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NEW INSIGHTS INTO THE ASSOCIATION BETWEEN CARDIOMETABOLIC INDEX WITH METABOLIC PROFILE, NUTRITIONAL STATUS, AND INFLAMMAGING IN OLDER

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ABSTRACT

The Cardiometabolic Index (CMI) has been highlighted as a promising tool for predicting cardiovascular and metabolic disease, but its relationship with systemic inflammatory status in older populations remains poorly understood. This study investigated the association between CMI and the triad of metabolic profile, body mass index (BMI), and inflammaging in older adults with and without obesity. A total of 132 older adults (68 women, 64 men; mean age 71.3 ± 6.5 years) participated. Anthropometric and demographic data were collected, and fasting blood samples were analyzed for glucose, lipids, proteins, and inflammatory markers. Participants were initially stratified by CMI values into G1 (lower CMI, < 50 % of mean) and G2 (higher CMI, > 50 % of mean).Regardless of sex, G2 individuals exhibited lower HDL-cholesterol and higher weight, BMI, total cholesterol, LDL-cholesterol, triglycerides, and TG/HDL ratio than G1. Correlation and multivariate regression analyses revealed a significant positive association between CMI and BMI, as well as with pro-inflammatory

cytokines across groups. When further stratified by BMI, subgroups with obesity and high CMI demonstrated generally higher levels of IL-1β, IL-6, IFN-γ, and TNF-α and a stronger association between CMI and pro-inflammatory status, especially in older women.These data not only reinforce the potential of CMI in cardiovascular risk evaluation but also suggest that CMI is associated with systemic pro-inflammatory status, particularly in the presence of obesity.

Keywords: Cytokines. Aging. Inflammation.

INTRODUCTION

Population aging is one of the most significant global health trends of the 21st century, driven by declining fertility and mortality rates. Estimates indicate that by 2030, one in six people worldwide will be over 60, increasing from 1 billion in 2020 to 1.4 billion, and reaching 2.1 billion by 2050. (1).

Although longevity is increasing, it does not necessarily translate into improved health outcomes. Aging is strongly associated with a rise in chronic non-communicable diseases (NCDs) — including diabetes, cardiovascular disease, cancer, and respiratory disease — which account for the majority of morbidity and mortality in older adults.(2)

Age-related diseases are influenced by genetic, metabolic, immunological, and inflammatory factors. A key concept in this context is inflammaging, a chronic, low-grade inflammatory state that contributes to the progression of age-related conditions.(3) This inflammation is driven in part by increased pro-inflammatory cytokines such as TNF-α and IL-6, which are closely linked to visceral adiposity — a condition that has increased globally among older adults over the past three decades. (4) Obesity promotes metabolic inflammation ("metaflammation"), which amplifies systemic inflammatory signaling and heightens cardiometabolic risk.(5)

While metaflammation is known to increase chronic disease risk, there is ongoing debate over biomarkers that accurately reflect the chronic inflammatory state and improve prognostic models in aging. (6)The Cardiometabolic Index (CMI) has emerged as a promising candidate because it integrates metabolic parameters (triglycerides, HDL-cholesterol) with anthropometric measures (waist circumference and height).(7) Measures of central obesity, such as Waist-to-Height Ratio (WHtR), more reliably predict cardiometabolic outcomes than BMI alone,(8) and CMI incorporates WHtR as a core component.(8) However, the ability of CMI to reflect cardiovascular risk in the context of chronic inflammation is under investigation.(6)

Sex differences are also notable: women generally accumulate more subcutaneous fat and maintain a relatively robust immune response, which may increase susceptibility to autoimmune disorders and age-related inflammation. Men tend to accumulate more visceral fat and exhibit a faster decline in immune efficiency with aging.(8)

Although CMI has been validated for cardiovascular and metabolic risk prediction, its role as an indicator of inflammaging and metaflammation in older adults

remains underexplored. This study aimed to investigate the association of CMI with metabolic profile, BMI, and inflammaging in older women and men, classified by obesity status.

MATERIALS AND METHODS

This study was a retrospective, cross-sectional, observational study involved 132 older adults (68 women, 64 men) aged 60–90 years. Fasting serum samples and clinical data were collected in early 2019 before the COVID-19 pandemic (Data and fasting serum samples were provided by Prof. Dr. Tábatta Renata Pereira de Brito from the Faculty of Nutrition at Universidade Federal de Alfenas (UFAL), Brazil), and the study followed the STROBE guideline. Participants were stratified by Cardiometabolic Index (CMI) into two groups: G1 (CMI <50 % below the mean) and G2 (CMI >50 % above the mean).

Inclusion criteria were age 60–90 years, absence of disease symptoms at sample collection, and no history of HIV, neurological, kidney, liver disease, or cancer. Exclusion criteria included recent (within two months) use of corticosteroids or other anti-inflammatory drugs, and failure to complete study procedures.

A sample size calculation using G*Power indicated that 124 participants would provide adequate statistical power (effect size = 0.30, $\alpha = 0.05$, power = 0.95).

Ethical approval was granted by the Ethics and Research Committee of UFAL (Protocol no. 2,668,936), and all volunteers provided written informed consent in accordance with the Declaration of Helsinki and Brazilian regulatory guidelines.

Anthropometric assessments included height and weight (measured using standard equipment) and BMI, classified according to WHO criteria. Waist circumference was measured with a non-elastic tape at the midpoint between the lowest rib and iliac crest. Clinical status and lifestyle data were self-reported.

Fasting blood samples were centrifuged, and serum stored at −80 °C until analysis. Biochemical measurements included glucose, lipid fractions (HDL, LDL, total cholesterol), triglycerides, and total proteins using colorimetric kits. Systemic cytokines (IL-1β, IL-6, IL-10, IFN-γ, TNF-α) were quantified by a multiplex bead assay and analyzed on a flow cytometer.

Statistical analyses included normality tests (Shapiro-Wilk), t-tests and ANOVA for parametric data, and Mann-Whitney/Kruskal-Wallis for non-parametric data. Correlations used Pearson or Spearman coefficients. Multivariate regression with CMI as the dependent variable was applied. A significance level of $p \leq 0.05$ was adopted.

Backward selection regression was used to explore subgroup predictors. Principal Component Analysis (PCA) of pro-inflammatory cytokines generated a Pro-inflammatory Gradient Score (PGS). ROC analyses assessed discriminatory ability of CMI and PGS. Interaction models examined whether IL-10 modified the association between PGS and CMI.

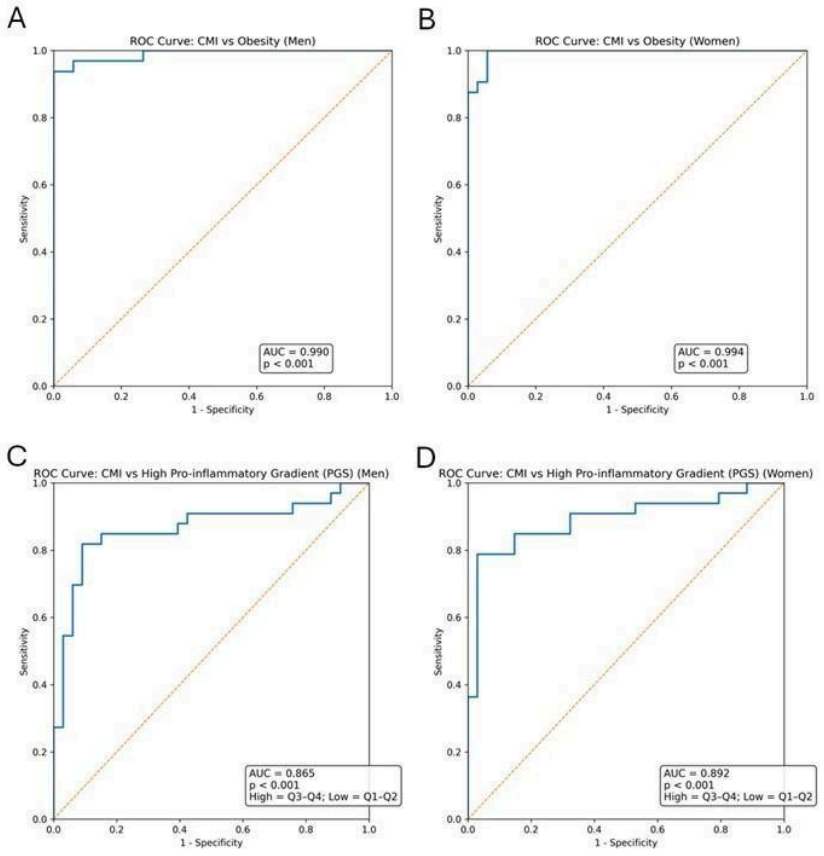
RESULTS

The table bellow summarizes demographic, anthropometric, cardiometabolic, biochemical, clinical, and lifestyle characteristics of the older adults in this study, both overall and by sex. Variables included age, weight, height, BMI, cardiometabolic index (CMI), glycemia, lipid profile (HDL-cholesterol, LDL-cholesterol, total cholesterol, triglycerides), total proteins, type 2 diabetes mellitus, arterial hypertension, cardiovascular diseases, physical activity, and smoking status. Older men had significantly higher weight and height than older women, while no other sex-related differences were observed.

Parameters	Volunteers			*p*-value[a]
	Total (n = 132)	Women (n = 68)	Men (n = 64)	
Age (years)	71.3 ± 6.5	70.9 ± 5.6	71.7 ± 7.4	0,5495
Weight (kg)	72.35 ± 17.86	66.87 ± 16.23[a]	78.44 ± 18.05	**0,0002**
Height (cm)	161.2 ± 9.90	154.9 ± 8.1[a]	167.9 ± 7.0	**<0,0001**
BMI (kg/m^2)	27.79 ± 6.10	27.88 ± 6.31	27.78 ± 5.90	0,9268
Glucose (mg/dL)	105.5 ± 33.73	103.1 ± 33.53	107.9 ± 34.03	0,4232
Total cholesterol (mg/dL)	193.8 ± 53.63	201.2 ± 55.74	186.0 ± 50.63	0,1038
HDL-cholesterol (mg/dL)	43.53 ± 8.30	43.35 ± 7.81	43.72 ± 8.82	0,7985
LDL-cholesterol (mg/dL)	113.4 ± 49.04	120.2 ± 52.17	107.7 ± 42.56	0,1356
Triglycerides (mg/dL)	184.2 ± 51.95	188.4 ± 52.60	179.8 ± 51.31	0,3447
TG/HDL ratio	6.86 ± 1.69	4.5 ± 1.6	4.3 ± 1.4	0,4095
Total protein (g/L)	4.4 ± 1.5	6.98 ± 1.62	6.75 ± 1.77	0,5324
CMI	2.8 ± 1.3	2.9 ± 1.3	2.7 ± 1.2	0,3078
Clinical (n)[b]				
Type 2 diabetes mellitus	48	20	28	0.0870
Arterial hypertension	90	42	48	0.1028
Cardiovascular disease	38	17	21	0.3218
Lifestyle (n)[a]				
Physical activity practice	41	20	21	0.6730
Current smoker	17	8	9	0.6937

[a]Comparison between the values obtained in the older women and older men groups.
[b]n = number of individuals.
BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG/HDL, Triglycerides and HDL-cholesterol; CMI, cardiometabolic index.
In bold are the values statistically significant.

ROC (Receiver Operating Characteristic) analyses demonstrated the excellent discriminatory ability of CMI to identify obesity in both sexes, with AUC values > 0.97 and narrow confidence intervals, indicating high sensitivity and specificity. These results confirm that CMI stratification into higher and lower groups reflects meaningful physiological differences rather than arbitrary categories. A PCA-derived pro-inflammatory axis (PC1_high_Q3-Q4), capturing shared variance among key pro-inflammatory cytokines, also showed strong discrimination for cardiometabolic burden (AUC = 0.86 in older men; AUC = 0.90 in older women), reinforcing that a composite inflammatory gradient retains cardiometabolic relevance.



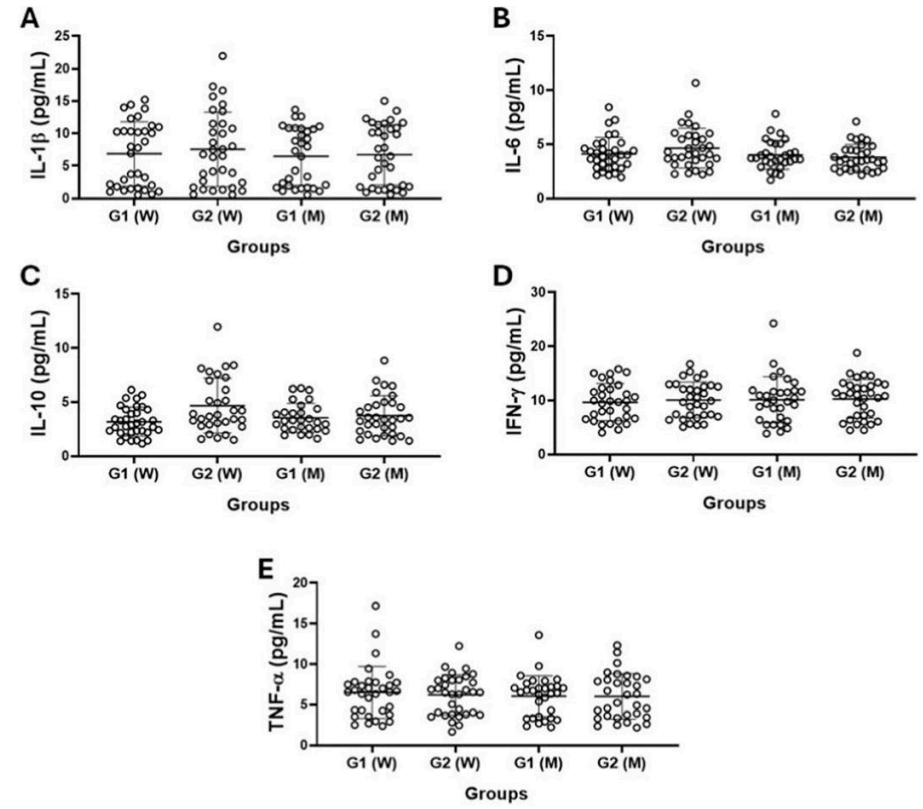
When volunteers were separated into higher CMI (G1) and lower CMI (G2) groups (Table 2), a consistent higher-risk profile emerged with elevated CMI. Regardless of sex, G2 participants had higher weight, BMI, total cholesterol, LDL-cholesterol, triglycerides, and TG/HDL ratio, lower HDL-cholesterol, and higher prevalence of arterial hypertension and cardiovascular diseases compared with G1. These findings support the interpretation that

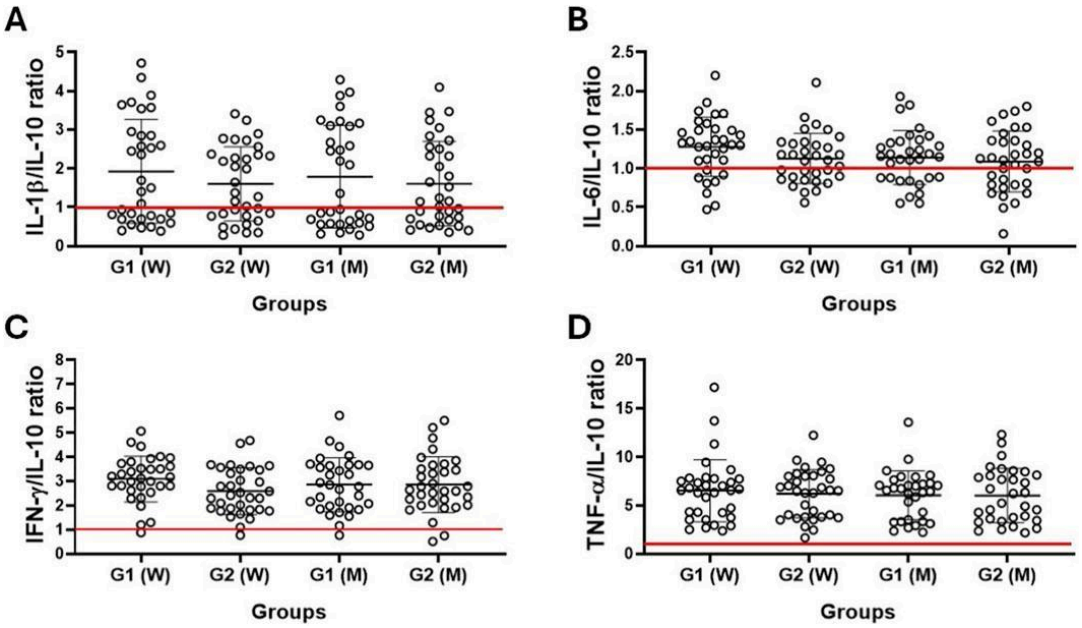
higher CMI integrates central adiposity and dyslipidemia, reflecting cardiometabolic stress beyond what BMI alone captures.

Parameters	Volunteers						
	Women G1 (n = 34)	Women G2 (n = 34)	*p*-value (intragroup)	Men G1 (n = 32)	Men G2 (n = 32)	*p*-values (intragroup)	*p*-value (intergroup)
Age (years)	71.4 ± 4.8	70.3 ± 6.4	0,4333	71.8 ± 6.8	71.8 ± 7.9	0,9944	0,7827/0,4197
Weight (kg)	54.72 ± 7.80	80.17 ± 12.03	**<0,0001**	64.40 ± 6.50	93.35 ± 13.88	**<0,0001**	**<0,0001/0,0001**
Height (cm)	156.2 ± 8.9	153.4 ± 6.9	0,3162	168.8 ± 6.4	167.0 ± 7.5	0,1650	**<0,0001/<0,0001**
BMI (kg/m^2)	22.58 ± 1.54	33.31 ± 3.02	**<0,0001**	22.37 ± 1.96	33.91 ± 2.95	**<0,0001**	0,6241/0,4282
Glucose (mg/dL)	104.73 ± 6.62	111.3 ± 31.19	0,4380	105.9 ± 34.26	100.1 ± 32.98	0,4818	0,8875/0,1703
Total cholesterol (mg/dL)	186.0 ± 46.72	215.1 ± 60.21	**0,0314**	172.0 ± 33.87	198.9 ± 59.78	**0,0318**	0,2642/0,1776
HDL-cholesterol (mg/dL)	48.43 ± 7.7	37.79 ± 1.64	**<0,0001**	48.52 ± 9.70	38.46 ± 2.81	**<0,0001**	0,9663/0,2552
LDL-cholesterol (mg/dL)	105.0 ± 42.31	134.1 ± 56.89	**0,0218**	97.11 ± 28.68	117.4 ± 50.63	**0,0493**	0,2044/0,3883
Triglycerides (mg/dL)	163.2 ± 44.41	216.0 ± 47.16	**<0,0001**	164.6 ± 48.84	196.6 ± 49.39	**0,0109**	0,9030/0,1155
TG/HDL ratio	3.4 ± 0.89	5.7 ± 1.2	**<0,0001**	3.4 ± 0.7	5.3 ± 1.4	**<0,0001**	0,9651/0,1682
Total protein (g/L)	6.92 ± 1.69	7.58 ± 0.67	0,4431	6.73 ± 1.57	6.81 ± 2.43	0,9062	0,6417/0,5512
Clinical (n)[a]							
Type 2 diabetes mellitus	7	13	0.1113	12	18	0.1329	0.1295/0.1428
Arterial hypertension	17	25	**0.0459**	20	28	**0.0209**	0.3065/0.1538
Cardiovascular disease	5	12	**0.0499**	6	15	**0.0166**	0.6595/0.3389
Lifestyle (n)*							
Physical activity practice	7	11	0.1684	7	14	0.0624	0.8983/0.3401
Current smoker	5	4	0.7192	4	4	0.9999	0.6479/0.9271

[a]n = number of individuals.
BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG/HDL, Triglycerides and HDL-cholesterol; CMI, cardiometabolic index. Red values present the p-values obtained in the comparison between women's groups (G1 × G2 groups). Blue values present the p-values obtained in the comparison between men´s groups (G1 × G2 groups).
In bold are the values statistically significant.

Figures bellow present cytokine profiles. The first figure displays serum concentrations of pro-inflammatory cytokines IL-1β, IL-6, IFN-γ, TNF-α, and the anti-inflammatory cytokine IL-10 across CMI groups and sex, with no significant differences between G1 and G2. The second figure shows ratios between pro-inflammatory cytokines and IL-10 (IL-1β/IL-10, IL-6/IL-10, IFN-γ/IL-10, and TNF-α/IL-10), and again, no group differences were observed. This pattern of modest between-group differences is consistent with inflammaging, a chronic low-grade systemic inflammation characteristic of aging, in which multiple mediators are moderately elevated rather than dominated by single spikes.





Despite the lack of striking differences in isolated cytokines, Spearman's correlation analyses revealed significant positive associations between CMI and BMI, and between CMI and both pro- and anti-inflammatory cytokines across sexes and CMI groups. These findings suggest that cardiometabolic load — as captured by CMI — is broadly linked to both adiposity and

systemic inflammation.

G1 group – older men			G2 group – older men		
Parameters	*rho*-value	*p*-value	Parameters	*rho*-value	*p*-value
CMI × BMI	0,7846	<0,0001	CMI × BMI	0,7667	<0,0001
CMI × IL-1β	0,6249	0,0001	CMI × IL-1β	0,7630	<0,0001
CMI × IL-1β/IL-10	0,7461	<0,0001	CMI × IL-6	0,4615	0,0068
CMI × IFN-γ	0,3766	0,0367	CMI × IL-6/IL-10	0,4976	0,0032
CMI × IFN-γ/IL-10	0,4854	0,0056	CMI × IL-10	0,6418	<0,0001
CMI × TNF-α/IL-10	0,5116	0,0032	CMI × TNF-α	0,6975	<0,0001
CMI × BMI	0,7400	<0,0001	CMI × IFN-γ	0,3766	0,0367
CMI × IL-1β	0,7126	<0,0001	CMI × BMI	0,7205	<0,0001
CMI × IL-1β/IL-10	0,5829	0,0002	CMI × IL-1β	0,7109	<0,0001
CMI × IL-6	0,4946	0,0025	CMI × IL-1β/IL-10	0,6616	<0,0001
CMI × IL-10	0,4378	0,0086	CMI × IL-6	0,4048	0,0238
CMI × IFN-γ	0,5417	0,0007	CMI × IFN-γ	0,7385	<0,0001
CMI × TNF-α	0,5591	0,0004	CMI × TNF-α	0,6738	<0,0001

Multivariate regression analyses adjusted for CMI showed that BMI was significantly associated with CMI in both older men and women, reinforcing that greater adiposity drives higher cardiometabolic burden. More nuanced inflammatory contributions emerged in subgroup analyses:

- Older men with normal weight (eutrophic): IL-6 and IL-10 remained in final models across CMI strata, suggesting that in non-obese men, CMI is influenced by a balance between pro-inflammatory and anti-inflammatory signals rather than by dominance of one marker. IL-6 plays both pro- and regulatory roles depending on context, while IL-10 moderates inflammatory signaling.

- Older men with obesity and high CMI: TNF-α and IFN-γ were primary predictors of CMI. TNF-α is a central mediator of obesity-related chronic inflammation, contributing to insulin resistance and endothelial dysfunction, while IFN-γ supports Th1-oriented pro-atherogenic immune responses. Their prominence suggests that inflammation in obese older men is skewed toward classical pro-inflammatory pathways that amplify cardiometabolic damage.

In older women, regression models were less stable but still informative. In normal-weight, lower-CMI women, IL-1β and TNF-α tended to remain in final models with borderline significance, implying that subtle inflammasome activation and TNF-α effects may

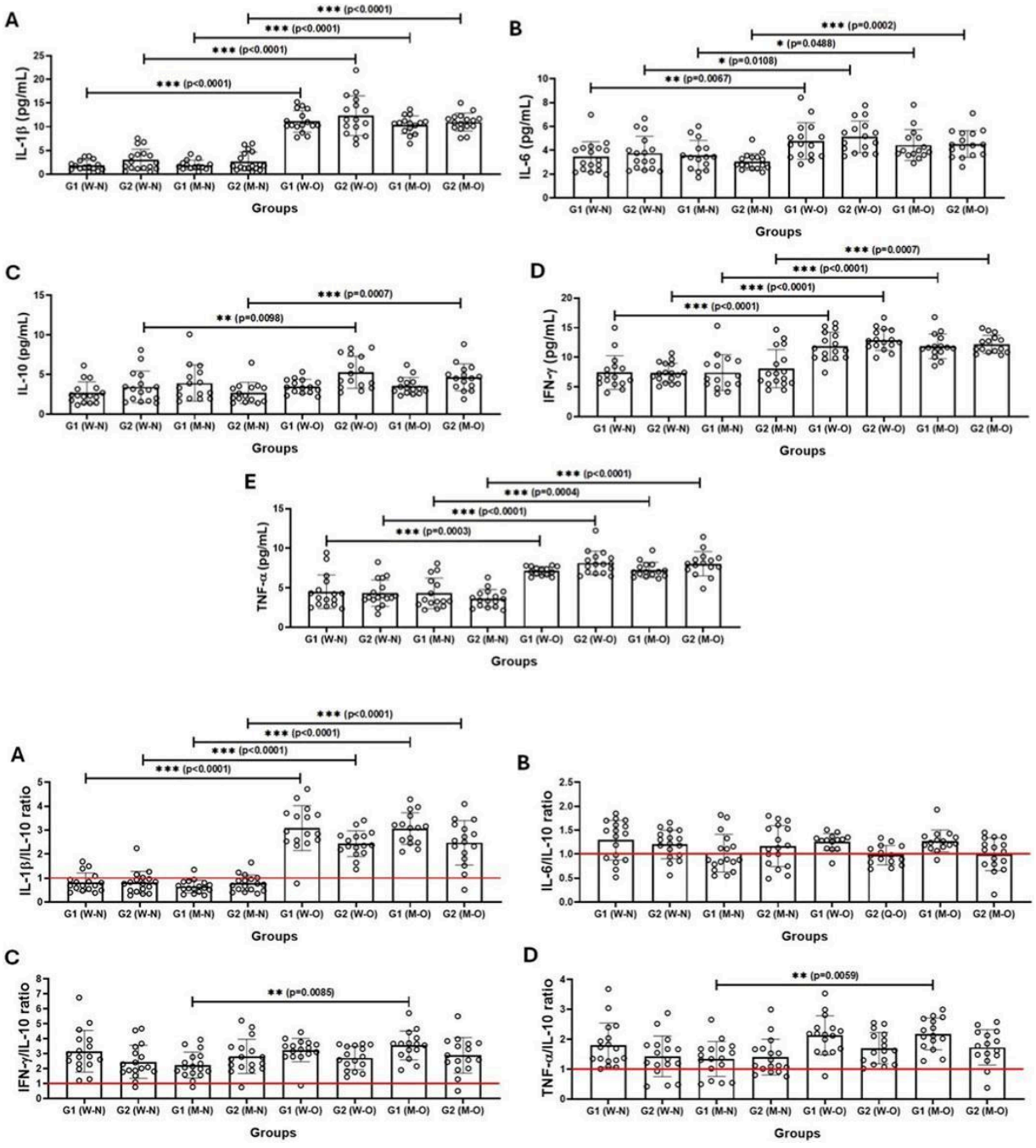
contribute even without obesity. In women with obesity, although individual predictors were weaker, overall patterns — including higher mean levels of pro-inflammatory cytokines and elevated pro/anti-inflammatory ratios — indicate that excess adiposity amplifies systemic inflammatory pressure, especially as regulatory networks shift with aging.

CMI-adjusted								
Parameters	G1 group – older men				G2 group – older men			
	β–value	CI[a] - 95%	*p*-value	R^2	β–value	CI[a] - 95%	*p*-value	R^2
BMI	0,0478	0.012 a 0.083	0.014	0,9396	0,0982	0.023 a 0.173	0.014	0,7656
IL-6	0,2058	0.059 a 0.352	0.012	0,9843				
IL-10	−0,2767	−0.438 a −0.114	0.004	0,9947				
IFN-γ	0,2473	0.142 a 0.352	0.001	0,9987				
IFN-γ/IL-10	0,5845	0.289 a 0.883	0.002	0,9810				
TNF-α	0,2286	0.120 a 0.337	0.001	0,9980				
IL-1β/IL-10	0,2855	0.016 a 0.554	0.039	0,9782				
BMI	0,0224	0.003 a 0.048	0.049	0,8614	0,2547	0.152 a 0.378	0,0001	0,9159
IL-1β	0,3128	0.054 a 0.571	0.021	0,9843				
IL-1β/IL-10	1,102	0.224 a 1,981	0.017	0,9520				
TNF-α	0,0151	0.005 a 0.024	0.006	0,9247				
TNF-α/IL-10	0,0444	0.019 a 0,0691	0.001	0,8955	0,02371	0.001 a 0.046	0.042	0,9662
IL-6/IL-10	0,8009	0.008 a 1,593	0.047	0,9595				

[a]CI, confidence interval.

To conceptualize overall inflammatory architecture, a Pro-inflammatory Gradient Score (PGS) was computed via principal component analysis incorporating IL-1β, IL-6, TNF-α, and IFN-γ. Composite indices like PGS integrate multiple biomarkers into a single gradient of inflammatory activation and have been associated with cardiometabolic risk and adverse outcomes in older populations. The association between PGS and CMI was stronger in subgroups with obesity, suggesting that similar levels of inflammatory activation may be more detrimental in the context of adiposity, consistent with evidence that adipose tissue amplifies systemic inflammation and associated metabolic dysfunction.

Figures bellow illustrates pro- to anti-inflammatory cytokine ratios in normal-weight and obese subgroups. IL-1β/IL-10 ratios were consistently higher in obese participants than in normal-weight individuals regardless of sex. Additionally, in older men, IFN-γ/IL-10 and TNF-α/IL-10 ratios were higher in the G2 obese group compared with the G1 normal-weight group, while IL-6/IL-10 did not differ significantly. These findings further support the impact of adiposity on the inflammatory balance toward pro-inflammatory pressure.



Spearman's correlations between CMI and inflammatory markers stratified by BMI and CMI groups revealed that in G2 obese subgroups, CMI was significantly positively correlated with cytokines and pro-inflammatory ratios. By contrast, in G1 normal-weight older women, CMI and the IL-1β/IL-10 ratio showed a significant negative correlation, suggesting that patterns of inflammatory contribution to cardiometabolic burden vary depending on adiposity and CMI category.

G1 group – older women with normal weight		
Parameters	*rho*-value	*p*-value
CMI x IL-1β/IL-10	–0,6396	0,0043
G2 group – older women with obesity		
Parameters	*rho*-value	*p*-value
CMI x IL-1β	0,6418	0,0095
CMI x IFN-γ	0,6632	0,0041
CMI x IL-6/IL-10	0,4978	0,0477
G2 group – older men with obesity		
Parameters	*rho*-value	*p*-value
CM x TNF-α	0,5625	0,0291
CMI x TNF-α/IL-10	0,4803	0,0491

Table analyses of regression models with CMI as the dependent variable in sex, CMI, and BMI stratifications showed that in G2 older men with obesity, IFN-γ and TNF-α were significantly associated with CMI, while in G2 older women with obesity, age was significantly associated with CMI. These results indicate that inflammatory factors and age contribute differentially to cardiometabolic burden depending on sex and adiposity.

Parameters	CMi-adjusted			
	G2 group – older men with obesity			
	β–value	CI[a] - 95%	*p*-value	R^2
IFN-γ	0,4945	0.164 a 0.823	0,0118	0,7199
TNF-α	0,1310	0.037 a 0.224	0,0153	0,1504
Parameters	G2 group – older women with normal weight			
	β–value	CI[a] - 95%	*p*-value	R^2
Age (years)	0,0681	0.003 a 0.132	0,0419	0,6422

[a]CI, confidence interval.

IL-10 appears to play a buffering role in modulating how pro-inflammatory activation translates into cardiometabolic impact. IL-10 facilitates macrophage polarization toward less inflammatory phenotypes and inhibits TNF-α, IL-1β, and IL-6 — mechanisms associated with improved metabolic outcomes. When CMI was modeled as a function of PGS and IL-10, volunteers with higher IL-10 exhibited smaller increases in CMI for a given inflammatory

gradient, whereas those with lower IL-10 had steeper rises in CMI, supporting the interpretation that IL-10 attenuates the cardiometabolic impact of inflammatory pressure.

Sex differences emerged: in women, the IL-10 effect was strong enough to be an independent predictor in some models, while in men it was more evident through interaction effects. These sex-dependent patterns align with evidence that inflammatory markers have stronger associations with adverse outcomes in older women and that women may exhibit greater regulatory responsiveness.

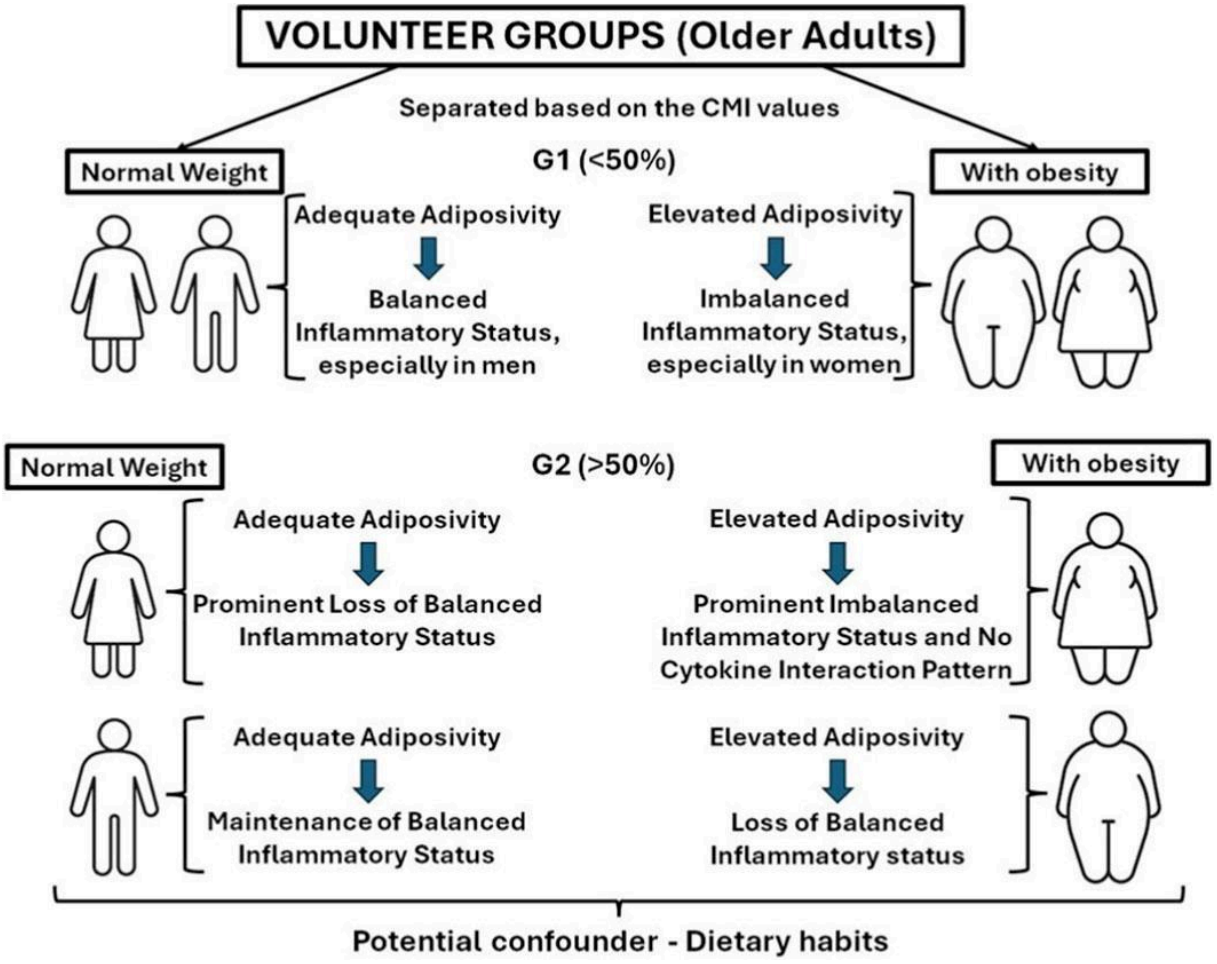
The integrated findings reinforce the potential of CMI as a simple, integrative index capturing both metabolic derangements and the interplay between adiposity, inflammation, and cardiometabolic risk. Incorporating inflammatory information — whether through composite scores like PGS or combined pro- and anti-inflammatory patterns — may further refine risk stratification beyond traditional metabolic markers. Composite biomarker indices have been shown in other cohorts to offer superior predictive value compared with individual markers alone.

From a clinical perspective, identifying subgroups with compromised regulatory capacity (e.g., low IL-10 responsiveness) could help target interventions for individuals who might benefit most from intensified lifestyle or pharmacological strategies. Evidence from randomized trials demonstrates that comprehensive approaches — including weight control, improved diet, physical activity, and management of comorbidities — effectively reduce cardiometabolic risk factors and markers of biological aging in older adults, and multidimensional assessment improves early identification of at-risk individuals for intervention.

CONCLUSION

In the present study, we were able to demonstrate that even though the isolated cytokine assessment presents valuable data, the integrative analysis performed here offers a plausible and testable mechanistic framework for understanding how inflammaging, obesity, and cardiometabolic risk interact in older men and women.

CMI emerges not only as a metabolic index but as an accessible index of the balance between the intensity of inflammatory signaling and the effectiveness of IL-10-mediated counter-regulation. The main findings are summarized in the figure below:



In summary, this study supports the Cardiometabolic Index as a simple, accessible tool that integrates not only central adiposity, dyslipidemia, and cardiometabolic risk, but also the low-grade inflammation in older adults, while revealing a mechanistic framework in which CMI could also reflect the systemic inflammatory status, particularly that involved in the (un)balance between pro-inflammatory cytokine and IL-10–mediated counter-regulation. Additionally, sex-dependent patterns further indicated more direct inflammation-CMI

coupling in older men and greater reliance on IL-10–driven regulatory capacity in older women.

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