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Adiposity and insulin resistance mediate the inverse association between legume intake and blood pressure: a cross-sectional analysis in secondary cardiovascular prevention

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Abstract

This study aimed to evaluate the association between legume intake and blood pressure, as well as the mediating role of cardiometabolic risk factors in patients in secondary cardiovascular prevention. Socio-demographic, anthropometric, clinical and food intake data were collected from the baseline of the multicentre study Brazilian Cardioprotective Nutritional Program Trial – BALANCE (RCT: NCT01620398). The relationships between variables were explored through path analysis. In total, 2247 individuals with a median age of 63·0 (45–91) years, 58·8 % (*n* 1321) male and 96·5 % (*n* 2168) with diagnosis of hypertension were included. Negative associations were observed between histidine intake and systolic blood pressure (SBP) (standardised coefficient (SC) = −0·057; $P = 0{\cdot}012$) and between legume intake and BMI (SC = −0·061; $P = 0{\cdot}006$). BMI was positively associated with triglycerides–glucose (TyG) index (SC = 0·173; $P < 0{\cdot}001$), SBP (SC = 0·144; $P < 0{\cdot}001$) and diastolic blood pressure (DBP) (SC = 0·177; $P < 0{\cdot}001$), and TyG index was positively associated with DBP (SC = 0·079; $P = 0{\cdot}001$). A negative indirect effect was observed between the intake of legumes, SBP and DBP, mediated by BMI (SC = −0·009; $P = 0{\cdot}011$; SC = −0·011; $P = 0{\cdot}010$, respectively). In addition, an indirect negative effect was found between the intake of legumes and the DBP, mediated simultaneously by BMI and TyG index (SC = −0·001; $P = 0{\cdot}037$). In conclusion, legume intake presented a negative indirect association with blood pressure, mediated by insulin resistance (TyG) and adiposity (BMI) in individuals of secondary care in cardiology.

Key words: Triglycerides–glucose (TyG) index: BMI: Path analysis: Food intake: Dietary plant proteins

Hypertension (HTN) is a multifactorial clinical condition characterised by sustained high blood pressure levels. It affects 1·13 million people worldwide and is considered one of the main risk factors for CVD(1,2). Moreover, the HTN is a recognised metabolic consequence of insulin resistance (IR), an impaired response to insulin stimulation in target tissues (liver, muscles and adipose tissue)(3). Among the various techniques used to assess IR, the triglycerides–glucose (TyG) index stands out as an easy-to-apply test with high sensitivity and specificity(4). The TyG index has already been associated with the presence of HTN or high blood pressure(5–8).

Excess weight and body fat also contribute to metabolic changes that lead to increased levels of insulin, IR and cardiometabolic risk(3). In a cross-sectional study with 1730 adults of both sexes, IR, assessed by the TyG index, was associated with the presence of HTN(9). In a cohort study of 6078 men and women that evaluated the role of the TyG index in predicting the development of CVD, it found that individuals in the higher TyG quartiles had higher systolic blood pressure (SBP) values and a higher risk for CVD(10). However, few studies have evaluated the interrelationship between IR, assessed by the TyG index, excess body weight and food consumption(11) on increased blood pressure.

Abbreviations DBP, diastolic blood pressure; HTN, hypertension; IR, insulin resistance; SBP, systolic blood pressure; SC, standardised coefficients; TyG, triglycerides–glucose; R24h, 24-hour dietary recalls.

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Food is an important adjustable factor for the prevention of cardiometabolic disorders, such as HTN, and the reduction in the recurrence of cardiac events in secondary care patients in cardiology(12). The legume food group, which consists of beans, peas and lentils(13), has important bioactive components, such as folate, Fe, K, Mg, soluble fibre and amino acids. These components have beneficial effects on energy regulation and metabolic functions, helping to maintain an adequate weight and, consequently, blood pressure(2,14,15). A higher consumption of vegetable protein (legumes and nuts) was associated with a lower incidence of the metabolic syndrome in disease-free adults followed for 11·2 years in Australia(16). After 15 years of follow-up, there was a reduction in the blood pressure of men (70·1 (SD 4·6) years of age) with a higher consumption of vegetable protein(17). A cohort study that examined the associations of protein intake with mortality risk in adult men and women without CVD also found a lower risk of CVD mortality in individuals with a higher intake of plant protein(18).

Amino acids can play an important role in CVD(19–21). Some amino acids with potential cardioprotective roles(19), such as glutamic acid, arginine, glycine, cysteine, leucine and histidine, are present in meat, fish, eggs, dairy products, vegetables, fruits, legumes, whole cereals and nuts. They act through the nitric oxide synthesis pathway(22,23), catecholamine synthesis control(24) and glycaemic control(25–27). However, studies that assess the relationship between the cardioprotective amino acids intake, their main dietary sources and cardiometabolic risk factors are scarce(19,28). Therefore, further studies are needed to investigate the relationships between amino acids and food groups with blood pressure levels, mainly in secondary care patients in cardiology. Therefore, the objective of the present study was to evaluate the association between legume intake and blood pressure, as well as the mediating role of cardiometabolic factors in individuals in secondary cardiovascular prevention.

Methods

This study was conducted with the baseline data of the multicentre study Brazilian Cardioprotective Nutritional Program Trial (BALANCE Program Trial). The BALANCE Program Trial was designed and coordinated by researchers from the Instituto de Pesquisa of Hospital do Coração in partnership with the Programa de Apoio ao Desenvolvimento Institucional do Sistema Único de Saúde (PROADI-SUS) of Brazilian Ministry of Health, registered on the ClinicalTrials.gov (NCT01620398). The study was a multicentre project conducted throughout the country, with thirty-four collaborating centres spread across the five regions of Brazil. The main objective of this study was to investigate the effects of the Brazilian cardioprotective food programme on the secondary prevention of cardiovascular events. The methodology of this project is detailed elsewhere(29).

Subjects

Adult and elderly individuals of both sexes, aged 45 years or older, who had at least one CVD (coronary disease, stroke and/or peripheral vascular disease) within the last 10 years were included. All eligibility criteria are reported in the study protocol(29).

Among the 2535 participants of the BALANCE Program Trial, 2247 had complete baseline data on food consumption and were included. Individuals who had non-plausible daily energetic intake (<2092 or >25104 kj/d - <500 or >6000 kcal/d) were excluded from the analyses(30).

Ethics

The study was approved by the Hospital do Coração Ethics Committee (Protocol number nº: 1.171.748), Human Research Ethics Committee of the Universidade Federal de Viçosa (Protocol number nº: 882,612 and 1,020,056) and all the ethics committees of the other participating centres, following Brazilian and international ethical principles(31). The study began only after all centres approved the protocols(29) and the patients signed an informed consent form.

Food assessment

Energy intake, contents of carbohydrates, fibres, proteins, cardioprotective amino acids (arginine, glutamic acid, cysteine, glycine, histidine, leucine and tyrosine), branched amino acids (isoleucine, leucine and valine) and lipids, and food groups (cereals, vegetables, nuts and seeds, dairy products, legumes, fruits, eggs and meats, and fish) were evaluated by the mean food consumption recorded in two 24-h dietary recalls (R24h). The method used to apply the R24h was based on the Automated Multiple-Pass Method(32). Quantitative analysis of the foods was performed on the Nutriquanti® software. The R24h were collected during the inclusion of patients in the study, and all seasons and periods of the year were considered. All centres participating in this study collected the same data.

Amino acid intake was estimated using the National Nutrient Database for Standard Reference (USDA)(33). The estimated composition of foods reported in the R24h, but not listed in the USDA table, was obtained by comparison with those that had similar nutritional compositions and cooking methods. The preparations were split into their constituent ingredients and, if no compositional match could be found for a prepared food, the composition of the raw ingredients was used instead. Amino acids intake was estimated with an electronic spreadsheet (Microsoft Excel®) developed especially for this purpose. Foods and preparations were categorised into food groups by compositional similarity(34). All food intake variables were adjusted for daily energy intake using the residual method(35).

Demographic and behaviour variables

Data on demographic characteristics (sex and age), health-related behaviour such as physical activity (evaluated through the International Physical Activity Questionnaire)(36,37) and smoking, medication usage (anti-diabetic and antihypertensive drugs) and history of CVD (coronary disease and peripheral vascular disease) were collected by structured questionnaires applied by trained interviewers.

Anthropometry and blood pressure

Weight (kg), height (m) and waist circumference (cm)(38) were measured by trained professionals. The BMI was calculated as

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weight/height^2 (kg/m^2), and participants were classified with excess body weight when BMI ≥ 25 kg/m^2 (adults – <60 years) or 27 kg/m^2 (elderly – ≥ 60 years)(39,40). The waist-to-height ratio was calculated by dividing waist circumference by height (cm)(41). Blood pressure was measured following the American Heart Association's recommendations. HTN was diagnosed when SBP ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg and/or use of the antihypertensive drug(42).

Metabolic biomarkers

Blood samples were collected after 12–14 h of fasting. Classical cardiovascular risk markers, such as fasting glycaemia, TAG, total cholesterol and HDL-cholesterol, were evaluated. LDL-cholesterol was determined by the Friedewald formula. TyG index was calculated by the formula: Natural Logarithm (Ln) (fasting TAG (mg/dl) × fasting glucose (mg/dl)/2)(4). The LDL-cholesterol/HDL-cholesterol ratio was also calculated. Dyslipidaemia was defined as the presence of one or more of the following conditions: TAG ≥ 150 mg/dl; LDL-cholesterol ≥ 130 mg/dl; HDL-cholesterol ≤ 45 mg/dl and use of lipid-lowering medication(43). Type 2 diabetes mellitus was diagnosed when fasting blood glucose ≥ 100 mg/dl or the patient was using anti-diabetic drugs(44).

Statistical analysis

All descriptive statistics were analysed on the SPSS v.23 software for Windows (SPSS, Inc.). The normality of the data was evaluated by the Shapiro–Wilk test. The data are presented here as mean values and standard deviation, median (interquartile range) or absolute and relative frequency, when appropriate. Comparisons across quartiles of legume intake, histidine intake and TyG index were assessed by Kruskal–Wallis test or the χ^2 test, for continuous and categorical variables, respectively.

The MPlus® software, version 5.0, was used to explore the interrelationships between variables through path analysis. Path analysis, a subset of structural equation modelling(45), is an extension of the regression analysis that simultaneously estimates the linear associations between all variables in a model(46), which allows the evaluation of the total, direct and indirect effects of each variable on the outcome. Direct effects represent the direct relationships between two variables, interpreted similarly to a regression coefficient. Indirect effects, on the other hand, express a sequence of paths with at least one intermediate or mediating variable and are obtained by multiplying the direct effects between the variables belonging to that path. Finally, the total effect is calculated from the sum of direct and indirect effects between two variables(47,48). In this study, the term 'effect' is used to indicate association, not causality.

To evaluate the relationships of the intake of proteins, amino acids or source foods with blood pressure levels (SBP and DBP), several theoretical models were constructed according to the scientific literature on these relationships. All variables collected and available in the database that could mediate the relationship between food consumption and blood pressure were included in the models. The possibility of constructing latent variables or constructs (sets of variables)(48), with food groups, branched amino acids and cardioprotective amino acids, was also evaluated; however, the construct variables showed excessively high correlations, indicating that, in this case, the indicators were measuring the same aspect of the constructs(47). Based on these findings, the intake of each amino acid was tested separately.

After finding a model with a good fit and with an amino acid (histidine) that was related to blood pressure, the correlation between histidine and groups of foods that are sources of protein and also had a relationship with the outcome (i.e. blood pressure) was evaluated. This procedure was implemented aiming at enriching the model and bringing more complex relationships between food consumption, the outcome and the potential mediators. Finally, the final model was constructed (Fig. 1), which presented a good fit and demonstrated the relationship of the consumption of legumes and histidine from food and blood pressure. Additional adjustments to the model were age, sex, physical activity, smoking, the use of anti-diabetic and antihypertensive drugs.

The results are presented as standardised coefficients (SC), with their respective standard error and *P* values. The robust maximum likelihood method was used to estimate the parameters. This is a robust estimator that does not require the assumption of normal multivariate data distribution(47). To verify the fit of the model, the root mean square error of approximation and standardised root mean square residual were evaluated. These values are based on model residuals, with values <0·06 indicating that the theoretical model fits the data(49,50). Finally, the Tucker–Lewis index and comparative fit index were estimated, with values above 0·90 indicating a good fit(47). For all analyses, the significance level was set at 5 %.

Results

The sample included 2247 participants who underwent secondary care for CVD. The median age was 63·0 (45–91) years, 58·8 % (*n* 1321) of the participants were male and 96·5 % (*n* 2168) were diagnosed with HTN. The mean of the SBP and DBP was 129·6 (SD 22·7) mmHg and 78·6 (SD 4·36) mmHg, respectively. The mean of the TyG index, BMI, and legume and histidine intake was 8·6(SD 1·9), 29·1 (SD 4·9) kg/m^2, 76·8 (SD 85·5) g/d and 1·79 (SD 0·96) g/d, respectively. The characteristics of the participants, according to quartiles of legume intake, histidine intake and TyG index (Q1 and Q4), are displayed in Table 1. Regarding legume intake, participants in the fourth quartile had lower BMI, waist-to-height ratio, total cholesterol and HDL-cholesterol than those in the first quartile. However, these individuals had higher values of LDL-cholesterol/HDL-cholesterol ratio compared with participants in the first quartile.

Participants in the fourth quartile of histidine intake had lower BMI, waist-to-height ratio, SBP, total cholesterol, LDL-cholesterol and HDL-cholesterol compared with the first quartile, and those with excess body weight were more often placed in the first quartile of histidine intake. Moreover, those in the fourth quartile of the TyG index presented higher values of anthropometry, blood pressure and metabolic markers compared with the first quartile. The use of anti-diabetic drugs and individuals with diabetes, dyslipidaemias and excess body weight were most often found in the fourth quartile (Table 1). The participants in the

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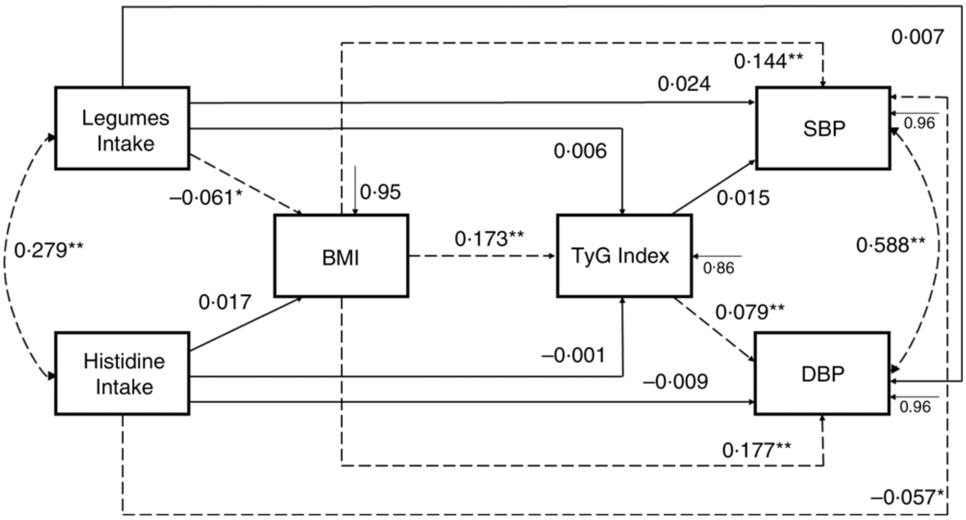

Dashed lines indicate paths with statistical significance. *p<0·05; **p<0·001. RMSEA/SRMR < 0·001; CFI/TLI = 1·000. R^2 BMI = 0·052; R^2 TyG index = 0·136; R^2 SBP and DBP = 0·043. The model was adjusted for sex (categorical variable: male or female), age (continuous variable), physical activity (categorical variable: sedentary lifestyle or physical activity practice), smoking (categorical variable: non-smoking or smokers) and use of antihypertensive and hypoglycemic agents (categorical variable: no or yes). BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure TyG: triglycerides/blood glucose index. Legumes intake, histidine intake, BMI, TyG index, SBP and DBP: continuous values.

Fig. 1. Path model of relationships between food intake, cardiometabolic risk factors and blood pressure, constructed based on the baseline data from the BALANCE Program Trial (*n* 2247). Dashed lines indicate paths with statistical significance. *P < 0·05; **P < 0·001. RMSEA/SRMR < 0·001; CFI/TLI = 1·000. R^2 BMI = 0 052; R^2 TyG index = 0·136; R^2 SBP and DBP = 0·043. The model was adjusted for sex (categorical variable: male or female), age (continuous variable), physical activity (categorical variable: sedentary lifestyle or physical activity practice), smoking (categorical variable: non-smoking or smokers) and use of antihypertensive and hypoglycaemic agents (categorical variable: no or yes). DBP, diastolic blood pressure; SBP, systolic blood pressure; TyG, triglycerides/blood glucose index. Legumes intake, histidine intake, BMI, TyG index, SBP and DBP: continuous values.

fourth quartile of legume intake exhibited higher values of intake of energy content, carbohydrates, fibre, proteins, cardioprotective amino acids, branched amino acids, cereals, vegetables, eggs and meats, when compared with the first quartile (Table 2). Furthermore, the subjects in the last histidine intake quartile had higher values of energetic and macronutrient intake, compared with the first quartile. Additionally, the participants in the fourth quartile of the TyG index displayed only lower values of carbohydrate intake (Table 2).

In the path analysis model (Fig. 1), histidine intake was negatively associated with SBP (SC = −0·057; P = 0·012) and legume intake was negatively associated with BMI (SC = −0·061; P = 0·006). Conversely, BMI was positively associated with TyG index (SC = 0·173; P < 0·001), SBP (SC = 0·144; P < 0·001) and DBP (SC = 0·177; P < 0·001). TyG index was positively associated with DBP (SC = 0·079; P = 0·001). Histidine and legume intake (r = 0·279; P < 0·05), and SBP and DBP (r = 0·588; P < 0·01) were positively correlated. In a second and third model (online Supplementary Material), additionally adjusted for fruit and vegetable intake, respectively, the present effects remained significant.

Table 3 presents the direct, indirect and total effects of the relationships between histidine and legume intake, BMI, TyG index, SBP and DBP. Significant negative indirect effects were observed for BMI-mediated relationships of legume intake with SBP (SC = −0·009; P = 0·011) and DBP (SC = −0·010; P = 0·011). An indirect negative effect of legume intake on DBP, mediated simultaneously by BMI and TyG index (SC = −0·001; P = 0·037), was also observed.

Discussion

This study contributes to the understanding of the relationships of intake of legumes and cardioprotective amino acids with blood pressure levels, as well as the mediating role of metabolic risk factors for HTN, such as adiposity (BMI) and IR (TyG index).

The first relevant results in the study are the negative indirect association of legume intake with SBP, mediated by BMI, and with DBP, mediated by BMI and TyG. Besides, the intake of legumes is negatively and directly associated with BMI. In this sense, legumes, which are rich in fibre, can control body weight owing to their reduced energy density, favouring the reduction of energy intake. Furthermore, legumes require more chewing before ingestion, increasing satiety and, thus, contributing to reducing the size of the consumed portions. Finally, nutrients from legumes are absorbed slowly, contributing to a greater feeling of satiety(51). Altogether, the consumption of legumes can directly influence body weight control, which in turn can prevent IR, both of which are important risk factors for the onset of uncontrolled blood pressure.

Additionally, legumes contain micronutrients, phytosterols and polyphenols, which bring other health benefits(52,53). Isoflavones and anthocyanins, bioactive compounds of the flavonoids class (polyphenols), have high antioxidant activity and can act on IR control. Anthocyanins activate the AMP-activated protein kinase, which in turn promotes the translocation of GLUT4 on the membrane, facilitating the transport and uptake of glucose to the muscle and, consequently, improving insulin sensitivity. Furthermore, the activation of AMP-activated protein

Table 1. Baseline characteristics of participants according to legume intake, histidine intake and TyG index quartiles, BALANCE Program Trial
(Medians and quartiles; frequencies and percentages)

	Legumes intake					Histidine intake					TyG index				
	Q1 (*n* 592)		Q4 (*n* 564)			Q1 (*n* 561)		Q4 (*n* 562)			Q1 (*n* 564)		Q4 (*n* 560)		
Variables *n*	Frequency	%	Frequency	%	*P*	Frequency	%	Frequency	%	*P*	Frequency	%	Frequency	%	*P*
Age (years)															
Median	62·0		62·0		0·246	63·0		62·0		0·590	63·0		61·0		0·009
Quartiles (p25–p75)	57·0–69·0		57·0–69·0			57·00–70·0		57·0–68·3			58·0–70·0		55·0–68·0		
Male (%)	321	24·3	407	30·8	<0·001	227	17·2	348	26·3	<0·001	338	25·6	335	25·4	0·725
Use of anti-diabetics (%)	240	25·9	248	26·7	0·498	231	24·9	230	24·8	0·932	153	16·5	368	39·7	<0·001
Use of antihypertensive (%)	558	26·2	535	25·2	0·156	532	25·0	523	24·6	0·306	519	24·4	537	25·3	0·072
Smokers (%)	366	26·3	376	27·1	0·119	327	23·5	361	26·0	0·185	332	23·9	368	26·5	0·160
Physical activity practice (%)	192	25·6	183	24·4	0·300	173	23·1	202	26·9	0·101	202	26·9	163	21·7	0·016
Diabetes (%)	318	26·9	307	26·0	0·565	298	25·2	294	24·9	0·994	179	15·1	456	38·5	<0·001
Dyslipidaemias (%)	482	26·2	479	26·0	0·164	448	24·4	482	26·2	0·040	344	18·7	550	29·9	<0·001
Hypertension (%)	569	26·2	548	25·3	0·469	544	25·1	538	24·8	0·558	536	24·7	543	25·0	0·381
Excess body weight (%)	376	27·0	321	23·1	0·070	377	27·1	343	24·7	0·023	285	20·5	406	29·2	<0·001
CAD (%)	554 (26·7		514	24·8	0·435	506	24·4	529	25·5	0·014	513	24·7	526	25·4	0·299
PAD (%)	69	26·8	62	24·1	0·851	69	26·8	58	22·6	0·738	63	24·5	71	27·6	0·761
	Median	Quartiles (p25–p75)	Median	Quartiles (p25–p75)		Median	Quartiles (p25–p75)	Median	Quartiles (p25–p75)		Median	Quartiles (p25–p75)	Median	Quartiles (p25–p75)	
Weight (kg)	74·9	65·5–86·0	74·7	65·2–84·2	0·265	73·2	64·9–83·4	77·7	68·6–86·5	<0·001	71·3	61·7–80·3	77·6	68·8–88·0	<0·001
BMI (kg/m^2)	28·7	28·8–32·4	28·0	25·1–31·1	0·003	29·3	26·3–32·5	28·3	25·6–31·8	0·001	27·2	24·4–30·2	29·8	26·9–32·9	<0·001
WC (cm)	99·8	91·5–108·0	98·5	91·0–105·8	0·395	99·3	92·0–107·1	100·0	92·7–108·0	0·119	95·8	88·0–102·8	102·5	95·5–110·7	<0·001
Waist-to-height ratio	0·61	0·57–0·67	0·60	0·56–0·65	0·002	0·63	0·58–0·68	0·61	0·57–0·65	<0·001	0·59	0·54–0·64	0·64	0·59–0·68	<0·001
SBP (mmHg)	130	120–140	130	120–140	0·893	130	120–145	127	116–140	<0·001	130	115–140	130	120–143	0·007
DBP (mmHg)	80	70–90	80	70–90	0·927	80	70–89	80	70–86	0·326	80	70–85	80	70–90	<0·001
Total cholesterol (mg/dl)	166	140–198	159	136–190	0·014	168	142–201	160	137–189	<0·001	150	131–176	181	156–213	<0·001
TAG (mg/dl)	137	98–187	139	96–194	0·733	135	95–191	136	94–192	0·864	77	60–91	244	192–315	<0·001
LDL-cholesterol (mg/dl)	86	66–112	85	64–109	0·257	89	69–116	84	65–111	0·003	79	57–101	89	65–114	<0·001
HDL-cholesterol (mg/dl)	42	35–51	39	32–47	<0·001	41	35–52	39	33–47	<0·001	44	34–56	37	32–44	<0·001
Blood glucose (mg/dl)	102·02	92–126	103	92–127	0·546	103	92–127	103	91–125	0·594	91	79–99	139	109–184	<0·001
TyG index	8·9	8·5–9·3	8·9	8·5–9·4	0·527	8·9	8·5–9·3	8·9	8·5–9·3	0·660	8·2	7·9–8·3	9·7	9·5–9·9	<0·001
LDL-cholesterol/HDL-cholesterol	3·4	2·2–4·8	3·7	2·4–5·4	0·040	3·3	2·1–5·1	3·5	2·3–5·1	0·427	1·7	1·3–2·2	6·7	4·6–9·0	<0·001

CAD, coronary disease; DBP, diastolic blood pressure; LDL-cholesterol/HDL-cholesterol, LDL-cholesterol/HDL-cholesterol ratio; PAD, peripheral artery disease; SBP, systolic blood pressure; TyG, triglycerides/blood glucose index; WC, waist circumference.

Data presented as frequency (%) or median and quartiles (p25–p75), when appropriate. *P* values according to χ^2 test for linear trends or Kruskal–Wallis test (by Mann–Whitney test of multiple comparison with Bonferroni correction). Legumes: Q1 (0·00–0·00 g/d) and Q4 (140·00–225·00 g/d); histidine Q1 (0·69–1·01 g/d) and Q4 (2·2·46–3·40 g/d); TyG index: Q1 (7·86–8·34) and Q4 (9·48–9·99).

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Table 2. Nutrients and food consumption of participants at baseline according to legume intake, histidine intake and TyG index quartiles, BALANCE Program Trial
(Medians and quartiles)

Variables	Legume intake					Histidine intake					TyG index				
	Q1 (*n* 592)		Q4 (*n* 564)			Q1 (*n* 561)		Q4 (*n* 562)			Q1 (*n* 564)		Q4 (*n* 560)		
	Median	Quartiles (p25–p75)	Median	Quartiles (p25–p75)	*P*	Median	Quartiles (p25–p75)	Median	Quartiles (p25–p75)	*P*	Median	Quartiles (p25–p75)	Median	Quartiles (p25–p75)	*P*
Energetic intake (kcal/d)	1374·2	1046·8–1853·6	1515·7	1227·9–1928·5	<0·001	1007·4	819·3–1268·6	1873·6	1504·4–229·1	<0·001	1439·9	1102·3–1785·7	1371·4	1047·7–1779·1	0·114
Carbohydrates (g/d)	184·1	142·8–253·9	213·5	170·5–277·2	<0·001	156·1	120·3–200·9	226·5	177·8–299·7	<0·001	200·5	150·5–258·6	184·6	145·2–237·3	0·010
Fibre (g/d)	12·5	8·0–17·5	28·8	22·3–35·4	<0·001	14·0	9·7–18·4	22·2	16·3–31·7	<0·001	17·8	12·6–24·9	17·5	12·8–24·8	0·168
Total lipids (g/d)	37·5	24·3–56·3	37·8	26·9–52·1	0·830	23·4	16·5–32·3	52·8	37·8–71·0	<0·001	35·4	23·9–49·3	36·8	25·7–54·4	0·152
Proteins (g/d)	63·6	45·9–88·5	75·4	58·4–102·8	<0·001	40·6	32·3–50·4	104·9	89·3–127·9	<0·001	67·1	49·8–87·8	65·2	48·1–91·5	0·558
Histidine (g/d)	1·4	0·9–2·0	2·0	1·5–2·7	<0·001	0·9	0·7–1·0	2·8	2·5–3·4	<0·001	1·6	1·1–2·2	1·6	1·1–2·2	0·837
Cardioprotective amino acids (g/d)	22·2	15·3–32·2	31·0	23·0–41·4	<0·001	13·9	10·9–16·0	41·8	36·6–50·7	<0·001	24·9	18·1–34·8	24·1	17·5–33·8	0·503
BCAA (g/d)	8·8	5·9–12·6	12·5	9·2–16·6	<0·001	5·4	4·2–6·3	17·2	14·9–20·4	<0·001	9·9	7·2–14·0	9·7	6·9–13·7	0·274
Cereals (g/d)	136·3	77·6–214·0	230·0	163·5–325·0	<0·001	142·5	87·5–195·0	222·0	150·0–324·6	<0·001	177·8	112·6–252·4	176·0	120·0–257·3	0·661
Vegetables (g/d)	64·5	6·5–156·4	90·8	32·1–184·8	<0·001	60·0	15·0–130·3	93·8	40·0–192·0	<0·001	75·0	22·5–155·5	75·0	24·3–160·8	0·278
Nuts and seeds (g/d)	0·0	0·0–0·0	0·0	0·0–0·0	0·210	0·0	0·0–0·0	0·0	0·0–0·0	0·426	0·0	0·0–0·0	0·0	0·0–0·0	0·329
Dairy products (g/d)	155·0	27·3–300·0	181·4	32·8–320·8	0·080	140·0	9·0–252·5	211·3	68·5–369·3	<0·001	185·0	40·0–333·8	155·0	35·0–310·0	0·210
Legumes (g/d)	0·0	0·0–0·0	160·0	140·0–225·0	<0·001	34·0	0·0–70·0	80·0	20·0–160·0	<0·001	52·5	0·0–105·0	65·0	0·0–130·0	0·124
Fruits (g/d)	196·3	40·0–370·0	205·5	55·0–410·0	0·381	155·0	40·0–335·0	252·5	70·0–441·3	<0·001	240·0	58·5–403·8	198·8	56·3–382·4	0·168
Eggs and meats (g/d)	100·0	40·0–169·5	136·0	77·2–210·0	<0·001	55·0	25·0–85·0	207·1	140·0–292·7	<0·001	110·0	58·1–170·0	118·8	60·0–180·0	0·239
Fish (g/d)	0·0	0·0–0·0	0·0	0·0–0·0	0·088	0·0	0·0–0·0	0·0	0·0–0·0	0·060	0·0	0·0–0·0	0·0	0·0–0·0	0·578

Data presented as frequency (%) or median and quartiles (p25–p75), when appropriate. *P* values according to χ^2 test for linear trends or Kruskal–Wallis test (by Mann–Whitney test of multiple comparison with Bonferroni correction). Legumes: Q1 (0·00–0·00 g/d) and Q4 (140·00–225·00 g/d); histidine Q1 (0·69–1·01 g/d) and Q4 (2·2 ·46–3·40 g/d); TyG index: Q1 (7·86–8·34) and Q4 (9·48–9·99). Food intake variables were adjusted for daily energy intake using the residual method.

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Table 3. Direct, indirect and total coefficients of the mediation relationships of the path model, using baseline data from the BALANCE Program Trial (*n* 2247)

Relationship	Mediators	Effects	Standardised coefficient	Standard error	*P*
Legume intake → SBP		Direct	0·024	0·022	0·269
	BMI	Indirect	−0·009	0·003	**0·011**
	TyG		0·000	0·0·00	0·774
	BMI → TyG		0·000	0·000	0·524
		Total	0·016	0·022	0·484
Histidine intake → SBP		Direct	−0·057	0·023	**0·012**
	BMI	Indirect	0·002	0·003	0·434
	TyG		0·000	0·000	0·954
	BMI → TyG		0·000	0·000	0·622
		Total	−0·054	0·023	**0·017**
Legume intake → DBP		Direct	0·007	0·022	0·749
	BMI	Indirect	−0·011	0·004	**0·010**
	TyG		0·001	0·002	0·756
	BMI → TyG		−0·001	0·000	**0·037**
		Total	−0·004	0·022	0·846
Histidine intake → DBP		Direct	−0·009	0·022	0·670
	BMI	Indirect	0·003	0·004	0·433
	TyG		0·000	0·002	0·954
	BMI → TyG		0·000	0·000	0·452
		Total	−0·006	0·022	0·779
BMI → SBP	TyG	Direct	0·144	0·022	<**0·001**
		Indirect	0·003	0·004	0·513
		Total	0·147	0·022	<0·001
BMI → DBP	TyG	Direct	0·177	0·023	<**0·001**
		Indirect	0·014	0·004	**0·002**
		Total	0·190	0·023	<**0·001**

DBP, diastolic blood pressure; SBP, systolic blood pressure; TyG, triglycerides/blood glucose index.
P values in bold have statistical significance ($P < 0·05$).

kinase contributes to the increasing of adiponectin in adipocytes. The adiponectin has documented anti-inflammatory and anti-diabetic effects. In turn, isoflavones can act on the adipose tissue by inhibiting the activity of the PPARγ, an essential regulator of adipocyte differentiation. PPARγ can decrease the accumulation of lipids in adipocytes, which contributes to glucose and lipid homoeostasis regulation. Also, isoflavones can act in the adipose tissue to reduce the concentration of resistin, an adipokine known to promote IR(54).

Legumes are also good sources of proteins, including histidine, a recognised cardioprotective amino acid(55). Based on that, another outstanding result was the direct and negative effect of histidine intake on SBP. Other authors have also found that a higher histidine intake was associated with lower values of SBP, DBP(19) and risk of CVD(19,28). The inverse association between serum concentrations of histidine and SBP has also been found(56). Histamine is a compound synthesised from histidine by the histidine decarboxylase. When the body release histamine, it can bind to the H3 receptor, a type of histaminergic receptor in the brain. As a consequence, the central nervous system signalling may result in increased nitric oxide concentrations(23), which has the effect of relaxing vascular smooth muscle, thereby reducing vascular resistance(57).

Positive direct associations between BMI and the TyG index and between BMI and SBP/DBP were observed as well. Individuals with excess weight and body fat, mainly visceral fat, have a low-grade chronic inflammation, which inhibits insulin signalling in the adipocytes. Lipolysis is more sensitive to the action of insulin. A failure to suppress lipolysis through the effect of insulin, especially in insulin-resistant visceral adipose tissue, leads to increased concentrations of free circulating fatty acids. These higher concentrations directly affect liver and muscle metabolism, further contributing to IR(3,58,59). In addition, the interaction of alterations caused by excess weight, such as IR, inflammation, oxidative stress and increased activity of the sympathetic nervous system, can result in endothelial dysfunction, changes in body haemodynamics and increased blood pressure levels(60,61). Moreover, the TyG index showed a positive direct association with DBP; other studies had already found an association between the TyG index and HTN(62–65). The IR may be involved in the molecular processes related to the development of HTN. Insulin, through the INSR-IRS1-PI3K-Akt-eNOS signalling pathway, stimulates the nitric oxide activation, favouring the vasodilation process of the vessels(66). However, there is a negative modulation of this pathway in IR conditions, reducing nitric oxide production. In this study, an association of IR (TyG index) was found only with DBP. This relationship can be justified by the fact that the increase in DBP or isolated diastolic HTN is mainly related to the rise in peripheral vascular resistance(67–69). It is known that IR favours the increase in peripheral vascular resistance through increased activity of the sympathetic nervous system(70).

The present study found relationships between legume intake and SBP (mediated by BMI) and DBP (mediated by BMI and IR). This finding was only possible through the application of path analysis, which allowed the verification of direct and indirect effects between two variables(71). It should be noted that both BMI and IR are important risk factors for HTN(2,3), and because the variables of food consumption assessed here have a direct effect on these risk factors, they can also contribute to the

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development of HTN. It is also noteworthy that dietary strategies are very important during the treatment of secondary care patients in cardiology to control blood pressure, aiming at a better quality of life and the prevention of the recurrence of cardiovascular events(12).

The strengths of the present study are its multicentre design, which evaluated a large number of individuals with CVD in all five regions of Brazil, and the robust data analysis strategy, including the path model analysis, which allows a simultaneous assessment of linear associations between all variables in a single model. The use of the TyG index making it a good method to predict IR(4,72,73) and cardiometabolic risk(5,62,64,74). This is one of the first studies to investigate the relationship between food intake and TyG index, and the first to indicate TyG as a metabolic pathway between food intake and blood pressure. However, there are also a few limitations. First, the cross-sectional design makes it hard to infer a cause–effect relationship between the results found here. Second, alcohol consumption and intake of Na, K, other nutrients related to cardiovascular health and use of dietary supplements were not evaluated. We really cannot rule out the possibility of residual confounding for these variables. Food consumption was assessed exclusively through the R24h; it does not provide an estimate of ‘usual or habitual intakes’, which would be important when investigating associations between food intake and health outcomes. However, when a study aims to determine the average intake for a group or population, only a single R24h can be performed, especially when the sample size is large enough(75). Additionally, this food survey has been used in epidemiological studies that evaluated the relation between food intake and cardiometabolic risk factors with promising results and acceptance by the scientific community(76–79). Finally, we did not measure serum histidine concentrations; however, plasma concentrations of amino acids may not directly reflect the consumption of these nutrients through the diet(20,80).

Conclusion

The higher consumptions of histidine and legumes have direct and mediated effects, respectively, that promote lower blood pressure. These results may contribute to the planning of dietary strategies for individuals with CVD, considering the beneficial effects of amino acids and vegetable food sources of protein on cardiovascular health.

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A. C. B.-F., C. R. T. and B. W. worked in the conception and design of the study. A. C. B.-F., C. R. T., B. W., H. H. M. H. and J. B. performed data collection. A. C. B-F., A. M., A. P. A., B. W., C. R. T., L. J. L., J. B. and H. H. M. H. performed the assembly, analysis and interpretation of the data. A. P. A. and H. H. M. H. wrote the manuscript. All authors read and approved the final manuscript.

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Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114521005018

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