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Original article

The association between genetic risk score and blood pressure is modified by coffee consumption: Gene–diet interaction analysis in a population-based study

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SUMMARY

Background & aim: Recent genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) that are associated with high blood pressure (BP). However, whether coffee consumption interacts with the genetic variants related to BP is yet unclear. Thus, this study aimed to investigate whether the association between genetic risk core (GRS) and blood pressure was modified by usual coffee consumption.

Methods: Data were from the 'Health Survey of São Paulo' a cross-sectional population-based survey, among 533 participants aged 20 years or older. Coffee consumption was estimated by two 24-h dietary recalls and categorized into <1, 1–3, and >3 cups/day. The GRS was calculated based on SNPs in previous GWAS [*CYP1A1/CYP1A2* (rs2470893, rs2472297); *CPLX3/ULK3* (rs6495122); *MTHFR* (rs17367504)]. Multiple logistic regression analysis were performed to estimate the associations between GRS with high BP, and both, high systolic BP (SBP) and diastolic BP (DBP); and the multiplicative interaction term between the GRS and coffee consumption were tested by including in the models.

Results: Higher GRS independently contributed to higher probability of elevated BP, SBP and DBP in this population (OR = 1.85, 95%CI = 1.19–2.87; OR = 2.30, 95%CI = 1.32–4.01 and OR = 1.66, 95%CI = 1.10–2.51; respectively). Moreover, there were a significant interaction effects for coffee consumption and GRS on the high BP, SBP and DBP. Individuals with higher BP increasing alleles in the GRS had a significantly high BP (OR = 5.09, 95%CI = 1.32–19.7), and both elevated SBP and DBP (OR = 2.14, 95% CI = 1.12–4.11; OR = 3.54, 95%CI = 1.17–10.75), among those with high coffee consumption (>3 cups coffee/day).

Conclusions: Consumption of coffee could interact with genetic predisposition in relation to BP. Thus, the GRS for high BP is modified by coffee consumption. Individuals with greater GRS appeared to have high BP associated with higher coffee consumption, highlighting the particular importance to reduce coffee intake in individuals genetically predisposed to this cardiovascular disease risk factor.

1. Introduction

High blood pressure (BP) has long been recognized as an important risk factor for cardiovascular disease (CVD). Data from epidemiological studies have established that the increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP), even within the normal range (between 130 and 139/85–89 mmHg), have a continuous and graded impact on CVD risk [1,2]. Elevated BP affects about one third of adults, decreasing life expectancy, and accounts for 7% of disease burden – as measured in disability-adjusted life-years (DALYS). Raised BP is estimated to cause 9.4 million deaths worldwide every year [3]. For every 20 mmHg systolic or 10 mmHg

Abbreviations: BP, blood pressure; CPLX3, complexin 3; CYP1A1, cytochrome P450 family 1 subfamily A member 1; CYP1A2, cytochrome P450 family 1 subfamily A member 2; CVD, cardiovascular disease; DBP, diastolic blood pressure; GRS, Genetic Risk Score; GWAS, genome-wide association studies; MTHFR, 5,10-methylenetetrahydrofolate reductase; SBP, systolic blood pressure; SNPs, single nucleotide polymorphisms; ULK3, unc-51 like kinase 3; 24HR, 24-h dietary recalls.

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diastolic increase in BP, there is a doubling of mortality from both ischaemic heart disease and stroke [2].

As a multifactorial condition, BP is influenced by environmental and genetic factors, as well as their interactions, and has long been recognized as an inheritable trait, suggesting a significant contribution of genetic factors to this complex phenotype [4]. The considerable heritability of BP (about 30–60 percent) has instigated extensive efforts to identify its genetic underpinnings but the vast majority of the genetic contribution to variation in BP, remains largely unknown or unexplained [4,5]. Therefore, the identification of susceptibility genes associated with inter-individual variation in BP in the general population could help elucidate the underlying molecular mechanisms of hypertension [5].

Over the last decade, several genetic loci or chromosomal regions were found to be associated with BP or hypertension through candidate gene and genome-wide linkage studies [6–9]. Large-scale genome-wide association studies (GWAS) have recently recognized to be an effective approach to identify novel genetic risk variants for various common diseases and traits, including continuous BP and dichotomous hypertension [10,11]. Subsequently, two large GWAS meta-analyses in European descendent, one by the CHARGE (Cohorts for Heart and Aging Research in Genome Epidemiology) Consortium (N = 29,136) [6] and the second by the Global BPgen (Blood Pressure Genetics) Consortium (N = 34,433) [7] identified 17 variants in 13 loci strongly associated with SBP and/or DBP [6,7]. More recently, the International Consortium for Blood Pressure Genome-Wide Association Studies [12] of SBP and DBP, in individuals of European descent, identified 16 novel loci, wherein six of these loci contain genes previously recognized or suspected to regulate BP; the other ten provide new evidences to BP physiology. A genetic risk score based on 29 independent genetic variants was significantly associated with hypertension, left ventricular wall thickness, stroke, and coronary artery disease [12].

Emerging data suggest that synergistic interactions of genetic predisposition with diet and lifestyle factors may play an important role in affecting BP and the pathogenesis of hypertension [13]. Coffee is among the most widely consumed beverages in the world and has received considerable attention regarding health risks and benefits [14]. The majority of recent observational studies have associated regular coffee consumption with reduced risk of hypertension and related cardiovascular disease [15–17], but the effect of long-term coffee consumption on BP is not entirely consistent [18–20]. Although the acute effect of caffeine intake is to increase BP by blocking adenosine receptors in the vascular tissue, which leads to vasoconstriction in the macro- and microcirculation [19,21], coffee is a blend of complex organic compounds (i.e., minerals, soluble fiber, and phenolic compounds) with strong antioxidant capacity [22], anti-inflammatory and antithrombotic properties [23]. Furthermore, such heterogeneous associations might be attributed, at least partly, to the modification effects of divergent genetic predispositions, as observed in previous studies showing coffee–gene interactions on different health outcomes [24–26]. Genetic factors could be especially valuable as they offer ways to explore the potential health effects of coffee through gene–diet interactions [27]. Therefore, the purpose of the current study was to investigate whether the association between GRS and blood pressure was modified by usual coffee consumption, in a representative sample of São Paulo population, Brazil.

2. Subjects and methods

2.1. Subject population

Data were derived from the 'Health Survey of São Paulo' (ISA-Capital), a cross-sectional population-based health survey conducted in 2008–2009. The study population comprised residents living in private households in the urban area of São Paulo City, south-eastern Brazil. This complex probabilistic sample was obtained by conglomerates, based on census tracts and household sectors using data from the 'National Household Sample Survey' (PNAD) conducted in 2005 [28]. The sample of ISA-Capital was defined for six domains defined by age groups and sex: females and males aged 12–19 years (adolescents), 20–59 years (adults) and 60 years or over (older adults). A sample size of 300 in each domain was estimated to be the minimum, based on a prevalence of 0.5 with a standard error of 0.07 at a 5% significance level and a design effect of 1.5.

A total of 2691 individuals, aged 12 years or over, were selected to answer questions about dietary intake, life conditions (e.g. physical activity, smoking and use of drugs) and socio-demographic characteristics (e.g. age, sex, self-reported skin color, educational attainment, and family income). Among these participants, 750 individuals donated a blood sample, completed two 24-h dietary recalls (24HR), and anthropometric data as well as BP were measured. Other details of the sampling have been previously published [29]. For the present study, we considered only participants aged 20 years or older at the time of collection. A total of 533 individuals responded to a social-economic survey, completed two 24-h dietary recalls (24HR), underwent anthropometric and blood pressure measurements and subsequently, blood samples were collected for DNA extraction and genotyping.

The study protocol (Protocol number 2001) was reviewed and approved by the Ethics Committee at the School of Public Health of the University of São Paulo. A written informed consent form was obtained from all participants.

2.2. Data collection and processing

Household information of demographic, socioeconomic, lifestyle, self-reported morbidity, family-history diseases, supplementation, use of drugs and food intake variables, were obtained using structured questionnaires applied by trained interviewers.

In a subsequent home visit, BP was measured, blood samples were collected, and anthropometric measurements were recorded.

2.2.1. Dietary assessment

The dietary intake was assessed using two non-consecutive 24HR collected on different day of the week, weekends and different seasons. The first was collected in the households using the Multiple Pass Method, and the second 24HR was performed through telephone based on the Automated Multiple Pass Method [30]. The Multiple-Pass Method uses a standardized process structured in five steps (quick listing, forgotten list foods, naming meals, detail cycle and general review) that keeps individuals interested and engaged in the interview, which helps them remember all items consumed.

Food items reported in each 24HR were critically reviewed to identify any failures in reporting related to the descriptions of the food consumed or to food preparation techniques, including their apportioning and quantification. Dietary data were estimated using the Nutrition Data System for Research (NDSR®) software program version 2007 (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN, USA), which is based on data from the United States Department of Agriculture (USDA) Food Composition Table, to obtain the nutritional information of the 24HR (energy and nutrient values). The nutritional adequacy of the food consumption data was verified using a national food composition table – *Tabela Brasileira de Composição de Alimentos* (available here: http://www.intranet.fcf.usp.br/tabela/).

Moreover, the Multiple Source Method (MSM) was used, that is, a statistical modeling technique to estimate the usual dietary intake of coffee, alcohol and total energy, and to remove within-person variation. This method uses two 24HR and a probability of intake. First, the MSM estimates the probability of eating the food and/or nutrient intake on a random day for each individual, allowing to calculate the usual daily intake, and then builds the population distribution based on individual data [31].

2.2.2. Coffee consumption

During the 24HR, the participants reported if they consumed coffee on the day before the interview using household measures, then, the quantity of coffee intake on each occasion was converted in mL, to enter the information at NDSR® software. Furthermore, information about the method of coffee preparation (filter, instant, espresso, moka pot, or other), whether this coffee contained caffeine (caffeinated or decaffeinated), and whether additional items were typically added to the coffee (milk, sugar, artificial sweetener, none), were probed during the detailed cycle of the multiple-pass method.

For this study, daily coffee intake (in mL) was categorized into three categories, according to the reference cup size of 50 mL, which is the household measure frequently used in Brazil: <1 cup/day (<50 mL), 1–3 cups/day (50–150 mL), and >3 cups/day (>150 mL). The <1 cup/day of coffee category was used as the reference group.

2.2.3. Blood pressure measurement

BP was measured according to the recommendations of the Fifth Brazilian Guidelines for Hypertension [32], using a validated automatic oscillometer (Omron®, model HEM-712 C, Omron Health Care, Inc., Vernon Hills, IL, USA) handled by a nursing technician, who also collected data on antihypertensive drugs use. High systolic blood pressure (SBP) was defined as a SBP more than or equal to 140 mm Hg, and high diastolic blood pressure (DBP) was defined as DBP more than or equal to 90 mmHg. Therefore, the participants were considered to have high BP if they had a SBP and/or a DBP higher or equal to 140 mmHg and 90 mmHg, respectively, according to the national and international recommendations [2,32].

2.2.4. Lifestyle and anthropometric measures

A structured questionnaire was used to gather information on lifestyle characteristics (physical activity, smoking habits and alcohol consumption).

The long version of the International Physical Activity Questionnaire (IPAQ), validated in Brazil [33], was used to collect data on physical activity and information from the leisure domain of the questionnaire (energy expenditure in leisure time by reporting type and duration of activity) was used to classify the level of physical activity. In the current study, physical activity level was categorized in low and moderate or high. The smoking status was ascertained from questions about current or past smoking, time from smoking cessation and the number of cigarettes smoked *per day*, and this variable was classified in three categories: non-smoker, former smoker and current smoker. Alcohol consumption was assessed from information about amount, frequency and preferences then, it was categorized as non-drinker and alcohol drinker.

A trained nurse technician, using a standardized protocol, measured body weight and height at the participants' homes. Body weight (kg) was measured using a digital balance (Tanita®, model HD-313, Tanita Corporation of America, Inc., Arlington Heights, IL, USA). Height (cm) was measured with a fixed stadiometer, with head, shoulders, buttocks, and heels pressed back against the wall (Seca®, model 208, Seca Brazil, São Paulo, Brazil). Then, these two measures were used to calculate the body mass index (BMI, kg/m^2), according to the Quetelet equation [BMI = weight (kg)/height (m)^2].

2.2.5. Blood samples collection

The blood samples were obtained through venipuncture after 12-h of overnight fasting by a trained nurse technician, according to the standardized procedures. Approximately 20 mL of blood were collected, in tubes containing EDTA (ethylenediaminetetraacetic acid) and plastic serum tubes which had spray-coated silica. The tubes were stored in styrofoam box with ice packs and transported within 2 h to the Laboratory of Human Nutrition at School of Public Health for immediate centrifugation at 3000 rpm for 15 min at room temperature. After centrifugation, serum and plasma samples were aliquoted and stored in a freezer at −80 °C until analysis.

2.2.5.1. DNA extraction and genotyping. The DNA was extracted using the salting out method [34]. Subsequently, the DNA integrity was observed using a 1% agarose gel whereas DNA concentration was quantified using a Nanodrop 8000 Spectrophotometer (Thermo Scientific, Waltham, MA, USA). The PCR-allele technique performed by the TaqMan Open Array (Life Technologies Corporation, Carlsbad, CA, USA), was used for genotyping of the SNPs [35].

2.2.5.2. Single nucleotide polymorphism selection and construction of genetic risk score. The GRS was created using four single nucleotide polymorphisms that reached genome-wide significance level with BP in previous GWAS [*CYP1A1/CYP1A2* (rs2470893, rs2472297); *CPLX3/ULK3* (rs6495122); *MTHFR* (rs17367504)] [6,7,9,12].

Each SNP was recoded as 0, 1 or 2 according to the number of risk alleles known to increase BP, i.e. BP increasing alleles. Thereafter, the unweighted GRS was determined by a simple summation of the number of risk alleles from the four SNPs. In our approach, no weighting of effects is used, and each SNP allele counts equally in the score. The GRS ranges from 0 to 8, and each point of the genetic risk score corresponded to each one risk allele, with higher scores indicating a greater genetic predisposition to high BP.

2.3. Statistical analysis

For each polymorphism in this population, the minor allele frequency (MAF) was calculated, and the Chi-square test with continuity correction was used to determine whether genotype frequencies followed the Hardy–Weinberg equilibrium.

The frequencies of sex, age group, self-declared skin color, smoking status, leisure-time physical activity levels, coffee and alcohol consumption, and medians and interquartile range (IQR) of BMI and total energy intake were described according to genotypes for each gene. The differences between characteristics of the studied population by genotypes were properly verified by Chi-square test and Kruskall–Wallis test for categorical variables and continuous variables, respectively.

Multiple logistic regression analysis were performed to estimate adjusted odds ratio (OR) and 95% confidence intervals (CI) for associations between high BP, and both, high SBP and DBP with the GRS, adjusting for potential confounders, described below. Thereafter, the effects of interactions between the GRS and coffee consumption on high BP, SBP and DBP were tested by including the respective multiplicative interaction term in the logistic regression models. Statistical adjustments for potential confounding factors were made for age (years), sex (male and female), self-declared skin color (White, Black and others: Mixed, Asian or Indigenous), smoking status (non-smoker, former and current smoker), leisure-time physical activity (low and moderate or high), body mass index (Kg/m^2), current use of alcoholic beverages (no and yes), total energy intake (kcal/day), sodium intake (mg/day), and use of

antihypertensive drugs (no and yes). After statistically significant interaction was found, the multiple logistic models were used to assess the associations of the GRS with high BP, stratified by categories of coffee consumption (<1 cup/day, 1–3 cups/day, and >3 cups/day).

All statistical analysis considered the appropriate sample weights to account for the complex survey design and were done using the STATA® software, version 13 (StataCorp LLC, College Station, TX, USA). A significance level of 5% was considered in all analysis.

3. Results

The current study involved 533 individuals as a representative sample of the population of São Paulo City, of which 54.1% of the participants were women, with a mean age of 44.9 years (SD = 16.1 years). In relation to skin color, most of the participants were self-declared White (59.9%), followed by Mixed, Asians or Indigenous (33.7%), and Black (6.4%). The non-smokers comprised 76.6% of the population. Regarding to the leisure-time physical activity 89.1% had low or moderate levels. The median of coffee consumption was 138.0 mL/day (IQR = 87.6, 185.9), and 87.6% of the individuals consumed coffee. The traditional brewing method of coffee in Brazil is filtering, so a minority of participants consumed espresso coffee (n = 4), and there were no decaffeinated coffee consumers in the current study population.

The information relating to the polymorphisms studied in this population, such as gene location, change of DNA molecule bases, Hardy–Weinberg equilibrium, and MAF, is listed in Table 1. The chi-square test revealed that genotype distributions were in Hardy–Weinberg equilibrium for all of the SNPs ($P > 0.05$). A linkage disequilibrium (LD) map of the three SNPs in and around the *CYP1A1/CYP1A2* region (15q24) investigated in this sample study is shown in Supplementary Material (Figure S1). The software Haploview was used to analyze and visualize patterns of LD and it was observed that SNPs (rs2470893, rs2472297 and rs6495122) were either weakly linked to each other or not linked at all, because all r^2 values were lower ($r^2 < 0.80$). Therefore, in the ISA-Capital study population, genotyped polymorphisms in the *CYP1A1/CYP1A2* gene were not in LD.

The genotype frequencies of the SNPs, regarding the final population and the sociodemographic, lifestyle and dietary characteristics of the study population according to genotypes, are summarized in Table 2. Individuals presenting genotypes AG and GG for the *MTHFR* polymorphism had higher caffeine intake than individuals with genotype AA. Participants with genotype TT for the *CYP1A1/CYP1A2* polymorphism (rs2470893) had higher BMI than individuals with genotype CC. For race and age groups were observed statistical differences in the genotypes of *CYP1A1/CYP1A2*, and *CPLX3/ULK3*. Moreover, for smoking status was a depicted statistical difference in the genotype of *CYP1A1/CYP1A2* (rs2472297) ($P = 0.003$). In relation to sex, a significant difference was only observed for *CPLX3/ULK3* polymorphism ($P = 0.031$). The major proportion of individuals with high BP had the CT genotype for the *CYP1A1/CYP1A2* (rs2470893) and the AA genotype for the *MTHFR* polymorphisms. For *CPLX3/ULK3* polymorphism the difference in BP was of borderline significance ($P = 0.068$). The other variables did not differ between the genotypes.

Crude and adjusted odds ratios for high BP, SBP and DBP across genetic risk score, are showed in Table 3. After adjustment for potential confounding factors, the findings suggested that higher GRS independently contributed to higher probability of elevated BP, SBP and DBP in this population (OR = 1.85, 95%CI = 1.19–2.87; OR = 2.30, 95%CI = 1.32–4.01 and OR = 1.66, 95%CI = 1.10–2.51; respectively).

Gene-coffee interactions and associations between high BP, SBP and DBP with genetic risk score stratified by categories of coffee consumption are depicted in Table 4. There were a statistically significant interaction effects for coffee consumption and GRS on the high BP (*P-interaction* = 0.026), and both high SBP (*P-interaction* = 0.035) and DBP (*P-interaction* = 0.026). Moreover, the positive associations between GRS and high BP differ by coffee consumption groups. A single point rise in the GRS increases the probability of high BP (OR = 5.09, 95% CI = 1.32–19.7) among participants with high coffee consumption (>3 cups coffee/day). In addition, higher BP increasing alleles in the GRS was also associated with high SBP (OR = 2.14, 95% CI = 1.12–4.11) and high DBP (OR = 3.54, 95%CI = 1.17–10.75), in individuals who drank more than 3 cups of coffee/day. For those individuals with low and moderate coffee consumption (<1 cups/day and 1–3 cups/day, respectively), the associations were not significant for high BP, SBP or DBP.

4. Discussion

The present study showed an association between GRS, derived from four SNPs related to BP, and high BP in a population-based study of residents in São Paulo City, Brazil. Furthermore, it also found a significant interaction between usual coffee consumption and genetic predisposition in relation to BP among this population.

Several epidemiological studies on the effect of coffee consumption on BP have been published, but they have provided inconsistent and contradictory results [18–20]. Some research suggested a positive association between coffee consumption and increase BP [21,36], whereas others reported an inverse association [16,17]. The acute effects of caffeine intake are well-known [19,21], but the effect of long-lasting coffee consumption on BP is still unclear [18–20]. This finding suggests that although the acute ingestion of caffeine increases BP, when ingested via coffee its hypertensive effect may be somehow attenuated, so, it seems that other compounds of coffee could potentially counterbalance the negative effect of caffeine. Coffee is a complex mixture of a wide number of different bioactive chemicals, rich in BP-lowering minerals (i.e., potassium and magnesium), soluble fiber, and polyphenols that may outweigh the pressor effects of caffeine [18].

Table 1
Panel of genetic variants, minor allele frequency and Hardy–Weinberg equilibrium of the polymorphisms used to calculate the genetic risk score for blood pressure. ISA-Capital 2008. São Paulo, Brazil.

Polymorphisms	Location	Gene	Changes in DNA	MAF	Position
rs2470893	15q24	*CYP1A1/CYP1A2*	C>T	0.22	Upstream variant
rs2472297	15q24	*CYP1A1/CYP1A2*	C>T	0.10	Intergenic variant
rs6495122	15q24	*CPLX3/ULK3*	A>C	0.07	Intergenic variant
rs17367504	1p36	*MTHFR*	A>G	0.12	Intron variant

All polymorphisms were in Hardy–Weinberg equilibrium (*P*-value >0.05).
CPLX3, complexin 3; *CYP1A1*, cytochrome P450 family 1 subfamily A member 1; *CYP1A2*, cytochrome P450 family 1 subfamily A member 2; *MAF*, minor allele frequency; *MTHFR*, 5,10-methylenetetrahydrofolate reductase; *ULK3*, unc-51 like kinase 3.

Table 2
Genotype frequencies of the polymorphisms (SNPs) and general characteristics of the study population according to genotypes (N = 533). ISA-Capital 2008. São Paulo, Brazil.

Characteristics	*CYP1A1/CYP1A2* C>T (rs2470893)			*p*-value[c]	*CYP1A1/CYP1A2* C>T (rs2472297)			*p*-value[c]	*CPLX3/ULK3* A>C (rs6495122)			*p*-value[c]	*MTHFR* A>G (rs17367504)			*p*-value[c]
	C:C	C:T	T:T		C:C	C:T	T:T		A:A	A:C	C:C		A:A	A:G	G:G	
Total, %	58.0	39.6	2.4		80.7	18.9	0.4		85.9	14.1	0.0		76.2	23.0	0.8	
Sex, % [a]																
Male	56.3	41.4	2.3	0.768	77.8	21.4	0.8	0.363	90.2	9.8	0.0	0.031	77.2	22.7	0.1	0.161
Female	59.5	38.0	2.5		83.3	16.7	0.0		82.4	17.6	0.0		75.3	23.3	1.4	
Age (years), median (IQR) [b]	36 (28−48)	57 (42−68)	53 (33−58)	<0.001	42 (31−56)	47 (34−57)	53 (53 −53)	0.179	43 (31−56)	47 (32−64)	–	0.241	43 (32−57)	42 (30−53)	52 (32−58)	0.390
Self-declared skin colour, % [a]																
White	53.0	43.4	35.7	0.040	75.4	23.9	0.6	0.063	81.7	18.3	0.0	0.019	78.0	21.1	0.9	0.372
Black	58.4	40.8	0.8		82.3	17.7	0.0		95.7	4.3	0.0		61.3	38.7	0.0	
Others (Mixed, Asian/Indigenous)	66.9	32.5	0.6		90.0	10.0	0.0		91.0	9.0	0.0		75.7	23.5	0.8	
Smoking status, % [a]																
Non-smoker	61.7	36.0	2.3	0.074	85.7	14.3	0.0		85.5	14.5	0.0		76.4	22.8	0.8	
Former smoker	46.6	48.0	5.4		84.0	14.0	2.0	0.003	80.3	19.7	0.0	0.161	76.2	22.0	1.8	0.779
Current smoker	58.1	41.5	0.4		66.1	33.9	0.0		91.0	9.0	0.0		75.7	24.3	0.0	
Leisure-time physical activity levels, % [a]																
Low	56.6	40.8	2.6	0.159	79.5	20.1	0.4	0.328	86.3	13.7	0.0	0.576	77.2	21.9	0.8	0.214
Moderate or high	69.3	29.9	0.8		90.7	9.3	0.0		82.8	17.2	0.0		67.7	31.8	0.5	
Blood pressure (mm Hg), % [a]																
Normal	65.0	32.2	2.8	0.007	81.6	17.9	0.5	0.708	84.9	15.1	0.0	0.068	74.7	24.3	1.0	0.027
High	37.3	62.7	0.0		76.6	23.4	0.0		92.4	7.6	0.0		91.7	8.3	0.0	
Coffee consumption (cups *per* day), % [a]																
<1	64.8	33.1	2.1		84.0	14.9	1.1		83.9	16.1			78.6	21.3	0.1	
1−3	55.2	41.8	3.0	0.310	81.0	19.0	0.0	0.430	85.4	14.6	0.0	0.638	76.8	22.3	0.9	0.646
>3	53.0	44.8	2.2		76.7	23.3	0.0		88.7	11.3	0.0		72.7	25.9	1.4	
Alcohol consumption (g/day), % [a]																
No	60.6	38.0	1.4	0.573	87.8	12.2	0.0	0.077	87.1	12.9	0.0	0.621	72.3	26.9	0.8	0.436
Yes	56.6	40.4	3.0		76.9	22.5	0.6		85.2	17.8	0.0		78.2	20.9	0.8	
Body Mass Index (kg/m^2), median (IQR) [b]	24.8 (22.5, 28.4)	26.1 (22.9, 29.9)	27.2 (23.9, 31.0)	0.017	25.8 (23.1, 29.9)	25.0 (22.7, 29.5)	–	0.770	25.8 (23.3, 29.5)	25.1 (22.8, 29.1)	–	0.480	25.6 (23.3, 29.4)	25.7 (21.3, 30.6)	28.7 (22.8, 33.9)	0.971
Caffeine intake (mg/d), median (IQR) [b]	91.0 (54.4123.7)	90.5 (63.0, 130.2)	95.3 (69.2, 114.1)	0.595	93.0 (58.8, 123.6)	85.7 (55.1, 132.4)	69.2 (69.2, 69.2)	0.948	92.8 (59.4, 130.2)	80.8 (33.2, 116.7)	–	0.178	87.8 (55.1, 118.0)	100.5 (69.7, 155.9)	112.7 (103.2, 139.7)	0.008
Total energy intake (kcal/d), median (IQR) [b]	1741.3 (1415.5, 2013.7)	1638.3 (1306.6, 2054.5)	1850.3 (1279.2, 2168.7)	0.348	1683.2 (1359.6, 2004.8)	1808.4 (1391.6, 2310.8)	1534.0 (1534.0, 1534.0)	0.189	1697.0 (1354.0, 2018.4)	1698.1 (1391.7, 2081.8)	–	0.831	1683.3 (1337.7, 2060.7)	1752.3 (1461.8, 2017.4)	1217.0 (1217.0, 1808.4)	0.416

The effect allele (EA) for rs2470893was T; the EA for rs2472297 was T; the EA for rs6495122 was A, and the EA for rs17367504 was G.
The sample weight was considered for statistical analysis.
[a] *p*-value for the Chi−Square test.
[b] *p*-value for the Kruskal−Wallis test.
[c] The p-value <0.05 was considered statistically significant.

Table 3
Crude and adjusted odds ratios (95% CI) for high blood pressure (BP), high systolic BP and high diastolic BP across genetic risk score (GRS). ISA-Capital 2008. São Paulo, Brazil.

GRS	High BP	*P*-value[a]	High Systolic BP	*P*-value[a]	High Diastolic BP	*P*-value[a]
Individuals, %	11.5		18.6		14.0	
OR (95% IC)						
Model 1 (crude)	2.52 (1.63, 3.90)	<0.001	1.31 (0.88, 1.96)	0.186	1.80 (1.26, 2.56)	0.001
Model 2 (adjusted)	1.85 (1.19, 2.87)	0.007	2.30 (1.32, 4.01)	0.004	1.66 (1.10, 2.51)	0.016

Odds ratio (OR) and 95% Confidence Interval (CI) were calculated by using multiple logistic regression.
Model 1 – Crude.
Model 2 – Adjusted for age, sex, race/skin color, smoking status, leisure-time physical activity, body mass index, current use of alcoholic beverages, total energy intake, sodium intake, and antihypertensive drugs.
The sample weight was considered for statistical analysis.
The reference category considered in logistic regression analysis was GRS equal to zero (GRS = 0).
High BP (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg); high SBP (≥140 mmHg); high DBP (≥90 mmHg).
[a] The *P*-value <0.05 was considered statistically significant.

Among these, polyphenols particularly phenolic acids, seem to have a protective role in the cardiovascular system due to their extensive antioxidant activity, anti-inflammatory properties, improvement in endothelial function and, inhibition of platelet aggregation and antithrombotic properties [22,23]. In recent years, epidemiological investigations have suggested that dietary consumption of chlorogenic acid (CGA) can has a considerable lowering effect on systolic and diastolic BP in humans [37,38]. Mechanistically, the CGA, particularly their metabolites caffeic and ferulic acids, attenuate oxidative stress (i.e., reactive oxygen species), which leads to the benefit of blood-pressure reduction through improved endothelial function and nitric oxide bioavailability in the arterial vasculature [23,38].

In this context, it is well known, that considerable variability exists in the cardiovascular responses to coffee drinking. In part, such variability is due to tolerance to caffeine and effects of BP-lowering compounds, such as phenolic acids, but there is evidence that some may have a genetic predisposition [39].

The BP associated loci were recently identified by genome-wide association studies [6,7,9]. GWAS have prompted improvements in hypertension genomics research, highlighting novel pathways influencing BP and clarifying genetic mechanisms underlying BP regulation [4]. The results of current study showed a significant and positive association between the combination of all four genetic risk variants and high BP in a Brazilian population, which showed consistent direction as reported in the Global BPgen and the CHARGE Consortiums [6,7]. However, the biological roles of these genetic loci in relation to high BP are poorly understood. The mechanisms by which these common variants contribute to affect higher BP remain unexplained and need to be investigated [6,8]. The *CPLX3/ULK3* polymorphism is associated with altered expression of *ULK3* in liver; however, little is know about *ULK3* and how variation in this gene might affect BP [6]. Other genetic variant considering in GRS was *MTHFR* gene. It has been described that the variant genotypes can decrease enzyme activity and reduce folate levels, and consequently result in hyperhomocysteinemia [40].

Table 4
Genetic risk score (GRS)-coffee consumption interaction and associations between the GRS with high blood pressure (BP), high systolic BP and high diastolic BP stratified by categories of coffee consumption. ISA-Capital 2008. São Paulo, Brazil.

GRS	Total population[a]	Coffee consumption, *cups per day*			*P*-value for interaction[b]
		<1	1–3	>3	
High BP					
High BP/normal BP, n	70/344	24/117	20/120	26/107	–
BP (mmHg), median (IQR)	198 (181, 216)	198 (179, 217)	196 (176, 210)	200 (186, 220)	
OR (95% CI)					
Model 1 (crude)	1.82 (1.28, 2.60)	1.94 (1.01, 3.72)	2.20 (1.08, 4.52)	3.57 (1.71, 7.45)	0.001
Model 2 (adjusted)	1.55 (1.06, 2.28)	1.15 (0.46, 2.87)	1.36 (0.58, 3.20)	5.09 (1.32, 19.7)	0.026
High Systolic BP					
High BP/normal BP, n	169/364	58/123	53/127	58/114	–
Systolic BP (mmHg), median (IQR)	121 (111, 134)	121 (108, 133)	120 (111, 130)	124 (113, 138)	
OR (95% CI)					
Model 1 (crude)	2.03 (1.42, 2.90)	1.26 (0.50, 3.20)	3.04 (1.49, 6.24)	3.86 (1.83, 8.17)	<0.001
Model 2 (adjusted)	1.38 (1.02, 1.87)	0.55 (0.27, 1.14)	2.01 (0.95, 4.24)	2.14 (1.12, 4.11)	0.035
High Diastolic BP					
High BP/normal BP, n	90/443	30/151	27/153	33/139	–
Diastolic BP (mmHg), median (IQR)	76 (69, 84)	76 (69, 85)	76 (68, 82)	76 (70, 85)	
OR (95% CI)					
Model 1 (crude)	1.45 (1.15, 1.82)	1.44 (0.91, 2.30)	1.68 (0.73, 3.84)	2.33 (1.44, 3.75)	0.002
Model 2 (adjusted)	1.36 (1.04, 1.78)	1.18 (0.63, 2.23)	1.56 (0.88, 2.78)	3.54 (1.17, 10.75)	0.026

Odds ratio (OR) and 95% Confidence Interval (CI) were calculated by using multiple logistic regression.
Model 1 – Crude.
Model 2 – Adjusted for age, sex, race/skin color, smoking status, leisure-time physical activity, body mass index, current use of alcoholic beverages, total energy intake, sodium intake, and antihypertensive drugs.
The sample weight was considered for statistical analysis.
High BP (SBP≥140 mmHg and/or DBP≥90 mmHg); high SBP (≥140 mmHg); high DBP (≥90 mmHg).
The reference category considered in logistic regression analysis was GRS equal to zero (GRS = 0).
The reported OR values are based on one-point increments in GRS.
[a] Interaction between coffee consumption and genetic risk score.
[b] The *P*-value <0.05 was considered statistically significant.

High levels of homocysteine has been linked to cardiovascular disease, namely, high BP, and hypertension in pregnancy (HIP) because it may induce vasoconstriction, arterial stiffness, renal dysfunction and increase sodium reabsorption, and also rise oxidative stress [41]. Thus, recent studies provide evidence that the *MTHFR* C677T polymorphism is associated with hypertension and HIP, particularly among East Asians and Caucasians [41], and the *MTHFR* A1298C mutation accompanied by hyperhomocysteinemia jointly elevated DBP [42].

Other polymorphisms are related to *CYP1A1* and *CYP1A2* genes. It is known that the cytochrome P450 enzymes in the liver have a key role in coffee metabolism [9]. *CYP1A2* is the main enzyme that metabolizes caffeine to the dimethylxanthine metabolites theobromine, paraxanthine, and theophylline [43]. Indeed, CYP1A2 has been shown to account for more than 95% of hepatic caffeine clearance [44], whereas its coregulated homolog *CYP1A1*, also known as AHH (aryl hydrocarbon hydroxylase), metabolizes polycyclic aromatic hydrocarbons such as benzo(a) pyrene, which is a component of coffee [45]. The *CYP1A1* T3801C polymorphism, associated with a higher *CYP1A1* inducibility and enhanced catalytic activity, has been linked to stroke, triple vessel disease and may therefore, be related with high BP [46]. Additionally, *CYP1A2* variants, and its activity, could influence BP through the effect of caffeine on renal segmental tubular sodium handling [47]. Polymorphisms in the *CYP1A2* gene are known to moderate the association between coffee consumption and hypertension [48] or myocardial infarction [24]. Thus, *CYP1A2* genotype may have relevant influences on the pressor effect of coffee [48].

Different individuals have different risks, and coffee or caffeine consumption can modulate the risk of developing cardiovascular disease from genetic predisposition [39]. In the current study, we provided novel evidence based on gene–diet interaction that usual coffee consumption and genetic predisposition may interact with each other and synergistically influence BP, that is, the coffee consumption could modify the associations between genetic risk and high BP. This interaction between coffee consumption and the genetic risk score to BP was independent of multiple sociodemographic, diet and lifestyle factors. We adjusted for the potential confounders factors that previously described in literature and showed a significant association with genetic predisposition to BP, and the results remained significant and unchanged. The observed interaction on BP might reflect the cumulative effects of multiple genetic variants rather than any single variant.

Determination of the precise mechanism underlying the identified interaction will require more studies, because until now the mechanisms involved in the interaction between coffee consumption and the genetic predisposition to BP are unclear and incompletely understood. Thus, future research is needed to explore the pathways underlying such gene–diet interactions that lead to high BP.

Some points should be considered in interpreting the findings of the present study. Firstly, our data are related to the cross sectional study design then inferences of causality among coffee consumption, genetic variants, and high BP are not allowed. Secondly, the unweighted GRS was considered because the relative effect size (β coefficient) to some SNPs was not available in the GWAS. Finally, the participants included in our study were adults and older adults of multiple ethnicities recruited in a Brazilian population, and it is unknown whether our findings could be generalized to other demographic or ethnic groups. On the other hand, considering the differences of genetic backgrounds between Europeans descendent and other ethnic populations, the contribution of these loci to BP in other ethnicities and the mechanisms by which they increase BP need to be investigated.

Notwithstanding these limitations, the major strength of the current study is that it offers findings of the gene–diet interactions, i.e. data-linking coffee intake, genetic predisposition and change in BP in a representative sample of São Paulo population. Furthermore, the present analyses include the use of a genetic risk score combining genetic information of four variants related with BP. The characterization of this new GRS can serve as a basis for future approaches to early detection of high risk in individuals, and for the development of novel therapies for the prevention or treatment of hypertension.

5. Conclusions

In summary, the present data provide evidence that usual coffee consumption and genetic predisposition to BP may interact with each other and influence BP in a Brazilian population, and the association between genetic risk and high BP is modified by coffee consumption level. Thus, individuals with higher GRS are associated with high BP, SBP and DBP, among those who drank more than 3 cups of coffee *per* day. Our findings further emphasize the importance to reduce coffee consumption in the prevention of high BP, particularly in individuals genetically predisposed to this cardiovascular disease risk factor.

Authors' contributions

A.M.M., R.M.F. and D.M.M. conceived and designed the research. A.M.M. drafted and wrote the manuscript, and has the primary responsibility for the final content. A.M.M., J.S. and M.M.N. analysed the data. J.S. and D.M.M. were responsible for critical analysis and final review. All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare that they have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.07.033.

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