BMJ Nutrition, Prevention & Health

Excessive dietary sodium intake and elevated blood pressure: a review of current prevention and management strategies and the emerging role of pharmaconutrigenetics

Olivia M Dong[1,2]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjnph-2018-000004).

[1]Center for Pharmacogenomics and Individualized Therapy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA
[2]Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Correspondence to
Olivia M Dong, Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA;
odong@email.unc.edu

Received 25 June 2018
Revised 1 August 2018
Accepted 2 August 2018
Published Online First 19 September 2018

To cite: Dong OM. *bmjnph* 2018;**1**:7–16.

INTRODUCTION

Precision medicine has the potential to improve current standard of care for patients, especially in the cardiovascular field. Better prevention and treatment of cardiovascular disease (CVD) remains a public health concern globally as the disease affects a considerable proportion of populations in many countries.[1] CVD progression can be in part prevented with effective management of blood pressure through nutritional, pharmacological and lifestyle approaches.[2 3] Nutritional approaches to reduce blood pressure has in part focused on sodium intake as part of a nutritional intervention plan, although this established approach may be more effective for individuals who are salt sensitive, a phenotype that is currently not considered clinically. Blood pressure for individuals who are salt sensitive will change depending on the level of sodium intake, while those who are salt resistant will not see a change in their blood pressure even when sodium intake varies. This difference in response to sodium and its associated effect on blood pressure makes it important to be able to stratify the population based on this response to be able to effectively guide dietary intake. Nutrigenetics, which incorporates genetic markers in dietary intervention approaches, is one promising way this salt sensitivity phenotype can be identified among individuals. In addition, for those receiving antihypertensive agents to control blood pressure, using genetic markers to help with drug selection, or using a pharmacogenetic approach, may be a better way of achieving improved efficacy, lower adverse events and lead to more efficient use of limited healthcare resources. Current methods to manage blood pressure and sodium intake and the emerging role of precision medicine will be explored. More specifically, the use of genetics in nutritional and pharmacological interventions, or pharmaconutrigenetics, to guide sodium intake and manage blood pressure will be discussed as a way to better prevent and manage CVD progression.

THE RELATIONSHIP BETWEEN HIGH SODIUM INTAKE, BLOOD PRESSURE AND CVD

Adequate intake (AI) of the essential nutrient sodium is crucial in sustaining health. Sodium is an electrolyte that is involved in vital physiological processes, including muscle and nerve function by controlling membrane potential of cells, active transport of molecules across cell membranes and controlling blood pressure through altering fluid and electrolyte balance in the body.[4] Low sodium intake may affect insulin resistance, blood lipids, CVD risk and increase plasma renin activity, although more evidence is needed to substantiate these adverse events.[4] Excessive intake of sodium is strongly associated with elevated blood pressure, which increases the risk for cardiovascular and renal diseases.[4]

Raised blood pressure and hypertension are major risk factors for CVD as they are underlying contributing factors in 62% of all stroke events and 49% of all coronary heart disease cases.[5] At the global level, the prevalence of raised blood pressure affects 40% of adults aged 25 years and older and accounts for 12.8% of all deaths.[6] In the USA, approximately one-third of the adult population suffers from hypertension with 76% taking medication to manage the disease.[7] Hypertension is prevalent in 7.3% of adults

Table 1 Sodium: UK dietary reference values levels[10]

Group	Reference nutrient intake levels, amount of sodium (g/day)	Tolerable upper intake levels, amount of sodium (g/day)
<1 year old	0.3	N/A
1–3 years old	0.5	0.8
4–6 years old	0.7	1.2
7–10 years old	1.2	2.0
>10 years old, pregnancy	1.6	2.5

aged 18 years and over, 32.4% of adults aged 40–59 years and 65% of adults aged 60 years and older.[7] Proper blood pressure control is critical in avoiding cardiovascular-related mortality and remains an area of great public health concern. For the past 40 years, heart disease has remained the top leading cause of mortality in the USA (23.4% of all deaths).[8] In 2015, stroke was ranked as the fifth cause of mortality in the USA (5.2% of all deaths).[8] Maintaining an optimal level of sodium intake can help manage blood pressure and prevent cardiovascular-related mortality since studies have shown that reducing sodium consumption can reduce blood pressure.[9] Given these data, it is imperative that healthcare professionals and public health efforts aim to ensure sodium intake among the population is within a healthy range.

RECOMMENDED DAILY INTAKE OF SODIUM FOR OPTIMAL PHYSIOLOGICAL HEALTH

Table 1[10] summarises the dietary reference values, including the reference nutrient intake (RNI) and tolerable upper intake levels (ULs) set by the UK government through the Committee on Medical Aspects of Food and Nutrition Policy for the UK population. Table 2[4] summarises the dietary reference intake (DRI) levels, including the AI and tolerable ULs of sodium set by the Institute of Medicine for the US population, which are similar to the guidelines recommended for Canadians.[11 12] In line with these DRI levels, the 2015–2020 Dietary Guidelines for Americans recommends that adults limiting sodium intake to less than 2.3 g per day as part of a healthy eating pattern.[13] The WHO recommends a level of sodium intake less than 2 g per day for adults in order to reduce blood pressure, risk of CVD, stroke and coronary heart disease.[14 15] There is insufficient high-quality data associating a low sodium diet (<2.3 g or <1.5 g per day) with an increased or reduced cardiovascular risk and mortality for the general population.[16 17] Better quality randomised trials and cohort studies are needed in this area to better understand the effects of low sodium intake on cardiovascular outcomes.[18]

Table 2 Sodium: US dietary reference intakes levels[4]

Group	Adequate intake levels, amount of sodium (g/day)	Tolerable upper intake levels, amount of sodium (g/day)
0–6 months old	0.12	N/A
6–12 months old	0.37	N/A
1–3 years old	1.0	1.5
4–8 years old	1.2	1.9
9–13 years old	1.5	2.2
14–50 years old	1.5	2.3
51–70 years old	1.3	2.3
>70 years old	1.2	2.3
Pregnancy, lactation	1.5	2.3

SODIUM CONSUMPTION LEVELS

Current sodium consumption levels around the world exceed recommendations and are above levels that are considered physiologically optimal. Global mean intake of sodium in 2010 was estimated to be almost twice the level recommended by WHO at 3.95 g per day.[19] Highest sodium intake levels were observed in central Asia (5.51 g per day) and lowest in east sub-Saharan Africa (2.18 g per day).[19] A similar trend of excessive consumption of sodium is observed in the USA, with approximately 90% of the US population over the age of 2 years old consuming on average 3.4 mg of sodium per day.[20 21] Main contributors of sodium in the diet for the US population comes from food bought from stores (~60.8%) and restaurants (~29.4%).[20]

INTERVENTIONS TO DECREASE DIETARY SODIUM INTAKE

Excessive sodium consumption is recognised as a global issue. A global initiative backed by the United Nations and the WHO aims to reduce salt intake at the population level by 30% by 2025, and 75 countries have already adopted national sodium reduction programme to help meet this goal.[22] Strategies to reduce sodium intake at the population level have taken different approaches, including working with industry to reformulate food products, establishing sodium content targets for foods, educating consumers, revising labelling schemes on food packages, taxing high-salt foods and developing interventions in public institutions.[22]

In the UK, the National Institute for Health and Clinical Excellence (NICE) has responded to this excessive sodium intake level with recommended policy goals. The UK has been aiming to reduce sodium intake among adults to 2.4 g per day by 2015 and down to 1.2 g per day by 2025.[23] The UK reported a population level reduction of sodium intake by 14.7% (3.8 g to 3.24 g) during 2001–2011.[22] This reduction in sodium intake is in part due to the UK Food Standards Agency's salt reduction

programme that were implemented 2003–2010. Sodium content in food items was reduced (some as high as 70%) and educational campaigns led to 43% of adults (vs 34% before the campaigns) making efforts to reduce sodium intake.[24]

In the US, the Food and Drug Administration (FDA) has responded to this excessive sodium consumption among the US population through a 2016 Draft Guidance for Industry that outlines short-term (2 years) and longer term (10 years) goals for sodium content reduction in commercially processed and packaged foods.[25] This guidance document recognises the importance of a supportive food environment through engagement with industry to help the US population meet the sodium intake levels recommended in the 2015–2020 Dietary Guidelines for Americans. Although voluntary, it will be imperative for food companies to recognise the need to reduce sodium levels in their food products in ways that will not compromise the integrity of their products since sodium serves many functions beyond affecting taste, including texture, preservation and microbial safety.[26]

In addition to addressing this issue from the food environment perspective, individuals with high blood pressure can work one-on-one with their dietitians to lower their sodium intake. A commonly prescribed heart-healthy diet for individuals with elevated blood pressure is the Dietary Approaches to Stop Hypertension (DASH) diet.[27] Broadly, the DASH diet emphasises the consumption of vegetables, fruits and whole grains while limiting foods high in saturated fat, sugar sweetened beverages and sweets. Low-fat and fat-free dairy products, fish, poultry, beans, nuts and vegetable oils are also emphasised.[27] One of the core recommendations of this diet is to consume less than 2.3 g of sodium each day and further recommends an intake of 1.5 g of sodium each day for better blood pressure control.[27] A major randomised controlled trial studying the effects of the DASH diet in comparison with a control diet high in sodium observed a 7.1 mm Hg drop in blood pressure for non-hypertensive subjects and a 11.5 mm Hg drop in blood pressure for subjects with hypertension.[28] The results of a meta-analysis that included 17 randomised controlled trials indicated that adhering to the DASH diet is associated with reduced blood pressure (6.74 mm Hg drop in systolic blood pressure and 3.54 mm Hg drop in diastolic pressure).[29] In addition to the DASH diet, sodium reduction, weight loss in overweight an obese individuals, potassium supplementation, limiting alcoholic drinks and increased physical activity are other non-pharmacological interventions that are recommended for US adults with elevated or blood pressure hypertension.[2] NICE guidelines recommend limiting alcoholic consumption and excessive caffeine-rich products, reducing sodium intake, avoiding calcium magnesium or potassium supplementation, smoking cessation, social support organisations that promote healthy lifestyle change, increasing exercise and engaging in relaxation therapies as non-pharmacological approaches to reducing blood pressure.[30]

SALT SENSITIVITY: AN INDEPENDENT RISK FACTOR FOR MORTALITY—NOT EVERYONE RESPONDS TO SODIUM WITH CHANGES IN BLOOD PRESSURE

While elevated blood pressure is an established surrogate marker for CVD and a risk factor meriting pharmacological and dietary interventions,[2 3 31] what tends to be ignored in discussions on this topic is the concept of salt sensitivity and the difference in response individuals can have to sodium intake. Considering the salt sensitivity phenotype is important since many dietary interventions aim to decrease sodium intake to lower blood pressure, but this assumes individuals are all salt sensitive, which is not the case for many.

Salt sensitivity is defined by a change in blood pressure in response to a change in sodium chloride intake. Salt sensitivity is influenced by many factors, including genetics, age, gender, race/ethnicity, body mass index and diet.[32] The exact numeric change in blood pressure to classify an individual as salt sensitive varies and is not consistently defined.[33] A 5%–10% blood pressure change or a >4 mm Hg in mean blood pressure are two commonly used cut-offs in response to a change in sodium chloride intake.[34 35] Salt sensitivity has also been defined by a >10 mm Hg increase in mean blood pressure by comparing blood pressure on a normal 2 L saline (0.9%) infusion over a 4-hour period to blood pressure on a combination of a low-sodium diet (10 mmol) and a loop diuretic.[34 35] Despite the numerous ways salt sensitivity can be determined, the most robust method for assessing salt sensitivity is through dietary sodium intake using a crossover study design where a 5–7 day intervention period is given for a normal (~3.6 g), low (~1.2 g) and high (~7.9 g) dietary sodium intake level.[34 35] When a change in blood pressure is not observed despite changes in sodium chloride intake, the individual is classified as salt resistant.

In a 27-year-long observational study, salt sensitivity was found to be an important risk factor for mortality independent of blood pressure level that mimics mortality risk observed in hypertensive and salt resistant individuals.[36] The survival curve with the best survival over the 27-year period was observed in individuals who were normotensive and salt resistant, and individuals with the worst survival were those who were hypertensive and salt sensitive.[36] Survival over this 27-year period was not significantly different between those who were normotensive plus salt sensitive and those who were hypertensive plus salt resistant.[36] Individuals who were normotensive and salt resistant had significantly better survival than the other three subgroups investigated (normotensive and salt sensitive, hypertensive and salt resistant, and hypertensive and salt sensitive) ($p<0.001$).[36] An OR of 1.73 (95% CI 1.02 to

2.94, p=0.042) for death was observed for individuals who were salt sensitive.[36] One major limitation of this observational study is the lack of dietary information on individuals in this cohort to understand the relationship between sodium intake levels and mortality risk for salt sensitive and resistant individuals. It has been shown, however, that salt-sensitive individuals tend to have higher blood pressures over time when compared with salt-resistant individuals, suggesting that reduced sodium intake interventions may reduce the progression of hypertension overtime for salt sensitive individuals.[37] In addition, numerous studies have also observed adverse effects of high sodium on organ damage independent of blood pressure.[38–41]

Given that sodium intake for most individuals is excessive, the majority of the population would benefit from an overall reduction in sodium intake towards UL levels. The salt sensitivity phenotype is an important factor to consider in determining optimal sodium intake levels instead of relying solely on blood pressure. In addition, focusing on aggressive salt intake reduction for salt resistant individuals may not be an effective dietary intervention strategy in managing blood pressure.

PREVALENCE AND IDENTIFICATION OF INDIVIDUALS WITH THE SALT SENSITIVITY PHENOTYPE

The salt sensitivity phenotype is more common in several subgroups, including individuals who are black, older adults and patients with hypertension.[41 42] In the USA, approximately 26.4% is salt sensitive (58 million), 30.4% is hypertensive (66.9 million) and 11.8% is both hypertensive and salt sensitive (26 million).[34]

Currently, there are no practical methods to assess this phenotype in the clinical setting as it involves weeks of careful dietary monitoring using a crossover study design. The genetics that characterise this phenotype has been extensively studied in an attempt to use genetic screening tools to predict this phenotype for more precise dietary and pharmaceutical interventions. Numerous genes have been identified and associated with the salt sensitivity phenotype.[34 35 43–48] Table 3[49–53] summarises the genetic variants with the strongest links to salt sensitivity.

Variants in the GRK4 and SLC4A5 genes have the strongest and most consistent genetic links to salt sensitivity.[49 50] The GRK4 gene codes for a protein that is responsible for regulating the dopamine D_1 receptor, which is involved with regulating the renal tubule ion transport.[51] The SLC4A5 gene codes for a protein that transports sodium and bicarbonate ions in renal tubule cells back into circulation.[49]

A randomised crossover study of blood pressure in response to a low (230 mg sodium/day) and high salt (6.9 g sodium/day) diet was conducted in 185 Caucasians (55 hypertensive; 130 normotensive).[49] Salt sensitivity defined by mean arterial pressure increase of ≥7 mm Hg on high versus low salt diet. Out of all the polymorphisms that were studied in the 17 genes, two single nucleotide polymorphisms (SNPs) in SLC4A5, rs7571842 and rs10177833 were found to be associated with salt sensitivity (p value 1.0×10^{-4} and 3.1×10^{-4}, respectively) in an unadjusted regression model.[49] G allele carriers for rs7571842 and rs10177833 had a protective effect against salt sensitivity even after adjusting for body mass index and age (OR=0.210, $p=8.9\times10^{-5}$ and 0.286, $p=2.6\times10^{-4}$, respectively).[49] These two SNPs were investigated for replication purposes in a second hypertensive cohort of 211 subjects (low sodium diet: 230 mg/day; high sodium diet: 4.6 g/day, salt sensitivity defined by mean arterial pressure increase of ≥7 mm Hg on high vs low salt diet).[49] G allele carriers also had a protective effect against salt sensitivity for rs7571842 (OR=0.32, p=0.02) and rs10177833 (OR=0.36, p=0.06).[49] Although these studies were well designed, one limitation to note with the SLC4A5 variants is the generalisability of this result since the two populations studied were Caucasian. Variants in the SLC4A5 gene have also been associated with hypertension.[54–56]

The GRK4 variants rs296036, rs1024323 and rs1801058 have been studied in three major ethnic groups (ie, Japanese, Italian and European American) and have been most consistently associated with salt sensitivity.[49 50 57] In the crossover study investigating these GRK4 SNPs in the Japanese cohort, 184 subjects followed a normal (3.6 g/day), low (1.2 g/day), and high (7.9 g/day) sodium diet to assess salt sensitivity.[50] Salt sensitivity was defined by a ≥10% change in mean arterial pressure going from a low to high sodium diet. It was found that Japanese subjects carrying three or more variants at any of the three sites were more likely to be salt sensitive than salt resistant. Using this criterion, 94% of the cohort was correctly classified by their response to sodium.[50] The GRK4 rs1024323 variant was the most accurate predictor of salt sensitivity, with a 78.4% accuracy rate among hypertensive Japanese.[50] Although the study was well conducted, replication of these findings in additional populations is needed to understand the extent to which these conclusions can be further generalised. Several studies have also found GRK4 variants to be associated with hypertension.[35]

CURRENT PRACTICE IN MANAGING SODIUM INTAKE IN HYPERTENSION AND CHANGES TO CURRENT PRACTICE WITH THE IDENTIFICATION OF THE SALT SENSITIVITY PHENOTYPE

Current standard of practice in the nutrition field intervenes on an individual's sodium intake when blood pressure is elevated. This standard of practice misses an opportunity to intervene and reduce sodium intake for approximately 14% of the population who are salt sensitive but normotensive.[34] In addition, this standard of practice is also ineffective for 16% of individuals who are hypertensive and salt resistant.[34] Current intervening strategies for elevated blood pressure is appropriate for 11.8% of adults who are both hypertensive and salt sensitive.[34] Excessive

Table 3 Summary of the strongest genetic markers associated with salt sensitivity

Gene	Gene function and association with salt sensitivity	rsID	Associated risk allele	Risk allele prevalence*	Magnitude of effect
Solute carrier family 4 member 5 (SLC4A5)	Encodes a protein that transports sodium and bicarbonate ions in renal tubule cells back into circulation.[49]	rs7571842	A	US Caucasian: 0.57. British Caucasian: 0.59. Asian: 0.34. African-American: 0.34.	OR=4.76 ($p=8.9\times10^{-5}$) for salt sensitivity.[49]
Solute carrier family 4 member 5 (SLC4A5)	Encodes a protein that transports sodium and bicarbonate ions in renal tubule cells back into circulation.[49]	rs10177833	A	US Caucasian: 0.62. British Caucasian: 0.60. Asian: 0.34. African-American: 0.52.	OR=3.50 ($p=2.6\times10^{-4}$) for salt sensitivity.[49]
G protein-coupled receptor kinase 4 (GRK4)	Codes for an enzyme that deactivates activated G protein-coupled receptors via phosphorylation. GRK4 regulates the dopamine D_1 receptor. The D_1 receptor plays a role in regulating the renal tubule ion transport.[51]	rs296036, rs1024323 and rs1801058.	A (rs296036), T (rs1024323), T (rs1801058).	rs296036: US Caucasian: 0.19. British Caucasian: 0.23. Asian: 0.15. African-American: 0.18. rs1024323 US Caucasian: 0.38. British Caucasian: 0.36. Asian: 0.20. African-American: 0.61. rs1801058 US Caucasian: 0.39. British Caucasian: 0.42. Asian: 0.53. African-American: 0.14.	Predictive of salt sensitivity with 94% accuracy if three or more variants are present.[50 52] Predictive of salt sensitivity with 78.4% accuracy if the rs1024323 variant is present.[50 52]

Ethnic groups defined by specific 1000 Genomes Project populations: *US Caucasian:* Utah residents with northern and western European ancestry (CEU); *British Caucasian:* British in England and Scotland (GBR); *Asian:* Han Chinese in Beijing, China (CHB); *African American:* Americans of African Ancestry in SW USA (ASW).
*Source: 1000 Genomes Project Samples.[53]

sodium intake can cause hypertension, but this threshold for what is considered excessive differs depending on how the body is able to handle sodium homeostasis. In addition, elevated blood pressure has traditionally been the marker for reduced sodium intake but perhaps the salt sensitivity phenotype should also be considered. This varied response to sodium intake highlights the need to move away from the current 'one-size-fits-all' approach in sodium recommendations to a paradigm that is more precise in characterising sodium response.

Current practice related to reducing sodium intake is appropriate for the subset of the population who are hypertensive and salt sensitive, but how would dietary recommendations change if we knew how individuals responded to salt? Knowing that salt sensitivity is an independent risk for mortality, it may be beneficial for salt sensitive individuals to follow a diet lower in salt regardless of blood pressure. There are no formal guidelines on the amount of dietary sodium intake that is appropriate for salt sensitive individuals, but keeping intake close to the AI/RNI and at the very least below the UL might be beneficial. For those who are hypertensive, it would be important to know whether blood pressure will be affected by sodium intake. For those who are salt resistant and hypertensive, focusing on dietary interventions beyond sodium intake may result in better control over blood pressure. Following a diet lower in sodium can be burdensome, so identifying those who would most benefit from such drastic dietary restrictions can focus healthcare resources to ensure this subpopulation is identified and managed appropriately. Being able to tease out someone's response to sodium can potentially better individualise dietary recommendations for optimal health outcomes. With current sodium intake well above the recommended amount, it would be imperative for salt-sensitive individuals to especially pay particular attention to this recommendation given their increased chances of mortality. Further research investigating the optimal level of sodium intake for salt sensitive individuals is needed.

PHARMACOLOGICAL INTERVENTIONS TO CONTROL BLOOD PRESSURE

A common approach to controlling blood pressure is through pharmacological agents, as 76% of hypertensive individuals are taking medication to manage the disease.[7] Most drugs achieve 10–15 mm Hg reduction in systolic blood pressure and 8–10 mm Hg reduction in diastolic blood pressure when used as monotherapy, although combination therapy has been found to be more effective in achieving target blood pressure control.[58 59] For first-line antihypertensive agents in the UK, NICE recommends an ACE inhibitor or ARB (angiotensin-receptor blockers) for individuals less than 55 years old and a CCB for blacks or for those 55 years old or older.[30] In the USA, a thiazide-type diuretic, ACE inhibitor, ARB or CCB are first-line antihypertensive agents for non-blacks; and a thiazide-type diuretic or CCB for blacks is recommended.[3]

Despite many pharmacological agents available to help control blood pressure, 60% of hypertensive individuals treated with pharmacological agents do not have their blood pressure controlled adequately.[60] Many factors can lead to this suboptimal control of blood pressure, including the lack of efficacy of antihypertensive agents in 40%–60% of patients.[61 62] The practice of pharmacogenetics, which attempts to tailor drug therapies based on genetic information, is one way for predicting efficacy and/or prevent adverse outcomes when selecting antihypertensive medications. Currently, there are no validated pharmacogenetic guidelines endorsed by the FDA or the international Clinical Pharmacogenetics Implementation Consortium (CPIC), but there are promising genetic markers associated with specific antihypertensive drug classes and blood pressure response and/or cardiovascular outcomes (online supplementary table 1[51 53 63–70]).[63] Replication is currently needed for these genetic markers to investigate the robustness of the ability for these genetic makers to predict blood pressure response and/or cardiovascular outcomes in the presence of antihypertensive agents before clinical validation is achieved. It has been hypothesised that the model that will guide antihypertensive a gene selection will likely use a combination of genetic variants, with each variant exerting a modest effect size on relevant outcomes, instead of using the traditional model that associates a single genetic marker to an outcome in the presence of a prescribed drug.[63] Therefore, drug prescribing of these agents will depend on the genetic make-up of the patient. The resulting guideline, like other CPIC guidelines, will translate pertinent genetic research into clear directions regarding which agents and doses are recommended based on genetic markers so that clinicians can implement the information directly into the drug prescribing process for their patients.

TREATMENT OF INDIVIDUALS WITH RESISTANT HYPERTENSION

Finding effective antihypertensive agents is especially important for individuals with resistant hypertension (uncontrolled hypertension despite use of three or more different classes of antihypertensive agents, including a diuretic) and refractory hypertension (uncontrolled hypertension despite use of five or more different classes of antihypertensive agents, including a diuretic).[71] The prevalence of resistant hypertension is estimated to affect 10%–15% of hypertensive patients treated with antihypertensive agents and approximately 3.6%–10% of these patients have refractory hypertension.[71]

Using pharmacogenetic information to guide selection of antihypertensive agents may be a way to help optimise blood pressure control and could potentially reduce the overall number of agents prescribed. Online supplementary table 1[51 53 63–70] lists a few genetic markers that are associated with response to antihypertensive agents and cardiovascular outcomes. This genetic testing would be beneficial for this population to receive to reduce the likelihood of being prescribed an ineffective antihypertensive agent. In addition, several genetic markers in candidate genes associated with resistant hypertension have been identified, although not ready for clinical implementation since these associations have not been replication and many of these studies lack adequate sample sizes.[72] Online supplementary table 2[53 67 72–80] summarises the genetic markers that have been associated with resistant hypertension.

According to the DASH diet on dietary sodium intake, consuming less than 2.3 g of sodium each day and further recommends an intake of 1.5 g of sodium each day for better blood pressure control is suggested for hypertensive individuals.[27] Sodium restriction in individuals with resistant hypertension has been shown to be an effective strategy to help decrease blood pressure.[81 82] In a crossover randomised controlled trial of 12 patients with resistant hypertension in the USA, blood pressure was monitored, while a low (1.15 g/day) and high (5.75 g/day) sodium diet were provided to subjects while maintaining their prescribed antihypertensive medication regimens.[82] Average blood pressure on entering the study was 145.8±10.8/83.9±11.2 mm Hg, which was being controlled with 3.4±0.5 antihypertensive agents.[82] Average blood pressure (mm Hg) on the high sodium diet was 145.6±15.1/84.0±12.1, and 122.8±14.0/74.9±12.5 on the low sodium diet.[82] Systolic (−22.7 mm Hg, (−33.5 to −11.8), p=0.0008) and diastolic (−9.1 mm Hg, (−15.1 to −3.1),[74] p=0.0065) blood pressure decreased significantly when subjects were on the low sodium diet in comparison with the high sodium diet.[82] Further research is needed to evaluate whether reducing sodium intake among this population is effective based on the salt sensitivity phenotype or if salt-sensitive individuals are more likely to have resistant hypertension.

Patients with resistant hypertension should work with registered dietitians to keep their sodium intake in line with the recommendations outlined in the DASH diet, especially if individuals are salt sensitive. As a result, assessing for salt sensitivity in this population would be beneficial in the management of blood pressure. In cases

Table 4 A proposed practice pattern if pharmaconutrigenetics was incorporated in patient care

Population	Daily sodium targets for adults	Genetic variants to test	Recommendations
General population	1.6–2.5 g (UK). 1.5–2.3 g (USA).	Salt sensitivity variants (table 3)[49–53]	► Ensure sodium intake is between the AI/RNI and the UL.[4 10 13 14] ► Assess genetic variants for salt sensitivity. ► *Salt-sensitive individuals*: it may be beneficial to reduce sodium levels closer to the AI/RNI than UL.*[34] ► *Salt-resistant individuals*: ensure sodium intake is below the UL.
Newly diagnosed with hypertension requiring pharmacological agents	1.6–2.5 g (UK). 1.5–2.3 g (USA).	Salt-sensitivity variants (table 3).[49–53] Response to antihypertensive agent variants (online supplementary table 1).[51 53 63–70] Resistant hypertension variants and response to antihypertensive agents (online supplementary table 2).	► Assess genetic variants for salt sensitivity, antihypertensive agent selection and resistant hypertension/response to antihypertensive agents.*[63 72] ► *Salt-sensitive individuals*: reduce sodium intake down towards AI/RNI with priority, along with other lifestyle changes.*[34] ► *Salt-resistant individuals*: reduce sodium down below UL and focus on dietary factors besides sodium intake and other lifestyle factors.*[34]
Resistant and refractory hypertension	1.6–2.5 g (UK). 1.5–2.3 g (USA).	Salt-sensitivity variants (table 3).[49–53] Response to antihypertensive agent variants (online supplementary table 1).[51 53 63–70] Resistant hypertension variants and response to antihypertensive agents (online supplementary table 2).	► Assess genetic variants for salt sensitivity, antihypertensive agent selection and resistant hypertension/response to antihypertensive agents.*[63 72] ► *Salt-sensitive individuals*: reduce sodium intake down towards AI/RNI with high priority, along with other lifestyle changes.*[34] ► *Salt-resistant individuals*: reduce sodium down below UL and focus on dietary factors besides sodium intake and other lifestyle factors to manage blood pressure.*[34]

*The proposed recommendation has not been clinically validated and presents as a potential way for precision medicine to be incorporated into patient care. Promising evidence for future incorporation into recommendations is cited.
AI, adequate intake.

where sodium intake is within recommended levels, it would also be important for registered dietitians to educate these individuals on the importance of maintaining their sodium intake at these levels.

STRATEGIES TO MANAGE SODIUM INTAKE AND BLOOD PRESSURE, INCLUDING THE POTENTIAL FOR PHARMACONUTRIGENETICS TO BE AN EFFECTIVE APPROACH

One of the top priorities at the moment for better cardiovascular health at the global level is reducing sodium intake since daily consumption far exceeds recommended levels. Public health interventions to help reduce sodium intake at the population level have been developed and implemented in many countries, and continued progress is needed.

Next, accounting for salt sensitivity in assessing cardiovascular health will be an important factor to consider. Salt sensitivity is an independent risk factor for mortality and provides information on how the individual will respond to restricting sodium intake and whether restricting sodium intake closer to the AI/RNI is warranted to control blood pressure. Currently, there is no practical method for assessing salt sensitivity, although genetic markers to predict this phenotype

have shown a lot of promise for individualising sodium recommendations.

Lastly, as many patients engage in pharmacological and dietary interventions to manage their blood pressure, using genetic information to help optimise efforts in these two fields could potentially lead to better blood pressure control and cardiovascular outcomes. Pharmacogenetic information can help guide antihypertensive medication selection to optimise drug efficacy and minimise adverse outcomes. Nutrigenetic information can help identify individuals who are salt sensitive among those who are normotensive and hypertensive, and dietitians can work with these patients to ensure reduced sodium intake is being followed. Taken together, the synergy of using pharmaconutrigenetics and nutrigenetics to manage blood pressure may be an effective approach since an optimal approach is selected in both fields based on genetics to maximise the response achieved in managing blood pressure. At the patient level, the synergy between these two fields working together to manage blood pressure more efficiently may result in scenarios such as patients requiring fewer pharmacological agents, or relying solely on sodium reduction given the presence of the salt sensitivity phenotype, among other possible outcomes. To this end, a better alignment of medication and nutrition decisions has the potential to help patients manage their blood pressure and sodium intake more optimally and ensure their cardiovascular risk is minimised.

Table 4[4 10 13 14 34 63 72] summarises what practice patterns could look like if precision medicine in this area became validated as currently known. Most notably, sodium target levels will not differ much from the established AI, RNI and UL levels, but having salt-sensitive individuals aim for sodium intake closer to the AI/RNI levels might be beneficial, while a focus on interventions beyond sodium intake level may be needed for salt-resistant individuals. The other major paradigm shift in this area is not relying on blood pressure to dictate sodium intervention, but instead using the salt sensitivity phenotype to guide the priority placed on sodium intake levels.

SUMMARY

CVD is a huge public health concern that affects a large proportion of the population in many countries, including the UK and the USA. Management of blood pressure through nutrition and pharmacological interventions has traditionally been the approach in reducing CVD. Although not yet commonly done, considering the salt sensitivity phenotype can point to individuals at highest risk for adverse health outcomes with high sodium intake and most likely to benefit from lower sodium intake targets. Several predictive genetic markers for probabilistic identification of the salt sensitivity phenotype have already been replicated and would become even more credible with further clinical validation. In addition, for those receiving antihypertensive agents, drug selection guided by such genetic markers promises better efficacy, lower risk of adverse events and more efficient use of limited healthcare resources. Precision medicine, in particular combining pharmacological and nutritional genetic information to guide individualised medication and nutritional decisions (pharmaconutrigenetics), can help improve blood pressure management.

Contributors OMD wrote the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

1. World Health Organization. 2017.Cardiovascular diseases (CVDs) http://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (accessed 17 Jul 2017).
2. Whelton PK, Carey RM, Aronow WS, *et al*. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;71:1269–324.
3. James PA, Oparil S, Carter BL, *et al*. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311:507–20.
4. Institute of Medicine (US). *Panel on Dietary Reference Intakes for Electrolytes and Water. DRI, dietary reference intakes for water, potassium, sodium, chloride, and sulfate*. Washington, DC: National Academies Press, 2005.
5. Mackay J, Mensah GA, Mendis S. *The atlas of heart disease and stroke*. Geneva: World Health Organization, 2004.
6. World Health Organization. *Global Health Observatory (GHO) Data: Raised blood pressure*, 2018.
7. Nwankwo T, Yoon SS, Burt V, *et al*. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011-2012. *NCHS Data Brief* 2013(133):1–8.
8. National Center for Health Statistics. *Health, United States, 2016: with Chartbook on Long-term Trends in Health*. Hyattsville, Maryland, 2017.
9. Aburto NJ, Ziolkovska A, Hooper L, *et al*. Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ* 2013;346:f1326.
10. Dietary reference values for food energy and nutrients for the United Kingdom. Report of the Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy. *Rep Health Soc Subj* 1991;41:1–210.
11. Government of Canada. 2013.Sodium: the basics https://www.canada.ca/en/health-canada/services/nutrients/sodium/sodium-basics.html.
12. The National Health Service. 2017.Salt: the facts https://www.nhs.uk/live-well/eat-well/salt-nutrition/ (accessed 17 Jun 2018).
13. U.S. Department of Health and Human Services and U.S. *Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans*. 8th edn, 2015.
14. World Health Organization. *Guideline: sodium intake for adults and children*. Geneva: World Health Organization, 2012.
15. Mozaffarian D, Fahimi S, Global Burden of Diseases Nutrition and Chronic Diseases Expert Group. Global sodium consumption and death from cardiovascular causes. *N Engl J Med* 2014;371:624–34.
16. Oparil S. Low sodium intake-cardiovascular health benefit or risk? *N Engl J Med* 2014;371:677–9.

17. McGuire S. Institute of Medicine. 2013. "Sodium intake in populations: assessment of evidence." Washington, DC: The National Academies Press, 2013. *Adv Nutr* 2014;5:19–20.
18. Graudal N. Dietary sodium and cardiovascular disease risk. *N Engl J Med* 2016;375:2406–7.
19. Powles J, Fahimi S, Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE). Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open* 2013;3:e003733.
20. Quader ZS, Zhao L, Gillespie C, *et al*. Sodium intake among persons aged ≥2 Years - United States, 2013-2014. *MMWR Morb Mortal Wkly Rep* 2017;66:324–238.
21. Jackson SL, King SM, Zhao L, *et al*. Prevalence of excess sodium intake in the United States - NHANES, 2009-2012. *MMWR Morb Mortal Wkly Rep* 2016;64:1393–7.
22. Trieu K, Neal B, Hawkes C, *et al*. Salt reduction initiatives around the world - a systematic review of progress towards the global target. *PLoS One* 2015;10:e0130247.
23. National Institute for Health and Care Excellence. 2010.Cardiovascular disease prevention June https://www.nice.org.uk/guidance/ph25/chapter/1-Recommendations (accessed 21 Jun 2018).
24. Wyness LA, Butriss JL, Stanner SA. Reducing the population's sodium intake: the UK Food Standards Agency's salt reduction programme. *Public Health Nutr* 2012;15:254–61.
25. US Food and Drug Adminstration. 2017.Voluntary sodium reduction goals: target mean and upper bound concentrations for sodium in commercially processed, packaged, and prepared foods https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm494732.htm (accessed 17 Jun 2018).
26. Doyle ME, Glass KA. Sodium reduction and its effect on food safety, food quality, and human health. *Compr Rev Food Sci Food Saf* 2010;9:44–56.
27. NIH. 2018.National heart, lung, and blood institute: DASH eating plan https://www.nhlbi.nih.gov/health-topics/dash-eating-plan (accessed 17 Jun 2018).
28. Sacks FM, Svetkey LP, DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001;344:3–10.
29. Saneei P, Salehi-Abargouei A, Esmaillzadeh A, *et al*. Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: a systematic review and meta-analysis on randomized controlled trials. *Nutr Metab Cardiovasc Dis* 2014;24:1253–61.
30. National Institute for Health and Care Excellence (NICE). 2016.Hypertension in adults: diagnosis and management https://www.nice.org.uk/guidance/cg127/chapter/1-Guidance-initiating-and-monitoring-antihypertensive-drug-treatment-including-blood-pressure-targets-2 (accessed 25 Jul 2018).
31. Weber MA, Schiffrin EL, White WB, *et al*. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens* 2014;16:14–26.
32. Sundeep Mishra SI, Jain R. Salt sensitivity and its implications in clinical practice. *Indian Heart Journal* 2017 (published Online First: 10 October 2017).
33. Kurtz TW, DiCarlo SE, Pravenec M, *et al*. An appraisal of methods recently recommended for testing salt sensitivity of blood pressure. *J Am Heart Assoc* 2017;6:e005653.
34. Felder RA, White MJ, Williams SM, *et al*. Diagnostic tools for hypertension and salt sensitivity testing. *Curr Opin Nephrol Hypertens* 2013;22:65–76.
35. Sanada H, Jones JE, Jose PA. Genetics of salt-sensitive hypertension. *Curr Hypertens Rep* 2011;13:55–66.
36. Weinberger MH, Fineberg NS, Fineberg SE, *et al*. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. *Hypertension* 2001;37(2 Pt 2):429–32.
37. Weinberger MH, Fineberg NS. Sodium and volume sensitivity of blood pressure. Age and pressure change over time. *Hypertension* 1991;18:67–71.
38. Farquhar WB, Edwards DG, Jurkovitz CT, *et al*. Dietary sodium and health: more than just blood pressure. *J Am Coll Cardiol* 2015;65:1042–50.
39. Imaizumi Y, Eguchi K, Murakami T, *et al*. High salt intake is independently associated with hypertensive target organ damage. *J Clin Hypertens* 2016;18:315–21.
40. Morimoto A, Uzu T, Fujii T, *et al*. Sodium sensitivity and cardiovascular events in patients with essential hypertension. *Lancet* 1997;350:1734–7.
41. Kanbay M, Chen Y, Solak Y, *et al*. Mechanisms and consequences of salt sensitivity and dietary salt intake. *Curr Opin Nephrol Hypertens* 2011;20:37–43.
42. Sanders PW. Dietary salt intake, salt sensitivity, and cardiovascular health. *Hypertension* 2009;53:442–5.
43. Beeks E, Kessels AG, Kroon AA, *et al*. Genetic predisposition to salt-sensitivity: a systematic review. *J Hypertens* 2004;22:1243–9.
44. Caprioli J, Mele C, Mossali C, *et al*. Polymorphisms of EDNRB, ATG, and ACE genes in salt-sensitive hypertension. *Can J Physiol Pharmacol* 2008;86:505–10.
45. Armando I, Villar VA, Jose P. Genomics and pharmacogenomics of salt-sensitive hypertension. *Curr Hypertens Rev* 2015;11:49–56.
46. Doaei S, Gholamalizadeh M. The association of genetic variations with sensitivity of blood pressure to dietary salt: A narrative literature review. *ARYA Atheroscler* 2014;10:169–74.
47. Gu D, Kelly TN, Hixson JE, *et al*. Genetic variants in the renin-angiotensin-aldosterone system and salt sensitivity of blood pressure. *J Hypertens* 2010;28:1–20.
48. Luft FC. Molecular genetics of salt-sensitivity and hypertension. *Drug Metab Dispos* 2001;29(4 Pt 2):500–4.
49. Carey RM, Schoeffel CD, Gildea JJ, *et al*. Salt sensitivity of blood pressure is associated with polymorphisms in the sodium-bicarbonate cotransporter. *Hypertension* 2012;60:1359–66.
50. Sanada H, Yatabe J, Midorikawa S, *et al*. Single-nucleotide polymorphisms for diagnosis of salt-sensitive hypertension. *Clin Chem* 2006;52:352–60.
51. Villar VA, Jones JE, Armando I, *et al*. G protein-coupled receptor kinase 4 (GRK4) regulates the phosphorylation and function of the dopamine D3 receptor. *J Biol Chem* 2009;284:21425–34.
52. Felder RA, Jose PA. Mechanisms of disease: the role of GRK4 in the etiology of essential hypertension and salt sensitivity. *Nat Clin Pract Nephrol* 2006;2:637–50.
53. Abecasis GR, Altshuler D, 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing. *Nature* 2010;467:1061–73.
54. Gröger N, Vitzthum H, Fröhlich H, *et al*. Targeted mutation of SLC4A5 induces arterial hypertension and renal metabolic acidosis. *Hum Mol Genet* 2012;21:1025–36.
55. Barkley RA, Chakravarti A, Family Blood Pressure Program. Positional identification of hypertension susceptibility genes on chromosome 2. *Hypertension* 2004;43:477–82.
56. Hunt SC, Xin Y, Wu LL, *et al*et al. Sodium bicarbonate cotransporter polymorphisms are associated with baseline and 10-year follow-up blood pressures. *Hypertension* 2006;47:532–6.
57. Bengra C, Mifflin TE, Khripin Y, *et al*. Genotyping of essential hypertension single-nucleotide polymorphisms by a homogeneous PCR method with universal energy transfer primers. *Clin Chem* 2002;48:2131–40.
58. Paz MA, de-La-Sierra A, Sáez M, *et al*. Treatment efficacy of anti-hypertensive drugs in monotherapy or combination: ATOM systematic review and meta-analysis of randomized clinical trials according to PRISMA statement. *Medicine* 2016;95:e4071.
59. Bronsert MR, Henderson WG, Valuck R, *et al*. Comparative effectiveness of antihypertensive therapeutic classes and treatment strategies in the initiation of therapy in primary care patients: a Distributed Ambulatory Research in Therapeutics Network (DARTNet) study. *J Am Board Fam Med* 2013;26:529–38.
60. Benjamin EJ, Virani SS, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation* 2018;137:e67–e492.
61. Materson BJ. Variability in response to antihypertensive drug treatment. *Hypertension* 2004;43:1166–7.
62. Ma J, Stafford RS. Screening, treatment, and control of hypertension in US private physician offices, 2003-2004. *Hypertension* 2008;51:1275–81.
63. Cooper-DeHoff RM, Johnson JA. Hypertension pharmacogenomics: in search of personalized treatment approaches. *Nat Rev Nephrol* 2016;12:110–22.
64. Pacanowski MA, Gong Y, INVEST Investigators. beta-adrenergic receptor gene polymorphisms and beta-blocker treatment outcomes in hypertension. *Clin Pharmacol Ther* 2008;84:715–21.
65. Johnson JA, Zineh I, Puckett BJ, *et al*. Beta 1-adrenergic receptor polymorphisms and antihypertensive response to metoprolol. *Clin Pharmacol Ther* 2003;74:44–52.
66. Vandell AG, Lobmeyer MT, Gawronski BE, *et al*. G protein receptor kinase 4 polymorphisms: β-blocker pharmacogenetics and treatment-related outcomes in hypertension. *Hypertension* 2012;60:957–64.

67. Svensson-Färbom P, Wahlstrand B, Almgren P, *et al*. A functional variant of the NEDD4L gene is associated with beneficial treatment response with β-blockers and diuretics in hypertensive patients. *J Hypertens* 2011;29:388–95.
68. McDonough CW, Burbage SE, Duarte JD, *et al*. Association of variants in NEDD4L with blood pressure response and adverse cardiovascular outcomes in hypertensive patients treated with thiazide diuretics. *J Hypertens* 2013;31:698–704.
69. Cusi D, Barlassina C, Azzani T, *et al*. Polymorphisms of alpha-adducin and salt sensitivity in patients with essential hypertension. *Lancet* 1997;349:1353–7.
70. Muskalla AM, Suter PM, Saur M, *et al*. G-protein receptor kinase 4 polymorphism and response to antihypertensive therapy. *Clin Chem* 2014;60:1543–8.
71. Siddiqui M, Dudenbostel T, Calhoun DA. Resistant and refractory hypertension: antihypertensive treatment resistance vs treatment failure. *Can J Cardiol* 2016;32:603–6.
72. El Rouby N, Cooper-DeHoff RM. Genetics of resistant hypertension: a novel pharmacogenomics phenotype. *Curr Hypertens Rep* 2015;17:583.
73. Oliveira-Paula GH, Lacchini R, Coeli-Lacchini FB, *et al*. Inducible nitric oxide synthase haplotype associated with hypertension and responsiveness to antihypertensive drug therapy. *Gene* 2013;515:391–5.
74. Lu H, Cassis LA, Kooi CW, *et al*. Structure and functions of angiotensinogen. *Hypertens Res* 2016;39:492–500.
75. Lynch AI, Irvin MR, Davis BR, *et al*. Genetic and adverse health outcome associations with treatment resistant hypertension in GenHAT. *Int J Hypertens* 2013;2013:578578–.
76. Fontana V, McDonough CW, Gong Y, *et al*. Large-scale gene-centric analysis identifies polymorphisms for resistant hypertension. *J Am Heart Assoc* 2014;3:e001398.
77. Butterworth MB. Regulation of the epithelial sodium channel (ENaC) by membrane trafficking. *Biochim Biophys Acta* 2010;1802:1166–77.
78. Jones ES, Owen EP, Rayner BL. The association of the R563Q genotype of the ENaC with phenotypic variation in Southern Africa. *Am J Hypertens* 2012;25:1286–91.
79. Fontana V, de Faria AP, Barbaro NR, *et al*. Modulation of aldosterone levels by -344 C/T CYP11B2 polymorphism and spironolactone use in resistant hypertension. *J Am Soc Hypertens* 2014;8:146–51.
80. Laffer CL, Elijovich F, Eckert GJ, *et al*. Genetic variation in CYP4A11 and blood pressure response to mineralocorticoid receptor antagonism or ENaC inhibition: an exploratory pilot study in African Americans. *J Am Soc Hypertens* 2014;8:475–80.
81. Agarwal R. Resistant hypertension and the neglected antihypertensive: sodium restriction. *Nephrol Dial Transplant* 2012;27:4041–5.
82. Pimenta E, Gaddam KK, Oparil S, *et al*. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. *Hypertension* 2009;54:475–81.