Association between stressor events and inflammatory and anti-inflammatory cytokines in long-lived older people

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Abstract

Objective: To investigate the association between the frequency of stressor events and cytokines in long-lived older people. *Methods*: The participants answered a questionnaire consisting of sociodemographic variables, indicated which stressor events included in the Stressor Life Events Inventory occurred in the last five years and answered the Geriatric Depression Scale (GDS). The following were measured by flow cytometry: interleukin (IL) 10, IL-6, IL-4, IL-2, tumor necrosis factor (TNF-α) and interferon gamma (IFN-γ). We carried out a descriptive statistical analysis in order to characterize the sample. To investigate the association between the variables, a multiple linear regression model was developed, using the *Backward* method. *Results*: 91 older people with an age average of 82 years participated in the research. More than half of the sample reported the death of a loved one as the most prevalent stressor event (61%). In this sample, it was possible to notice that the more stressor events were reported, the lower the level of IL-4 (p=0.046), as well as the marital status of widowhood, where data showed that those who are widowed have fewer stressor events in comparison to who is married (p=0.037). *Conclusion*: The importance of a more careful look by health professionals in older people multidimensional assessment was evidenced, so that subsidies are obtained for the implementation of specific programs and interventions that can ease the perception of the stressor events experienced, collaborating with less resulting damage of immunosenescence.

Keywords: Health of the Elderly. Emotional stress. Cytokines. Interleukin-4. Older adults.

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INTRODUCTION

Emotional stress carries strong connotations of usual performance breakdown, but it is an inevitable factor during life[1] and aging itself can be considered a stressor factor, as it relates to increased dependence, diseases, losses of occupational and affective roles[2]. The experience of these events entails greater or lesser demand for emotional, social, and intellectual resources depending on the value that is attributed to them[3,4].

Life event was a term created by Aldwin[5] and Baltes[6] to designate a phase of change that occurred between relatively stable periods in the individual's life. Some of these events are typically expected such as menopause, university entry and retirement, others are unexpected, such as accidents, natural disasters and unemployment[6].

Unexpected and unpredictable events enhance the perception of uncontrollability, ineffectiveness of coping or excessive burden of demands[2], thereby having greater potential to be experienced as stressful[2,6,7]. The stress resulting from these events can reduce the immune system's ability to respond to an injury[8]. There are interactions between the endocrine, the immunological, and the Central Nervous System (CNS) that are necessary to obtain adequate responses to stressor events. Thus, the presence of these events can affect the circulation and the activity of immune system cells[9].

On the other hand, during systemic infections, cancer or autoimmune diseases, immunological repercussions lead to CNS stimulation that can lead to the development of symptoms of depression in vulnerable individuals. Inflammation is therefore an important risk factor for major depressive episodes, as well as more traditional psychosocial factors[8].

Physiological aging is related to changes in the immune system, which characterizes the process known as immunosenescence. These changes result in greater susceptibility of the older person to infectious diseases, degenerative diseases, cardiovascular diseases, autoimmune diseases and cancer[10]. Among the changes in immunosenescence, we highlight the increase of 2 to 4 times in plasma levels of cytokines both pro and anti-inflammatory[11].

The imbalance in the production and release of inflammatory mediators characterizes low-grade, clinically undetectable inflammation, called *inflammaging* [11,12]. This pro-inflammatory state occurs in older people even in the absence of associated diseases, and it is related to the increased risk of chronic diseases[12].

Among the fundamental principles of this paradigm is the increase of pro-inflammatory cytokines and the decrease in anti-inflammatory cytokines[13,14]. Pro-inflammatory cytokines include IL-1, IL-2, IL-6, IL-12, IL-15, IL18, IL-22, IL-23, TNF-α, IFN-γ and among anti-inflammatory drugs, il-1Ra, IL-4, IL-10, TGF-β [15].

These changes can be analyzed from an evolutionary perspective and not just as harmful[16]. The accumulated knowledge suggests that without the existence of double immunosenescence and *inflammaging*, human longevity would be greatly reduced which suggests that attempts to intervene in the immune system in aging aimed at rejuvenation should be based on the maintenance of general homeotase to adequately improve inflammatory immune functions[16].

Recognizing sources related to immunosenescence has been the basis for many studies in the field of human aging, but the relationship between the impact of stress on the immune system in older people, especially those with older age are still poorly understood. This study aimed to investigate the association between the frequency of stressor events and pro- and anti-inflammatory cytokines in long-lived old people.

METHOD

This is a cross-sectional, quantitative study. The sample was obtained for convenience and recruited from the Geriatrics and Internal Medicine outpatient clinic of the Catholic University Hospital of Brasília (HUCB) between March 2016 and May 2018. The older people who were already being taken care in the outpatient clinic were invited, personally or by telephone, to participate in the research on a voluntary basis.

Training was conducted with the field researchers' team to standardize data collection and apply the instruments to minimize evaluation errors and problems in filling out the database.

As inclusion criteria, we chose to select, preferably, those older than 80 years old, not being excluded those who would miss less than one and a half years to complete the desired age. Thus, older people aged 78 years and older and who were followed at the HUCB outpatient clinic were included.

Cognitive deficit was used as an exclusion criterion. Therefore, the 227 old people who initially consented to participate in the study and signed the consent form passed the global cognitive screening, where the Mini Mental State Examination (EMSE) was used, consisting of 30 questions that assess orientation in time and space, episodic memory, immediate repetition, praxia, visuospatial functions and language[17].

Of the 227 older people who participated in global cognitive screening, those who scored below the cut-off score for their level of education were excluded, 17 points for illiterate, 22 points for older with 1 to 4 years of education, 24 points for those with 5 to 8 years of education and 26 points for those who have 9 years or more of education, thus, the sample started to include 144 older people.

The 144 selected participants answered an interview consisting of sociodemographic variables: age, gender, self-declared color, whether they work or if they are retired, as well as about the presence of chronic diseases (heart disease, arterial hypertension, ischemic stroke, diabetes, cancer, rheumatoid arthritis, lung diseases, depression and osteoporosis).

To evaluate the presence of stressful events, we used the Life Course Stressor Events Inventory, validated by Aldwin[18], consisting of 31 items that present stressor events potentially experienced in the last 5 years prior to data collection. The instrument evaluates the frequency of stressor events and the level of stress attributed by the respondent. The answers were grouped into 9 categories: death of a loved one, illness of a loved one, illness of the person, care of a family person, loss of purchasing power, family conflicts, suffering from some type of violence, uncontrollable events that affect descent, loss of activity or friendship appreciated. Older people indicated which events listed were present in their lives in the last five years, or if they did not happen.

The geriatric depression scale (GDS) was also applied, an instrument used to track depression in older people, and the short version, consisting of 15 questions was also used, and it should be answered by assigning grade 1 for no and 0 for yes, where the sum greater than or equal to 5 is indicative of suspected depression[19-21].

For cytokine dosage, blood collection was pre-scheduled with participants for a second moment in a Sabin Laboratory unit. All collections were performed in the morning by qualified professionals.

A total blood sample was collected from each participant in tubes with coagulation activator and centrifuged. These venous total blood samples were transported to the Immunogerontology Laboratory of UCB and, at the time of biochemical evaluation, serum samples were obtained, being kept at the temperature of -80°C until thawed for evaluation of inflammatory mediators.

Cytokine dosages were obtained by flow cytometry using multiplex system with a ball-based immunoassay set (Human Th1/Th2/TH17, BD Biosciences, San Diego, California, USA). Laboratory procedures followed the protocols provided by the kit manufacturer. This allowed measurements for six different circulating mediators: IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α. Lyophilized cytokine patterns and serum samples were processed together, following the manufacturer's protocol, and the results obtained used the BD FACSCalibur flow cytometer, FL4 channel. The data were analyzed using the FCAP software, version 3.0, (BD Biosciences).

All responses were recorded electronically by Google form and sent to the search database worksheet. To ensure data security against unauthorized access, alteration, disclosure, or unauthorized destruction of information, documents have been encrypted, with restricted access and two-step verification and safe browsing feature. At the end of the search, the data was downloaded to a local device and the data was erased from the cloud.

53 out of 144 participants were excluded because they did not show up for blood collection for cytokine dosages. The final analysis was performed with data referring to 91 long-lived old people.

To verify the difference in the dosage of biomarkers with the number of life stressful events, the Kruskal Wallis test was used.

The association between categorical variables was verified using the Chi-Square Person test, and when it was not possible to use it, Fisher's exact test was performed.

At the end, the variables with *p*-value less than 0.20 for linear regression analysis were selected. Then, a table was elaborated, removing the variables with higher values of *p* until reaching a model with all variables with p value less than 0.05, using *Backward* method.

The research was approved by the Research Ethics Committee of UCB, under opinion No. 3,061,534, meeting the requirements of Resolution No. 466/12 of the National Health Council, which provides for the rules and guidelines regulating research involving human beings.

RESULTS

The participants of the research were mostly female, corresponding to 61.5% of the sample, concentrating on the age group of 80 to 84 years, 48.4%, with the majority self-declared white, 68.1%. Singles represented 43.1% of the sample, with a majority of 59.7% having 4 children or more. Most of them do not work and receive retirement (Table 1).

Table 1. Sociodemographic variables of long-lived old people attended at the HUCB outpatient clinic, 2016.

Variables	Frequency
Age (in years)	
78 to 79	14 (15.4%)
80 to 84	44 (48.3%)
> 85	32 (35.2%)
Not reported	1 (1.1%)
Gender	
Male	34 (37.4%)
Female	56 (61,5%)
Not reported	1 (1.1%)
Color	
White	62 (68.1%)
Black	2 (2.2%)
Mixed	23 (25.3%)
Indigenous	1 (1.1%)
Yellow	2 (2.2%)
Not reported	1 (1.1%)
Work	
Yes	12 (13.2%)
No	78 (85.7%)
Not reported	1 (1.1%)
Retired	
Yes	75 (82,4%)
No	14 (15,4%)
Not reported	2 (2.2%)

The most reported chronic diseases were hypertension, 80.5%, osteoporosis, 36.3%, and diabetes, present in 28.9% of the sample.

Regarding the stressor events experienced in the last five years, more than half reported death of a loved one (61%). Other frequent events were loss of activity or friendship that he liked very much (48%), illness in a loved one (47%), illness in the person himself (38%), events that occurred in the offspring (34%) and loss of purchasing power (33%). The least reported events were violence to the older people (27%), family conflicts (21%) and care provided to some family member (3%). The percentages of stressful events are represented in Figure 1.

The mean cytokine values were 6.12 pg/mL for IFNγ, 3.32 pg/mL for TNF, 3.54 pg/mL for IL-10, 12.27 pg/mL for IL-6, 1.70 pg/mL for IL-4 and 9.10 pg/mL for IL-2.

The influence of the set of variables was verified: gender, age group, years of study, marital status, color, number of children, work, retirement, suspicion of depression by GDS, family arrangement and inflammatory biomarkers in the presence of stressor events. This association was made according to the number of events thus divided: 0 to 2; 3 and 4; 5 and more. In it, the number of stressor events was directly related to higher chances of depression and the fact that these long-lived older people were not working (Table 2).

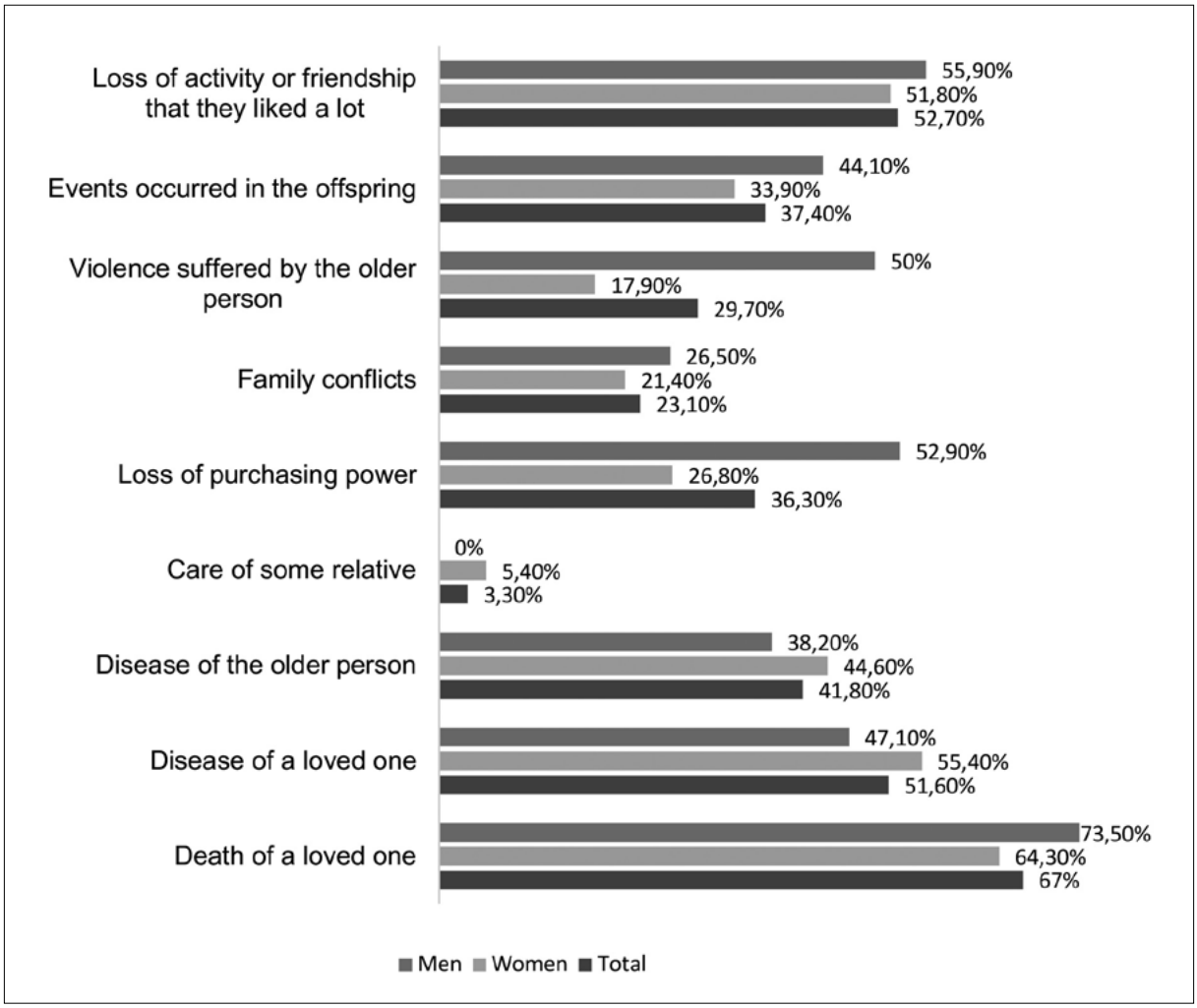

Figure 1. Number of stressor events presented by long-lived older people attended at the HUCB outpatient clinic, 2016.

Table 2. Analysis of the relationship between the number of life stressor events and inflammatory biomarkers and sociodemographic variables in long-lived older people attended at the HUCB outpatient clinic, 2016.

Variable	0 to 2 life stressor events	3 to 4 life stressor events	5 and more life stressor events	Total	*p*-value
Total	9	32	31	91	
IFN-γ					0.700[KW]
Median (IQR)	5.7 (4.8-6.5)	5.9 (5.4-6.6)	5.9 (5.5-6.4)	5.9 (5.4-6.5)	
TNF-α					0.680[KW]
Median (IQR)	2 (1-3.1)	2 (1.3-2.5)	1.8 (1.1-2.4)	1.9 (1.3-2.5)	
IL-10					0.572[KW]
Median (IQR)	3.2 (3-3.3)	3.7 (3-3.9)	3.6 (2.9-3.8)	3.6 (2.9-4)	
IL-6					0.933[KW]
Median (IQR)	5.2 (3.8-5.6)	4.8 (3.4-8.7)	4.6 (3.1-7.9)	4.8 (3.2-7.2)	
IL-4					0.307[KW]
Median (IQR)	1.9 (1.9-2.7)	1.6 (1.3-2.1)	1.5 (1.2-2)	1.6 (1.3-2.1)	
IL-2					0.699[KW]
Median (IQR)	8.9 (8.8-9.1)	9.2 (8.6-9.7)	8.9 (8.6-9.5)	8.9 (8.6-9.4)	
Gender					0.978[Qq]
Male	4 (44.4%)	13 (40.6%)	13 (41.9%)	30 (41.7%)	
Female	5 (55.6%)	19 (59.4%)	18 (58.1%)	42 (58.3%)	
Age group (years)					0.555[TF]
78 to 79	1 (11.1%)	4 (12.5%)	6 (19.4%)	11 (15.3%)	
80 to 84	3 (33.3%)	16 (50.0%)	17 (54.8%)	36 (50.0%)	
85 and more	5 (55.6%)	12 (37.5%)	8 (25.8%)	25 (34.7%)	
Years of Education					0.944[TF]
None	1 (11.1%)	7 (21.9%)	8 (25.8%)	16 (22.2%)	
1 to 4	4 (44.4%)	14 (43.8%)	11 (35.5%)	29 (40.3%)	
5 to 8	2 (22.2%)	6 (18.8%)	8 (25.8%)	16 (22.2%)	
9 and more	2 (22.2%)	5 (15.6%)	4 (12.9%)	11 (15.3%)	
Marital status					0.074[TF]
Married	1 (11.1%)	1 (3.1%)	4 (12.9%)	6 (8.3%)	
Single	1 (11.1%)	17 (53.1%)	13 (41.9%)	31 (43.1%)	
Divorced	1 (11.1%)	1 (3.1%)	5 (16.1%)	7 (9.7%)	
Widow/Widower	6 (66.7%)	13 (40.6%)	9 (29.0%)	28 (38.9%)	
Number of children					0.423[TF]
0 to 1	2 (22.2%)	4 (12.5%)	3 (9.7%)	9 (12.5%)	
2 to 3	4 (44.4%)	9 (28.1%)	7 (22.6%)	20 (27.8%)	
4 and more	3 (33.3%)	19 (59.4%)	21 (67.7%)	43 (59.7%)	
Work					**0.022**[TF]
Yes	4 (44.4%)	4 (12.5%)	2 (6.5%)	10 (13.9%)	
No	5 (55.6%)	28 (87.5%)	29 (93.5%)	62 (86.1%)	
Retirement					0.083[TF]
Yes	6 (66.7%)	30 (93.8%)	27 (90.0%)	63 (88.7%)	
No	3 (33.3%)	2 (6.2%)	3 (10.0%)	8 (11.3%)	

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Continuation of Table 3

Variable	0 to 2 life stressor events	3 to 4 life stressor events	5 and more life stressor events	Total	*p*-value
Depression					**0.013**[Qq]
Yes	0 (0)	5 (16.7%)	13 (41.9%)	18 (25.7%)	
No	9 (100%)	25 (83.3%)	18 (58.1%)	52 (74.3%)	
Without assistance					0.964[Qq]
Yes	3 (33.3%)	10 (31.2%)	9 (29.0%)	22 (30.6%)	
No	6 (66,7%)	22 (68,8%)	22 (71,0%)	50 (69,4%)	
Partner					0.332[Qq]
Yes	2 (22.2%)	16 (50.0%)	14 (45.2%)	32 (44.4%)	
No	7 (77,8%)	16 (50,0%)	17 (54,8%)	40 (55,6%)	
Children					0.574[TF]
Yes	6 (66,7%)	15 (46,9%)	17 (54,8%)	38 (52,8%)	
No	3 (33.3%)	17 (53.1%)	14 (45.2%)	34 (47.2%)	
Grandchildren					0.561[Qq]
Yes	4 (44,4%)	10 (31,2%)	8 (25,8%)	22 (30,6%)	
No	5 (55,6%)	22 (68,8%)	23 (74,2%)	50 (69,4%)	
Great-grandchildren					0.184[TF]
Yes	1 (11.1%)	2 (6.2%)	0 (0.0)	3 (4.2%)	
No	8 (88.9%)	30 (93.8%)	31 (100.0%)	69 (95.8%)	
Other relative					0.626[TF]
Yes	0 (0.0)	1 (3.1%)	3 (9.7%)	4 (5.6%)	
No	9 (100.0%)	31 (96.9%)	28 (90.3%)	68 (94.4%)	
Friend					0.724[TF]
Yes	1 (11,1%)	2 (6,2%)	3 (9,7%)	6 (8,3%)	
No	8 (88.9%)	30 (93.8%)	28 (90.3%)	66 (91.7%)	

IQR: Interquartile range; KW: Kruskal-wallis; Qq: Chi-square; TF: Fisher Test.

Then, data with *p* values lower than 0.20 were submitted to linear regression, with the number of stressor events added to all inflammatory biomarkers as a dependent variable. Depression was the only significant variable in this linear regression analysis, evidencing that the more stressor events, the higher the GDS score.

In a second round, data with *p* values lower than 0.20 were again removed, reserving only the variables corresponding to inflammatory biomarkers, until the most significant variables were reached, all having a *p* value lower than 0.05. The data obtained are shown in Table 3.

Table 3. Factors associated with the number of stressor events among long-lived old people in the Federal District.

Variables	Coefficient (95% CI)	*p*-value
IFN	0.34 (-0.21-0.89)	0.224
TNF	-0.02 (-0.06-0.02)	0.406
IL-10	0.16 (-0.49-0.8)	0.624
IL-6	0.03 (-0.05-0.12)	0.428
IL-4	-0.66 (-1.3- -0.01)	**0.046**
IL-2	0 (-0.72-0.72)	1
Marital status*		
Single	-0.51 (-2.06-1.03)	0.508
Divorced	-0.23 (-2.08-1.62)	0.804
Widow/Widower	-1.73 (-3.36- -0.11)	**0.037**
Depression		
Yes vs No	1,35 (0,42-2,29)	**0,005**

* Reference for marital status: being married; IC: Confidence Interval.

In the end, the variables that were statistically significant were IL-4, widowhood and depression. Thus, the more stressor events were reported, the lower the IL-4 count. Regarding widowhood, the data showed that widowers have 1.63% fewer stressor events compared to those who are married. The data also showed that those who tested positive for depression (GDS score≥5) have 1.17% more stressor events when compared to those without depression.

DISCUSSION

The main objective of the present study was to evaluate the relationship between cytokines and stressor events in long-lived older people, where a significant relationship was observed between the highest number of events and lower il-4 concentrations.

Our results also showed that there is a strong association between the number of stressor events and the presence of depressive symptoms, observed in 25.7% of the sample. A similar fact also observed in a study conducted with 385 Chinese older people living in the community, where it was observed that the increase in the number of life stressor events and lower levels of resilience were significantly associated with higher levels of depressive symptomatology[22].

Stress can also become an aggravating factor for immunological alterations, especially in old age, which is also characterized by immunosenescence. Among the inflammatory mediators analyzed, IL-4 presented an association inversely proportional to stressor events.

In addition to the known anti-inflammatory immunological functions, IL-4 shows signs of relationship with depressive behaviors, as observed in research by Wachholz et al[23]. These authors, using interferon-α in rats, observed that a lower responsiveness to il-4 of the microglia was specifically related to the development of depressive behavior. Thus, IL-4 seems to be related to the regulation of depressive behavior in an untreated condition. However, this effect was evident only in combination with an additional genetic disposition that seems to be absent in a certain strain of mice[23].

Now, in a study conducted by Lee et al.[24] in mice submitted to immobilization stress, there was a significant decrease in IL-4 secretion in the brain stem in relation to the control group, and inverse relationship between the activation of the primary neuroendocrine and neuronal components of stress response and IL-4 concentration.

This interleukin was first discovered as a factor secreted by T cells, promoting the increase in the proliferation of B cells stimulated by anti-IgM in 1982[25]. It is now recognized as a regulator of a wide variety of functions in immune cells such as Th2

lymphocytes, basophils, eosinophils, and mast cells, has receptors expressed in many cell types, and can stimulate cell proliferation and differentiation, tissue regeneration and neurological functions[25,26].

IL-4 is a regulatory cytokine par excellence, playing a vast role in immune function, with increasingly recognized anti-inflammatory functions[26]. At the time of its discovery, little was imagined how broad its functionality would be, nor was it foreseen that blocking its receptor proved to be a valuable strategy, as demonstrated with the efficacy of creating a drug to moderate to severe asthma and atopic dermatitis[26].

Inflammatory immune activation has often been associated with the development of major depression, and microglia (brain immunological cells) can serve as an important interface in the communication of this system with the brain. IL-4, the main cytokine of type Th2, can act as a protector against depression due to the ability to negatively regulate inflammatory processes and inhibit serotonin carrier activity[24].

Regarding marital status, widowers had a lower number of stressor events when compared to married patients. This fact can be compared with a result obtained by a study by Trevisan et al[27] that showed that while older men may suffer negative consequences after the death of their partner, widowed older women appeared to become healthier.

Although this study did not reveal in its results the marital status of the participants according to male or female gender, most of the sample was composed of women who, due to traditionally typical social functions as caregivers of partner and descendants assuming household tasks with weight of "obligation," tend to suffer more fatigue and anxiety[27].

Several studies relate emotional stress and changes in the immunological pattern, where IL-1 cytokines stand out as more studied, IL-6 and TNF-α[28], among which we can mention a meta-analysis performed by Black and Miller[29], where high levels of IL-1β and IL-6 were observed in brain and blood samples after the death of people with suicidal tendencies compared to healthy controls without suicide and IL-8 levels cerebrospinal fluid in individuals exhibiting suicidal behavior.

However, the limited number of studies relating other cytokines such as IL-4 to neurological alterations in response to stress suggests a wide knowledge gap. This situation highlights researchs that investigate the theme in specific populations such as this, focusing on older populations.

The *inflammaging* has great impact for the older person, culminating in baseline levels of increased pro-inflammatory cytokines[10-12.15], with more intense changes in age, especially in the age group studied, a fact observed in the high dosage levels of these cytokines in the sample.

The imbalance in cytokine production may also be exacerbated by the presence of events with stressful potential, which can act as potentiators of inflammatory activity[9]. In the present study, a relationship was observed between lower IL-4 concentrations and a higher number of stressor events.

Given the high frequency of women in the sample, the number of events presented, the relationship of this number with marital status and the report of violence highlights the need for public policies that focus on the protection of older people rights, especially women.

In addition, a more careful view of health professionals in the multidimensional evaluation of the older person, so that subsidies are obtained for the implementation of specific programs and interventions that can soften the perception of stressor events experienced, identifying them early and strengthening coping mechanisms[22,28] for a more active old age, and even with less damage from immunosenescence.

The present study presents some limitations, such as sample size. We believe that this is due to the older person's profile in this study (long-distance) and the dependence of third parties to participate in data collection, where many older people stopped participating in the stages. Regarding the validation stage of the Inventory of Life Stressor Events, no publications were found for the Brazilian population, although it is already widely used in research in this population. In addition, the level of stress attributed to each event was not evaluated, only the presence or not of the occurrence of each stressor event.

Similar studies in humans specifically relating IL-4 to stressor events have not been found in the literature, for this reason we consider that the present study gains great relevance because it is a subject that has not yet been studied, and the need to present data from older people with an average age of more than eighty years in Brazil.

CONCLUSION

The performance of this study allowed verifying the relationship between the presence of stressor events and inflammatory biomarkers, where the decrease in IL-4 was highlighted, which has anti-inflammatory function, with the increase in the number of events. Thus, it is noted the relevance in the continuity of studies that deepen the relationship between this cytokine and psychological aspects, especially in long-lived older people.

By knowing the frequency of events, it was possible to verify a higher frequency relationship of depressive symptoms and lower risk to these events among older widowers when compared to married people.

The results bring important contributions to the development of public policies to improve the quality of life of the older people population, such as the evidence of the importance of investigating stressor events in this population.

Therefore, it is understood the need for reception and follow-up by health professionals in clinical practice, considering events with stressor potential to create a framework that helps them to live or even overcome, favoring resilience.

Public investment in coping strategies and the creation of support networks as a health promotion action can optimize public health resources, due to the potential to mitigate the damage resulting from the negative effects related to immunosenescence.

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