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Original Article

Are dietary amino acids prospectively predicts changes in serum lipid profile?

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ABSTRACT

Background: Besides of dietary fat and carbohydrate, amino acids(AAs), as constituent components of dietary protein have been related with serum lipid levels. This study aims to examine the association between dietary AAs and prospective changes in serum lipid profile in adults.
Methods: Analyses were conducted on 3881 participants aged, 18–75 years of Tehran lipid and Glucose study, at baseline (2008–2011) and were followed for 3 years (2011–2014) to ascertain serum lipid profile changes. Dietary intakes of AAs were collected at baseline using food frequency questionnaire. Multiple linear regression adjusted for age, sex, body mass index, physical activity, smoking and daily intakes of energy, total fat, and fiber were used.
Results: The median(IQR) changes in triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) were 6.0(-19.0, −35.5), 9.0(7.0, −24.0), 1.0(-3.0, −6.0), and 5.2(-8.0, −18.6) mg/dl, respectively. Higher intakes of isoleucine, lysine, tyrosine, alanine, threonine, methionine, valine, histidine, aspartic acid, and branched chain, alkaline, and alcoholic AAs were positively associated with TGs-changes in the final adjusted model, whereas tryptophan, glutamic acid, and acidic AAs were negatively related to TG-changes. Alanine and tryptophan were associated with higher and lower LDL-C-changes, respectively. Lysine, alanine, methionine, aspartic acid, and alkaline AAs showed positive association with changes in TC, whereas tryptophan and glutamic acid had a negative association with TC-changes.
Conclusion: Our findings showed that some dietary amino acids have the potential to increase or decrease serum lipid profile.

1. Introduction

Elevated serum lipid concentrations are one of the well-known complications of global healthcare system and are known as main risk factor for cardiovascular disease [1,2]. This complication has attracted great attentions to look for every eventual serum lipid treatment or risk factor modification. The nutritional factors are recognized as one of the main determinants of serum lipid levels, which has been widely shown to have relationship with serum lipid profile in previous studies [3].

Serum lipid levels are modified not only by dietary fat and carbohydrate but also by dietary protein [4]. Regarding protein, attentions mostly have been paid to the animal and plant sources of dietary protein. However some researchers have found that protein source is not always important, and amino acids (AAs) and their balance are responsible for the protein effect on lipid metabolism [4,5].

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The protein intake and lipid profile associations have been extensively investigated [6]; whether as protein foods like soy, individual and group of AAs as a part of diet, or dietary supplement in animals and humans [7–9]. Few epidemiologic studies investigated the relation between serum lipid profile with usual amino acids intake [5,10–12]. Javadian et al. demonstrated that some dietary amino acids were associated with serum triglycerides (TGs), high density lipoprotein cholesterol (HDL-C), and total cholesterol (TC), however they observed no relation with low density lipoprotein cholesterol (LDL-C) [11]. In a cross sectional study in Brazilian adults, higher dietary intakes of branched chain amino acids (BCAA) in particular leucine was associated with lower TC/HDL-C and TG/HDL-C ratios [12].

Many nutrients and phytochemicals were investigated to detect their associations with lipid profile; however limited epidemiologic investigations were conducted to elucidate relation of usual dietary amino acids with lipid rpofile.

This prospective study was conducted for assessing the association between dietary amino acids and 3-year-change in plasma lipid profile among participants of the Tehran Lipid and Glucose Study (TLGS).

2. Methods

2.1. Participants

This study was conducted within the framework of the TLGS, a prospective study initiated in 1999 and aimed to determine the prevalence of non-communicable disease risk factors among Tehran's urban population [13], with participants monitored every 3 years; the baseline survey was a cross-sectional study (1999–2001), and surveys II (2002–2005), III (2006–2008), and IV (2009–2011) were prospective follow-up surveys (see Figs. 1).

In the fourth survey of the TLGS (2009–2011), from 12823 participants, 7956 randomly selected, agreed to complete dietary assessment. For the present study, from 6813 individuals, aged 18–75 years, those with prevalent cancer (n = 11), cardiovascular disease (n = 47), diabetic participants (n = 480), pregnant and lactating women (n = 106), participants taking corticosteroid, thyroid, hormone drugs, and lipid lowering drugs (n = 973), participants with under- or over-reported dietary intakes (less than 800 kcal/d or more than 4200 kcal/d, respectively) (n = 465), those on hyperlipidemia diet (n = 558), and those who had not

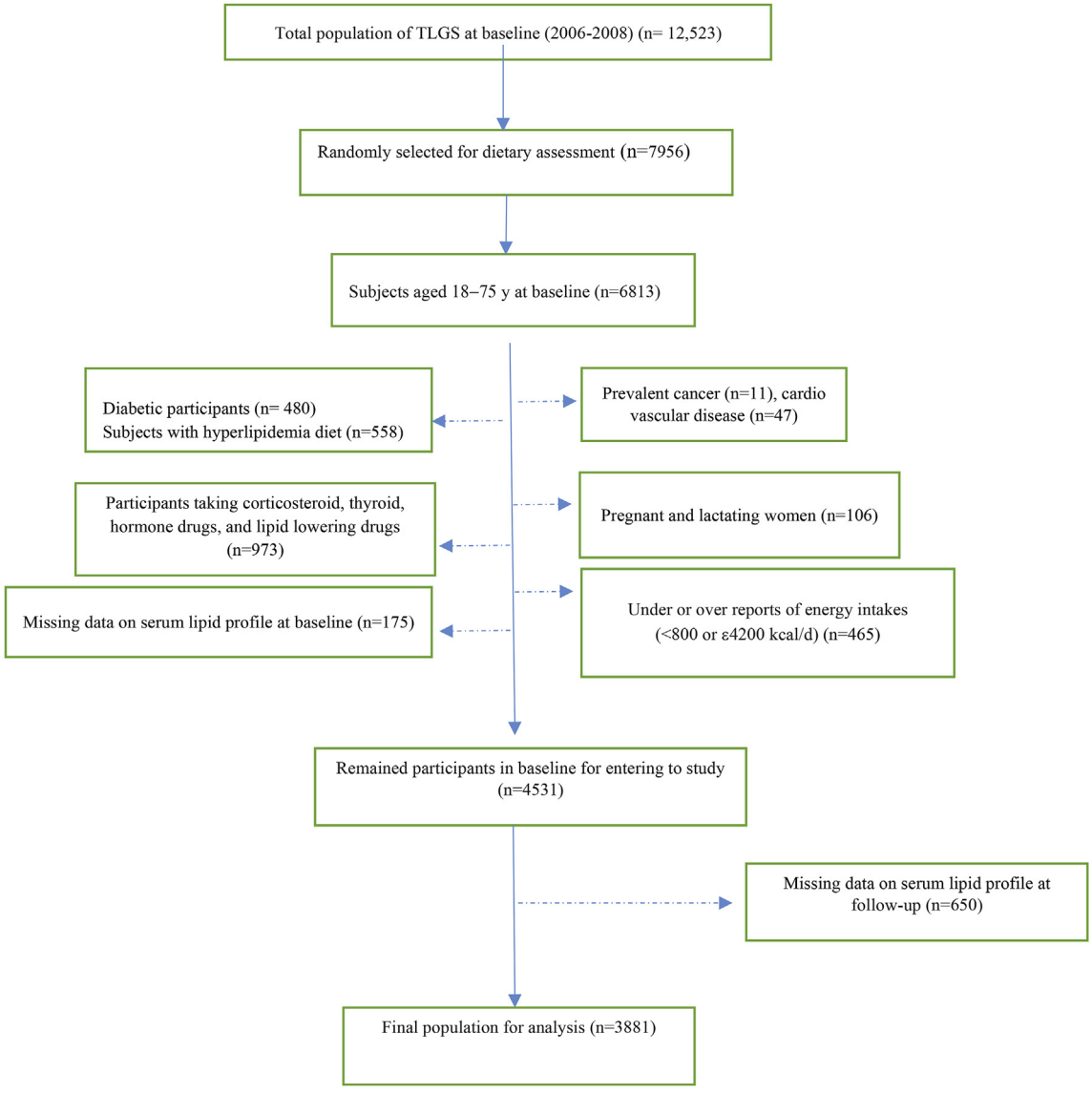

Fig. 1. The diagram of the study participants and follow-up.

data on lipid profile (n = 175) were excluded. of 4531 participants followed through the fifth survey (2012–2014), 650 subjects who had missing data on lipid profile in the follow-up assessment were excluded, remaining 3881 participants for the final analysis (Follow up rate: 85.6%). Some individuals fell into more than one category. Written informed consents were obtained from all participants and the study protocol was reviewed and approved by the ethics research council of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences.

2.2. Dietary intake assessment

Dietary intakes were assessed using valid and reliable semi-quantitative food frequency questionnaire (FFQ). The reliability and validity of the FFQ has been previously reported [14,15]. During face-to-face interview, consumption frequency for each food item during the previous year on a daily, weekly, or monthly basis of participants was collected by trained and experienced dieticians. Portion sizes of consumed foods, reported in household measures were then converted to grams. Using the United States Department of Agriculture (USDA) food composition table (FCT), energy and nutrients content were computed. For local food items that were not available in USDA FCT, The Iranian FCT [16] was used. Data on amino acids was calculated using USDA (USDA National Nutrient Database for Standard Reference, Release 28) FCT of 2015 (http://www.ars.usda.gov/ba/bhnrc/ndl), which is based on the chemically analyse of amino acids composition of over 5000 food items from all food groups. Dietary intakes during the fourth phase (2008–2011) assessment of TLGS were considered as dietary intake exposure at baseline.

2.3. Physical activity assessment

Using the Modifiable Activity Questionnaire, which previously modified and validated among Iranians estimating of physical activity levels was done [17]. Individuals were asked to report and identify the frequency and time spent during the past 12 months on activities of light, moderate, hard, and very hard intensity, according to a list of common activities of daily life; physical activity levels were expressed as metabolic equivalent hours per week (MET-h/wk).

2.4. Clinical and biological measurements

Information on age, sex, medical history, medication use, and smoking habits of participants were collected by trained interviewers, using pretested questionnaires. Anthropometric measures including weight, height, and waist circumference (WC) were measured, and body mass index (BMI) was computed. Weight was measured with light clothing and accuracy of up to 100 g using a SECA digital weighing scale (Seca 707; Seca Corporation, Hanover, Maryland; range, 0.1–150 kg). Height measurement conducted while participants were in standing position, without shoes and shoulders in normal alignment, using a stadiometer with a minimum measurement of 1 mm. Body mass index was calculated as weight in kilograms, divided by height in meters squared. Waist circumference was measured to the nearest 0.1 cm using an unstretched shape tape meter, on the level of the umbilicus, over light clothing, without any pressure to body surface.

All subjects' blood samples were collected after a 12–14 h of overnight fast in a sitting position between 7:00 and 9.00 a.m., intermediately, centrifuged within 30–45 min of collection. All blood samples were analysed at the TLGS research laboratory on the day of blood collection by using of Selectra 2 auto-analyzer (Vital Scientific, Spankeren, Netherlands). Triglyceride (TGs) levels were measured using the enzymatic calorimetric method with glycerol phosphate oxidase. Inter- and intra-assay CVs for TGs were 0.6 and 1.6%, respectively. Serum high-density lipoprotein-cholesterol (HDL-C) was measured after precipitation of the apolipoprotein B-containing lipoproteins with phosphotungstic acid. Enzymatic colorimetric tests were used to assay total cholesterol (TC) with cholesterol esterase and cholesterol oxidase. Inter- and intra-assay CVs for both TC and HDL-C were 0.5 and 2% respectively. Friedewald formula were used to calculate low-density lipoprotein-cholesterol (LDL-C) and expressed in mg/dL, analyses performed using commercial kits (Pars Azmoon Inc., Tehran, Iran).

2.5. Statistical analysis

Data analyses were conducted using Statistical Package for Social Sciences (version 15.0; SPSS Inc, Chicago IL). We used Kolmogorov–Smirnov analysis and histogram charts for assessing the normality of variables. Baseline characteristics of subjects were expressed as mean ± SD or median (25–75 interquartile range) for continuous variables, and percentage and number for categorical variables. Amino acids intake was reported as percentage of total protein intake. The correlation between dietary individual and groups of amino acids with serum lipid profile in the cross sectional analysis were measured using partial correlation analysis adjusted for probable confounders including age, gender, BMI, and dietary intake of total energy and Spearman's p values were reported. The three year changes of serum TG, HDL-C, LDL-C, and TC were ascertained and dietary individual and amino acids groups categorized based on quartiles cut off points. Multiple linear regression analysis was conducted with lipid profile change values as dependent variable and quartiles of AAs as independent continuous variable. Analysis was adjusted for potential confounders including age, sex, BMI, physical activity, smoking and daily energy, total fat, and fiber intake. Beta coefficient (unstandardized) and their respective confidence intervals 95% (95% CI) was reported and P-values <0.05 were considered as statistically significant.

3. Result

Table 1 presents the baseline characteristics and dietary intakes of study population. The mean ± SD age and BMI of participants (46.5% males) were 38.4 ± 12.7 years and 26.8 ± 4.7 kg/m^2, respectively. Protein intake was 13.6 ± 2.2% of total energy.

Glutamic acid and aspartic acid were the most predominant dietary AAs (21.90 ± 1.76 and 8.58 ± 0.76% of protein) and tryptophan and cysteine were the least (1.15 ± 0.07 and 1.52 ± 0.15% of protein). Among amino acid groups, the highest and lowest contribution to the total protein intake were related to acidic and sulfuric AAs, respectively.

The association between dietary AAs with serum lipid profile at baseline was shown in Table 2. After adjusting for confounders, a weak positive significant correlation observed between cysteine, glycine, and sulfuric AAs with TGs, methionine and sulfuric AAs with TC, sulfuric AAs with LDL-C, lysine, threonine, histidine, and aspartic acid with HDL-C. Whereas cysteine, glutamic acid, and sulfuric AAs were negatively correlated with HDL-C.

Table 3 demonstrates the association between per one quartile increase in dietary AAs with changes in lipid profiles. Isoleucine, lysine, tyrosine, alanine, threonine, methionine, valine, histidine, aspartic acid, and BCAAs, alkaline, and alcoholic AAs were positively associated with TGs changes after adjusting for confounders; whereas tryptophan, glutamic acid, and acidic AAs were negatively related to TGs changes. Alanine and tryptophan were associated with higher and lower LDL-C changes, respectively. Lysine, alanine,

Table 1
Baseline characteristics and dietary intakes among 3881 participants 18–75 years of fourth phase of Tehran Lipid and Glucose Study after excluding criteria for assessment of population serum lipid profile[a].

Variables	
Characteristics	
Age (years)	38.4 ± 12.7
Men (%)	1816 (46.5)
Body mass index (kg/m^2)	26.8 ± 4.7
Smoking (%)	433 (11.1)
Physical activity (MET.h/week)	65.9 (33.4, 101.2)
lipid markers	
Triglyceride (mg/dl)	109.0 (77.0, 156.0)
Total cholesterol (mg/dl)	180.9 ± 35.3
HDL- cholesterol (mg/dl)	47.7 ± 11.2
LDL- cholesterol (mg/dl)	107.9 ± 30.7
Dietary intake	
Energy (kcal)	2414 ± 716
Carbohydrates (% of energy)	58.7 ± 8.4
Total protein (% of energy)	13.6 ± 2.2
Total fat (% of energy)	30.2 ± 14.3
Fiber (g/1000 kcal)	15.0 ± 5.1
Tryptophan (% protein/d)	1.15 ± 0.07
Isoleucine (% protein/d)	4.53 ± 0.20
Lysine (% protein/d)	6.11 ± 0.66
Cysteine (% protein/d)	1.52 ± 0.15
Tyrosine (% protein/d)	3.53 ± 0.23
Arginine (% protein/d)	5.29 ± 0.45
Alanine (% protein/d)	4.46 ± 0.24
Glutamic acid (% protein/d)	21.90 ± 1.76
Threonine (% protein/d)	3.72 ± 0.17
Leucine (% protein/d)	7.87 ± 0.39
Methionine (% protein/d)	2.16 ± 0.16
Phenylalanine (% protein/d)	4.70 ± 0.19
Valine (% protein/d)	5.55 ± 0.36
Histidine (% protein/d)	2.52 ± 0.10
Aspartic acid (% protein/d)	8.58 ± 0.76
Glycine (% protein/d)	3.80 ± 0.30
Serine (% protein/d)	5.04 ± 0.27
Proline (% protein/d)	7.70 ± 0.80
Amino acid groups	
Branched chain AAs (% protein/d)	17.96 ± 0.93
Aromatic AAs (% protein/d)	9.39 ± 0.38
Alkaline AAs (% protein/d)	13.94 ± 0.83
Acidic AAs (% protein/d)	30.48 ± 1.40
Sulfuric AAs (% protein/d)	3.69 ± 0.16
Alcoholic AAs (% protein/d)	8.77 ± 0.37

[a] Data represented as mean ± SD or number and percent.

methionine, aspartic acid, and alkaline AAs showed positive association with changes in TC, whereas there were a negative association of tryptophan, and glutamic acid with TC changes in the adjusted model. No association was found between AAs and HDL-C changes (see Figs. 2).

4. Discussion

In the current study among adults of TLGS, we observed a direct association between several AAs including isoleucine, lysine, tyrosine, alanine, threonine, methionine, valine, histidine, aspartic acid, and BCAAs, alkaline, and alcoholic AAs with TG changes; whereas tryptophan, glutamic acid, and acidic AAs were negatively related to TGs changes after adjusting for potential confounders. Although our study did not observe any association between AAs and HDL-C changes, alanine and tryptophan were associated with higher and lower LDL-C changes, respectively. Changes in serum TC had positive association with lysine, alanine, methionine, aspartic acid, and alkaline AAs, whereas negatively associated with dietary intakes of tryptophan, and glutamic acid.

Some epidemiologic studies with cross-sectional design indicated inconsistent findings on dietary AAs with serum levels of lipid profile [5,10–12]. Although our findings on TC, LDL-C, and HDL-C are inconsistent with previous study in Iran [11], both ones showed direct association of some AAs including isoleucine, lysine, tyrosine, alanine, and asparagine with serum TGs. These inconsistent results could be justified by different study design, methods of dietary measurements, and study population. Another cross-sectional study in 454 European adolescents, showed no association between dietary AA intake using two 24-h dietary recalls with serum lipid profile after adjusting for dietary fat [5]; however in our cohort study with a large population of Iranian adults, we observed diverse relations between some AAs with lipid profile after adjusting several anthropometric and dietary factors such as fat. In addition above mentioned differences of the European adolescents study to ours, there is evidence of overt differences between patterns of serum lipid profile between adolescents and adults [18]. Other two cross-sectional studies conducted in female twins of UK and Brazilian middle-aged men indicated that higher dietary BCAAs had inverse association with dyslipidaemia, metabolic syndrome, and insulin resistance [10,12]; which are incompatible the current findings and our recent study that observed a direct association between higher intakes of BCAAs and insulin resistance [19].

Findings about dietary BCAAs and chronic disease are much controversial; completely opposite associations were reported on dietary BCAAs relationship with diabetes [20,21] and cardiometabolic factors [12,19]. However, most serum BCAAs studies demonstrate an adverse relation between BCAAs and chronic diseases such as hyperlipidemia [22–25]. Similar to ours, Yamakado et al. indicates that higher serum levels of leucine, isoleucine, valine, tyrosine, and alanine are positively associated with risks of dyslipidaemia [22]. Furthermore, Mook-Kanamori showed that serum levels of leucine, valine, isoleucine, and lysine were significantly associated with an increased risk of hypertriglyceridemia after 7-year follow-up [24].

Higher tryptophan intake in our study showed negative association with changes in serum levels of TG, LDL-C, and TC. This may be explained by tryptophan roles as precursor of serotonin, which is recognized as new therapeutic target for the treatment of lipid metabolic disorders [26,27].

Glutamic acid showed a weak negative correlation with HDL-C in the cross-sectional analysis, and an inverse relation with TGs and TC changes in the 3-year follow up analysis. Several mechanisms have been proposed to explain the beneficial effects of glutamic acid in multiple metabolic processes [28,29]. Glutamic acid is a precursor of glutathione, a major natural scavenger, which could attenuates the inflammatory response by regulating nitric oxide synthase [29]. It also could take part both as a substrate or a modulator of glucose metabolism and contribute to whole-body glucose homeostasis [28,29].

In our study, alanine showed a direct association with TGs, TC, and LDL-C and actually was the only AA, which had positive association with LDL-C changes. Alanine is a lipogenic AA and recently observed that alanine supplementation increased TC, LDL-C, and adiposity [30].

Consistent with our cross-sectional and follow-up analysis, previous studies demonstrate that methionine rich diets are responsible for increasing the cholesterol levels of serum [31,32]. In addition, in the cross-sectional analysis, sulfuric AAs had a positive weak correlation with both TGs and TC, methionine with TC, and cysteine with TGs. A positive correlation between cysteine and TG levels were previously reported by Javadian et al. [11]. It has been shown that cysteine increases digestibility of fat and starch and could affect TG levels [33].

Previous animal studies reported adverse effects of lysine on hypercholesterolemia and hypertriglyceridemia [34,35], as shown in our results. This association also observed for total basic AAs. It is noteworthy to mention that 44% of total basic AAs in our study

Table 2
The association between dietary amino acids intake with serum lipid profile after adjustment for confounders age, gender, BMI, and dietary intake of total energy in 3881 participants 18–75 years of fourth phase of Tehran Lipid and Glucose Study.

Amino Acid	TG	HDL-C	LDL-C	TC
Tryptophan	0.325	0.658	0.100	0.083
Isoleucine	0.986	0.195	0.944	0.525
Lysine	0.580	**0.022 (r = 0.03)**	0.262	0.106
Cysteine	**0.031 (r = 0.03)**	**0.001 (r = -0.04)**	0.866	0.850
Tyrosine	0.488	0.335	0.645	0.553
Arginine	0.206	0.608	0.407	0.790
Alanine	0.060	0.806	0.354	0.097
Glutamic acid	0.211	**0.047 (r = -0.02)**	0.755	0.684
Threonine	0.321	**0.030 (r = 0.03)**	0.668	0.417
Leucine	0.870	0.935	0.659	0.492
Methionine	0.298	0.405	0.129	**0.034 (r = 0.03)**
Phenylalanine	0.710	0.122	0.722	0.646
Valine	0.890	0.956	0.575	0.464
Histidine	0.855	**0.034 (r = 0.03)**	0.930	0.487
Aspartic acid	0.084	**0.047 (r = 0.03)**	0.850	0.832
Glycine	**0.040 (r = 0.03)**	0.985	0.933	0.470
Serine	0.353	0.520	0.990	0.695
Proline	0.925	0.478	0.892	0.798
Amino acid groups				
Branched chain AAs	0.899	0.730	0.673	0.473
Aromatic AAs	0.661	0.933	0.837	0.848
Alkaline AAs	0.822	0.074	0.653	0.223
Acidic AAs	0.522	0.158	0.625	0.535
Sulfuric AAs	**0.002 (r = 0.05)**	**0.026 (r = -0.03)**	0.165	**0.047 (r = 0.03)**
Alcoholic AAs	0.246	0.604	0.835	0.935

Numbers indicate P-values which stand for partial correlation analysis with controlling for probable confounders.
HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; TC: Total cholesterol; TG: triglyceride.

Table 3
Multiple linear regression analysis evaluating the association between individual and amino acids groups as continues values (per one quartiles increase) and lipid profile factors in 3881 participants 18–75 years of Tehran Lipid and Glucose Study [beta coefficient (unstandardized) and their respective confidence intervals 95% (95% CI)].

	Triglyceride changes		HDL-cholesterol changes		LDL-cholesterol changes		Total cholesterol changes	
	unadjusted	adjusted[a]	unadjusted	adjusted[a]	unadjusted	adjusted[a]	unadjusted	adjusted[a]
	B (95% CI)	*B (95% CI)*	*B (95% CI)*	*B (95% CI)*	*B (95% CI)*	*B (95% CI)*	*B (95% CI)*	*B (95% CI)*
Tryptophan	−1.02 (−2.79, 0.75)	**−1.90 (-3.70, -0.10)**	−0.17 (−0.39, 0.04)	−0.01 (−0.23, 0.20)	−0.57 (−1.17, 0.03)	**−0.71 (-1.32, -0.09)**	**−0.97 (-1.64, -0.31)**	**−1.08 (-1.76, -0.40)**
Isoleucine	**1.92 (0.13, 3.70)**	**2.77 (0.87, 4.67)**	0.06 (−0.15, 0.28)	−0.09 (−0.32, 0.14)	0.08 (−0.52, 0.69)	0.14 (−0.51, 0.80)	0.45 (−0.21, 1.13)	0.47 (−0.25, 1.19)
Lysine	**2.19 (0.40, 3.97)**	**3.38 (1.50, 5.27)**	0.17 (−0.05, 0.39)	−0.02 (−0.26, 0.20)	0.26 (−0.34, 0.87)	0.41 (−0.24, 1.04)	**0.85 (0.17, 1.52)**	**0.96 (0.25, 1.68)**
Cysteine	0.17 (−1.62, 1.96)	−1.18 (−3.06, 0.69)	**−0.38 (-0.60, -0.15)**	−0.12 (−0.36, 0.10)	0.10 (−0.50, 0.71)	0.03 (−0.60, 0.68)	−0.38 (−1.05, 0.29)	−0.40 (−1.12, 0.30)
Tyrosine	**1.96 (0.17, 3.75)**	**2.64 (0.75, 4.53)**	0.06 (−0.15, 0.29)	−0.07 (−0.31, 0.15)	−0.12 (−0.73, 0.48)	−0.07 (−0.72, 0.57)	0.08 (−0.59, 0.75)	0.06 (−0.65, 0.78)
Arginine	-.00 (−1.79, 1.79)	−0.17 (−1.97, 1.62)	−0.03 (−0.25, 0.19)	0.03 (−0.19, 0.25)	0.47 (−0.14, 1.08)	0.53 (−0.08, 1.14)	0.47 (−0.20, 1.15)	0.55 (−0.12, 1.23)
Alanine	1.41 (−0.37, 3.21)	**1.85 (0.03, 3.67)**	0.00 (−0.21, 0.22)	−0.05 (−0.27, 0.17)	0.57 (−0.03, 1.19)	**0.64 (0.01, 1.26)**	**1.01 (0.34, 1.69)**	**1.08, (0.39, 1.76)**
Glutamic acid	−1.04 (−2.84, 0.74)	**−1.84 (-3.68, -.00)**	−0.13 (−0.35, 0.08)	0.02 (−0.20, 0.24)	−0.02 (−0.63, 0.59)	−0.19 (−0.83, 0.43)	−0.56 (−1.23, 0.11)	**−0.69 (-1.39, 0.00)**
Threonine	1.63 (−0.16, 3.42)	**2.77 (0.87, 4.67)**	0.17 (−0.05, 0.39)	−0.02 (−0.25, 0.21)	0.09 (−0.52, 0.70)	0.13 (−0.51, 0.78)	0.61 (−0.06, 1.29)	0.63 (−0.08, 1.35)
Leucine	1.30 (−0.48, 3.09)	1.85 (−0.03, 3.73)	−0.06 (−0.28, 0.15)	−0.20 (−0.43, 0.02)	0.03 (−0.58, 0.64)	0.06 (−0.57, 0.71)	0.03 (−0.63, 0.71)	0.00 (−0.71, 0.71)
Methionine	**2.20 (0.42, 3.98)**	**2.82 (0.91, 2.73)**	0.04 (−0.17, 0.26)	−0.06 (−0.30, 0.17)	0.23 (−0.37, 0.84)	0.33 (−0.32, 0.99)	**0.66 (-.00, 1.33)**	**0.74 (0.02, 1.47)**
Phenylalanine	−0.95 (−2.74, 0.83)	−1.15 (−2.96, 0.64)	−0.17 (−0.39, 0.05)	−0.14 (−0.36, 0.07)	−0.10 (−0.71, 0.50)	−0.17 (−0.79, 0.44)	−0.58 (−1.26, 0.08)	−0.67 (−1.35, 0.01)
Valine	**2.12 (0.33, 3.90)**	**2.81 (0.97, 4.66)**	−0.03 (−0.25, 0.18)	−0.18 (−0.41, 0.04)	0.36 (−0.24, 0.97)	0.44 (−0.18, 1.08)	0.53 (−0.14, 1.20)	0.54 (−0.15, 1.24)
Histidine	1.49 (−0.29, 3.28)	**2.02 (0.19, 3.85)**	−0.07 (−0.29, 0.14)	−0.17 (−0.40, 0.04)	0.05 (−0.55, 0.64)	0.02 (−0.60, 0.65)	0.24 (−0.42, 0.92)	0.18 (−0.51, 0.87)
Aspartic acid	0.90 (−0.89, 2.70)	**2.22 (0.38, 4.07)**	0.15 (−0.07, 0.37)	−0.05 (−0.27, 0.17)	0.16 (−0.44, 0.78)	0.39 (−0.23, 1.03)	**0.68 (0.00, 1.35)**	**0.88 (0.18, 1.58)**
Glycine	1.00 (−0.79, 2.80)	0.37 (−1.44, 2.20)	**−0.22 (-0.44, 0.00)**	−0.06 (−0.28, 0.16)	0.51 (−0.10, 1.12)	0.53 (−0.09, 1.16)	0.54 (−0.13, 1.21)	0.63 (−0.05, 1.32)

(*continued on next page*)

Table 3 (*continued*)

	Triglyceride changes		HDL-cholesterol changes		LDL-cholesterol changes		Total cholesterol changes	
	unadjusted	adjusted[a]	unadjusted	adjusted[a]	unadjusted	adjusted[a]	unadjusted	adjusted[a]
	B (95% CI)	*B (95% CI)*	*B (95% CI)*	*B (95% CI)*	*B (95% CI)*	*B (95% CI)*	*B (95% CI)*	*B (95% CI)*
Serine	0.05 (−1.73, 1.84)	0.31 (−1.50, 2.12)	−0.04 (−0.26, 0.17)	−0.13 (−0.36, 0.08)	−0.01 (−0.62, 0.59)	−0.05 (−0.67, 0.57)	−0.22 (−0.89, 0.45)	−0.32 (−1.01, 0.36)
Proline	−0.45 (−2.23, 1.33)	−0.74 (−2.53, 1.04)	−0.16 (−0.38, 0.05)	−0.09 (−0.31, 0.12)	−0.04 (−0.65, 0.56)	−0.19 (−0.81, 0.42)	−0.54 (−1.21, 0.13)	−0.66 (−1.33, 0.01)
Amino acid groups								
Branched chain AAs	1.62 (−0.16, 3.40)	**2.38 (0.49, 4.26)**	0.00 (−0.21, 0.22)	−0.15 (−0.38, 0.07)	0.08 (−0.52, 0.69)	0.13 (−0.51, 0.78)	0.24 (−0.43, 0.91)	0.22 (−0.49, 0.93)
Aromatic AAs	0.83 (−0.95, 2.62)	0.97 (−0.85, 2.79)	−0.10 (−0.32, 0.11)	−0.16 (−0.38, 0.06)	−0.26 (−0.87, 0.35)	−0.27 (−0.90, 0.35)	−0.37 (−1.05, 0.29)	−0.43 (−1.12, 0.25)
Alkaline AAs	2.22 (0.44, 4.01)	**3.04 (1.20, 4.89)**	0.10 (−0.12, 0.32)	−0.04 (−0.27, 0.17)	0.38 (−0.22, 0.99)	0.53 (−0.10, 1.16)	**0.92 (0.25, 1.59)**	**1.03 (0.34, 1.73)**
Acidic AAs	−1.40 (−3.19, 0.38)	**−1.85 (-3.70, -.00)**	−0.08 (−0.30, 0.13)	0.02 (−0.20, 0.25)	0.04 (−0.56, 0.65)	−0.08 (−0.71, 0.55)	−0.39 (−1.07, 0.27)	−0.48 (−1.18, 0.21)
Sulfuric AAs	**2.05 (0.26, 3.84)**	1.23 (−0.63, 3.11)	−0.14 (−0.36, 0.08)	0.01 (−0.21, 0.24)	0.03 (−0.57, 0.65)	0.06 (−0.57, 0.71)	0.11 (−0.56, 0.78)	0.16 (−0.54, 0.87)
Alcoholic AAs	1.19 (−0.58, 2.98)	**2.01 (0.16, 3.87)**	0.00 (−0.21, 0.22)	−0.16 (−0.39, 0.06)	0.10 (−0.50, 0.71)	0.10 (−0.53, 0.74)	0.19 (−0.48, 0.86)	−0.11 (−0.58, 0.28)

[a] Lipid profile factors change values in follow up time was entered as dependent variable and dietary amino acids and lipid factor values in baseline of study were entered to analysis as independent variables. This analysis was adjusted for potential confounders: age, sex, body mass index, physical activity, smoking (yes or no) and daily energy intake, total fat and fiber intake. Significant associations are in bold.

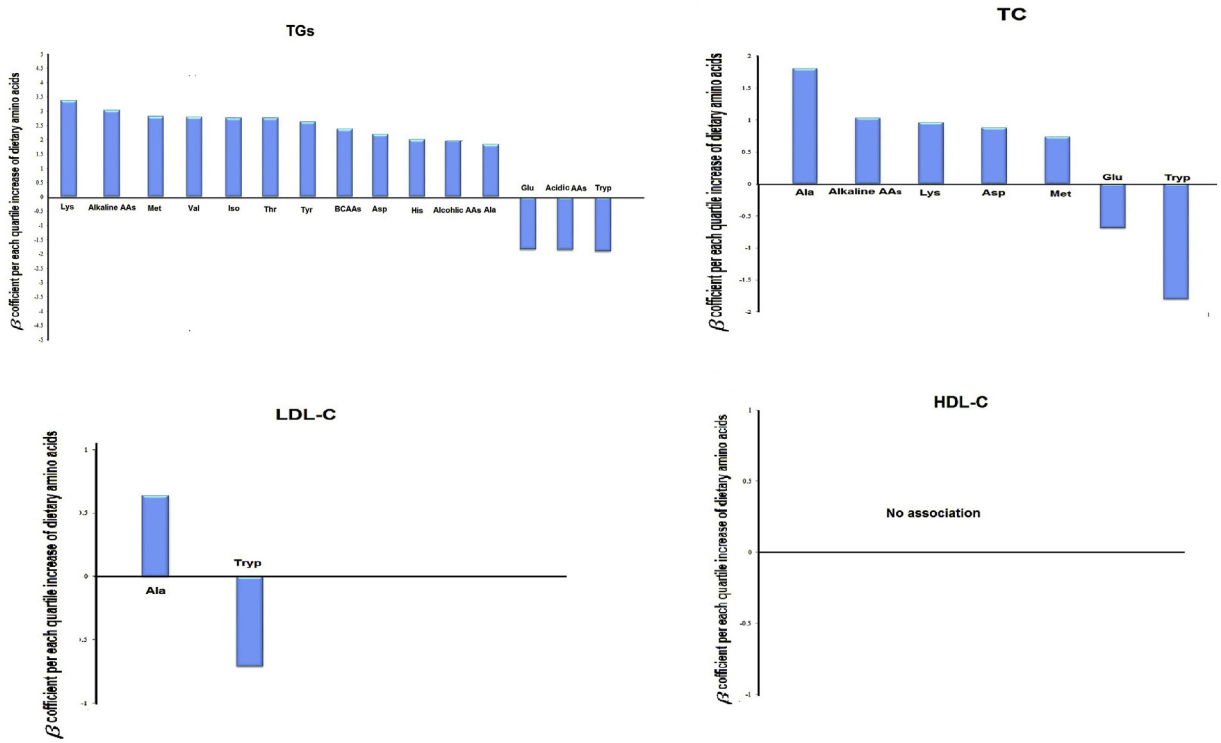

Fig. 2. The statistically significant B coefficients for 3 years changes in lipid profile factors per increase the each quartile of dietary amino acids intake in the full adjusted model.

supplied from lysine and it seems that hypercholesterolemic effects of basic AAs mostly was related to lysine. Furthermore, histidine, another basic AA, also showed positive association with TGs changes.

In the current study, cross-sectional analysis indicates weak correlations between several AAs and lipid profile, which is expectable. Previous studies may also confirm these weak correlations [11,36]. Therefore, this analysis set a pay as hypothesis synthesizing and considered as exploratory analysis rather than confirmatory ones. In the next step, we designed the follow-up analysis to illustrate the casual effect association between AAs and lipid profile. The latter design has great clinical importance because 3-year changes of serum lipid levels was investigated.

This study has some noteworthy strengths. First, compared to other cross-sectional studies on the association between AAs and serum lipid levels, to our knowledge, this is the first study which investigated the association between dietary AAs and serum lipid profile changes in frame of a prospective cohort study. Furthermore, dietary intakes were collected by trained dieticians rather than individual self-reports which increased the validity of our

results. However, our study has some limitations. First, no data on serum AAs were available for better interpretation of the AAs-lipid profile association. Second, despite adjusting of a wide variety of variables, the confounding effect of some unknown and unmeasured residual confounders may have occurred.

In conclusion, higher dietary intakes of some AAs has the potential to increase or decrease serum lipid profile including TGs, TC, and LDL among general population. We also observed that several dietary AAs have correlations with serum lipid factors in particular HDL, as well as TGs and TC. Our findings have important clinical implications; more prospective studies in other populations should be conducted to determine the beneficial and detrimental AAs associations with serum lipid profile.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.04.013.

References

[1] Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2001;104:1108–13.
[2] Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. Lancet 2011;377:578–86.
[3] Hegsted DM, Kritchevsky D. Diet and serum lipid concentrations: where are we? Am J Clin Nutr 1997;65:1893–6.
[4] Oda H. Functions of sulfur-containing amino acids in lipid metabolism. J Nutr 2006;136. 1666s-9s.
[5] Bel-Serrat S, Mouratidou T, Huybrechts I, Cuenca-Garcia M, Manios Y, Gomez-Martinez S, et al. The role of dietary fat on the association between dietary amino acids and serum lipid profile in European adolescents participating in the HELENA Study. Eur J Clin Nutr 2014;68:464–73.
[6] El Khoury D, Anderson GH. Recent advances in dietary proteins and lipid metabolism. Curr Opin Lipidol 2013;24:207–13.
[7] Potter SM. Soy protein and serum lipids. Curr Opin Lipidol 1996;7:260–4.
[8] Sugino T, Shirai T, Kajimoto Y, Kajimoto O. L-ornithine supplementation attenuates physical fatigue in healthy volunteers by modulating lipid and amino acid metabolism. Nutr Res 2008;28:738–43.
[9] Kawasaki M, Miura Y, Funabiki R, Yagasaki K. Effects of simultaneous dietary fish oil ingestion and sulfur amino acid supplementation on the lipid metabolism in hepatoma-bearing rats with hyperlipidemia. J Nutr Sci Vitaminol (Tokyo) 2010;56:247–54.
[10] Jennings A, MacGregor A, Pallister T, Spector T, Cassidy A. Associations between branched chain amino acid intake and biomarkers of adiposity and cardiometabolic health independent of genetic factors: a twin study. Int J Cardiol 2016;223:992–8.
[11] Javidan AN, Sabour H, Nazari M, Soltani Z, Heshmat R, Larijani B, et al. Is the pattern of dietary amino acids intake associated with serum lipid profile and blood pressure among individuals with spinal cord injury? J. Spinal Cord. Med 2017;40:201–12.
[12] Cogate PG, Natali AJ, de Oliveira A, Alfenas RC, Hermsdorff HH. Consumption of branched-chain amino acids is inversely associated with central obesity and cardiometabolic features in a population of Brazilian middle-aged men: potential role of leucine intake. J Nutr Health Aging 2015;19:771–7.
[13] Azizi F, Ghanbarian A, Momenan AA, Hadaegh F, Mirmiran P, Hedayati M, et al. Prevention of non-communicable disease in a population in nutrition transition: Tehran Lipid and Glucose Study phase II. Trials 2009;10:5.
[14] Asghari G, Rezazadeh A, Hosseini-Esfahani F, Mehrabi Y, Mirmiran P, Azizi F. Reliability, comparative validity and stability of dietary patterns derived from an FFQ in the Tehran Lipid and Glucose Study. Br J Nutr 2012;108:1109–17.
[15] Esfahani FH, Asghari G, Mirmiran P, Azizi F. Reproducibility and relative validity of food group intake in a food frequency questionnaire developed for the Tehran Lipid and Glucose Study. J Epidemiol 2010;20:150–8.
[16] Azar M, Sarkisian E. Food composition table of Iran, vol. 65. Tehran: National Nutrition and Food Research Institute, Shaheed Beheshti University; 1980.
[17] Momenan AA, Delshad M, Sarbazi N, Rezaei Ghaleh N, Ghanbarian A, Azizi F. Reliability and validity of the Modifiable Activity Questionnaire (MAQ) in an Iranian urban adult population. Arch Iran Med 2012;15:279–82.
[18] American Academy of Pediatrics. National cholesterol education program: report of the expert panel on blood cholesterol levels in children and adolescents. Pediatrics 1992;89:525–84.
[19] Asghari G, Farhadnejad H, Teymoori F, Mirmiran P. In: High dietary intake of branched-chain amino acids is associated with an increased risk of insulin resistance in adults, vol. 10; 2018. p. 357–64.
[20] Nagata C, Nakamura K, Wada K, Tsuji M, Tamai Y, Kawachi T. Branched-chain amino acid intake and the risk of diabetes in a Japanese community: the Takayama study. Am J Epidemiol 2013;178:1226–32.
[21] Zheng Y, Li Y, Qi Q, Hruby A, Manson JE, Willett WC, et al. Cumulative consumption of branched-chain amino acids and incidence of type 2 diabetes. Int J Epidemiol 2016;45:1482–92.
[22] Yamakado M, Nagao K, Imaizumi A, Tani M, Toda A, Tanaka T, et al. Plasma free amino acid profiles predict four-year risk of developing diabetes, metabolic syndrome, dyslipidemia, and hypertension in Japanese population. Sci Rep 2015;5:11918.
[23] Ntzouvani A, Nomikos T, Panagiotakos D, Fragopoulou E, Pitsavos C, McCann A, et al. Amino acid profile and metabolic syndrome in a male Mediterranean population: a cross-sectional study. Nutr Metabol Cardiovasc Dis 2017;27:1021–30.
[24] Mook-Kanamori DO, Romisch-Margl W, Kastenmuller G, Prehn C, Petersen AK, Illig T, et al. Increased amino acids levels and the risk of developing of hypertriglyceridemia in a 7-year follow-up. J Endocrinol Investig 2014;37:369–74.
[25] Siomkajlo M, Rybka J, Mierzchala-Pasierb M, Gamian A, Stankiewicz-Olczyk J, Bolanowski M, et al. In: Specific plasma amino acid disturbances associated with metabolic syndrome, vol. 58; 2017. p. 553–62.
[26] Watanabe H, Rose MT, Aso H. Role of peripheral serotonin in glucose and lipid metabolism. Curr Opin Lipidol 2011;22:186–91.
[27] Colotto M, Vinci F, Vo Hong N, Raimo O, Castello A, Carnovale A, et al. [Effect of treatment with selective serotonin reuptake inhibitors on lipid profile: state of the art]. Clin Ter 2012;163:e41–5.
[28] Roth E. Nonnutritive effects of glutamine. J Nutr 2008;138. 2025s-31s.
[29] Young VR, Ajami AM. Glutamine: the emperor or his clothes? J Nutr 2001;131. 2449S-59S; discussion 86S-7S.
[30] Coqueiro AY, Raizel R, Bonvini A, Godois ADM, Hypolito TM, Pereira JRR, et al. Effects of glutamine and alanine supplementation on adiposity, plasma lipid profile, and adipokines of rats submitted to resistance training. J Diet Suppl 2018:1–13.
[31] Sugiyama K, Mizuno M, Muramatsu K. Effect of individual amino acids on plasma cholesterol level in rats fed a high cholesterol diet. J Nutr Sci Vitaminol (Tokyo) 1986;32:623–33.
[32] Sugiyama K, Muramatsu K. Significance of the amino acid composition of dietary protein in the regulation of plasma cholesterol. J Nutr Sci Vitaminol (Tokyo) 1990;36(Suppl 2):S105–10.
[33] Nordrum S, Krogdahl Å, Røsjø C, Olli JJ, Holm H. Effects of methionine, cysteine and medium chain triglycerides on nutrient digestibility, absorption of amino acids along the intestinal tract and nutrient retention in Atlantic salmon (Salmo salar L.) under pair-feeding regime. Aquaculture 2000;186:341–60.
[34] Leszczynski DE, Kummerow FA. Excess dietary lysine induces hypercholesterolemia in chickens. Experientia 1982;38:266–7.
[35] Giroux I, Kurowska EM, Carroll KK. Role of dietary lysine, methionine, and arginine in the regulation of hypercholesterolemia in rabbits. J Nutr Biochem 1999;10:166–71.
[36] de Moraes AC, Bel-Serrat S, Manios Y, Molnar D, Kafatos A, Cuenca-Garcia M, et al. Dietary protein and amino acids intake and its relationship with blood pressure in adolescents: the HELENA STUDY. Eur J Public Health 2015;25:450–6.