Association and Interaction Between Dietary Patterns and Gene Polymorphisms in Liangshan Residents with Hyperuricemia

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ABSTRACT

Background: Hyperuricemia (HUA) is caused by genetic and dietary factors. However, little is known about the ways in which diet and gene interactions influence HUA or the role of dietary patterns in HUA.

Objectives: We aimed to explore the association between dietary patterns and HUA as well as dietary patterns and gene interactions in HUA among the Yi ethnic group of China.

Methods: Food consumption information was collected using a semi-quantitative food frequency questionnaire. Vein blood samples were collected after overnight fasting from all participants and DNA was extracted from peripheral blood leukocytes. Dietary patterns were derived using factor analysis.

Results: The study included 2646 participants aged 18–88 years with a HUA prevalence of 26.8%. Three major dietary patterns were identified and shown to be associated with HUA prevalence, with meat-based diets having a higher association with HUA than plant-based or regionally specific diets. The frequency of the T allele at *ABCG2* rs2231142 and *SLC2A9* rs11722228 loci was higher in HUA than in non-HUA populations. An additive interaction between a meat-based diet and the rs2231142 locus was associated with the risk of HUA. The relative excess risks of interaction (RERI), attributable proportion of interaction (AP), and synergy index (S) were 0.482 (95% CI = 0.012,0.976),0.203 (95% CI = 0.033,0.374), 1.544 (95% CI = 1.012,2.355), respectively.

Conclusions: The meat-based dietary pattern was associated with an increased risk of

HUA. There was an additive interaction between a meat-based dietary pattern and the *ABCG2* rs2231142 locus in study participants. Individuals with the rs2231142 T allele had a higher frequency of HUA than those with the rs2231142 GG allele. Individuals with the rs2231142 T allele but a healthy dietary pattern could have a reduced HUA risk.

Keywords: dietary pattern; hyperuricemia; gene; interaction; factor analysis

Introduction

Hyperuricemia (HUA) is a purine metabolic disorder. The most well-known disease induced by HUA is gout, but many studies have reported that HUA also plays important roles in cardiac-kidney-vascular system diseases and metabolic syndromes (Mets) [1]. A meta-analysis in 2015 reported that the pooled prevalence of HUA is 13.3% in China [2]. A national survey in the US found that the prevalence of HUA is substantial, with 20.2% in males and 20.0% in females aged 20 years and older [3]. HUA has become the second most common metabolic disease after diabetes mellitus [1].

The known risk factors for developing HUA include genetic and environmental factors as well as interactions between them [1]. Recent genome-wide association studies (GWAS) have identified significant associations between single nucleotide polymorphisms (SNPs) in *ABCG2* and *SLC2A9* in HUA cases [4]. Studies have shown that a mutation at the rs2231142 locus of *ABCG2* can cause a 53% reduction in *ABCG2*-mediated serum uric acid (SUA) transport [5], and that a variation at the rs11722228

55 locus of *SLC2A9* can also affect the transport and reabsorption of SUA [6].

56 Along with inherited genetic variants, specific dietary components also play a
57 significant role in the development of HUA [7]. Previous studies have reported that red
58 meat, seafood, and alcohol consumption are associated with the risk of HUA [8,9].
59 However, most of the existing research focuses on the effects of a single food or nutrient
60 rather than the interaction between multiple food items, which may be more relevant to
61 the study of disease association [10,11]. The dietary pattern method uses complex
62 combinations of foods and nutrients to investigate the association between multiple
63 food items and disease [12]. A cross-sectional study found that the 'animal and fried
64 foods' pattern was associated with a higher prevalence of HUA [13], while another
65 study demonstrated that there was no significant association between dietary patterns
66 and HUA in Chinese participants [11]. Hence, the association between dietary patterns
67 and HUA remains unclear.

68 Potential gene–environment interactions are key features in the development of
69 complex diseases, including HUA and gout [14]. Evidence has suggested that the intake
70 of sugar-sweetened beverages and *SLC2A9* variants interact in the pathogenesis of gout
71 [15]. However, there are few studies on diet and gene interaction in HUA [7,14-16] and
72 to our knowledge, no previous study has examined the relationship of dietary patterns
73 and gene interaction in HUA risk in the Chinese population.

74 The Liangshan Yi Autonomous Prefecture is located in southwestern Sichuan
75 province, where the aboriginal Yi people maintain a unique dietary culture and customs
76 [17]. Our previous study found that the prevalence of HUA among adult Yi people was

22%, which was significantly higher than that in other areas of China [18]. Therefore, we aimed to identify their major dietary patterns and assess the association between dietary patterns and the risk of HUA among adult Yi people in China. We also explore the effects of dietary patterns and gene interactions on HUA.

Methods

Participants

A cross-sectional study was conducted on the Yi people located in the Liangshan District, Sichuan Province, China, from July 2014 to February 2016. A representative sample was obtained using a multistage stratified cluster sampling method. Details of the study design were described in our previous study [19]. We excluded participants who had unretained blood samples or dietary questionnaires that were more than 50% incomplete. Of the 3188 participants, 2646 were included in the analyses. The protocol of this study was approved by the Ethics of Research Committee of Southwest Medical University. All methods were performed in accordance with the relevant guidelines and regulations of the Ethics of Research Committee of Southwest Medical University. Informed consent was obtained from all participants.

Questionnaire survey

The on-site survey was conducted by well-trained investigators through face-to-face interviews. Participants were asked to complete a questionnaire that included demographic and lifestyle information. Their dietary intake was assessed using a semi-

quantitative 52-item food frequency questionnaire (FFQ) that inquired about the types of food items, frequency (daily, weekly, monthly, yearly, or never), and amount of food consumed over the past year (serving size per gram). The FFQ was designed based on culture-specific dishes and tested on local samples to check its applicability under the Yi culture. Alcohol consumption was calculated based on the drinking frequency and consumption of different alcoholic beverages.

Physical examination

Height and weight were measured by trained professionals to the nearest 0.1 cm and 0.01 kg, respectively. Body mass index (BMI) was calculated by weight/height^2 (kg/m^2). Blood pressure (BP) was measured twice from the upper left arm after 5 min rest in a seated position. Waist circumference was measured with a non-retractable tape measure to the nearest 0.1 cm at the umbilical level with the participants standing and breathing normally. Hip circumference was measured to the nearest 0.1 cm around the symphysis pubis and the posterior gluteus maximus.

Assessment of hyperuricemia and other variables

HUA was defined as serum uric acid (SUA) concentrations >420 μmol/L (7.0 mg/dL) for males and >360 μmol/L (6.0 mg/dL) for females [1]. Overnight fasting blood samples were collected from each participant. SUA, triglycerides (TG), total cholesterol (TC), fasting plasma glucose (GLU), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using an

automatic biochemical analyzer (Mindary, BS-820, Shenzhen, China).

Genomic DNA extraction and genotyping

Genomic DNA was extracted from peripheral blood leukocytes and a Nano Drop 2000 ultraviolet spectrophotometer was used to measure its quantity and quality. Genotyping was performed by Kompetitive Allele Specific PCR (KASP). The detection success rates of the *ABCG2* rs2231142 and *SLC2A9* rs11722228 loci were 99% and 97.2%, respectively. The SNPs were selected based on the following criteria: 1) SNP with $P<1.0 \times 10–5$ for all GWAS samples; 2) when multiple SNPs had a strong LD ($r^2 \geq 0.8$), SNPs previously reported in the literature were used prior to selection; 3) clear genotyping clusters; and 4) Minor Allele Frequency(MAF)≥0.05. Based on quality control criteria, SNPs were excluded when the $P<0.001$ for the Hardy-Weinberg equilibrium (HWE) test, MAF<0.01, or genotype call rate<95%.

Identification of dietary patterns

According to the Food Composition Table, similarity of nutrient profiles, and purine contents, we collapsed 52 food items into 17 food groups. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's sphere test were used to evaluate the adequacy of correlation matrices with the data. Principal component factor analysis (PCFA) was applied to derive dietary patterns. Moreover, varimax rotation was applied for greater interpretability. After evaluation of eigenvalues >1, the cumulative contribution rate, and the scree plot, three factors were determined. Food items with a

143 factor loading >0.30 (absolute value) were regarded as the main components of each
144 pattern. The higher the factor loading of a food group, the greater the contribution of
145 that group to the pattern. The labeling of dietary patterns was based on the interpretation
146 of foods with high factor loadings for each pattern [20]. Dietary pattern scores were
147 calculated by summing the product of the standardized intake for each group multiplied
148 by the regression coefficients before they were categorized into quartiles (Qs).
149
150 **Statistical analyses**
151 The factor scores of each dietary pattern were divided into quartiles with Q4 and Q1
152 the highest and lowest categories for the intake of each dietary pattern, respectively.
153 The association between the quartile categories of dietary pattern scores and HUA was
154 examined using logistic regression analysis. Data for continuous variables are presented
155 as mean ± standard deviation. Categorical variables were generally reported as the sum
156 (percentage) and analyzed using a chi-square test. The Kaiser-Meyer-Olkin(KMO)
157 measure of sampling adequacy (0.727) and Bartlett's test of sphericity (P <0.001)
158 showed that the factor model as a whole was significant. The additive interaction was
159 measured using the Delta method described by Rothman et al. [21], while the parameter
160 estimates and covariance matrix of the logistic regression model were substituted in the
161 Excel program developed by Andersson et al. [22] to calculate the additive interaction
162 index. The indicators used for evaluating the additive interaction included the excess
163 relative risk (RERI), attribution ratio (AP), and interaction index (S). If the 95% CI of
164 RERI and AP were > 0, and the 95% CI of S > 1, there was a synergistic interaction

between the dietary pattern and the gene in HUA. Data were analyzed using SPSS software (SPSS Inc. Version 24). All P values were two-tailed, and the difference was considered significant when P<005.

Results

Participants

A total of 2646 subjects were included in this study, including 1445 males and 1201 females. The prevalence of HUA was 26.8% in all participants, but 34.9% in males and 17.2% in females. Participants with and without HUA showed significant differences in age, gender, ethnicity, education, and occupation. Compared with non-HUA participants, patients with HUA showed higher expression of SUA, TC, and TG, as well as higher WC, WHR, BMI, and BP **(Table 1)**. The participant flowchart is shown in **Figure 1**.

Extraction of dietary patterns

Three major dietary patterns were identified by factor analysis in the tested population (**Table 2**). Factor 1 was defined as the 'meat-based' pattern and characterized by a high intake of animal organs, seafood, fresh meat, and eggs; factor 2 was characterized as a 'plant-based' pattern and included the intake of mushroom algae, beans and their products, nuts, and fruits; and factor 3, was the 'local special' pattern was characterized by the intake of marinated smoked meat and grease. These three patterns accounted for 33·87% of total variance, with the 'meat-based,' 'plant-

based,' and 'local special' dietary patterns constituting 12.64%, 12.54%, and 8.69% of the total variance, respectively.

Association between dietary patterns and HUA

As shown in **Table 3**, there was a significant association between the 'meat-based' pattern and a high prevalence of HUA. Compared with the participants in the lowest quartile, the OR for the highest quartile was 1.878 (95% CI = 1.461, 2.415, P <0001) and 1.385 (95% CI = 1.052, 1.823, P <005) before and after adjustment for age, sex, and ethnicity, respectively. The other two dietary patterns were not related to the prevalence of HUA in the participant population after adjustment.

Hardy-Weinberg equilibrium test and genotype frequency distribution

The allele frequencies for both SNPs in the *ABCG2* case group (χ^2=0156，P=0.925), control group (χ^2=0.303，P=0.859), *SLC2A9* case group (χ^2=0.156, P=0.925), and control group (χ^2=0.683, P=0.711) were in Hardy-Weinberg equilibrium (P>0.05). The results reveal that the population used in the present study exhibited adequate group representation. **Table 4** displays the genotype frequency distribution of the *ABCG2* and *SLC2A9* genes. For both loci, the T allele in the HUA group was higher than that in the non-HUA group.

Different genotypes and HUA

As shown in **Figure 2**, when the GG wild-type genotype at the rs2231142 locus in

ABCG2 was used as a reference, the risk of HUA increased with the number of T alleles. Additionally, compared with the GG wild-type genotype, the risk of HUA in individuals with GT and TT mutant genotypes was 1.784 times (95% CI = 1.471,2.163) and 2.993 times (95% CI = 2.015,4.445), respectively. After adjustment for age, sex, and ethnicity, the association between the rs2231142 locus and HUA was still significant (P<0.001).

A similar relationship was observed in the rs11722228 locus in *SLC2A9*. Compared with the CC wild-type genotype, the CT and TT mutant genotypes increased the risk of HUA by 22.5% (OR: 1.225, 95% CI = 1.015,1.478) and 39.2% (OR: 1.392, 95% CI = 1.029,1.884), after adjustment for confounders, respectively.

Interaction analysis between dietary patterns and genetics

There was no evidence that the three dietary patterns had multiplication interaction effects on HUA risk in combination with the *ABCG2* rs2231142 and *SLC2A9* rs11722228 loci. Therefore, we next examined whether there were additive dietary and genetic interactions associated with HUA in the tested population.

The three dietary pattern factor scores were divided into two quantiles, with the low quantile as the reference and the rs2231142 locus referenced with the GG wild-type genotype. There was an additive interaction between the pattern of ‘meat-based’ and the rs2231142 locus associated with the risk of HUA; the RERI, AP, and S were 0.482 (95% CI = 0.012,0.976), 0.203 (95% CI = 0.033,0.374), and 1.544 (95% CI = 1.012,2.355), respectively (**Table 5, Figure 3**). The other two dietary patterns had no additive interactions with the rs2231142 locus, with the 95% CI of RERE and AP

including 0 and the interaction coefficient S including 1. Using the CC wild-type genotype as a reference, the results showed no additive interaction between the rs11722228 locus and the three dietary patterns.

When the average SUA levels of each genotype at the *ABCG2* rs2231142 locus was compared under the "animal diet pattern" quartile, that SUA levels increased with the number of T risk alleles (GG→GT→TT). In addition, the SUA level increased as the "meat-based pattern" factor score increased in the same genotype (**Figure 4**).

Discussion

In this study, three major dietary patterns were identified in the Yi people of the Liangshan District, Sichuan Province, China that were mainly meat-based, plant-based, or associated with regionally specific cuisine. The main finding of this study is that the meat-based food pattern, which is characterized by high intake of animal organs, seafood, fresh meat, and eggs was positively associated with an elevated risk of HUA, whereas no significant association was found between the other two patterns and HUA risk.

To date, several studies have explored the association between diet and HUA. A cross-sectional study demonstrated that animal products and fried food patterns that are rich in pork, eggs, animal giblets, poultry, and fried wheat, was positively associated with a higher prevalence of HUA [13]. He et al. [23] found that a meat food pattern characterized by the intake of poultry, beef, processed and cooked meat, eggs, and fats, was associated with an elevated risk of HUA. In contrast, a study in Taiwan showed no significant association between any dietary pattern and HUA after adjustment [11].

Another study suggested that compared with individuals in the lowest quintile, those in the highest quintile of meat and seafood intake experienced increased risk of gout [8].

Our study found a positive association between the 'meat-based' dietary pattern and the prevalence of HUA, which is consistent with previous reports [13,23]. The mechanism that has been proposed to explain this connection is related to the high purine content of animal meat-based foods because excessive intake of purines may increase the level of SUA and thus, increase the risk of HUA [8]. Our previous study found that people in the Liangshan area are more likely to drink broth and the meat consumed is mainly fresh pork fat [17], which contains more purines and saturated fatty acids. The consumption of animal food products, especially the calories and fat in red meat, leads to centripetal obesity, which is a strong stimulus for increased plasma insulin levels that could lead to HUA [13,24]. A previous study found that a dietary pattern of soybean products and fruit was negatively associated with the prevalence of HUA [13]. Fruits and vegetables can provide rich dietary fiber and their antioxidant components have a protective effect against HUA [10]. However, we found no significant association between the other plant-based and regional dietary patterns and HUA in the present study, indicating that further research is still needed to clearly understand how diet patterns affect HUA prevalence.

The heritability of SUA concentration is approximately 40%-70% [25]. Previous GWAS studies have suggested an association between HUA susceptibility relative to dysfunctional *ABCG2* variants, with the rs2231142 locus being the most common variant [26]. In our study, we found that individuals with the *ABCG2* rs2231142 T allele

had a higher frequency of HUA and SUA than those with the rs2231142 GG allele, which was consistent with results reported in the United States [27] and Mexico [28]. *ABCG2* is a high-capacity urate transporter that plays a key role in renal urate overload [26]. The risk of HUA that is attributed to *ABCG2* variants is 29.2%, which is much higher than other typical environmental risks [29]. Our findings indicate that the rs2231142 locus variants of *ABCG2* are extremely important in HUA pathogenesis, consistent with the reported importance of *ABCG2* genotyping in the screening of HUA high-risk individuals [26].

The *SLC2A9* gene encodes two GLUT9 isoforms of the class II facilitative glucose transport family [7]. A previous study reported that the rs11722228 locus of *SLC29* can explain 1.03% of the variation in SUA levels in the Chinese population [30]. Doring et al. reported that the most significant SNPs associated with SUA were within the *SLC2A9* gene [31]. Our study also found that the SUA level in individuals with the rs11722228 locus showed increased instances of the T allele and was higher in the HUA population than in the non-HUA population.

Longitudinal studies have found that some individuals are more sensitive to unhealthy diets, reflecting the complex interaction between genetic factors and diet [14]. In this study, we found an additive interaction between a meat-based dietary pattern and the rs2231142 locus of *ABCG2*. Under the same dietary pattern factor score, the increase of the T allele at the rs2231142 locus was associated with increased SUA levels. Moreover, individuals with this genotype also exhibited SUA levels that increased with the dietary pattern factor score. Similar to our results, Beydoun et al. [7] reported that

12 SNP sites (including *ABCG2* and *SLC2A9*) are closely related to SUA and found that there was a synergistic interaction between the genetic risk score (GRS) and red meat intake that increased the risk of increased SUA among women. In addition, a population-based study in Malaysia (32) showed that SUA concentration is affected by the interaction of a 'fruit diet pattern' and the *VEGFR-2* rs2071559 locus, suggesting that fruit consumption may play a role in enhancing or suppressing the effects of *VEGFR-2* polymorphisms.

To the best of our knowledge, there are four main studies that examined the interaction effect of diet and gene expression on HUA [7,14-16]. These results support the hypothesis that different dietary intake can enhance or weaken the effect of genes on blood UA level and HUA. However, only one study included the rs2231142 and rs11722228 loci [7], and none of these studies were conducted among a Chinese population. Our study used a large sample size and careful study design to add new evidence of diet and genetic interactions on HUA prevalence in the Chinese population to the field. The findings of this study will provide new and necessary insight into HUA and assist in the development of intervention strategies.

Most studies on the interaction between diet and genetics in China have focused on diseases such as Mets [33] and obesity [34]. Our study is among the few to explore the influence of dietary patterns and gene interactions on HUA. We also evaluated dietary patterns using FFQ, which consists of purine-containing foods and beverages commonly consumed by the Chinese population. This is important because dietary structure is a key factor for assessing the prevalence of HUA within populations [35].

In addition, information from the questionnaires was collected by trained investigators, and thus our results are reliable.

This study had several limitations. First, it is a cross-sectional study and therefore cannot refer to causality. Second, although we adjusted for potential confounding variables in the multivariate adjusted model, we were unable to control for the effect of unmeasured confounding factors.

In conclusion, higher adherence to meat-based dietary pattern was associated with a higher prevalence of HUA in a Chinese population. There was a significant additive interaction between the meat-based dietary pattern and the *ABCG2* rs2231142 locus on the risk of HUA in the Yi ethnic group of China. These findings may provide new insights into health policy and intervention strategies for controlling HUA among the Chinese population. Further prospective studies will be needed to validate our findings.

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Author contributions

HJ: designed the research project; LJL: provided comments and critical review of the manuscript; TTL: analyzed the data and was primarily responsible for the final content

of the manuscript. All authors wrote the paper and read and approved the final manuscript.

Conflicts of interest

The authors report no conflicts of interest.

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Data Share Statement

Data described in the manuscript, code book, and analytic codes cannot be made available due to the University Institution Review Board requirement.

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Tables

Table 1 Socio-demographic and clinical characteristics of participants

Variables	Participants with HUA	Participants without HUA	*P* value
	n=710	n=1,936	
Age (years)	42.70±15.06	44.62±14.09	0.003
Gender (%)			**<0.001**
Male	504 (71.0)	941 (48.6)	
Female	206 (29.0)	995 (51.4)	
Ethnic groups (%)			**<0.001**
Han	351 (49.4)	687 (35.5)	
Yi	359 (50.6)	1249 (64.5)	
Education (%)			**<0.001**
≤ primary school	276 (38.9)	1142 (59.0)	
≥ junior high school	434 (61.1)	794 (41.0)	
Occupation (%)			**<0.001**
Farmer	251 (35.6)	1046 (54.3)	
Non-farmer	454 (64.4)	882 (45.7)	
Waistline (cm)	84.53±10.15	78.49±9.21	**<0.001**
WHR	0.89±0.06	0.86±0.06	**<0.001**
BMI (Kg/m^2)	24.21±3.60	22.43±3.11	**<0.001**
SBP (mmHg)	131.94±19.49	126.45±18.57	**<0.001**
DBP (mmHg)	80.91±15.82	77.13±13.97	**<0.001**
SUA (μmol/L)	466.40±72.71	306.27±60.61	**<0.001**
LDL (mmol/L)	3.08±0.84	2.92±0.80	**<0.001**
HDL (mmol/L)	1.25±0.32	1.35±0.33	**<0.001**
GLU (mmol/L)	5.51±1.39	5.51±1.54	**0.985**
TC (mmol/L)	5.10±1.02	4.93±1.01	**<0.001**
TG (mmol/L)	2.01±1.45	1.40±1.15	**<0.001**

WHR: waist–hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; GLU: glucose; TC: serum cholesterol; TG: serum triglycerides. LDL-cholesterol: low-density lipoprotein cholesterol; HDL-cholesterol: high-density lipoprotein cholesterol.

480 **Table 2** Factor loading matrix for the tested dietary patterns

Food groups	Meat-based	Plant-based	Local special
Viscera	**0.577**	—	—
Snacks and pastries	**0.539**	—	—
Fish, shrimp, crab and shellfish	**0.537**	—	—
Fresh meat	**0.521**	—	—
Eggs	**0.505**	—	—
Cereals	**0.457**	—	—
Grain	**0.451**	—	—
drinks	**0.357**	—	—
Mushrooms and algae	—	**0.716**	—
Beans and their products	—	**0.640**	—
Nuts	—	**0.520**	—
Fruits	—	**0.503**	—
Vegetables	—	**0.487**	—
Milk and dairy products	—	**0.396**	—
Marinated and smoked meat	—	—	**0.727**
Grease	—	—	**0.588**
Alcoholic beverages	—	—	—
Contribution rate (%)	12.640	12.542	8.686
The cumulative contribution rate (%)	12.640	25.182	33.869

481 **Factor loading > 0.30 are listed.**

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Table 3 Association between dietary patterns and HUA

dietary pattern	Quartile	Crude model		Adjusted model	
		OR（95% CI）	*P* value	OR（95% CI）	*P* value
Meat-based	Q_1	1.00		1.00	
	Q_2	1.446（1.118~1.870）	0.005	1.307（1.003~1.702）	0.048
	Q_3	1.644（1.275~2.119）	**＜0.001**	1.288（0.984~1.685）	0.065
	Q_4	1.878（1.461~2.415）	**＜0.001**	1.385（1.052~1.823）	0.020
Plant-based	Q_1	1.00		1.00	
	Q_2	1.119（0.875~1.432）	0.371	1.086（0.842~1.401）	0.525
	Q_3	1.076（0.841~1.379）	0.559	0.960（0.741~1.245）	0.760
	Q_4	1.268（0.994~1.617）	0.056	1.080（0.831~1.404）	0.566
Local special	Q_1	1.00		1.00	
	Q_2	0.932（0.735~1.181）	0.558	1.069（0.837~1.365）	0.592
	Q_3	0.871（0.686~1.105）	0.255	1.111（0.864~1.429）	0.412
	Q_4	0.635（0.495~0.815）	**＜0.001**	0.865（0.662~1.131）	0.289

Crude model: no adjustments are made. Adjusted model: adjusted for age (continuous), gender (male/female), and ethnicity.

Table 4 Frequency distribution of *ABCG2* rs2231142 and *SLC2A9* rs11722228 loci

SNP sites	Genotype/Allele	HUA group	Non-HUA group	P value
rs2231142	G:G	374 (52.7)	1349 (69.7)	**＜0.001**
	G:T	278 (392)	528 (27.3)	
	T:T	58 (8.2)	59 (3.0)	
	G	1026 (72.3)	3226 (83.3)	**＜0.001**
	T	394 (27.7)	646 (16.7)	
rs11722228	C:C	301 (42.4)	904 (46.7)	0.074
	C:T	328 (46.2)	854 (44.1)	
	T:T	81 (11.4)	178 (9.2)	
	C	930 (65.5)	2662 (68.8)	0.025
	T	490 (34.5)	1210 (31.2)	

518 **Table 5** Additive interaction of dietary patterns with *ABCG2* rs2231142 and *SLC2A9*

519 rs11722228 loci

SNP site	Dietary patterns	RERI	AP	S
rs2231142	Meat-based	0.482 (0.012~0.976)	0.203 (0.033~0.374)	1.544 (1.012~2.355)
	Plant-based	0.049 (-0.421~0.519)	0.022 (-0.183~0.227)	1.041 (0.713~1.520)
	Local special	-0.140 (-0.496~0.215)	-0.099 (-0.353~0.156)	0.750 (0.367~1.534)
rs11722228	Meat-based	0.024 (-0.551~0.600)	0.009 (-0.208~0.226)	1.015 (0.713~1.446)
	Plant-based	-0.033 (-0.367~0.302)	-0.022 (-0.244~0.201)	0.941 (0.501~1.764)
	Local special	-0.052 (-0.298~0.194)	-0.055 (-0.315~0.205)	14.979(0.000~33.426)

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Figure Legends

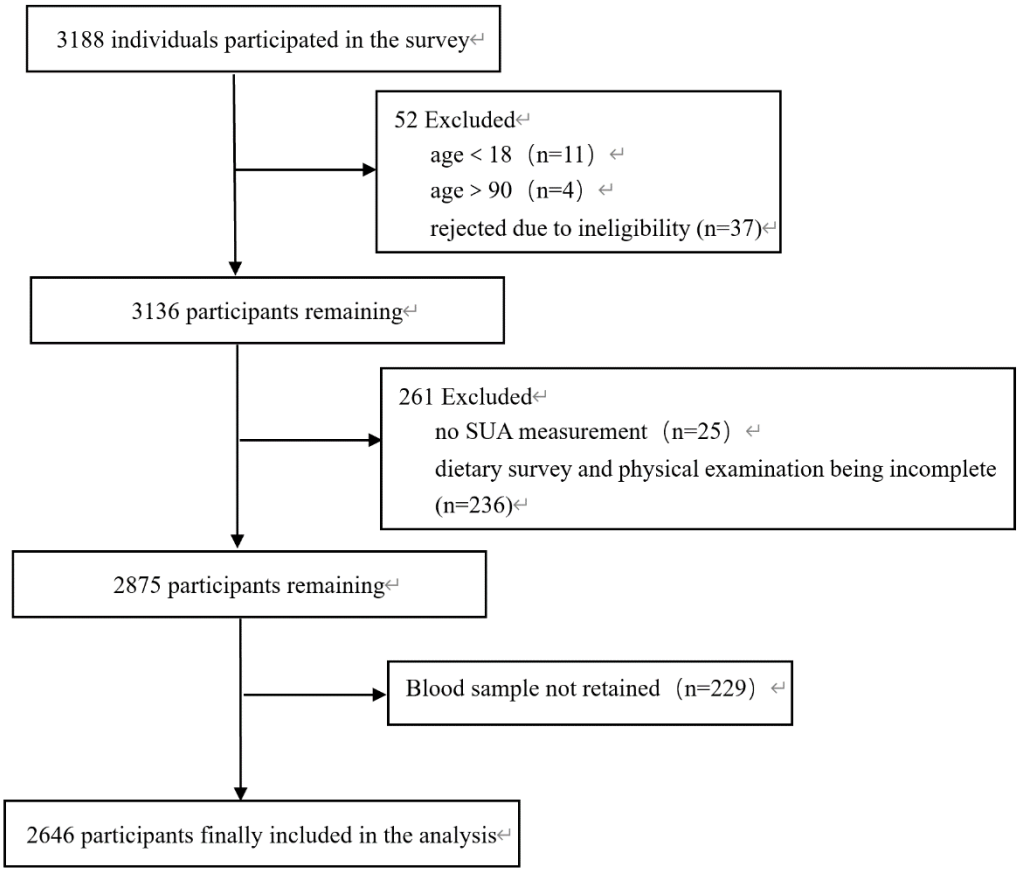
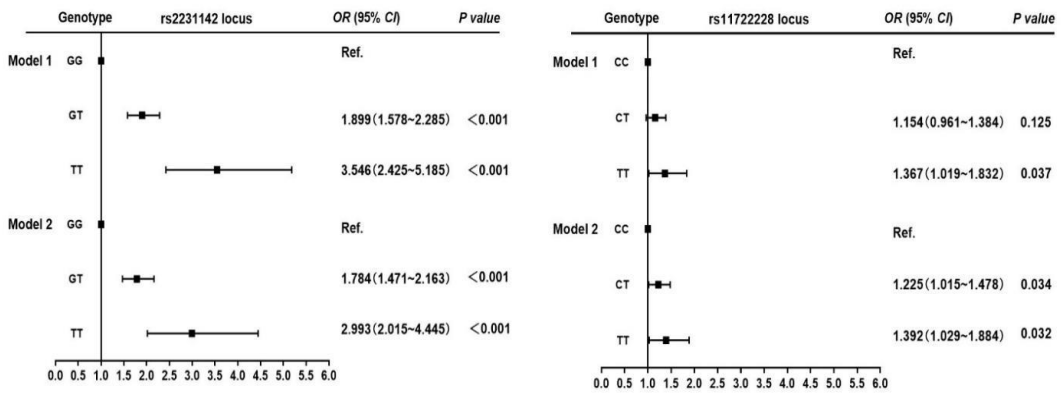
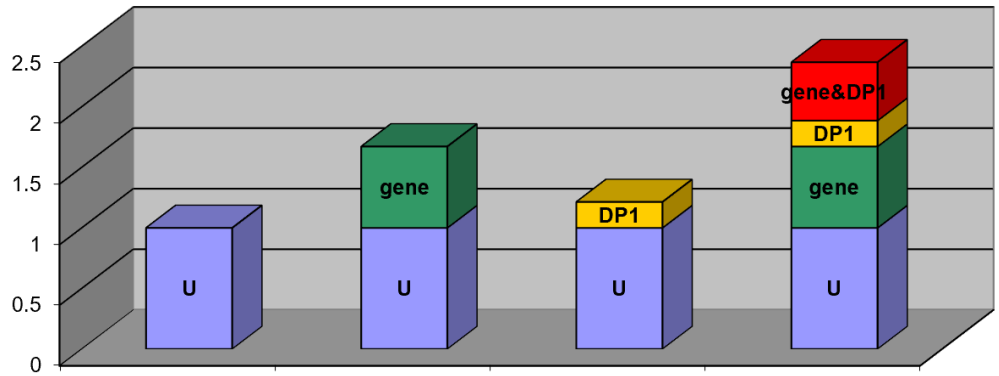


Figure 1 Participant flowchart



Model 1: not adjusted are made. Model 2: adjusted for age, gender, and ethnicity.

Figure 2 The relationship between *ABCG2* rs2231142 and *SLC2A9* rs11722228 loci with HUA



U: Baseline; gene: *ABCG2* rs2231142locus; DP1: Dietary pattern 1 (Meat-based pattern); gene&DP1: Additive interaction between the 'Meat-based' pattern and *ABCG2* rs2231142 locus.

Figure 3 Additive interaction between the 'Meat-based' pattern and *ABCG2* rs2231142 locus

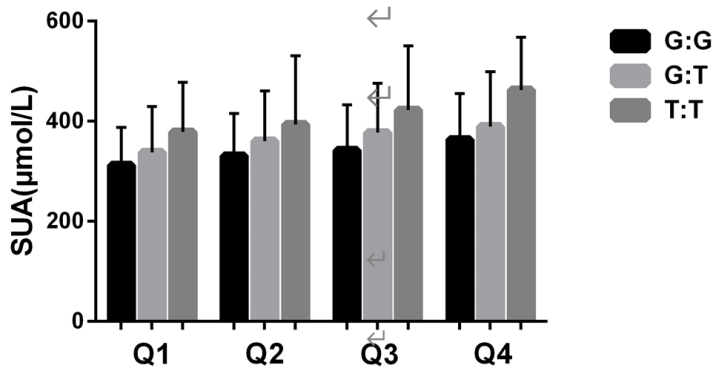


Figure 4 The SUA level of *ABCG2* rs2231142 locus in 'Meat-based' pattern quartile