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ALLOSTATIC LOAD AS A BIOLOGICAL SUBSTRATE TO INTRINSIC CAPACITY: A SECONDARY ANALYSIS OF CRELES

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Abstract: *Objectives:* Intrinsic capacity (IC) is one of the latest views of positive aging. In its current status lacks a biological substrate amenable to be intervened. The aim of this study was to determine the association of allostatic load (AL) with IC. *Design:* We present a cross-sectional analysis of the Costa Rican Longevity and Healthy Aging Study. *Setting:* This report is from a representative sample of Costa Rican older adults; one of the countries that integrate the Central America region. *Participants:* 2,827, 60-year or older community-dwelling individuals. *Methods:* An IC index was gathered and validated, including different domains: cognitive, psychological, sensory, vitality and locomotion. AL was integrated with: blood pressure, abdominal obesity, body mass index, HDL-cholesterol, glycosylated hemoglobin, DHEAS, cortisol, epinephrine and norepinephrine. AL was grouped in three categories according to the number of abnormal biomarkers (0-1, 2-3 and ≥4). Chronic diseases, socioeconomic level, sex and age were the adjusting variables. Ordinal logistic regression models were estimated in order to test the strength of the association. *Results:* From a total sample of 1,888 individuals, 51% (n=962) were women, 36.4% were in the 60-69 age category. The mean score of the IC index was of 6.6 (±2.2). Odds ratio (OR) of the adjusted models were significant for the group of those with 2-3 abnormal biomarkers of AL (OR 0.67, p=0.007) and also for those with ≥4 (OR 0.56, p=0.002), when compared to the reference group of AL (0-1 abnormal biomarkers). *Conclusions and implications:* AL showed an incremental association with IC, even when adjusted for factors such as socioeconomic status and chronic diseases. Targeting therapeutically AL could potentially improve IC in older adults and therefore decreasing the progression to disability or to overt dependency.

Key words: Intrinsic capacity, healthy aging, allostasis, aging.

Older adults are a continuously growing fraction of the population worldwide, challenging the society because of special health needs (1, 2). Along with chronic diseases –mainly present as two or more (multimorbidity)– the aging biological changes (3) give older adults specific health features. Therefore health care paradigms of younger humans may not apply to older adults, and special approaches are needed in order to fulfill their needs (4).

In the framework of the study of health in old age, mainly negative aspects of health, and the consequences of lifetime insults to the building blocks of function (5, 6); have been studied. From these perspectives, old age is seen as a negative stage of life that implies an inevitable deterioration, leaving behind the possibility of a productive and active aging (2, 7). In this sense, the integral perspective of healthy aging that focus on the positive aspects of an individual –that are the result of the accumulation of different skills on diverse levels (i.e., psychologic, social, biologic)– in which best case scenario make it possible to live this period of life as well as possible (2, 8). Moreover, having a positive approach to aging, may help in improving health policies and aid in substituting the belief that older age is a burden for the society (9).

The model of healthy aging is defined as the process of promoting and maintaining the functional capacity that allows well-being in old age. Moreover, functional capacity is defined as the attributes related to health that allow a person to carry out their activities, which is made up of the intrinsic capacity (IC), the environment and the interaction between them (2). The IC is defined as a set of physical and mental skills that a certain individual has acquired and modified throughout life (10). As previously mentioned, this concept emphasizes the positive attributes of individuals in relation to the environment and throughout life as part of a longitudinal vision (2). In fact, through the review of recent empirical evidence (10), the risk factors that indicate disability, functional loss and dependence in older adults were identified (11-13). Accordingly, five domains were determined to be part of IC: 1) cognition, 2) psychological, 3) Sensory, 4) vitality and 5) locomotion.

However, a biological substrate amenable to be intervened in order to improve IC, was not included. In this sense, allostatic load (AL) is a biological expression result of both the genetic background of an individual and the (positive and negative) impact of social determinants and environmental characteristics (14). Seeman et al., combined 10 parameters of physiological activity according to regulatory systems, proposing a measure of AL as an index of body endurance from a biological point of view, and with the possibility to be medically intervened (15-17).

Currently there is a lack of data on IC and how could it be related to a biological substrate. Therefore, the objective of this manuscript is to determine if AL has an incremental association with IC, even when adjusted to other important social and

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Table 1
Socioeconomic level and demographic variables in total sample and subsample with intrinsic capacity evaluation

Variables	Total sample 2,827		Subsample with intrinsic capacity evaluation 1,888	
n				
Sex	n	%	n	%
Male	1,293	45.7	926	49.1
Female	1,534	54.3	962	51.0
Age (years)				
60-69	843	29.8	687	36.4***
70-79	940	33.3	673	35.7
80-89	765	27.1	445	23.6
90+	279	9.9	83	4.4
Education				
None	561	19.8	312	16.5
Elementary	1,891	66.9	1,302	69.0
Secondary +	375	13.3	274	14.5
Residence				
Lowlands	1,097	38.8	783	41.5
Highlands	1,044	36.9	636	33.7
Metro San Jose	686	24.3	469	24.8
Wealth (14 goods)				
Poor	674	23.8	403	21.4
Middle	1,881	66.5	1,283	68.0
Rich	272	9.6	202	10.7
Socioeconomic level				
Low	902	31.9	574	30.4
Middle	1,569	55.5	1,050	55.6
High	356	12.6	264	14.0

***p<0.05 test of proportions between total sample and subsample

demographic determinants of health.

Methods

Design and Sample

This is a cross-sectional analysis of the Costa Rican Longevity and Healthy Aging Study (CRELES). CRELES is a cohort of a national representative sample of 9,000 ≥60-year adults residing in Costa Rica. For this study, sociodemographic, health, food frequency, anthropometric and biomarker measurements from the baseline assessment were used (18).

Variables

Intrinsic Capacity

For the construction of the IC, the five domains proposed by Cesari (10) were considered from the first wave of CRELES (Table A1). Each domain was further divided in three categories, assigning a numerical score for each one as follows: optimal=0, mild impairment=1 and sever impairment=2. The sum of each domain was then integrated as a complete IC index, going from zero (worst IC possible) to ten (highest IC possible). This index was further divided into groups (see below). With the exception of the cognitive domain, the domains and the IC index were divided in groups using main component analysis and clustering by k-means. Those subjects with missing values for a given dominion were imputed with zero (<5% of the cases).

Cognitive Domain

A modified version of the Mini Mental Status Examination was used. Scores were standardized and stratified by education in order to define 3 cut-off points (severe deterioration [>2.5 SD], slight deterioration [≥1.5 to ≤2.5], optimal [<1.5SD]).

These categories were assigned values from 0 to 2, respectively.

Psychological Domain

For this domain, a summary index was built on the basis of four indicators: 1) depression (15-item Geriatric Depression Scale [GDS-15]) 19, 2) self-reported life satisfaction, 3) locus of control and 4) social participation (Table 1).

Life satisfaction was measured with the question «In general, how do you feel about your life», with a 4-point possible score. It was inverted and transformed into a 0 to 1 scale: very satisfied = 1, somewhat satisfied = 0.66, somewhat dissatisfied = 0.33 and very dissatisfied = 0 (20).

Locus of control was measured with eight items, that were summed (after reversing the coding for those external locus of control questions) and then divided by 8; resulting in a score ranging from 1 to 4. A higher score reflects greater internal locus (i.e., less of a sense that one is in control of his or her life) (21).

Social participation was evaluated by the average number of hours dedicated in the last 12 months to the following activities: providing help to other adults, church, child care, civic activities, watching TV, sports, daily tasks, recreational activities. If they dedicated at least one hour, it was defined as if the activity was carried out. Three categories were defined: no activities = 0, participation in 1 or 2 activities = 1, and participation in 3 or more activities = 2.

Sensory Domain

Self-reported vision in a Likert scale was used (1=poor-7=excellent). The following questions were asked: «how do you see it for seeing far (with glasses) and to recognize a friend on the other side of the street? « and « how your sight is for seeing near (with glasses) and to read the newspaper or to see photographs in a magazine?». An average of the vision was calculated with the two scores, and those who were not asked about far vision if they saw up close, were assigned a score of 6 considering that they only use glasses for reading. Those participants that reported themselves as blind were considered to have the lowest score (0). Self-reported hearing (1=poor-7=excellent) was evaluated with the following question: «how is your hearing is in general (with hearing aid)».

Vitality Domain

Three variables were used for this domain: peak flow test (L/min), handgrip strength (kg) and body mass index (BMI) (kg/m2). Regarding BMI values, the following categories were gathered: underweight or obese = 0 (<18.5 and ≥30), overweight = 0.5 (≥25 and <30), and normal = 1 (18.5-25). Peak flow test and handgrip strength were standardized.

Locomotion Domain

Three tests were considered in this domain: chair-rising, gait speed and pick-pencil. Regarding the first test, the number of times an individual rose from a chair divided by time (seconds) was the score. Gait speed was measured with the time (seconds) taken to walk 3-meters at normal pace; the time was divided by 3, resulting in gait speed (m/s). For the pick pencil test, the inverted time taken to lift a pencil from the floor was the score used for the summary index of this domain.

Covariables

Allostatic Load

For the construction of the AL, the proposed biomarkers of Seeman et al. 2001 were used. However, to determine the parameters of higher risk, the highest to sex-specific quartiles were used (with the exception of HDL-cholesterol and DHEA-S, highest risk was defined as the lower quartile) (22). As a previous step, the AL was calculated with three forms: original (16), cut-off points from previous studies in the Costa Rican population (18) and according to the highest to sex-specific quartiles. The average estimated score was 3.7, 3.5 and 2.4 respectively. For this analysis, the proposal of the sex-specific parameters was used (see Table A2).

Socioeconomic Level

A socioeconomic level index was constructed based on three variables: place of residence, education and household wealth. The defined place of residence, was categorized as follows: less developed lowland = 0 (including coastal regions at the Pacific Ocean and Caribbean); rest of highlands at the Central Valley = 1 (including suburbs of San Jose) and metropolitan area of San Jose = 2. The educational level was as follows: none = 0, elementary = 1, some secondary = 2, and secondary and more = 3. Household wealth was defined by the number of goods and conveniences in the household, and categorized as follows: poor (0-8), middle (9-11) and rich (12-14) 18. Again, a summary index was estimated based on main component (50% variance explained), defining three levels (low, middle and high) by means of cluster analysis by k-means.

Chronic Diseases

Self-reported chronic diseases were also included in the analysis as covariates. We considered the following conditions: hypertension, high cholesterol, diabetes, cancer, asthma or chronic bronchitis/chronic obstructive pulmonary disease, heart attack, other heart diseases, stroke, arthritis and osteoporosis. A summary variable based on the number of chronic diseases was used for analysis: 0, 1-2, and ≥3.

Statistical Methods

In order to have a robust IC, a validity analysis was performed as follows. For internal consistency of IC evaluation, the Cronbach alpha was 0.73. All items of the five domains were correlated to the scale´s total score (rho ranging from 0.49 to 0.73) The differences between mean value IC between age groups were also analyzed to assess the validity of the following hypothesis: the IC is expected to be higher among

Table 2
Variables of intrinsic capacity domains and parameters of allostatic load according to age categories

Variables of domains intrinsic capacity		**Age categories (years)**			
	n	**60-69**	**70-79**	**80-89**	**90+**
Cognitive					
% Severe impairment	2,827	2.61	7.02	22.8	63.1
Psychological					
Geriatric depression	2,114	9.6	7.7	8.0	10.7
% Life Satisfaction	2,111	73.5	75.8	75.0	73.2
% More Social Participation	2,827	53.0	43.3	21.7	5.7
% internal locus control	2,112	51.9	41.7	36.3	26.8
Sensory					
%Vision Impairment	2,727	6.5	10.7	22.2	41.0
% Optima vision		56.8	51.1	33.1	21.9
% Hearing Impairment	2,750	2.2	5.8	13.4	35.0
% Hearing		74.2	63.8	47.2	25.1
Vitality					
Normal	2,698	27.6	33.3	46.2	57.2
Obesity		26.4	20.0	13.9	3.1
% Lowest quartile hand grip strength	2,518	9.6	18.2	38.5	65.6
% Highest quartile hand grip strength		37.7	30.8	10.3	2.1
% Lowest quartile breathing flow	2,281	11.9	21.7	39.8	58.9
% Highest quartile breathing flow		38.2	26.5	11.5	3.6
Locomotion					
% Lowest quartile chair speed	2,062	13.4	23.5	41.2	54.0
% Highest quartile chair speed		34.5	25.4	13.0	9.5
% Lowest quartile gait speed	2,234	11.2	20.9	42.2	67.3
% Highest quartile gait speed		37.8	23.4	12.2	8.9
% Lowest quartile pick-pencil	2,828	33.6	24.4	14.9	3.8
% Highest quartile pick-pencil		15.1	23.2	38.6	50.6
Allostatic Load					
%High systolic blood pressure	2,793	19.3	28.0	29.5	22.9
%High diastolic blood pressure	2,793	30.9	27.8	21.2	12.2
%Obesity	2,563	22.9	31.9	26.3	24.9
%Low HDL	2,654	29.6	26.1	25.3	25.1
%High cholesterol ratio	2,654	30.5	23.2	22.8	21.1
%High glycosylated hemoglobin					
%Low DHEAS-S	2,621	14.7	23.9	30.3	46.8
%Hight cortisol	2,616	26.4	27.3	19.2	18.0
%High epinephrine	1,522	23.0	23.2	28.2	28.8
% High norepinephrine	1,572	22.3	24.0	26.7	33.6

Table 3
Ordinal logistic models assessing effect of component of allostatic load, health, demographic and socioeconomic factors in Intrinsic Capacity (n= 970)

Variables	Ordinal IC				IC (Low (0-6) - High (7-10)				IC (Low (0-4) / Mild (5-6) / High (7-10)			
	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	OR	Sig.	OP	Sig.	OR	Sig.	OR	Sig.	OR	Sig.	OR	Sig.
Allostatic load (0-1 reference category)												
2-3	0.68	0.003	0.74	0.023	0.63	0.002	0.67	0.025	0.62	0.001	0.70	0.007
4+	0.62	0.000	0.70	0.027	0.55	0.001	0.56	0.006	0.56	0.001	0.62	0.002
Chronic diseases (none reference category)												
1 or 2			0.82	0.197			0.81	0.290			.83	0.315
3 or more			0.51	0.000			0.49	0.002			.49	0.001
Sex (male reference category)												
Female			0.27	0.000			0.28	0.000			0.35	0.000
Age groups (60-69 reference category)												
60-69												
70-79			0.56	0.000			0.76	0.114			0.71	0.043
80+			0.11	0.000			0.12	0.000			0.13	0.000
Socioeconomic Level (low reference category)												
Middle			2.23	0.000			2.36	0.000			2.15	0.000
High			5.50	0.000			4.09	0.000			4.49	0.000
Goodness of fit												
-2 log-likelihood			4080	3497			1319	1009			1878	1517
AIC			4104	3535			1325	1029			1886	1539
BIC			4163	3627			1340	1077			1905	1592

the youngest to check this value. Then, a ROC curve was constructed to determine the sensibility and specificity of the IC index in predicting mortality in follow up (0.732). For purposes of this validation only, two waves were utilized in order to register the follow-up status: alive, lost to follow-up or death (n = 501). Data available upon request.

Descriptive analysis of the variables included for each domain according to age, sex, socioeconomic level and AL categories was performed. Categorization for IC by cluster analysis k-means was defined in two (low=0-6 and high=7-10) and three groups (low=0-4, mild=5-6 high=7-10), in order to perform the multivariate analyses. To analyze the effect of the AL socioeconomic and demographic factors on IC, ordinal logistic regressions were estimated.

Ethical issues

CRELES was approved by the Ethical Science Committee of the University of Costa Rica (VI-763- CEC-23-04). All subjects signed informed consent, and all procedures of the study are according to the last version of Helsinki declaration.

Results

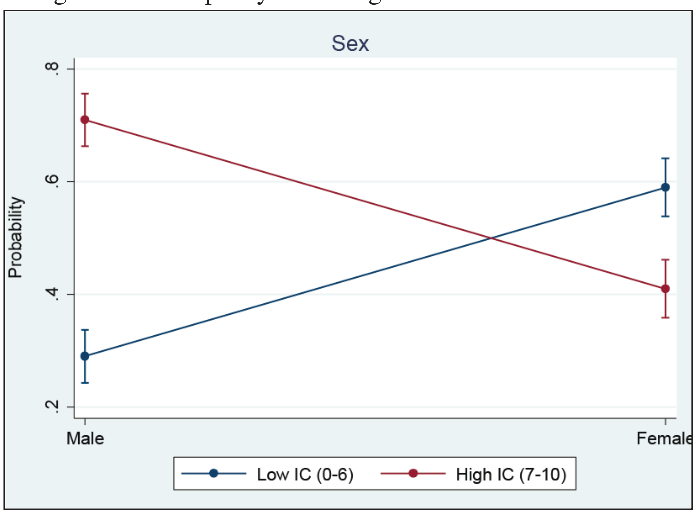
From a total of 1,888 60-year of older adults 51% (n=962) were women and the age group from 60 to 69 years had the highest frequency 36.4% (n=687) in subsample with IC evaluation. Regarding the IC index, the mean for all the sample was of 6.6 (±SD 2.2). Elementary school was the most frequent (69%) level of education and the majority of the older adults lived in the Lowlands (41.5%). Up to 55.6% (n=1,050) of the individuals were considered to have an intermediate socioeconomic level (see Table 1).

As depicted in both Fig. A1 and Fig. A2, IC index has higher scores in those younger older adults (60-69 group) and tends to have lower scores in the female group. Accordingly, those older adults 80-year or older seem to have higher frequencies of very low scores of the IC index. Similarly, Fig. A3 shows how each domain is more impaired in the oldest age group, with a linear trend for the distribution between age groups. As shown in table A3 the lowest mean IC index score was found for those older adults 90-years or older (2.9 ±SD 2.3). It also shows that health conditions reduce the IC. Socioeconomic level and AI seem to have association with IC index (see Table A3). This pattern is also evident for each component of the domains of IC, the higher the age group, the worse the performance in individual tests. For example, from the vitality domain, the frequency of having a low handgrip strength (lowest quartile), is 9.6% for those in the 60-69 age group, 18.2% for those in the 70-79 age group, 38.5% for those in the 80-89 age group and 65.6% for those in the 90-year or older group. Similar patterns are present in the rest of the components (see Table 3).

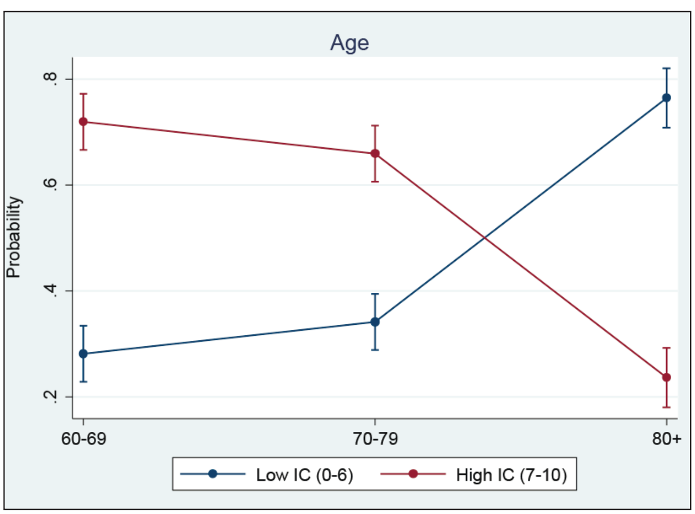
Figure 1

Predicted probabilities with 95% confidence intervals of low or high intrinsic capacity according to different variables: a) sex; b) age groups; c) categories of allostatic load; d) health conditions; e) socioeconomic level

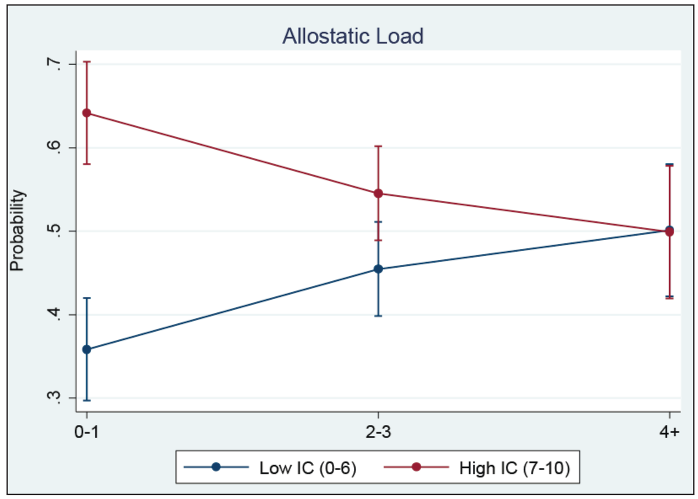
A) Predicted probabilities with 95% confidence intervals of low or high intrinsic capacity according to sex



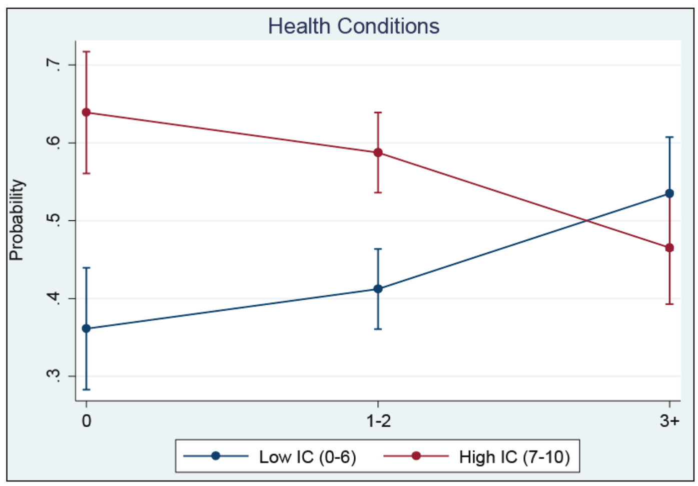
B) Predicted probabilities with 95% confidence intervals of low or high intrinsic capacity according to age group



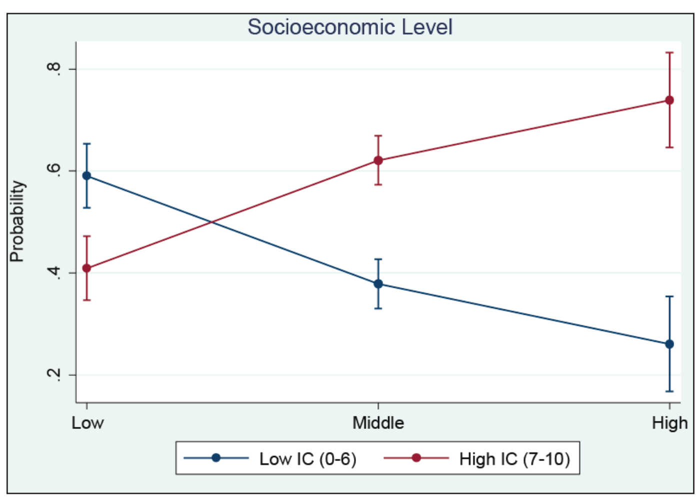
C) Predicted probabilities with 95% confidence intervals of low or high intrinsic capacity according to categories of allostatic load



D) Predicted probabilities with 95% confidence intervals of low or high intrinsic capacity according to health conditions



E) Predicted probabilities with 95% confidence intervals of low or high intrinsic capacity according to health conditions



Regarding the association of IC index and AL, there was a significant association. In the model with best fit (Model 4) regarding lower value AL, the OR of having greater IC evaluation decrease by 33% in the category of 2-3 abnormal biomarkers (p=.008), and 44% for ≥4 abnormal biomarkers (p=.002). Controlling for chronic diseases,

IC tends to decrease as the number of diseases increases. When compared with those not having any declared condition, the odds of having a significant decrease in IC score rise significantly (51%) among those with 3 or more conditions.

In women, the odds of having a lesser IC score are 72% higher than those among men. As age increases, the IC score decreases significantly among those aged 80 and over (p=0.000). On the other hand, socioeconomic condition (SEC) level is closely related with the IC score, the higher the SEC level the higher the IC score (see Table 3).

When considering all the potential confounding variables (i.e., model 4) the probabilities of having a greater IC score (7-10) increase among men, in those in the age group of 60-69 years, in those with a low AL (0-1) and or higher socioeconomic level (see Fig. 1A-D).

Discussion

There is an independent and significant inverse association between AL and IC. To our knowledge this is the first work to demonstrate the possible biologic substrate of IC, and its potential to be intervened by modifying these biological parameters. In addition to already known properties of IC, our results point to the fact that changes in simple biomarkers could change the disabling process of an older adult. For example, if an individual has abnormal blood pressure, correcting it could result in better IC and therefore a lower probability of changing from disability to dependency.

IC is better understood in the context of general approaches to the older adult health, rather than in the classical reductionist way of modern medicine (23). It gives an opportunity to advance in the integrated care of older adults, recognizing the value of looking at "the whole picture" rather than to individual components (24). In addition, it could be used in a younger population, since the components of its domains, are constructed along the life course; with the potential of reducing the burden of chronic disease in older adults (25).

It is important to recognize that this novel concept arrives to an era of different terms that somehow deviate the attention from the important issue: older adult care (26). However, since it is composed of well-known domains that are already evaluated in the so-called geriatric assessment, it could provide a new frame for primary care practice in caring for older adults (27). Moreover, according to our results, IC could be explained by biological factors, a crucial issue in the understanding a phenomenon for those used to mechanistic approaches, it helps to provide already known interventions (i.e., lower blood pressure) that seem to work in comparison to ambiguous or general interventions (i.e., changes in lifestyle).

On the other hand, there is a potential overlapping of the IC concept with other well-established conditions. Nevertheless, clear definitions and differences are available, and the research and implementation of one concept does not preclude the others, they complement each other (10, 28, 29).

Apart from being the first work to identify a biological substrate for IC, this work has other advantages. It uses data from a representative sample of a middle-income country, that has in-depth exploration of variables that are not usually available in these data sets. Moreover, the process of integration and validation of IC was carefully performed in order to have a robust index that could be tested across other cohorts. Finally, it provides information that could be translated in the short term into actions or policies for older adults, not only from the region, but from other countries. Further research should aim at testing our methodology in other environments in addition to demonstrate if changes in AL impact IC and finally the incidence of disability and dependency (among other outcomes of interest in older adult care).

On the other hand, this study has several limitations, that could limit the interpretation of our results. Sample comes from a region with special characteristics, that could preclude generalization of our results or at least careful interpretation. The data set had a considerable number of subjects without complete information that were dropped from the analysis. Cut-off points used for the biomarkers of AL may not be the same to those previously used in order to integrate this concept. Finally, many variables were self-reported, having the potential of memory bias.

Conclusions and Implications

In conclusion, the IC is a novel concept that seems to have the potential of boosting care for older adult from a holistic point of view, it's clear association with AL may provide a target to be intervened and halt the progress of disability in older adults. Further research on this matter could lead to the implementation of this approach (i.e., intervening in specific AL components to impact general IC) in primary care settings and delay the progression to disability of older adults.

Conflict of Interest: Authors declare no conflict of interest.

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Ethical Standards: CRELES was approved by the Ethical Science Committee of the University of Costa Rica (VI-763- CEC-23-04). All subjects signed informed consent and procedures were according to Helsinki´s declaration.

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