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Associations of microRNA Gene Polymorphisms With Salt Sensitivity, Longitudinal Blood Pressure Changes, and Hypertension Incidence in the Chinese Population

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Keywords: blood pressure | gene polymorphism | microRNA | potassium | salt

ABSTRACT

MicroRNAs (miRNAs) are small endogenous RNA molecules that play an essential role in various disease processes including elevated blood pressure (BP). Although the effects of dietary salt and potassium intake on BP regulation have been established, their co-interaction with miRNAs are still unclear. The purpose of the current study was to explore the connection between miRNA gene polymorphisms and BP response to salt and potassium intake, and the relationship between miRNA gene polymorphisms and long-term BP changes and hypertension development. A total of 333 participants underwent a chronic sodium-potassium dietary intervention trial, which included a 3-day normal diet, followed by a 7-day low-salt diet, then a 7-day high-salt diet, and finally a 7-day high-salt with potassium-supplemented diet. This cohort was subsequently followed for up to 14 years. Single-nucleotide polymorphisms (SNPs) rs115254818 in miR-26b-3p, rs11191676 and rs2292807 in miR-1307-5p, and rs4143957 in miR-382-5p were significantly correlated with systolic BP (SBP) and mean arterial pressure (MAP) responses to high-salt intake, whereas rs11191676 and rs2292807 in miR-1307-5p exhibited significant associations with SBP response to potassium-supplemented diet. Furthermore, SNPs rs2070960 in miR-3620-5p and rs12364149 in miR-210-3p demonstrated significant correlations with diastolic BP and MAP alterations at 14 years of follow-up. Generalized linear mixed model analysis revealed a significant association between rs2070960 in miR-3620-5p and hypertension development over a 14-year period. Our study indicates that miRNA gene polymorphisms are pivotal in the salt and potassium sensitivity of BP, as well as in the longitudinal BP progression and hypertension incidence.

Trial Registration: ClinicalTrials.gov identifier: NCT02734472

Xi Zhang and Shi Yao contributed equally to this study.

1 | Introduction

The global prevalence of hypertension in adults aged 30–79 is approximately 33%. High systolic blood pressure (SBP ≥ 110–115 mmHg) leads to more than 10 million deaths worldwide annually [1]. Blood pressure (BP) is regulated by the complex physiological system, while being determined by both genetic and environmental factors [2]. High salt consumption is a long-known critical environmental factor affecting BP levels, with the phenomenon of elevated BP caused by excessive sodium intake being termed salt sensitivity [3]. Inadequate potassium intake is also a recognized risk factor for elevated BP. A recent clinical study found that replacing 25% of the salt in food with potassium reduced BP levels and the risk of fatal cardiovascular events [4]. Prior animal research studies demonstrated that insufficient potassium intake triggered tubulointerstitial damage and increased renin-angiotensin-aldosterone activity, which in turn promoted salt sensitivity [5]. Furthermore, certain genetic variants have been found to produce a marked effect in the BP changes induced by salt and potassium intake.

MicroRNAs (miRNAs) are a group of non-coding RNA molecules with a length of 19 to 25 nucleotides. miRNAs have a wide distribution throughout the genome and bind to the 3′-untranslated region (3′-UTR) of target mRNA transcripts to perform post-transcriptional regulatory functions [6]. Numerous studies have reported their regulatory roles in cell proliferation, differentiation, apoptosis, and lipid metabolism. In addition, miRNAs are pivotal for the physiological and pathophysiological processes in cardiovascular diseases, including atherosclerosis, arrhythmias, and hypertension [7, 8]. Research involving a spontaneously hypertensive rat model reported that miR-21 lowered BP by upregulating mitochondrial translation [9]. Functional experiments showed that miR-663 and miR-181a regulated renin expression by targeting the 3′-UTR of REN mRNA [10].

Genome-wide association studies (GWAS) are a valuable approach for determining genetic variations linked to the risk for complex diseases, with single-nucleotide polymorphisms (SNPs) being the most frequent variations in the genome [11]. Multiple studies demonstrated that SNPs in miRNAs could affect gene expression function by regulating the transcription of primary transcripts, the processing and maturation of pri- and pre-miRNAs, or targeted binding to mRNAs [12]. 3′-UTR SNPs in miRNA binding sites have been associated with various complicated human diseases, including cancer [13], rheumatic disease [14], and Alzheimer's disease [15]. A recent study identified that SNP rs41291957 located at the miR-143/145 locus modulated miR-143 and miR-145 expression, ultimately influencing the risk of coronary heart disease [16]. However, the specific biological mechanisms by which miRNAs SNP are involved in BP regulation have not yet been delineated at the population scale.

The current study conducted a dietary intervention trial to examine the relationship between miRNA-SNPs and BP response to sodium-potassium intake in participants from a Chinese cohort. Furthermore, we explored the associations of miRNA-SNPs with longitudinal BP progression and hypertension onset by conducting a 14-year cohort study.

2 | Methods

2.1 | Study Cohort

In 2004, 514 adults from 124 households in the rural areas of Shaanxi Province were enrolled in the Baoji Salt-Sensitive (SS) Study [17, 18]. Briefly, the inclusion criteria were Han nationality, 18 to 60 years of age, normotension or SBP between 130 and 160 mmHg, diastolic BP (DBP) between 85 and 100 mmHg, and no antihypertensive treatment. Participants who matched any of the following criteria were excluded: secondary hypertension, severe cardiovascular disease or diabetes mellitus, hepatic or renal dysfunction, alcoholism, or pregnancy.

From this cohort, 333 non-parental participants underwent a chronic sodium-potassium dietary intervention trial in 2004 to investigate the correlation between miRNA genetic variation and BP response to sodium-potassium intake. The general process of this trial is illustrated in Figure 1. More detailed information can be found in previous publications [17, 18]. This trial was divided into four phases: a 3-day normal diet with baseline measurements, a 7-day low-salt diet (3 g of NaCl or 51.3 mmol of sodium per day), a 7-day high-salt diet (18 g of NaCl or 307.8 mmol of sodium per day), and a 7-day high-salt with potassium-supplemented diet (4.5 g of KCl or 60 mmol of potassium per day based on a high-salt diet). Subsequently, the cohort was visited in 2009, 2012, and 2018 to examine the connections between miRNA-SNPs and long-term BP variation and hypertension development.

2.2 | BP Measurements and Definitions

BP was assessed on the right arm of the participant by a medical professional using a mercury sphygmomanometer according to the Korotkoff method. The participants were prohibited from drinking coffee, smoking, and exercising before the measurement. BP was measured thrice daily in basal period and on days 5, 6, and 7 of every dietary phase. The average of the nine BP values estimated at each phase was ultimately included in the study. Mean arterial pressure (MAP) was calculated as: MAP = DBP + (SBP − DBP)/3. Additionally, the following computations were performed to objectively estimate the contribution of salt and potassium intake on BP: BP response to low-salt = BP on low-salt diet − BP at baseline; BP response to high-salt = BP on high-salt diet − BP on low-salt diet; BP response to high-salt plus potassium = BP on high-salt with potassium-supplemented diet − BP on high-salt diet. Given the lack of universal consensus on the definition of the salt sensitivity of BP, subjects with a ≥5 mmHg increase in MAP from the low- to high-salt diet were classified as SS and those with a <5 mmHg increase as salt-resistant (SR) [18, 19].

2.3 | Urine and Blood Biochemistry Tests

On the third day of the basal period and the last day of each dietary phase, 24-h urine samples were collected, and urine volume was measured. The concentrations of urinary sodium and potassium were measured by Flame photometry. And the 24-h urinary sodium/potassium excretion values were calculated by

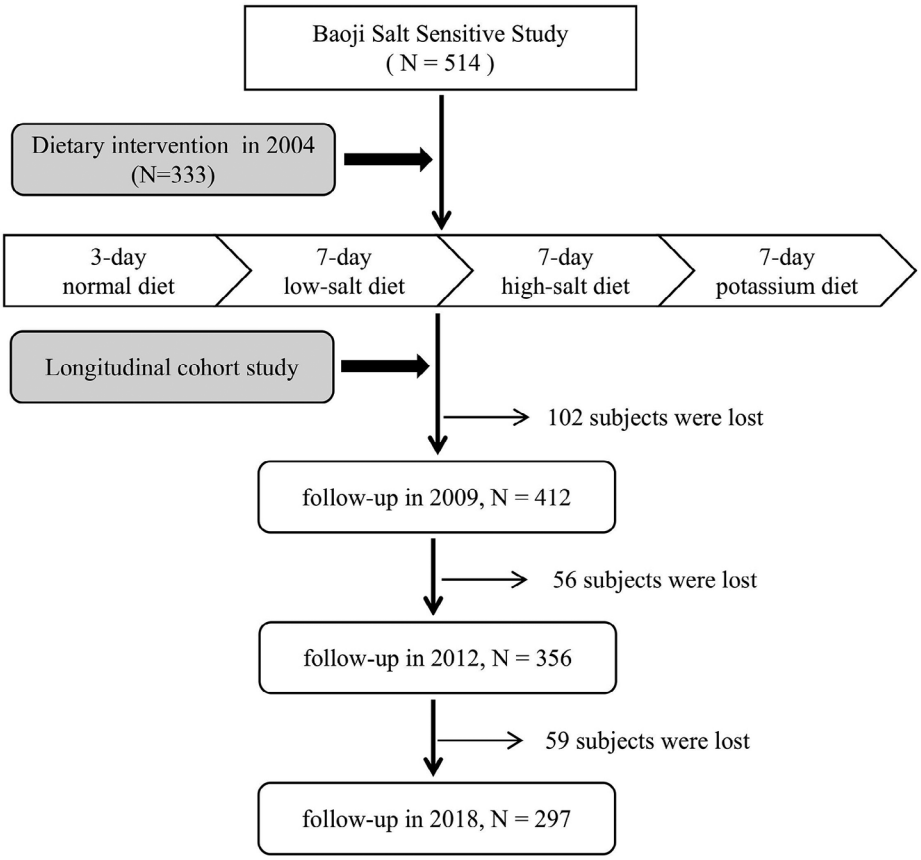

FIGURE 1 | The protocol of Baoji Salt-Sensitive Cohort Study. A cohort of 514 adults from 124 households in the rural areas of Shaanxi Province were enrolled in the Baoji Salt-Sensitive Study. A total of 333 non-parental participants underwent a chronic sodium and potassium intervention trial, including a 3-day normal diet, a 7-day low-salt diet, a 7-day high-salt diet, and a 7-day high-salt plus potassium diet. This cohort was subsequently followed up in 2009, 2012, and 2018.

multiplying the 24-h urine volume by its respective concentration. Additionally, 4 mL of venous blood was collected after fasting on the third day of the basal period and the last day of each dietary phase. After centrifuging the blood at 3000 rpm for 15 min, collected the supernatant and stored it at −80°C.

2.4 | SNP Selection and Genotyping

Twelve miRNAs linked to BP salt sensitivity were identified from the literature review. Further, we searched the National Center for Biotechnology Information and Genome Variation Server databases and screened the SNP sites in miRNA genes according to the following criteria: (1) frequency distribution of the SNP complies with Hardy–Weinberg equilibrium (HWE) at a p value of ≥0.05; (2) minor allele frequency (MAF) ≥0.05; and (3) linkage disequilibrium coefficient r^2 ≥0.8. Finally, 19 SNPs in 12 miRNAs were included for subsequent analysis: miR-3620-5p (rs2070960), miR-26b-3p (rs115254818), miR-15b-5p (rs10936201), miR-143 (rs4705342), miR-4638-3p (rs6601178), miR-1307-5p (rs11191676 and rs2292807), miR-210-3p (rs7935908, rs7395206, rs12364149, and rs10902173), miR-19a-3p (rs4284505), miR-382-5p (rs4906032, rs12886869, rs4143957, and rs77282763), miR-4508 (rs12439354), miR-423-5p (rs6505162), and miR-361-5p (rs62608229). DNA from peripheral venous blood was extracted utilizing the GoldMag-Mini purification kit, and miRNA-SNPs were genotyped using the MassARRAY platform.

2.5 | Statistical Analysis

Mean ± standard deviation was employed to indicate continuous values, whereas frequency and percentage were employed to represent categorical variables. The Student's t-test was utilized to compare data between two groups, while the analysis of variance was performed to compare data between various categories. p Value less than 0.05 indicates statistical significance. The above analyses were performed with the software SPSS 26.0. Further, HWE and Mendelian consistency tests were performed for SNP genotypes by PLINK software, and the MAF was calculated. After adjusting for age, sex, body mass index, and familial correlations, the PLINK software was used to conduct mixed linear regression analyses in three genetic models (additive, recessive, and dominant) to link each miRNA-SNP with BP response to salt or potassium dietary intervention and prospective BP progression. Lastly, the associations between each miRNA-SNP and hypertension onset were examined using generalized linear mixed models, with adjustment for multifactorial variables via R software. Bonferroni correction was used for adjustment of multiple testing.

TABLE 1 | Characteristics of study participants during dietary intervention trial.

	Proband	Sibling	Spouse	Offspring	Parent
Participants (*n*)	99	167	18	49	181
Gender (male/female)	69/30	81/86	5/13	24/25	88/93
Age (years)	41.8 ± 8.4	39.8 ± 7.4	47.4 ± 6.1	23.3 ± 6.9	66.1 ± 8.3
BMI (kg/m^2)	23.0 ± 2.8	22.2 ± 2.9	23.1 ± 4.7	20.1 ± 2.7	20.4 ± 2.6
BP at baseline (mmHg)					
SBP	120.9 ± 12.5*	107.6 ± 11.1	108.6 ± 12.2	102.7 ± 10.7	123.2 ± 21.3
DBP	79.0 ± 8.3*	70.1 ± 8.1	70.6 ± 6.9	63.4 ± 8.9	70.5 ± 10.5
MAP	93.0 ± 9.0*	82.6 ± 8.7	83.3 ± 7.9	76.5 ± 9.2	88.0 ± 13.1
BP response to low-salt diet (mmHg)					
SBP	111.7 ± 10.0*,&	103.4 ± 9.1&	102.5 ± 7.7&	100.3 ± 9.4&	—
DBP	72.8 ± 9.3*,&	66.4 ± 7.7&	67.1 ± 5.8&	60.7 ± 8.3&	—
MAP	85.7 ± 9.0*,&	78.7 ± 7.6&	78.9 ± 5.4&	73.9 ± 8.3&	—
SBP change	−8.65 ± 9.52*	−3.90 ± 5.41	−6.15 ± 7.88	−2.38 ± 4.79	—
DBP change	−6.00 ± 6.71*	−3.64 ± 4.83	−3.48 ± 6.36	−2.70 ± 5.21	—
MAP change	−6.88 ± 7.07*	−3.73 ± 4.55	−4.37 ± 6.52	−2.59 ± 4.56	—
BP response to high-salt diet (mmHg)					
SBP	118.9 ± 11.2*,#	108.5 ± 11.1#	108.4 ± 10.9#	102.0 ± 10.0#	—
DBP	76.2 ± 8.1*,#	68.7 ± 9.3#	68.6 ± 7.5	60.9 ± 8.3	—
MAP	90.4 ± 8.5*,#	82.0 ± 9.5#	81.9 ± 8.0#	74.6 ± 8.4	—
SBP change	7.16 ± 7.40*	5.09 ± 6.50	5.93 ± 7.90	1.72 ± 4.07	—
DBP change	3.49 ± 7.33*	2.29 ± 5.73	1.51 ± 4.69	0.22 ± 4.52	—
MAP change	4.71 ± 6.86*	3.22 ± 5.60	2.98 ± 5.61	0.72 ± 3.79	—
BP response to high-salt with potassium supplement diet (mmHg)					
SBP	112.2 ± 8.6*,§	103.1 ± 8.9§	102.8 ± 9.4§	101.0 ± 9.6§	—
DBP	73.0 ± 7.7*,§	66.1 ± 7.9§	65.9 ± 7.1	59.9 ± 8.0§	—
MAP	86.1 ± 7.4*,§	78.4 ± 7.8§	78.2 ± 7.2§	73.6 ± 8.1§	—
SBP change	−6.54 ± 5.65	−5.48 ± 5.86	−5.59 ± 7.10	−1.02 ± 4.15	—
DBP change	−3.21 ± 4.76	−2.63 ± 4.88	−2.69 ± 4.42	−1.02 ± 4.25	—
MAP change	−4.32 ± 4.40	−3.58 ± 4.77	−3.66 ± 5.05	−1.02 ± 3.35	—

Note: Continuous variables are expressed as mean ± SD.

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

*$p < 0.05$ versus the siblings, spouses or offspring.

&$p < 0.05$ versus the baseline period.

#$p < 0.05$ versus the low-salt diet.

§$p < 0.05$ versus the high-salt diet.

3 | Results

3.1 | Baseline Characteristics and BP Response to Dietary Intervention

Table 1 displays the basal characteristics of all participants and the BP changes following the salt and potassium dietary intervention. This study involved 514 participants, of which 99 were probands and 181 were the parents of the probands. At baseline, the probands had the highest DBP and MAP among all groups (i.e., 93.0 ± 9.0 mmHg and 79.0 ± 8.3 mmHg, respectively), while the SBP of the parent group was the most elevated at 123.2 ± 21.3 mmHg. During the sodium-potassium dietary intervention for the 333 non-parent participants, BP was altered at all intervention stages. The trend in BP level declined in the low-salt diet, ascended in the high-salt diet, and further declined in the potassium supplementation diet.

3.2 | Dietary Intervention Effects on 24-h Urinary Sodium and Potassium Excretion

The 24-h urinary sodium and potassium excretion values of the participants at baseline and during the dietary intervention trial

are presented in Table S1. The 24-h urinary sodium excretion during the low-salt phase was much lower than the basal excretion, while after the high-salt intervention, urinary sodium excretion elevated significantly. In addition, the 24-h urinary potassium excretion after potassium supplementation was significantly higher than before. The above data demonstrated that the participants exhibited good dietary adherence.

3.3 | Associations of miRNA-SNPs With BP Responses to Sodium and Potassium Intervention

As summarized in Table S2, 19 SNPs in 12 miRNAs were investigated in this study. The genotype distribution frequencies of these SNPs were in accordance with HWE ($p > 0.05$), demonstrating that the genomes of the participants were representative of the population.

Table 2 provides the results of the association analysis between the miRNA-SNPs and the BP changes induced by sodium or potassium intake. SNP rs12364149 in miR-210-3p was significantly correlated with SBP, DBP, and MAP responses to low-salt intake. After the high-salt diet, rs115254818 in miR-26b-3p was significantly correlated with SBP, DBP, and MAP responses, while rs11191676 and rs2292807 in miR-1307-5p showed significant correlations with SBP and MAP responses. Furthermore, rs4906032 and rs4143957 in miR-382-5p were significantly correlated with SBP response to high-salt intake. Following the potassium-supplemented intervention, rs115254818 in miR-26b-3p was significantly correlated with SBP and MAP responses, while rs11191676 and rs2292807 in miR-1307-5p were significantly correlated with SBP response. In addition, the subjects were classified into SS and SR groups according to the BP changes after salt intervention. As shown in Table S3, SNPs rs10936201 in miR-15b-5p and rs6505162 in miR-423-5p were significantly correlated with SBP and MAP responses to low-salt diet in the SS group, while rs10902173 in miR-210-3p was significantly correlated with DBP and MAP responses to high-salt diet in the SR group. After potassium supplement, rs62608229 in miR-361-5p was significantly correlated with BP responses in the SS group, while rs12364149 in miR-210-3p showed significant correlations with SBP response in the SR group.

3.4 | Associations of miRNA-SNPs With Longitudinal BP Progression and Hypertension Incidence

The characteristics of the cohort at baseline (2004) and follow-up visits (2009, 2012, and 2018) are displayed in Table 3. For 14 years of follow-up, average SBP, DBP, and MAP values elevated by 21.2, 7.9, and 12.3 mmHg, respectively. Furthermore, excluding the 51 participants with hypertension at baseline, 160 (53.9%) participants developed hypertension over the 14-year period.

Table 4 presents the correlations between miRNA gene polymorphisms and BP variations in the 5th year (2009), 8th year (2012), and 14th year (2018) of follow-up. SNP rs4906032 in miR-382-5p was significantly correlated with SBP variations over 5 years, 8 years, and 14 years. SNP rs7395206 and rs10902173 in miR-210-3p were significantly correlated with DBP and MAP changes over 8 years. At the 14th year of visit, rs2070960 in miR-3620-5p and rs12364149 in miR-210-3p demonstrated significant correlations with DBP and MAP changes. Further analysis of the correlation between miRNA-SNPs and the development of hypertension found that rs6505162 in miR-423-5p was significantly correlated with hypertension incidence at the 8-year visit, while rs2070960 in miR-3620-5p was significantly correlated with hypertension incidence over 14 years (Table 5).

4 | Discussion

In this dietary intervention trial, we identified multiple SNPs in miRNAs that were significantly correlated with changes in BP due to salt and potassium intake. Based on the 14-year follow-up period, several miRNA-SNPs exhibited significant associations with long-term BP variations and hypertension development. Our findings imply that miRNAs may be responsible for the salt and potassium sensitivity of BP and highlight the possible predictive value of miRNA gene polymorphisms for longitudinal BP regulation and hypertension onset.

According to the GenSalt study, approximately 32.4% of Chinese individuals exhibit salt sensitivity [20]. Both genetic and environmental variables are implicated in influencing the salt sensitivity of BP, with available evidence suggesting the crucial involvement of miRNAs in this phenomenon [21, 22]. For instance, previous animal studies showed that miR-133a bound to the 3′-UTR of angiotensinogen mRNA and attenuated high salt-induced BP elevation by inhibiting angiotensinogen expression [23]. Functional studies demonstrated that overexpressing the miR-429 transgene in the kidneys could alleviate hypertension in Dahl SS rats by improving the pressor-diuretic response and promoting urinary sodium excretion [24]. Based on bioinformatics prediction analyses, miR-23a targeted sodium-hydrogen exchanger 1 (a protein involved in sodium reabsorption and BP regulation) mRNA and repressed its expression [25]. For many years, the screening of candidate genes for salt sensitivity has mainly focused on genes associated with membrane sodium transport, abnormal sodium metabolism, and renal sodium excretion disorders. Currently, there is a lack of recognized evidence of pathogenic genes directly related to human SS hypertension. Our study showed that rs115254818 in miR-26b-3p, rs11191676 and rs2292807 in miR-1307-5p, and rs6601178 in miR-4638-3p were significantly correlated with BP responses to high-salt intake. Prior case-control research comparing the rs11191676-C allele in miR-1307-5p with the rs11191676-A wild-type allele revealed that the rs11191676-A wild-type allele was linked to a 1.424-fold higher risk of salt sensitivity [26]. Further bioinformatics analysis results indicated that the SNP rs6601178 in miR-4638-3p may affect the binding of early growth response protein 1, which functioned as a transcriptional regulator.

Dietary potassium intake is inversely correlated with BP, and potassium supplementation can lower BP levels in both hypertensive and normotensive individuals, a phenomenon called potassium sensitivity [27]. Similar to salt sensitivity, the potassium sensitivity of BP is a complex phenotype driven by environmental and genomic determinants along with their interactions. Genetic linkage results indicate that candidate genes in multiple chromosomal regions are associated with potassium intake, suggesting

TABLE 2 | Associations between miRNA-SNPs and BP responses to sodium and potassium intake.

miRNA	SNP	SBP response		DBP response		MAP response	
		β	*p*	*β*	*p*	*β*	*p*
Low-salt diet							
miR-3620-5p	rs2070960	−0.116	0.272	−0.148	0.160	−0.14	0.163
miR-26b-3p	rs115254818	0.192	0.067	0.193	0.069	0.210	**0.047**
miR-15b-5p	rs10936201	0.089	0.429	0.033	0.768	0.060	0.594
miR-143	rs4705342	0.041	0.609	−0.010	0.895	0.010	0.895
miR-4638-3p	rs6601178	0.367	**0.045**[b]	0.117	0.168	0.136	0.109
miR-1307-5p	rs11191676	−0.073	0.374	−0.041	0.612	−0.058	0.476
miR-1307-5p	rs2292807	−0.073	0.372	−0.038	0.634	−0.056	0.487
miR-210-3p	rs7935908	0.024	0.772	0.088	0.291	0.068	0.411
miR-210-3p	rs7395206	0.025	0.764	0.083	0.322	0.065	0.434
miR-210-3p	rs12364149	0.626	**0.040**[b]	0.227	**0.021**	0.202	**0.041**
miR-210-3p	rs10902173	0.005	0.950	0.121	0.154	0.082	0.332
miR-19a-3p	rs4284505	0.029	0.712	0.014	0.848	0.022	0.777
miR-382-5p	rs4906032	−0.098	0.426	−0.092	0.450	−0.103	0.402
miR-382-5p	rs12886869	−0.064	0.465	−0.097	0.271	−0.092	0.298
miR-382-5p	rs4143957	−0.089	0.303	−0.113	0.190	−0.113	0.191
miR-382-5p	rs77282763	−0.002	0.988	−0.272	0.089	−0.182	0.259
miR-4508	rs12439354	0.054	0.496	−0.005	0.947	0.019	0.805
miR-423-5p	rs6505162	0.075	0.451	0.004	0.965	0.035	0.726
miR-361-5p	rs62608229	0.046	0.733	−0.027	0.838	0.001	0.991
High-salt diet							
miR-3620-5p	rs2070960	0.129	0.231	0.132	0.213	0.140	0.186
miR-26b-3p	rs115254818	−0.266	**0.011**	−0.221	**0.035**	−0.254	**0.015**
miR-15b-5p	rs10936201	−0.048	0.671	0.045	0.685	0.012	0.909
miR-143	rs4705342	0.009	0.904	−0.066	0.412	−0.042	0.604
miR-4638-3p	rs6601178	0.022	**0.048**[a]	0.103	0.230	0.129	0.135
miR-1307-5p	rs11191676	0.400	**0.009**[b]	0.035	0.665	2.121	**0.034**[b]
miR-1307-5p	rs2292807	0.396	**0.010**[b]	0.043	0.599	2.104	**0.036**[b]
miR-210-3p	rs7935908	−0.041	0.623	−0.020	0.809	−0.029	0.722
miR-210-3p	rs7395206	−0.026	0.761	−0.015	0.853	−0.020	0.807
miR-210-3p	rs12364149	−0.239	**0.019**	−0.114	0.257	−0.170	0.091
miR-210-3p	rs10902173	−0.071	0.409	−0.075	0.381	−0.079	0.356
miR-19a-3p	rs4284505	−0.122	0.126	−0.049	0.531	−0.081	0.306
miR-382-5p	rs4906032	0.261	**0.048**[a]	0.076	0.537	0.136	0.271
miR-382-5p	rs12886869	0.118	0.190	0.084	0.339	0.103	0.244
miR-382-5p	rs4143957	0.250	**0.026**[a]	0.125	0.145	0.228	**0.040**[a]
miR-382-5p	rs77282763	−0.174	0.289	−0.024	0.880	−0.083	0.607
miR-4508	rs12439354	0.021	0.789	−0.026	0.736	−0.010	0.897
miR-423-5p	rs6505162	−0.144	0.154	−0.080	0.420	−0.111	0.269
miR-361-5p	rs62608229	0.041	0.764	−0.031	0.813	−0.006	0.963

(Continues)

TABLE 2 | (Continued)

miRNA	SNP	SBP response		DBP response		MAP response	
		β	*p*	*β*	*p*	*β*	*p*
High-salt with potassium supplement diet							
miR-3620-5p	rs2070960	0.047	0.659	−0.031	0.763	−0.001	0.985
miR-26b-3p	rs115254818	−0.281	**0.008**	−0.205	0.050	−0.262	**0.012**
miR-15b-5p	rs10936201	−0.212	0.066	−0.004	0.971	−0.092	0.413
miR-143	rs4705342	0.018	0.827	−0.103	0.198	−0.064	0.428
miR-4638-3p	rs6601178	0.085	0.336	0.086	0.314	0.096	0.267
miR-1307-5p	rs11191676	0.177	**0.034**	0.006	0.936	0.079	0.332
miR-1307-5p	rs2292807	0.183	**0.028**	0.011	0.891	0.085	0.298
miR-210-3p	rs7935908	−0.014	0.862	0.026	0.748	0.012	0.883
miR-210-3p	rs7395206	−0.011	0.898	0.022	0.785	0.011	0.894
miR-210-3p	rs12364149	−0.186	0.071	−0.148	0.138	−0.182	0.071
miR-210-3p	rs10902173	−0.012	0.884	0.010	0.905	0.001	0.984
miR-19a-3p	rs4284505	−0.253	**0.001**	−0.095	0.223	−0.174	**0.027**
miR-382-5p	rs4906032	0.137	0.274	−0.001	0.998	0.058	0.638
miR-382-5p	rs12886869	0.105	0.243	0.102	0.244	0.116	0.190
miR-382-5p	rs4143957	0.132	0.135	0.132	0.122	0.148	0.087
miR-382-5p	rs77282763	−0.244	0.139	−0.110	0.494	−0.180	0.267
miR-4508	rs12439354	−0.064	0.430	−0.036	0.642	−0.052	0.508
miR-423-5p	rs6505162	−0.158	0.122	−0.131	0.188	−0.158	0.115
miR-361-5p	rs62608229	0.013	0.924	0.092	0.487	0.070	0.604

Note: A total of 333 non-parental participants took part in the sodium-potassium dietary intervention trial and were included in the analysis. For associations that were not significant under any model, *β* and *p* values for an additive model are listed.

Abbreviations: DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; SNP, single nucleotide polymorphism.

The bold digits represent that the *p* value is less than 0.05.

[a]dominant model.

[b]recessive model.

TABLE 3 | Characteristics of the study participants during follow-ups in the longitudinal cohort study.

	Baseline in 2004	Follow-up in 2009	Follow-up in 2012	Follow-up in 2018
Participant (Male)	514 (267)	412 (208)	356 (185)	297 (155)
Age (years)	48.6 ± 19.8	53.3 ± 14.2	56.6 ± 19.0	62.3 ± 12.1
BMI (kg/m^2)	22.2 ± 3.1	22.4 ± 3.3	23.6 ± 3.5	24.6 ± 3.7
SBP (mmHg)	115.2 ± 17.6	120.0 ± 17.3	129.6 ± 18.7	136.4 ± 17.4
DBP (mmHg)	71.3 ± 10.0	75.8 ± 10.4	77.9 ± 10.9	79.2 ± 11.2
MAP (mmHg)	86.0 ± 11.5	90.5 ± 11.7	95.1 ± 11.9	98.3 ± 12.0
Fasting glucose (mmol/L)	4.8 (4.5–5.2)	5.1 (4.8–5.5)	5.1 (4.8–5.6)	5.0 (4.7–5.4)
Total cholesterol (mmol/L)	4.0 (3.6–4.6)	4.1 ± 0.8	4.2 (3.8–4.8)	4.6 ± 0.9
Triglycerides (mmol/L)	1.27 (0.9–1.8)	1.5 (1.1–2.0)	1.3 (1.0–1.9)	1.4 (1.0–2.0)
High-density lipoprotein (mmol/L)	1.2 ± 0.3	1.3 ± 0.3	1.3 (1.1–1.5)	1.3 (1.1–1.6)
Hypertension at baseline (*n*, %)	51 (9.9)	–	–	–
Hypertension incidence (*n*, %)*	–	77 (18.7)	103 (28.9)	160 (53.9)

Note: Non-normally distributed variables are expressed as the median (interquartile range). All other values are expressed as mean ± SD or *n*, %. Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

*Participants with hypertension at baseline were excluded.

TABLE 4 | Associations between miRNA-SNPs and BP changes in the longitudinal follow-up cohort.

miRNA	SNP	BP change (2004–2009)			BP change (2004–2012)			BP change (2004–2018)		
		SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
miR-3620-5p	rs2070960	0.486	0.311	0.813	0.756	0.673	0.684	0.178	**0.035**[a]	**0.041**[a]
miR-26b-3p	rs115254818	0.436	0.330	0.338	0.755	0.134	0.297	0.578	0.069	0.418
miR-15b-5p	rs10936201	0.763	0.695	0.705	0.553	0.240	0.320	0.212	0.777	0.428
miR-143	rs4705342	0.819	**0.048**[b]	0.995	0.621	0.838	0.896	0.564	0.981	0.783
miR-4638-3p	rs6601178	0.056	0.272	0.110	0.432	0.511	0.432	0.075	0.559	0.215
miR-1307-5p	rs11191676	0.609	0.787	0.679	0.591	0.990	0.780	0.415	0.296	0.301
miR-1307-5p	rs2292807	0.469	0.651	0.531	0.647	0.996	0.815	0.416	0.331	0.322
miR-210-3p	rs7935908	0.535	0.208	0.676	0.315	**0.039**	0.085	0.630	0.356	0.756
miR-210-3p	rs7395206	0.887	0.113	0.398	0.136	**0.024**	**0.037**	0.768	0.362	0.690
miR-210-3p	rs12364149	0.622	0.428	0.479	0.747	0.908	0.817	0.436	**0.034**[b]	**0.043**[b]
miR-210-3p	rs10902173	0.629	0.460	0.853	0.086	**0.027**	**0.029**	0.614	0.644	0.980
miR-19a-3p	rs4284505	0.339	0.797	0.530	0.974	0.328	0.580	**0.049**	0.102	0.051
miR-382-5p	rs4906032	**0.028**[b]	0.843	0.966	**0.002**[b]	0.180	**0.029**[b]	**0.004**[b]	0.496	**0.034**[b]
miR-382-5p	rs12886869	0.555	0.458	0.467	0.523	0.725	0.595	0.250	0.537	0.345
miR-382-5p	rs4143957	0.654	0.681	0.643	0.635	0.819	0.708	0.167	0.377	0.223
miR-382-5p	rs77282763	0.505	0.133	0.227	0.419	0.897	0.627	0.858	0.350	0.517
miR-4508	rs12439354	0.151	0.707	0.349	0.632	0.581	0.932	0.637	0.661	0.978
miR-423-5p	rs6505162	0.198	0.172	0.150	**0.019**	0.090	**0.029**	0.209	0.128	0.123
miR-361-5p	rs62608229	**0.032**	0.742	0.376	0.367	0.654	0.848	0.116	0.099	0.076

Note: For associations that were not significant under any model, β and p values for an additive model are listed.

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; SNP, single nucleotide polymorphism.

[a]dominant model.

[b]recessive model.

that genetic variation regulates BP phenotypes with potassium sensitivity [28]. GWAS investigations showed that each copy of the CDCA7 rs10930597-T allele was associated with reductions of 3.2 mmHg in DBP and 3.5 mmHg in MAP during potassium intervention. In addition, each copy of the rs16890334-C allele in the IRAKBP1 gene locus was linked with a decline of 5.4 mmHg in SBP during potassium intervention [29]. Gu et al. have also determined that the BP response induced by dietary potassium supplementation has moderate heritability in the Chinese population [30]. The GenSalt study identified that APLN and ACE2 genetic variations were closely related to the hypotensive response to potassium supplementation [31]. However, the relationship between miRNA gene polymorphisms and potassium sensitivity remains obscure. Our results showed for the first time that rs115254818 in miR-26b-3p, rs11191676, and rs2292807 in miR-1307-5p were significantly correlated with the decrease in BP after potassium supplementation. SNP rs115254818, rs11191676, and rs2292807 loci are also closely related to salt sensitivity, implying a common genetic mechanism for BP response phenotypes with sodium and potassium sensitivity.

The biological significance of miRNAs in the pathophysiology of hypertension has been recognized, and they participate in the BP regulation by modulating several molecular pathways. A previous case-control study found that miR-1283 might play a role in essential hypertension by targeting activating transcription factor 1 to modulate the ROS expression [32]. The positive correlations between mir-505 expression levels in human plasma and SBP and C-reactive protein concentrations have been reported by researchers. Subsequent in vitro experiments demonstrated that miR-505 mediated endothelial inflammation activation in a cellular autonomous manner, which might lead to endothelial dysfunction and, to some extent, elevated BP [33]. In addition, miR-124-3p was found to suppress angiotensin II-dependent hypertension via the downregulation of early growth response protein 1 [34]. However, few studies have focused on the potential miRNA regulation of long-term BP progression. The present study followed a Chinese cohort for up to 14 years and identified significant associations of rs2070960 in miR-3620-5p and rs12364149 in miR-210-3p with BP alterations. Interestingly, rs2070960 in miR-3620-5p was significantly correlated with the occurrence of hypertension in 14 years. Tian et al. found that miR-3620-5p inhibited monoamine oxidase B expression by binding to the 3'UTR of monoamine oxidase B mRNA, thus exerting a certain anti-atherosclerosis effect [35]. Exosomal miR-210-3p was found to promote atrial fibrosis in atrial fibrillation by inhibiting glycerol-3-phosphate dehydrogenase 1-like gene in atrial fibroblasts [36]. Our study provides a novel perspective on the potential role of miRNA gene polymorphic loci in long-term BP progression, and it appears that the regulation of inflammatory

TABLE 5 | Associations between miRNA-SNPs and hypertension incidence in the longitudinal follow-up cohort.

		Incident hypertension (2004–2009)		Incident hypertension (2004–2012)		Incident hypertension (2004–2018)	
miRNA	**SNP**	**OR (95%CI)**	***p***	**OR (95%CI)**	***p***	**OR (95%CI)**	***p***
miR-3620-5p	rs2070960	0.25 (−0.24 to 0.74)	0.304	0.02 (−0.42 to 0.47)	0.900	0.54 (−0.12 to 0.92)	**0.037**
miR-26b-3p	rs115254818	−0.02 (−0.59 to 0.51)	0.936	0.17 (−0.29 to 0.65)	0.458	−0.40 (−0.90 to 0.08)	0.109
miR-15b-5p	rs10936201	0.20 (−0.33 to 0.72)	0.438	−0.16 (−0.66 to 0.30)	0.498	−0.20 (−0.68 to 0.26)	0.396
miR-143	rs4705342	−0.08 (−0.48 to 0.30)	0.684	0.10 (−0.23 to 0.44)	0.525	0.02 (−0.33 to 0.38)	0.910
miR-4638-3p	rs6601178	0.28 (−0.11 to 0.68)	0.158	−0.06 (−0.42 to 0.28)	0.702	−0.11 (−0.48 to 0.25)	0.532
miR-1307-5p	rs11191676	0.27 (−0.10 to 0.66)	0.152	0.03 (−0.29 to 0.37)	0.824	0.11 (−0.24 to 0.47)	0.530
miR-1307-5p	rs2292807	0.29 (−0.08 to 0.68)	0.122	0.04 (−0.29 to 0.37)	0.805	0.12 (−0.23 to 0.48)	0.491
miR-210-3p	rs7935908	0.36 (−0.05 to 0.78)	0.090	−0.12 (−0.50 to 0.24)	0.517	0.15 (−0.23 to 0.54)	0.447
miR-210-3p	rs7395206	0.29 (−0.11 to 0.71)	0.159	−0.16 (−0.54 to 0.20)	0.388	0.11 (−0.27 to 0.50)	0.572
miR-210-3p	rs12364149	0.25 (−0.26 to 0.77)	0.328	−0.33 (−0.82 to 0.14)	0.176	−0.01 (−0.48 to 0.47)	0.973
miR-210-3p	rs10902173	0.31 (−0.10 to 0.74)	0.140	−0.11 (−0.50 to 0.26)	0.558	0.19 (−0.20 to 0.59)	0.339
miR-19a-3p	rs4284505	−0.07 (−0.44 to 0.29)	0.694	0.07 (−0.25 to 0.40)	0.658	0.01 (−0.33 to 0.34)	0.965
miR-382-5p	rs4906032	−0.01 (−0.64 to 0.58)	0.974	−0.15 (−0.70 to 0.37)	0.575	0.08 (−0.48 to 0.64)	0.776
miR-382-5p	rs12886869	0.31 (−0.10 to 0.72)	0.141	0.06 (−0.30 to 0.43)	0.738	0.19 (−0.18 to 0.59)	0.314
miR-382-5p	rs4143957	0.32 (−0.09 to 0.73)	0.124	0.10 (−0.25 to 0.47)	0.569	0.21 (−0.16 to 0.60)	0.278
miR-382-5p	rs77282763	−0.11 (−0.92 to 0.59)	0.766	0.23 (−0.39 to 0.86)	0.453	−0.02 (−0.73 to 0.68)	0.936
miR-4508	rs12439354	0.06 (−0.31 to 0.43)	0.750	0.18 (−0.15 to 0.51)	0.286	0.11 (−0.24 to 0.48)	0.518
miR-423-5p	rs6505162	0.14 (−0.34 to 0.61)	0.562	0.54 (−0.11 to 0.98)	**0.014**	0.31 (−0.12 to 0.76)	0.160
miR-361-5p	rs62608229	0.12 (−0.31 to 0.54)	0.561	−0.40 (−0.85 to 0.01)	0.060	0.03 (−0.34 to 0.42)	0.844

Note: Generalized linear mixed models were used to examine the associations between each miRNA-SNP and hypertension onset, after adjustment for age, sex, body mass index, and familial correlations.

Abbreviations: CI, confidence interval; OR, Odds ratio; SNP, single nucleotide polymorphism.

factors, oxidative stress molecules, and transcription factors plays a role, and further functional studies of these loci are needed.

A strength of this study is that it was focused on family lineage and performed in the Han Chinese population, thus reducing the possibility of bias due to population stratification. Another strength is that the strict monitoring of urinary sodium and potassium excretion ensured good compliance with the dietary intervention regimen and facilitated more reliable results. However, the present study has several limitations that need to be taken into account. The population investigated in this study was limited to rural Shaanxi, China. Thus, our results require validation in other ethnic populations. Moreover, only a limited number of salt sensitivity-related miRNAs were included in this study, and the analyzed SNP loci did not cover the entire length of miRNA genes. Therefore, more detection sites should be added in future research.

5 | Conclusions

Our population-based study on a chronic dietary intervention revealed significant correlations between miRNA genetic variations and BP responses to dietary sodium and potassium intervention, indicating that miRNAs might participate in the formation of salt and potassium sensitivity of BP. Furthermore, multiple SNP loci in miRNAs were significantly correlated with long-term BP changes and hypertension development during the 14-year cohort follow-up, suggesting that miRNAs may be implicated in longitudinal BP regulation.

Ethics Statement

The Academic Committee of the First Affiliated Hospital of Xi'an Jiaotong University approved the study protocol (code: 2015–128).

Consent

The present study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Each participant provided informed consent for the interventional experiment and subsequent follow-ups.

Conflicts of Interest

The authors declare that there is no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.