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Salt consumption in children and adolescents – impact on blood pressure and cardiovascular health

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Resumo

Introdução: O sódio é o principal catião do líquido extracelular e desempenha um papel fisiológico na manutenção do volume plasmático, no equilíbrio ácido-base, na transmissão de impulsos nervosos e no normal funcionamento das células. Ainda que a ingestão de sódio seja fundamental para o correto funcionamento do corpo humano, atualmente, em todo o mundo, a quantidade de sódio consumida é superior à quantidade recomendada pela Organização Mundial de Saúde. O consumo exagerado de sódio representa uma preocupação importante, tendo em conta que, em adultos, uma maior ingestão de sódio está relacionada com o aumento da pressão arterial e o desenvolvimento/progressão de doença cardiovascular. Em crianças com pressão arterial elevada existe um maior risco de, na idade adulta, a pressão arterial se manter elevada, por um fenómeno conhecido como *tracking*. Por este motivo torna-se fundamental compreender qual a implicação de um consumo de sódio exagerado durante a infância e adolescência, na pressão arterial e na saúde cardiovascular. No entanto, a evidência disponível relativa a esta temática em idade pediátrica é significativamente mais escassa do que a existente na idade adulta.

Objetivo: Elaborar uma revisão abrangente e atualizada acerca do impacto da ingestão de sódio na pressão arterial e saúde cardiovascular, durante a infância e adolescência.

Metodologia: Procedeu-se a uma pesquisa metódica da literatura publicada na plataforma digital de publicações científicas *PubMed*. Foram incluídos artigos escritos em Inglês, Francês, Espanhol ou Português e que datavam, preferencialmente, dos últimos 20 anos.

Discussão: A pressão arterial pode ser programada através de fatores maternos e/ou placentários e pode manter-se elevada desde a infância até à idade adulta visto seguir um padrão de *tracking*. Diversos estudos realizados com o intuito de compreender como a ingestão de sal afeta a pressão arterial durante a infância e a adolescência, demonstram uma relação positiva e significativa entre estas duas variáveis. Outros estudos também demonstraram que os eventos cardiovasculares na infância estão associados a um maior consumo de sódio, embora o número de estudos realizados neste âmbito seja diminuto. Desta forma, as intervenções para a redução de consumo do sódio devem ser implementadas e integradas na sociedade, dirigidas a toda a população, incluindo indivíduos com uma idade jovem, com o intuito de prevenir o desenvolvimento de hipertensão e de doenças cardiovasculares associadas. Estas intervenções além de serem pouco dispendiosas, provaram ser eficazes e com elevado potencial para reduzir carga global de doença, com implicações a vários níveis.

Palavras-chave: Consumo de sal; Cloreto de sódio; Pressão Arterial; Risco Cardiovascular; Crianças; Adolescentes.

Abstract

Introduction: Sodium is the major cation of the extracellular fluid and has a physiological role in the organism through the maintenance of plasma volume, acid-base balance, transmission of nerve impulses and normal cell function. Even though dietary sodium intake is crucial for the organism, nowadays around the world, it exceeds the amount of consumption recommended by World Health Organization. This represents a great concern since that, in adulthood, sodium intake is associated with elevated blood pressure and poorer outcomes regarding cardiovascular health. Knowing that blood pressure follows a tracking pattern from childhood to adulthood, it is fundamental to understand the effects of sodium intake in children's and adolescent's blood pressure and the cardiovascular events related to sodium intake. However, the evidence, in this age group is scarcer and more controversial compared to the literature in adults.

Objectives: To provide a comprehensive and updated overview about how sodium intake, during childhood and adolescence, affects blood pressure and cardiovascular health.

Methodology: A methodical search of the published literature was conducted on the electronic database PubMed. The included articles dated preferentially from the last 20 years and were written in English, French, Spanish or Portuguese.

Discussion: Blood pressure can be programmed due to maternal and placental factors and follows a programming pattern, suggesting that children with elevated blood pressure levels will most likely maintain high blood pressure in adulthood. Several studies that analyzed how high dietary salt intake affected blood pressure during childhood, demonstrated a positive and significant relation between these variables. Additionally, studies have also shown that cardiovascular events in childhood are related to high sodium intake and increased BP, even though the number of studies regarding this issue is limited. Therefore, sodium intake reduction programs should be implemented since an early age, in order to prevent hypertension and, moreover, cardiovascular disease. These programs are cost-effective and have the potential to reduce the overall burden of disease.

Key-words: Salt intake; Sodium Chloride; Blood Pressure; Cardiovascular Risk; Children; Adolescents.

List of Abbreviations

ACE – Angiotensin Converting Enzyme
ACE2 – Angiotensin Converting Enzyme 2
ANP – Atrial Natriuretic Peptide
AT₁R – Angiotensin II Type 1 Receptor
AT₂R – Angiotensin II Type 2 Receptor
BMI – Body Mass Index
BNP – Brain Natriuretic Peptide
BP – Blood Pressure
CI – Confidence Interval
CKD – Chronic Kidney Disease
CNP – C-type Natriuretic Peptide
COX – Cyclooxygenase
CV – Cardiovascular
DBP – Diastolic Blood Pressure
ENaC – Epithelium Sodium Channel
ET – Endothelin
GFR – Glomerular Filtration Rate
IUGR – Intrauterine Growth Restriction
LBW – Low Birth Weight
MAP – Median Arterial Pressure
NO – Nitric Oxide
PGI₂ – Prostacyclin
RAAS – Renin Angiotensin Aldosterone System
RNI – Reference Nutrient Interval
SBP – Systolic Blood Pressure
SDS – Standard Deviation Score
SNS – Sympathetic Nervous System
SR – Salt Resistant
SS – Salt Sensitive
WHO – World Health Organization

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1. Introduction and aims

Since primordial times, salt or sodium chloride has been integrated in human civilizations¹. Following agricultural revolution and until the discovery of refrigerators, salt was used to preserve food and therefore was considered a valuable trade product¹. Nowadays, almost 70% of the daily salt intake is related with the consumption of processed foods, 15% is attributable to the sodium naturally present in food, and the remaining can be explained by intentional addition during the cooking process, being related to the individual/cultural eating habits^{2,3}. Even though sodium is necessary for the physiological needs, evidence shows that the majority of countries have an exaggerated sodium intake with mean estimated values ranging between 9 to 12 g/day, even reaching over 12 g/day in some Asian countries⁴.

It is suggested that elevation of blood pressure (BP) might, in some settings, start during childhood, with the contribution of events from the prenatal and postnatal period, besides following a tracking pattern from childhood into adulthood afterwards⁵. In adults, excessive sodium intake is a major issue, namely due to its BP elevation effect and influence in target organ damage, particularly in salt-sensitive (SS) individuals⁶. In children and adolescents, the evidence on the impact of salt intake in BP is scarce and controversial⁵; although reduction in sodium intake has a lowering effect in BP, many of the studies have methodological problems, frequently with short follow-up periods and poorly representative samples⁵.

Hypertension persists as a critical public health problem, being the largest contributor to cardiovascular (CV) disease and the major modifiable risk for CV mortality worldwide⁷, despite the fact that some of the most effective actions to prevent hypertension are fairly inexpensive, such as weight loss, exercise, and sodium restriction⁷. Reducing sodium intake has shown not only to decrease BP values but also to have beneficial effects on CV health, particularly in vascular function and arterial elasticity⁸. The World Health Organization (WHO) has been recommending the reduction of sodium intake for the last 3 decades, and more recently, as a result of several studies, defined levels of consumption by age groups^{9,10}. Prevention of salt-associated raise in BP in early ages is essential, since it can prevent the development of hypertension later in life and attenuate the public health onus of all its associated diseases and complications⁵.

Contemplating the importance of this topic, the present review aims to provide an updated overview about the evidence relating sodium intake and health, particularly focusing on BP and CV health, with particular emphasis in the period of childhood and adolescence.

2. Methods

For this review, it was conducted a methodical search of scientific articles on the electronic database PubMed, with the following key words: “infants”, “children”, “childhood”, “adolescents”, “adults”, “adulthood”, “blood pressure”, “hypertension”, “sodium intake”, “salt intake”, “cardiovascular events”, “salt sensitivity”, “tracking” and “programming”. Additionally, in the selected articles, it was performed a search in their references in order to find other important articles not included in the results from the primary search.

The present review included articles written in English, French, Spanish or Portuguese and preferentially dated from the last 20 years (2001-2021). However, a few articles prior to that date, considered especially relevant were also included.

3. Sodium balance and salt intake

3.1 Physiological role and homeostasis

Many mechanisms and systems are involved in the regulation of the levels of sodium in the organism, namely the renin-angiotensin-aldosterone system (RAAS), the tubuloglomerular feedback, nitric oxide (NO) and endothelin (ET), prostaglandins, vasopressin, natriuretic peptides and the sympathetic nervous system.

The RAAS is an essential system to the organism since it regulates the plasma sodium concentration, extracellular volume and BP¹¹. Renin is secreted by the granular cells of the kidney and its secretion is triggered by low BP, low sodium chloride concentration at the macula densa, hypovolemia and stimulation of the sympathetic nervous system (SNS)^{11,12}. The active form of renin metabolizes angiotensinogen, forming angiotensin I that will be converted to angiotensin II by angiotensin-converting enzyme (ACE)¹². Angiotensin II interacts with 2 types of receptors: the angiotensin II type 1 receptor (AT₁R) and the angiotensin II type 2 receptor (AT₂R)¹². Actions resulting from the interaction with AT₁R include sodium retention, vasoconstriction, stimulation of thirst and desire for salt intake, stimulation of SNS activity, aldosterone secretion, as well as pro-inflammatory and pro-fibrotic effects¹². In the kidney, the principal effect of angiotensin II includes vasoconstriction of the interlobular artery as well as the afferent and efferent arterioles, increased afferent arteriolar response to tubuloglomerular feedback, and constriction of glomerular mesangium, leading to augmented BP¹². When angiotensin II interacts with the AT₂R, the resulting actions are counterregulatory to the ones produced with activation of the AT₁R, promoting vasodilatory effects as well as anti-inflammatory and anti-fibrotic effects¹². Even though the RAAS is activated in the presence of low sodium chloride concentrations, it has been described that high sodium diet might also promote RAAS activation¹³. The mechanism is not completely understood but it may be linked to the decreased amount of circulating angiotensin II that upregulates the AT₁R¹³. The RAAS also has a counterregulatory arm¹⁴, which includes the angiotensin-converting enzyme 2 (ACE2). This enzyme preferentially degrades angiotensin II to produce angiotensin 1-7, a heptapeptide, which activates the Mas receptor promoting the inhibition of tubular sodium and HCO₃⁻ transport, resulting in increased diuresis and natriuresis, vasodilation and antihypertensive actions¹⁵. The RAAS included aldosterone, which is produced in the presence of high concentrations of angiotensin II or increased extracellular potassium concentration, and constitutes a vital regulator

of sodium, potassium and fluid balance¹². This hormone leads to potassium excretion and increased reabsorption of sodium and water leading to high BP¹².

The macula densa tubuloglomerular feedback is a physiological mechanism involved in the autoregulation of glomerular blood flow¹⁶. When the glomerular filtration rate (GFR) is elevated or in states of volume overload, the amount of sodium that reaches the macula densa is increased, leading to augmented uptake in the loop of Henle with consequent release of adenosine¹⁶. Adenosine acts in receptors located on extraglomerular mesangial cells causing elevations in the concentration of intracellular calcium that in smooth muscle cells of the afferent arteriole, promoting vasoconstriction and decrease of GFR¹⁶. Additionally, adenosine modulates renin secretion through negative feedback by acting in the renin secreting cells¹⁷.

NO and ET act as regulators of sodium and water homeostasis and the impairment of these pathways may play a role in SS hypertension¹⁸. NO plays an important role in sodium balance, promoting its excretion via renal blood flow, GFR, direct tubular effects or by inhibition of SNS activity¹⁸. Dysfunction of the NO system might be linked to the progression of salt-induced kidney disease¹⁸. NO acts as a key signaling mediator of pressure-natriuresis and has a direct action in sodium transport in multiple nephron segments¹⁸. In the thick ascending loop of Henle, NO inhibits sodium transport through the Na-K-2Cl cotransporter and the Na/H exchanger¹⁸. In the proximal tubule, NO effects in sodium transport are controversial with both stimulatory and inhibitory actions being reported¹⁸. The ET system acts as a regulator of vascular tone and fluid balance¹⁸. ET-1, ET-2 and ET-3 are the three known isoforms of ET, with ET-1 being the predominant isoform found in the kidney, more specifically in the renal medulla¹⁸. High dietary intake of sodium increases renal synthesis of ET-1 that binds ET_A and ET_B receptors¹⁸. ET_A receptors are located in vascular smooth muscle and mediate vasoconstriction, while ET_B receptors mediate vasodilation through activation of the NO system and negative feedback on the amount of circulating ET¹⁸. However, ET_B receptors can also produce vasoconstriction since they are present in sympathetic ganglia and vascular smooth muscle¹⁸. Sodium intake can trigger the production of ET-1 that activates the NO system in the renal inner medulla leading to sodium excretion¹⁸. The dysfunction of this pathway can lead to sodium accumulation in the organism, that can result in SS hypertension¹⁸.

Studies aiming to understand the effect of prostaglandins in sodium homeostasis, revealed that their inhibition translates into decreased excretion of sodium and water by the kidneys¹⁹. Also, it is known that the pressure-natriuresis response is dependent on prostaglandins²⁰. PGE₂ and prostacyclin (PGI₂) are vasodilatory prostaglandins known to regulate vascular tone, water and sodium balance and to adjust the function of the distal nephron²⁰. PGE₂ stimulates sodium excretion

at the thick ascending limb of the loop of Henle through inhibition of the Na-K-2Cl cotransporter, and inhibits the effect of vasopressin in water reabsorption²⁰. PGI₂ is a potent vasodilator that maintains GFR and renal blood flow and stimulates RAAS leading to potassium secretion and sodium reabsorption²⁰. The basal production of prostaglandins is relatively low in healthy individuals²¹ but it increases in states of volume depletion due to gastrointestinal or renal losses, heart failure, cirrhosis or others²¹.

Vasopressin is secreted by the pituitary gland as a consequence of the thirst reflex induced by RAAS stimulation in hypothalamus¹¹. The thirst reflex occurs when there is an increase in plasma osmolality, hypovolemia or hypernatremia²². Vasopressin acts in two receptors; the V1 receptor is located in smooth muscle cells and the V2 receptor is located in epithelial cells, such as the principal cells in the distant nephron²³. Stimulation of V1 receptors promotes sodium excretion through increases in BP, hypervolemia, decreases in the GFR and vasoconstriction in the vasa recta system, while stimulation of V2 receptors promotes water reabsorption and sodium reabsorption mediated by the epithelium sodium channel (ENaC)²³. Vasopressin promotes water conservation at the expense of less efficient sodium excretion which can lead to increases in BP through V2 receptors effects²².

Natriuretic peptides are also relevant for sodium balance and homeostasis. The atrial natriuretic peptide (ANP) is produced and stored in the atrial granules and is secreted in response to augmented tension in atrial wall, although its secretion is also influenced by age, sex, renal function, heart rate, hypoxia, glucocorticoid stimuli, vasopressin, ET A, angiotensin II and catecholamines²⁴. Low levels of brain natriuretic peptide (BNP) are stored in atrial granules together with ANP, but it is the cardiac ventricle that secretes most of the BNP to the organism²⁴. Unlike the other natriuretic peptides, C-type natriuretic peptide (CNP) is not stored in atrial granules, but is produced and secreted from endothelial cells and some neurons in the central nervous system²⁵. All of the natriuretic peptides are present in different renal tubular segments and have cardiorenal protective effects, with CNP presenting the less marked renal effects^{24,26}. These peptides act after binding with specific plasma membrane receptors, the natriuretic peptide receptors A (NPR-A), B (NPR-B) and C (NPR-C)²⁶. ANP and BNP are more likely to interact with NPR-A while NPR-B acts as a specific CNP receptor²⁶. The natriuretic peptides have equal affinity to bind with NPR-C, which is the most expressed receptor in the atrial myocardium²⁷. These interactions between the natriuretic peptides and their receptors produce multiple effects among the kidney, the blood vessels, the heart, the endocrine metabolism, cell growth and tissue remodelling²⁸. In the kidney, natriuretic peptides act mostly in the glomerular and tubular segments, inducing afferent arteriole vasodilation with augmented glomerular filtration and decreased tubular reabsorption of sodium and water²⁸. These

peptides also inhibit the RAAS, reduce SNS activity, and antagonize the effects of ET and arginine-vasopressin²⁸. Natriuretic peptides represent the major system protecting from sodium retention, especially in heart failure²⁶.

Baroreceptors are mechanoreceptors that are sensitive to changes in BP, being stimulated by stretching of the vessel wall²⁹. There are two types of baroreceptors, the high pressure arterial baroreceptors located in the carotid sinuses and aortic arch, and the low pressure volume baroreceptors located in the atria, ventricles and pulmonary vasculature²⁹. When BP raises, baroreceptors inhibit SNS activity resulting in vasodilation and diminished peripheral vascular resistance, while if BP falls or hypovolemia/hyponatremia is present, baroreceptors trigger SNS activity²⁹. In the spontaneously hypertensive rat, carotid sinus denervation attenuated the development of hypertension and lowered sympathetic vasomotor tone, suggesting that hypertension might result from an inappropriately activated baroreceptor mechanism and hyperactivity of the SNS³⁰. Indeed, hyperactivity of the SNS plays a role on BP regulation, by acting on the blood vessels, the kidney and the heart³¹. Renal nerves have sympathetic (efferent) and sensory (afferent) fibers that control renal function, central hemodynamics and BP³¹. The activation of efferent sympathetic fibers increases noradrenaline production and its spillover³². When renal sympathetic nerves are activated, β_1 adrenergic receptors increase renin secretion, while α_1 -adrenoceptors stimulate sodium and water reabsorption, as well as decrease in renal blood flow³². Activity of afferent sensory renal nerves has proved to be elevated in studies with hypertensive rats and may be linked to the regulation of systemic vascular resistance and BP control, through vasopressin and oxytocin release³².

3.2 Dietary salt intake during childhood and adolescence

3.2.1 Physiological needs and daily recommended intake

According to the WHO, adults should ingest a maximum of 5g of salt per day (equivalent to 2 g/day of sodium) and for children the upper level of maximum intake should be adjusted downward based on their energy requirements¹⁰.

Throughout the years, additional guidelines were published aiming to recommend the ideal value ranges of sodium consumption according to age groups. The most recent guideline is the Dietary Guidelines for Americans 2020-2025 that recommends that above 14 years old, the sodium intake should be inferior to 2.3 g/day of sodium.³³ For the age groups of as 6 to 11 months, 1 to 3 years, 4

to 8 years and 9 to 13 years, the daily sodium goal should be 0.37 g/day, 1.2 g/day, 1.5 g/day and 1.8 g/day correspondingly.³³ Other guidelines such as the one released in 2003 by the Scientific Advisory Committee on Nutrition and a consensus study report dating from 2019 present with different range of values as can be seen in Table I.

Even though, the three reports presented in Table I recommend slightly different value ranges regarding sodium intake, the values are concordant to the ones recommend by WHO. Sodium consumption below the recommended minimal value or above the upper limit might be associated with several deleterious effects³⁴. However, it is important to underline that these limits might need to be adjusted, according to interindividual variability, which is dependent of several factors such as age, genetic predisposition and environmental conditions. Therefore, the recommended levels of sodium intake should take into account this variability and be adapted accordingly.

3.2.2 Methods to assess sodium intake

An accurate measure of sodium intake is crucial to evaluate its impact in individuals, to compare/discuss results from different studies, to set more specific goals, and to guide the evaluation of sodium intake reduction. Currently, there are some methods for measuring dietary sodium intake including self-report assessments and biochemical measures, although there are still challenges associated with the precise quantification⁴⁰.

The most objective method to assess sodium intake and, therefore the actual gold standard, is the quantification of the excretion in a 24h urine collection, as 90% of the salt consumed is excreted in urine⁴¹. This method is expensive, a considerably hassle for subjects, and unpractical when contemplating large populations or when multiple measurements are needed^{40,41}. Additionally, in infants, 24h urine collection presents numerous problems such as contamination, leakage and micturition loss⁴². Even with the use of tools designed to help urine collection, 24-hour collection is generally considered not to be sufficiently reliable in small children⁴². As an alternative, biochemical analysis might be performed on 12h urine samples, spot urine and/or overnight urine samples⁴¹. These methods are less reliable comparing to 24h urine collection because the rate of renal sodium excretion is inconstant throughout the day due to the salt intake pattern, individual posture, and neurohormonal influence⁴¹.

Self-report methods include dietary recalls (24h or 48h), food records (3, 4 or 7 days), food frequency questionnaires and discretionary salt use. These are widely applied since they are easy, practical and very low cost⁴¹. However, a possible change of behavior during this type of data collection, with a under-report of sodium intake, represents one of the major disadvantages inherent to this methods⁴⁰. Previous studies have shown that under-reporting is mostly observed

in individuals with high body mass index (BMI), which might be particularly relevant in high and middle income countries, where the prevalence of obesity and overweight is very high⁴⁰.

3.2.3 Salt intake in the world

In 2009, Brown et al published an overview of salt intake worldwide³⁵, as a result of several published studies, and concluded that in the majority of populations worldwide, salt intake was greater than the recommended dietary intake³⁵. In adulthood, the average sodium intake was approximately 2.3 g/day (equivalent to 100 mmol/day of sodium) and in some Asian countries, it reached approximately 4.6 g/day (equivalent to 200 mmol/day of sodium)³⁵. During childhood, sodium intake above 100 mmol/day was commonly found among 5 year old children and the tendency was to increase from that age³⁵. Regarding the main dietary sources of sodium, in European and Northern American countries a significant quantity of the ingested sodium is added in food manufacture, while in developing countries the sodium intake is mainly associated with the addition of salt in meal preparation and sauces³⁵.

Powles et al conducted a study comparing the amount of salt intake between 1990 and 2010, in 66 countries (74% of the global adult population) and demonstrated that in this 20 years period there was a statistically non-significant increase in sodium intake³⁶. The mean sodium intake in men was 4.02 g/day (3.93 g/day to 4.11 g/day, 95% CI) in 1990 and 4.14 g/day (4.04 g/day to 4.23 g/day, 95% CI) in 2010³⁶, while that of women was 3.63 g/day (3.55 g/day to 3.71 g/day, 95% CI) in 1990 and 3.77 g/day (3.69 g/day to 3.85 g/day, 95% CI) in 2010³⁶. In 2010, mean sodium intake in adults was 3.95 g/day (3.89 g/day to 4.01 g/day, 95% CI) equivalent to 10.06 g/day of salt (9.88 g/day to 10.21 g/day, 95% CI)³⁶. East Asia and Europe were the regions with the higher sodium intake increase in the period studied and were two of the regions reportedly to have the highest sodium intakes, which suggested a “silk road” pattern.³⁶

The Portuguese HYPertension and SALT (PHYSA) Study in 2014 provided the first national data on prevalence, awareness and control of hypertension as well as on salt intake based on 24h urine samples.³⁷ Overall, in the tested sample (n = 2568) the average daily intake of sodium was 4.2 g/day (equivalent to an intake 10.7 g/day of salt and a sodium excretion of 182.5 ± 64.7 mmol/24h), demonstrating an exaggerated consumption of this element according to the WHO recommendations³⁷. In hypertensive individuals, urinary sodium excretion (185.4 ± 64.8 mmol/24h) was significantly higher than in normotensive participants (177.8 ± 64.5 mmol/24h) and gender differences were also found with men presenting greater urinary sodium excretion, most likely related to higher food and energy intake³⁷.

In 2016, another Portuguese study with 298 Portuguese children aged between 8-9 years determined salt intake based in 24h urinary sodium excretion³⁸. The average amount of salt intake was 6.5 ± 2.2 g/day and similarly to other studies, significantly gender differences were found with boys having a higher salt consumption (6.8 ± 2.4 g/day) opposed to girls (6.1 ± 1.9 g/day)³⁸. Moreover, significant disparities in overweight/obese children (6.8 ± 2.4 g/day) versus normal weight children (6.1 ± 2.0 g/day) were also observed³⁸. Almost 75% of the children that participated in this study had a consumption of salt above the upper limit value recommended for adults, indicating that Portuguese children consume large quantities of sodium, which are much superior to the daily intake recommended³⁸.

More recently, Thout et al identified 13 nationally representative studies from 13 different countries that exceeded the WHO recommended salt intake of 5g/day³⁹. Only in 4 countries (Italy, England, Canada and Barbados) the amount of salt intake was lower than in previous reports, namely in The Global Burden of Disease 2010, probably due to the implementation of salt intake reduction programs in these countries³⁹. Divergently, in Fiji, Benin and Samoa, the amount of salt intake reported in the presented study was higher than the one found in The Global Burden of Disease 2010, which could be explained by the nutritional transition from traditional to processed foods, happening in many low and middle income countries³⁹.

In the Dietary Guidelines for Americans 2020-2025, the average sodium intake was reported by group age³³. Between 2 and 4 years, the average intake in males was 2.274 g/day and in females was 2.061 g/day³³. Among males with ages between 5 and 8 years an average intake of 2.785 g/day was reported, while in females the average intake was of 2.525 g/day³³. In 9 to 13 years old children, the mean sodium intake was 3.451 g/day in males and 3.030 g/day in females³³. Adolescents aged 14 to 18 years had a mean sodium intake of 3.888 g/day in males and 2.875 g/day in females³³. Young adults (19 – 30 years) had an average of sodium intake of 4.274 g/day and 3.142 g/day in males and females, respectively³³. In adults aged 31 to 59 years, the mean sodium intake was 4.172 g/day in males and 3.062 g/day in females³³. Interestingly, in elderly (60 years and older) the average sodium intake decreased (3.799 g/day in males and 2.802 g/day in females), but to values still above the WHO recommendations³³.

4. Effects of salt on blood pressure

4.1 Evidence during adulthood

In the last decades, a large number of studies have provided solid and reliable evidence regarding the relationship between salt and BP in adulthood. Some of the most important and recent reports are described below.

One of the oldest studies in this field is the INTERSALT study, published in 1997⁴³. This study aimed to test, in a population of over 10 000 participants, if systolic blood pressure (SBP) and diastolic blood pressure (DBP) were directly and independently related to the 24h urinary sodium excretion, urinary excretion of sodium/potassium ratio, BMI and alcohol use, and inversely related to potassium excretion⁴³. INTERSALT was a worldwide large epidemiologic study, with a sample of 10 079 individuals aged between 20 and 59 years, from 32 different countries, that demonstrated a significant positive relationship between urinary sodium excretion and BP as well as an inverse relationship between 24h potassium excretion and BP⁴³. BMI and alcohol intake also showed significant and independent relationships with BP⁴³. The association between urinary sodium excretion and BP remained significant after adjustment for several potential confounders, such as BMI, alcohol intake and urinary potassium excretion⁴³. The INTERMAP was another epidemiological study; it included 4680 participants from Japan, People's Republic of China, United Kingdom and United States of America, aged 40 to 59 years old⁴⁴. INTERMAP intended to analyze the relation between BP and 24-hour urine sodium excretion and the urinary sodium/potassium ratio, but also to evaluate if the consumption of several macro and micronutrients interfered with the sodium and BP relation⁴⁴. The results of the INTERMAP were similar to those from the INTERSALT study, with a significant direct association of BP and 24-hour urine sodium excretion and urinary sodium/potassium ratio, apparently not affected by other micro or macro nutrients⁴⁴.

One of the latest meta-analysis on the association between BP and salt consumption was conducted by He et al, in 2013, with the objective of clarifying the effects of a modest salt intake reduction (in average, 4.4 g/day of salt) on BP, plasma renin activity, aldosterone, noradrenaline, adrenaline, total cholesterol, low density and high density lipoprotein cholesterol and triglycerides⁴⁵. The authors analyzed 34 trials, 22 in hypertensive individuals and 12 in normotensive individuals, which gathered a total of 3230 participants with a mean age of 50 years (ranging from 22 to 73 years)⁴⁵. In both groups, the mean decrease in urinary sodium was -75 mmol/24h, which is equivalent to a salt intake reduction of 4.4g/day, but the mean decrease in BP was higher among individuals with

hypertension (-5.39 mmHg (-6.62 to -4.15, 95% CI) in SBP and -2.82 mmHg (-3.54 to -2.11, 95% CI) in DBP), when compared to normotensive subjects (mean decrease in SBP of -2.42 mmHg (-3.56 to -1.29, 95% CI) and of -1.0 mmHg (-1.85 to -0.15, 95% CI) in DBP)⁴⁵. The most recent meta-analysis conducted, reviewed 30 trials in order to assess how a “Dietary Approaches to Stop Hypertension (DASH) diet”, which includes salt intake reduction, could modify BP in adults with and without hypertension⁴⁶. All studies reviewed showed that the DASH diet, when compared with a control diet, significantly reduced SBP (mean difference of -3.2 mmHg; -4.2 to -2.3, 95% CI) and DBP (mean difference of -2.5 mmHg; -3.5 to -1.5, 95% CI) in individuals with or without hypertension⁴⁶.

Jackson et al developed a cross-sectional study which analyzed BP values and 24 hour urine sodium excretion measurements of 766 adults (ages ranging from 20 to 69 years), from the 2014 National Health and Nutrition Examination Survey (NHANES)⁴⁷. The results obtained were consistent with previous studies, demonstrating a direct association between the two studied variables and an inverse relation between potassium excretion and SBP⁴⁷. Previous cohort studies, such as the one developed by Welsh et al in 2019, also reported a reliable and linear relationship between sodium intake and BP⁴⁸.

Even though the aforementioned studies differ in several methodological characteristics and type of design (observational, meta-analysis, interventional, cross-sectional and cohort studies), the available data evidences a direct, strong and linear association between sodium intake and BP. Additionally, an inverse relation between urinary potassium and BP and a positive relation between sodium/potassium ratio and BP has also been reported.

4.2 Evidence during childhood and adolescence

It is known that children and adolescents with increased BP have a higher risk to develop hypertension in adult life^{49,50}. Additionally, several studies analyzed and demonstrated the importance of salt intake as a contributing factor to develop changes in BP in children and adolescents.

Pomenraz et al conducted an observational study with 867 fourth and fifth graders that showed changes in BP when children ingested water containing high levels of sodium and nitrate⁵¹. In another study, Pomeranz et al evaluated if feeding neonates with milk formula diluted with low-sodium mineral water (LSMW) or with high-sodium tap water (HSTW) would change BP when compared with neonates feed with breast milk (control group)⁵². This prospective study included

58 Jewish neonates randomly assigned to the two intervention groups; milk formula diluted with LSMW or HSMW was given for the first 8 weeks of life, and after, group 1 (LSMW) changed to a diet similar to group 2 (HSTW)⁵². At week 8, the participants from group 2 presented significantly greater urinary sodium/creatinine ratios and significant changes in their BP levels, with increases in mean arterial pressure (MAP), SBP and DBP⁵². Interestingly, at week 24, participants of group 1 showed results similar to those of group 2⁵².

Yang et al led an observational study in the US, which included 6235 children and adolescents aged 8 to 18 years, from the National Health and Nutrition Examination Survey (NHANES) of 2003-2008. The study population included 37% of overweight or obese individuals⁵³. The studied population consumed an average of 3.387 g/day of sodium and increments of 1 g/day of sodium were associated with an increase in SBP of approximately 1.0 mmHg (SDS increasing 0.097; 0.006 to 0.188, 95% CI) among all participants, and approximately 1.5 mmHg (SDS increasing 0.141; -0.010 to 0.298, 95% CI) among overweight/obese individuals⁵³. The increases in BP were more evident among individuals in the highest sodium intake quartile and among overweight/obese participants⁵³.

Another observational study, which included 1424 healthy Italian children and adolescents, aged 6-18 years old, aimed to investigate the relation between dietary sodium and potassium intake, BMI and BP, concluded that the high sodium intake verified among the participants was directly associated to BP and BMI levels⁵⁴.

The evidence available in children and adolescents, despite scarcer, appears to be comparable to that from adult studies, demonstrating that the linear positive association between BP and sodium intake is present from early ages.

4.3 Tracking and programming

Events or exposures that occur in the prenatal and postnatal period of human life are considered to be a key component to the development of diseases in adulthood, such as high BP and hypertension⁵⁵. Besides having its roots in early life, BP additionally follows a tracking pattern, implying that children and adolescents with high values of BP will most likely maintain them in adulthood⁵⁶. Both experimental and clinical studies support this evidence⁵⁷⁻⁵⁹. Taking in consideration that hypertension is one of the major risk factors for CV disease and that the obesity

epidemic is strongly related to higher values of BP in childhood, the phenomenon of BP tracking has important public health repercussions, and should be comprehensively studied⁵⁷.

The mechanisms of BP programming are dependent of maternal and placental factors that can independently or co-dependently control the in utero and postnatal environment, influencing the risk of CV development later in life⁵⁵. The main systems affected by early life environmental factors that can lead to hypertension are the renal and the vascular systems, and many of the early changes possibly involve epigenetic mechanisms⁵⁵. Some variables that can affect BP tracking and programming include low birth weight (LBW), uteroplacental insufficiency and exposure to glucocorticoids, as described below.

LBW is defined by WHO as a weight under 2500g due to intrauterine growth restriction (IUGR) or prematurity^{60,61}. LBW linked with IUGR suggests intrauterine stress during the last stages of pregnancy, differing from LBW in prematurity which may indeed represent an appropriate weight for the gestational age⁶². Several studies, performed both during childhood or adulthood, consistently demonstrated that LBW has an inverse relation with hypertension even after correction for gender, current weight at the moment, smoking status and use of oral contraceptives^{63–67}. Huxley et al concluded that postnatal catch-up growth is associated with BP, this relation being greater among individuals with LBW and subsequently accelerated postnatal growth⁶⁸. Experimental studies support the clinical evidence and suggest that the explanation for this phenomenon lies on nephron deficit^{69,70}, since impaired nephrogenesis is believed to lead to a less efficient kidney excretion of salt and, consequently, to a higher risk of developing hypertension and chronic kidney disease (CKD)⁷¹. Studies such as the ones developed by Keller et al⁷², Hoy et al⁷³ and Kazanki et al⁷⁴ suggested that the quantity of glomeruli is lower in the kidneys of hypertensive individuals, when compared to normotensive individuals, however birthweight was not considered in these analysis. In a cohort study, Hughson et al found a relation between the development of hypertension, low nephron number and LBW in Caucasian participants but not in African Americans, even though these latter presented twice the prevalence of hypertension and a nephron number below the mean⁷⁵. Another plausible mechanism to explain the association between LBW and hypertension is a compromised endothelial function, which was found in young adults born with LBW⁷⁶. The alterations in endothelial function could also be due to impaired angiogenesis during fetal development or to a decrease in the production of NO⁶¹.

Uteroplacental insufficiency results from inadequate blood flow from the mother to the fetus and therefore can result in IUGR with associated LBW⁶¹. The greatest impact on adult BP appears to be when IUGR happens synchronized with the period of nephrogenesis, which results in reduced

nephron endowment, reduced renal mass and increased protein excretion, pointing to the key role of the kidney in the programming of hypertension⁶¹. Interestingly, there seems to be sex-specific differences in the development of programmed hypertension in IUGR offspring⁷⁷. Ojeda et al demonstrated that while postpubertal male IUGR offspring maintained hypertension in adulthood, postpubertal female tended to normalize BP values⁷⁷. These findings suggest that estrogen has a protective role in the development of hypertension⁷⁷. In another study, Ojeda et al showed that testosterone contributes to elevations of MAP in postpubertal male IUGR offspring probably due to inappropriate stimulation of the RAAS and degradation of vasopressin in the hypothalamic-pituitary-adrenal axis⁷⁸.

Glucocorticoids are potent regulators of fetal growth, having the power to restrict it when blood levels are excessive⁶¹. Increased levels of glucocorticoids in fetal circulation can be achieved by diminished placental or maternal nutrient supply or by exposure to exogenous glucocorticoids, for example when the maternal active form crosses placental barrier due to deficit in 11- β -hydroxysteroid dehydrogenase type 2⁶¹. This exposure has effects on the kidney and on the kidney development that might lead to increased oxidative stress and activation of the RAAS⁷⁹. An animal study with sheep revealed that glucocorticoid exposure can result in nephron deficit and increased expression of renal sodium channels, which can lead to hypertension through limited glomerular filtration and potentially increased sodium reabsorption in the postnatal period⁸⁰.

4.4 Salt sensitivity and special populations

According to the American Heart Association, salt sensitivity is a physiological trait that in some individuals leads to BP changes that parallel changes in salt intake⁸¹, representing an independent risk to CV disease and mortality⁸². Therefore, considering a population with high salt intake, some individuals can excrete salt without increasing BP (salt – resistant, SR) while others (SS) cannot⁸³. Even though there is large interindividual variability and there is not an uniform definition or a standard diagnostic method, salt sensitivity prevalence is projected to be 25% in the general population and 50% in individuals with hypertension⁸⁴. Weinberger et al conducted a 27-year follow-up study of 430 normotensive and 278 hypertensive individuals and concluded that salt sensitivity is associated with a worse prognosis even for normotensive individuals, with an increased mortality risk ratio and similar cumulative mortality among normotensive and hypertensive groups⁸⁵. This authors had already suggested in a previous study that the SS individuals experience an accentuated increase in BP during life, compared to the SR ones⁸⁶. In

another long-term follow up study of 18 years, Mu et al investigated the effects of salt sensitivity on the development of hypertension in 310 adolescents (101 being SS and 209 SR) and established that SS participants had a higher incidence rate of hypertension than the SR ones⁸⁷.

There are several risk factors associated with salt sensitivity (physiological, environmental, genetic and demographic such as sex, race and age)⁸² which makes this phenomenon phenotypically heterogeneous⁸³. Salt sensitivity has been linked to ethnicity (specially people of African origins), obesity, kidney disease or LBW⁸⁶.

4.4.1 Ethnicity

BP among people of African origin (black) is indisputably higher than in people of European origin (white) with this ethnic difference presumably being explained by how the kidney handles sodium⁸⁸. A study hinted that the sodium retention found among black individuals was possibly imputable to an adaptive mechanism for regions with hot environments, where salt was a rarer resource⁸⁸. Nowadays, this mechanism is considered to be unfit, leading to increased extracellular fluid volume and hypertension⁸⁸. Moreover, plasma levels of renin and aldosterone are consistently lower in black people, with no appearing association between plasma renal activity and sodium intake⁸⁸. In fact, renin levels do not respond to the increase in sodium intake and volume depletion, but when sodium is reduced in black hypertensive subjects the decrease in BP is higher, suggesting that RAAS is suppressed as a compensatory mechanism to sodium retention⁸⁸. The ENaC is responsible for reabsorbing sodium exchanging it for potassium and plays a central role in the physiology of SS hypertension among black individuals as it represents a limitative factor for sodium reabsorption⁸⁹. Localized in the cortical collecting duct of the kidney, the expression of ENaCs is promoted by aldosterone and degraded by a ubiquitin E3 ligase protein⁸⁹. Mutations in the ENaC binding site prompt an overexpression since the degradation protein cannot bind and eliminate this channels resulting in sodium retention⁸⁹. Tu et al in a prospective observational study with black and white children assessed the role of aldosterone in regulating BP⁹⁰. It was demonstrated that the levels of aldosterone and renin were significantly lower in both black adults and children and that in black individuals, BP and plasma aldosterone levels had a significant association⁹⁰. Additionally, after 2 weeks of administration of an agonist of aldosterone, BP in white participants did not change while in black participants not only increased by around 5 to 6 mmHg but also higher levels of natriuretic peptides and weight were found, pointing towards a significant relation between BP and aldosterone levels⁹⁰.

4.4.2 Obesity

Visceral obesity is known to be related with hypertension and directly associated with sodium intake⁹¹. In 2009, Chen et al documented a positive and significant association between metabolic syndrome (for which obesity and insulin resistance are the most important risk factors) and SS hypertension⁹². In an early phase, obese individuals have an elevated GFR and renal blood flow which enhances sodium reabsorption and the maintenance of excessive weight leads to severe hypertension and loss of nephrons and kidney function⁹¹. The mechanisms that explain increased sodium reabsorption include the compression of kidneys due to excessive weight, the activation of SNS, overactivation of the RAAS and of the aldosterone/mineralocorticoid receptor system⁹¹.

The adipose tissue produces many RAAS components such as angiotensin II which will contribute to SNS activation and increase in sodium retention⁹³. An experimental study in male C57BL/6 mice showed a positive association between angiotensin II and SBP, with the adipose tissue representing a major source of angiotensin II in the development of hypertension linked with obesity⁹³. Aldosterone has a central role in electrolyte and fluid volume regulation and maintenance of BP while the complex aldosterone/mineralocorticoid receptor interfere in CV and renal disease⁹⁴. In obese individuals, hyperaldosteronism is correlated with the amount of adipocytes, independently of plasma renin activity⁹⁴. Rossi et al demonstrated an association between BMI and aldosterone in the overweight/obese group of this study, suggesting that a pathological connection between fat deposition and aldosterone secretion exists⁹⁵. Numerous studies suggested that adipocytes also release adipokines that promote aldosterone secretion from adrenal glands⁹⁴. Aldosterone can also act in the mineralocorticoid receptor promoting white adipose cell differentiation, leading to a selective adipocyte distribution⁹⁵. In the kidney, aldosterone acts as the ligand for the mineralocorticoid receptor that when activated causes podocyte injury with consequent proteinuria, glomerulosclerosis and proinflammatory compensatory mechanisms⁹⁴. In obese and spontaneously hypertensive rats, high levels of salt intake increase BP and exacerbate cardiorenal damage, that can be prevented by the use of mineralocorticoid antagonists⁹¹. Therefore, the activation of mineralocorticoid receptors induced by sodium intake may result in inappropriate aldosterone circulating levels and consequently contribute to SS hypertension⁹¹.

Activation of SNS is another mechanism that can lead to obesity induced hypertension. Obese hypertensive individuals often present with SS BP and increased renal SNS activity, indicating that these two mechanisms might be linked⁹¹. Moreover, pharmacological blockade of adrenergic activity and denervation of the kidneys reduce sodium reabsorption and BP⁹⁶. Leptin is a hormone with multiple roles, predominantly secreted by adipocytes that inhibits feeding behavior and

induces thermogenesis mediated through SNS⁹⁷. Leptin has been shown to increase sympathetic nerve activity in the kidneys and in the adrenal glands⁹⁷. Additionally, leptin has a clear association with BP independently of weight, with this relationship being more clear in children, thus suggesting an early role of leptin in inducing BP⁹⁷. Even though obese individuals exhibit high concentrations of leptin, the adipocyte mass remains relatively equal in most individuals, which suggests resistance to leptin's actions⁹⁷. However, in this individuals leptin effects on BP are maintained⁹⁷. Therefore, obesity leads to hyperleptinemia with selective leptin resistance that induces SNS activation and consequent hypertension⁹⁷.

4.4.3 Chronic Kidney Disease

CKD is often related with the presence of SS hypertension resistant to treatment, which further contributes to the evolution of kidney injury and CV disease in this group of patients⁹⁸. In a study with participants with CKD (not in dialysis) it was demonstrated that the salt sensitivity of BP increased as renal function declined⁹⁹. The mechanisms involved in SS hypertension in CKD are believed to include distal nephron sodium controlling changes induced by CKD itself, associated with renin-independent aldosterone secretion, activation of intrarenal RAAS, high sodium intake, metabolic acidosis and proteinuria-induced sodium reabsorption⁹⁸.

CKD induces changes in sodium handling in the distal nephron, causing sodium reabsorption that leads to hypertension but does not explain how CKD leads to SS hypertension⁹⁸. Aldosterone is mostly regulated by the presence of angiotensin II and plasma levels of potassium, however in some individuals with CKD and without hyperreninemia or hyperkalemia, hyperaldosteronism was present, resulting in hypertension and disease progression⁹⁸. These studies suggest that it is likely that in patients with CKD other factors can promote aldosterone secretion, with the candidates being metabolic acidosis, ET-1, adrenocorticotrophic hormone (ACTH), catecholamines, vasopressin and factors related with adipocytes⁹⁸.

In SS individuals, increased salt intake might promote sodium reabsorption, independently of the RAAS, by direct activation of the mineralocorticoid receptor, in opposition to SR individuals whereas increased salt intake promotes natriuresis and suppression of RAAS⁹⁸. This leads to renal damage that is associated with infiltration of macrophages and T lymphocytes, suggesting an immune mechanism¹⁰⁰. This immune mechanism is suggested to have a role in hypertension since immune-deficient mice are resistant to hypertensive stimulation and since in mice with high dietary salt intake but without T cells, BP did not increase as it did in the control group (high dietary salt intake and immunocompetent mice)¹⁰⁰.

Moreover, CKD conducts to chronic metabolic acidosis with diminished HCO_3^- and systemic pH levels¹⁰¹, which leads to the activation of compensatory mechanisms to increase the acidification of urine⁹⁸. Angiotensin II leads to enhanced HCO_3^- reabsorption and ammonium production in the proximal tubules, while aldosterone is responsible for increasing distal acidification of urine directly through activation of H^+ -ATPases and indirectly via sodium reabsorption mediated by ENaC ⁹⁸. The combined actions of angiotensin II and aldosterone lead to acid-base equilibrium but with augmented reabsorption of sodium in distal nephron⁹⁸. In 2014, Krupp et al conducted a study in 257 healthy children that showed a significant association between dietary renal acid load and increased BP¹⁰². In individuals with hypertensive nephropathy, studies have shown a reduction in BP with ACE inhibition and dietary acid intake restriction, giving further evidence on the association between metabolic acidosis and BP^{103,104}.

4.4.4 Low Birth Weight

It is thought that the relation between LBW and salt sensitivity of BP is caused by a shift in the pressure-natriuresis curve, which can be explained by several mechanisms such as congenital nephron deficit¹⁰⁵. As previously mentioned, nephron deficit can lead to hypertension due to compensatory glomeruli hyperfiltration and hypertrophy that, over time, results in a shift in the pressure-natriuresis curve and lower GFR in LBW¹⁰⁵. Uric acid can also incite a pressure-natriuresis shift due to microvascular renal injury¹⁰⁵. Knowing this, De Boer et al, led a research aiming to prove that LBW was associated with salt sensitivity of BP and to explore the association between LBW and the levels of uric acid¹⁰⁵. This study concluded that an inverse relation between birth weight and salt sensitivity of BP is present and regarding uric acid, a positive association was also found¹⁰⁵. Additionally, renal microvascular injury caused by elevated levels of fetal uric acid can result in nephron deficit, which along with a significant association between salt sensitivity of BP and uric acid found in this study, suggest that elevated levels of uric acid can be a risk factor for the development of SS hypertension¹⁰⁵. In 2008, Simonetti et al conducted a study with 50 children, 35 of them born with LBW and further showed that children with LBW had impaired kidney size, which was inversely related to salt sensitivity increase in BP¹⁰⁶. Even though reduced renal mass is not a clear indicator of GFR or number of nephrons, in this study, children born with LBW presented reduced GFR when compared to children with adequate weight for gestational age¹⁰⁶. Recently, Ruys et al led a cohort study that showed that in 16% of the children under evaluation, salt sensitivity of BP was associated with LBW, lower fat mass and BMI¹⁰⁷. Another mechanisms that can relate salt sensitivity of BP and LBW is endothelial dysfunction¹⁰⁷. Endothelial dysfunction can result from decreased vasodilation mediated by NO or insulin insensitivity, and might lead to an increase in renal vascular resistance and, as consequence, augmented BP¹⁰⁷.

4.5 Impact of salt on cardiovascular risk

In spite of the fact that the relationship between salt intake and BP is well recognized, the association between salt intake and CV events and mortality is controversial with prospective cohort studies demonstrating varying associations between salt intake and rates of CV events and death^{108,109}.

4.5.1 Evidence in adulthood

Using data from two randomized trials of hypertension prevention (TOPH I and II), a group of researchers examined how reducing sodium intake would affect CV health¹¹⁰. TOPH I evaluated the viability and effectiveness of non-pharmacological interventions (three life style interventions: weight loss, sodium reduction and stress management, and nutritional intervention with supplements of calcium, magnesium, fish oil and potassium) in decreasing BP in 744 participants with high to normal BP¹¹⁰. TOPH II assessed how weight loss and salt reduction affected incident hypertension and BP in 2382 participants¹¹⁰. Both TOPH I and II showed significant reduction among salt intake and BP¹¹⁰. On follow-up, data regarding CV events was obtained for 2415 individuals (77%) and, after adjustment for baseline characteristics, the analysis showed a significant estimated reduction in the relative risk for CV events of around 25%, between the sodium intervention and the control groups¹¹⁰. These studies concluded that a reduction in dietary salt may in fact reduce, not only BP levels, but also the long-term risk of CV events¹¹⁰. Furthermore, using the same data, Cook et al explored the association between salt intake and all-cause mortality rate and showed a linear relation between high sodium intake and mortality (for every 1g/day increase in salt intake, all-cause mortality increased 12%)¹¹¹. In a study with 3505 participants, published in 2015, the authors did not find an relation between salt intake and CV outcomes, but salt intake was significantly associated with all-cause mortality¹¹². These results may be explained by confounding factors that can underestimate the significance of an association, such as measurements errors, individual variability, and single measurements of baseline characteristics¹¹². A prospective study with 7543 adults (28 to 75 years) that had participated in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, did not find an association between urinary sodium excretion and the risk of coronary heart disease¹¹³. However, among hypertensive individuals or those with high levels of NT-proBNP, there was a higher risk of coronary heart disease associated with excessive sodium intake¹¹³.

4.5.2 Evidence during childhood

During childhood and adolescence CV events are very rare. Nonetheless, BP values have been reported to be associated with subclinical CV disease that can start during childhood and led to increased risk of adverse CV events during adulthood¹¹⁴

A review conducted by Emmerik et al summarized the existing evidence on the association between sodium intake in the beginning of life (first 6 months) and CV health outcomes later in life¹¹⁵. This review included 25 studies (18 human studies and 7 animal studies) and the authors concluded that higher amounts of sodium intake may in fact increase the risk for CV events later in life¹¹⁵.

Pulse wave velocity is considered the most accurate non-invasive method to assess arterial stiffness and has been associated not only to CV events but also to CV mortality, in adult studies¹¹⁶. Lurbe et al conducted a research, including children and adolescents with normal BP, high-normal BP and hypertension, and showed that pulse wave velocity was increased in the hypertensive and in the high-normal BP groups, demonstrating the presence of vascular function abnormalities at an early age¹¹⁶. The authors also reported that in obese individuals with high-normal BP or with hypertension, the increase in pulse wave velocity values was of less magnitude than in their normal weight counterparts, suggesting that the association of BP and arterial stiffness might be modified in the presence of obesity¹¹⁶. Seeking to prove that the well-known association of left ventricular mass and CV events in adulthood is also present in childhood and adolescence, Urbina et al completed an investigation with a total of 723 participants¹¹⁷. Left ventricular mass index was shown to be increased in the groups with pre-hypertension and hypertension; additionally diastolic function and lipid profile were better among the normotensive individuals¹¹⁷. High BP values in childhood have been reported to be associated with atherosclerosis later in life. A cohort study including 4210 participants showed that increased carotid intima media thickness was higher among individuals with persistently elevated BP, both in childhood and adulthood and among individuals with elevated BP in adulthood but normal values during childhood. Those with higher BP values during childhood but normal BP in adulthood did not have a significantly increased risk of higher carotid intima media thickness¹¹⁸.

Although some evidence exists on the association between childhood BP and CV events later in life, very few studies have tried to ascertain the impact of salt intake on the risk of subclinical or overt CV disease. Since the evidence for this association is very limited more well-designed studies, relating salt intake and CV events, with adequate follow-up periods are required in order to achieve stronger evidence regarding this issue.

5. Impact of strategies for dietary salt intake reduction

Dietary salt intake reduction can be achieved through different strategies such as public education, individual dietary counselling, food labelling, government policies and regulations, as well as sodium reduction in the food industry¹¹⁹.

Huang et al conducted a systematic review and meta-analysis with the goal of exploring the dose-response relation between diminished sodium intake and BP changes along with the impact of the duration of the intervention¹²⁰. This work analyzed 133 studies (including 12 197 participants) and demonstrated that after reduction in sodium intake, an overall mean change in 24 hour urinary sodium of -130 mmol (-145 mmol to -115 mmol, 95% CI) was observed, together with a mean change of -4.26 mmHg in SBP (-4.89 mmHg to -3.62 mmHg, 95% IC) and -2.07 mmHg in DBP (-2.48 mmHg to -1.67 mmHg, 95% CI)¹²⁰. The effect of reduction of sodium intake on BP was significant both among female and male participants, among hypertensive and normotensive groups, and in all ethnic groups¹²⁰. Overall, this work did not identify a relation between the duration of the intervention (salt reduction) and changes in BP, except that in trials with interventions lasting less than 15 days, the effect of sodium restriction in BP may possibly be undervalued¹²⁰. As stated by the authors, sodium reduction has benefits among normotensive participants, therefore it could be a significant element in delaying the development of hypertension with aging¹²⁰. He et al, in another systematic review and meta-analysis, this including 34 trials (3230 participants), reported that with long-term (4 weeks or more) modest (within the range of 2.3 to 7.0 g/day of salt, equivalent to 40 to 120 mmol) reduction in salt intake there were no significant difference in the concentration of plasma hormones (plasma renin, aldosterone, noradrenaline and adrenaline) or lipids (total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglycerides)⁴⁵. Differently, in short-term trials with important changes (for example, from 20 g/day to less than 1g/day for 4 to 5 days) in sodium intake, the concentration of plasma lipids and hormones was altered⁴⁵. Indeed, renin activity, aldosterone and noradrenaline levels increase, representing a compensatory response which occurs with the increase of extracellular volume and subsequently activation of RAAS and sympathetic nervous system⁴⁵. Likewise, Rhee et al concluded that long-lasting salt intake reduction is unlikely to be associated with increased plasma renin levels¹²¹.

Dietary sodium intake reduction can also have positive effects in the CV health, that can be independent or cumulative to the ones observed in BP¹²². Salt intake reduction can, for example, have a positive impact on the risk of stroke, left ventricular hypertrophy, renal disease and proteinuria¹²². Supporting this evidence, a 10-15 years follow-up study of TOHP I and II revealed

that the participants with prehypertension designated to the intervention group (individuals submitted to dietary sodium reduction) had a 25% to 30% reduction in risk of developing CV events¹¹⁰. Also, a study by Jablonski et al, demonstrated that macro and micro vascular endothelial dysfunction can be reversed in middle age/older individuals with elevated SBP by a dietary sodium reduction approach, through reducing oxidative stress and increasing bioavailability of NO and one of its cofactors, tetrahydrobiopterin¹²³.

In a cluster randomized trial (School-EduSalt), He et al analyzed if an educational program targeted at schoolchildren could decrease salt intake in children and their families¹²⁴. Children (n=279) from 28 primary schools in China (mean age of 10.1 years) and 553 adults (mean age of 43.8 years) participated in the trial for a period of 3.5 months¹²⁴. The intervention group was firstly educated about the harmful effects of salt and how to reduce its intake, and then the children presented the information to their families¹²⁴. The results demonstrated that salt intake decreased in the intervention group (both in the children and in the adults) and increased in the control group, with the differences between the two groups being of 1.9 g/day (-2.6 to -1.3 g/day, 95% CI) in children and of 2.9 g/day (-3.7 to -2.2 g/day, 95% CI) in adults¹²⁴. In the intervention group, SBP decreased 0.8 mmHg (-3.9 to -1.5 mmHg, 95% CI) in children and 2.3 mmHg (-4.5 to -0.04 mmHg, 95% CI) in adults, proving that educational programs are effective at reducing salt intake and therefore decreasing BP¹²⁴.

He and MacGregor published a meta-analysis in 2006 reviewing 13 trials in order to assess the effects of salt restriction in infants, children and adolescents on BP¹²⁵. In the 3 trials including infants (total of 551 participants), the median salt intake reduction was of 54 % and had a median duration of 20 weeks (extending from 8 weeks to 6 months)¹²⁵. The analysis showed a significant decrease in SBP of approximately - 2.47 mmHg (-4.00 to -0.94, 95% CI)¹²⁵. In the other 10 trials that comprehended children and adolescents (total of 966 participants), with a median age of 13 years (ranging from 8 to 16 years), the salt intake reduction was in median 42% and had a median duration of 4 weeks (extending from 2 weeks to 3 years)¹²⁵. The analysis showed a significant reduction in SBP of approximately -1.17 mmHg (-1.78 to -0.56, 95% CI) and approximately -1.29 mmHg (-1.94 to -0.65, 95% CI) in DBP¹²⁵.

6. Conclusions

Sodium intake is present among all cultures and countries worldwide. It is mostly consumed in processed foods and snacks, but it is also added to home cooked meals. Even though physiological quantities of sodium are required for the organism, in general, dietary salt intake is above the recommended values by WHO. This large consumption of sodium has negative effects in adults but also in children and adolescents. Several studies demonstrated that high dietary sodium intake is associated with higher values of BP. Children and adolescents with increased BP are at a higher risk of developing hypertension later in life, since BP follows a tracking pattern. Moreover, BP can be programmed depending on maternal and placental factors that control the in utero and postnatal environment. Hypertension prevalence is increasing, rendering this disease a global health problem. Sodium intake and BP during childhood are also known to be linked to CV events later in life but studies regarding this topic are limited. Yet there is enough evidence to suggest that prevention and treatment of hypertension are crucial to prevent CV events and CKD.

Taking into account that high sodium intake is related to hypertension and CV health, the amount of sodium ingested should be reduced in order to prevent these diseases. Programs targeting a reduction of sodium intake are cost-effective and have the potential to reduce the prevalence of CV diseases and consequently reduce health care costs.

7. Appendix

Table I: Recommendations for daily intake of sodium based on age groups. Adapted from ^{33,34,126}.

<i>“Dietary Guidelines for Americans 2020-2025”, U.S. Department of Health and Human Services³³</i>	
Age	Recommended Daily Intake of Sodium
6 – 11 months	0.37 g/day
1 – 3 years	1.2 g/day
4 – 8 years	1.5 g/day
9 – 13 years	1.8 g/day
≥ 14 years	< 2.3 g/day
<i>“Dietary Reference Intakes for Sodium and Potassium”, National Academies of Sciences, 2019¹²⁶</i>	
Age	Recommended Daily Intake of Sodium
0 – 6 months	0.11 g/day
7 – 12 months	0.37 g/day
1 – 3 years	0.8 g/day
4 – 8 years	1 g/day
9 – 13 years	1.2 g/day
14 – 18 years	1.5 g/day
<i>“Salt and Health”, Scientific Advisory Committee on Nutrition, 2003³⁴</i>	
Age	Recommended Daily Intake of Sodium
0 – 6 months	0.24 g/day
7 – 12 months	0.336 g/day
1 – 3 years	0.512 g/day
4 – 6 years	0.72 g/day
7 – 10 years	1.224 g/day
11 – 14 years	1.632 g/day
≥ 15 years	2.4 g/day

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