectively, of participants using these on a weekly basis.

1.16 Cost-effectiveness of salt reduction

Population reductions in dietary salt intake are recommended by a variety of major scientific and public health organizations. The proposal was made based on the available evidence, which has shown that significant population-based reductions in salt consumption could lower the blood pressure of enough people to produce a substantial public health benefit in both developed and developing countries. Indeed, even a modest reduction in the population intake of salt worldwide could produce a major improvement in public health.

Several studies have demonstrated that a reduction in population salt intake is very cost-effective. Murray et. al. (214) performed a global analysis, reporting estimates of the population health effects and costs of selected interventions to reduce the risks associated with high blood pressure and hypercholesterolemia. Effect sizes were derived from systematic reviews or meta-analyses, and the effect on health outcomes projected over time for populations with differing age, sex, and epidemiological profiles. Incidence data from estimates of burden of disease were used to calculate disability-adjusted life years (DALYs) averted

and patients treated, while cost incurred were either estimated based on previous publication or by local experts. The results revealed that non-personal health interventions, including government action to stimulate a reduction in the salt content of processed foods, were cost-effective ways to limit CVD and could avert over 21 million disability-adjusted life years per year worldwide. Furthermore, the combination of personal (such as treatment of individuals with high systolic blood pressure) and non-personal health interventions provide additional health benefits by reducing the global incidence of cardiovascular events by as much as 50%.

In United Kingdom, Barton et. al. (139) in a recent study indicated that by reducing salt intake by 3 g/day might reduce mean population systolic blood pressure by approximately 2.5 mmHg, equivalent to a 2% decrease in the risk reduction model. This would prevent approximately 4450 deaths from cardiovascular disease, with total discounted savings overall of approximately £347 million over a decade, representing equivalent annual savings of approximately £40 million. Any salt reduction intervention totalling up to £40m a year would therefore still be cost saving.

Other studies in Norway, Canada, and the United States have all demonstrated that salt reduction not only saves lives, but also saves money. A recent study in the US showed that collaboration with industry that decreases mean population sodium intake by 9.5% prevents 513 885 strokes and 480 358 myocardial infarctions over the lifetimes of adults aged 40–85 years who are alive today, increasing QALYs by 2.1 million and could save more than USD32 billion in medical expenses in the US alone (215).

A simulation study, also from the United States, suggested that achieving a salt reduction of 3 g/day in the American diet would be either similar in magnitude or greater than those projected for interventions targeting tobacco or obesity, interventions involving primary prevention with statins, and the pharmacologic treatment of hypertension. The study conducted by Bibbins-Domingo et. al. (216) used Markov modelling applied to US residents aged 35 years or older to assess the impact of reducing dietary salt by 3 g per day on the annual number of new cases of coronary heart disease, stroke, and myocardial infarction and on reducing annual deaths from any cause. These researchers found that a

regulatory intervention targeting a daily reduction of 3 g of salt would save, on an annual basis, 194 000 to 392 000 quality-adjusted life-years (QALYs) and US$ 10–24 billion in healthcare costs. Such an intervention would save costs even if the reduction was just 1 g per day, achieved on a gradual basis between 2010 and 2019, and it would be more cost-effective than a program of using drugs to lower blood pressure in the entire hypertensive population.

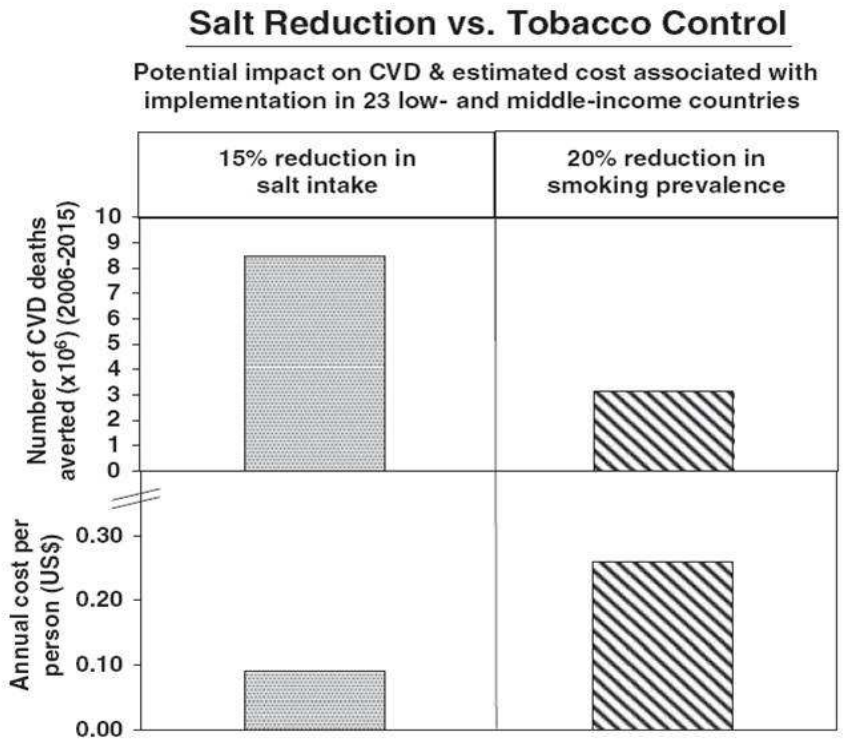
In Canada, Joffres et. al. (217) estimated the impact of dietary sodium reduction on the prevalence of hypertension and medical cost savings. The authors discovered that sodium reduction of 1840 mg/day might decrease the prevalence of hypertension by 30%, translating to a reduction of 1 million hypertensive patients in Canada, and it would almost double the rates of treatment and control for hypertensive persons. The authors estimated direct cost savings from less physician visits and laboratory tests and fewer use of drugs to be about US$ 430 million annually. They also estimated that the total costs of physician visits and laboratory services would decrease by 6.5% and predicted that among patients receiving treatment for hypertension, 23% fewer would need drugs to control their blood pressure.

Selmer et. al. (218) from Norway estimated the economic and health consequences (reduced risk of myocardial infarction and stroke due to lowered blood pressure) of interventions designed to reduce individual daily sodium intake in the Norwegian population by 6 g. Health promotion (informational campaigns), the development of new recipes for foods by the industry, reporting the salt content of foods, and levying taxes on salty food/providing subsidies for products with less salt were the possible interventions. The net cost of the interventions was minus US$ 118 million indicating cost saving. Thus, the costs of population interventions were much lower than the cost savings from fewer strokes and heart attacks.

In developing countries, where the healthcare resources are very limited, a reduction in salt intake is one of the most cost-effective interventions to reduce CVD. Asaria et. al. (219) estimated the effects and cost of strategies to reduce salt intake and to control tobacco use for 23 low- and middle income countries that account for 80% of chronic disease burden in the developing world. They demonstrated that, over 10 years (from 2006 to 2015), a 15% reduction in

population salt intake could prevent 8.5 million CVD deaths while a 20% reduction in smoking prevalence could avert 3.1 million CVD deaths. The modest reduction in salt intake could be achieved by a voluntary reduction in the salt content of processed foods and condiments by manufacturers, together with a sustained mass-media campaign aimed to encourage dietary change within households and communities. The cost for implementing such salt reduction programmes was estimated to be US$0.09 per person per year. The cost for tobacco control including both price and non-price measures was US$0.26 per person per year (Figure 1-15). These figures clearly suggest that a reduction in salt intake is more or at the very least just as cost-effective as tobacco control in terms of reducing CVD on its own, which is the leading cause of death and disability worldwide.

Figure 1-15. Number of cardiovascular disease deaths averted and financial costs associated with implementation of salt reduction and tobacco control.



From (219).

1.17 Methods for measuring dietary sodium intake

There are various ways of measuring patients' compliance towards advice to reduce dietary salt intake. A number of objective and subjective methods have

been used, and each method has its own advantages as well as disadvantages (Figure 1-16). Measurement tools have ranged from objective measures such as a 24-hour urine sodium to subjective measures such as dietary self-report through 24-hour recall or food diaries. In general, however, the choice of method involves a compromise between accuracy and ease-of-use, with relatively precise methods being difficult to perform whereas simpler methods being less reliable. Moreover, because salt intake is not fixed in each person and demonstrates considerable individual variation and daily fluctuations in the same individual, its assessment is naturally subject to limitations in accuracy.

Figure 1-16. General assessment on various methods of salt intake estimation.

Evaluation method	Reliability	Convenience
Evaluations based on dietary contents		
Weighing method	◎	×
Questionnaire method	○	△
Measurement before intake	◎	×
Evaluation using test paper or salt sensor	×	◎
Evaluations based on the measurement of urinary Na excretion		
24-h pooled urine	◎	×
Nighttime or early morning urine	○	△
The second urine sample after waking	○	△
Spot urine	△ (○*)	○
Evaluation using test paper or salt sensor	× (△**)	◎

◎, excellent; ○, good; △, fair; ×, poor. *When a formula for the estimation of the daily creatinine (Cr) excretion is used. **When a salt sensor installed with the formula is used.

From (220).

1.17.1 24-hour urine collection

The “gold standard” method of obtaining data on sodium intake in population surveys is the 24-hour urinary sodium excretion (17). In a healthy individual, urine is the major route of sodium excretion. A 24-hour period is required to capture the pattern of sodium excretion since there is marked diurnal variation in sodium, chloride and water excretion (221). Electrolytes excretion in healthy individuals reaches a maximum at or before midday, and a minimum at night towards the end of sleep. This cycle of excretion is present regardless of either sodium restricted or sodium-supplemented diet and unaffected by moderate

activity although severe exercise may produce decreased excretion of sodium and chloride (222). Certain circumstances however, may trigger the cycle disruption causing reversed pattern of the electrolytes excretions. These include healthy individuals taking large doses of cortisone, patients diagnosed with both Cushing's disease and primary aldosteronism, and night workers (223).

Typically, 24-hour urine sodium excretion can account for ~95% of dietary sodium intake. However, the within-person sodium excretion may be varied as high as 30% (224). Hence, multiple observations may assist in increasing precision in the overall mean for individuals. Since the 24-hour urine collections method takes no account of electrolytes loss via other routes other than the kidneys, there is possibility that the true sodium intake will be slightly underestimated (17).

Holbrook et. al. (225) in a study revealed that among 28 adults, average urinary excretion of sodium from seven consecutive 24-hour urine collections was 86% of that estimated from chemical analysis of duplicate diets collected over the same seven-day period. In temperate climates it is assumed that skin losses of sodium are insignificant. Sodium losses through faeces is considered small under normal condition and over wide range of consumption (226). Other losses can be regarded as negligible except those from excessive sweating which in certain circumstances (as previously stated) can be considerable.

The 24-hour urine collection offers the main advantage of not being affected by subjective reporting of dietary intakes. Nevertheless, it is subjected to a few limitations such as high participant burden which may lead to incomplete collection or attrition, complete collection must be done with no more than a few drops lost or otherwise the excretion estimate will be biased, there is no absolute check on completeness; though good survey technique may help to minimize the levels of incompleteness, and the collection must be accurately timed to avoid over- as well as under-collection (221).

The 24-hour urine collection may also be used to validate the accuracy of dietary assessment methods such as food diary or food frequency questionnaire. Validity and reliability are both important in any biochemical measurement as both imply that the data are true, unbiased measures of the variable (224).

Validity may be difficult to achieve because most biochemical measurements involve multiple stages and bias may enter the process at any point in time. National quality control schemes have led to improved quality of work in laboratories. This has led to improvement in relative validity between methods (224).

Factors other than laboratory quality control may influence the validity of a 24-hour urine sodium as a measure of dietary sodium intake. Partially collected urine specimens, heavy perspiration, secretion into breast milk, and chronic diarrhoea may interfere with the agreement between 24-hour urine excretion and dietary intake (227).

Completeness of 24-hour urine sampling may be verified by an objective marker such as para-aminobenzoic acid (PABA). Bingham and Cummings (228) had proposed the use of PABA as an objective biomarker to confirm the completeness of 24-hour urine collections, as an alternative to the creatinine method. PABA which is a B-complex vitamin, was chosen as it was considered to be non-toxic in human. Pharmacokinetically, it is proposed to be absorbed and almost entirely excreted within 24-hours and can be quantitatively measured. The excretion of PABA in the urine was found to be dose dependent (221). Normally, three 80 mg of PABA tablet are taken orally in conjunction with main meals on the day of urine collection. At this particular dose, Bingham and Cummings (228) discovered that mean PABA recovery over 24-hour period was 93% ± 4% in 33 individuals. The range between minimum and maximum values was 15% of the mean compared with 70% for creatinine excretion. The investigators then concluded that in the general population, urine collections containing more than 85% (205 mg) of the administered dose can be considered complete (with a 5% chance of incorrectly excluding a complete sample).

Although the use of PABA has proved to be valuable in validation studies, its wider use in population surveys may be more challenging. Bingham et. al. (229) reported that PABA recovery was lower in patients with renal disease with increased creatinine excretion compared to those with normal creatinine excretion. Jacobsen et. al. (230) found a gradual decline of PABA recovery with age, at a rate of approximately 1% per year from the age of 30 onwards.

Consequently, some 24-hour urine collection in older individuals might be falsely rejected (false-negative).

PABA is metabolized in the liver to p-aminohippuric acid (PAHA), and both PAHA and PABA are acetylated (221). Hydrolysis of acetylated metabolites of PABA occurs in the urine, and the free amine groups become available for detection by chemical analysis. A few drugs including sulphonamides, folic acid, paracetamol, phenacetin and furosemide contain amine groups or may be metabolized to them. As a result, erroneously high PABA recovery rates might therefore be discovered in individuals taking these drugs (228).

Since the PABA technique requires the participants taking the PABA tablets, informed consent and ethics committee approval is required (192). The technique relies on the participants taking the tablets as instructed at appropriate intervals during the 24-hour period. Non-compliance such as missing a dose or taking the tablets at the wrong times, might result in complete urine collections being falsely rejected (221). In the 2000-2001 British National Diet and Nutrition Survey, the PABA method was initially used to validate the 24-hour urine collections. However, during the first wave of data collection, one participant exhibited an acute allergic reaction presenting with generalised urticaria and periorbital oedema, leading to the procedure being discontinued for the remainder of the survey (192). Thus the utility and safety of the PABA technique for population surveys have not been established.

Overall, although PABA verification has proved to be a useful objective marker, the 24-hour urine specimens could potentially be unjustly excluded (false-negative) or included (false positive) depending on confounding factors such as non-compliance or variability in pharmacokinetics of PABA.

1.17.2 Spot urine collection

Overnight and spot (casual or single) urine collections have been proposed as low-burden alternatives to the 24-hour collection (231). In these techniques fewer voidings are required and the participant does not have to continue the collection during daily activities.

A single voiding of the bladder is all that is required for a spot urine collection. Sodium concentration and ratios to creatinine and potassium are obtained from laboratory analysis. Time of day of the collection should be standardized to minimize error introduced by diurnal variation in urinary solute excretion (232). The results of Stanbury and Thomson (233) allow estimations of variability in the ratios of sodium: potassium (Na:K) and sodium:creatinine (Na:Cr) across different urine specimens throughout the day. Large variations are apparent, not only between individuals but also within individuals in adjacent time periods.

Cummins et. al. (234) were sceptical of the use of sodium concentration from spot urines as a proxy for sodium excretion. They argued that sodium concentration relies not only on the quantity of sodium, but also the volume of fluid ingested (which varies greatly throughout the day along with sodium consumption), and the amount of water required by the kidneys to excrete a given quantity of sodium. The wide variation in Na:K and Na:Cr ratios within individuals reflect the fact that both numerator and denominator are dynamic variables.

Nonetheless, Walker et. al. (235) reported significant correlations between Na:Cr ratios in spot urine and 24-hour urine collections. For 18 individuals with normal blood pressure the correlation coefficient was 0.62 while for 37 hypertensive individuals the coefficient was 0.56. Moore et. al. (236) reported a significant correlation between 24-hour urinary sodium and the Na:Cr ratio of the next voided (morning) spot urine (r = 0.84) in eight individuals under 30 years of age with essential hypertension, but no significant correlations were apparent in 18 older people. In another study, Milne et. al. (237) reported on a study of 97 men showing significant correlations (r = 0.25 to 0.52) between sodium excretion in urine samples at different times of the day and in 24-hour collections of urine. They suggested that spot urine specimens might be useful in differentiating between individuals with large differences in electrolyte excretion.

Widdowson et. al. (232) collected single specimens of urine to study the excretion of urinary electrolytes by young children in Uganda and Cambridge, United Kingdom, and concluded that the method was useful for a group, although not necessarily for individuals. Dauncey et. al. (238) used single urine

specimens to estimate electrolyte excretion in five British towns. In a small validation study in 10 men, they found non-significant differences in estimated sodium excretion over 24 hours on comparing spot values with those measured in 24-hour urine collections. Ratios for Na:Cr ranged from 2.1 to 2.9 in four spot urine collections over a 24-hour period.

In an analysis of the 10 079 men and women from 52 population samples of the INTERSALT Study, the investigators found the ratio of sodium to creatinine assessed by spot urine to be positively correlated with sodium excretion from an independent 24-hour collection (r = 0.82 between population samples and r = 0.37 between individuals) (221). Khaw et. al.(33) reported similar estimates of mean sodium excretion based on spot urines and repeated 24-hour urine collections.

The Japanese investigators have been pioneers in developing methods to estimate sodium excretion based on spot urine samples. Kawasaki et. al. (239) reported a method of estimating 24-hour urinary sodium and potassium excretion from second morning voiding urine in adults. The study involved analysis of 24-hour urine samples and second morning voiding urine (SMU) specimen collected within 4 h after the first voiding upon awakening (but before breakfast) in 159 participants. Results from the study revealed a strong, positive and significant association between sodium concentration from both estimated and measured ($r = 0.728$, $p < 0.001$).

More recently, Tanaka et. al. (240) proposed a method of estimating the 24-hour urinary sodium and potassium excretion based on casual spot urine collection. The investigators demonstrated that Na:Cr ratio in the casual spot urine samples correlates relatively well with the Na:Cr ratio in 24-hour urine sampling ($r = 0.65$, $p < 0.01$). The estimated sodium excretion calculated based on formula incorporating the estimated 24-hour urinary creatinine excretion is also reportedly close to the actually measured 24-hour urinary sodium excretion ($r = 0.54$, $p < 0.01$). It has been suggested that this method of sodium assessment, though limited in reliability, is simple enough to be implemented and practical in clinical settings (220).

1.17.3 Food diary and 24-hour recall

Food diary is another commonly used method to assess dietary sodium intake. In this method, subjects are taught to describe and provide an estimate of the portion size or weight of the food eaten. Information about the weight of food consumed may be obtained either by requesting subjects to weigh the food or to describe portions of food in terms of household measures, pictures, food models, or pack sizes. Typically, these descriptions are then incorporated into computer programs to generate information regarding nutrient intake (224).

The number of days in which dietary intake is recorded may vary. The research question may play a role in determining the number of days for food intake to be recorded. The ideal number of daily food records will differ according to the researcher's aim of either investigating the mean of a population or an individual. The number of daily food records may also vary depending on whether the investigator is interested in a person's single day's diet or typical eating habits of an individual or population (227).

An important issue to consider is whether a single day food record estimates dietary intake as well as multiple day food records. Caggiula et. al. (241) conducted a study in which single versus multiple-day food records were compared for estimates of intake for sodium, potassium, and calories. For sodium, the averages from the one, two, and three days of food records all correlated strongly with the six-day average. Correlations ranged from 0.81 – 0.93 with the strongest correlation between the three and six-day averages. This is an expected finding since each day represented a portion of the variability in the six-day mean (227). As the number of days is increased, more of the variability was accounted for and the resulting correlation should be improved. These results indicate that when estimating group averages for sodium intake, the one-day record provided a value nearly as close to the six-day mean as a three-day average.

The same conclusion however, cannot be applied if the goal is to estimate individual intake (241). Absolute differences and mean percent differences were calculated between the one, two, and three-day means and the six-day mean. The largest absolute difference was obtained with the one-day mean. This

difference was decreased by 40-50% when the number of days was increased to three. The three-day record had the smallest mean percent difference from the six-day record. The inability of a one-day food record to closely approximate another day or days is largely due to the high degree of intrasubject variability between days.

Measures of daily nutrient intake have low reliability due to the intrasubject variability. A single day dietary record should not be obtained if the goal of the investigator is to evaluate whether or not an individual has changed their usual diet as a result of an intervention (227).

Acheson et. al. compared variation of intake among periods of one day and one, two, three, and four weeks (242). The coefficient of variation improved dramatically between one day and one week. The coefficient of variation did not improve significantly for periods longer than one week. It may be suggested, based on these data, that the determination of habitual or usual intake should be one week. However, there are several limitations to this study (227). First, the focus of this study was energy intake. It was not specific to sodium. Second, the sample consisted of only 12 men with a mean age of 24. Third, the study sample was confined to an Antarctic base and the diet was fairly limited, consisting mostly of tinned and dehydrated food supplemented by frozen meat two to three times a week.

Another common method to be used in dietary assessment is the 24-hour recall. This method may be an interview or written information concerning the previous day's intake. The actual foods consumed within the previous 24 hours were described and information on portion sizes or weights were obtained (227). This particular technique provides an ideal method and commonly employed by government agencies for national surveys (e.g. US National Health and Nutrition Examination Survey).

Both food diary and 24-hour recall depend on the ability of the participant to provide accurate information. Nelson reported the reliability, or repeatability, of 24-hour recalls to generally be good (243). Other studies have reported sodium estimates by dietary recall ($r = 0.19 – 0.28$) to be less repeatable than by urine ($r = 0.24 – 0.30$) (244;245). Nonetheless, good reliability does not imply

validity. It is therefore necessary to establish the validity of the responses obtained. A valid external measure would be ideal to assess the validity of the measurements. A 24-hour urine, if correctly collected, is often used as an external measure to assess validity of these measures (241). Another consideration is whether dietary recalls and food diaries should include weekdays and weekends. The variability of daily intakes may be high due to differing intakes during weekdays and weekends. Acheson et. al. found a significantly higher intake on Saturdays compared to Tuesdays ($P<0.05$) (242).

1.17.4 Food Frequency Questionnaire

Food Frequency Questionnaire (FFQ) is defined as " A questionnaire in which the respondent is presented with a list of foods and is required to indicate how often each is eaten in broad terms such as *x* times per day/per week/per month, etc" (246). Commonly, it is designed to assess nutrient intake including both macro- and micro-nutrients, and foods/food groups consumptions. Questionnaires used may either be developed from basic principles or adapted from existing questionnaires. They may either be interviewer- or self-administered according to the need of the study.

FFQ has been widely used among epidemiologists as a means to characterize the 'usual' dietary pattern of free living individuals. From a statistical perspective, FFQ's are the only dietary intake measure with the potential to minimize the very high intra-individual, day-to-day variability in nutrient intake without relying on multiple-day assessments of actual foods consumption (e.g. 7-day dietary record) (247). The earliest approach to quantifying usual dietary intake was the diet history, developed by Burke et. al. (248). These were professionally administered, 1½ hour interviews, eliciting descriptions of 'usual' meals and snacks, portion sizes, frequency of food consumption from broad food groups (e.g. meat, fish) and frequency of deviations from usual patterns. These data were combined to generate estimates of usual nutrient intake, based on hand-calculations from food tables.

Progressing through 1950s and 1960s, nutritionists then started to develop questionnaires for the assessment of habitual food intake based on a checklist of foods consumed over a set time period. These attempts allowed for

standardization of the data collected and reduced both cost and bias when collecting these data (247). Later in 1970's through 1980s, the 'semi-quantitative' FFQ was introduced, in which the standardized list of foods was more comprehensive, the nutrient databases were more carefully constructed, and portion sizes and seasonability were incorporated into software that generated nutrient estimates (249;250). After further refinement, revision and appraisal during the 1980's and 1990's, FFQ has become one of the key research tools in nutrition epidemiology (251).

The analytic strategy is the same for all FFQs. The frequency of consumption is multiplied by portion size and by nutrient density, and these later are summed to obtain nutrient totals. Some of the FFQs may include supplementary questions such as the types of milk usually consumed and whether chicken is eaten with or without skin. Answers to these questions are incorporated into analysis software to better refine calculation of nutrient intakes (247).

In general, a food frequency questionnaire (FFQ) is used in large-scale epidemiological studies. FFQs are often used because they are more cost-effective and easier to administer compared to other methods of dietary assessment such as weighed dietary records (WDR) or 24-hour recall (252). Other benefits and limitation of FFQs are summarized in Table 1-7.

Table 1-7. Summary of comparison between advantages and limitations of FFQs.

Advantages	Limitations
➢ Suitable for population surveys ➢ Relatively inexpensive ➢ Most amenable to web-based administration ➢ Recent improvement include on-line and web-based versions (provide convenient) ➢ Ability to capture intake of all nutrients of interest, and can provide information on overall dietary adequacy ➢ Supplementary questions may be included	➢ Typically long in view of the need to be comprehensive of common food products ➢ Should the questionnaire be administered by interviewers, an extensive training is required to ensure data consistency ➢ Usually requires validation against food diaries or biochemistry analysis in a sub-sample of the same population. ➢ Depending on the period of assessment, may be subjected to recall bias (especially when diet is assessed over long periods of time e.g. previous 12 months)

Adapted from WHO (253).

1.18 Aims of the thesis:

The specific aims of this thesis are:

1) To develop/modify a food frequency questionnaire (FFQ) for sodium intake assessment tailored to local UK foods and common portion sizes.

2) To validate the modified version of the FFQ against corrected spot urine for sodium.

3) To investigate the status of sodium intake among hypertensive patients by using modified FFQ as the assessment tool.

4) To determine patients knowledge, attitude and perception regarding dietary sodium intake.

5) To investigate the impact of sodium consumption (as estimated from the modified FFQ and spot urine sodium) on blood pressure control among hypertensive patients.

6) To explore the relationship between serum sodium and mortality.

Hypotheses:

1) Modified Food Frequency Questionnaire (FFQ) can help assess awareness of sodium intake.

2) Sodium consumption (as estimated from the modified FFQ) will predict longitudinal blood pressure control in hypertensive patients.

3) Serum sodium levels will predict mortality in hypertensive patients due to its adverse effect on blood pressure control.

2 Materials and methods

2.1 Patient recruitment for questionnaires-related study

All subjects were recruited from the Glasgow Blood Pressure Clinic, Western Infirmary, Glasgow. The clinic appointment list for the coming month (containing patient's name, registration number and time of appointment) was obtained from the BP clinic's office. Based on the list provided, the patients' address was traced by using the NHS PAS system.

2.2 Questionnaires

2.2.1 Questionnaire to estimate sodium intake

For the salt consumption assessment, the sodium Food Frequency Questionnaire (FFQ) developed by Charlton et. al. (254) was used. The investigators constructed the questionnaire based on a cross-sectional validation study in 324 conveniently sampled men and women. A repeated 24-hour urinary sodium values and 24-hour dietary record, obtained on 3 occasions were used to validate the questionnaire. Food items consumed by equals or more than 5% of the sample and which contributed ≥ 50mg sodium per serving were included in the questionnaire in 42 different categories. These included both food sources with inherent sodium, such as milk, as well as food items with a high added salt content, such as processed meat.

Patients were instructed to recall their diet for the past seven days, and marked each relevant food category with matched frequency. For each food category on the list, there is a sodium conversion factor. Total sodium consumption was derived based on sodium content of one index food per category multiply by frequency of consumption. Results were presented as X g of sodium per day.

2.2.2 Modification of the original questionnaire

2.2.2.1 Food elimination

The food items listed on the original questionnaire were screened and with the help of an expert dietician, foods which are not a custom to the locals were eliminated. Foods which were eliminated from the original version of the

questionnaire include koeksister, biltong/ dry wors, chakalaka, and monkey gland.

2.2.2.2 Category substitution

The ‘biltong/dry wors/fish biltong’ category from the original questionnaire was removed and a category of ‘dried salted meat, beef jerky and smoked fish’ was added as a substitute.

2.2.2.3 Brand substitution and addition

The following brand substitution and addition were made from the original questionnaire; ProVita® were changed to Tac®, Simba® were changed to Walkers® and McVitie’s® was added as an example of biscuit brand.

2.2.2.4 Modification of sodium content in each food category

Since the original version of the FFQ was constructed based on South African MRC Food Composition Table, a modification of sodium content in each food category was made based on UK Food Composition Table. The following steps were undertaken to convert the sodium content of each food category from the original FFQ:

- **Step 1**

  For each of the food item listed in the modified version of the FFQ, the exact-matched food was searched from the UK Food Composition table. All varieties of the particular food were also included. The amount of sodium in the UK Food Composition table was listed as mg per 100g serving. The average amount of sodium for each food category were then calculated (e.g. for white bread, there were 14 varieties of white bread listed in the UK Food Composition table. Sodium content for each of the bread ranges from 439mg to 710mg (per 100g serving). The total amount of sodium (per 100g serving) for all of these white bread were summed up, then later divided by 14, which represents the sodium content (per 100g serving) for white bread category).

- **Step 2**

To estimate average portion size of food consumption, the Food Portion Size book (255) was used along with the consultation from the dietician.

- **Step 3**

Sodium content for common portion size for each food category was finally calculated based on the following formula (Refer Chapter 3 Table 3-1 for detailed listing):

$$\frac{\text{Average sodium for each food category}}{100\ \text{gm}} \times \text{Common portion sizes (gm) estimated from Step 2}$$

2.2.3 Pilot study

The modified version of sodium intake questionnaires was then distributed among 14 healthy volunteers at the Glasgow Cardiovascular Research Centre for a pilot study. Minor changes were made to the questionnaire based on the feedbacks given by the participants. These include font sizes and spacing. The final version of the questionnaire after the amendment is included in Appendix 1.

2.2.4 Questionnaire related to salt intake awareness

A total of eight questions related to general information on salt were included in this section. This questionnaire was adapted based on Consensus Action on Salt and Health (CASH) study (256), which covers four main aspects related to sodium intake awareness, knowledge, attitude and perception (KAP). For KAP questionnaire, patients were requested to select one answer for each question, excluding the question on possible complications of hypertension where patients may select more than one answer (Appendix 2).

2.3 Mailing of the questionnaire

A cover letter, salt estimation and KAP questionnaires were mailed to the patients at pertaining address one week prior to their clinic appointment. In the cover letter, all patients were invited to participate in the study. Patients were instructed to complete the questionnaires and return to the clinic during their appointment. Alternatively, they can return the questionnaires via mail at the address as stated.

2.4 Data entry

For sodium intake FFQ, each individual response from patients were transferred to an excel file where total sodium consumption per day were calculated. This result was then transferred to the SPSS program together with the response from KAP questionnaire.

2.5 Questionnaire feedbacks

All patients were offered feedbacks regarding the questionnaires that had been completed. Patients had the options of having a personal session during their next clinic visit or being notified via mail. Each patient received a summary of personalized daily salt intake status and was offered advice regarding a healthy salt intake. A leaflet containing information regarding low-salt diet was also distributed to the patients.

2.6 Laboratory tests

2.6.1 24-hour urine collection

A single 24-hour urine sample was collected from sub-sample of the study population. Subjects were provided with a plastic container. On the day of the collection, patients were instructed to discard their first urine of the day upon awakening. The collection was then started from the second time the patient passed urine, and continues for the next 24 hours including the first urine of the next morning. Patients were instructed to store the container in a cool, dark place before returning them to the clinic on the following day. The collected

urine was then sent to the Biochemistry laboratory in the Gartnavel General Hospital for electrolyte measurements.

2.6.2 Spot urine samples

Spot urine samples were obtained from patients upon the collection of the completed questionnaire, when they arrived for clinic's appointment at the Glasgow Blood Pressure Clinic. A plastic vial is provided to each patient, and they were instructed to collect a midflow sample.

2.6.3 Urinary electrolyte and creatinine

Urinary electrolyte (sodium, potassium, urea and chloride) were measured in the routine clinical biochemistry laboratory, Gartnavel General Hospital, Glasgow, using an Ion specific electrode method. Creatinine was measured using the colorimetric method.

2.7 Data from Glasgow Blood Pressure Clinic Database

2.7.1 Study setting and study population

The Glasgow blood pressure clinic (GBPC) provides secondary and tertiary level service to individuals with hypertension from the West of Scotland. Data from patients attending the clinic are stored in a computerised database, which contains information of individuals attending the clinic from the mid 1970s until 2011. Record linkage with the office of the Register General for Scotland allows identification of all deaths and causes of death in clinic attendees.

2.7.2 Collection of data and follow up

All patients were treated at GBPC until they achieve target BP and are maintained at that level for at least three months. The frequency of visits to GBPC mainly depends on individual patients BP levels and presence of other co-morbidities. Patients who achieved the target BP level were transferred back to the referring physician for ongoing management.

2.7.3 Clinical measurements

Blood pressure measurements were taken manually 3 times, using standardized sphygmomanometers at each visit by specialist hypertension nurses; the mean of the last 2 measurements is recorded at each visit. Patients attending the clinic were advised to take their regular medications as usual. Height and weight of all patients were measured using standardized equipment during each visit. Blood samples were collected at baseline and at regular intervals for estimation of routine haematological and biochemical indices. Estimated glomerular filtration rate (eGFR) was calculated from the baseline serum creatinine values using the Modification of Diet in Renal Disease Study Group (MDRD) equation (257). A structured format was used to assess the presence of existing cardiovascular disease, tobacco (any versus none) and alcohol use (any versus none). All data were electronically captured and maintained as a large single database.

2.7.4 Outcome assessment

Records kept by the General Register Office for Scotland ensured notification of a subject's death (provided that it occurred in the United Kingdom) together with the primary cause of death according to the International Classification of Diseases, 10th Revision, Version for 2007 (ICD-10), codes. We considered cardiovascular deaths (CVD mortality; ICD-10 codes I00-I99), ischemic heart disease deaths (IHD mortality; ICD-10 codes 120-I25), and stroke deaths (stroke mortality; ICD-10 codes I60-I69) in the analysis. Deaths other than due to cardiovascular causes are classified as non-CVD deaths. Mortality data were collected up to April 2011 allowing a maximum of 35 years for participants who had been under follow up for the longest time.

2.8 Statistical analysis

Statistical Package for the Social Sciences (SPSS. version 18.0) and Data Analysis and Statistical Software (STATA Version 12.0) were used for data recording and analysis. Details on specific analysis used were described in each chapter under the 'statistical analysis' section.

3 Modification and validation of questionnaire to estimate sodium intake

3.1 Introduction

Estimation of salt intake among hypertensive patients is important for accurate advice concerning the need for reduction. Daily salt intake may be estimated using food consumption data collected from interviews and diaries, spot urine collection or from 24 hour urinary sodium excretion. Each method has its own advantages and disadvantages, with some relatively more inconvenient to perform than the others (227).

There are various issues concerning the methods for dietary sodium measurement. High intra-subject (45%) and inter-subject (45-56%) variability for reporting of non-discretionary salt usage may influence reliability of food record estimates (258). It has been suggested that 81 days of dietary recording would be required to estimate an individual's intake within 10% of the observed mean. For this reason, the gold standard for assessment of salt intake is considered to be repeated 24-hour urinary sodium excretion (259). This method, though accurate, is not ideal for large community-based studies since it is time-consuming and inconvenient to the individual performing the collections. Incomplete urine collections are also quite common, resulting in under-estimation.

A simple method to estimate population mean levels of 24-hour urinary sodium excretion from spot urine specimens has been developed by Japanese investigators (240). This particular method has been suggested to be more convenient and applicable for an out-patient setting. The investigators estimated daily salt intake by using formulas comprising of predicted creatinine excretion multiply by sodium to creatinine ratio, derived from a "spot" urine specimen. The results showed a high correlation between spot urine sodium concentration and 24 hour urinary sodium excretion. Despite the reliability of the spot urine method in estimating salt consumption has been confirmed in population studies, its role in estimating individual salt intake remains uncertain (254).

The food frequency questionnaire (FFQ) has been proposed as a precise measure for the evaluation of the intake of nutrients, and has been used extensively for various purposes (246). For example, Charlton et. al. (254) developed a short

FFQ for dietary salt intake assessment among multi-ethnic, economically active South African sample. The questionnaire was constructed based on repeated 24-hour urinary values and dietary recalls obtained on 3 occasions. Results from the study revealed that FFQ performs as well as the dietary recalls against urinary sodium excretion and shows an acceptable correlation against the repeated dietary recalls.

In an out-patient hypertension clinic setting, the estimation of salt intake should ideally be accomplished for all patients so as to complement patient's optimum hypertensive management. While time constraints in clinics make this difficult, short questionnaires such as those previously discussed, suitably adapted to local foods, could be used for this purpose. Therefore, the aim of the present study was to modify the FFQ for salt intake estimation which has been developed by Charlton & colleagues and have it validated against spot urine sodium among out-patient hypertensive patients.

3.2 Methods

Detail methods for this chapter regarding questionnaire modification have been previously discussed in Chapter 2 Section 2.1 up to 2.6. In total, 997 questionnaires we mailed to patients at the Glasgow Blood Pressure Clinic between the periods of 1st May 2009 to 30th June 2010.

3.2.1 Corrected spot urine for sodium concentration

Biochemistry result for sodium concentration from the spot urine collections were corrected based on formula by Tanaka et. al. (240). Detail discussions were outlined in Chapter 5, Section 5.2.2.

3.2.2 Sub-samples for repeat FFQ (Reproducibility test)

For repeat FFQ assessments, an interval of 1 year was used to administer the repeat questionnaires for two reasons. 1) According to Cade et. al. it is not recommended to administer a repeated FFQ at a very short interval as respondents may still remember, and tend to repeat their previous responses

(251), 2)At GBPC, repeat clinic appointments are commonly scheduled at 6 to 12-monthly interval. Therefore, a one year interval was chosen to address the first issue and also to ensure that all subjects were administered the repeat questionnaire at approximately similar interval periods. A total of 62 patients completed the questionnaire in May 2009, hence the repeated FFQ were sent to all of these patients 12 months later (May 2010). From published literature, reproducibility testing of questionnaires is done with around 20-25 samples. In this study 62 subjects completed the repeat questionnaires and all of them were included to assess reproducibility.

3.2.3 Sub-samples for 24-hour urine collection

Patients who returned the questionnaires and provided spot urine samples were approached to provide a single 24-hour urine collection. A random sampling method has been attempted, however, due to poor patient compliance with this procedure, complete 24-hour urine collection were only available for eight patients. This is a limitation of the study and other methods to improve patient compliance with 24-hour urine collection will need to be explored in future studies.

3.2.4 Data analysis

Mean, standard deviation, median and range were used to describe the results of sodium intake estimation based on FFQ and corrected spot urine. Pearson's correlation was used to investigate the association between FFQ, corrected spot urine, and 24-hour urine collection. To test the agreement, kappa analysis was performed while paired sample t-test was used to identify any discrepancy between the two measurements from the FFQ in the subsample analysis. For Kappa analysis, sodium levels were categorized accordingly. For FFQ, patients who consumed more than 2.4 g of sodium/day (equivalent to 6g of salt/day) were labelled as 'high' while those with 2.4 g of sodium/day and below were categorized as 'not high'. Similarly, for corrected spot urine, patients with more than 100 mEq of sodium/day (equivalent to 6g of salt /day) were considered as 'high' while those with 100 mEq of sodium/day and below were categorized as 'not high'. Sensitivity and specificity analysis were also performed to test the

precision of the modified FFQ. All results were analysed using SPSS version 18 and tables and figures were presented as the followings.

3.3 Results

Out of 997 questionnaires being sent throughout the study period, 632 were returned to the clinic. Three questionnaires were rejected since the patients did not answer the FFQ section at all or replied ‘never’ for all of the foods listed, and two questionnaires were returned to the clinic due to unknown address. Total FFQ included in the final analysis was 627, providing a response rate of 63%. With regards to subsample of patients where the FFQ were mailed for a second time at 12 months later, thirty one out of sixty two patients replied, providing a response rate of 50%. Spot urine samples were collected on 234 patients, whereas only eight patients agreed to provide 24-hour urine samples. Detailed demographic of patients who completed the FFQ were presented in Chapter 5 Table 5-2.

The various food items included in the FFQ, common portion size and average sodium content per serving were all listed in Table 3-1. There were 42-categories of items listed in the questionnaire, mainly consisting of processed foods such as meat products, snacks and fast foods. Patients were asked how frequently each food category was consumed during the past seven days, with options for response ranging from ‘never’ up to ‘three times or more daily’. Detail methods on how the FFQ provides estimate for daily sodium consumption were discussed in Chapter 2 Section 2.2.1.

3.3.1 Determination of average Na content for each food category

Table 3-1. Various food items, common portion sizes, and sodium content per serving as listed in the modified version of the FFQ.

Food	Average sodium content (mg) /100g	Common portion sizes	Average sodium content/ serving
White bread/ white bread rolls/ pita /croissants	545.5	2 slices = 72g	392.8
Brown/ wholewheat bread/ rolls	543.1	2 slices = 72g	391.1
Breakfast cereal (processed eg. cornflakes, rice crispies)	452.6	30g	135.8
Breakfast cereal (minimally processed-weetbix, muesli, etc.)	337.4	50g	168.7
Crackers (Tac, etc.)	650.5	3 pieces = 21g	136.6
Cookies, biscuits, rusks (McVitie's, etc.)	314.3	3 pieces = 30g	94.3
Cake/ scone/ muffin/ puddings/ pancake/ fruit pie/ tarts	283.0	60g	169.8
Roti/ samosa/ spring roll/ doughnut	253.1	130g	329.0
Pizza	319.6	2 slices = 167g	533.7
Pasta or noodle dishes with cheese sauces (macaroni cheese, lasagne, noodle salad, spaghetti bolognaise etc.)	247.9	230g	570.1
Popcorn	30.0	75g	22.5
Crisps (Walkers,etc.)	794.3	40g	317.7
Beef sausages	1096.7	2 pieces = 80g	877.3
Processed meat, cooked, smoked or canned eg Salami/ bacon/ pork sausages	1076.9	46g	495.4
Meat or chicken pies/ sausage rolls	502.3	130g	653.0
Chicken – battered (KFC, etc.) or chicken burger	405.6	2 pieces =140g	567.8
Meat and meat dishes (steaks, minced meat, cottage pie, mince, meatballs, stew, chicken stew etc.)	144.2	310g	447.0
Gravy, made with stock or gravy powder	3395.0	50g	1697.5
Dried salted meat/ beef jerky/ smoked fish	2127.1	56g	1191.2

Food	Average sodium content (mg) /100g	Common portion sizes	Average sodium content/ serving
Milk (all types, also dairy fruit juice, malted milk, milk shakes, chocolate drinks, evaporated & condensed milk)	130.0	200g	260.1
Fermented milk/ sour milk	0.01g/65 ml bottle	1 bottle	0.01
Cheese	693.7	40g	277.5
Yogurt	82.9	125g	103.7
Eggs (any preparation)	380.7	50g	190.4
Tinned fish (tuna, sardines, etc.)	628.6	100g	628.6
Other fish and seafood (eg battered fish, prawns, crabs, mussels)	244.2	150g	366.3
Potato chips/ French fries or potato salad	67.7	165g	111.7
Canned vegetables, including baked beans, tomato paste, sweet corn, olives etc.	359.6	135g	485.5
Soup (all types)	1263.6	220g	2780.0
Salad dressing/ mayonnaise	806.9	30g	242.1
Ice cream (all types)	68.2	75g	51.1
Margarines, all types, also butter	656.6	14g	91.9
Worcester sauce/relish/ barbecue or steak sauce	922.1	20g	184.4
Savoury sauces (mushroom, white, cheese)	766.5	62g	475.2
Tomato sauce/ Ketchup	985.0	20g	197.0
Salt (added to cooking or at the table)	38850.0	1g	388.5
Mustard/ all purpose seasoning mix	2285.0	2g	45.7
Peanuts (salted/unsalted/raw)	260.6	50g	130.3
Peanut butter	360.0	25g	90.0
Marmite/ Bovril	4335.0	9g	390.2
Chocolate - sweets or sauce	103.5	54g	55.9
Beer and cider	7.2	1 pint = 574g	41.5

3.3.2 Validating the questionnaire

3.3.2.1 Sodium estimation from FFQ and corrected spot urine for sodium

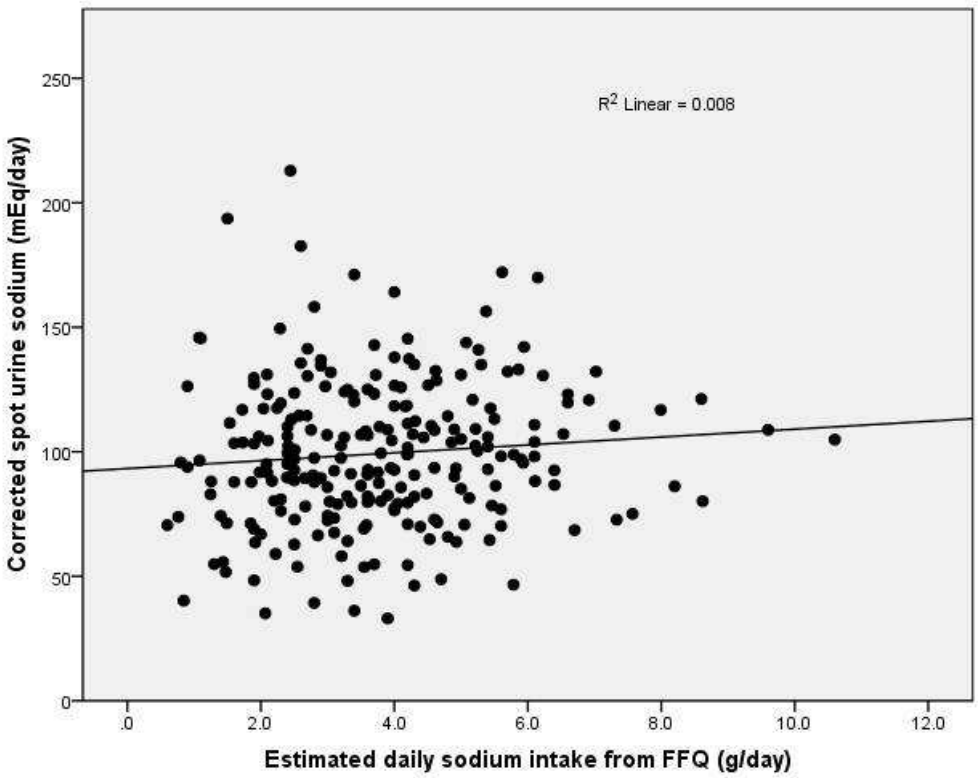
Table 3-2. Comparison between sodium estimation based on the FFQ and corrected spot urine for sodium.

	Spot urine (mmol/day)	Spot urine (g/day equivalent)	FFQ (g/day)
N	234	234	234
Mean **Overall** **Men** **Women**	 99.08 103.53 95.13	 2.279 2.381 2.188	 3.779 4.008 3.580
SD	30.938	0.712	1.695
Median	97.10	2.23	3.60
Range	33 - 262	0.76 – 6.03	0.6 – 10.6

Sodium estimation based on questionnaire revealed higher results for the overall mean, men and women when compared against the results from corrected spot urine for sodium. Further analysis showed a significant difference between the average sodium intake between men and women based on corrected spot urine ($p = 0.020$), but not according to the FFQ ($p = 0.408$).

3.3.2.2 Correlation between FFQ and corrected spot urine sodium

Figure 3-1. Scatter plot showing the correlation between FFQ and adjusted spot urine sodium (n=234).



There appears to be little correlation between sodium intake estimation from the FFQ and corrected spot urine sodium ($r = 0.092$, $p = 0.155$).

3.3.2.3Test of agreement (Kappa) between FFQ and corrected spot urine sodium

Table 3-3. Kappa analysis between FFQ and corrected spot urine sodium (n=234).

Symmetric Measures

		Value	Std. Error	CI	Approx. Sig.
Measure of Agreement	Kappa	.056	.052	-0.046 to 0.158	.281
N of Valid Cases		234			

Kappa analysis revealed only slight agreement between the FFQ and corrected spot urine for sodium (260). The result however was found to be non-significant ($p = 0.281$).

3.3.2.4 Sensitivity and specificity of FFQ

Table 3-4. Crosstabulation between categories of sodium intake as assessed by FFQ and corrected spot urine sodium.

			Corrected spot urine sodium		Total
			High	Not High	
FFQ	High	Count	85	95	180
		% of total	36.3%	40.6%	76.9%
	Not High	Count	21	33	54
		% of total	9.0%	14.1%	23.1%
Total		Count	106	128	234
		% of total	45.3%	54.7%	100.0%

A sensitivity and specificity values were derived based on the above crosstabulation table. The questionnaire was demonstrated to have a sensitivity value of 80.2% and specificity of 25.8% against corrected spot urine sodium. Positive predictive value was found to be 47.2% and negative predicted value was 61.1%.

3.3.2.5 Reproducibility test

Figure 3-2. Scatterplot showing correlation between results of daily sodium intake derived from baseline FFQ compared to the same FFQ administered at 12-months later.

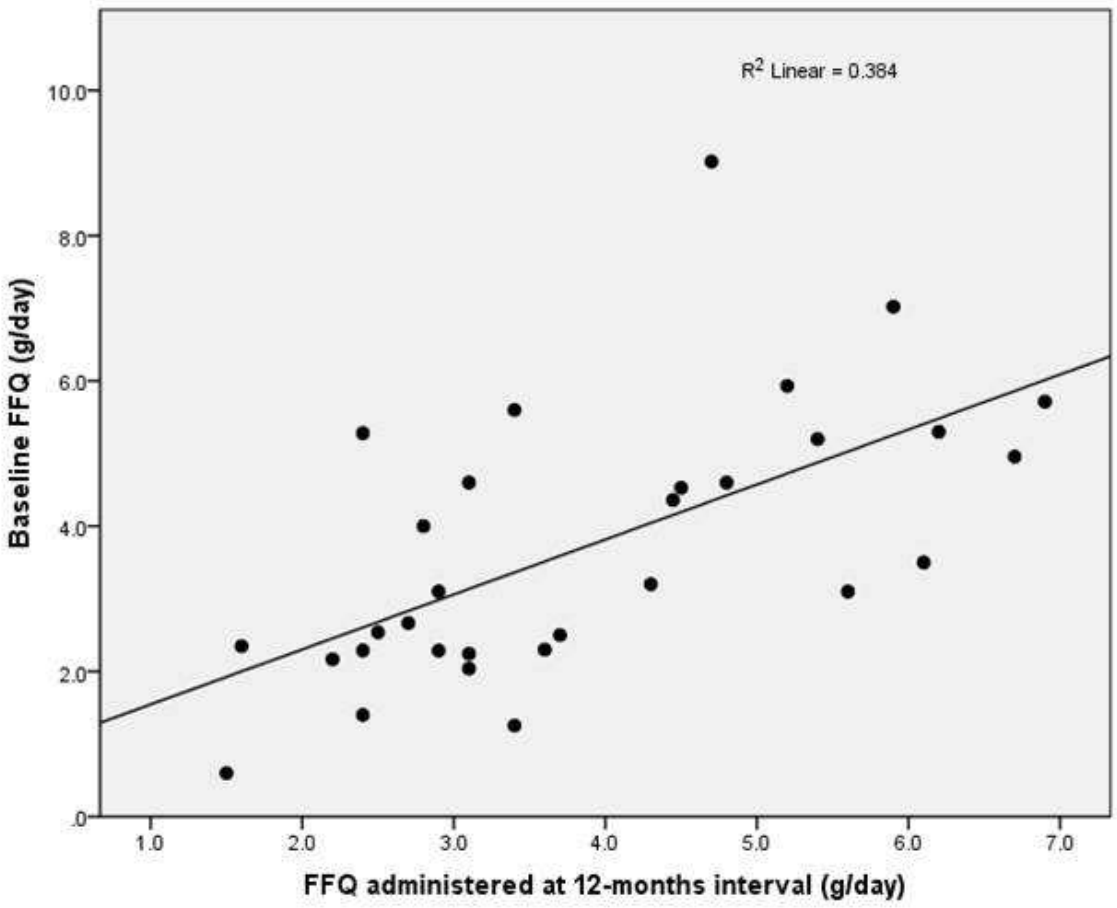


Figure 3-2 illustrates the correlation between the results from FFQ administered at baseline, and the same FFQ which was administered at 12 months later. The correlation between the two results were found to be moderate and significance ($r = 0.619$ and $p = 0.000$).

3.3.2.6 Test of agreement (Kappa) between first FFQ and second FFQ

Table 3-5. Crosstabulation between the results from the first administered FFQ compared against the results from the same FFQ administered at 12-months interval.

			FFQ2		Total
			High	Not High	
FFQ1	High	Count	20	1	21
		% of total	64.5%	3.2%	67.7%
	Not High	Count	5	5	10
		% of total	16.1%	16.1%	32.3%
Total		Count	25	6	31
		% of total	80.6%	19.4%	100.0%

Table 3-6. Kappa analysis between the first FFQ and second FFQ.

Symmetric Measures

		Value	Std. Error[a]	CI	Approx. Sig.
Measure of Agreement	Kappa	.505	.168	0.176 to 0.834	.003
N of Valid Cases		31			

Based on the crosstabulation table as demonstrated in Table 3-5, a Kappa analysis was computed. The results revealed a moderate and significant agreement between the two measurements (K = 0.505, p = 0.003).

3.3.2.7 Paired t-test between baseline FFQ and FFQ administered at 12 months later

Table 3-7. Paired samples t-test result for the first FFQ administered at baseline and second FFQ administered at 12 months later.

Paired Samples Test

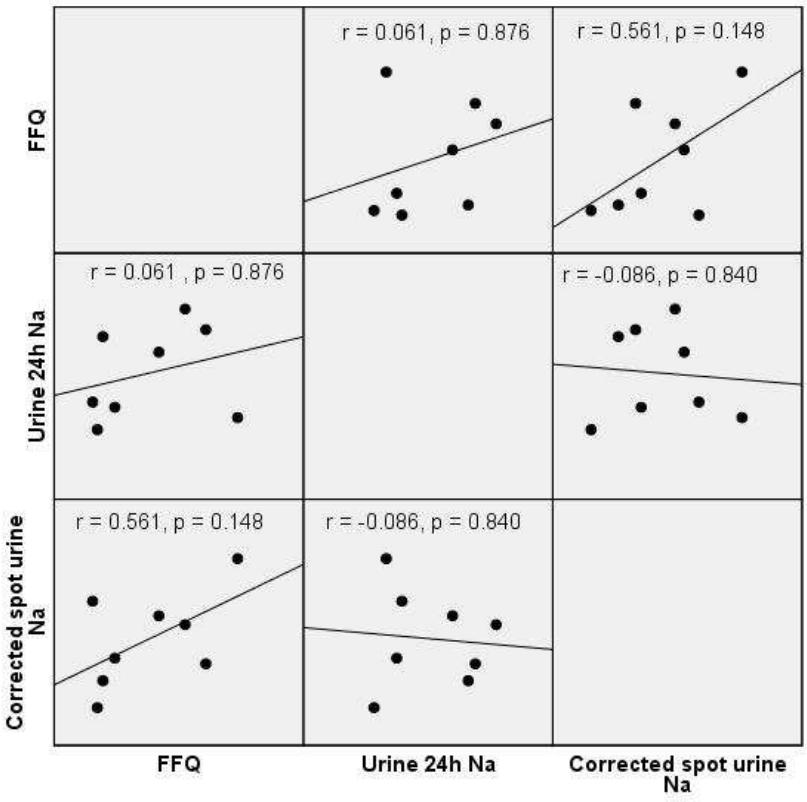
		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	FFQ 1 and FFQ2	-.1549	1.5109	.2714	-.7091	.3993	-.571	30	.572

Paired samples t-test between the results from the first FFQ administered at baseline and second FFQ which was administered at 12 months later showed no significant difference between the two measurements ($p = 0.572$).

3.3.3 Sub-sample analysis

3.3.3.1 Correlation between 24-hour urine sodium, spot urine sodium and FFQ

Figure 3-3. Scatter plot of sodium intake as estimated according to FFQ compared against urine 24-hour urine and corrected spot urine for sodium.



Pearson correlation showed a positive, moderate correlation (though non-significance) between sodium estimation from FFQ and corrected spot urine sodium in our sub-sample analysis. Other correlations (FFQ vs. corrected spot urine sodium, 24-hour urine sodium vs. corrected spot urine sodium) revealed poor, non-significant association.

3.3.4 Discussion

Accurate estimation of sodium intake is challenging due to varied sodium distribution in foods, widespread use of sodium chloride in cooking and as table salt, and the extensive use of sodium compounds in food processing (254). In United Kingdom, the average salt intake as determine from by 24-hour urinary sodium was 9.5 g/day (261) which was higher than current recommended value of no more than 6 g/day (13). Processed foods are thought to account for as much as 80% of total salt intake, followed by discretionary salt usage (15%) and naturally presence in foods (5%).

Determination of salt intake among hypertensive patients is important since dietary salt restriction had been proven to improve blood pressure control in conjunction with optimum pharmacological management. In order for advice to reduce salt intake to be targeted to those with excessive intakes, reliable estimations of habitual intake are required. We developed a modified version of sodium intake assessment tool based on the original FFQ developed by Charlton et. al. (254). This fast and convenient instrument of sodium intake measurement may be used as a motivational tool to quantify daily dietary salt intake and to set targets for lifestyle changes within out-patient clinic setting.

Urinary sodium is considered to be the ‘gold-standard’ for estimation of sodium intake, although it does not provide information regarding the quantity of nutrients consumed, nor what dietary habits are involved. It is therefore of limited value in planning educational including diet intervention (262). In this study, we use the modified sodium FFQ containing list of foods which were mainly high in sodium content. This FFQ was validated against spot urine sodium which had been corrected according to Tanaka et. al. (240). This method of correction allows the urine sample to be collected at ‘one-off’ point and can be performed at any time of day which provides convenient to the patients.

Results from our study revealed that mean sodium intake as estimated from the FFQ was higher compared to mean sodium level based on corrected spot urine sodium (3.786 g vs. 2.279 g, respectively). This is in contrary with the findings from the original study (254) where mean sodium from FFQ were found to be lower than 24-hour urine sodium. Modification to the original questionnaire by

including average sodium content of all foods listed in each category, rather than using the exact sodium content based on an index food as a representative of the category as per original FFQ, might have contributed to such findings. Men were found to have significantly higher sodium consumption compared to women as evident by spot urine. This correlates with FSA report which indicated that average salt intake in the UK for men as reflected by 24-hour urine collection was 166 mmol/day compared to 131 mmol/day in women (263). Reasons being men in general had higher caloric intake, leading to higher total sodium consumption (264), lack of awareness of good dietary practice, and little understanding of the effect of high salt consumption on health status (202). Furthermore, gender differences in sensitivity to salt may have contributed to an increased use of discretionary salt amongst male (61).

Our analysis also demonstrated a poor, non-significant correlation between reported sodium intakes from the FFQ compared against the corrected spot urine for sodium. In addition, Kappa analysis showed very little and non-significant agreement exist between the two methods of sodium assessment. The discrepancy between the questionnaire estimation of sodium and the urinary excretion could possibly be attributable to the time reflective between the two measurements. The spot urine samples collected during the clinic appointment were most likely suggest the amount of sodium consumed during breakfast, up until the period before lunch time. Whereas the questionnaire represents the average of daily sodium consumption based on the frequency intake of various foods which had been consumed for the past seven days. In addition, our version of modified FFQ contained the average amount of sodium content for all of the food listed within each category, which would contribute to the higher overall sodium estimation as compared to the urinary measure.

Other similar studies also revealed low correlations between dietary reports and urinary estimations of sodium. Sowers et. al. (265) in a cross-over study, provided a diet containing either 2000 or 3500 mg of sodium for 7 days and sodium intake was estimated from seven 24-hour urinary sodium collections per diet period. Urinary sodium analyses were significantly associated with duplicate chemical food analysis ($r = 0.61$), but not with sodium intake estimated from food composition tables ($r = 0.05$). Thus, even under strictly controlled environment, whereby food not provided by the research centre was obtained in

duplicate and accounted for, where monitoring of intake and wastage took place daily, and where added salt intake was carefully measured, dietary analyses did not correlate with urinary sodium excretion. These findings imply that dietary assessment methods that rely on food composition tables are unable to accurately calculate the sodium content of foods, probably due to the large variation in portion sizes and huge range of sodium content in processed foods (254).

Based on the categorisation of sodium intake as represented by Table 3-4, the FFQ has a high sensitivity (80.2%) but low specificity (25.8%). Out of 106 urine sample that was tested high on sodium content, 80.2% was correctly identified by the questionnaire. The negative predictive value indicates that, provided a questionnaire result of less or equal to 2.4 g/day (not high category), there is 61.1% chance than a patient will have a corrected spot urinary sodium concentration below 100 mmol/day. The positive predictive value however is only moderate, suggesting that those with questionnaire results more than 2.4 g/day, had a 47.2% probability that the corrected spot urinary sodium concentration would be above 100 mmol/day. With a strong sensitivity, and high negative predictive value, the questionnaire therefore would be a useful initial screening tool to classify patients as having high or desirable sodium intake. Patients who were tested low sodium intake from the FFQ, were more likely to comply with the sodium restriction, whereas those who score more than 2.4 g requires further evaluation such as urinary analyses or screening of food consumption pattern from the FFQ. The low Kappa value between the questionnaire and corrected spot urine samples further indicates that the FFQ needs additional refinement.

The reproducibility of FFQs has generally been assessed by administering them at two points in time to the same group of people and correlation coefficients used to assess the association between the two responses. The reproducibility of salt intake from repeat FFQ administered at least 12 months apart was moderate with r = 0.619 and kappa = 0.505. Paired sample t-test showed no significant difference between the 2 measurements. According to Cade et. al. (251) correlation coefficients between two administrations of an FFQ of 0.5 to 0.7 are quite common. Repeat administration of the FFQ at 1 month or less were more likely to results in higher correlation coefficients compared to repeat

administrations further apart. The fact that correlations results in this study were moderate and comparable with other studies shows that the FFQ provides reliable estimates of salt intake in our study.

There are, however, a few limitations to be considered in the present study. The FFQ sodium assessment offers the advantages of being simple, quick, and easy to understand and convenient to administer. The questionnaire reflects overall sodium intake over the past 7-days period which include weekend days when sodium consumption may differ. Nevertheless, we are only measuring a single nutrient (sodium) rather than a combination of other micronutrients. The current version of the questionnaire, which mainly includes lists of sodium-rich foods, does not allow provision for the testing of hypotheses of other nutrients such as potassium or calcium (254). Another potential limitation to consider is that the FFQ did not take into consideration total energy intake nor did it consider sodium intake as a function of estimated energy requirements, as been attempted by other studies (265;266). Rationally, the more foods a person consumes, the more likely they are to have a higher intake of sodium.

Due to staff, technique, and time restriction, we were only able to perform cross validation against 24-hour urine sample in 8 subjects. Results from the analysis revealed a weak positive association with FFQ and a weak negative association with corrected spot urine sample. None of the correlations were significant due to small sample size. It is recommended for future studies, to include more 24-hour urine samples as this would greatly improve the validity of the modified questionnaire. In addition, patients own dietary record should be incorporated to provide a clear idea on the type of foods consumed together with exact portion sizes. As suggested by Ferreira-Sae et. al. (267), the use of more than one measure in validating a food frequency questionnaire would strengthen its validity since it is able to capture all different dimensions of the actual total intake of sodium.

Finally, the use of morning spot urine sodium as a method of validation for the questionnaire should be given a fair valuation. Previous studies have reported that this approach provides a valid estimate of sodium intake in healthy control participants (239) and patients taking antihypertensive therapy (268), and has been used in previous research (269;270). Nevertheless, Mann et. al. (271)

suggested that random urine sample was not significantly correlated with actual 24-hour sodium excretion. Alternatively, urine samples obtained late afternoon/early evening should be used instead as they were found to be strongly correlated with actual 24-hour sodium excretion ($r = 0.86$, $p < 0.001$).

In, summary the modified FFQ can be a useful tool for quick assessment of sodium intake in hypertensive population. For more accurate estimation of sodium consumption, the FFQ should be used in conjunction with other robust dietary measure such as serial spot urine measurements or 24-hour urine collection.

4 Knowledge, attitude and perception study in relation to salt intake

4.1 Introduction

High-salt diet has been associated with elevated blood pressure level (30;41). Hence, reducing salt intake with the ultimate aim of decreasing chronic illness, is an important public health intervention. Strategies to reduce population salt consumption should be multi-faceted, with public education being targeted as one of the fundamental approach.

Awareness regarding dietary salt intake is essential among general public, in particular individuals with high blood pressure. Optimum pharmacological management coupled with strict dietary salt control have been shown to improve blood pressure control in hypertensive patients (272). It is therefore important to determine the patterns of salt intake, both discretionary and consumption of processed foods, being frequently consumed by this specific population. Acquiring this data will enable health educators to target advice at the relevant patients groups. It can also be used to persuade the government and food manufacturers in relation to understanding how to reduce the salt content of processed foods frequently consumed by particular groups of consumers.

Findings from a questionnaire by Tilston et. al. (273) suggested concern among consumers regarding the impact of high salt intake on health. Despite awareness of the potential harmful effects of salt, findings showed a low use of salt alternatives and limited awareness of reducing salt consumption. Consumer knowledge of the salt content of specific processed foods was assessed revealing a poor level of knowledge. The same study also reported high levels of awareness of low salt foods, but low levels of purchase.

A recent study by CASH (202) revealed that whilst as many as 9 out of 10 people in the UK knew that too much salt is harmful, very few have any idea how it can affect their health. The study, which included all adults aged 16 and over in Wales, England and Scotland, was conducted to investigate public awareness regarding the danger of high-salt diet. Men, young adults and those from lower socio-economic groups appear to be much less aware of the effects of salt on their health. Knowledge regarding osteoporosis and stomach cancer is also low despite the evidence linking salt intake to both conditions is very compelling.

The studies available to date provide useful information in relation to awareness and salt consumption patterns and related issues among general public. With a lack of recent research targeting specific hypertensive population, it was the objective of this research study to establish current trends in awareness and practice regarding salt consumption among hypertensive patients.

4.2 Methods

The detail methods for this chapter have been previously described in Chapter 2, Section 2.2.4. Out of 997 KAP questionnaires being sent throughout the study period, 632 were returned to the clinic. Five questionnaires were rejected due to incomplete response (patient failed to answer at least 5 out of eight questions), and two questionnaires were returned to the clinic due to unknown address. Total KAP questionnaires included in the final analysis was 625, providing a response rate of 63%. Results from the questionnaires collected were analysed and presented as follows.

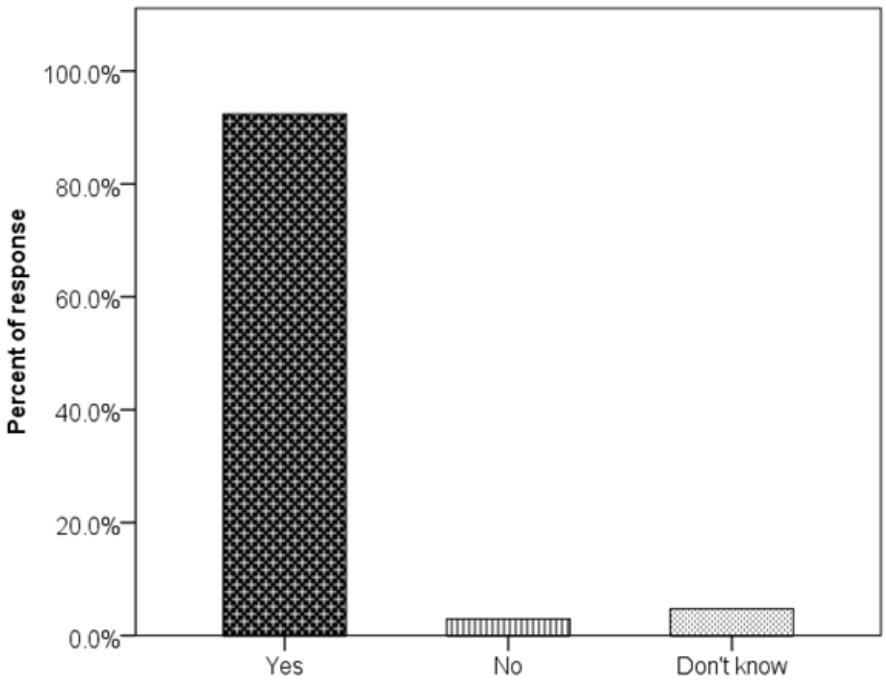
4.3 Results

4.3.1 Demographic characteristics

Details demographic of responders were presented in Chapter 5 Section 5.3.1.

4.3.2 Awareness on the harmful effects of high salt intake

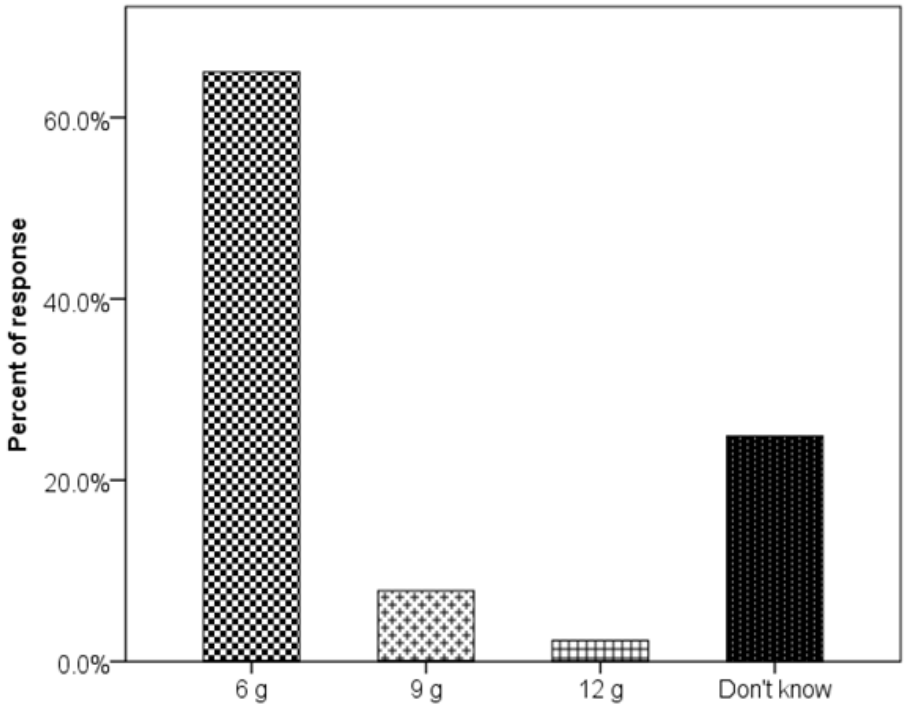
Figure 4-1. Patients' response regarding the awareness of harmful effects of too much salt in the diet.



Majority of patients (92.2%) were aware regarding the harmful effects of having too much salt in the diet, while only 18 patients disagreed to the statement.

4.3.3 Knowledge of UK salt recommendation

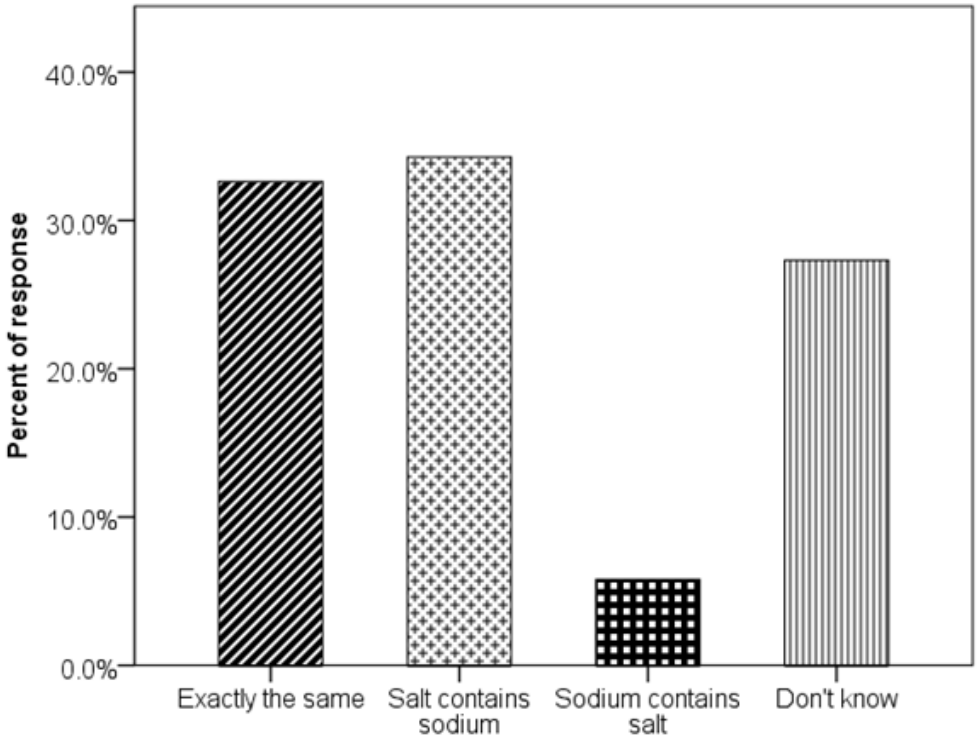
Figure 4-2. Patients' knowledge on current recommended level of salt intake.



A total of 64.5% of respondents knew that that maximum recommended daily intake of salt is no more than 6g per day. Twenty five percent indicated that they did not know the current recommended value while others thought that daily limit of salt intake is more than 6 grams/day.

4.3.4 Knowledge on the difference between salt and sodium

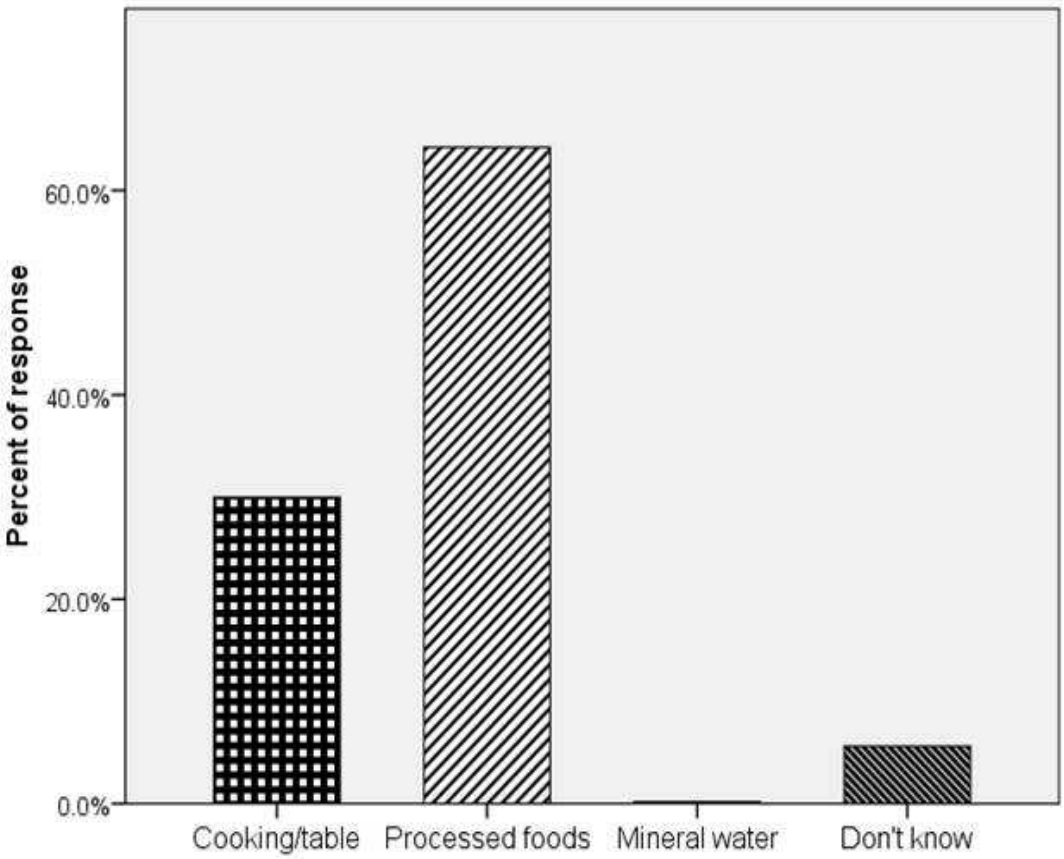
Figure 4-3. Patients' knowledge regarding the difference between sodium and salt.



Only 34.2% of patients were able to correctly identify that salt contains sodium. About a quarter of respondents did not know the relationship between the two entities, while other 38.4% have the wrong perception about salt and sodium.

4.3.5 Knowledge on the main source of salt

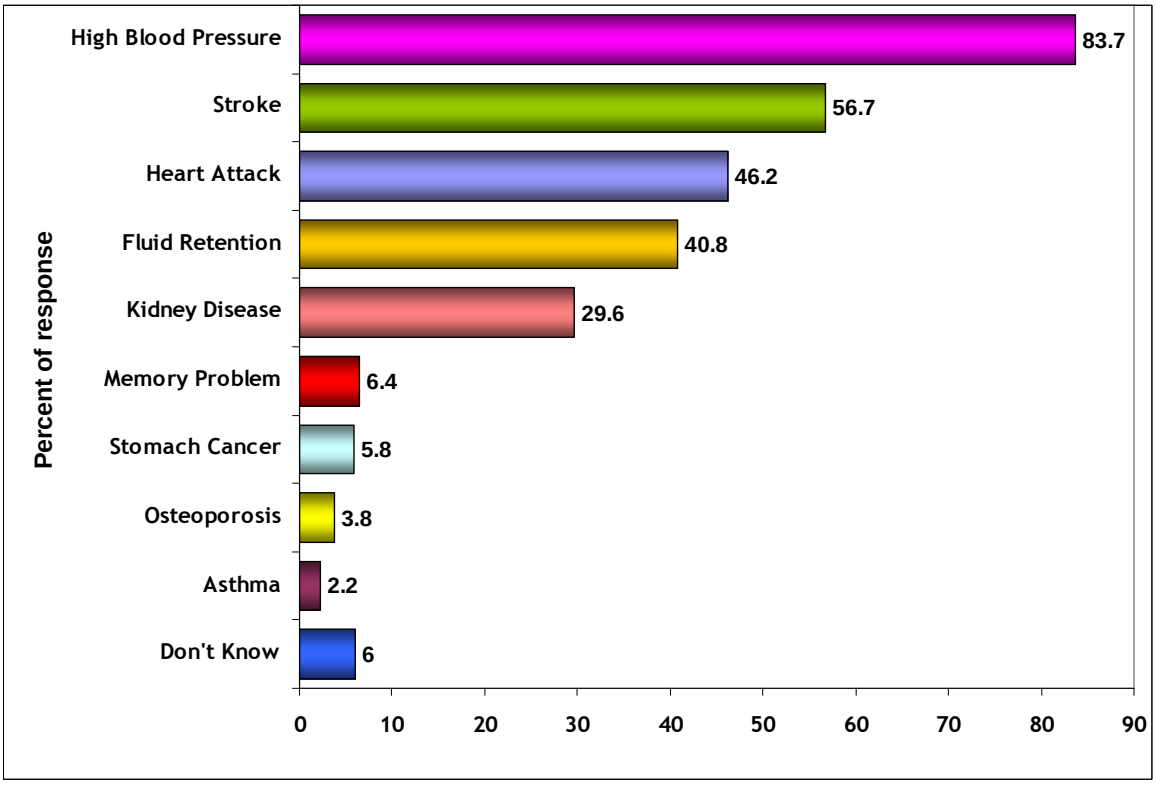
Figure 4-4. Patients' knowledge regarding various sources of sodium in daily diet.



Most respondents (64%) knew that processed foods contributed as the main source of salt in daily diet. Thirty percent chose discretionary salt while only one respondent opted for mineral water as the main source of salt.

4.3.6 Knowledge on possible complications from high salt diet

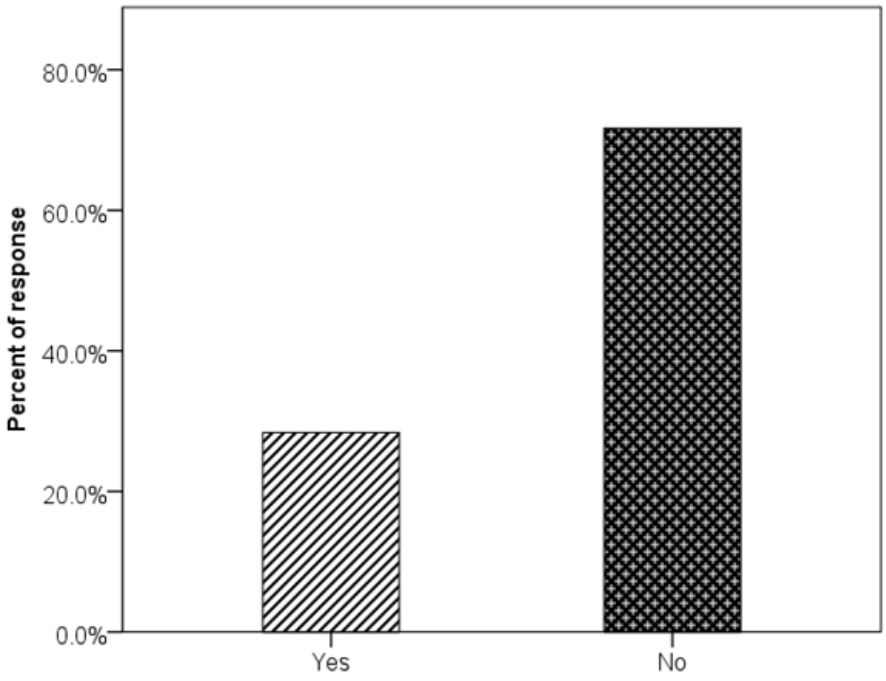
Figure 4-5. Patients' response regarding all the possible complications arising from high salt diet.



Majority of patients (83.7%) claimed to know that high salt intake can be associated with high blood pressure. This is followed by stroke, myocardial infarction, fluid retention and kidney disease. Less than 10% of the respondents knew that high salt consumption can also be associated with other conditions such as dementia, stomach cancer, osteoporosis and asthma.

4.3.7 Attitude regarding salt information on food labels

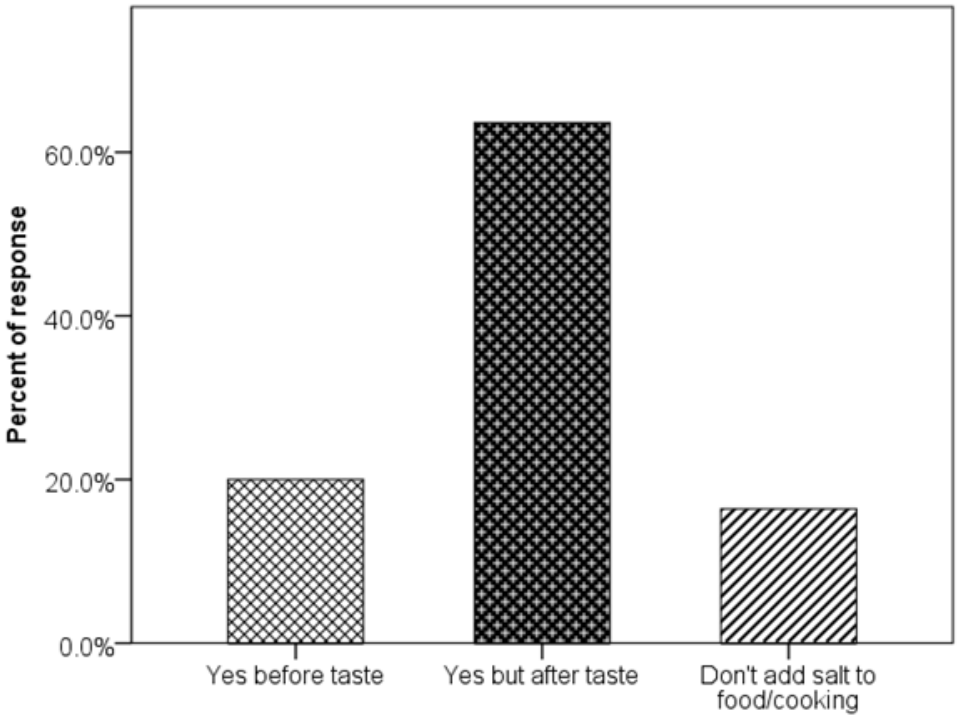
Figure 4-6. Patients' attitude regarding reading the food labels.



Seventy percent of respondents did not refer to label for salt content upon food purchasing.

4.3.8 Attitude regarding adding salt in foods

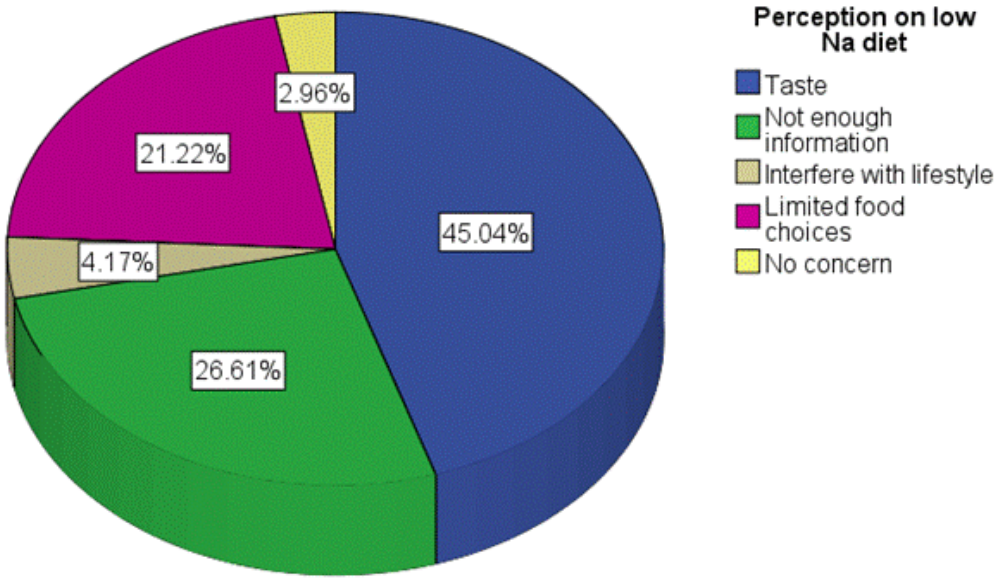
Figure 4-7. Patients' attitude regarding adding salt during cooking or at the table.



Only 16% of respondents did not use salt at all either during cooking or at the table. Most patients (83.5%) did add salt at one point of food preparation with majority (63.5%) had the food tasted before adding them.

4.3.9 Perception on low salt diet

Figure 4-8. Patients' perception regarding low salt diet.



Forty-five percent of patients were concerned regarding the taste of food without the addition of salt. This is followed by not having enough information about the diet and limited availability of low-salt foods on the market. Only 3% of patients indicated that they had no concern over the low salt diet.

4.3.10 KAP results in relation to levels of salt intake

Table 4-1. Comparison of KAP variables against high vs. low sodium intake group.

Variables	High Salt Intake	Low Salt Intake	P-value
n	498 (80.3%)	122 (19.7%)	
Male : Female	254 : 244 (51.0% : 49.0%)	52 : 70 (42.6% : 57.4%)	0.097
Agree that high salt is harmful	454 (91.2%)	105 (86.1%)	0.090
Know the recommended 6g/day	319 (64.1%)	69 (56.6%)	0.125
Know that salt contains sodium	167 (33.5%)	38 (31.1%)	0.616
Know the main source of salt	278 (55.8%)	63 (51.6%)	0.405
Look for salt content on label	124 (24.9%)	45 (36.9%)	0.011*
Add salt at table/cooking	428 (85.9%)	96 (78.7%)	0.047*

All variables measured from the KAP questionnaire were cross-tabulated against the level of salt intake based on the FFQ results. FFQ was chosen as a marker for comparison since it estimates sodium consumption for the past 7 days (including weekend) which are more likely to represent patients' habitual dietary pattern. Respondents having a sodium intake of more than 2.4 g/day were considered as high salt group and those with 2.4 g/day or less were considered as low salt group. No significant difference in level of salt intake between genders was observed. Awareness and knowledge regarding salt intake between the high- and low-salt groups were also non-significant. Nevertheless, there was a significant difference with regards to attitude between the groups. Patients with low salt intake are more likely to look at the food label for salt content ($p = 0.011$) while those in high-salt group tend to use discretionary salt more often than those in the low salt group ($p < 0.05$).

4.4 Discussion

Published studies related to KAP in hypertensive patients are very limited. Assessment on current level of awareness and practice regarding healthy salt intake is important as this will encourage patients to take active control over their own BP management. In this study, awareness regarding dangers of too much salt in the diet appears to be high among hypertensive patients. Nine out of ten patients agreed that having a high salt diet is detrimental to their health. This is comparable to results from the CASH survey (202) which revealed that 92% of the Great Britain population were aware of the harmful effects of salt.

Knowledge concerning the dietary recommendation for salt is crucial for patients to engage in low-salt diet. More than half of the respondents in our study knew about the 6 gram/day limit and only 1 in 3 respondents indicated that they did not know the dietary recommendation for salt. This figure is slightly higher compared to the recent survey by CASH (274), which indicated that only 15% of the population studied knew 6g as the daily limit of salt intake. The difference could possibly be attributed to patients in our sample being closely-monitored at the clinic, and therefore they frequently received counselling or advice regarding healthy diet including salt intake, from their healthcare professionals.

Majority of respondents selected processed foods as the main contributor to daily salt intake while 1 in 3 patients claimed that they did not know the source. It is estimated that 75% of salt consumed contained in processed foods (275). Many patients may be unaware that some of the main sources of salt in our diet are 'hidden' in everyday food items, hence explaining why many did not consider salt as a problem in their diet. For example, a recent survey revealed that more than 1 in 4 (28%) loaves of bread contain as much salt, or even more, per slice than a packet of crisps (276). The survey was conducted to investigate the salt content of 292 fresh and packaged loaves from supermarkets and their in-store bakeries as well as chain and independent high street bakeries. These findings were disclosed soon after the Department of Health announced that bread is the largest contributor of salt to our diet, providing almost a fifth (18%) of current daily salt intake among UK populations (207).

Despite the high rate of awareness regarding salt, majority of the patients (62%) either did not know or had the wrong perception about salt and sodium when they were asked regarding the difference between the two elements. This could be a potential problem when patients are referring to food labelling, as sodium content could easily be interpreted as equivalent to salt. Essentially, this highlights the fact that the current method of labelling sodium on foods may serve to mislead the public into thinking that they are consuming less salt than they actually are. Patients therefore need to be educated regarding the '2.5 conversion factor' from sodium to salt. Alternatively, they can opt for green colouring for salt content from the traffic light labelling system and avoid those with red colour, indicating foods with high salt content.

Although most of the patients knew that salt leads to high blood pressure, they did not appear to have made a strong association with other serious complications such as stroke, heart or kidney disease. Very few patients recognized that salt can be associated with other conditions such as osteoporosis, asthma, stomach cancer and dementia. This is in parallel with findings from study by Carley et. al. (277) which revealed that general public tend to associate excessive salt intake with high blood pressure (88%) compared to other health complications, with osteoporosis being the least. Similarly, results from CASH survey highlighted that general publics' knowledge regarding osteoporosis and stomach cancer is worryingly low, despite the evidence linking salt intake to both conditions is very compelling (202). Other evidence of salt and its associated health complications has been well documented.

Previous study had suggested that the practice of reading food labels for sodium content among UK population was satisfactory (278). Grimes et. al. (2009) demonstrated that there was a significant association between knowledge of some of the health risks of salt intake and salt label usage. Despite this, our findings indicate only 30% of patients referred to label for salt content upon food purchasing, with significant higher percentages among patients with low salt intake ($p<0.05$). Even though similar studies could potentially over estimate actual salt label use as measures rely on self-reported behaviour, the fact that our results yield a small number should be a major concern. Reading food labels for salt content is vital for individual to successfully reduce salt intake (278;278). By having a continuous exposure to this habit, patients will have a

better understanding and knowledge regarding salt intake status, hence able to apply the label information to make inference about the healthiness of the product (209).

Majority of patients surveyed claimed to be adding salt either during cooking or at the table, and the difference is significant between the high- and low-salt intake groups. This findings correlates with previous study by Grimes et. al. (2010), looking at frequency of discretionary salt use among Australian adults. The investigators reported that almost 50% of the sample used salt both at the table and cooking. The trend in discretionary salt usage among public could be due to lack of awareness of good dietary practice and little understanding of the effect of high salt consumption on health status. Shepherd and Farleigh (1989) have commented that 'for many people adding salt to food may be more a habit than a conscious decision'. Consequently, habitual use of salt may increase tolerance to salt and in turn increase consumption. Since there is positive evidence linking the exposure to highly salty foods and an increased in preference, a comprehensive salt reduction policy should include both reduction in discretionary salt practice and low-salt product reformulation.

The taste of food without salt was the biggest barrier (45%) to pursuing low salt diet according to the patients. This provides a huge area of intervention for health care professionals as patients can be advised regarding the alternative ways of food seasoning and taste sensory adaptation. Many of us have developed a preference for the taste of salt in our diet following years of consuming manufactured foods with high salt content and the use of salty seasonings. When salt is abruptly removed, the foods can initially taste bland. In spite of this, the taste receptors can be re-programmed in two to three weeks to adjust to a diet lower in salt content. In addition, there are many alternative ways of adding flavours to food such as using spices and natural flavours e.g. lemon juice and fresh herbs. Once the taste sensory is adjusted, foods will no longer deemed 'tasteless' and one will begin to appreciate the natural flavours.

In conclusion, even though reported awareness regarding harmful effects of excessive salt seems to be high, patients overall knowledge and practice regarding healthy salt intake is still unsatisfactory. Health care professionals, community health-workers and public health agencies need to be actively

involved in educating hypertensive populations to improve current status of salt awareness.

5 Dietary sodium intake – Demographics and effect on longitudinal patterns of blood pressure in a hypertensive cohort

5.1 Introduction

Excessive dietary sodium consumption increases BP, which subsequently increases the risk for stroke, coronary heart disease, heart failure, and renal disease (279). Importantly, the risk of CVD increases throughout the range of BP, beginning at 115/75mmHg (280). High salt intake, in combination with other factors such as low potassium consumption (from fresh fruits and vegetables), obesity, excess alcohol intake and sedentary lifestyle have been shown to contribute to the development of high BP. Nevertheless, the diversity and strength of the evidence is much greater for salt compared to the others.

The INTERSALT study was one of the landmark international trial which showed a significant positive relationship between BP and salt intake (30). The study, which used a standardized method for measuring BP and 24-hour urinary sodium, was conducted to investigate communities with a wide range of salt consumption, varying from 0.5 to 25 g/day. Among all the communities recruited into the study, only four had a low salt intake (3 g per day or less) whereas the majority lay between 6 and 12 g/day. None had the high salt intake as initially anticipated. Results from the study demonstrated that reducing dietary salt intake by 5.8 g was associated with a 3.1 mmHg decrease in systolic blood pressure (31). There was also a highly significant positive relationship between dietary salt intake and the increase in blood pressure with age.

Numerous studies have been published since the INTERSALT looking at the effects of salt intake and its impact on BP and/or cardiovascular outcomes; all with various conflicting results. For example, recently, a study by O'Donnell et. al. (281) suggested that a J-shaped association exist between estimated urinary sodium excretion and CV events in individual at increased CV risk. Compared to those with moderate sodium excretion, the investigators found an association between high sodium excretion and CV events. However, they also discovered that low sodium excretion was positively linked to CV death (hazard ratio = 1.19 and 1.37, for sodium excretion = 2-2.99 g/day and <2 g/day, respectively), and increased in the rate of hospitalization for patients with congestive heart failure. The study had been criticised as patients included in the study already had established severe cardiovascular disease and were prescribed with various

cardiovascular treatments including Angiotensin Receptor Blockers, ACE inhibitors and diuretics which did not reflect the general population (282).

Due to uncertainty regarding issues related to sodium intake and the outcome, it is therefore essential to clarify the pattern of daily intake for sodium, particularly in patients who are at risk of CV complications such as hypertensive patients. These patients are more likely to be vulnerable to the CV effects of high and low sodium intake, and are most likely to receive recommendations concerning dietary sodium restriction.

This chapter reports the association between daily sodium consumption and related clinical outcomes in a cohort of hypertensive patients attending the Glasgow Blood Pressure Clinic, using FFQ as measure of sodium intake.

5.2 Methods

Detail methods for this chapter have been previously discussed in Chapter 2 Section 2.2 and 2.7. In summary, data obtained from the FFQ for sodium estimation and spot urine analysis were merged to the corresponding dataset from Glasgow Blood Pressure Clinic database.

5.2.1 Scottish Index of Multiple Deprivation (SIMD)

The SIMD is the Scottish Government's official measure for identifying areas of deprivation within Scotland. The SIMD divides Scotland into a few geographical areas identified as 'datazones' and assigns each datazone with a deprivation score. There are 6,505 datazones covering the whole of Scotland, with each comprising, on average, populations of between 500 and 1,000 household residents. SIMD scores are based on 37 indicators of deprivation across 7 categories known as 'domains' which includes current income, employment, health, education, housing, geographic access to services, and crime (283). For this particular study, SIMD ranking were presented as quintiles; Quintiles 1 containing the 20% most deprived datazones, while Quintile 5 containing the 20% least deprived datazones in Scotland.

5.2.2 Estimation of 24-hour urinary sodium and potassium excretion

The formula developed by Tanaka et. al. (2002) was used to estimate 24-hour urinary sodium and potassium excretion from a random spot urine specimen. These formulas were based on a similar method reported by Kawasaki et. al., except that the second morning voiding urine (SMU) was replaced with casual ('spot') urine specimen, which were collected during patient's clinic appointment. The collection time of the spot urine ranged from 9.00 am to 12.00pm. The detail formula for the estimation was shown in Table 5-1.

Table 5-1. Formula used to estimate 24-hour urinary Na and K excretion.

(1) PRCr (mg/day) = -2.04 x age + 14.89 x weight (kg) + 16.14 x height (cm) – 2244.45 (2) Estimated 24-HUNaV (mEq/day) = 21.98 x $XNa^{0.392}$ (3) Estimated 24-HUKV (mEq/day) = 7.59 x $XK^{0.431}$
PRCr = predicted value of 24-hour urinary creatinine (mg/day) SUNa = Na^+ concentration in the spot voiding urine (mEq/day) SUK = K^+ concentration in the spot voiding urine (mEq/day) SUCr = creatinine concentration in the spot voiding urine (mg/dl) XNa (or XK) = SUNa (or SUK)/SUCr x PRCr Estimated 24-HUNaV = 24-hour urinary sodium Estimated 24-HUKV = 24-hour urinary potassium

5.2.3 Statistical methods

Average daily sodium intake was estimated from the dietary survey data using FFQ. This dataset was then merged to the corresponding blood pressure clinic data. ANOVA was used to assess the difference in demographic characteristics, BP pattern and SIMD quintiles, while chi-square was used to determine differences in terms of sodium consumption between males and female in the samples. The study population was then divided into three groups based on tertiles of estimated daily sodium intake. Repeat measurement data (serum sodium, serum chloride, serum potassium, systolic blood pressure and diastolic blood pressure measured at 0, 3, 6, 12, 24, 36, 48, 60 months and after 60 months) are then converted from wide format to long format for further analysis.

5.2.3.1 Analysis of longitudinal measures of BP, serum electrolytes using generalized estimating equations (GEE)

GEE were developed by Liang and Zeger (284) as a means of testing hypotheses regarding the influence of factors on binary and other exponentially (e.g., Poisson, Gamma, negative binomial) distributed response variables collected within subjects across time. They are an extension of generalized linear models, which allow correlated observations. Often this method account for the correlation between observations in generalized linear regression model by use of empirical variance estimator.

GEE also develops a population average or marginal model. Marginal models give an average response for observations sharing the same covariates as a function of the covariates (285). In other words, for every one-unit increase in a covariate across the population, GEE tells the user how much the average response would change (286). It also estimates regression coefficients and standard errors with sampling distributions that are asymptotically normal can be applied to test main effects and interactions, and can be used to evaluate categorical or continuous independent variables (284).

In this study, since there are multiple observations at different time points, it is not possible to assume independence among the different measurement available on an individual. Ignoring the dependency will result in overestimation

of the standard errors of the regression estimates. Therefore, in longitudinal repeat measures correlation between observations on a given subject exists and need to be accounted for in the regression model. To study the effect of repeat measurement outcome variables (systolic blood pressure, diastolic blood pressure, serum sodium, serum potassium, and serum chloride) by tertiles of sodium intake the generalized estimating equations (GEE) models were employed for the different outcome variables with sodium intake in tertiles as the principal independent variable and after incorporating all covariates that are believed to be confounders. The corresponding regression coefficients for sodium intake in tertile 2 and three in comparison to the tertile 1 was used for explaining the fixed effect of the sodium intake on the outcome variables.

5.3 Results

5.3.1 Overall demographics

On average, the age of patients being follow-up at the Glasgow Blood Pressure Clinic was 62 years old with BMI score more than 25. Both systolic and diastolic BP were beyond the ideal target BP of 140/90 mmHg. Mean sodium intake estimation based on questionnaire was higher compared to mean urinary sodium obtained from spot urine sample (3.8 g vs. 2.0 g, respectively). Other relevant demographic details were summarized in Table 5-2.

5.3.2 Demographic by sodium intake

Results from univariate analysis comparing all variables against the three tertiles of sodium intake revealed significant differences in terms of BMI, amount of sodium intake (from FFQ), spot urine Na/K ratio, prevalence of CVD and prevalence of LVH across all three tertiles of sodium consumption. Tertile 1 had the highest mean BMI (29.72), tertile 2 revealed the highest number of reported LVH and CVD cases (41 vs. 55, respectively), and tertile 3 had the highest mean for spot urine Na/K ratio. There were significant differences in terms of BMI, average daily sodium intake, Na/K ratio, prevalence of CVD and LVH across the three tertiles. Details of the analysis were summarized in Table 5-3.

5.3.3 Sodium intake by gender

Based on the FFQ results, male in general had a higher average intake of sodium (3.82 g/day) compared to female (3.75 g/day) though the difference was non-statistically significant. Conversely, corrected spot urine for sodium and potassium were found to be significant. Other pertinent variables were found to be insignificant when compared against gender, as listed in Table 5-4.

5.3.4 Sodium intake by SIMD 2009 quintiles

Patients residing in the area classified in quintile 3 appeared to be consuming the highest amount of sodium on average. However, when mean sodium intake was compared against all the 5 quintiles, no significant difference were observed (Table 5-5).

Table 5-2. Overall baseline demographic characteristics.

Variables	**Mean (SD)**
Age (years)	62.09 (13.73)
BMI (kg/m^2)	28.89 (5.93)
Cholesterol (mmol/L)	5.59 (1.12)
eGFR (mls/min/1.73m^2)	73.62 (16.90)
SBP (mmHg)	155.67 (21.42)
DBP (mmHg)	94.81 (10.72)
Sodium intake (g/day)	3.79 (1.64)
U Na (mmol/L)	86.87 (46.07)
U K (mmol/L)	49.77 (32.50)
U Cl (mmol/L)	92.95 (52.94)
U Cr (mg/dL)	9.85 (8.61)
Na/Cr ratio	12.90 (11.73)
Na/K ratio	2.75 (3.60)
Estimated 24-h Na (mmol)	99.08 (30.94)
Estimated 24-h K (mmol)	37.51 (9.65)
	Frequencies
Male : Female	337: 349
Prevalence - IHD	IHD – 24 MI – 19
Prevalence- CVA	TIA – 15 Stroke – 6
Prevalence -CVD	Yes – 142 No – 363
Prevalence -LVH	Yes – 100 No - 289
Alcohol status	Yes – 369 No - 103
Smoking status	Yes – 191 No – 310

BMI = body mass index, eGFR = estimated glomerular filtration rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, U Na = spot urine sodium, U K = spot urine potassium, U Cl = spot urine chloride, U Cr = spot urine creatinine, Na/Cr ratio = Sodium/Creatinine ratio, Na/Potassium ratio, IHD = ischemic heart disease, CVA = cerebrovascular accident, CVD = cardiovascular disease, LVH = left ventricular hypertrophy

Table 5-3. Patients' demographics by tertiles of sodium intake.

	Tertile 1 ≤ 2.9		**Tertile 2 3.0 – 4.3**		**Tertile 3 ≥ 4.4**		**P-value**
	Mean (SD)	%	**Mean (SD)**	%	**Mean (SD)**	%	
N	209	33.3	215	34.3	203	32.4	
Age (years)	61.7 (13.03)		62.2 (12.78)		64.2 (14.03)		0.136
Male : Female	102:107	48.8:51.2	102:113	47.4:52.6	105:98	51.7:48.3	0.672
BMI (kg/m^2)	29.72 (6.99)		28 (5.44)		29.14 (5.42)		**0.015**
Smoking status	162	77.5	156	72.6	156	76.8	0.438
Alcohol status	154	73.7	147	68.4	150	73.9	0.414
Cholesterol (mmol/L)	5.53 (1.03)		5.697 (1.12)		5.501 (1.21)		0.268
eGFR (mls/min/1.73m^2)	73.12 (16.78)		74.37 (16.26)		72.69 (17.44)		0.669
SBP (mmHg)	154.8 (21.49)		155.96 (20.71)		157.06 (21.58)		0.568
DBP (mmHg)	95.17 (10.92)		94.76 (10.87)		94.84 (10.53)		0.919
Sodium intake from FFQ (g/day)	2.1 (0.60)		3.6 (0.41)		5.6 (1.21)		**0.000**
U Na (mmol/L)	86.82 (48.29)		80.64 (44.50)		91.75 (44.68)		0.303
U K (mmol/L)	51.14 (33.75)		50.75 (30.83)		42.27 (25.19)		0.108
U Cl (mmol/L)	92.02 (54.67)		85.87 (49.55)		93.38 (48.57)		0.603
U Cr (mg/dL)	9.97 (8.28)		9.28 (6.16)		9.76 (11.80)		0.880
Na/Cr ratio	12.93 (10.20)		11.62 (7.60)		13.24 (7.59)		0.440
Na/K ratio	2.79 (3.63)		2.10 (1.62)		3.51 (4.96)		**0.049**
Estimated 24-h Na (mmol)	99.16 (33.11)		96.08 (27.82)		102.69 (26.18)		0.371
Estimated 24-h K (mmol)	37.88 (10.86)		38.12 (8.71)		36.29 (8.82)		0.432
Prevalence - IHD	14	6.7	14	6.5	12	5.9	0.914
Prevalence - CVA	5	2.4	7	3.3	8	3.9	0.347
Prevalence -CVD	37	17.7	55	25.6	44	21.7	**0.046**
Prevalence -LVH	26	12.4	41	19.1	28	13.8	**0.035**

BMI = body mass index, eGFR = estimated glomerular filtration rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, FFQ = food frequency questionnaire, U Na = spot urine sodium, U K = spot urine potassium, U Cl = spot urine chloride, U Cr = spot urine creatinine, Na/Cr ratio = Sodium/Creatinine ratio, Na/Potassium ratio, IHD = ischemic heart disease, CVA = cerebrovascular accident, CVD = cardiovascular disease, LVH = left ventricular hypertrophy

Table 5-4. Sodium intake by gender.

Variables	Male Mean (SD)	Female Mean (SD)	P-value
Sodium intake (g/d)	3.82 (1.57)	3.75 (1.71)	0.378
U Na (mmol/L)	96.99 (45.92)	78.10 (44.63)	0.317
U K (mmol/L)	52.88 (31.17)	47.13 (33.58)	0.495
U Cl (mmol/L)	104.81 (54.01)	82.67 (50.03)	0.306
U Creatinine (mg/dL)	11.21 (9.74)	8.65 (7.34)	0.567
Na/Cr ratio	11.79 (7.86)	13.90 (14.27)	0.490
Na/K ratio	2.70 (3.24)	2.80 (3.91)	0.344
Estimated 24-h Na (mmol)	103.53 (29.12)	95.13 (32.14)	0.022
Estimated 24-h K (mmol)	38.97 (9.41)	36.22 (9.73)	0.014
Sodium tertiles (≤2.9/3.3-4.3/≥4.4)	102/102/105	107/113/98	0.672

Table 5-5. Sodium intake based on SIMD 2009 Quintiles.

SIMD 2009 Quintiles	N	Mean (SD)	Min	Max
1	125	3.80 (1.74)	0.6	10.0
2	91	3.81 (1.44)	1.1	8.9
3	67	3.95 (1.72)	0.8	8.6
4	86	3.48 (1.63)	0.3	9.6
5	207	3.81 (1.60)	0.4	10.6

*** (p = 0.435)**

5.3.5 Longitudinal BP pattern by sodium intake

Table 5-6 showed the results of mean BP measurement at 12 months interval from baseline up to 5th year of follow-up across all 3 tertiles of sodium consumption. Mean systolic blood pressure appears to be different between the three tertiles at 12 months of follow-up (p = 0.024). However, after Bonferroni adjustment with p = 0.004 (0.05/12), the systolic blood pressure difference were insignificant. Mean diastolic blood pressure did not appear to be affected by different level of sodium intake throughout the 5 years.

Complete data for all covariates were available in 439 subjects. Table 5-7 summarises the results of the Generalised Estimating Equation (GEE) analysis between longitudinal measures of BP and serum sodium and tertiles of dietary sodium. There is no significant association between serial serum sodium measures and dietary sodium intake.

Serial SBP measurements in treated hypertensive subjects show a significant association with tertiles of dietary sodium. Tertile 2 and tertile 3 are significantly associated with a 2.28 (95% CI: -4.24;-0.32; p=0.02) and 3.4 (-5.38;-1.43; p=0.001) mmHg lower SBP during the follow-up period respectively. There was no significant association with DBP.

Spot urine sodium did not show any association with longitudinal SBP or DBP measures in this population.

Table 5-6. Longitudinal BP pattern by sodium intake at baseline and every 12-month interval.

	Tertile 1 Mean (SD) ≤ 2.9	**Tertile 2 Mean (SD) 3.0 – 4.3**	**Tertile 3 Mean (SD) ≥ 4.4**	**P-value**
N	209	215	203	
SBP 0m (mmHg)	154.80 (21.49)	155.96 (20.71)	157.06 (21.58)	0.568
SBP 12m (mmHg)	143.93 (20.18)	139.94 (19.14)	137.95 (16.91)	0.024
SBP 24m (mmHg)	140.78 (17.19)	139.93 (18.42)	138.86 (16.53)	0.715
SBP 36m (mmHg)	138.49 (16.99)	137.62 (18.54)	135.09 (13.33)	0.379
SBP 48m (mmHg)	137.41 (18.07)	136.76 (18.22)	134.77 (14.89)	0.605
SBP 60m (mmHg)	137.19 (15.53)	135.70 (18.04)	134.50 (12.41)	0.489
DBP 0m (mmHg)	95.17 (10.92)	94.76 (10.87)	94.84 (10.53)	0.919
DBP 12m (mmHg)	89.65 (10.20)	88.08 (10.71)	87.10 (8.37)	0.088
DBP 24m (mmHg)	88.28 (9.69)	87.87 (9.96)	87.35 (9.23)	0.773
DBP 36m (mmHg)	86.24 (9.96)	86.95 (12.18)	86.16 (7.82)	0.853
DBP 48m (mmHg)	85.57 (9.98)	87.49 (9.75)	87.12 (8.85)	0.434
DBP 60m (mmHg)	86.66 (8.05)	86.36 (9.79)	86.31 (8.35)	0.956

Figure 5-1. Longitudinal change in SBP by tertiles of sodium intake.

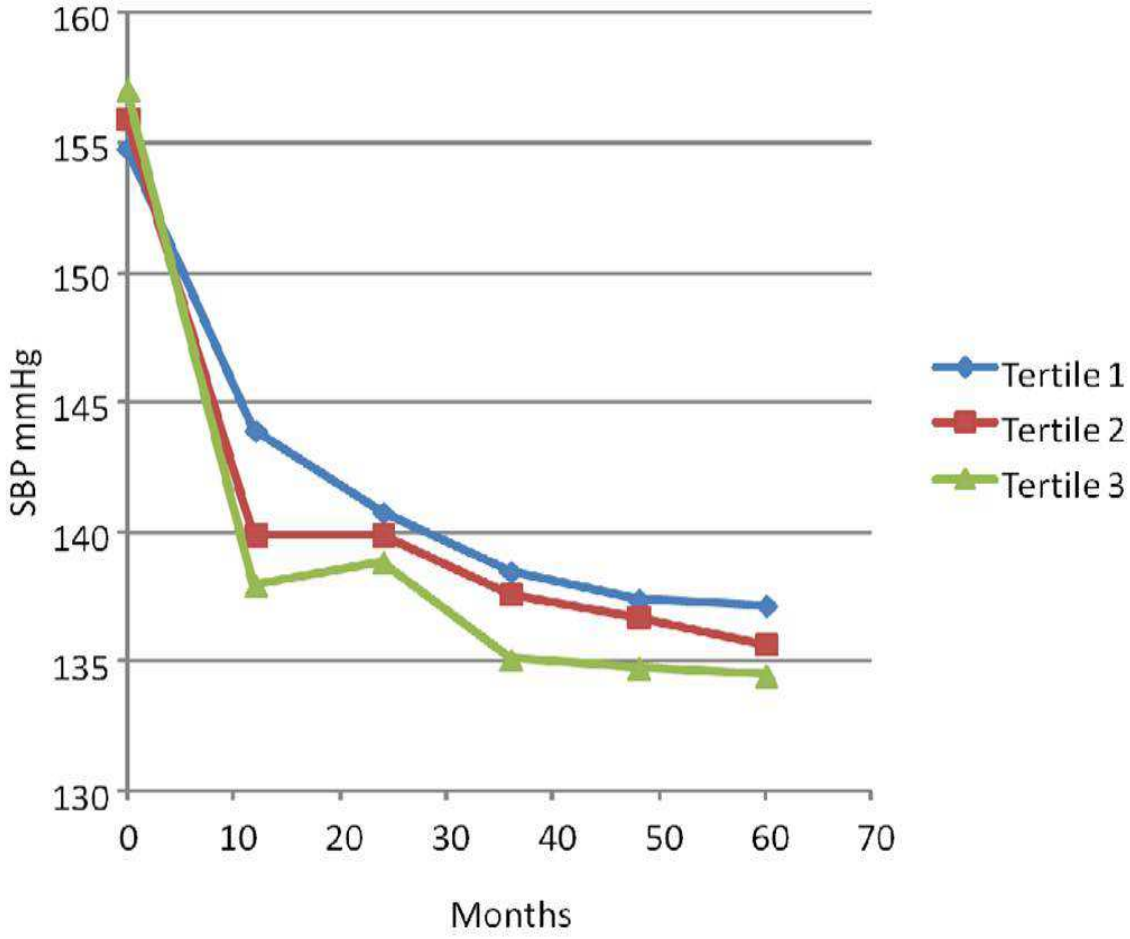


Table 5-7. Generalised Estimating Equation (GEE) - Analysis of longitudinal measures of blood pressure and serum sodium by tertiles of dietary sodium intake and tertiles of spot urine sodium excretion.

Serum Na		Coef.	Std.Err	P>|z|	[95%CI]		
	FFQ DietNa_Tertile2 (g/day)	0.11	0.23	0.642	-0.34	0.56	Obs 2621 Groups 437 Min 1 Max 5
	FFQ DietNa_Tertile3 (g/day)	0.23	0.23	0.302	-0.21	0.68	
	Sex	-1.03	0.20	**<0.0001**	-1.42	-0.65	
	Baseline SBP (mmHg)	-0.01	0.00	0.174	-0.01	0.00	
	Age_first_visit (years)	-0.03	0.01	**<0.0001**	-0.05	-0.01	
	BMI (kg/m^2)	0.00	0.01	0.84	-0.02	0.03	
	Smoking_status	-0.05	0.19	0.809	-0.42	0.33	
	eGFR_0m (mls/min/1.73m^2)	-0.01	0.01	0.059	-0.02	0.00	
SBP		Coef.	Std.Err	P>|z|	[95%CI]		
	FFQ DietNa_Tertile2 (g/day)	-2.28	1.00	**0.023**	-4.24	-0.32	Obs 2128 Groups 439 Min 1 Max 7
	FFQ DietNa_Tertile3 (g/day)	-3.40	1.01	**0.001**	-5.38	-1.43	
	Sex	4.00	0.85	**<0.0001**	2.34	5.65	
	Age_first_visit (years)	0.28	0.04	**<0.0001**	0.21	0.36	
	BMI (kg/m^2)	-0.13	0.07	0.06	-0.26	0.01	
	Smoking_status	0.75	0.84	0.374	-0.90	2.40	
	eGFR_0m (mls/min/1.73m^2)	0.09	0.03	**0.001**	0.04	0.15	
DBP		Coef.	Std.Err	P>|z|	[95%CI]		
	FFQ DietNa_Tertile2 (g/day)	-0.55	0.51	0.282	-1.55	0.45	Obs 2128 Groups 439 Min 1 Max 7
	FFQ DietNa_Tertile3 (g/day)	-0.42	0.51	0.411	-1.43	0.58	
	Sex	-1.29	0.43	**0.003**	-2.13	-0.44	
	Age_first_visit (years)	-0.24	0.02	**<0.0001**	-0.28	-0.20	
	BMI (kg/m^2)	0.02	0.03	0.634	-0.05	0.08	
	Smoking_status	0.33	0.43	0.445	-0.51	1.17	
	eGFR_0m (mls/min/1.73m^2)	0.04	0.01	**0.003**	0.01	0.07	
SBP		Coef.	Std.Err	P>|z|	[95%CI]		
	UrineNa_Tertile2 (mmol/L)	-0.07	1.63	0.966	-3.27	3.13	Obs 811 Groups 168 Min 1 Max 7
	UrineNa_Tertile3 (mmol/L)	1.43	1.71	0.404	-1.93	4.79	
	Sex	2.39	1.39	0.085	-0.33	5.12	
	Age_first_visit (years)	0.36	0.06	**<0.0001**	0.24	0.48	
	BMI (kg/m^2)	-0.19	0.10	0.057	-0.38	0.01	
	Smoking_status	-0.67	1.35	0.621	-3.32	1.98	
	eGFR_0m (mls/min/1.73m^2)	0.11	0.04	**0.011**	0.03	0.20	
DBP		Coef.	Std.Err	P>|z|	[95%CI]		
	UrineNa_Tertile2 (mmol/L)	2.00	0.84	**0.017**	0.36	3.64	Obs 811 Groups 168 Min 1 Max 7
	UrineNa_Tertile3 (mmol/L)	0.95	0.88	0.28	-0.77	2.67	
	Sex	-1.94	0.71	**0.006**	-3.34	-0.54	
	Age_first_visit (years)	-0.20	0.03	**<0.0001**	-0.26	-0.14	
	BMI (kg/m^2)	-0.02	0.05	0.677	-0.12	0.08	
	Smoking_status	0.54	0.69	0.437	-0.82	1.90	
	eGFR_0m (mls/min/1.73m^2)	0.06	0.02	**0.015**	0.01	0.10	

5.4 Discussion

The role of dietary sodium chloride in the regulation of blood pressure has been difficult to elucidate for several reasons. Population science is limited by the narrow range of dietary sodium intake by most populations and individuals and the multiple confounders in those populations at the extremes of intake. For example in isolated hunter-gatherer populations in Africa, the Americas, Asia and the Pacific region, blood pressure raised little or not at all with age and hypertension was distinctly uncommon. These communities have a low-salt intake, usually less than 40 mEq/day and when these individuals migrated to an urban environment blood pressure increased(287). However, Hollenberg et. al.(288) showed the Kuna Indian tribe which demonstrated low BP and low salt intake in the original studies, have acculturated in-situ, enjoying a very-high salt intake while living in their original island homes. Despite the high salt intake among the Kuna, BP remains low and does not rise with age(288). This raises the question that the rise in BP seen on migration to the urban environment may not be due to salt alone as migration involves far more changes than just a change in salt intake.

Results from clinical trials have been rather challenging to interpret because of the difficulty in maintaining a given level of sodium intake over a period of time sufficient for study. In 167 controlled, randomized trials in which the effect of a reduction in salt intake on blood pressure in subjects with hypertension and normotension was assessed, in hypertensive subjects (whites), the mean reduction was 5.5/2.8 mmHg and the mean reductions in normotensive subjects (whites) were smaller or 1.3/0.1 mmHg(78). In addition they showed that salt restriction resulted in significant increases in renin and aldosterone levels as well as increases in catecholamines and lipids(78).

The relationship between sodium intake and cardiovascular outcomes is still controversial (69;70;78;281). Furthermore, basic science studies have been challenged by identification of appropriate models that mimic salt-sensitive hypertension in humans. The relationship between renal handling of sodium and blood pressure is apparently influenced by a complex combination of factors

including nutritional, environmental, genetic, neurohormonal, and metabolic factors.

In this analysis of hypertensive adults with detailed diet estimates of sodium intake, there were no significant differences in sodium intake by deprivation scores. However, corrected urine sodium and potassium excretion were found to be statistically significant between genders with males appeared to have higher sodium excretion. This could be attributed to lack of awareness of good dietary practice and little understanding on the effect of high salt consumption on health status. Furthermore, gender differences in salt preference may have contributed to an increased use of discretionary salt amongst males in general. This suggestion is supported by findings from other study which indicated that male respondents were more inclined to add salt to their food before even tasting it.

Analysing BP control during follow-up, a significant reduction of 3.4 mmHg in the highest tertile of sodium intake was observed compared to the lowest tertile of intake. Hypertensives subjects who are in the highest tertile of salt intake based on FFQ show the highest early drop in SBP and the lowest BP over time. Table 5-6 shows similar starting BP in all three tertiles of sodium intake, indicating that the observed difference in longitudinal SBP cannot be due to differences in initial BP between groups. However, the highest tertile of sodium intake is also associated with a significantly higher prevalence of cardiovascular disease and LVH. This would imply that the greater reduction in BP seen in those in the highest tertile of sodium intake is likely to be due to more aggressive management of BP in these individuals given their associated risk factors.

As this is an observational study, it is impossible to attribute causality to the higher prevalence of CVD in the highest tertile of sodium intake. Nevertheless, in real-life treated hypertensive patients, at least in the Glasgow cohort, it appears that sodium intake may not be a major factor in resistance to antihypertensive treatment. Additionally, FFQ was administered at only one point during follow-up and it may not be representative of sodium intake during the entire period of follow-up. An important future analysis will be to analyse anti-hypertensive prescriptions to see if there are differences in prescribing diuretics among the different groups. Major limitation of this study is the observational nature of the cohort which can be confounding. Randomised control studies are needed to further validate these findings.

6 Serum sodium levels and long-term mortality: 35 year follow-up study in a treated hypertensive population in Glasgow

6.1 Introduction

Worldwide, hypertension and elevated blood pressure together attribute to 7.6 million premature deaths annually. While the available anti-hypertensive agents reduce the blood pressure and curtail the risk of cardiovascular complications, the mortality burden remains relatively high in hypertensive population. Risk stratification and identification of factors associated with mortality outcomes are therefore important strategies for delaying the mortality events in hypertensive population.

The normal serum sodium distribution in healthy individuals is between 135-145 mmol/L. Both renal and extra-renal mechanisms play important role in maintenance of sodium content in body fluids. A surplus of sodium, the main extracellular cation, increases arterial blood pressure and cited as an important mechanisms associated with pathogenesis of hypertension. A relative excess or deficiency of total body water content to sodium is often seen in hypertensive population either as a consequence of hypertension or due to the effect of anti-hypertensive medication especially the diuretics.

While hyponatremia is associated with increased mortality outcomes in heart failure patients and also in adult hospitalized patients, serum sodium and its association with mortality outcomes are not studied in detail in hypertensive population. We therefore studied this association in an uncontrolled hypertensive cohort of nearly 15,000 adults in Glasgow, United Kingdom.

6.2 Methods

6.2.1 Study settings

The Glasgow blood pressure clinic (GBPC) provides secondary and tertiary level service to individuals with hypertension from the West of Scotland. Data from patients attending the clinic are stored in a computerized database, which contains information of individuals attending the clinic from the mid 1970s until 2011. Record linkage with the office of the Register General for Scotland allows identification of all deaths and causes of death in clinic attendees.

6.2.2 Collection of data and follow up

All patients were treated at GBPC until they achieve target BP and are maintained at that level for at least three months. The frequency of visits to GBPC mainly depends on individual patients BP levels and presence of other co-morbidities. Patients who achieved the target BP level were transferred back to the referring physician for ongoing management.

6.2.3 Clinical measurements

Blood pressure measurements were taken manually 3 times, using standardized sphygmomanometers at each visit by specialist hypertension nurses; the mean of the last 2 measurements is recorded at each visit.

Patients attending the clinic were advised to take their regular medications as usual. Height and weight of all patients were measured using standardized equipment during each visit. Blood samples were collected at baseline and at regular intervals for estimation of routine haematological and biochemical indices. Estimated glomerular filtration rate (eGFR) was calculated from the baseline serum creatinine values using the Modification of Diet in Renal Disease Study Group (MDRD) equation (289).

A structured format was used to measure tobacco (any versus none) and alcohol use (quantity and frequency of consumption). All data were electronically captured and maintained as a large single database.

6.2.4 Outcome assessment

Records kept by the General Register Office for Scotland ensured notification of a subject's death (provided that it occurred in the United Kingdom) together with the primary cause of death according to the International Classification of Diseases, 10th Revision, Version for 2007 (ICD-10), codes. We considered cardiovascular deaths (CVD mortality; ICD-10 codes I00-I99), ischemic heart disease deaths (IHD mortality; ICD-10 codes 120-I25), and stroke deaths (stroke mortality; ICD-10 codes I60-I69) in the analysis. Deaths other than due to cardiovascular causes are classified as non-CVD deaths. Mortality data were collected up to April 2011 allowing a maximum of 35 years for participants who had been under follow up for the longest time.

6.2.5 Statistical analysis

The normal serum sodium range is 135-145 mmol/L. The study population was divided into four groups based on baseline serum sodium levels (quartiles). The approximately equal sample sizes in each cohort will allow reliable risk estimates to be calculated in survival analyses. The baseline characteristics of study subjects in different sodium quartiles were compared using one way analysis of variance (ANOVA) for continuous variables and Chi-Square test for categorical variables. Kaplan-Meir (KM) curves were generated to plot the time to mortality outcomes across serum sodium quartiles. A log-rank test for multiple groups was employed to determine whether the KM curves for groups based on serum sodium quartiles are statistically equivalent. The cause-specific mortality event rates per 1000 person-years of follow-up and their 95% confidence interval were also estimated.

Cox proportional hazards models were set up to analyse the influence of baseline sodium on all-cause, CVD, ischaemic heart disease (IHD), stroke and non-CVD mortality. The covariates included were baseline age, gender, body mass index (BMI), smoking status, systolic and diastolic blood pressure (SBP and DBP), alcohol use, tobacco use, eGFR, and cardiovascular co-morbidity. A variable on year of first visit strata (epochs) was used to adjust the secular trend in mortality and was divided into three categories (first visit 1986 or before, between years 1987-1996, 1997 and after). Hazard ratios were then generated.

Initially, hazard rate of second, third and fourth sodium quartiles were generated in comparison to the first quartile after adjustment for the above mentioned baseline variables (Model 1). A second model was generated (Model 2) after incorporating baseline total cholesterol also in the model. Baseline serum chloride, potassium and bicarbonate were also incorporated in the model 1 and generated a new model (Model 3). Finally, baseline total cholesterol was also incorporated in the model 3 and generated the model 4. Since concomitant diuretic use can influence serum sodium levels, all the above models were repeated after stratifying for baseline diuretic use.

The proportional hazard (PH) assumption is tested by comparing the estimated –ln(-ln) survivor curves of groups based on serum sodium in quartiles and also by the goodness-of-fit (GOF) tests. The coefficient of variation (CoV) of serum sodium levels in the initial five years was estimated for each individual based on available data at the following time points; 3 months, 6 months, 12 months, 24 months, 36 months, 48 months, 60 months and above 60 months. The population was then divided into three categories based on the CoV of serum sodium (<50^{th} percentile, 50^{th}-75^{th} percentile, >75^{th} percentile). This variable was replaced with the baseline sodium variable in model 4 and the corresponding HRs were generated (Model 5). All analysis for this section was performed using STATA Software (Version 12.0, Statacorp, Texas, USA).

6.3 Results

A total of 13,380 patients with baseline serum sodium values were included in the current analysis. The full demographic and clinical characteristics for men and women are given in Table 6-1. The mean age of the study population was 50.6 years (range 14-93). More than half of the study patients were females (52.3%, n=6996). The population was overweight (mean BMI 27.53 (5.68)), hypertensive with baseline BP >166/98 mmHg and eGFR>70 mL/min per 1.73 m^2. There were 5911 smokers (45%) and 7756 people (61%) drank alcohol.

There were 3470 all-cause deaths in 202,114 person-years of follow-up. Of these, 2030 were cardiovascular deaths (IHD deaths=1138; stroke deaths=488) and 1440 were non-cardiovascular deaths. Survival analysis was performed after grouping the population into serum sodium quartiles. Univariate analysis was

performed by calculating deaths per 1000 person-years and with Kaplan Meier analysis. Univariate analysis showed a U-shaped pattern in all-cause, cardiovascular and non-cardiovascular mortality (Table 6-2, Figure 6.1 to 6.5).

Multivariate adjusted survival analysis was performed used Cox-proportional hazards model. Five different models were employed of which two models were essentially replicates by the addition of baseline cholesterol which was available in only a subset of subjects. Model 1 (3470 all-cause deaths) was adjusted for conventional cardiovascular covariates and model 2 (2874 all-cause deaths) was the same as model 1 but including serum cholesterol. Model 3 (3337 all-cause deaths) included all conventional cardiovascular covariates but also included other serum electrolytes – potassium, chloride, bicarbonate (as serum potassium levels can be artefactually elevated by haemolysis from delay in analyses, we excluded all serum potassium>6). Model 4 (2750 all-cause deaths) was the same as model 3 but including cholesterol. Finally we were able to assess the longitudinal variability in serum sodium which would reflect on how representative our analysis based on baseline sodium could be generalisable to hypertensive patients. We classified patients based on the coefficient of variation of serial sodium measurements (minimum 3 sodium in the first 5 years of follow-up at-least a year apart) and tested whether the level of variability in serum sodium had an impact on survival (model 5 – 2750 all-cause deaths).

Models 1 and 2 showed decrease in mortality with each increasing quartile of serum sodium (Table 6-3). However this association completely disappeared when adjusted for other electrolytes (models 3 and 4). Potassium and bicarbonate independently predicted mortality in models 3 and 4 unsurprisingly. Finally in model 5, variability in longitudinal sodium levels did not predict mortality in the hypertensive population. Repeating the analyses after stratifying by diuretic use did not substantially change the results.

Table 6-1. Baseline characteristics stratified by serum sodium in quartiles.

Variables	Total (N=13380)	Na<=138 (N=3385)	Na=139-140 (N=4050)	Na=141-142 (N=3767)	Na>=143 (N=2178)	P Value
Age at first visit (years), mean (SD)	50.62 (14.24)	51.23 (14.94)	48.86 (14.31)	50.59 (13.77)	53.02 (13.33)	<0.001
Men, n(%)	6384 (47.71)	1437 (42.45)	1945 (48.02)	1848 (49.06)	1154 (52.98)	<0.001
BMI (Kg/m^2), mean (SD)	27.53 (5.68)	27.46 (6.02)	27.40 (5.56)	27.69 (5.70)	27.59 (5.34)	0.12
SBP (mmHg), mean (SD)	166.26 (29.13)	166.40 (28.98)	164.62 (28.69)	166.34 (28.80)	168.97 (30.53)	<0.001
DBP (mmHg), mean (SD)	98.41 (15.06)	97.54 (14.99)	97.54 (14.99)	98.73 (14.88)	99.49 (15.73)	<0.001
Total cholesterol (mmol/l), mean (SD)	5.95 (1.46)	6.02 (1.50)	5.93 (1.28)	5.90 (1.24)	5.94 (1.95)	0.01
eGFR (mL/min per 1.73 m2), mean (SD)	73.82 (32.96)	74.91 (31.29)	74.97(21.98)	73.08 (36.95)	71.19 (43.65)	<0.001
eGFR <60 mL/min per 1.73 m2, n(%)	2227 (17.62)	659 (20.56)	777 (20.16)	558 (15.69)	233 (11.50)	<0.001
Alcohol Use, n (%)	7756 (61.04)	1901 (59.46)	2449 (63.54)	2165 (60.32)	1241 (60.04)	0.002
Tobacco Use, n (%)	5911 (45.08)	1515 (45.90)	1806 (45.47)	1641 (44.45)	949 (44.20)	<0.001
CVD, n (%)	2424 (18.12)	608 (17.96)	657 (16.22)	710 (18.85)	449 (20.62)	0.50
Year of first visit						
First visit <= Year 1987, n (%)	6260 (46.88)	1391 (41.17)	1880 (46.50)	1901 (50.59)	1088 (50.07)	
First visit between years 1988 - 1997, n (%)	3351 (25.10)	1086 (32.14)	1118 (27.65)	761 (20.25)	386 (17.76)	
First visit >= Year 1998, n (%)	3742 (28.20)	902 (26.69)	1045 (25.85)	1096 (29.16)	699 (32.17)	<0.001
Serum Chloride, mean (SD)	102.74 (3.53)	100.71 (3.77)	102.59 (3.11)	103.63 (3.02)	104.50 (3.16)	<0.001

Variables	Total (N=13380)	Na<=138 (N=3385)	Na=139-140 (N=4050)	Na=141-142 (N=3767)	Na>=143 (N=2178)	P Value
Serum Potassium, mean (SD)	4.11 (0.46)	4.09 (0.49)	4.11 (0.44)	4.10 (0.44)	4.13 (0.47)	0.01
Serum Bi-carbonate, mean (SD)	26.02 (3.08)	25.69 (3.14)	25.86 (3.02)	26.16 (2.98)	26.65 (3.19)	0.002

BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, eGFR=estimated glomerular filtration rate based on MDRD equation, Baseline CVD=prevalent cardiovascular disease at baseline, SD=standard deviation

Table 6-2. Person years of follow-up and mortality event rates.

Follow-up and event rates	Na^+<=138 (N=3385)	Na^+=139-140 (N=4050)	Na^+=141-142 (N=3767)	Na^+>=143 (N=2178)	Total (N=13380)
Person years of follow-up (p-y)	48740.84	62359.80	58613.16	32400.33	202114.14
IHD mortality, n/1000 p-y (95% CI)	7.16 (6.45-7.95)	6.54 (5.94-7.21)	6.40 (5.78-7.08)	7.35 (6.47-8.34)	6.78 (6.43-7.15)
Stroke mortality, n/1000 p-y (95% CI)	3.06 (2.60-3.59)	2.87 (2.48-3.32)	3.09 (2.67-3.57)	3.95 (3.32-4.70)	3.15 (2.92-3.41)
CVD mortality, n/1000 p-y (95% CI)	12.88 (11.92-13.93)	11.63 (10.81-12.50)	12.15 (11.29-13.07)	13.67 (14.46-15.01)	12.41 (11.93-12.90)
Non-CVD mortality, n/1000 p-y (95% CI)	9.23 (8.42-10.13)	7.94 (7.27-8.67)	7.85 (7.16-8.60)	9.01 (8.04-10.11)	8.40 (8.01-8.81)
All-cause mortality, n/1000 p-y (95% CI)	22.12 (20.84-23.48)	19.56 (18.50-20.69)	20.00 (18.88-21.17)	22.69 (21.10-24.39)	20.81 (20.19-21.44)

CVD=Cardiovascular disease and IHD=Ischemic heart disease

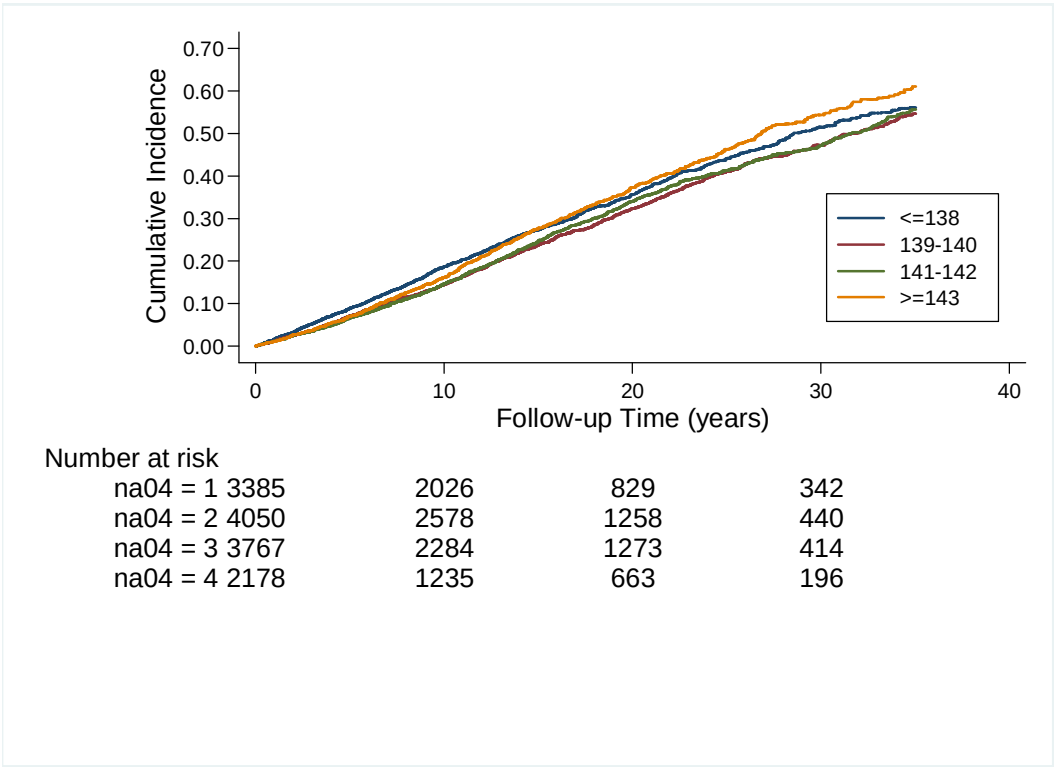
Table 6-3. Cox regression analysis for the association between serum sodium and mortality.

Cox-PH Models	All-cause mortality		CVD mortality		IHD mortality		Stroke Mortality		Non-CVD mortality	
	N=3470/11288		N=2030/11288		N=1138/11288		N=488/11288		N=1440/11288	
Baseline Serum Sodium (Model 1)	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Na<=138	1		1		1		1		1	
Na=139-140	0.87*	0.79-0.95	0.88*	0.78-0.99	0.88	0.76-1.04	0.89	0.70-1.15	0.86*	0.75-0.99
Na=141-142	0.80*	0.73-0.88	0.83*	0.74-0.94	0.81*	0.69-0.95	0.88	0.68-1.13	0.76*	0.66-0.87
Na>=143	0.80*	0.72-0.89	0.80*	0.70-0.92	0.76*	0.63-0.92	1.05	0.80-1.37	0.80*	0.68-0.95
Baseline Serum Sodium (Model 2)	N=2874/10009		N=1646/10009		N=911/10009		N=409/10009		N=1228/10009	
Na<=138	1		1		1		1		1	
Na=139-140	0.90*	0.82-0.99	0.91	0.80-1.04	0.94	0.79-1.12	0.93	0.71-1.22	0.89	0.77-1.04
Na=141-142	0.84*	0.76-0.93	0.89	0.78-1.02	0.87	0.73-1.04	0.97	0.74-1.27	0.78*	0.67-0.91
Na>=143	0.85*	0.75-0.95	0.87	0.75-1.01	0.82	0.67-1.01	1.15	0.86-1.54	0.82*	0.69-0.97
Baseline Serum Sodium (Model 3)	N=3337/8939		N=1971/8939		N=1108/8939		N=473/8939		N=1366/8939	
Na<=138	1		1		1		1		1	
Na=139-140	1.02	0.93-1.12	1.06	0.93-1.20	1.06	0.89-1.25	1.06	0.82-1.39	0.96	0.83-1.12
Na=141-142	1.05	0.95-1.16	1.15*	1.01-1.31	1.16	0.97-1.38	1.09	0.83-1.44	0.92	0.78-1.08
Na>=143	1.11	0.99-1.25	1.20*	1.03-1.40	1.16	0.94-1.43	1.41*	1.03-1.92	0.99	0.83-1.20
Baseline Serum Sodium (Model 4)	N=2750/7822		N=1589/7822		N=883/7822		N=396/7822		N=1161/7822	
Na<=138	1		1		1		1		1	
Na=139-140	1.02	0.92-1.13	1.05	0.91-1.20	1.06	0.88-1.27	1.06	0.80-1.42	0.98	0.84-1.15
Na=141-142	1.02	0.91-1.14	1.12	0.96-1.29	1.10	0.91-1.34	1.12	0.82-1.51	0.89	0.74-1.05
Na>=143	1.08	0.95-1.24	1.17	0.98-1.39	1.11	0.88-1.40	1.41*	1.01-1.97	0.97	0.80-1.19

Cox-PH Models	All-cause mortality		CVD mortality		IHD mortality		Stroke Mortality		Non-CVD mortality	
	N=2750/7822		N=1589/7822		N=883/7822		N=396/7822		N=1161/7822	
Coefficient of Variation of Serum Sodium (Model 5)	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
<50th percentile	1.06	0.98-1.17	1.11	0.99-1.25	1.09	0.93-1.28	0.97	0.77-1.22	1.01	0.88-1.16
50th-75th Percentile	0.96	0.86-1.06	0.99	0.87-1.14	1.04	0.87-1.24	0.80	0.61-1.05	0.90	0.77-1.06
>75th Percentile	1		1		1		1		1	

***p value <0.05, Model 1 is adjusted for age at first visit, gender, BMI=body mass index, baseline cardiovascular disease, CKD=Chronic kidney disease, tobacco smoking, alcohol use, year of first visit (epochs), SBP=systolic blood pressure, and DBP=diastolic blood pressure. Model 2 is adjusted all variables in model 1 and total cholesterol. Model 3 is adjusted for all variables in model 1 and serum chloride, serum potassium and serum bi-carbonate. Model 4 is adjusted for all variables in model 3 and total cholesterol. In Model 5 baseline sodium in quartiles as in the Model 4 is replaced by categories**

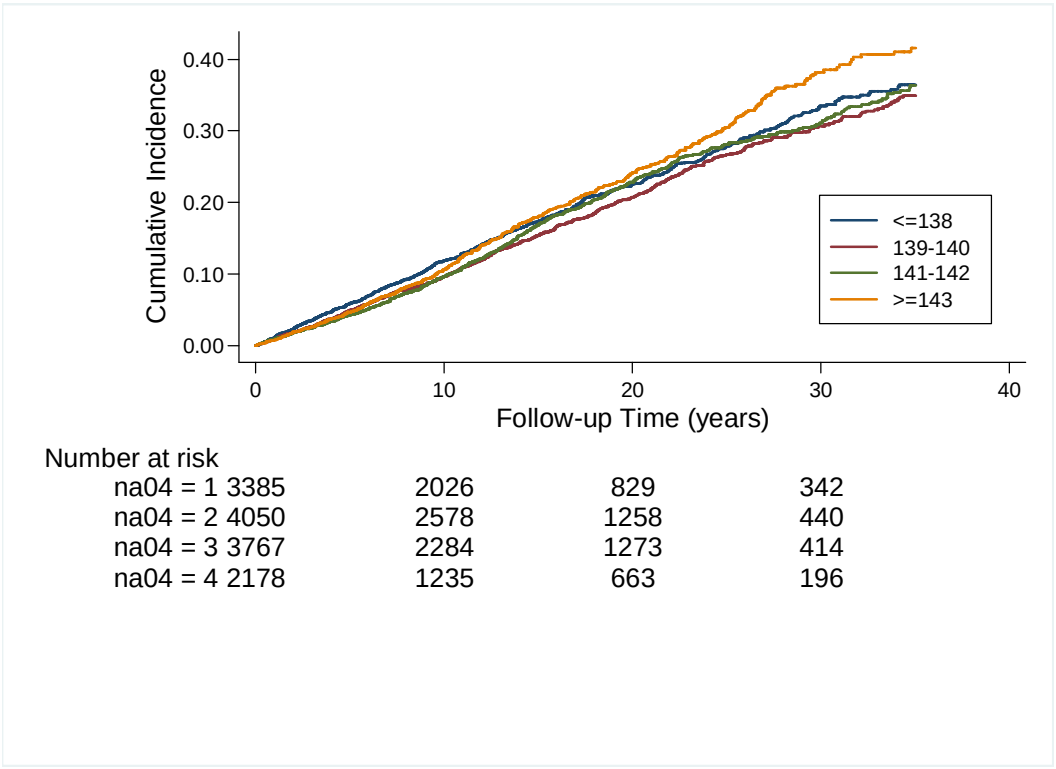
Figure 6-1. Kaplan Meier Plot serum Sodium quartiles and all-cause mortality.



Number at risk

na04 = 1	3385	2026	829	342
na04 = 2	4050	2578	1258	440
na04 = 3	3767	2284	1273	414
na04 = 4	2178	1235	663	196

Figure 6-2. Kaplan Meier Plot serum Sodium quartiles and cardiovascular mortality.



Number at risk

na04 = 1	3385	2026	829	342
na04 = 2	4050	2578	1258	440
na04 = 3	3767	2284	1273	414
na04 = 4	2178	1235	663	196

Figure 6-3. Kaplan Meier Plot serum Sodium quartiles and ischaemic heart disease mortality.

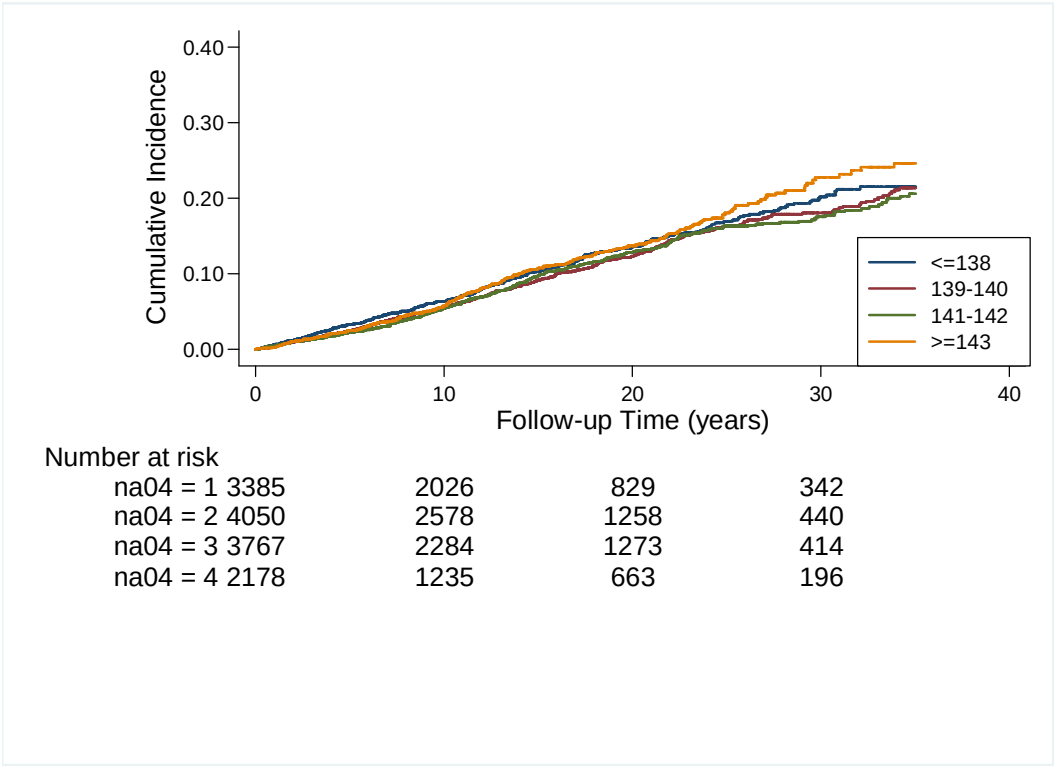


Figure 6-4. Kaplan Meier Plot serum Sodium quartiles and non-cardiovascular mortality.

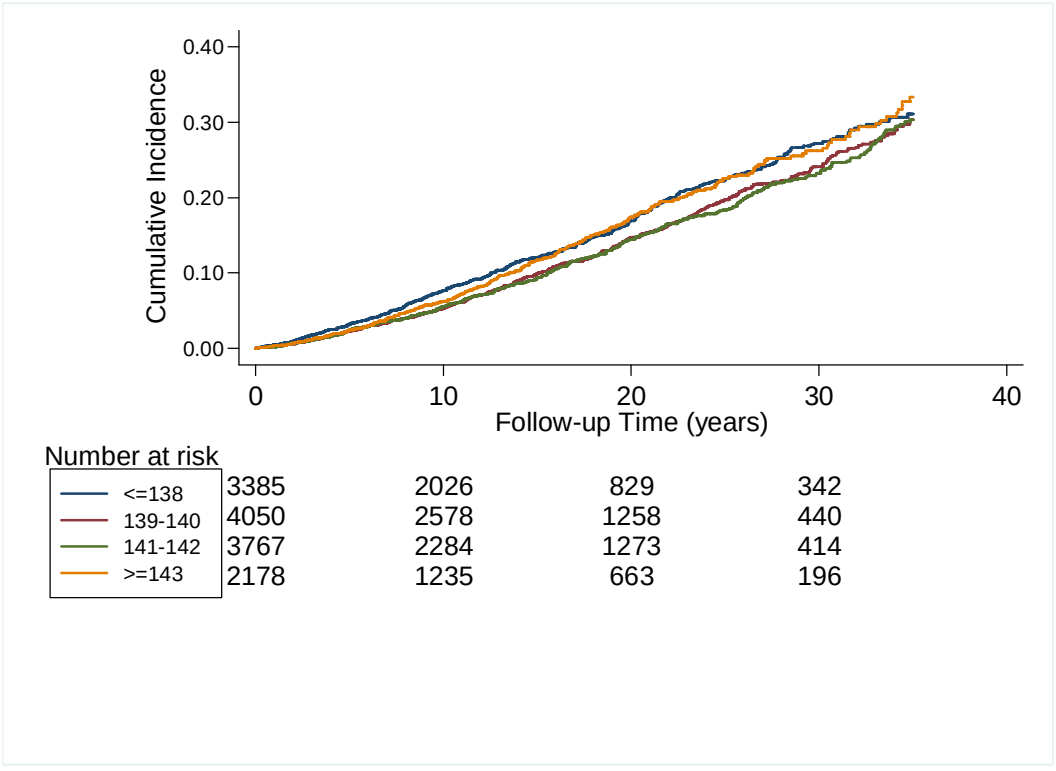
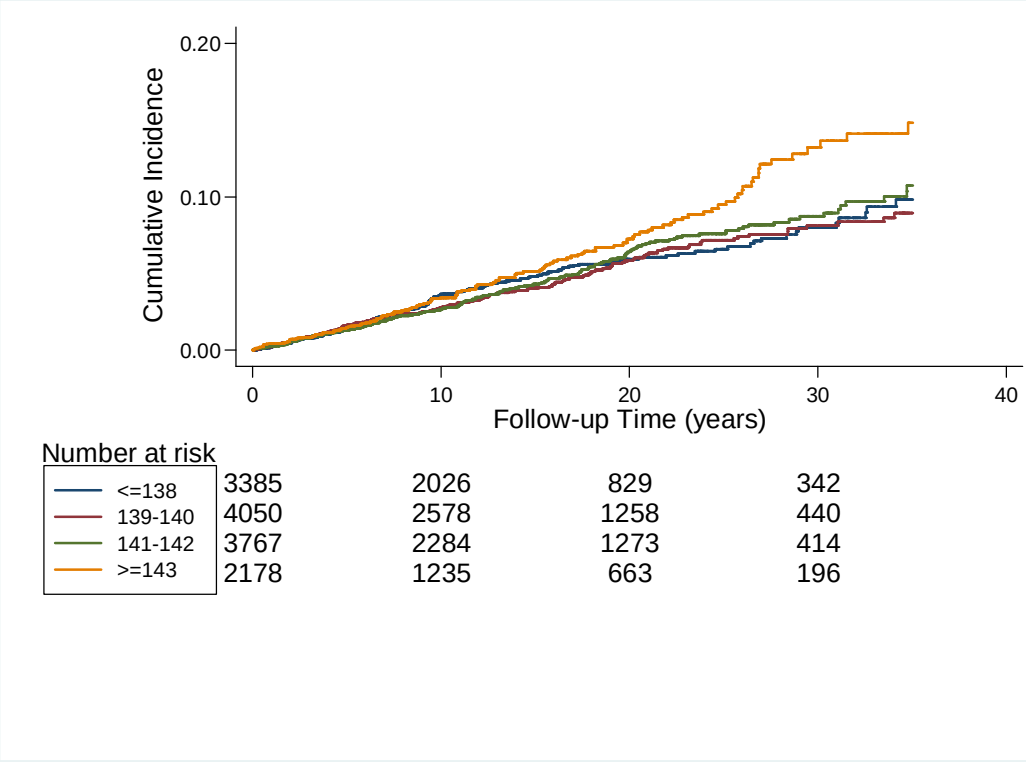


Figure 6-5. Kaplan Meier Plot serum Sodium quartiles and stroke mortality.



6.4 Discussion

The primary finding from this study is that among treated hypertensive patients, lower serum sodium is associated with a higher mortality risk which disappears when adjusted for other serum electrolytes. The univariate results from Kaplan Meier analysis and event-rates by serum sodium quartiles show a U shaped relationship which disappears after multivariate adjustment. In the multivariate analysis, the long ascertainment period was adjusted for by using a time-covariate and after accounting for other factors that affect mortality the adjusted hazard estimates reflect the true relationship between serum sodium and mortality. The results show that hyponatremia is associated with higher risk, which is not novel.

Previous studies have shown that hyponatremia is a significant predictor of mortality in hospitalised patients (290), patients with heart failure and renal failure. In a prospective cohort study of 98,411 adults hospitalized between 2000 and 2003 at 2 teaching hospitals in Boston, Massachusetts, Waikar et. al.(290) showed that patients with hyponatremia had higher in-hospital, 1-year, and 5-year mortality rates than patients without hyponatremia. They only adjusted for age, sex and co-morbidities only and did not adjust for other serum electrolytes. As all the subjects were hospitalised, they categorised patients into categories based on change in serum sodium between the first and final measurement and showed that mortality was highest in those with persistent or acquired hyponatremia. In this study, after adjustment for other electrolytes and stratifying by diuretic use, the relationship between sodium and mortality disappears, indicating that perhaps serum sodium is not a sensitive nor independent marker of risk.

In the current study of Glasgow hypertensive subjects, despite the use of diuretics as an antihypertensive agent, the prevalence of hyponatremia defined as serum sodium<135 was 2.8% (n=386) which is much lower than 13% as reported by Waikar et. al.(290). However this is similar to the prevalence of hyponatremia found in hospitalised patients (0.97% to 2.48%)(291). Wald et. al.(292) estimated the prevalence of community-acquired hyponatremia, defined as serum sodium <138, to be 37.9% which is comparable to 30% in the Glasgow hypertensive population using the same definition which corresponds to quartile

1. Thus our analysis reflects the spectrum of serum sodium in the general population albeit in a high cardiovascular risk group.

Hyperglycemia can result in misclassification of hyponatremia(293), however the hypertensive subjects in this cohort had a very low prevalence of diabetes. Also, as glucose data was not available in all the subjects it was not possible to adjust for it. Waikar et. al.(290) found only a minor level of miss-classification of hyponatremia due to hyperglycemia and this had no effect on the association between hyponatremia and mortality. It is unlikely that the results in this study will be confounded by glycemia because of the low prevalence of hyponatremia in the hypertensive cohort. The relationship between serum sodium and mortality in hospitalised patients is not valid across all diagnosis. There is clear evidence that hyponatremia is associated with increased mortality in patients with heart failure (294-296) and possibly in liver disease (297-300).

Although 135 to 145 mEq/L is frequently used as the reference range for serum sodium, Wald et. al.(292) showed an increase in mortality as serum sodium values declined below 138 mEq/L or rose above 142 mEq/L. The definition of serum sodium quartiles in this study reflected this definition, though it was selected primarily based on the distribution of serum sodium in this cohort.

None of the studies which analysed mortality outcomes in relation to serum sodium have adjusted for other serum electrolytes. The rationale for adjusting for serum electrolytes in the hypertensive population is related to the interconnectedness of the pathways that affect these electrolytes. For example, diuretics can decrease Na and K but can also increase bicarbonate. Potassium sparing diuretics can increase potassium in the presence of ACEI or ARBs. Aldosterone is a key hormone in sodium balance and primarily works through exchanging sodium for potassium in the distal tubules. Serum potassium and acidosis have been independently associated with mortality. In the hypertensive population we show that after correction for other serum electrolytes, serum sodium loses any effect on mortality. This is a novel finding from this study. It raises the question of interactions with other dietary or environmental factors. There is compelling evidence of an interaction between alcohol intake, potassium and magnesium, saturated or polyunsaturated, calcium, dietary fibre, and the accompanying anion, and salt-sensitivity of blood pressure.

Kurtz et. al. showed that in salt-sensitive individuals, replacement of sodium chloride with equimolal sodium bicarbonate (administered as sodium citrate) did not replicate the blood pressure influence of sodium chloride. When bicarbonate was the anion, sodium was much less likely to influence blood pressure (301). Moreover, the pressor response to norepinephrine and catecholamines were similar with dietary sodium chloride or sodium citrate indicating that increased pressor responsiveness alone cannot account for the sodium chloride-induced rise in resting blood pressure (302). Hence, this can be a possible explanation for the lack of association between serum sodium and mortality in the presence of other electrolytes. Further studies are needed to disentangle these effects.

There are several strengths and limitations to this study. The strengths include the large cohort with long follow-up and high event rates. The limitations are that this is a hypertensive cohort and hence the results may not be generalisable. The GBPC database only captures medication related to hypertension. Therefore, data pertaining to other concomitant drugs usage which may cause hyponatremia (such as selective serotonin reuptake inhibitors and antiepileptic drugs e.g. carbamazepine) are not available. We did not have diet information on all the subjects nor did we have measurements of renin aldosterone.

In summary, low serum sodium is associated with mortality in hypertensive patients, which is explained by the effect of other electrolytes. Thus this limits the prognostic value of serum sodium in hypertensive patients.

7 Conclusion

The issues regarding sodium intake and its relationship to blood pressure still continues to be a subject of controversy with some countries implementing regulatory interventions to reduce salt-intake on a population wide level. The evidence-base for sodium and blood pressure comes from epidemiological studies and randomised controlled trials of salt intervention. Estimates of sodium intake were done using diet questionnaires, food diaries, urinary sodium excretion (both spot urine and 24 hour urine) and combinations of these. Not all of the observational studies found an association between sodium intake and blood pressure. Observational studies showed that a 100 mmol rise in sodium intake led to a rather modest rise in systolic blood pressure in the range of 1–3 mmHg and diastolic blood pressure of 0–2 mmHg (303). A Cochrane review of 167 studies(78) of salt intervention showed a heterogenous effect on BP: in normotensive Caucasians blood pressure fell 1.3/0.05 mmHg, in blacks 4/2 mmHg, and Asians 1.3/1.7 mmHg. The fall in systolic pressure in blacks was significant. In hypertensives the falls were more impressive: Caucasians 5.5/2.8 mmHg, Blacks 6.4/2.4 mmHg and Asians 10.2/2.6 mmHg. There were predictable rises in plasma, renin, aldosterone, catecholamines, and lipids. The relationship between sodium intake and cardiovascular events appear to be J-shaped with higher risk with urinary sodium excretion of >7g/day or <3g/day.

In this project I have studied dietary sodium intake using a food frequency questionnaire that was adapted for use in UK. Though food frequency questionnaire alone is not reliable for estimating sodium intake, it is useful in assessing sodium intake in treated hypertensive patients both as a tool to create awareness and facilitate healthy diet. The application of this questionnaire, when used in conjunction with other dietary measures such as serial spot urine measurement or 24-hour urine collection, can be extremely helpful in monitoring excessive dietary salt intake among hypertensive patients.

The knowledge and understanding of health risks associated with salt was unsatisfactory despite the population being a high cardiovascular risk hypertensive population attending a specialist hypertension clinic. The findings from our study indicate that there is a need for increased education and awareness campaigns to increase patients understanding of the health risks associated with high-salt diet and how excessive intake could potentially

jeopardizing their health. Health care professionals, community health-workers and public health agencies need to actively inform the public regarding the recommended salt intake and the importance of reading food labels to identify for salt contents. As with other lifestyle interventions, problems can be anticipated from patients pertaining to the adjustment in taste to a lower salt diet and compliance with it. Nevertheless, with greater awareness from the media, and sensible advice from healthcare professionals, salt reduction may prove to be a readily accessible, non-pharmacological intervention, as well as a significant way of reducing public health concern in the long term.

Dietary sodium intake did not appear to have a significant effect on longitudinal blood pressure during follow-up in the hypertensive population. The decreased SBP during follow-up in the highest tertile of sodium intake was confounded by the greater prevalence of LVH and cardiovascular disease in this group. There appeared to be no association between dietary sodium intake and serum sodium (both single-point measurement and serial measurements). In multivariate adjusted survival analysis, serum sodium showed an inverse relationship to mortality with hyponatremia associated with increased risk. However, after adjusting for other electrolytes serum sodium was no longer a predictor of mortality. This is a novel finding and raises the prospect that other electrolytes may have an impact on blood pressure and cardiovascular risk – not sodium in isolation.

Whilst the current study is observational it has raised interesting insights into sodium and blood pressure which can inform future studies. A priority would be to correlate food questionnaire with a more robust estimation of dietary sodium intake such as 24 hour urinary sodium estimation, in a serial measurements. The effect of drugs especially diuretics on sodium balance and outcomes need to be studied. This will inform whether population based interventions for salt reduction will be beneficial over focussed diuretic based intervention in higher risk hypertensive individuals. Issues pertaining to confounding factors can be addressed through randomised control studies. Randomised controlled sodium intervention studies are feasible, although large sample sizes of ~15,000–20,000 are needed to detect benefits in the magnitude of 12–15% over 5 years.

8 Appendices

8.1 Appendix 1: Modified FFQ for sodium assessment

SALT INTAKE QUESTIONNAIRE
.

During the PAST 7 days (1 week) did you eat any of the following? Please put a tick (√) in the appropriate box

Food Item	NEVER	NOT EVERY DAY		EVERY DAY		
		1-3 times/week	4-6 times/ week	1 time a day	2 times a day	3+ times a day
White bread/ white bread rolls/ pita /croissants						
Brown/ wholewheat bread/ rolls						
Breakfast cereal (processed eg. cornflakes, rice crispies)						
Breakfast cereal (minimally processed-weetbix, muesli, etc.)						
Crackers (Tac, etc.)						
Cookies, biscuits, rusks (McVitie's, etc.)						
Cake/ scone/ muffin/ puddings/ pancake/ fruit pie/ tarts						
Roti/ samosa/ spring roll/ doughnut						
Pizza						
Pasta or noodle dishes with cheese sauces (macaroni cheese, lasagne, noodle salad, spaghetti bolognaise etc.)						
Popcorn						
Crisps (Walkers,etc.)						
Beef sausages						
Processed meat, cooked, smoked or canned eg Salami/ bacon/ pork sausages						
Meat or chicken pies/ sausage rolls						
Chicken – battered (KFC, etc.) or chicken burger						
Meat and meat dishes (steaks, minced meat, cottage pie, mince, meatballs, stew, chicken stew etc.)						
Gravy, made with stock or gravy powder						
Dried salted meat/ beef jerky/ smoked fish						
Milk (all types, also dairy fruit juice, malted milk, milk shakes, chocolate drinks, evaporated & condensed milk)						
Fermented milk/ sour milk						
Cheese						
Yogurt						
Eggs (any preparation)						
Tinned fish (tuna, sardines, etc.)						
Other fish and seafood (eg battered fish, prawns, crabs, mussels)						
Potato chips/ French fries or potato salad						
Canned vegetables, including baked beans, tomato paste, sweet corn, olives etc.						
Soup (all types)						
Salad dressing/ mayonnaise						
Ice cream (all types)						
Margarines, all types, also butter						
Worcester sauce/relish/ barbecue or steak sauce						
Savoury sauces (mushroom, white, cheese)						
Tomato sauce/ Ketchup						
Salt (added to cooking or at the table)						
Mustard/ all purpose seasoning mix						
Peanuts (salted/unsalted/raw)						
Peanut butter						
Marmite/ Bovril						
Chocolate - sweets or sauce						
Beer and cider						

8.2 Appendix 2: KAP Questionnaire

1. **Do you think eating too much salt affects your health?**

   Yes [ ] No [ ] I don't know [ ]

2. **A high salt intake can cause (you may choose more than one answer)**

High blood pressure	[ ]	Kidney disease	[ ]
Stroke	[ ]	Memory/concentration problems	[ ]
Osteoporosis	[ ]	Asthma	[ ]
Fluid retention	[ ]	Heart attacks	[ ]
Stomach cancer	[ ]	I don't know	[ ]

3. **What is the maximum recommended daily amount of salt for an adult in the UK?**

6 grams (1 teaspoonful)	[ ]	15 grams (2 ½ teaspoons)	[ ]
9 grams (1 ½ teaspoons)	[ ]	I don't know	[ ]
12 grams (2 teaspoons)	[ ]		

4. **What is the main source of salt in the diet of an average person?**

Salt added during cooking and at the table	[ ]
Salt in processed foods (including takeaway, fast food, catered food)	[ ]
Salt in mineral water	[ ]
I don't know	[ ]

5. **Do you add salt to food before tasting them?**

   Yes [ ] No [ ] I don't add salt at the table or in cooking [ ]

6. **Which of these statements best describes the relationship between salt and sodium?**

Exactly the same	[ ]	Sodium contains salt	[ ]
Salt contains sodium	[ ]	No idea about the relationship	[ ]

7. **Do you look for the sodium content of the product when shopping?**

   Yes [ ] No [ ]

8. What is your greatest concern related to low salt diet?

The taste of food without salt	[ ]
Don't have enough information on low salt diet	[ ]
Worry that low salt diet would interfere with your daily lifestyle	[ ]
Limited low salt food choices on the market	[ ]

8.3 Appendix 3: Cover letter

Glasgow Blood Pressure Clinic
Western Infirmary
Glasgow
G11 6NT

NHS
Greater Glasgow and Clyde

Dear Sir/Madam

I am writing to you with regard to your next appointment at the Glasgow Blood Pressure Clinic in the Western Infirmary. Enclosed with this letter is a questionnaire related to salt consumption. Many individuals are not aware of their daily salt intake. Studies have shown that high salt diet is related to poor blood pressure control and may affect how well the blood pressure medicine works. The purpose of this questionnaire is to find out the average daily salt intake amongst patients attending the Glasgow Blood Pressure Clinic. Your participation in this questionnaire, when combined with the others, could help, leading to the development of methods to help promote healthier living in people with high blood pressure.

The questionnaire will take approximately 10 minutes to read and answer the questions. Do not worry if you make a mistake, simply cross it out and tick your new answer. All the information provided will be kept confidential. Kindly be informed that a urine sample will also be requested upon your next appointment at the clinic.

The completed questionnaire can be returned to the clinic during your next appointment. Otherwise it can be mailed to the following address:

Adyani Md. Redzuan
Room 416
BHF Glasgow Cardiovascular Research Centre,
University of Glasgow,
Glasgow
G12 8TA

I would be happy to inform you personally regarding the result of your average daily salt intake, upon the completion of the study. This can either be discussed during clinic time or by mail. Should you have any questions regarding the questionnaire, please call me (Adyani Redzuan) at 0141-330-5074. I really appreciate your time in reading this letter and look forward to your participation.

Thank you.

Yours sincerely,

Adyani Redzuan

For Dr Sandosh Padmanabhan
Consultant,
Glasgow Blood Pressure Clinic
Western Infirmary

Reference List

(1) OED Online. "sodium, n.". Oxford English Dictionary 2012;Available from: URL: http://www.oed.com/view/Entry/183873?redirectedFrom=sodium

(2) BBC. Sir Humphry Davy (1778 - 1829). http://www bbc co uk/history/historic_figures/davy_humphrey shtml 2012;Available from: URL: http://www.bbc.co.uk/history/historic_figures/davy_humphrey.shtml

(3) He FJ, MacGregor GA. Reducing Population Salt Intake Worldwide: From Evidence to Implementation. Progress in Cardiovascular Diseases 2010;52(5):363-82.

(4) DeSanto NG, Bisaccia C, Cirillo M, DeSanto RM, DeSanto LS, DeSanto D et al. A contribution to the history of common salt. Kidney international Supplement 1997;59:S127-S134.

(5) Rodriguez-Iturbe B, Romero F, Johnson RJ. Pathophysiological mechanisms of salt-dependent hypertension. American Journal of Kidney Diseases 2007;50(4):655-72.

(6) Wormer E. A taste for salt in the history of medicine. http://www tribunes com/tribune/sel/worm htm 2012;Available from: URL: http://www.tribunes.com/tribune/sel/worm.htm

(7) Roberts WC. High salt intake, its origins, its economic impact, and its effect on blood pressure. American Journal of Cardiology 2001;88(11):1338-46.

(8) Ritz E. Salt--friend or foe? Nephrol Dial Transplant 2006 August 1;21(8):2052-6.

(9) Encyclopaedia Britannica Online. salt (NaCl) 2012. Encyclopædia Britannica Online 2012;Available from: URL: http://www.britannica.com/EBchecked/topic/519712/salt

(10) Adrogue HJ, Madias NE. Mechanisms of disease: Sodium and potassium in the pathogenesis of hypertension. New England Journal of Medicine 2007;356(19):1966-78.

(11) Joossens JV, Geboers J. Salt and Hypertension. Preventive Medicine 1983;12(1):53-9.

(12) Brown IJ, Tzoulaki I, Candeias V, Elliott P. Salt intakes around the world: implications for public health. International Journal of Epidemiology 2009;38(3):791-813.

(13) He FJ, MacGregor GA. How far should salt intake be reduced? Hypertension 2003 December;42(6):1093-9.

(14) Mohan S, Campbell NRC. Salt and high blood pressure. Clin Sci 2009;117(1-2):1-11.

(15) Ministry of Agriculture, Fisheries and Food. National Food Survey 2000. 2000.

(16) Cotton PA, Subar AF, Friday JE, Cook A. Dietary sources of nutrients among US adults, 1994 to 1996. J Am Diet Assoc 2004 June;104(6):921-30.

(17) WHO. Reducing Salt Intake In Populations. WHO Document Production Services, Geneva, Switzerland; 2006 Oct.

(18) Zhou BF, Stamler J, Dennis B, Moag-Stahlberg A, Okuda N, Robertson C et al. Nutrient intakes of middle-aged men and women in China, Japan, United Kingdom, and United States in the late 1990s: the INTERMAP study. Journal of Human Hypertension 2003;17(9):623-30.

(19) Kerry SM, Emmett L, Micah FB, Martin-Peprah R, Antwi S, Phillips RO et al. Rural and semi-urban differences in salt intake, and its dietary sources, in Ashanti, West Africa. Ethn Dis 2005;15(1):33-9.

(20) WHO. Reducing Salt Intake In Populations. WHO Document Production Services, Geneva, Switzerland; 2007.

(21) Dotsch M, Busch J, Batenburg M, Liem G, Tareilus E, Mueller R et al. Strategies to Reduce Sodium Consumption: A Food Industry Perspective. Critical Reviews in Food Science and Nutrition 2009;49(10):841-51.

(22) Daniels D, Fluharty SJ. Salt appetite: a neurohormonal viewpoint. Physiol Behav 2004 April;81(2):319-37.

(23) McCaughey SA, Scott TR. The taste of sodium. Neuroscience and Biobehavioral Reviews 1998;22(5):663-76.

(24) Lindemann B. Sodium taste. Current Opinion in Nephrology and Hypertension 1997;6(5):425-9.

(25) Watanabe E, Fujikawa A, Matsunaga H, Yasoshima Y, Sako N, Yamamoto T et al. Na(v)2/NaG channel is involved in control of salt-intake behavior in the CNS. Journal of Neuroscience 2000;20(20):7743-51.

(26) Mccance RA. Medical problems in mineral metabolism (Reprinted from The Lancet, vol 1, pg 823-830, 1936). Netherlands Journal of Medicine 2001;58(3):95-102.

(27) Beauchamp GK, Engelman K. High salt intake. Sensory and behavioral factors. Hypertension 1991 January;17(1 Suppl):I176-I181.

(28) Harrison-Bernard LM. The renal renin-angiotensin system. Advances in Physiology Education 2009;33(4):270-4.

(29) Page LB, Vandevert DE, Nader K, Lubin NK, Page JR. Blood-Pressure of Qash-Qai Pastoral Nomads in Iran in Relation to Culture, Diet, and Body Form. American Journal of Clinical Nutrition 1981;34(4):527-38.

(30) Elliott P. Intersalt - An International Study of Electrolyte Excretion and Blood-Pressure - Results for 24 Hour Urinary Sodium and Potassium Excretion. British Medical Journal 1988;297(6644):319-28.

(31) Dyer AR, Elliott P, Shipley M. Urinary Electrolyte Excretion in 24 Hours and Blood-Pressure in the Intersalt Study .2. Estimates of Electrolyte Blood-Pressure Associations Corrected for Regression Dilution Bias. American Journal of Epidemiology 1994;139(9):940-51.

(32) Stamler J, Elliott P, Dennis B, Dyer AR, Kesteloot H, Liu K et al. INTERMAP: background, aims, design, methods, and descriptive statistics (nondietary). Journal of Human Hypertension 2003;17(9):591-608.

(33) Khaw KT, Bingham S, Welch A, Luben R, O'Brien E, Wareham N et al. Blood pressure and urinary sodium in men and women: the Norfolk Cohort of the European Prospective Investigation into cancer (EPIC-Norfolk)(1-3). American Journal of Clinical Nutrition 2004;80(5):1397-403.

(34) Poulter NR, Khaw KT, Hopwood BEC, Mugambi M, Peart WS, Rose G et al. The Kenyan Luo Migration Study - Observations on the Initiation of A Rise in Blood-Pressure. British Medical Journal 1990;300(6730):967-72.

(35) He J, Tell GS, Tang YC, Mo PS, He GQ. Effect of migration on blood pressure: the Yi People Study. Epidemiology 1991 March;2(2):88-97.

(36) Forte JG, Miguel JMP, Miguel MJP, Depadua F, Rose G. Salt and Blood-Pressure - A Community Trial. Journal of Human Hypertension 1989;3(3):179-84.

(37) Takahashi Y, Sasaki S, Okubo S, Hayashi M, Tsugane S. Blood pressure change in a free-living population-based dietary modification study in Japan. Journal of Hypertension 2006;24(3):451-8.

(38) Cappuccio FP, Kerry SM, Micah FB, Plange-Rhule J, Eastwood JB. A community programme to reduce salt intake and blood pressure in Ghana [ISRCTN88789643]. Bmc Public Health 2006;6.

(39) Jessani S, Hatcher J, Chaturvedi N, Jafar TH. Effect of Low vs. High Dietary Sodium on Blood Pressure Levels in a Normotensive Indo-Asian Population. American Journal of Hypertension 2008;21(11):1238-44.

(40) Geleijnse JM, Kok FJ, Grobbee DE. Blood pressure response to changes in sodium and potassium intake: a metaregression analysis of randomised trials. Journal of Human Hypertension 2003;17(7):471-80.

(41) He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. Cochrane Database Syst Rev 2004;(3):CD004937.

(42) Hooper L, Bartlett C, Smith GD, Ebrahim S. Systematic review of long term effects of advice to reduce dietary salt in adults. British Medical Journal 2002;325(7365):628-632A.

(43) Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. New England Journal of Medicine 2001;344(1):3-10.

(44) Vollmer WM, Sacks FM, Ard J, Appel LJ, Bray GA, Simons-Aaorton DG et al. Effects of diet and sodium intake on blood pressure: Subgroup analysis of the DASH-Sodium Trial. Annals of Internal Medicine 2001;135(12):1019-28.

(45) He FJ, MacGregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. Journal of Human Hypertension 2009;23(6):363-84.

(46) Anon. The Hypertension Prevention Trial - 3-Year Effects of Dietary-Changes on Blood-Pressure. Archives of Internal Medicine 1990;150(1):153-62.

(47) [Anon]. The Hypertension Prevention Trial - 3-Year Effects of Dietary-Changes on Blood-Pressure. Archives of Internal Medicine 1990;150(1):153-62.

(48) Whelton PK, Appel L, Charleston J, Dalcin AT, Ewart C, Fried L et al. The Effects of Nonpharmacologic Interventions on Blood-Pressure of Persons with High Normal Levels - Results of the Trials of Hypertension Prevention, Phase-I. Jama-Journal of the American Medical Association 1992;267(9):1213-20.

(49) Whelton PK, Appel L, Charleston J, Dalcin A, Haythornthwaite J, Rosofsky W et al. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure - The trials of hypertension prevention, phase II. Archives of Internal Medicine 1997;157(6):657-67.

(50) Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH, Kostis JB et al. Sodium reduction and weight loss in the treatment of hypertension in older persons - A randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). Jama-Journal of the American Medical Association 1998;279(11):839-46.

(51) Dosh. **The Diagnosis of Essential and Secondary Hypertension in Adults**. The Journal of Family Practice 50[8]. 2001.
Ref Type: Journal (Full)

(52) Sacks FM, Campos H. Dietary Therapy in Hypertension. New England Journal of Medicine 2010;362(22):2102-12.

(53) Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Blood 2011;118(15):1206-52.

(54) Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: An overview. American Journal of Clinical Nutrition 1997;65(2):S643-S651.

(55) Pimenta E, Gaddam KK, Oparil S, Aban I, Husain S, Dell'Italia LJ et al. Effects of Dietary Sodium Reduction on Blood Pressure in Subjects With Resistant Hypertension Results From a Randomized Trial. Hypertension 2009;54(3):475-81.

(56) Alderman MH. Dietary sodium and cardiovascular health in hypertensive patients: The case against universal sodium restriction. Journal of the American Society of Nephrology 2004;15(1):S47-S50.

(57) Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell 2001;104(4):545-56.

(58) Sabath E, Meade P, Berkman J, Heros Pdl, Moreno E, Bobadilla NA et al. Pathophysiology of functional mutations of the thiazide-sensitive Na-Cl cotransporter in Gitelman disease. American Journal of Physiology - Renal Physiology 2004 August 1;287(2):F195-F203.

(59) Stein LJ, Cowart BJ, Beauchamp GK. The development of salty taste acceptance is related to dietary experience in human infants: a prospective study. The American Journal of Clinical Nutrition 2012 January 1;95(1):123-9.

(60) Davies D. Review of the UK marketplace for convenience foods. Nutrition & Food Science 2001;31(6):322-3.

(61) Purdy J, Armstrong G. Dietary salt and the consumer: reported consumption and awareness of associated health risks. Reducing Salt in Foods: Practical Strategies 2007;99-123.

(62) Henchion M. Meals for cash rich, time poor consumers. http://www teagasc ie/publications/readymeals2000/readymealsconf pdf 2000;Available from: URL: http://www.teagasc.ie/publications/readymeals2000/readymealsconf.pdf

(63) CASH. Salt content reduced in UK ready meals. http://www actiononsalt org uk/Docs/34003 doc 2007 November 23;

(64) Alderman MH, Madhavan S, Cohen H, Sealey JE, Laragh JH. Low Urinary Sodium Is Associated with Greater Risk of Myocardial-Infarction Among Treated Hypertensive Men. Hypertension 1995;25(6):1144-52.

(65) Cook NR, Cutler JA, Hennekens CH. An Unexpected Result for Sodium - Causal Or Casual. Hypertension 1995;25(6):1153-4.

(66) Stolarz-Skrzypek K, Kuznetsova T, Thijs L, Tikhonoff V, Seidlerova J, Richart T et al. Fatal and Nonfatal Outcomes, Incidence of Hypertension, and Blood Pressure Changes in Relation to Urinary Sodium Excretion. Jama-Journal of the American Medical Association 2011;305(17):1777-85.

(67) Gina Kolata. Low-Salt Diet Ineffective, Study Finds. Disagreement Abounds. The New York Times 2011 May 3.

(68) Willet. **Flawed Science on Sodium from JAMA**. http://www hsph harvard edu/nutritionsource/salt/jama-sodium-study-flawed/ 2011 May;Available from: URL: http://www.hsph.harvard.edu/nutritionsource/salt/jama-sodium-study-flawed/

(69) Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced Dietary Salt for the Prevention of Cardiovascular Disease: A Meta-Analysis of Randomized Controlled Trials (Cochrane Review). Am J Hypertens 2011 August;24(8):843-53.

(70) He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. Lancet 2011;378(9789):380-2.

(71) Jenner K. Comment on new Cochrane Review on reduced dietary salt. http://www actiononsalt org uk/news/Salt%20in%20the%20news/2011/58269 html 2011 July 6;Available from: URL: http://www.actiononsalt.org.uk/news/Salt%20in%20the%20news/2011/58269.html

(72) Alderman MH, Cohen H, Madhavan S. Dietary sodium intake and mortality: the national health and nutrition examination survey (NHANES I). Lancet 1998;351(9105):781-5.

(73) Cohen HW, Hailpern SM, Fang J, Alderman MH. Sodium intake and mortality in the NHANES II follow-up study. American Journal of Medicine 2006;119(3).

(74) Cohen HW, Hailpern SM, Alderman MH. Sodium intake and mortality follow-up in the Third National Health and Nutrition Examination Survey (NHANES III). Journal of General Internal Medicine 2008;23(9):1297-302.

(75) De Wardener HE. Salt reduction and cardiovascular risk: the anatomy of a myth. Journal of Human Hypertension 1999;13(1):1-4.

(76) Poulter NR. Dietary sodium intake and mortality: NHANES. Lancet 1998;352(9132):987-8.

(77) He J, Whelton PK. What is the role of dietary sodium and potassium in hypertension and target organ injury? American Journal of the Medical Sciences 1999;317(3):152-9.

(78) Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of Low-Sodium Diet vs. High-Sodium Diet on Blood Pressure, Renin, Aldosterone, Catecholamines, Cholesterol, and Triglyceride (Cochrane Review). Am J Hypertens 2012 January;25(1):1-15.

(79) MacGregor G. CASH comments on new Cochrane paper (9th November). http://www actiononsalt org uk/news/Salt%20in%20the%20news/2011/58991 html 2011 November 10;Available from: URL: http://www.actiononsalt.org.uk/news/Salt%20in%20the%20news/2011/58991.html

(80) Norman M.Kaplan, Ronald G.Victor. Treatment of Hypertension: Lifestyle Modifications. Kaplan's Clinial Hypertension.Philadelphia: Lippincott Williams & Wilnkins; 2010. p. 168-91.

(81) Tayie FAK, Jourdan K. Hypertension, Dietary Salt Restriction, and Iodine Deficiency Among Adults. American Journal of Hypertension 2010;23(10):1095-102.

(82) Vanderpump MPJ, Lazarus JH, Smyth PP, Laurberg P, Holder RL, Boelaert K et al. Iodine status of UK schoolgirls: a cross-sectional survey. Lancet 2011;377(9782):2007-12.

(83) MacGregor G. CASH comments - **Iodine deficiency in UK** adolescents highlighted in Lancet paper. http://www actiononsalt org uk/news/Salt%20in%20the%20news/2011/58276 html 2011 June

2;Available from: URL: http://www.actiononsalt.org.uk/news/Salt%20in%20the%20news/2011/58276.html

(84) He FJ, Markandu ND, Sagnella GA, De Wardener HE, MacGregor GA. Plasma sodium - Ignored and underestimated. Hypertension 2005;45(1):98-102.

(85) Van Vliet BN, Montani JP. The time course of salt-induced hypertension, and why it matters. International Journal of Obesity 2008 December;32:S35-S47.

(86) Dahl LK, Thompson K, Heine M. Genetic Influence of Renal Homografts on Blood-Pressure of Rats from Different Strains. Proceedings of the Society for Experimental Biology and Medicine 1972;140(3):852-&.

(87) Dahl LK, Heine M, Thompson K. Genetic Influence of Kidneys on Blood-Pressure - Evidence from Chronic Renal Homografts in Rats with Opposite Predispositions to Hypertension. Circulation Research 1974;34(1):94-101.

(88) Curtis JJ, Luke RG, Dustan HP, Kashgarian M, Whelchel JD, Jones P et al. Remission of Essential-Hypertension After Renal-Transplantation. New England Journal of Medicine 1983;309(17):1009-15.

(89) Guyton AC. Blood-Pressure Control - Special Role of the Kidneys and Body-Fluids. Science 1991;252(5014):1813-6.

(90) Bulpitt CJ, Shipley MJ, Semmence A. Blood-Pressure and Plasma Sodium and Potassium. Clinical Science 1981;61:S85-S87.

(91) Komiya I, Yamada T, Takasu N, Asawa T, Akamine H, Yagi N et al. An abnormal sodium metabolism in Japanese patients with essential hypertension, judged by serum sodium distribution, renal function and the renin-aldosterone system. Journal of Hypertension 1997;15(1):65-72.

(92) Lago RM, Pencina MJ, Wang TJ, Lanier KJ, D'Agostino RB, Kannel WB et al. Interindividual variation in serum sodium and longitudinal blood pressure tracking in the Framingham Heart Study. Journal of Hypertension 2008;26(11):2121-5.

(93) De Wardener HE, He FJ, MacGregor GA. Plasma sodium and hypertension. Kidney International 2004;66(6):2454-66.

(94) Friedman SM, Mcindoe RA, Tanaka M. The Relation of Blood Sodium Concentration to Blood-Pressure in the Rat. Journal of Hypertension 1990;8(1):61-6.

(95) Gu JW, Anand V, Shek EW, Moore MC, Brady AL, Kelly WC et al. Sodium induces hypertrophy of cultured myocardial myoblasts and vascular smooth muscle cells. Hypertension 1998;31(5):1083-7.

(96) Li J, White J, Guo L, Zhao X, Wang J, Smart EJ et al. Salt Inactivates Endothelial Nitric Oxide Synthase in Endothelial Cells. Journal of Nutrition 2009;139(3):447-51.

(97) Oberleithner H, Riethmueller C, Schillers H, MacGregor GA, de Wardener HE, Hausberg M. Plasma sodium stiffens vascular endothelium and reduces nitric oxide release. Proceedings of the National Academy of Sciences of the United States of America 2007;104(41):16281-6.

(98) Dickinson KM, Keogh JB, Clifton PM. Effects of a low-salt diet on flow-mediated dilatation in humans. American Journal of Clinical Nutrition 2009;89(2):485-90.

(99) Tzemos N, Lim PO, Wong S, Struthers AD, MacDonald TM. Adverse cardiovascular effects of acute salt loading in young normotensive individuals. Hypertension 2008;51(6):1525-30.

(100) Meneton P, Jeunemaitre X, De Wardener HE, MacGregor GA. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. Physiological Reviews 2005;85(2):679-715.

(101) Barker DJP. In utero programming of chronic disease. Clin Sci 1998;95(2):115-28.

(102) Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ 1989 March 4;298(6673):564-7.

(103) Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. Journal of Hypertension 2000;18(7):815-31.

(104) Alexander BT. New Investigator Award in Regulatory and Integrative Physiology of the Water and Electrolyte Homeostasis Section, 2005 - Fetal programming of hypertension. American Journal of Physiology-Regulatory Integrative and Comparative Physiology 2006;290(1):R1-R10.

(105) de Boer MP, IJzerman RG, de Jongh RT, Eringa EC, Stehouwer CDA, Smulders YM et al. Birth weight relates to salt sensitivity of blood pressure in healthy adults. Hypertension 2008;51(4):928-32.

(106) Simonetti GD, Raio L, Surbek D, Nelle M, Frey FJ, Mohaupt MG. Salt sensitivity of children with low birth weight. Hypertension 2008;52(4):625-30.

(107) Kimura G, Brenner BM. Implications of the linear pressure-natriuresis relationship and importance of sodium sensitivity in hypertension. Journal of Hypertension 1997;15(10):1055-61.

(108) Flack JM, Grimm RH, Staffileno BA, Elmer P, Yunis C, Hedquist L et al. New salt-sensitivity metrics: Variability-adjusted blood pressure change and the urinary sodium-to-creatinine ratio. Ethnicity and Disease 2002;12(1):10-9.

(109) Weinberger MH, Miller JZ, Luft FC, Grim CE, Fineberg NS. Definitions and Characteristics of Sodium Sensitivity and Blood-Pressure Resistance. Hypertension 1986;8(6):127-34.

(110) Weinberger MH. Salt sensitivity of blood pressure in humans. Hypertension 1996;27(3):481-90.

(111) Beeks E, Kessels AGH, Kroon AA, van der Klauw MM, de Leeuw PW. Genetic predisposition to salt-sensitivity: a systematic review. Journal of Hypertension 2004;22(7):1243-9.

(112) Miller JZ, Weinberger MH, Christian JC, Daugherty SA. Familial Resemblance in the Blood-Pressure Response to Sodium Restriction. American Journal of Epidemiology 1987;126(5):822-30.

(113) Kaplan. Primary Hypertension: Pathogenesis. Clinical Hypertension. 2010.

(114) Mayer G. An update on the relationship between the kidney, salt and hypertension. Wien Med Wochenschr 2008;158(13-14):365-9.

(115) Hall JE, Guyton AC, Brands MW. Pressure-volume regulation in hypertension. Kidney International 1996;S35-S41.

(116) Cowley AW. Renal Medullary Oxidative Stress, Pressure-Natriuresis, and Hypertension. Hypertension 2008;52(5):777-86.

(117) Dickhout JG, Mori T, Cowley AW. Tubulovascular nitric oxide crosstalk - Buffering of angiotensin II-induced medullary vasoconstriction. Circulation Research 2002;91(6):487-93.

(118) Crowley SD, Coffman TM. In hypertension, the kidney breaks your heart. Curr Cardiol Rep 2008 November;10(6):470-6.

(119) Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: From physiology to the pathobiology of hypertension and kidney disease. Pharmacological Reviews 2007;59(3):251-87.

(120) Carey RM, Padia SH. Angiotensin AT(2) receptors: control of renal sodium excretion and blood pressure. Trends in Endocrinology and Metabolism 2008;19(3):84-7.

(121) Rutledge DR, Sun YM, Ross EA. Polymorphisms Within the Atrial-Natriuretic-Peptide Gene in Essential-Hypertension. Journal of Hypertension 1995;13(9):953-5.

(122) Beige J, Ringel J, Hohenbleicher H, Rubattu S, Kreutz R, Sharma AM. HpaII-polymorphism of the atrial-natriuretic-peptide gene and essential hypertension in whites. American Journal of Hypertension 1997;10(11):1316-8.

(123) Greenfield JR, Miller JW, Keogh JM, Henning E, Satterwhite JH, Cameron GS et al. Modulation of Blood Pressure by Central Melanocortinergic Pathways. New England Journal of Medicine 2009;360(1):44-52.

(124) Dibona GF. Physiology in perspective: The Wisdom of the Body. Neural control of the kidney. American Journal of Physiology-Regulatory Integrative and Comparative Physiology 2005;289(3):R633-R641.

(125) Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009;373(9671):1275-81.

(126) Majid DSA, Kopkan L. Nitric oxide and superoxide interactions in the kidney and their implication in the development of salt-sensitive hypertension. Clinical and Experimental Pharmacology and Physiology 2007;34(9):946-52.

(127) Bankir L, Perucca J, Weinberger MH. Ethnic differences in urine concentration: Possible relationship to blood pressure. Clinical Journal of the American Society of Nephrology 2007;2(2):304-12.

(128) McKeigue PM, Reynard JM. Relation of nocturnal polyuria of the elderly to essential hypertension. Lancet 2000;355(9202):486-8.

(129) Fukuda M, Goto N, Kimura G. Hypothesis on renal mechanism of non-dipper pattern of circadian blood pressure rhythm. Medical Hypotheses 2006;67(4):802-6.

(130) Langenfeld MRW, Schmieder RE. Salt and Left-Ventricular Hypertrophy - What Are the Links. Journal of Human Hypertension 1995;9(11):909-16.

(131) Schmieder RE, Messerli FH. Hypertension and the heart. Journal of Human Hypertension 2000;14(10-11):597-604.

(132) Du CG, Ribstein J, Daures JP, Mimran A. Sodium and left ventricular mass in untreated hypertensive and normotensive subjects. Am J Physiol 1992 July;263(1 Pt 2):H177-H181.

(133) Gerdts E, Svarstad E, Aanderud S, Myking OL, Lund-Johnnsen P, Omvik P. Factors influencing reduction in blood pressure and left ventricular mass in hypertensive type-1 diabetic patients using captopril or doxazosin for 6 months. American Journal of Hypertension 1998;11(10):1178-87.

(134) Fields NG, Yuan BX, Leenen FHH. Sodium-Induced Cardiac-Hypertrophy - Cardiac Sympathetic Activity Versus Volume Load. Circulation Research 1991;68(3):745-55.

(135) Drayer JIM, Gardin JM, Weber MA. Echocardiographic Left-Ventricular Hypertrophy in Hypertension. Chest 1983;84(2):217-21.

(136) Gasowski J, Fagard RH, Staessen JA, Grodzicki T, Pocock S, Boutitie F et al. Pulsatile blood pressure component as predictor of mortality in hypertension: a meta-analysis of clinical trial control groups. J Hypertens 2002 January;20(1):145-51.

(137) Safar ME, Thuilliez C, Richard V, Benetos A. Pressure-independent contribution of sodium to large artery structure and function in hypertension. Cardiovascular Research 2000;46(2):269-76.

(138) Simon G, Illyes G. Structural vascular changes in hypertension - Role of angiotensin II, dietary sodium supplementation, and sympathetic stimulation, alone anti in combination in rats. Hypertension 2001;37(2):255-60.

(139) Barton P, Andronis L, Briggs A, McPherson K, Capewell S. Effectiveness and cost effectiveness of cardiovascular disease prevention in whole populations: modelling study. British Medical Journal 2011;343.

(140) Avolio AP, Clyde KM, Beard TC, Cooke HM, Ho KKL, Orourke MF. Improved Arterial Distensibility in Normotensive Subjects on A Low Salt Diet. Arteriosclerosis 1986;6(2):166-9.

(141) He FJ, Markandu ND, MacGregor GA. Modest salt reduction lowers blood pressure in isolated systolic hypertension and combined hypertension. Hypertension 2005;46(1):66-70.

(142) Gates PE, Tanaka H, Hiatt WR, Seals DR. Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. Hypertension 2004;44(1):35-41.

(143) He FJ, Burnier M, MacGregor GA. Nutrition in cardiovascular disease: salt in hypertension and heart failure. European Heart Journal 2011;32(24):3073-U179.

(144) Frohlich ED, Tarazi RC, Dustan HP. Clinical-Physiological Correlations in Development of Hypertensive Heart Disease. Circulation 1971;44(3):446-&.

(145) He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Dietary sodium intake and incidence of congestive heart failure in overweight US men and women - First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Archives of Internal Medicine 2002;162(14):1619-24.

(146) Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients - An underrecognized public health problem. Archives of Internal Medicine 2000;160(6):777-84.

(147) Ahn J, Varagic J, Slama M, Susic D, Frohlich ED. Cardiac structural and functional responses to salt loading in SHR. American Journal of Physiology-Heart and Circulatory Physiology 2004;287(2):H767-H772.

(148) Marcus ML, Doty DB, Hiratzka LF, Wright CB, Eastham CL. Decreased Coronary Reserve - A Mechanism for Angina-Pectoris in Patients with Aortic-Stenosis and Normal Coronary-Arteries. New England Journal of Medicine 1982;307(22):1362-6.

(149) Houghton JL, Frank MJ, Carr AA, Vondohlen TW, Prisant LM. Relations Among Impaired Coronary Flow Reserve, Left-Ventricular Hypertrophy and Thallium Perfusion Defects in Hypertensive Patients Without Obstructive Coronary-Artery Disease. Journal of the American College of Cardiology 1990;15(1):43-51.

(150) Willey RM. Managing Heart Failure: A Critical Appraisal of the Literature. J Cardiovasc Nurs 2011 November 2.

(151) Strazzullo P. Compelling evidence for salt-dependence of blood pressure from GENSALT. Journal of Hypertension 2009;27(1):22-3.

(152) De Wardener HE, MacGregor GA. Harmful effects of dietary salt in addition to hypertension. Journal of Human Hypertension 2002;16(4):213-23.

(153) Xie JX, Sasaki S, Joossens JV, Kesteloot H. The Relationship Between Urinary Cations Obtained from the Intersalt Study and Cerebrovascular Mortality. Journal of Human Hypertension 1992;6(1):17-21.

(154) Perry IJ, Beevers DG. Salt Intake and Stroke - A Possible Direct Effect. Journal of Human Hypertension 1992;6(1):23-5.

(155) Gow IF, Dockrell M, Edwards CRW, Elder A, Grieve J, Kane G et al. The Sensitivity of Human Blood-Platelets to the Aggregating Agent Adp

During Different Dietary-Sodium Intakes in Healthy-Men. European Journal of Clinical Pharmacology 1992;43(6):635-8.

(156) Gow IF, Padfield PL, Reid M, Stewart SE, Edwards CR, Williams BC. High sodium intake increases platelet aggregation in normal females. Journal of hypertension Supplement : official journal of the International Society of Hypertension 1987;5(5):S243-S246.

(157) Nara Y, Kihara M, Nabika T, Mano M, Horie R, Yamori Y. Dietary-Effect on Platelet-Aggregation in Men with and Without A Family History of Essential-Hypertension. Hypertension 1984;6(3):339-43.

(158) Ashida T, Tanaka T, Yokouchi M, Kuramochi M, Deguchi F, Kimura G et al. Effect of Dietary-Sodium on Platelet Alpha-2-Adrenergic Receptors in Essential-Hypertension. Hypertension 1985;7(6):972-8.

(159) Wright JA, Cavanaugh KL. Dietary Sodium in Chronic Kidney Disease: A Comprehensive Approach. Seminars in Dialysis 2010;23(4):415-21.

(160) Swift PA, Markandu ND, Sagnella GA, He FJ, MacGregor GA. Modest salt reduction reduces blood pressure and urine protein excretion in black hypertensives - A randomized control trial. Hypertension 2005;46(2):308-12.

(161) He FJ, Marciniak M, Visagie E, Markandu ND, Anand V, Dalton RN et al. Effect of Modest Salt Reduction on Blood Pressure, Urinary Albumin, and Pulse Wave Velocity in White, Black, and Asian Mild Hypertensives. Hypertension 2009;54(3):482-8.

(162) Cianciaruso B, Bellizzi V, Minutolo R, Tavera A, Capuano A, Conte G et al. Salt intake and renal outcome in patients with progressive renal disease. Mineral and Electrolyte Metabolism 1998;24(4):296-301.

(163) NHS. **Statistics on Obesity, Physical Activity and Diet: England, 2006** . The Information Centre, Lifestyle Statistics; 2006.

(164) Thornton SN. Sodium and Cardiovascular Disease[colon] A Mismatch of Physiological Regulation and Hydration. Am J Hypertens 2012 January;25(1):18.

(165) Karppanen H, Mervaala E. Sodium intake and hypertension. Progress in Cardiovascular Diseases 2006;49(2):59-75.

(166) James J. Preventing childhood obesity by reducing consumption of carbonated drinks: cluster randomised controlled trial (vol 328, pg 1237, 2004). British Medical Journal 2004;328(7450):1236.

(167) He FJ, Marrero NM, MacGregor GA. Salt intake is related to soft drink consumption in children and adolescents - A link to obesity? Hypertension 2008;51(3):629-34.

(168) National Osteoporosis Society. Osteoporosis Facts and Figures. http://www nos org uk/NetCommunity/admin/Document Doc?id=47 2009;Available from: URL: http://www.nos.org.uk/NetCommunity/admin/Document.Doc?id=47

(169) Massey LK, Whiting SJ. Dietary salt, urinary calcium, and bone loss. Journal of Bone and Mineral Research 1996;11(6):731-6.

(170) Itoh R, Suyama Y. Sodium excretion in relation to calcium and hydroxyproline excretion in a healthy Japanese population. American Journal of Clinical Nutrition 1996;63(5):735-40.

(171) Devine A, Criddle RA, Dick IM, Kerr DA, Prince RL. A Longitudinal-Study of the Effect of Sodium and Calcium Intakes on Regional Bone-Density in Postmenopausal Women. American Journal of Clinical Nutrition 1995;62(4):740-5.

(172) Wasnich R, Davis J, Ross P, Vogel J. Effect of Thiazide on Rates of Bone-Mineral Loss - A Longitudinal-Study. British Medical Journal 1990;301(6764):1303-5.

(173) Joossens JV, Hill MJ, Elliott P, Stamler R, Stamler J, Lesaffre E et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. International Journal of Epidemiology 1996;25(3):494-504.

(174) Fox JG, Dangler CA, Taylor NS, King A, Koh TJ, Wang TC. High-salt diet induces gastric epithelial hyperplasia and parietal cell loss, and enhances Helicobacter pylori colonization in C57BL/6 mice. Cancer Research 1999;59(19):4823-8.

(175) Palli D. Epidemiology of gastric cancer: an evaluation of available evidence. J Gastroenterol 2000;35 Suppl 12:84-9.

(176) Tsugane S. Salt, salted food intake, and risk of gastric cancer: Epidemiologic evidence. Cancer Science 2005;96(1):1-6.

(177) Takachi R, Inoue M, Shimazu T, Sasazuki S, Ishihara J, Sawada N et al. Consumption of sodium and salted foods in relation to cancer and cardiovascular disease: the Japan Public Health CenterΓÇôbased Prospective Study. The American Journal of Clinical Nutrition 2010 February 1;91(2):456-64.

(178) Strumylaite L, Zickute J, Dudzevicius J, Dregval L. Salt-preserved foods and risk of gastric cancer. Medicina (Kaunas) 2006;42(2):164-70.

(179) Burney P. A Diet Rich in Sodium May Potentiate Asthma - Epidemiologic Evidence for A New Hypothesis. Chest 1987;91(6):S143-S148.

(180) Carey OJ, Locke C, Cookson JB. Effect of Alterations of Dietary-Sodium on the Severity of Asthma in Men. Thorax 1993;48(7):714-8.

(181) Corbo GM, Forastiere F, De Sario M, Brunetti L, Bonci E, Bugiani M et al. Wheeze and asthma in children - Associations with body mass index, sports, television viewing, and diet. Epidemiology 2008;19(5):747-55.

(182) Mickleborough TD, Lindley MR, Ray S. Dietary salt, airway inflammation, and diffusion capacity in exercise-induced asthma. Medicine and Science in Sports and Exercise 2005;37(6):904-14.

(183) James WPT, Ralph A, Sanchezcastillo CP. The Dominance of Salt in Manufactured Food in the Sodium-Intake of Affluent Societies. Lancet 1987;1(8530):426-9.

(184) Gilbert PA, Heiser G. Salt and health: the CASH and BPA perspective. Nutrition Bulletin 2005;30(1):62-9.

(185) Frisoli TM, Schmieder RE, Grodzicki T, Messerli FH. Beyond salt: lifestyle modifications and blood pressure. European Heart Journal 2011;32(24):3081-U187.

(186) Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. The Lancet 2006 May 27;367(9524):1747-57.

(187) WHO. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva, Switzerland; 2002.

(188) WHO. Diet, nutrition, and the prevention of chronic diseases WHO technical report series, No 916. Geneva: World Health Organization; 2003.

(189) He FJ, Jenner KH, MacGregor GA. WASH-World Action on Salt and Health. Kidney International 2010;78(8):745-53.

(190) Webster JL, Dunford EK, Hawkes C, Neal BC. Salt reduction initiatives around the world. Journal of Hypertension 2011;29(6):1043-50.

(191) MacGregor GA, Sever PS. Salt - Overwhelming evidence but still no action: Can a consensus be reached with the food industry? British Medical Journal 1996;312(7041):1287-9.

(192) Henderson, L and et al. *National Diet and Nutrition Survey: Adults aged 19 to 64 Years. Vitamin and Mineral Intake and Urinary Analytes. Vol 3.* London: The Stationery Office; 2003.

(193) Food Standards Agency. Salt reduction targets, 2009. http://collections europarchive org/tna/20100927130941/http://food gov uk/healthiereating/salt/saltreduction 2009;Available from: URL: http://collections.europarchive.org/tna/20100927130941/http://food.gov.uk/healthiereating/salt/saltreduction

(194) Girgis S, Neal B, Prescott J, Prendergast J, Dumbrell S, Turner C et al. A one-quarter reduction in the salt content of bread can be made without detection. European Journal of Clinical Nutrition 2003;57(4):616-20.

(195) Food Standards Agency. Agency publishes 2012 salt reduction targets. http://www food gov uk/news/newsarchive/2009/may/salttargets 2009;Available from: URL: http://www.food.gov.uk/news/newsarchive/2009/may/salttargets

(196) Food Standards Agency. Dietary sodium levels surveys. http://www food gov uk/science/dietarysurveys/urinary 2008;Available from: URL: http://www.food.gov.uk/science/dietarysurveys/urinary

(197) National Institute for Health and Clinical Excellence (NICE). Guidance on the prevention of cardiovascular disease at the population level. http://guidance nice org uk/PH25 2010;Available from: URL: http://guidance.nice.org.uk/PH25

(198) Food Standards Agency. Traffic light labelling, Signposting. http://www food gov uk/foodlabelling/signposting/ 2010;Available from: URL: http://www.food.gov.uk/foodlabelling/signposting/

(199) Food Standards Agency. Citizens' forums on food: Front of Pack (FoP) Nutrition Labelling. http://www food gov uk/multimedia/pdfs/citforumfop pdf 2010;Available from: URL: http://www.food.gov.uk/multimedia/pdfs/citforumfop.pdf

(200) Young L, Swinburn B. Impact of the Pick the Tick food information programme on the salt content of food in New Zealand. Health Promotion International 2002;17(1):13-9.

(201) CASH. Salt Awareness Week 2012 - Reducing salt; preventing stroke. http://www actiononsalt org uk/awareness/Salt%20and%20stroke%202012/55601 html 2012;Available from: URL: http://www.actiononsalt.org.uk/awareness/Salt%20and%20stroke%202012/55601.html

(202) CASH. **Salt and Your Health**. http://www actiononsalt org uk 2010 February 1;Available from: URL: http://www.actiononsalt.org.uk/Docs/33386.pdf

(203) Addison A. Voluntary - Salt Reduction Strategy Reformulation Targets. http://www bis gov uk/assets/biscore/better-regulation/docs/v/10-

1283-voluntary-salt-reduction 2010;Available from: URL: http://www.bis.gov.uk/assets/biscore/better-regulation/docs/v/10-1283-voluntary-salt-reduction

(204) Food Standards Agency. UK Salt Reduction Initiatives. http://www food gov uk/multimedia/pdfs/saltreductioninitiatives pdf 2009;Available from: URL: http://www.food.gov.uk/multimedia/pdfs/saltreductioninitiatives.pdf

(205) Food Standards Agency. Food Standards Agency salt campaign: measuring success. FHA Newsletter - Issue 14 2009;Available from: URL: http://www.fhascot.org.uk/Resource/food-standards-agency-salt-campaign-measuring-success

(206) Wyness LA, Butriss JL, Stanner SA. Reducing the population's sodium intake: the UK Food Standards Agency's salt reduction programme. Public Health Nutrition 2012;15(2):254-61.

(207) National Diet and Nutrition Survey. **National Diet and Nutrition Survey: Headline results from Years 1 and 2 (combined) of the rolling programme 2008/9 - 2009/10**. http://www dh gov uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_128166 2011 July 21;Available from: URL: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_128166

(208) Mahtani KR. Simple advice to reduce salt intake. British Journal of General Practice 2009;59(567):786-7.

(209) Grunert KG, Wills JM, Fernandez-Celemin L. Nutrition knowledge, and use and understanding of nutrition information on food labels among consumers in the UK. Appetite 2010;55(2):177-89.

(210) Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM et al. A clinical trial of the effects of dietary patterns on blood pressure. New England Journal of Medicine 1997;336(16):1117-24.

(211) British Heart Foundation. Food Eaten Outside the Home Policy Statement. http://www bhf org uk/pdf/Public%20Out%20of%20home%20food%20policy%20recommendation%20 pdf 2010;Available from: URL: http://www.bhf.org.uk/pdf/Public%20Out%20of%20home%20food%20policy%20recommendation%20.pdf

(212) CASH. Takeaway foods very high in salt. http://www actiononsalt org uk/news/surveys/2006/takeaway/index html 2006;Available from: URL: http://www.actiononsalt.org.uk/news/surveys/2006/takeaway/index.html

(213) Mackison D, Wrieden W, Anderson A. Making an informed choice in the catering environment: what do consumers want to know? Journal of Human Nutrition and Dietetics 2009;22(6):567-73.

(214) Murray CJL, Lauer JA, Hutubessy RCW, Niessen L, Tomijima N, Rodgers A et al. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. Lancet 2003;361(9359):717-25.

(215) Smith-Spangler CM, Juusola JL, Enns EA, Owens DK, Garber AM. Population Strategies to Decrease Sodium Intake and the Burden of Cardiovascular Disease A Cost-Effectiveness Analysis. Annals of Internal Medicine 2010;152(8):481-U21.

(216) Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ et al. Projected Effect of Dietary Salt Reductions on Future Cardiovascular Disease. New England Journal of Medicine 2010;362(7):590-9.

(217) Joffres MR, Campbell NRC, Manns B, Tu K. Estimate of the benefits of a population-based reduction in dietary sodium additives on hypertension and its related health care costs in Canada. Canadian Journal of Cardiology 2007;23(6):437-43.

(218) Selmer RM, Kristiansen IS, Haglerod A, Graff-Iversen S, Larsen HK, Meyer HE et al. Cost and health consequences of reducing the population intake of salt. Journal of Epidemiology and Community Health 2000;54(9):697-702.

(219) Asaria P, Chisholm D, Mathers C, Ezzati M, Beaglehole R. Chronic diseases 3 - Chronic disease prevention: health effects and financial costs of strategies to reduce salt intake and control tobacco use. Lancet 2007;370(9604):2044-53.

(220) Kawano Y, Tsuchihashi T, Matsuura H, Ando K, Fujita T, Ueshima H. Report of the Working Group for Dietary Salt Reduction of the Japanese Society of Hypertension: (2) Assessment of Salt Intake in the Management of Hypertension. Hypertens Res 2007 October;30(10):887-93.

(221) Elliott, P and Brown, I. Sodium intakes around the world. WHO; 2007.

(222) Oconnor WJ. Normal Sodium Balance in Dogs and in Man. Cardiovascular Research 1977;11(5):375-408.

(223) Wesson LG. Electrolyte Excretion in Relation to Diurnal Cycles of Renal Function - Plasma Electrolyte Concentrations + Aldosterone Secretion Before + During Salt + Water Balance Changes in Normotensive Subjects. Medicine 1964;43(5):547-&.

(224) Bates C, Thurnham D, Bingham S, Margetts B, Nelson M. Biochemical markers of nutrient intake. Oxford, NY: Oxford University Press, Inc; 1997.

(225) Holbrook JT, Patterson KY, Bodner JE, Douglas LW, Veillon C, Kelsay JL et al. Sodium and Potassium Intake and Balance in Adults Consuming Self-Selected Diets. American Journal of Clinical Nutrition 1984;40(4):786-93.

(226) Baldwin D, Alexander RW, Warner EG. Chronic Sodium Chloride Challenge Studies in Man. Journal of Laboratory and Clinical Medicine 1960;55(3):362-75.

(227) Bentley B. A review of methods to measure dietary sodium intake. J Cardiovasc Nurs 2006 January;21(1):63-7.

(228) Bingham S, Cummings JH. The Use of 4-Aminobenzoic Acid As A Marker to Validate the Completeness of 24 H Urine Collections in Man. Clin Sci 1983;64(6):629-35.

(229) Bingham SA, Murphy J, Waller E, Runswick SA, Neale G, Evans D et al. Para-Amino Benzoic-Acid in the Assessment of Completeness of 24-Hour Urine Collections from Hospital Outpatients and the Effect of Impaired Renal-Function. European Journal of Clinical Nutrition 1992;46(2):131-5.

(230) Jakobsen J, Pedersen AN, Ovesen L. Para-aminobenzoic acid (PABA) used as a marker for completeness of 24 hour urine: effects of age and dosage scheduling. European Journal of Clinical Nutrition 2003;57(1):138-42.

(231) Watson RL, Langford HG. Usefulness of Overnight Urines in Population Groups - Pilot Studies of Sodium, Potassium, and Calcium Excretion. American Journal of Clinical Nutrition 1970;23(3):290-&.

(232) Widdowso EM, Mccance RA. Use of Random Specimens of Urine to Compare Dietary Intakes of African and British Children. Archives of Disease in Childhood 1970;45(242):547-&.

(233) Stanbury SW, Thomson AE. Diurnal Variations in Electrolyte Excretion. Clin Sci 1951;10(3):267-93.

(234) Cummins RO, Shaper AG, Walker M. Methodological Problems with Estimation of Salt Intake. Lancet 1981;1(8234):1373-4.

(235) Walker WG, Whelton PK, Saito H, Russell RP, Hermann J. Relation Between Blood-Pressure and Renin, Renin Substrate, Angiotensin-Ii, Aldosterone and Urinary Sodium and Potassium in 574 Ambulatory Subjects. Hypertension 1979;1(3):287-91.

(236) Moore M, Burgess R, Volosin K, Buckalew V. Spot Urinary Sodium-Creatinine Ratio Predicts Previous Days 24 Hour Sodium Excretion in Young Essential Hypertensives. Preventive Medicine 1979;8(2):200.

(237) Milne FJ, Gear JSS, Laidley L, Ritchie M, Schultz E. Spot Urinary Electrolyte Concentrations and 24 Hour Excretion. Lancet 1980;2(8204):1135.

(238) Dauncey MJ, Widdowso EM. Urinary-Excretion of Calcium, Magnesium, Sodium, and Potassium in Hard and Soft Water Areas. Lancet 1972;1(7753):711-&.

(239) Kawasaki T, Itoh K, Uezono K, Sasaki H. A Simple Method for Estimating 24-H Urinary Sodium and Potassium Excretion from 2Nd Morning Voiding Urine Specimen in Adults. Clinical and Experimental Pharmacology and Physiology 1993;20(1):7-14.

(240) Tanaka T, Okamura T, Miura K, Kadowaki T, Ueshima H, Nakagawa H et al. A simple method to estimate populational 24-h urinary sodium and potassium excretion using a casual urine specimen. Journal of Human Hypertension 2002;16(2):97-103.

(241) Caggiula AW, Wing RR, Nowalk MP, Milas NC, Lee S, Langford H. The Measurement of Sodium and Potassium Intake. American Journal of Clinical Nutrition 1985;42(3):391-8.

(242) Acheson KJ, Campbell IT, Edholm OG, Miller DS, Stock MJ. The Measurement of Food and Energy-Intake in Man - An Evaluation of Some Techniques. American Journal of Clinical Nutrition 1980;33(5):1147-54.

(243) Bates C, Thurnham D, Bingham S, Margetts B, Nelson M. Design concepts in nutritional epidemiology. Oxford, NY: Oxford University Press, Inc; 1997.

(244) Espeland MA, Kumanyika S, Wilson AC, Reboussin DM, Easter L, Self M et al. Statistical issues in analyzing 24-hour dietary recall and 24-hour urine collection data for sodium and potassium intakes. American Journal of Epidemiology 2001;153(10):996-1006.

(245) Espeland MA, Kumanyika S, Wilson AC, Wilcox S, Chao D, Bahnson J et al. Lifestyle interventions influence relative errors in self-reported diet intake of sodium and potassium. Annals of Epidemiology 2001;11(2):85-93.

(246) Cade J, Thompson R, Burley V, Warm D. Development, validation and utilisation of food-frequency questionnaires ΓÇô a review. Public Health Nutrition 2002;5(04):567-87.

(247) Kristal A, et al. Food frequency questionnaires for diet intervention research. 17th National Nutrient Databank Conference Proceedings; 1992.

(248) Burke BS, Stuart HC. A method of diet analysis: Application in research and pediatric practice. The Journal of pediatrics 12[4], 493-503. 1-4-1938. Ref Type: Abstract

(249) Willett Wc, Sampson Laur, Stampfer Mj, Rosner Bern, Bain Chri, Witschi Jeli Et Al. Reproducibility And Validity Of A Semiquantitative Food Frequency Questionnaire. American Journal of Epidemiology 1985 July 1;122(1):51-65.

(250) Block G, Woods M, Potosky A, Clifford C. Validation of A Self-Administered Diet History Questionnaire Using Multiple Diet Records. Journal of Clinical Epidemiology 1990;43(12):1327-35.

(251) Cade JE, Burley VJ, Warm DL, Thompson RL, Margetts BM. Food-frequency questionnaires: a review of their design, validation and utilisation. Nutrition Research Reviews 2004;17(1):5-22.

(252) Kobayashi T, Tanaka S, Toji C, Shinohara H, Kamimura M, Okamoto N et al. Development of a food frequency questionnaire to estimate habitual dietary intake in Japanese children. Nutrition Journal 2010;9.

(253) WHO. A review of methods to determine the main sources of salt in the diet. 2010.

(254) Charlton KE, Steyn K, Levitt NS, Jonathan D, Zulu JV, Nel JH. Development and validation of a short questionnaire to assess sodium intake. Public Health Nutrition 2008 January;11(1):83-94.

(255) Helen Crawley, Ministry of Agriculture FaF. Food Portion Sizes. HMSO, 1993; 1993.

(256) CASH. Older People Survey 2004. http://www actiononsalt org uk/less/what/older/index html 2004;

(257) Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999 March 16;130(6):461-70.

(258) Mattes RD, Donnelly D. Relative Contributions of Dietary-Sodium Sources. Journal of the American College of Nutrition 1991;10(4):383-93.

(259) WHO. **Reducing Salt Intake In Populations**. WHO Document Production Services, Geneva, Switzerland; 2006 Oct.

(260) Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977 March;33(1):159-74.

(261) Henderson L, Irving K Gregory J et al. National Diet and Nutrition Survey: Adults Aged 19 to 64. Vitamin and Mineral Intake and Urinary Analytes. 2012.

(262) Laviolle B, Froger-Bompas C, Guillo P, Sevestre A, Letellier C, Pouchard M et al. Relative validity and reproducibility of a 14-item semi-quantitative food frequency questionnaire for cardiovascular prevention. European Journal of Cardiovascular Prevention & Rehabilitation 2005;12(6):587-95.

(263) Food Standards Agency. An assessment of dietary sodium levels among adults (aged 19-64) in the UK general population in 2008, based on analysis of dietary sodium in 24 hour urine samples. 2008.

(264) McCarron DA, Geerling JC, Kazaks AG, Stern JS. Can Dietary Sodium Intake Be Modified by Public Policy? Clinical Journal of the American Society of Nephrology 2009 November 1;4(11):1878-82.

(265) Sowers M, Stumbo P. A Method to Assess Sodium-Intake in Populations. Journal of the American Dietetic Association 1986;86(9):1196-202.

(266) Hsu-Hage BHH, Wahlqvist ML. A food frequency questionnaire for use in Chinese populations and its validation. Asia Pacific Journal of Clinical Nutrition 1992;(1):211-23.

(267) Ferreira-Sae MCS, Gallani MCBJ, Nadruz W, Rodrigues RCM, Franchini KG, Cabral PC et al. Reliability and validity of a semi-quantitative FFQ for sodium intake in low-income and low-literacy Brazilian hypertensive subjects. Public Health Nutrition 2009;12(11):2168-73.

(268) Kawamura M, Kusano Y, Takahashi T, Owada M, Sugawara T. Effectiveness of a Spot Urine Method in Evaluating Daily Salt Intake in Hypertensive Patients Taking Oral Antihypertensive Drugs. Hypertension Research 2006;29(6):397-402.

(269) Iseki K, Iseki C, Itoh K, Uezono K, Sanefuji M, Ikemiya Y et al. Urinary excretion of sodium and potassium in a screened cohort in Okinawa, Japan. Hypertension Research 2002;25(5):731-6.

(270) Hashimoto T, Yagami F, Owada M, Sugawara T, Kawamura M. Salt preference according to a questionnaire vs. dietary salt intake estimated by a spot urine method in participants at a health check-up center. Internal Medicine 2008;47(5):399-403.

(271) Mann SJ, Gerber LM. Estimation of 24-Hour Sodium Excretion from Spot Urine Samples. Journal of Clinical Hypertension 2010;12(3):174-80.

(272) Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH, Jr., Kostis JB et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. JAMA 1998 March 18;279(11):839-46.

(273) Tilston C, Neale F, Gregson K, Bourne S. Salt - a challenge to food manufacturers. Food Marketing Research Group, University of Nottingham, Bradford, Horton Publishing; 1993.

(274) CASH. **Salt intake survey 2011**. http://www actiononsalt org uk/less/what/Salt%20intake%20survey%202011/index html# 2011 January 31;Available from: URL: http://www.actiononsalt.org.uk/less/what/Salt%20intake%20survey%202011/index.html#

(275) Dyer A, Elliott P, Chee D, Stamler J. Urinary biochemical markers of dietary intake in the INTERSALT study. American Journal of Clinical Nutrition 1997;65(4):S1246-S1253.

(276) CASH. **Consumers advised to use their loaf when choosing bread**. http://www actiononsalt org uk/news/surveys/2011/bread/index html 2011 September 2;Available from: URL: http://www.actiononsalt.org.uk/news/surveys/2011/bread/index.html

(277) Grimes CA, Riddell LJ, Nowson CA. Consumer knowledge and attitudes to salt intake and labelled salt information. Appetite 2009;53(2):189-94.

(278) Ayala C, Tong X, Valderrama A, Ivy A, Keenan N. Actions Taken to Reduce Sodium Intake Among Adults With Self-Reported Hypertension: HealthStyles Survey, 2005 and 2008. Journal of Clinical Hypertension 2010;12(10):793-9.

(279) Sodium intake among adults - United States, 2005-2006. MMWR Morbidity and mortality weekly report 2010;59(24):746-9.

(280) Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360(9349):1903-13.

(281) O'Donnell MJ, Yusuf S, Mente A, Gao P, Mann JF, Teo K et al. Urinary Sodium and Potassium Excretion and Risk of Cardiovascular Events. Jama-Journal of the American Medical Association 2011;306(20):2229-38.

(282) MacGregor G. **CASH response to JAMA paper examining urinary sodium and cardiovascular disease risk - 23rd November 2011**. CASH 2011 November 23;Available from: URL:

http://www.actiononsalt.org.uk/news/Salt%20in%20the%20news/2011/59619.html

(283) The Scottish Government. Scottish Index of Multiple Deprivation. 26-6-2012. Ref Type: Online Source

(284) LIANG KY, ZEGER SL. Longitudinal data analysis using generalized linear models. Biometrika 1986 April 1;73(1):13-22.

(285) ZEGER SL, LIANG KY, Albert PS. Models for Longitudinal Data: A Generalized Estimating Equation Approach. Biometrics 1988 December 1;44(4):1049-60.

(286) Ballinger GA. Using Generalized Estimating Equations for Longitudinal Data Analysis. Organizational Research Methods 2004 April 1;7(2):127-50.

(287) Page LB. Epidemiologic evidence on the etiology of human hypertension and its possible prevention. Am Heart J 1976 April;91(4):527-34.

(288) Hollenberg NK, Martinez G, McCullough M, Meinking T, Passan D, Preston M et al. Aging, Acculturation, Salt Intake, and Hypertension in the Kuna of Panama. Hypertension 1997 January 1;29(1):171-6.

(289) The Renal Association. Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral. 8-8-2005. Ref Type: Online Source

(290) Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. Am J Med 2009 September;122(9):857-65.

(291) Anderson RJ, Chung HM, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. Ann Intern Med 1985 February;102(2):164-8.

(292) Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated hyponatremia on selected outcomes. Arch Intern Med 2010 February 8;170(3):294-302.

(293) Katz MA. Hyperglycemia-induced hyponatremia--calculation of expected serum sodium depression. N Engl J Med 1973 October 18;289(16):843-4.

(294) Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH et al. Predictors of in-hospital mortality in patients hospitalized for heart failure: insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). J Am Coll Cardiol 2008 July 29;52(5):347-56.

(295) Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA 2003 November 19;290(19):2581-7.

(296) Milo-Cotter O, Cotter G, Weatherley BD, Adams KF, Kaluski E, Uriel N et al. Hyponatraemia in acute heart failure is a marker of increased mortality but not when associated with hyperglycaemia. Eur J Heart Fail 2008 February;10(2):196-200.

(297) Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology 2005 January;41(1):32-9.

(298) Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology 2004 October;40(4):802-10.

(299) Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008 September 4;359(10):1018-26.

(300) Porcel A, Diaz F, Rendon P, Macias M, Martin-Herrera L, Giron-Gonzalez JA. Dilutional hyponatremia in patients with cirrhosis and ascites. Arch Intern Med 2002 February 11;162(3):323-8.

(301) Kurtz TW, Al-Bander HA, Morris RC, Jr. "Salt-sensitive" essential hypertension in men. Is the sodium ion alone important? N Engl J Med 1987 October 22;317(17):1043-8.

(302) Sharma AM, Schattenfroh S, Thiede HM, Oelkers W, Distler A. Effects of sodium salts on pressor reactivity in salt-sensitive men. Hypertension 1992 June;19(6 Pt 1):541-8.

(303) Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. BMJ 1988 July 30;297(6644):319-28.