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Correlation Between Different Dietary Indexes, and Their Association with An Anti-inflammatory Biomarker in Older Adults: An Exploratory Study

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Abstract

Objective: Aging is associated with low-grade systemic inflammation (LGSI), and nutrition has been recognized as a crucial modifiable factor concerning LGSI. The aims of this study are to (i) identify the dietary quality of community-dwelling older adults using three approaches; two conventional *a priori* indexes and a ratio between minimally processed and ultra-processed foods (UPR; based on the NOVA classification); (ii) explore some differences and similarities among the approaches; (iii) investigate the association of DII and MDS with a biomarker of systemic inflammation, and investigate if UPR could be used in a complementary way to these associations.

Materials and Methods: We studied independent (non-frail) older adults, both genders, without any inflammatory disease. Variables investigated: - The anti-inflammatory index (AII = IL-10/IL-6 ratio); - Two 24h-food recall, from which we calculated: The dietary inflammatory index (DII); the Mediterranean Diet Scale (MDS); and the ratio between unprocessed or minimally processed/ultra-processed food (UPR). Single and multiples linear regression models, crude or adjusted by age and sex, were adopted to test the associations between the approaches and the anti-inflammatory biomarker. The differences and similarities between the approaches were explored using correlation analyses and the regression models.

Results: The MDS and DII showed the same trend to indicate the inflammatory potential; the UPR presented a non-significant correlation with the others. Only the MDS positively and significantly explained the AII values; the combination between MDS or DII with UPR did not change the association level with the anti-inflammatory index.

Conclusion: The only significant correlation was found between MDS and DII, however in different directions; only the MDS showed a significant association with our anti-inflammatory marker and the inclusion of UPR in our regression models did not add any improvement to the models. More studies are necessary with more robust and representative samples.

Keywords: Aging, dietary inflammatory index, low-grade systemic inflammation, Mediterranean diet, NOVA classification

Introduction

Aging is generally associated with low-grade systemic inflammation (LGSI), which has been pointed out to be responsible for several aging-related adverse outcomes (1). Diet quality has been recognized as an essential modifiable factor concerning LGSI, contributing to health (2); however, most studies have investigated specific nutrients or foods instead of considering broader diet features.

A comprehensive investigation of diet quality may be performed from two different approaches: *a posteriori* analysis consists of data reduction through other statical models, for instance, cluster analysis, factor analysis, or principal component analysis (3); *a*

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priori analysis takes into account different indexes previously developed based on previous hypotheses (4,5). As such, *a priori* analyses consider different concepts, enabling the population's diet to be compared with healthy eating recommendations (4,6-8). The indexes consider nutrients, food groups, and dietary patterns (9,10). For instance, the Mediterranean dietary pattern (MDP) considers adherence to different food groups, which is widely recognized models of healthy eating. Many studies have associated MDP indexes with benefits in chronic diseases and pro-inflammatory markers (11,12). Another frequently *a priori* index used is the dietary inflammatory index (DII) (13). This tool has been proposed as applicable to verify the inflammatory potential of the diet. It is calculated from a list of 45 food, nutrients, and food components considered pro- or anti-inflammatory and have also demonstrated a good association with health outcomes and inflammatory biomarkers (14,15).

The Dietary Guidelines for the Brazilian Population (DGBP) introduced a new approach to dietary recommendations, which has been associated with the assessment of diet quality. Instead of using the "conventional" food groups based on nutrients, DGBI explores the extent of food processing (16). As such, four groups are proposed by this guide: Unprocessed or minimally processed, culinary ingredients, processed, and ultra-processed food. Studies have demonstrated the association between high consumption of ultra-processed foods and chronic diseases (17-19).

Exploring the association between different dietary indexes with LGSI can contribute to planning healthy aging strategies (20). In this regard, some important points must be highlighted: (i) different indexes are used to discuss the quality and adequacy of dietary intake; however, few publications have compared these indexes regarding their correlation and their association with inflammatory biomarkers; (ii) The NOVA classification is innovative and incorporates one of the critical points of the nutritional transition - the damage to health caused by the excessive intake of ultra-processed foods (21); we consider relevant to investigate some possibilities to use this classification as a complement to the dietary indexes. We hypothesize that NOVA classification could be used together with the other indexes.

As such, in this exploratory study, we aimed to: (i) identify the dietary quality of community-dwelling older adults using three approaches, that is, two conventional *a priori* indexes and a ratio between minimally processed and ultra-processed foods (UPR; based on the NOVA classification); (ii) explore correlations among the approaches; (iii) investigate the association of DII and MDS with a biomarker of systemic inflammation, and investigate if the UPR could be used in a complementary way to these associations.

Materials and Methods

Sample

This study was conducted with secondary baseline data from an already finished clinical study (22). The original study (ReBec Clinical register RBR-6qr9xx) investigated the effects of a symbiotic supplementation in community-dwelling older adults, both genders, independent (non-frail), without reference to inflammatory disease (i.e., bowel disease or joint diseases) and not taking any antibiotics, or laxative substances, or food supplements. Regarding chronic diseases, considering the most common ones (hypertension, type 2 diabetes, and dyslipidemias), we only included those who controlled these diseases with appropriate medicines. In the present exploratory study, we had that previous project's baseline (n=73) data. We, therefore, define the current sample as a convenience and secondary sample.

Blood Collection and Analyses

The participant's blood was collected after 8-12 h fasting. After the collection, the blood was centrifuged and stored at -80 °C; from these samples, we analyzed the interleukin-6 (IL-6) and interleukin-10 (IL-10) by Multiple Analyte Profiling method (HCYTMAG-60K-03; Millipore®). These variables were treated as an anti-inflammatory index (AII) from the IL-10/IL-6 ratio (23).

Dietary Analyses

Two 24-hour dietary recalls (24HR) assessed the diet, applied in non-consecutive days, with a minimum of two week-interval. The information was first converted from home to standard measures (grams and milliliters) following specific technical publications. Other corrections and adjustments to the 24HR were conducted according to a particular manual developed by the Research Group of Food Intake, University of São Paulo (GAC-USP). After the adjustments needed, the 24HR were calculated for energy, macronutrients, micronutrients, and bioactive compounds, using the Nutrition Data System for Research (NDSR) software. Some flavonoid compounds not present in the NDSR database were calculated using data from the USDA Food Composition Databases as the first option and Brazilian Table of Food Composition as the second option. Afterward, each dietary variable was organized in statistical software (STATA®14) to gather each component's total consumption in each 24HR. The habitual intake was obtained using the multiple source method (MSM) software; this stage was mandatory to correct intraindividual variability.

The DII was developed by Cavicchia et al. (24) and Shivappa et al. (13). This index investigates the intake of 45 dietary components (which includes food, nutrients, and other compounds) derived from a previous systematic review and adjusted for population's data from eleven countries worldwide, which the authors considered as global intake. The DII can be calculated from different tools of dietary investigation, and here we used the 24HR. The dietary data were organized in a pre-developed Excel file, following the information given by Shivappa et al. (13). First, we calculated each dietary component individually; then, we used the global daily mean intake and its standard deviation and overall inflammatory effect to perform this calculation. To do so, we took the following steps:

(i) Z-score calculation: Subtraction of the global mean intake of the component from the individual's usual intake divided by the global standard deviation of the same component.

Z-score= [(usual intake of the component - global daily mean intake of the component)/global standard deviation of the component]

(ii) Percentile: Conversion of Z-score in percentile.

Percentile (in excel command) = DIST.NORMP.N (Z-score;TRUE)

(iii) Transformation of the percentile in a centralized percentile.

Centralized Percentile =(Percentile*2)-1

(iv) Effect score: Multiplication of centralized percentile by the inflammatory score of each component (also described in Shivappa's publication)

Effect score=Centralized percentile*(inflammatory factor of the component)

(v) The overall DII is obtained from summating all the components included.

When considering all the 45 food parameters, DII scores can range from -8.87 (a more anti-inflammatory diet) to +7.98 (a more pro-inflammatory diet).

The MDS was assessed according to the proposal by Trichopoulou et al. (12). The consumption of fish, vegetables, legumes, fruits and nuts, cereals, and the monounsaturated: saturated fat ratio, situated below or above the median (adjusted for energy intake by both sexes) of the own group, received scores zero and one, respectively. An inverse assignment was attributed to meat and dairy products, above or below the median. Alcohol intake of 10 to 50 g/day and 5 to 25 g/day, respectively, for men and women, were considered moderate and received the value of one; the consumption below or above these intervals received zero value. Thus, the total MDS ranged from 0 to 9, with higher scores indicating greater adherence to the MDP. As recommended by the author (12,25), for the construction of the MDS, we included only the authentic foods of the Mediterranean diet (maintaining as much as possible the statement of being fresh, locally produced, and not modified or with minimal modifications from their natural state).

The NOVA classification was performed according to Monteiro et al. (16) and supported by the second edition of DGBP, 2014. The individuals' food constituted four groups: Group 1 - unprocessed or minimally processed foods; Group 2 - processed culinary ingredients; Group 3 - processed foods and Group 4 - ultra-processed foods. Based on the "golden rule" of the DGBP ("always prefer natural or minimally processed foods and freshly made dishes and meals to ultra-processed foods"), we calculated the ratio between the diet energy density of the two main groups, unprocessed and minimally processed foods (UMF) and ultra-processed foods (UPF). We provisionally named this calculation "ultra-processed ratio" (UPR), and it is detailed below:

UPR= (energy density (g/kcal) of UMF /energy density (g/kcal) of UPF)

Higher ratio values represent a higher intake of UMF (healthy diet) than UPF, while lower values represent a higher consumption of UPF (unhealthy diet).

The participants had their weight and height evaluated, following standard recommendations. These values were used to calculate the body mass index (BMI) (weight/height^2) and were classified according to the proposal of the Pan American Health Organization (2002) for older adults (BMI <23 kg/m^2, low body weight; 23≤ BMI ≤28 kg/m^2, within the normality range; 28< BMI ≤30 kg/m^2, overweight and BMI >30 kg/m^2, obesity).

Age, gender, years of formal schooling, and individual monthly income were obtained, in the original study, by applying a structured questionnaire with the participants' information.

Statistics

Continuous variables were presented as median and range intervals, while categorical ones were presented as absolute and relative frequency. The normality of the continuous variables was investigated using the Kolmogorov-Smirnov test. We performed correlation analysis (Pearson correlation) to compare the three dietary indexes' directions. To test the association between the dietary indexes and the plasma AII, we run three single linear regression models between each dietary index and the AII. To investigate the complementarity potential of UPR to the two indexes, we run multiple linear regression models, including UPR + DII (Multiple Model 1) and UPR + MDS (Multiple Model 2). The multiple models were run as unadjusted and adjusted (by sex and age) fashion. To meet the assumptions of regression models, the variables that did not present normal distribution were Box-cox normalized. To investigate the models' quality and adequacy, we investigated the existence of multicollinearity (from tolerance and inflation factor analyses) and the independence from the residues (from Durbin-Watson test and ANOVA test). To explore the importance of adding the

UPR in multiple models, we investigated the difference between the R^2 from single and the R^2 from multiple models, observing the significance of these differences (ANOVA test). The analyses were performed with TIBCO Statistica software (version 13) and IBM SPSS statistics software (version 22); the significance of the analyses was established in p-value <0.05.

Results

The baseline characteristics of participants are described in Table 1. Seventy-three older adults were studied, with a mean age of 76 (63.0-89.0) years old and females' predominance (76.7%). Although most were classified as within the normality range (45.2%), a high prevalence of overweight (34.2%) and one-fifth of low body weight was observed. Formal schooling was highly heterogeneous between participants, while almost half of the sample reported monthly income between six and ten minimum wages. The UPR showed a mean ratio of 0.29 (0.0-1.3), demonstrating a predominant intake of unprocessed or minimally processed foods. The DII had a median of 0.51 [(-2.99) - (+3.14)], indicating a slight trend to be more pro-inflammatory. The MDS showed a median range of 4.0 (1.0-7.0), indicating a moderate adherence to this dietary pattern. In turn, the AII showed a mean value of 2.50 (0.35-14.88), indicating, in general terms, a sample with an anti-inflammatory profile.

Table 2 depicts the Pearson correlation analyses between the indexes. The only correlation that showed a significant result was MDS vs. DII, with a negative correlation (r=-0.40; p=0.003), indicating that both showed a similar trend to predict the diet quality. It is relevant to consider the direction of the different indexes' scores; lower values of DII indicate more anti-inflammatory diets; in contrast, the higher scores of MDS indicate a more anti-inflammatory profile.

Table 3 depicts the regression models investigated, taking the AII as the dependent variable. All models met the assumptions of collinearity and independence of residuals. The single models showed only the MDS as significantly associated with the AII. On average, each one-unit increase in the MDS was associated with a 0.25 unit increase in the AII. The MDS maintained the significance when added to the multiple models, both unadjusted and adjusted. However, the UPR did not add any significant increase in the Beta values, in none of the models.

Discussion

This exploratory study investigated correlations and complementarities between two a priori dietary indexes, named MDS, DII, and an indicator of ultra-processed foods intake (UPR); we investigated the association of these dietary indexes with plasma AII in a convenience sample of community-

Table 1. General description of the study's participants (n=73)

Variable	Categories	Median (range) or number (%)
Age (years)	-	76.0 (63.0-89.0)
Sex	Male	17 (23.3)
	Female	56 (76.7)
BMI[a]	Low body weight	15 (20.5)
	Normality range	33 (45.2)
	Overweight	25 (34.2)
Years of formal schooling	None	1 (1.4)
	1 to 4	12 (16.4)
	5 to 8	13 (17.8)
	9 to 11	18 (24.6)
	12 or more	29 (39.7)
Monthly income[b]	≤1	5 (6.8)
	>1 - ≤5	16 (21.9)
	≥6 - ≤10	35 (47.9)
	>10	17 (23.4)
UPR	-	0.29 (0.0-1.3)
DII	-	0.51 [(-2.99) - 3.14]
MDS	-	4.0 (1.0-7.0)
AII (IL-10/IL-6)	-	2.50 (0.35-14.88)

AII: Anti-inflammatory index, BMI: Body mass index, DII: Dietary inflammatory index, MDS: Mediterranean diet scale, UPR: Ultra-processed ratio, [a]classification according to PAHO, 2002, [b]number of minimal wages

Table 2. Correlation matrix between the indexes

Dietary indexes (a)	MDS	DII	NOVA
	r- values (p-value)		
MDS	1.0	**-0.40 (0.003)**	-0.04 (0.74)
DII		1.0	0.16 (0.89)
NOVA			1.0

(a) Scores normalized. Values in bold mean p<0.05. DII: Dietary inflammatory index, MDS: Mediterranean diet scale, UPR: Ultra-processed ratio

Table 3. Regression analysis between the inflammatory outcome (AII) and the dietary indexes investigated (a)

Models	Predictors	Single models			Multiple models			Adjusted multiple models (b)			Models quality (c)
		β	95% CI	p-value	Adj. β	95% CI	p-value	Adj. β	95% CI	p-value	
Single model 1	UPR	-0.066	-0.085 to 1.426	0.93							R^2=0.00; 0.93 DW=1.9
Single model 2	DII	-0.046	-0.051 to 1.632	0.18							R^2=0.025; 0.18 DW=1.9
Single model 3	MDS	0.086	**0.090 to 0.164**	**0.03**							R^2=0.252;0.03 DW=2.0
Multiple model 1 (DII + UPR)	DII				-0.186	-0.124 to 3.612	0.13	-0.176	-0.122 to 3.599	0.15	
	UPR				-0.009	-1.541 to 1.424	0.94	-0.12	-1.565 to 1.416	0.92	R^2 adjusted model= [-0.008] R^2 change=0.003 (0.95) DW=1.9
Multiple Model 2 (MDS+ UPR)	MDS				0.247	**0.005 to 0.163**	**0.04**	0.247	**0.005 to 0.163**	**0.04**	
	UPR				-0.003	-1.479 to 1.444	0.99	-0.006	-1.503 to 1.430	0.96	R^2 adjusted model=0.219 R^2 change=0.000 (0.99) DW=2.0

(a)Dietary indexes Box-Cox transformed; (b) Models adjusted by age and sex; (c) R^2= relative to the single or multiple adjusted model; R^2 change= difference between R^2 from single model and R^2 from adjusted multiple model and significance of this difference (ANOVA), AII- plasma anti-inflammatory index (IL-10/IL-6), DII: Dietary inflammatory index, MDS: Mediterranean diet scale, UPR: Ultra-processed ratio, DW: Durbin-Watson test. Negative values are [in brackets]. Values in bold mean p<0.05

dwelling older adults. As the main results, the MDS and DII indexes showed the same trend to indicate healthy (or anti-inflammatory) and unhealthy (or pro-inflammatory) diets; the UPR presented a non-significant inverse direction when tested against the other two (MDS and DII). Finally, only the MDS positively and significantly explained the AII values in single, and in unadjusted and adjusted multiple models. The inclusion of UPR in the multiple models did not significantly change the R^2 values, therefore, not confirming our hypothesis of using UPR as a complementary index to be associated with our plasma inflammatory indicator.

It is important to highlight some conceptual differences between the indexes and the ratio adopted in our work. The DII and the MDS include potentially inflammatory and anti-inflammatory foods in their construction; the DII considers nutrients, foods, and bioactive compounds singly, while the MDS considers food groups and nutrients ratio. Additionally, they also differ regarding the scoring system. While the DII works with the intakes standardization and includes energy as a component, the MDS is constructed based on the habitual intake and uses the median adjusted for energy intake. Nevertheless, the negative correlation between DII and MDS was coherent, with the lowest scores for DII and higher scores for MDS, meaning both an anti-inflammatory potential. On the other hand, the NOVA classification characterizes food by the extent of processing, being a broader approach to identifying possible inflammatory food components.

Our MDS results agree with other studies. A recent cross-sectional descriptive study compared different dietary indexes as predictors of inflammatory biomarkers (26). This study included 73 subjects aged >50 years without diseases; only the MDS indexes were inversely associated with serum IL-8 concentrations [β= (-0.251); p=0.018 and β= (-0.221); p=0.017]; the two dietary inflammatory indexes explained only the marker of oxidative stress (malondialdehyde). The authors hypothesized an explanation of MDP's anti-inflammatory role in intestinal microbiota change. The study used indexes of adherence to the MDP, which were derived from the one adopted in the present study (25). Our MDS results agree with other studies. A recent cross-sectional descriptive study compared different dietary indexes as predictors of inflammatory biomarkers (26). This study included 73 subjects aged >50 years without diseases; only the MDS indexes were inversely associated with serum IL-8 concentrations [β= (-0.251); p=0.018 and β= (-0.221); p=0.017]; the two dietary inflammatory indexes explained only the marker of oxidative stress (malondialdehyde). The authors hypothesized an explanation of MDP's anti-inflammatory role in intestinal microbiota change. The study used indexes of adherence to the MDP, which were derived from the one adopted in the present study (25).

Our sample, composed of older adults, did not present high values of UPR, which align with the last Brazilian family budgets survey (POF - 2017-2018) (27); older adults consume more energy from the unprocessed and minimally processed groups than ultra-processed ones. This can be one of the reasons for our non-significant results related to this ratio.

A Brazilian study with a robust sample derived from the ELSA-Brazil cohort found a significant association between higher consumption of ultra-processed products (caloric percentage) and C-reactive protein levels in women without adjusting BMI (28). We hypothesized that the NOVA index could be used as a complementary analysis of the other indexes since it classifies the diet according to the degree of processing without considering the intake of traditional food groups. We included MDS, or DII, to test this hypothesis in combined models with UPR. However, the combination of the MDS and the UPR in these models did not increase the degree of the association. The single model with MDS explained 6% (R^2=0.06) of the association, while including the UPR in the model explained 4% (adjusted R^2=0.04). Therefore, our hypothesis was not confirmed; an explanation for this non-significance may be that the MDS does not consider, in its calculation, the consumption of foods other than fresh, minimally processed, and Mediterranean foods (therefore, unprocessed, or minimally processed).

Concerning DII, da Silva et al. (29), different from our results, found a significant and inverse association between this index and the consumption of ultra-processed food and culinary ingredients in a cross-sectional study with 2.359 patients with cardiovascular diseases, mostly older adults (64.2%) and overweight (68.8%). Patients in the third tertile of DII (DII >0.91) were more likely to have two or more cardiovascular events and more likely to consume a higher percentage of processed ultra-processed, and culinary ingredients compared with the patients in the first DII tertile (DII ≤0.91). Also, UPF consumption higher than three servings/day was associated with higher odds for short telomeres in a Spanish sample of 645 men and 241 women with a mean age of 67.7±6.1 years. Besides not being a direct marker of inflammation, telomeres are markers of the aging process. The shortening of the telomeres is known to be associated with inflammation and oxidative stress (30).

Study Limitations

It is essential to highlight some limitations in discussing our results. Our sample consisting by older adults showed a non-expressive intake of ultra-processed food, which in combination with our small sample size, could not be enough to give statistical power to our analysis.

The sample's inflammatory profile indicated a sample with a more anti-inflammatory profile, possibly healthy. Also, it is known that many other covariates not considered in our study, could interfere with inflammatory profile, such as chronic diseases, medicaments, or even genetic aspects.

Additionally, in older adults, the characteristic of a monotonous diet may have influenced the minor changes in all indexes' scores, particularly DII. On the other hand, as far as we know, our study is the first exploratory attempt to develop an index that uses the NOVA classification and verifies the agreement between dietary indexes in a sample of older adults. The search for an appropriate index from the DGBP can contribute to expanding the possibilities of its use.

Conclusion

The three indicators of healthy/anti-inflammatory potential tested in our study led to the following conclusions. The only significant correlation was found between MDS and DII, however in different directions; only the MDS showed a significant association with our anti-inflammatory marker and the inclusion of UPR in our regression models did not add any improvement to the models. More studies are necessary with more robust and representative samples.

Ethics

Ethics Committee Approval: The original was approved by the Research Ethics Committee of the School of Arts, Sciences and Humanities, University of São Paulo (process 200.870/2013).

Informed Consent: The participants signed a consent form, and the procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept and Design: B.M.V., S.M.L.R., Analysis or Interpretation: B.M.V., A.A.B, C.M.M., S.M.L.R., Writing: B.M.V., A.A.B, C.M.M., R.C.A., S.M.L.R., Supervision: S.M.L.R.

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