Scoping Review

Nutrigenetics and Nutritional Strategies in Systemic Arterial Hypertension: Evidence From a Scoping Review

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Nutrition and genetics have individual roles in systemic arterial hypertension (SAH); however, they can interact, influencing the regulation of blood pressure (BP) levels. The aim of this study was to evaluate the available evidence regarding gene–nutrient interactions in modulating BP levels in adults with SAH. The review followed the recommendations of the Joanna Briggs Institute and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews. Twelve studies met the inclusion criteria for this review, reporting on 20 genes and 31 single nucleotide polymorphisms (SNPs), with 19 of them associated with BP variations. The most frequently evaluated SNPs were ACE *rs4646994 and* AT1R *rs5186. Among the nutritional interventions, dietary sodium content was the focus of most studies (n = 11). Interactions with sodium consumption were observed for the following SNPs:* KDM1A *rs587168,* EDNRB *rs5351,* LSS *rs2254524,* IRS1 *rs1801278,* KCNK9 *rs6997709,* ACE *rs4646994,* GNB3 *rs5443,* PPARG *rs4684847,* EDN1 *rs5370,* BCAT1 *rs7961152,* IL18 *rs5744292,* NOS3 *rs2070744, and* AT1R *rs5186. In the presence of a diet rich in fruits and vegetables, moderate alcohol consumption, and reduced sodium intake, the SNP* AT2R *rs11091046 was associated with a decrease in BP levels. Furthermore, the SNP* MTHFR *rs1801133 exhibited an interaction with riboflavin supplementation in affecting BP levels. The evidence regarding the interaction between genetics and diet on BP levels remains limited. Among the existing findings, an interaction was observed between sodium, calcium, riboflavin, and specific polymorphisms; however, the underlying mechanisms for these interactions have yet to be identified. Note: This paper is part of the Nutrition Reviews Special Collection on Precision Nutrition.*

Key words: *systemic arterial hypertension, blood pressure, diet, genetic polymorphism, gene-nutrient interaction.*

INTRODUCTION

Chronic noncommunicable diseases account for 74% of annual global mortality. Among these, the silent epidemic of systemic arterial hypertension (SAH) is particularly noteworthy, contributing to 19% of global premature death, with an even more pronounced impact in middle- and low-income nations.[1,2] Systemic arterial hypertension, characterized by clinical blood pressure (BP) levels readings of ≥140/90 mmHg,[3] represents an independent risk factor for cardiovascular and renal diseases, early decline in work capacity, a higher burden of disability-adjusted life-years, and premature mortality.[4]

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Systemic arterial hypertension arises from a combination of lifestyle and genetic factors.[5,6] Adopting unhealthy eating habits, such as high-energy diets and excessive alcohol and sodium intake, while not getting enough potassium, are classic examples of how diet directly contributes to the risk of developing or exacerbating this condition.[5]

Numerous studies, including those using the genome-wide association approach, have been dedicated to unraveling the intricate genetic underpinnings that influence BP regulation and their role in the development of SAH.[7–10] These efforts have yielded significant insights by identifying genes linked to BP control, revealing that genetic factors contribute to approximately 20% to 30% of BP variation.[6,7] These findings underscore the importance of understanding the interplay between genetics and environmental factors, particularly diet, in the onset of SAH. Therefore, it is crucial to investigate this relationship, exploring potential associations or interactions between dietary patterns, nutrients, bioactive compounds, gene expression, and genetic polymorphisms.[5,7,8]

Dietary approaches, such as vegetarianism, the Mediterranean diet, and the Dietary Approaches to Stop Hypertension (DASH) diet, have demonstrated their effectiveness in lowering BP levels.[11–13] They are now included in guidelines for managing and controlling SAH in various countries. However, these recommendations were originally designed for the general population and may not account for individual variations in characteristics such as race/skin color, geographic location, and genetics.[3,14,15]

Nutrigenetics aims to explore minor variations in DNA nucleotide sequences that can modulate specific metabolic pathways, leading to varying nutritional requirements, responses to food intake, and susceptibility to chronic diseases. Among the genetic variations under scrutiny, single nucleotide polymorphisms (SNPs) are prominent. Single nucleotide polymorphisms are substitutions of a single nucleotide at a specific position in the DNA and are found in more than 1% of the population.[16]

To date, much of the research on nutrigenetics and SAH has primarily focused on exploring interactions between genetic polymorphisms and the consumption of sodium and potassium. Subsequent studies have delved into the effects of various foods and nutrients, including coffee, protein, and riboflavin.[17–20]

While there has been considerable progress in understanding the relationships between diet, genetics, and BP levels, research involving this trio in patients diagnosed with SAH remains limited. A substantial portion of the literature exploring this relationship stems from the GenSalt study,[21] which mainly included individuals of a single ethnicity (Chinese) and probands with SAH and their family members. Furthermore, the Prevention of Obesity Using Novel Dietary Strategies (POUNDS LOST) trial[20] involved North American participants, some of whom had SAH, while others did not.

The future of BP management in patients with SAH must extend beyond traditional medical and dietary approaches to encompass individual genetic variations. This approach will enable the development of more tailored nutritional strategies for the personalized treatment of this condition and the promotion of overall health. However, the limited research in this field remains a substantial constraint, underscoring the need for increased investment in this area to enhance the quality of evidence. Currently, there is limited knowledge regarding the impact of the interplay between genetic variability and diet on optimizing outcomes for SAH control.

While conducting a preliminary search in major databases, no systematic or scoping reviews addressing the specific topic of gene–nutrient interactions in SAH management were found. This observation underscores the need for a comprehensive examination of the existing evidence in this area. Therefore, this scoping review aimed to thoroughly assess the available evidence regarding the interplay between genes and nutrients in the regulation of BP among individuals diagnosed with SAH.

Specifically, the objectives were to identify genetic variants associated with responses to nutritional interventions or the consumption/supplementation of specific nutrients and their underlying mechanisms. Additionally, this scoping review intended to explore how habitual dietary patterns and nutritional interventions impact BP control in relation to genetic polymorphisms. The primary research question was as follows: Which genetic polymorphisms may influence clinical biomarkers related to SAH in response to various diets and nutritional interventions in adults and the elderly? By addressing this question, the aim was to bridge the current knowledge gap, focusing on the intricate relationship between genetic variability and the effects of dietary interventions on BP regulation in patients diagnosed with SAH.

METHODS

Protocol and registration

This scoping review was conducted following the recommendations of the Joanna Briggs Institute[22] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).[23] The comprehensive protocol for this

review was registered in the Open Science Framework (OSF) on April 14, 2023, and is accessible via the following link: https://osf.io/kp3qa/. The Digital Object Identifier (DOI) record for this protocol is DOI: 10.17605/OSF.IO/KP3QA.

Eligibility criteria

Inclusion. Both experimental and observational studies were included, as well as systematic reviews provided they were relevant to the research question and focused on the target population of adults aged 19 years or older with a diagnosis of SAH.

Exclusion. The following types of studies were excluded: those involving animals, in vitro with cells or tissues; narrative reviews, opinion articles, editorials, letters, conference or congress summaries, and case reports; those focused on other types of hypertension; that did not provide separate results for individuals diagnosed with SAH or over 19 years of age; and that were unavailable in full or had data that could not be extracted, even after attempting to contact the authors.

Search strategy

The search strategy was initiated on March 1, 2023, in the MEDLINE database to identify relevant articles and gather key words and common terms for describing the conditions under study. Key words, descriptors, and terms extracted from the titles and abstracts of selected articles in this preliminary phase were used to create a specific search strategy for MEDLINE (Table S1).[24–35] This search strategy was adjusted, incorporating all key words and indexing terms, as needed for other databases. Furthermore, a supplementary search was conducted by analyzing the reference lists of included articles.

A comprehensive search for relevant articles was conducted on March 15, 2023, in the following databases: PubMed, Embase, Science Direct, Web of Science, Scopus, ClinicalTrials.gov, Brazilian Registry of Clinical Trials (REBEC), and Google Scholar, without restrictions on publication date or language.

Selection of studies/sources of evidence

A systematic and rigorous selection of studies and sources of evidence was conducted. Initially, all search results were organized into folders corresponding to their source database. Subsequently, Mendeley (Elsevier, Amsterdam, NL) reference management software[36] was used to identify and remove duplicates. The same procedure was followed using Rayyan software,[37] which was also used in later stages to ensure blinded review by the evaluators. After de-duplicating the records, 2 reviewers (L.C.H. and P.N.B.-L.) independently assessed the titles and abstracts of the articles. Any discrepancies in their evaluations were resolved by consulting a third reviewer (G.B.S.D.).

After completing the initial screening, the selected studies underwent a detailed review of their full versions by both reviewers, following the same independent process. Once more, the third reviewer assisted in resolving discrepancies. During this second stage, a thorough assessment was conducted based on the inclusion and exclusion criteria. Any exclusions were documented along with the reasons, which were included in the results of this review.

Data extraction

Data extraction was independently performed by both reviewers and recorded in Excel spreadsheets (Microsoft Corporation, Redmond, WA, USA). These spreadsheets included the following key topics: author and year, title, study design, objectives, population, dietary assessment methods, nutritional interventions, presence of diseases, medication use, evaluated SNPs, genotyping results, statistical analyses, observed outcomes, results, limitations, and conclusions (Table S2). Any discrepancies between the independent reviewers during data extraction were resolved through discussions involving the third reviewer.

To summarize the results, the studies were categorized based on the type of nutritional intervention and the evaluated genes or SNPs.

RESULTS

Selection of evidence sources

The results of the search and study selection process are depicted in Figure 1. Initially, 3233 articles were obtained from the search, and following the elimination of duplicates, 2186 articles remained. These were subjected to the initial screening of the titles and abstracts, which resulted in the selection of 118 articles for thorough examination. Subsequently, 12 articles aligned with the inclusion criteria were chosen for the review. Details concerning the exclusion of 107 articles and the associated reasons can be found in Table S3.[S1–S106]

Summary of results

Characteristics of the studies. The summary of the primary characteristics of the included studies is presented in Table 1. The temporal scope of these studies spans

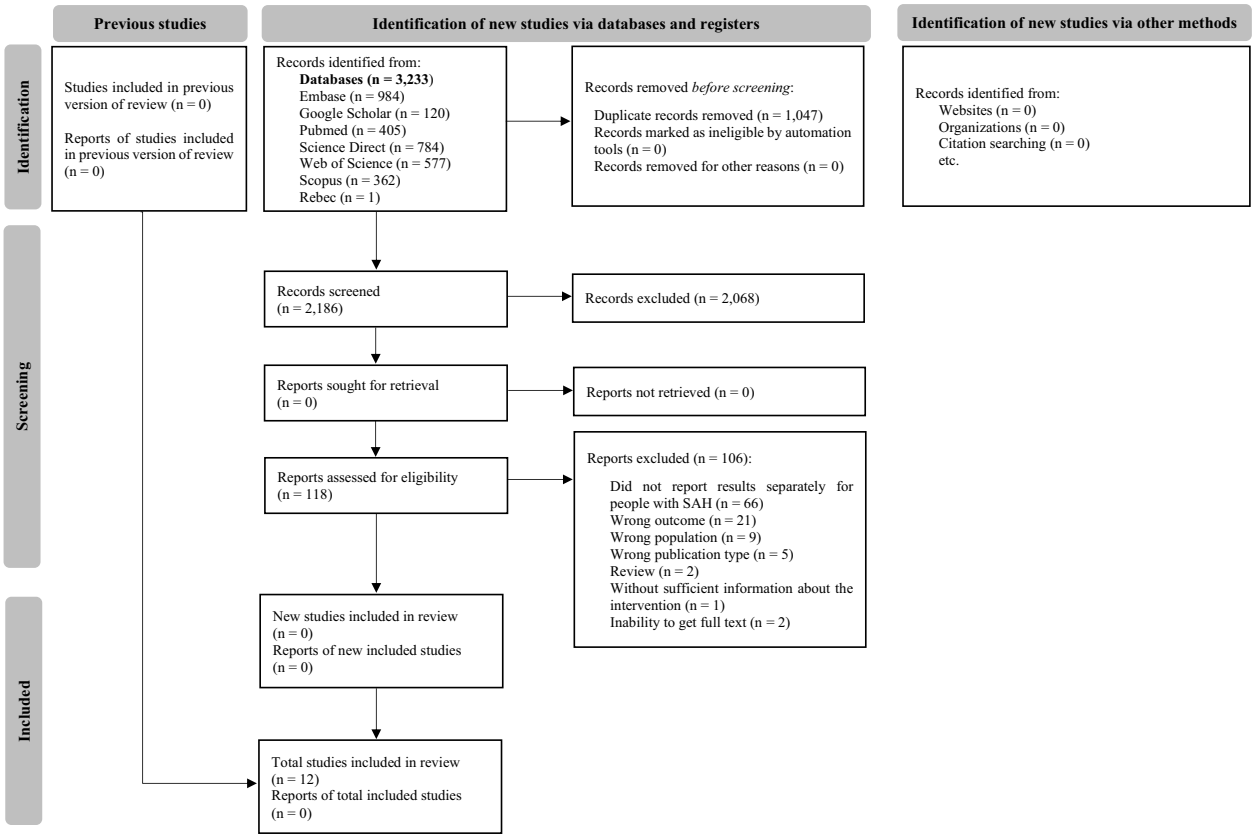

Figure 1. Flowchart of the Search Strategy and Inclusion and Exclusion of Studies. *Abbreviation:* SAH, systemic arterial hypertension

from the year 2000[24,25] to 2016.[26] These studies were conducted in 8 different countries, with 6 of them taking place in Europe,[24–29] 4 in North America,[30–33] 1 study in Asia,[34] and 1 study in Africa.[35] In terms of study design, 6 (50%) of them were longitudinal studies,[24–26,28,30,34] 3 (25%) were randomized clinical trials,[29,31,32] 2 (16.7%) were double-blind randomized clinical trials,[33,35] and 1 (8.3%) was a case-control study.[27]

Participant characteristics. The studies collectively assessed a total of 1648 participants who had been diagnosed with SAH. Information on the skin color of the participants was available in 60% of the studies. Among these, 4 studies were conducted with White individuals,[24,27,30,31] 1 with individuals of Asian descent,[34] 1 with Black individuals,[35] and another study included both White and Black participants.[32] Sex distribution among participants was fairly even, with men comprising 57.7% ($n = 702$) of the sample in studies where sex was identified ($n = 1217$), whereas women made up 42.3% ($n = 515$) of the participants. However, in 2 studies, this information was not available.[26,28] The mean age of participants with SAH was 53.1 ± 12.56 years, with a range spanning from 25.6 to 69 years. The smallest study included 28 participants,[33] while the largest involved the evaluation of 722 participants.[32]

Genes, SNPs, and responses to interventions. Twenty different genes were examined in the selected studies. Among these, only polymorphisms in angiotensin I converting enzyme (*ACE*), angiotensin II receptor type 1 (*AT1R*), and angiotensinogen (*AGT*) were found to be shared in 2 or more studies.[25,29,31,32] None of the included studies evaluated BP genetic risk scores. A total of 31 SNPs were examined across the 12 articles. The polymorphism *ACE* rs4646994 was assessed in 3 studies,[27,31,32] and the SNP *AT1R* rs5186 was also investigated in 3 studies.[25,27,31] While there was diversity in the number of SNPs studied, only 19 of them showed significant associations with BP. Among these, 7 were linked to SBP, 5 to diastolic BP (DBP), and another 7 to both SBP and DBP, as illustrated in Figure 2.

The most frequently applied intervention consisted of manipulating dietary sodium content.[25–35] Other interventions tested were based on changes in the content of other nutrients, such as calcium, potassium, magnesium, and riboflavin supplementation, and guidance on healthier eating habits.[29,34,35] The shortest intervention period was 6 days,[27] and the longest was 270 days.[32]

Table 1. Main Characteristics of Studies on Gene–Nutrient Interactions in the Modulation of Blood Pressure Levels in Individuals With Systemic Arterial Hypertension Included in the Scoping Review

Study (year)	*n*	Design	Country	Race	Age, y	Nutritional intervention	Intervention time, d	Gene/polymorphism	Results
Williams et al (2012)[30]	63	L	USA	Caucasian, Black, Amerindians	45.8 ± 1.4	High-Na diet: 200 mmol/d Low-Na diet: 10 mmol/d	7	*KDM1A* rs587168 and rs671357	rs587168: Individuals carrying the minor allele (*CC*) had ↑ variation in SBP in response to the high-Na diet
Caprioli et al (2008)[27]	104	CC	Italy	Caucasian, Europeans	NM	Normal Na levels: 150 mmol/d + infusion of 2 L physiological solution + furosemide (3 doses) the next day	6	*EDNRB* rs5351, *ACE* rs4646994, *AGT* rs699	Both SNPs associated with BP *EDNRB* rs5351 *GG* genotype related to Na sensitivity and showed ↑ risk of SAH *AGT* rs699 *TT* genotype was more frequent in individuals with SAH
Pescatello et al (2007)[31]	50	RCT	USA	Caucasian	40.5 ± 2.3	High-Ca diet: ≥880 mg/d Low-Ca diet: ≤880 mg/d Co-intervention: differentiated levels of physical exercise		*ACE* rs4646994, *AT1R* rs5186	Low-Ca diet: ↓ SBP for all *ACE* rs4646994 genotypes. AA homozygotes for *AT1R* rs5186 showed less ↓ of SBP than those carrying the C allele High-Ca diet: *DD* homozygotes for *ACE* rs4646994 had ↓ in SBP and DBP; *AA* homozygotes for *AT1R* rs5186 had ↓ of SBP
Lanzani et al (2016)[26]	394	L	Italy	NM	44.9 ± 8.9	Reduced dietary Na intake	30	*LSS* rs2254524	*AA* homozygotes showed higher ↓ in SBP and DBP
Dziwura et al (2007)[28]	115	L	Poland	NM	27.5 ± 5.2	Normal Na diet: 100–120 mmol/d Low-Na diet: 10–20 mmol/d High-Na diet: 220–240 mmol/d	7	*IRS1* rs1801278	Individuals with the *GA* genotype showed ↑ of MBP and MNBP with high-Na diet *GG* homozygotes had ↑ in MBP and MDBP and ↓ in MNBP with a high-Na diet
Kostis et al (2013)[32]	722	RCT	USA	White and Black	66.0 ± 4.7	Low-Na (<80 mmol/d) and low-energy diet	270	*EDN1* rs5370, *IL6* rs1800796, *BCAT1* rs7961152, *KCNK9* rs6997709, *ACE* rs4646994, *AT1R* rs5186, *RY2* rs2820037, *GNB3* rs5443, *EDN1* rs1937506, *PPARG* rs4684847, *MYBPC1* rs11110912, *NOS3* rs1799983, *IL18* rs5744292, *AGT* rs699, *ADD1* rs4961, *IL6* rs1800795, *TGFB1* rs1982073, *IL10* rs1800896, *IL18* rs187238	Association of 4 SNPs with SBP (rs6997709, rs4646994, rs5443, rs4684847) and 3 with DBP (rs5370, rs7961152, rs5744292) with low-Na diet

(continued)

Table 1. Continued

Study (year)	*n*	Design	Country	Race	Age, y	Nutritional intervention	Intervention time, d	Gene/polymorphism	Results
Wilson et al (2013)[29]	91	RCT	Ireland	NM	69.8 ± 7.0	Riboflavin supplementation (1.6 mg/d)	112	*MTHFR* rs1801133	*TT* homozygotes showed ↓ of SBP
Rayner et al (2012)[35]	78	DB RCT	South Africa	Black	60.4 ± 7.4	Changes in the amount of Na, K, Ca, and Mg	56	*GRK4* rs1024323 and rs2960306	↓ of BP after intervention for those carrying the C allele of rs1024323 and the G allele of rs2960306
Dengel et al (2007)[33]	28	DB RCT	USA	African American and Caucasian	NM	Diet 1: 20 mmol Na/d Diet 2: 200 mmol Na/d	8	*NOS3* rs2070744	↑ of DBP and MBP in individuals carrying the C allele and under high-Na diet
Spiering et al (2000)[25]	42	L	Netherlands	NM	NM	High-Na diet	7	*AT1R* rs5186	↑ of SBP in individuals with *AC* genotype
Poch et al (2000)[24]	352	L	Spain	White	52.0 ± 8.0	Diet 1: 20 mmol Na/d + placebo tablet Diet 2: 20 mmol Na/d + tablets with 240 mmol Na/d	7	*SCNN1G*C649G	No differences were observed in BP after the intervention
Kitaoka et al (2015)[34]	39	L	Japan	Japanese	NM	Diet with 2 servings of fruit and 5 servings of vegetables/d and moderate alcohol consumption, ↓ salt intake (2–3 g Na/meal)	150	*AT2R* rs11091046	Individuals carrying the C allele showed ↓ in DBP and SBP

Abbreviations: BP, blood pressure; Ca, calcium; CC, case-control; DB, double-blind; DBP, diastolic blood pressure; K, potassium; L, longitudinal; MBP, mean blood pressure; MDBP, mean daytime blood pressure; Mg, magnesium; MNBP, mean nighttime blood pressure; Na, sodium; NM, not mentioned; RCT, randomized clinical trial; SAH, systemic arterial hypertension; SBP, systolic blood pressure; SNP, single nucleotide polymorphism; ↑, increase; ↓, reduction.

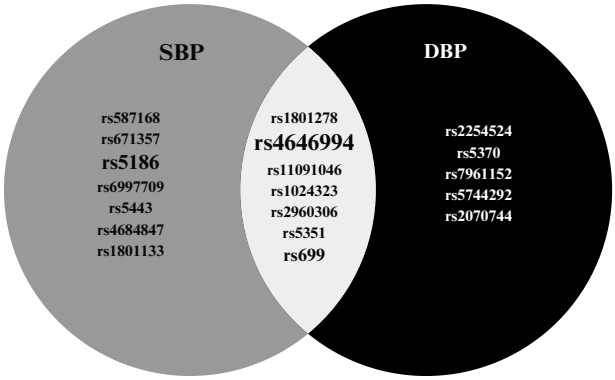

Figure 2. Diagram of SNPs Associated With BP in the Studies Included in the Scoping Review. SNPs identified with larger font sizes were reported more frequently in the studies. Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SNP, single nucleotide polymorphism

Among the studies that incorporated alterations in dietary sodium content and explored the influence of the polymorphism *ACE* rs4646994, no distinctions were detected in genotype distribution between individuals with sodium-sensitive and sodium-resistant SAH. Furthermore, there were no discernible differences, not even between individuals with SAH and those with normal BP levels. Additionally, there was no identified association of this polymorphism with either SBP or DBP.[27,32] However, in the context of a diet rich in calcium combined with physical exercise, individuals with the *DD* genotype experienced a reduction in both SBP and DBP. This effect was not observed in carriers of the I allele.[31]

Studies involving the SNP *AT1R* rs5186 and dietary sodium modifications yielded contrasting outcomes. In 1 study, individuals with the *AC* genotype exhibited higher SBP compared to the *AA* group after consuming a high-sodium diet for 7 days.[25] However, in another study that conducted a 9-month intervention, no association with BP was observed.[32]

Results from individual sources of evidence. In a study conducted by Williams and colleagues,[30] the relationship between dietary salt consumption and the activity of the enzyme lysine-specific demethylase 1 (LSD-1), previously linked to sodium-sensitive hypertension in animals,[38] was investigated. Individuals carrying the risk allele (*CC*) of the SNP rs587168 (A > C) in the lysine demethylase 1A gene (*KDM1A*) presented a more substantial reduction in SBP when consuming diets with varying levels of sodium (200 mmol sodium/d × 10 mmol sodium/d).

Caprioli and colleagues[27] conducted a study to investigate the influence of polymorphisms in the endothelin receptor type B gene (*EDNRB*), *ACE*, and *AGT* on sodium-sensitive hypertension in humans. Participants followed a diet with normal amounts of sodium along with a physiological solution infusion. Those with high sodium sensitivity exhibited a more significant increase in BP and a higher prevalence of the *GG* genotype of the SNP *EDNRB* rs5351 in comparison to those in the sodium-resistant group. The rs5351 was also linked to an increased risk of developing SAH. Additionally, the frequency of the *TT* genotype of the SNP *AGT* M235T rs699 was found to be higher among individuals with SAH in comparison to normotensive individuals, with no significant variation based on sodium sensitivity. In contrast, for the polymorphism *ACE* I/D rs4646994, no notable differences were observed in genotype distribution between participants with and without SAH. Overall, no associations were identified that would suggest synergistic effects between the evaluated genotypes.

Pescatello and colleagues[31] assessed the impact of calcium consumption and polymorphisms in genes associated with the renin-angiotensin-aldosterone system (RAAS) on BP response following physical activity. Participants were divided into 2 groups according to the mineral intake: a high-calcium-diet group (HighCa: ≥880 mg/d) and a low-calcium-diet group (LowCa: <880 mg/d). One SNP in *ACE* and another in *AT1R* were evaluated. When assessing the polymorphism *ACE* I/D, individuals in the HighCa group and carrying the I allele did not exhibit significant differences in SBP and DBP during periods without exercise, with exercise at 40% of maximal oxygen uptake (VO_{2max}) and at 60% of VO_{2max}. However, among individuals carrying the *DD* genotype, a notable reduction in SBP (7.5 mmHg) and DBP (4.5 mmHg) occurred following exercise at 60% of VO_{2max} compared with baseline (no exercise). In the LowCa group, for the *II/ID* genotype, SBP decreased by 5.7 mmHg after exercise at 60% of VO_{2max} compared with the non-exercise period. Among carriers of the *DD* genotype, a reduction in SBP (9.8 mmHg) was observed following exercise at 40% of VO_{2max}. For the SNP *AT1R* (A/C), individuals within the HighCa group carrying the *AA* genotype exhibited a reduction in SBP (6.9 mmHg) after exercise at 60% of VO_{2max} compared with baseline, with no significant differences in DBP. However, for carriers of the C allele, no notable changes were observed in SBP and DBP following exercise compared with baseline. Individuals in the LowCa group and carrying the *AA* genotype also experienced a reduction in SBP (7.5 mmHg) after exercise at 60% of VO_{2max} compared with the non-exercise period. In individuals carrying the C allele, a reduction in SBP (7.5 mmHg) was noted following exercise at 40% of VO_{2max} compared with baseline.

Lanzani and collaborators[26] investigated the influence of the SNP rs2254524 (A > C) in the lanosterol synthase gene (*LSS*) on the response of BP and endogenous ouabain to a diet low in sodium (<100 mEq/d) in individuals with SAH. Participants adhering to the low-sodium diet had a greater reduction in SBP (–5.17 mmHg) and DBP (–2.63 mmHg) compared with those nonadherent to the intervention. Individuals carrying the *AA* genotype adhering to a low-sodium diet had a significant reduction in SBP ($P = .005$) and DBP ($P = .071$) when compared with the other genotypes, with a considerable effect of the A allele. After the intervention, there was a significant increase in circulating endogenous ouabain ($P = .05$) in individuals carrying the *AC* and *CC* genotypes.

In the study conducted by Dziwura and colleagues[28] involving Polish participants with SAH, the investigation focused on the effects of diets with varying sodium contents (10–20, 100–120, and 220–240 mmol/d) on the frequency of insulin resistance and the impact of the SNP rs1801278 (G > A) in the insulin receptor substrate 1 gene (*IRS1*). When comparing participants carrying the *GA* and *GG* genotypes at baseline while consuming a diet with normal levels of sodium (100–120 mmol), no differences were observed in SBP and DBP. However, when these participants consumed a diet with high sodium concentrations (220–240 mmol/d), a significant increase in 24-hour BP and mean nocturnal BP was noted. In addition, only individuals carrying the *GA* genotype experienced an increase in the homeostatic model assessment of insulin resistance (HOMA-IR) after consuming high amounts of sodium.

Kostis and colleagues[32] conducted a study to investigate the association of polymorphisms with BP sensitivity to weight loss and sodium intake in 722 North American individuals with SAH, aged between 60 and 80 years. Participants were categorized into 4 distinct groups based on the presence or absence of obesity and the type of intervention carried out, primarily involving changes in body weight and sodium consumption. In the groups subjected to reduced sodium consumption, SBP exhibited a strong association with specific SNPs, including rs6997709 in the potassium two pore domain channel subfamily K member 9 gene (*KCNK9*), *ACE* rs4646994, rs4684847 in the peroxisome proliferator activated receptor gamma gene (*PPARG*), and rs5443 close to the G protein subunit beta 3 (*GNB3*) and cell division cycle associated 3 (*CDCA3*) genes. For DBP, the most notable association was observed with the SNP rs5744292 in the interleukin 18 gene (*IL18*), followed by rs5370 in the endothelin 1 gene (*EDN1*) and rs7961152 in the branched chain amino acid transaminase 1 gene (*BCAT1*).

Wilson and colleagues[29] evaluated Irish individuals with SAH who carried the *TT* genotype of the SNP rs1801133 (C677T) in the methylenetetrahydrofolate reductase gene (*MTHFR*) regarding the potential of riboflavin supplementation to lower BP levels over a 16-week intervention period. After the intervention, a notable reduction in SBP was observed in the riboflavin-supplementation group when compared with baseline (141.8 ± 19.4 mmHg × 137.1 ± 20.3 mmHg; $P = .003$). However, there was no significant difference in DBP for this group. In contrast, the placebo group did not exhibit any significant changes in BP levels.

Rayner and colleagues[35] conducted a study involving Black individuals from Cape Town, South Africa, focusing on the BP response to diets varying in micronutrient content. One group (intervention) received a diet with 41% less sodium, 826% more potassium, 388% more calcium, and 368% more magnesium compared with the control group over 8 weeks. Subgroups were created within each group based on the genotype for the SNPs A142V and R65L in the G protein-coupled receptor kinase 4 gene (*GRK4*). In the intervention group, a continuous decrease in BP was observed throughout the study. Among those carrying the C allele of the SNP A142V, higher mean daytime BP levels were noted, along with a smaller reduction in DBP and SBP compared with those with the *TT* genotype. Still, in the intervention group, individuals carrying the G allele of the SNP R65L exhibited a substantial reduction of 10.6 mmHg ($P = .004$) in SBP and 5.8 mmHg in DBP ($P = .006$), while no significant response was observed in the *TT* genotype group. The authors concluded that individuals carrying the C allele of the SNP A142V and the G allele of the SNP R65L are particularly responsive to nutritional interventions involving reduced sodium and increased potassium, calcium, and magnesium.

In the study led by Dengel and colleagues,[33] the investigation focused on the influence of the SNP rs2070744 (T-786C) in the nitric oxide synthase 3 gene (*NOS3*) on changes in renal hemodynamics and BP in response to varying salt loads in 28 Black and White men. These participants underwent an 8-day diet with 200 mmol/d of sodium followed by another 8-day diet containing only 20 mmol/d of sodium. The results revealed that individuals carrying 1 or 2 C alleles exhibited an increase in DBP and mean arterial pressure in response to the higher sodium load, an effect not observed in participants carrying the *TT* genotype. This effect was attributed to the inductive role of the SNP T-786C on the *NOS3* transcriptional activity. The C allele appeared to be associated with impaired nitric oxide (NO) production and a decrease in glomerular filtration rate (GFR). It is worth emphasizing that NO plays a significant role in blood vessel dilation, the stimulation of

hormone release, as well as the signaling and regulation of neurotransmission. However, the authors concluded that the response of BP levels to dietary sodium is influenced by many other genes and not solely by *NOS3*.

Similarly, Spiering and colleagues[25] investigated the influence of the SNP *AT1R* A1166C on the responsiveness to angiotensin II infusion in Dutch individuals with SAH who were consuming high sodium amounts. Initially, participants underwent 7 days of a high-sodium diet (220 mmol sodium and 80 mmol potassium/d). On the eighth day, they received increasing doses of angiotensin II (ranging from 0.3 to 3.0 ng/kg/min), under the hypothesis that carriers of the C allele would exhibit heightened responsiveness. Although SBP was higher in the individuals carrying the *AC* genotype compared with the *AA* group, no significant differences in BP responses to the supplemented doses of angiotensin II were observed between the genotypes. However, individuals carrying the *CC* genotype displayed higher GFR and plasma atrial natriuretic peptide levels, along with lower plasma aldosterone concentrations in comparison to individuals with the other genotypes (*AA* or *AC*). The authors concluded that the C allele of the SNP *AT1R* A1166C is associated with increased sensitivity to angiotensin II and, consequently, volume-dependent renal hypertension.

In contrast, no alterations in BP were noted in response to sodium intake in the study conducted by Poch and colleagues[24] involving Spanish individuals and the SNP C649G in the sodium channel epithelial 1 subunit gamma gene (*SCNN1G*). Participants with SAH were subjected to a high-sodium diet (260 mmol/d) for 7 days. Furthermore, no changes were observed in other assessed parameters, such as plasma renin activity, urinary albumin excretion, and plasma aldosterone concentration. These findings suggest that the SNP is not associated with the development of SAH, even though the function of this gene is linked to the net renal reabsorption of sodium in the distal tubules.

Finally, Kitaoka and colleagues[34] investigated the impact of the SNP C3123A in the angiotensin II receptor type 2 gene (*AT2R*) on the BP of Japanese men with SAH. This SNP influences the RAAS, potentially disrupting BP regulation. Participants underwent a 5-month intervention that prioritized lifestyle modifications, such as a diet rich in fruits, vegetables, and dairy products, along with moderate alcohol consumption. Additionally, they were provided with guidance on preparing meals with an average energy content of 600–700 kcal and a salt intake of 2–3 g per large meal. They also received medical and nutritional support, with regular consultations and group meals, in addition to engaging in physical activity sessions involving stretching, resistance training, and walking (targeting 10 000 steps/d). Individuals carrying the C allele exhibited a reduction in SBP and DBP compared with individuals with the A allele. Consequently, lifestyle modifications including dietary changes and physical activity were found to be beneficial for managing BP by affecting urinary salt excretion and contributing to weight and body fat reduction.

DISCUSSION

Given the high prevalence and associated risks of SAH, a comprehensive understanding of the mechanisms governing BP regulation is essential. Although a wide variety of genes and SNPs have previously been identified as factors in this regulation, the results from this scoping review show that little has been reported about the relationship between these SNPs and dietary factors, as well as their impact on BP levels.

In terms of genetic variation associated with SAH among different races, it is known that a few genetic loci exhibit substantial differences among races. These differences may stem from 4 key factors: (1) the absence of target variants in other ethnic groups, which can lead to variations in disease prevalence and drug response; (2) the presence of allelic heterogeneity; (3) differences in the linkage disequilibrium structure, which can affect genetic susceptibility to SAH; and (4) gene–gene and gene–environment interactions, which involve complex interactions between multiple genes and influence the risk and management of SAH. Therefore, caution is necessary when attributing BP control or SAH solely to genetic susceptibility. Furthermore, meta-analysis studies have revealed that many loci identified as associated with these parameters are common among Europeans, East Asians, and South Asians.[39–43]

While the scientific literature consistently reports positive outcomes associated with alterations in dietary patterns for BP control,[44,45] it is noteworthy that the majority of studies have primarily focused on changes in dietary sodium levels.[24–27,30,31,33] A notable finding is that those incorporating a broader spectrum of micronutrient adjustments in their interventions yielded more significant reductions in BP.[35] Micronutrients play a crucial role in BP regulation, affecting various pathways, including modulation of the sympathetic nervous system, the RAAS, vascular function, diuretic effects, and antioxidant/anti-inflammatory properties.[46] The role of sodium was notably emphasized in 9 out of the 12 studies, while studies incorporating micronutrients were limited. This underscores the importance of considering a broader range of micronutrients in interventions aimed at managing BP.

A recent systematic review indicates that adherence to a low-sodium diet presents challenges encompassing

individual, therapeutic, and social factors, with less than 50% of individuals with heart conditions able to maintain good adherence.[47] In contrast, systematic reviews and meta-analyses underscore the efficacy of dietary pattern–based nutritional strategies, which yield positive outcomes in BP control for both individuals with and without SAH, even in the long term.[48–50] One key reason behind the superiority of dietary pattern modifications is that diets consist of a complex interplay of foods rather than isolated nutrients. Furthermore, individuals who follow healthier dietary patterns are more likely to adopt a healthy lifestyle, including regular physical exercise and maintaining a healthy weight, which are factors strongly linked to BP regulation.[51]

Some of the genes under study exert direct influence on the RAAS, including *ACE*, *AT1R*, *AGT*, and *AT2R*.[52] Modulating the expression of these genes has a significant impact on the signaling of aldosterone, the hormone responsible for enhancing sodium and water re-absorption in renal tubules.[53] When considering the interaction between the DASH diet and RAAS, evidence has shown improvements in renal blood flow, plasma renin activity, and aldosterone sensitivity to angiotensin II, all of which are critical components of RAAS and are influenced by the expression of the mentioned genes.[54] A systematic review with meta-analysis suggests that adherence to the DASH diet positively affects the reduction in SAH risk compared with low adherence to this dietary intervention.[55] However, limited research has explored the association between dietary patterns and SNPs related to the RAAS.

The studies included in this scoping review identified genes associated with vasoconstriction (*NOS3*, *EDNRB*, *EDN1*) and the inflammatory process, including transforming growth factor beta 1 (*TGFB*), and interleukins-1, 6, and 18 (*IL6*, *IL10*, and *IL18*). Among these, genes related to endothelin and the endothelin B receptor (*EDN1* and *EDNRB*) are responsible for maintaining vascular tone, while *NOS3* is involved in NO production, promoting vasodilation and directly influencing BP levels.[27] Genes associated with the inflammatory process encode proteins linked to the expression and activation of growth factors, interferon-gamma, and tumor necrosis factor alpha. These factors contribute to an increased and sustained inflammatory response and other characteristics associated with SAH, such as endothelial dysfunction, thrombogenesis, and fibrosis.[56,57]

This scoping review has some limitations. First, the evidence regarding gene–nutrient interactions in SAH is limited, as indicated by the small number of studies included in this review. Second, the included studies primarily focused on a restricted set of genes and dietary interventions, particularly modifications in dietary sodium. Moreover, only a few studies addressed specific racial groups, with just 1 conducted among Asian populations, thereby limiting the generalizability of the findings. Third, the studies varied in their objectives and outcome measures, making it challenging to compare and synthesize the findings.

Last, only a few studies delved into the underlying mechanisms of gene–nutrient interactions in SAH. The utilization of medications, particularly antihypertensive drugs, plays a pivotal role in BP regulation.[58,59] Nevertheless, in 6 studies, no information regarding the medication usage among the evaluated individuals was provided.[24,25,27,30,31,35]

Little information is available regarding drug–nutrient–genome interactions in the literature. Genes associated with cytochrome P450 (CYP) enzymes primarily govern drug metabolic reactions, making them some of the most studied.[58] Polymorphisms in CYP family genes can alter the rate of metabolism and serum concentration of drugs. Moreover, the response to diuretics may be linked to variants in the neural precursor cell expressed, developmentally downregulated 4-like (*NEDD4L*) and protein kinase C alpha (*PRKCA*) genes.[59] Challenges, such as study design and methods, the number of different alleles, variable frequency across populations, and the lack of validation of findings in large cohorts, hinder the development of usage recommendations.[58,59]

With these limitations in mind, consolidating all of the information in this scoping review could potentially enable the application of these findings in the field of disease prevention or treatment. Identifying a selected few SNPs that have demonstrated association with SAH could potentially contribute to improving the effectiveness of nutrigenetic tests. This could lead to more efficient and effective management of SAH in adults and elderly individuals, improving outcomes and reducing healthcare costs.

CONCLUSION

Considering all of these observations, the current scientific literature remains limited, leaving a significant gap to be addressed concerning potential gene–nutrient interactions and their mechanisms in BP control. More comprehensive studies in this area are imperative. As of now, certain genetic polymorphisms, such as *KDM1A* rs587168 and rs671357, *EDNRB* rs5351, *AGT* rs699, *ACE* rs4646994, *AT1R* rs5186, *LSS* rs2254524, *IRS1* rs1801278, *MTHFR* rs1801133, *GRK4* rs1024323 and rs2960306, *NOS3* rs2070744, *AT2R* rs11091046, *KCNK9* rs6997709, *GNB3* rs5443, *EDN1* rs5370, *BCAT1* rs7961152, and *IL18* rs5744292 have been associated

with clinical biomarkers related to BP responses to various nutrient and dietary interventions.

Author Contributions

L.C.H., C.C., and M.M.R. designed the research. L.C.H., P.N.B.-L., and G.B.S.D. conducted the research and analyzed the data. L.C.H., P.N.B.-L., and G.B.S.D. wrote the article. M.M.R. and C.C. critically reviewed the article. All authors read and approved the final manuscript.

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Conflicts of Interest

None declared.

Data Availability

Data sharing is not applicable to this article as no new data were generated. All data used in this scoping review were extracted from published studies included in the systematic search. The search strategy and eligibility criteria are fully reported in the methods section of this article.

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