npj | aging

Article

Published in partnership with the Japanese Society of Anti-Aging Medicine

https://doi.org/10.1038/s41514-026-00340-6

Biological age and immunosenescence in Colombian centenarians

Juan-Manuel Anaya[1,2] ✉, Edward A. Ruiz-Narváez[3], Ivan David Lozada-Martinez[1,2], Manuel Rojas[1,4,5], Diana M. Monsalve[1,4], Jesús Armando Álvarez-Álvarez[1,6], María José Díaz Gutiérrez[1,7], Olianis Pájaro[1,7], Brenda Guerra[1,7], Juan Esteban Gallo[1,8], Isaura Torres[1,8,9], Carolina Ramírez-Santana[1,4], Andres Angelo Cadena Bonfanti[1,7,10] & Yeny Acosta-Ampudia[1,4]

Biological aging and immunosenescence are central to longevity, yet their interplay in centenarians remains unclear. We conducted a cross-sectional study in 160 Colombian centenarians to examine associations between biological age (PhenoAge), immunosenescence and age-related clinical variables. Cytokine profiling (n = 114) and lymphocyte immunophenotyping (n = 42) were assessed. It was observed that better QoL and well-being were significantly associated with lower biological age, while depressive symptoms, prior tobacco use, elevated levels of RANTES and G-CSF as well as a distinct CD8+ T cell phenotype including greater CD27− CD28+ central memory, effector memory, and KLRG1− CD57+ terminally differentiated effector memory T cells (TEMRA), and fewer KLRG1+ CD57+ TEMRA cells were linked to higher biological age. Centenarians were classified into three categories: vigorous (10%), resilient (46.25%), and vulnerable (43.75%). Cytokine levels were similar across the groups. These findings challenge the notion of immunosenescence in centenarians and highlight the value of translational research in geroscience.

Aging is a complex biological process resulting from the interaction of genetic, epigenetic, and environmental factors[1]. The most extreme phenotype of human survival, centenarians (those who have lived to 100 years of age), offer a natural experiment to examine the biological, immunological, psychological, and environmental mechanisms that enable some people to live very long lives with preserved function[2].

This population provides an exceptional opportunity to analyze the factors contributing to healthy aging[2]. Unlike chronological age, biological age more accurately reflects the physiological and functional state of the organism[3], allowing for an assessment of the cumulative impact of genetic load, lifestyle factors, and environmental exposures throughout life[4].

One of the key processes involved in aging is immunosenescence[5], a progressive set of modifications in the immune system affecting both the innate and adaptive functions. This condition has been associated with numerous age-related chronic diseases due to changes in the immune response[6], alteration of cellular regulation, and loss of autophagy and cellular waste lysis capabilities[5]. This phenomenon involves a state of chronic, low-grade inflammation known as inflammaging[7]. Whether immunosenescence is an inevitable hallmark of extreme longevity remains an open question in geroscience[5].

Among immune cell subsets, T cells are consistently regarded as occupying a predominant role in aging research. Impaired proliferation of naïve T cells, expansion of memory T cell clones, and a consequent reduction in immune repertoire diversity limit immune adaptability and foster the emergence of senescent T cell phenotypes, which in turn contribute to the chronic pro-inflammatory milieu characteristic of inflammaging[8]. Despite these changes, some individuals reach 100 years of age with a still functional immune system, indicating the presence of adaptive mechanisms that may counteract the detrimental effects of immunosenescence[9]. This observation presents an intriguing paradox that warrants further investigation to better understand potential protective mechanisms against immunosenescence and the acceleration of biological aging[9].

Quality of life (QoL) has been identified as a key determinant of healthy and active aging[10]. Older persons who maintain high levels of physical, psychological, and social well-being may exhibit a more favorable

[1]Colombian Centenarians Alliance, Bogotá, Colombia. [2]Universidad de la Costa, Barranquilla, Colombia. [3]Department of Nutritional Sciences, University of Michigan School of Public Health, Ann Arbor, MI, USA. [4]Center for Autoimmune Diseases Research, School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia. [5]Division of Rheumatology, Allergy and Clinical Immunology, University of California, Davis, Davis, CA, USA. [6]Grupo de Errores Innatos de la Inmunidad, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia. [7]Clínica de la Costa, Barranquilla, Colombia. [8]ASRT Laboratories, ASRT Inc., Birmingham, AL, USA. [9]Universidad EIA, Medellín, Colombia. [10]Universidad Simón Bolívar, Barranquilla, Colombia. ✉e-mail: anayajm@gmail.com

Table 1 | Baseline characteristics of the population studied (*N* = 160)

Variable	*n*	%
Age (years), mean SD	102	2
Sex		
Male	45	28
Female	115	72
Residential area		
Urban	127/158	80
Rural	31/158	20
Health insurance status		
Contributory	20/158	13
Subsidized	138/158	87
Marital status		
Single	22/152	14
Married	18/152	12
Divorced	3/152	2
Widowed	107/152	70
Free union	2/152	1
Educational level		
Without education	96/153	63
Primary education	49/153	32
Secondary education or higher	8/153	5
Religious belief		
No	3/159	2
Yes	156/159	98
Household economic income		
<1 minimum wage	107/157	68
1 minimum wage	28/157	18
1–2 minimum wage	16/157	10
>2 minimum wage	6/157	4
Socioeconomic status		
Low/very low	122/158	78
Middle/high	36/158	22
Occupation		
Farmers, agricultural, forestry and fishing	37	24
Home and child care	35	22
Elementary occupations	34	22
Officials, operators, craftsmen and related	23	15
Others	31	17

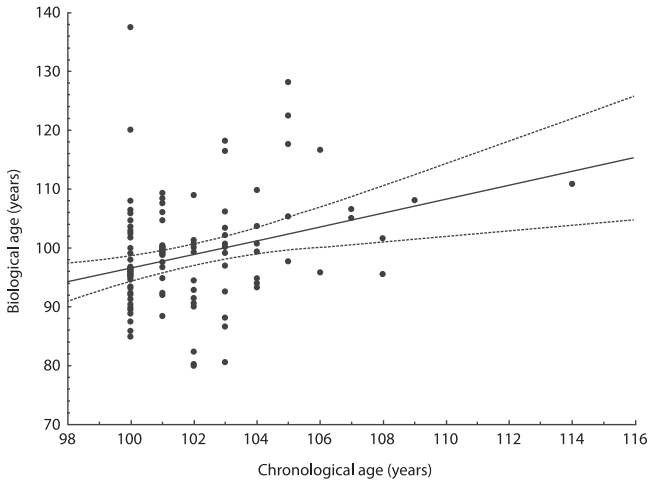

Fig. 1 | Regression of biological age on chronological age. The scatter plot illustrates the relationship between biological (98.7 ± 9.6 years) and chronological age (102 ± 2 years, $r = 0.3$, $p = 0.002$). The upward slope of the regression line suggests a positive correlation between chronological and biological age. As chronological age increases, biological age tends to increase as well. The scatter of the points around the regression line indicates the strength of the correlation. If the points are tightly clustered around the line, the correlation is strong. If they are widely scattered, the correlation is weak. The dotted lines represent the confidence intervals around the regression line. They indicate the range within which the true regression line is likely to fall. The wider the confidence intervals, the more uncertainty there is about the relationship between chronological and biological age.

immunological profile, reflecting a lower inflammatory burden and greater biological resilience[11]. However, the association between QoL, biological age, and immunosenescence in centenarians has not yet been fully elucidated, but a hypothesis suggests that healthy lifestyles, stress reduction, and psychosocial support may modulate the rate of biological aging and immune function[12].

Although multiple studies on extreme longevity have been conducted in high-income countries[13], knowledge about the biology of aging in populations from low- and middle-income countries remains limited[13]. Colombia, as a country with a growing aging population[14], represents a relevant setting to explore these interactions. Understanding the characteristics that contribute to the longevity of Colombian centenarians would advance global scientific understanding of healthy aging and provide crucial insights for developing public policies and health initiatives to increase the healthy lifespan of older persons. Therefore, this study aimed to investigate the relationship between biological age, immunosenescence, and age-related clinical variables, including QoL, in Colombian centenarians.

This study was reported according to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines[15].

Results

A total of 160 Colombian centenarians were included in the study, with a mean age of 102 years (standard deviation [SD] = 2); 72% were women (Table 1). Regression of biological age on chronological age is shown in Fig. 1. Most participants resided in urban areas and were affiliated with the subsidized healthcare regime. Widowed status, low educational attainment, low socioeconomic level, and limited household income were predominant. Nearly all participants reported religious beliefs, and the majority had no access to private transportation. In terms of occupation, farming, domestic work, and elementary occupations were the most frequently reported (Table 1).

Clinical status is shown in Table S1, 35% were considered free of age-related chronic diseases. Polypharmacy (defined as the use of five or more medications) was observed in 23% of participants, with an average medication count of 3.2 (SD = 2.4) among those with prescriptions. Dental loss was widespread, with 79% missing all upper teeth and 65% all lower teeth, although just over half used dental prostheses (Table S1).

In terms of QoL and functionality, 62% reported favorable self-perceived health, while 56% considered their memory favorable (Table 2). The World Health Organization Quality of Life AGE (WHOQOL-AGE) scale scores averaged 51.3 (SD = 14.9), reflecting moderate perceived QoL. High prevalence of frailty (77%) and sarcopenia (75%) was noted. Only 11% of participants were functionally independent, and 87% exhibited inadequate physical performance (Table 2). The risk of falls was high in over half of the population. Cognitive impairment was frequent: 23% met criteria for severe dementia, and only 9% scored in the normal range based on the Clinical Dementia Rating Sum of Boxes (CDR-SB) (Table 2). Despite this, over two-thirds reported being satisfied or extremely satisfied with life, reflecting a high level of resilience in this population (Table 2).

Substantial heterogeneity was observed in circulating cytokine levels (Supplementary Data 1). Notably, interleukin (IL)-1β, tumor necrosis factor

Table 2 | Quality of life, life satisfaction and health-related outcomes in centenarians (*N* = 160)

Variable	*n*	%
Favorable self-perceived health	95/154	62
Favorable self-perceived memory	85/153	56
Favorable self-perceived vision	62/157	30
Favorable self-perceived hearing	57/157	36
WHOQOL-AGE score, mean SD (*n* = 150)	51.3	14.9
Frailty	117/152	77
Sarcopenia	120	75
Nutritional status		
Malnutrition	55/158	35
Nutritional risk	77/158	49
Good nutrition	26/158	16
Functional independence		
Independent	18/159	11
Mild dependence	54/159	34
Moderate dependence	18/159	11
Severe dependence	23/159	14
Total dependence	46/159	29
Physical performance		
Inadequate performance	137/158	87
Adequate performance	21/158	13
Fall risk		
Low fall risk	71/156	45
High fall risk	85/156	55
Cognitive status according to CDR-SB		
No dementia	15/160	9
Questionable dementia	61/160	38
Mild dementia	32/160	20
Moderate dementia	16/160	10
Severe dementia	36/160	23
Cognitive status according to MMSE		
Normal	7/160	4
Mild impairment	33/160	21
Moderate impairment	64/160	40
Severe impairment	56/160	35
Depression		
Normal	128/151	85
Moderate depression	18/151	12
Severe depression	5/151	3
Anxiety	2/152	1.3
Insomnia	28/158	18
Life satisfaction		
Extremely satisfied	26/147	18
Satisfied	77/147	52
Somewhat satisfied	23/147	16
Neutral	6/147	4
Somewhat dissatisfied	10/147	7
Dissatisfied	3/147	2
Extremely dissatisfied	2/147	1

CDR-SB clinical dementia rating sum of boxes, *MMSE* mini-mental state examination, *WHOQOL-AGE* World Health Organization Quality of Life AGE.

(TNF)-α, IL-6, IL-8, and regulated on activation, normal T cell expressed and secreted (RANTES) showed high variability, with RANTES presenting particularly elevated mean values (7681.6 pg/mL, SD = 1565.6), suggesting an ongoing low-grade inflammatory state (Table S2 and Supplementary Data 1). The CD4/CD8 ratio was on average 4.8 (SD = 5.6), indicating a healthy immune system (i.e., good immune health grade [IHG] status and optimal immune resilience) (Table 5). Naïve and memory T cell subpopulations were detected in all participants, although with varying proportions (Supplementary Data 2).

Correlation analyses revealed that biologicalage residuals were negatively associated with WHOQOL-AGE scores ($r = -0.338$, $p = 0.004$), indicating that better QoL was related to lower biological aging (Table 3). A positive and significant correlation was observed between biological-age residuals and RANTES levels ($r = 0.318$, $p = 0.003$), as well as with G-CSF ($r = 0.252$, $p = 0.023$), suggesting that higher expression of these inflammatory markers was associated with accelerated biological aging (Table 3). In contrast to the predominantly non-significant associations observed for most cytokines and lymphocyte subpopulations, several CD8+ T-cell subsets showed significant correlations with biological-age residuals. Specifically, CD8+ CD27− CD28+ central memory (CM) T cells and CD8+ effector memory (EM) T cells displayed positive correlations, indicating that higher frequencies of these subsets were linked to accelerated biological aging. Additionally, CD8+ KLRG1+ CD57+ terminally differentiated effector memory T cells (TEMRA) showed a negative correlation, whereas CD8+ KLRG1− CD57+ TEMRA cells correlated positively with biological-age residuals. These findings point to targeted shifts in CD8+ memory and terminal differentiation dynamics, indicating a specific CD8+ differentiation pattern rather than a generalized pro-inflammatory profile (Table 3).

Three new categories of centenarians are presented: vigorous (10%), resilient (46.25%), and vulnerable (43.75%) (Fig. 2). No significant differences in cytokine levels were observed among these categories (Table 4). The limited number of vigorous centenarians included in the immunosenescence study precluded a statistical analysis of the cell populations examined (Table 4).

Group comparisons using one-way analysis of variance (ANOVA) indicated that centenarians with a history of previous tobacco consumption exhibited significantly higher biological-age residuals compared to those who had never smoked (mean difference = 0.46, $p = 0.01$), suggesting lasting effects of past smoking on biological aging (Table 5). Although current smoking did not show a significant effect, the small number of active smokers may have limited statistical power. A trend toward lower biological-age residuals was observed in individuals reporting regular physical activity two to three times per week (mean = −0.701, $p = 0.06$) (Table 5). In terms of mental health, a significant difference in biological aging was found across categories of depressive symptoms ($p = 0.03$), with those classified as having severe depression presenting markedly elevated biological-age residuals (mean = 2.371), indicating a potential link between depressive symptoms and accelerated aging (Table 5).

No significant associations were identified between biological-age residuals and current or past alcohol use, insomnia, frailty status, nutritional status, or most measures of cognitive function, including MMSE and CDR-SB categories (Table 5). However, centenarians who reported being "dissatisfied" or "extremely dissatisfied" with their lives showed extreme biological-age values, though group sizes were small (Table 5). No differences in biological-age residuals were observed across IHGs, suggesting that subjective and biological markers of immune resilience may not always align.

Discussion

This study assessed the relationship between biological age (PhenoAge), immunosenescence (encompassing immune cell populations and a cytokine panel), and age-related clinical variables within a cohort of Colombian centenarians. The results provide novel insights into the complexity of biological aging during extreme longevity and challenge prevailing assumptions about the inevitability of immunosenescence in advanced age. These findings underscore the need to evaluate not only biological age as a static endpoint but also to consider its dynamic progression, namely, the pace of aging.

Table 3 | Correlations of cognitive health and immune-senescence markers with biological age

Variable	Correlation	*p*-Value
QoL (WHOQOL-AGE)	−0.338	**0.004**
Well-being (SWLS)	−0.096	0.325
Depression (GDS-15)	0.110	0.251
Cytokines (n = 114)		
RANTES	0.318	**0.003**
G-CSF	0.252	**0.023**
IL-1β	0.178	0.110
IL-2	−0.059	0.599
IL-4	0.100	0.372
IL-5	0.066	0.555
IL-6	0.120	0.282
IL-7	0.049	0.657
IL-8	0.100	0.373
IL-9	−0.091	0.414
IL-10	0.157	0.160
IL-12p70	0.088	0.433
IL-13	0.114	0.307
IL-17A	0.091	0.415
TNFα	0.147	0.189
GM-CSF	−0.074	0.508
MCP-1	0.093	0.406
IFNα	0.1295	0.249
IFNγ	0.034	0.760
MIG	−0.007	0.948
Immune cell populations (n = 42)		
Lymphocytes (%)	−0.285	0.088
CD19+ B cells (%)	−0.236	0.160
Double-negative B cells (%)	0.186	0.270
Naive B cells (%)	−0.276	0.099
Switched memory B cells (%)	0.155	0.359
Unswitched memory B cells (%)	−0.192	0.255
CD3+ T cells (%)	0.111	0.515
CD3+ CD27+ CD28+ T cells (%)	−0.067	0.692
CD3+ CD27+ CD28− T cells (%)	−0.070	0.683
CD3+ CD27− CD28+ T cells (%)	0.018	0.914
CD3+CD27- CD28- T cells (%)	0.085	0.619
CD3+ CD95+ T cells (%)	0.013	0.938
CD3+ KLRG1+ CD57+ T cells (%)	−0.096	0.571
CD3+ KLRG1+ CD57- T cells (%)	0.007	0.967
CD3 + KLRG1− CD57 + T cells (%)	0.252	0.133
CD3 + KLRG1− CD57− T cells (%)	−0.037	0.826
CD4+ T cells (%)	0.049	0.772
CD4+ CD27+ CD28+ T cells (%)	-0.132	0.435
CD4+ CD27+ CD28− T cells (%)	-0.114	0.498
CD4+ CD27− CD28+ T cells (%)	0.009	0.954
CD4+ CD27- CD28− T cells (%)	0.144	0.392
CD4+ CD95+ T cells (%)	−0.092	0.585
CD4+ KLRG1+ CD57+ T cells (%)	0.088	0.604
CD4+ KLRG1 + CD57− T cells (%)	0.053	0.751
CD4+ KLRG1- CD57+ T cells (%)	0.090	0.595

Table 3 (continued) | Correlations of cognitive health and immune-senescence markers with biological age

Variable	Correlation	*p*-Value
CD4+ KLRG1- CD57- T cells (%)	-0.100	0.554
CD4+ CM T cells (%)	−0.143	0.395
CD4+ CD27 + CD28 + CM T cells (%)	0.094	0.577
CD4+ CD27+ CD28− CM T cells (%)	−0.155	0.357
CD4+ CD27− CD28+ CM T cells (%)	0.228	0.173
CD4+ CD27− CD28− CM T cells (%)	−0.152	0.366
CD4+ CD95+ CM T cells (%)	−0.078	0.643
CD4+ KLRG1 + CD57 + CM T cells (%)	0.010	0.949
CD4+ KLRG1+ CD57− CM T cells (%)	0.130	0.442
CD4+ KLRG1− CD57+ CM T cells (%)	0.180	0.285
CD4+ KLRG1− CD57− CM T cells (%)	−0.150	0.376
CD4+ EM T cells (%)	0.150	0.375
CD4+ CD27+ CD28+ EM T cells (%)	–	–
CD4+ CD27+ CD28− EM T cells (%)	–	–
CD4+ CD27− CD28+ EM T cells (%)	−0.120	0.476
CD4+ CD27− CD28− EM T cells (%)	0.120	0.477
CD4+CD95+EM T cells (%)	−0.071	0.675
CD4+ KLRG1+ CD57+ EM T cells (%)	0.012	0.940
CD4+ KLRG1+ CD57− EM T cells (%)	−0.006	0.968
CD4+ KLRG1− CD57+ EM T cells (%)	0.266	0.111
CD4+ KLRG1− CD57− EM T cells (%)	−0.113	0.505
CD4+ Naïve T cells (%)	−0.178	0.289
CD4+ CD27+ CD28+ Naïve T cells (%)	0.070	0.679
CD4+ CD27+ CD28− Naïve T cells (%)	−0.144	0.394
CD4+ CD27- CD28+ Naïve T cells (%)	0.145	0.391
CD4+CD27− CD28− Naïve T cells (%)	−0.062	0.711
CD4+ CD95+ Naïve T cells (%)	0.169	0.316
CD4+ KLRG1+ CD57+ Naïve T cells (%)	0.039	0.815
CD4+ KLRG1+ CD57− Naïve T cells (%)	−0.106	0.531
CD4+ KLRG1− CD57+ Naïve T cells (%)	−0.123	0.467
CD4+ KLRG1− CD57− Naïve T cells (%)	0.045	0.792
CD4+ TEMRA T cells (%)	0.008	0.957
CD4+ CD27+ CD28+ TEMRA T cells (%)	–	–
CD4+ CD27+ CD28− TEMRA T cells (%)	–	–
CD4+ CD27− CD28+ TEMRA T cells (%)	0.001	0.998
CD4+ CD27− CD28− TEMRA T cells (%)	0.022	0.896
CD4+ CD95+ TEMRA T cells (%)	0.071	0.672
CD4+ KLRG1+ CD57+ TEMRA T cells (%)	0.228	0.174
CD4+ KLRG1+ CD57− TEMRA T cells (%)	−0.219	0.192
CD4+ KLRG1− CD57+ TEMRA T cells (%)	0.079	0.639
CD4+ KLRG1− CD57− TEMRA T cells (%)	−0.135	0.423
CD8+ T cells (%)	0.039	0.814
CD8+ CD27+ CD28+ T cells (%)	−0.177	0.295
CD8+ CD27+ CD28− T cells (%)	−0.033	0.848
CD8+ CD27− CD28+ T cells (%)	0.014	0.933
CD8+ CD27− CD28− T cells (%)	0.162	0.338
CD8+ CD95+ T cells (%)	0.056	0.743
CD8+ KLRG1+ CD57+ T cells (%)	−0.221	0.189
CD8+KLRG1+CD57- T cells (%)	0.124	0.467
CD8+ KLRG1- CD57+ T cells (%)	0.282	0.091

Table 3 (continued) | Correlations of cognitive health and immune-senescence markers with biological age

Variable	Correlation	*p*-Value
CD8+ KLRG1− CD57− T cells (%)	−0.008	0.961
CD8+ CM T cells (%)	−0.095	0.576
CD8+ CD27+ CD28+ CM T cells (%)	−0.142	0.402
CD8+ CD27+ CD28− CM T cells (%)	−0.020	0.908
CD8+ CD27− CD28+ CM T cells (%)	0.330	**0.046**
CD8+ CD27− CD28− CM T cells (%)	0.249	0.137
CD8+CD95+CM T cells (%)	0.054	0.750
CD8+KLRG1+CD57+CM T cells (%)	0.217	0.198
CD8+KLRG1+CD57- CM T cells (%)	0.049	0.772
CD8+KLRG1- CD57+CM T cells (%)	0.074	0.663
CD8+KLRG1- CD57- CM T cells (%)	−0.126	0.457
CD8+ EM T cells (%)	0.454	**0.005**
CD8+ CD27+ CD28 + EM T cells (%)	–	–
CD8+ CD27+ CD28− EM T cells (%)	–	–
CD8+ CD27− CD28 + EM T cells (%)	−0.175	0.301
CD8+ CD27− CD28− EM T cells (%)	0.163	0.336
CD8+ CD95+ EM T cells (%)	−0.093	0.584
CD8+ KLRG1+ CD57 + EM T cells (%)	−0.145	0.391
CD8+ KLRG1+ CD57- EM T cells (%)	0.116	0.496
CD8+ KLRG1- CD57 + EM T cells (%)	0.213	0.205
CD8+ KLRG1- CD57- EM T cells (%)	−0.044	0.797
CD8+ Naïve T cells (%)	−0.299	0.072
CD8+ CD27+ CD28+ Naïve T cells (%)	−0.269	0.107
CD8+ CD27+ CD28− Naïve T cells (%)	0.264	0.114
CD8+ CD27− CD28+ Naïve T cells (%)	0.036	0.833
CD8+ CD27− CD28− Naïve T cells (%)	0.127	0.454
CD8+ CD95+ Naïve T cells (%)	−0.056	0.743
CD8 + KLRG1+ CD57+ Naïve T cells (%)	−0.070	0.680
CD8+ KLRG1+ CD57− Naïve T cells (%)	−0.134	0.431
CD8+ KLRG1− CD57+ Naïve T cells (%)	0.053	0.754
CD8+ KLRG1- CD57− Naïve T cells (%)	0.148	0.381
CD8+ TEMRA T cells (%)	−0.147	0.386
CD8+ CD27+ CD28+ TEMRA T cells (%)	–	–
CD8+ CD27+ CD28− TEMRA T cells (%)	–	–
CD8+ CD27− CD28 + TEMRA T cells (%)	−0.103	0.545
CD8+ CD27− CD28− TEMRA T cells (%)	0.117	0.490
CD8+CD95+TEMRA T cells (%)	0.169	0.318
CD8+KLRG1+CD57+TEMRA T cells (%)	−0.390	**0.017**
CD8+KLRG1+CD57- TEMRA T cells (%)	−0.018	0.914
CD8+KLRG1- CD57+TEMRA T cells (%)	0.347	**0.035**
CD8+KLRG1- CD57- TEMRA T cells (%)	0.304	0.067
CD4/CD8 ratio	0.103	0.540
Vitamins (n = 143)		
Vitamin D	−0.047	0.624
Vitamin B12	0.111	0.249

The regression of biological age on chronological age depicted in Fig. 1 establishes a mathematical connection that elucidates the changes in biological age as chronological age advances and helps in understanding the variety of aging processes among the evaluated centenarians and identifying factors that may expedite or mitigate biological aging in relation to chronological aging. Consistent with previous findings in extreme longevity[16], our estimation of biological age using PhenoAge revealed considerable inter-individual variability among centenarians, even after adjusting for sex and chronological age[16]. Importantly, the biological-age residuals were significantly associated with markers of immune system dysregulation, particularly elevated levels of RANTES and G-CSF, suggesting that immune-inflammatory activity remains a component of the biological aging phenotype in late life[5].

In our centenarian group, high RANTES levels were correlated with accelerated biological age (Table 3). When compared with previous studies, our values are much higher than those reported in healthy older adults (≈830 pg/mL), but still lower than the extreme elevations described in conditions such as early Alzheimer's disease (≈75,000 pg/mL)[17]. Other reports in vascular disease also describe values in the 10,000–15,000 pg/mL range[18]. This means that Colombian centenarians show an intermediate pattern: RANTES levels are substantially above what is expected in healthy aging, but below those seen in major pathological states[17,18]. From a biological perspective, this suggests a chronic, but not overwhelming, pro-inflammatory activation.

This may indicate that centenarians sustain an 'intermediate' state of controlled inflammation, suggesting an immunological resilience mechanism that permits a degree of activation without progressing to overt damage. RANTES could act as a signal for immune recruitment and tissue repair. The intermediate levels observed in centenarians may therefore represent a balance between chronic inflammation and compensatory repair mechanisms.

Also, average G-CSF levels were close to 0.9 ng/mL (≈900 pg/mL). Comparative studies in healthy adults indicate that baseline values are frequently very low or undetectable, usually below 100 pg/mL[19]. In special conditions such as substance use disorders, control subjects without comorbidities show average concentrations around 2000 pg/mL, while affected patients may present reduced values closer to 1400 pg/mL[20]. This means that centenarians from our study lie between what is considered a normal resting state and the higher levels seen in clinical populations, suggesting a persistent though moderate activation of this growth factor. Biologically, G-CSF supports granulocyte production and the mobilization of bone marrow cells[19]. While this is protective in acute stress, its chronic elevation may contribute to "myeloid skewing" and reduced lymphocyte renewal, phenomena that have been described as hallmarks of immune aging[19]. Supporting this notion, senescent cells have been shown to markedly increase G-CSF secretion, and genetic studies in telomerase-deficient mice revealed that telomere dysfunction elevates serum G-CSF, thereby reinforcing this myeloid skewing phenotype[21,22].

Interestingly, a paradoxical decline in circulating neutrophils despite elevated G-CSF, together with evidence that blood neutrophils from aged rhesus macaques are less functional, has been reported[23]. Aging disrupts neutrophil homeostasis, reduces their chemotaxis and antimicrobial function, and prolongs of inflammatory responses[24]. Nevertheless, evidence from a study in healthy centenarians showed that this group displayed superior neutrophil function compared with middle-aged adults, with levels approaching those of young subjects, suggesting that extreme longevity may involve compensatory mechanisms that counterbalance age-associated decline[25]. Finally, the observed positive correlation between G-CSF and biological age in our data suggests that, even at modestly elevated levels, this factor could act as a signal of accelerated immune aging in extreme longevity.

In large population studies, aging is consistently associated with a decline in CD8 + T cells, an expansion of the CD4+/CD8+ ratio, loss of naive T cells, and accumulation of terminally differentiated subsets, together with an increase in NK cells and a reduction in circulating B cells[26,27]. In our data, centenarians followed these general trajectories: CD8+ counts were at the lower limit of normal, the CD4+/CD8+ ratio was markedly elevated, and naïve subsets were diminished but not absent. Interestingly, residual pools of central memory and NK cells remained detectable (Table 3), suggesting that, even at extreme ages, the immune system retains functional

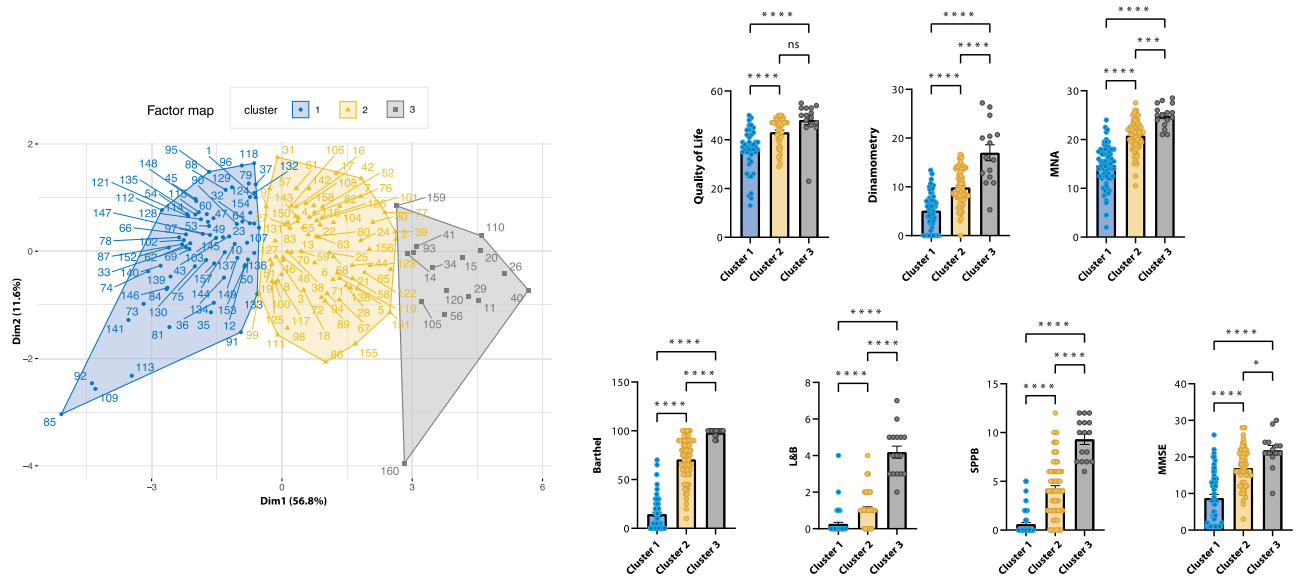

Fig. 2 | Multivariate centenarians cluster classification. Factor map for obtained clusters of centenarians by mixed-cluster methodology using the total scores of Quality of Life, Mini Nutritional Assessment (MNA), Barthel Index, Lawton & Brody scale (L&B), Short Physical Performance Battery (SPPB), and the Mini-Mental State Examination (MMSE). A total of three clusters were obtained through this methodology: Vulnerable (Cluster 1, $n = 70$, 43.75%), Resilient (Cluster 2, $n = 74$, 46.25%), and Vigorous (Cluster 3, $n = 16$, 10%). $^{*}p < 0.05$, $^{**}p < 0.005$, $^{***}p < 0.0005$, $^{****}p < 0.0001$ by two-way ANOVA adjusted for multiple comparisons with the Tukey Test.

Table 4 | Age and sex-adjusted means (SE) of immune-senescence markers by cluster

Variable	Cluster			*p*-Value
	Vulnerable	Resilient	Vigorous	
Cytokines	$n = 49$	$n = 50$	$n = 15$	
RANTES	7445 (253)	7796 (232)	7433 (407)	0.50
G-CSF	0.53 (0.28)	0.86 (0.26)	0.77 (0.46)	0.66
IL-1β	2.2 (6.6)	8.9 (6.0)	4.8 (10.6)	0.72
IL-2	1.0 (1.1)	2.6 (1.0)	0.20 (1.7)	0.35
IL-4	0.54 (0.22)	0.69 (0.20)	0.44 (0.35)	0.77
IL-5	0.27 (0.15)	0.43 (0.14)	0.75 (0.24)	0.25
IL-6	201.8 (121.5)	42.5 (111.5)	22.2 (195.6)	0.54
IL-7	2.0 (0.2)	2.3 (0.2)	2.3 (0.4)	0.38
IL-8	1833 (4128)	4753 (3788)	523 (6648)	0.79
IL-9	0.05 (0.04)	0.33 (0.22)	0 (0)	0.45
IL-10	1.27 (0.33)	0.95 (0.31)	0.87 (0.54)	0.70
IL-12p70	0.10 (0.05)	0.17 (0.04)	0.04 (0.08)	0.23
IL-13	0.029 (0.015)	0.035 (0.014)	0.005 (0.025)	0.58
IL-17A	0.07 (0.63)	0.95 (0.58)	1.12 (1.02)	0.49
TNFα	13.9 (8.3)	13.7 (7.6)	11.3 (13.4)	0.99
GM-CSF	0.53 (0.28)	0.86 (0.26)	0.77 (0.46)	0.66
MCP-1	50.3 (7.7)	47.8 (7.1)	50.5 (12.4)	0.96
IFNα	0.27 (0.42)	0.66 (0.38)	0.95 (0.67)	0.63
IFNγ	0 (0)	0.29 (0.21)	0.15 (0.36)	0.43
*Immune cell populations**	$n = 11$	$n = 29$	$n = 2$	
Leukocytes	6.19 (0.30)	6.17 (0.26)	5.69 (0.53)	N.A.
Lymphocytes	1.75 (0.13)	1.75 (0.12)	1.93 (0.23)	N.A.
CD19+ B cells (%)	6.96 (0.97)	5.97 (0.60)	8.39 (2.32)	N.A.
Double-negative B cells (%)	39.23 (4.79)	42.40 (2.95)	43.37 (11.47)	N.A.
Naive B cells (%)	29.29 (4.49)	26.19 (2.77)	33.11 (10.75)	N.A.
Switched memory B cells (%)	30.46 (3.40)	29.88 (2.10)	22.37 (8.14)	N.A.
Unswitched memory B cells (%)	1.56 (0.38)	1.52 (0.23)	1.17 (0.91)	N.A.

Table 4 (continued) | Age and sex-adjusted means (SE) of immune-senescence markers by cluster

Variable	Cluster			*p*-Value
	Vulnerable	Resilient	Vigorous	
CD3+ T cells (%)	46.87 (3.27)	47.52 (2.02)	54.74 (7.83)	N.A.
CD3+ CD27+ CD28+ T cells (%)	58.25 (4.44)	51.20 (2.74)	41.85 (10.63)	N.A.
CD3+ CD27+ CD28- T cells (%)	4.61 (2.77)	8.15 (1.71)	2.23 (6.62)	N.A.
CD3+ CD27- CD28 + T cells (%)	12.37 (1.57)	12.54 (0.97)	13.23 (3.75)	N.A.
CD3+ CD27- CD28- T cells (%)	23.70 (4.36)	28.17 (2.69)	42.63 (10.45)	N.A.
CD3+ CD95+ T cells (%)	10.21 (2.05)	9.86 (1.27)	11.74 (4.92)	N.A.
CD3+ KLRG1+ CD57+ T cells (%)	8.24 (2.30)	10.74 (1.42)	25.21 (5.52)	N.A.
CD3+ KLRG1+ CD57− T cells (%)	18.34 (1.72)	13.97 (1.06)	15.34 (4.11)	N.A.
CD3+ KLRG1- CD57+ T cells (%)	3.53 (0.94)	5.91 (0.58)	3.87 (2.24)	N.A.
CD3+ KLRG1- CD57− T cells (%)	69.02 (3.56)	69.42 (2.20)	55.48 (8.54)	N.A.
CD4+ T cells (%)	41.57 (8.85)	34.69 (5.46)	26.34 (21.20)	N.A.
CD4+ CD27+ CD28+ T cells (%)	47.9 (11.2)	41.5 (6.9)	33.3 (26.9)	N.A.
CD4+ CD27+ CD28- T cells (%)	3.1 (4.1)	8.4 (2.5)	1.2 (9.8)	N.A.
CD4+ CD27- CD28+ T cells (%)	8.8 (2.4)	11.5 (1.5)	10.6 (5.8)	N.A.
CD4+ CD27- CD28- T cells (%)	38.03 (12.14)	38.73 (7.48)	54.70 (29.07)	N.A.
CD4+ CD95+ T cells (%)	3.49 (1.25)	2.95 (0.77)	2.56 (3.00)	N.A.
CD4+ KLRG1+ CD57+ T cells (%)	12.57 (6.94)	19.27 (4.28)	41.97 (16.64)	N.A.
CD4+ KLRG1+ CD57− T cells (%)	18.44 (5.31)	15.50 (3.28)	11.70 (12.73)	N.A.
CD4+ KLRG1- CD57+ T cells (%)	3.87 (2.32)	6.71 (1.43)	1.13 (5.56)	N.A.
CD4+ KLRG1- CD57− T cells (%)	86.49 (5.06)	85.55 (3.12)	86.81 (12.12)	N.A.
CD4+ CM T cells (%)	38.83 (9.08)	39.19 (5.60)	29.40 (21.75)	N.A.
CD4+ CD27+ CD28+ CM T cells (%)	85.95 (4.91)	78.95 (3.03)	79.97 (11.76)	N.A.
CD4+ CD27+ CD28- CM T cells (%)	4.75 (4.33)	9.48 (2.67)	1.79 (10.36)	N.A.
CD4+ CD27- CD28+ CM T cells (%)	8.47 (1.79)	9.17 (1.11)	13.28 (4.30)	N.A.
CD4+ CD27− CD28− CM T cells (%)	0.40 (1.33)	2.43 (0.82)	4.93 (3.18)	N.A.
CD4+ CD95+ CM T cells (%)	8.86 (2.36)	8.21 (1.45)	11.23 (5.65)	N.A.
CD4+ KLRG1+ CD57+ CM T cells (%)	1.23 (1.06)	2.57 (0.65)	1.66 (2.54)	N.A.
CD4+ KLRG1+ CD57- CM T cells (%)	10.05 (3.85)	10.14 (2.37)	12.40 (9.22)	N.A.
CD4+ KLRG1- CD57+ CM T cells (%)	1.43 (0.87)	1.77 (0.54)	0.00 (0.00)	N.A.
CD4+ KLRG1− CD57− CM T cells (%)	86.49 (5.06)	85.55 (3.12)	86.81 (12.12)	N.A.
CD4+ EM T cells (%)	37.22 (9.06)	41.93 (5.59)	37.43 (21.71)	N.A.
CD4+ CD27+ CD28+ EM T cells (%)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	N.A.
CD4+ CD27+ CD28− EM T cells (%)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	N.A.
CD4+ CD27− CD28+ EM T cells (%)	51.06 (10.15)	46.87 (6.26)	47.60 (24.30)	N.A.
CD4+ CD27- CD28- EM T cells (%)	48.91 (10.15)	53.13 (6.26)	52.40 (24.31)	N.A.
CD4+ CD95+ EM T cells (%)	3.87 (1.74)	4.02 (1.07)	5.14 (4.17)	N.A.
CD4+ KLRG1+ CD57+ EM T cells (%)	19.75 (6.97)	25.52 (4.30)	39.50 (16.69)	N.A.
CD4+ KLRG1+ CD57- EM T cells (%)	29.28 (5.09)	23.34 (3.14)	23.34 (3.14)	N.A.
CD4+ KLRG1- CD57+ EM T cells (%)	7.52 (2.73)	9.76 (1.69)	0.00 (0.00)	N.A.
CD4+ KLRG1- CD57- EM T cells (%)	41.63 (8.99)	41.44 (5.55)	35.25 (21.54)	N.A.
CD4+ Naïve T cells (%)	13.60 (3.03)	10.84 (1.87)	4.82 (7.27)	N.A.
CD4+ CD27+ CD28+ Naïve T cells (%)	85.87 (8.13)	75.69 (5.02)	70.78 (19.49)	N.A.
CD4+ CD27+ CD28- Naïve T cells (%)	6.86 (5.03)	13.64 (3.10)	7.23 (12.05)	N.A.
CD4+ CD27− CD28+ Naïve T cells (%)	4.14 (2.92)	4.46 (1.80)	1.80 (7.01)	N.A.
CD4+ CD27− CD28− Naïve T cells (%)	3.03 (4.57)	6.21 (2.82)	20.20 (10.94)	N.A.
CD4+ CD95+ Naïve T cells (%)	2.91 (1.21)	1.73 (0.75)	1.08 (2.91)	N.A.
CD4+ KLRG1+ CD57+ Naïve T cells (%)	4.24 (4.01)	5.30 (2.47)	21.63 (9.60)	N.A.
CD4+ KLRG1+ CD57- Naïve T cells (%)	2.13 (2.11)	3.81 (1.30)	0.66 (5.06)	N.A.
CD4+ KLRG1- CD57+ Naïve T cells (%)	1.77 (1.69)	2.73 (1.04)	0.00 (0.00)	N.A.
CD4+ KLRG1- CD57− Naïve T cells (%)	91.85 (5.40)	88.16 (3.33)	79.07 (12.94)	N.A.
CD4+ TEMRA T cells (%)	6.05 (4.90)	8.26 (3.02)	28.00 (11.74)	N.A.
CD4+ CD27+ CD28 + TEMRA T cells (%)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	N.A.

Table 4 (continued) | Age and sex-adjusted means (SE) of immune-senescence markers by cluster

Variable	Cluster			*p*-Value
	Vulnerable	Resilient	Vigorous	
CD4+ CD27+ CD28− TEMRA T cells (%)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	N.A.
CD4+ CD27− CD28+ TEMRA T cells (%)	48.81 (8.51)	41.44 (5.25)	4.42 (20.39)	N.A.
CD4+ CD27− CD28− TEMRA T cells (%)	53.20 (8.52)	58.46 (5.25)	95.80 (20.41)	N.A.
CD4+ CD95+ TEMRA T cells (%)	7.42 (2.17)	2.14 (1.34)	0.01 (5.19)	N.A.
CD4+ KLRG1+ CD57+ TEMRA T cells (%)	30.24 (9.29)	31.97 (5.73)	42.63 (22.25)	N.A.
CD4+ KLRG1+ CD57− TEMRA T cells (%)	29.26 (6.31)	23.94 (3.89)	26.90 (15.11)	N.A.
CD4+ KLRG1− CD57+ TEMRA T cells (%)	11.67 (3.59)	10.78 (2.21)	24.71 (8.60)	N.A.
CD4+ KLRG1− CD57− TEMRA T cells (%)	26.64 (9.22)	33.44 (5.68)	5.52 (22.08)	N.A.
CD8+ T cells (%)	30.67 (3.33)	28.90 (2.05)	37.54 (7.97)	N.A.
CD8+ CD27+ CD28+ T cells (%)	37.62 (3.89)	28.91 (2.40)	27.54 (9.31)	N.A.
CD8+ CD27+ CD28- T cells (%)	9.33 (2.73)	13.18 (1.68)	3.76 (6.54)	N.A.
CD8+ CD27− CD28+ T cells (%)	10.35 (2.40)	9.38 (1.48)	6.08 (5.75)	N.A.
CD8+ CD27− CD28− T cells (%)	42.92 (4.85)	48.54 (2.99)	62.68 (11.63)	N.A.
CD8+ CD95+ T cells (%)	1.14 (0.50)	1.30 (0.31)	1.10 (1.20)	N.A.
CD8+ KLRG1+ CD57+ T cells (%)	19.27 (3.59)	22.63 (2.21)	38.46 (8.59)	N.A.
CD8+ KLRG1+ CD57- T cells (%)	39.82 (2.75)	31.68 (1.70)	29.24 (6.59)	N.A.
CD8+ KLRG1- CD57+ T cells (%)	4.10 (1.46)	9.44 (0.90)	5.97 (3.49)	N.A.
CD8+ KLRG1- CD57- T cells (%)	36.48 (3.84)	36.25 (2.37)	26.35 (9.19)	N.A.
CD8+ CM T cells (%)	40.75 (4.01)	35.87 (2.47)	23.51 (9.60)	N.A.
CD8+ CD27+ CD28+ CM T cells (%)	82.36 (3.28)	76.28 (2.02)	88.15 (7.85)	N.A.
CD8+ CD27+ CD28− CM T cells (%)	8.70 (2.88)	14.21 (1.78)	3.84 (6.91)	N.A.
CD8+ CD27− CD28+ CM T cells (%)	6.88 (1.09)	6.26 (0.67)	5.85 (2.60)	N.A.
CD8+ CD27− CD28− CM T cells (%)	1.79 (0.60)	3.26 (0.37)	2.14 (1.43)	N.A.
CD8+ CD95+ CM T cells (%)	3.25 (1.22)	3.55 (0.75)	6.65 (2.91)	N.A.
CD8+ KLRG1+ CD57+ CM T cells (%)	3.44 (0.78)	4.32 (0.48)	5.61 (1.86)	N.A.
CD8+ KLRG1+ CD57- CM T cells (%)	42.52 (3.43)	34.46 (2.11)	38.12 (8.20)	N.A.
CD8+ KLRG1- CD57+ CM T cells (%)	1.66 (0.68)	3.01 (0.42)	-0.14 (1.64)	N.A.
CD8+ KLRG1- CD57- CM T cells (%)	51.70 (3.85)	58.26 (2.37)	56.34 (9.23)	N.A.
CD8+ EM T cells (%)	30.42 (3.67)	28.38 (2.26)	25.73 (8.79)	N.A.
CD8+ CD27+ CD28+ EM T cells (%)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	N.A.
CD8+ CD27+ CD28− EM T cells (%)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	N.A.
CD8+ CD27- CD28 + EM T cells (%)	41.69 (5.71)	34.22 (3.52)	38.54 (13.68)	N.A.
CD8+ CD27- CD28- EM T cells (%)	57.54 (5.65)	65.82 (3.49)	61.39 (13.55)	N.A.
CD8+ CD95+ EM T cells (%)	1.75 (1.05)	2.94 (0.64)	2.24 (2.50)	N.A.
CD8+ KLRG1+ CD57+ EM T cells (%)	29.38 (5.02)	31.67 (3.10)	48.56 (12.03)	N.A.
CD8+ KLRG1+ CD57− EM T cells (%)	43.33 (3.17)	26.81 (1.96)	28.92 (7.61)	N.A.
CD8+ KLRG1− CD57 + EM T cells (%)	6.87 (2.85)	15.42 (1.76)	4.63 (6.82)	N.A.
CD8+ KLRG1− CD57− EM T cells (%)	23.26 (3.54)	25.94 (2.19)	18.15 (8.49)	N.A.
CD8+ Naïve T cells (%)	6.18 (1.49)	6.22 (0.92)	7.76 (3.56)	N.A.
CD8+ CD27+ CD28+ Naïve T cells (%)	63.68 (5.08)	58.40 (3.13)	61.48 (12.17)	N.A.
CD8+ CD27+ CD28- Naïve T cells (%)	23.88 (4.03)	25.37 (2.49)	21.85 (9.66)	N.A.
CD8+ CD27- CD28+ Naïve T cells (%)	4.86 (1.57)	5.97 (0.97)	4.11 (3.75)	N.A.
CD8+ CD27− CD28− Naïve T cells (%)	7.71 (1.90)	10.25 (1.17)	12.56 (4.55)	N.A.
CD8+ CD95+ Naïve T cells (%)	0.60 (0.45)	1.03 (0.28)	0.03 (1.08)	N.A.
CD8+ KLRG1+ CD57+ Naïve T cells (%)	5.26 (2.05)	7.85 (1.27)	3.67 (4.92)	N.A.
CD8+ KLRG1+ CD57- Naïve T cells (%)	37.59 (6.67)	35.21 (4.11)	24.71 (15.97)	N.A.
CD8+ KLRG1- CD57+ Naïve T cells (%)	0.84 (0.67)	1.98 (0.41)	5.46 (1.60)	N.A.
CD8+ KLRG1- CD57- Naïve T cells (%)	57.11 (7.35)	54.92 (4.53)	66.17 (17.60)	N.A.
CD8+ TEMRA T cells (%)	25.14 (4.76)	29.42 (2.94)	43.25 (11.41)	N.A.
CD8+ CD27+ CD28+ TEMRA T cells (%)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	N.A.
CD8+ CD27+ CD28− TEMRA T cells (%)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	N.A.
CD8+ CD27- CD28+ TEMRA T cells (%)	20.88 (3.98)	18.94 (2.45)	10.29 (9.52)	N.A.

Table 4 (continued) | Age and sex-adjusted means (SE) of immune-senescence markers by cluster

Variable	Cluster			*p*-Value
	Vulnerable	Resilient	Vigorous	
CD8+ CD27- CD28- TEMRA T cells (%)	79.69 (3.98)	81.03 (2.45)	89.78 (9.53)	N.A.
CD8+ CD95+ TEMRA T cells (%)	0.38 (0.14)	0.32 (0.09)	0.40 (0.34)	N.A.
CD8+ KLRG1+ CD57+ TEMRA T cells (%)	38.33 (6.07)	34.19 (3.74)	52.07 (14.53)	N.A.
CD8+ KLRG1+ CD57− TEMRA T cells (%)	40.11 (4.52)	33.55 (2.79)	23.54 (10.82)	N.A.
CD8+ KLRG1- CD57+ TEMRA T cells (%)	7.25 (3.23)	14.41 (1.99)	14.43 (7.74)	N.A.
CD8+ KLRG1− CD57- TEMRA T cells (%)	16.98 (5.27)	17.73 (3.25)	10.26 (12.63)	N.A.
CD4+ CD8+ T cells (%)	0.50 (0.16)	0.49 (0.10)	0.14 (0.37)	N.A.
CD4/CD8 ratio	1.67 (0.44)	1.40 (0.27)	0.64 (1.06)	N.A.
Vitamins	*n* = 61	*n* = 67	*n* = 15	
Vitamin D	29.71 (6.53)	41.37 (5.62)	32.58 (11.67)	0.35
Vitamin B12	467.45 (43.85)	417.04 (37.70)	713.11 (78.31)	**0.004**
Inflammation/acute-phase	*n* = 62	*n* = 67	*n* = 16	
C-reactive protein	5.39 (1.39)	2.69 (1.21)	5.86 (2.42)	0.23
ESR	32.22 (3.55)	35.10 (2.99)	23.95 (5.55)	0.21
Ferritin	188.28 (21.83)	195.35 (18.47)	128.83 (38.29)	0.30

*Spite of low sample size it should be noticed that vigorous centenarians disclosed higher levels of memory T cells (CD4+ TEMRA, CD3+ KLRG1+ CD57+ , CD8+ KLRG1− CD57+ Naive T cells) and less CD8+ KLRG1+ CD57− T cells and CD8+ KLRG1− CD57+ EM T cells as compared with vulnerable and resilient centenarians. Vulnerable centenarians had higher levels of CD8+ KLRG1+ CD57− T cells, while resilient centenarians disclosed higher levels of CD8+ KLRG1− CD57+ T cells.

CM central memory, *EM* effector memory, *ESR* erythrocyte sedimentation rate, *G-CSF* granulocyte colony-stimulating factor, *GDS-15* geriatric depression scale-15 items, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *IFN-γ* interferon-gamma, *IL* interleukin, *MCP-1* monocyte chemoattractant protein-1, *N.A.* not applicable, *QoL* quality of life, *RANTES* regulated on activation, normal T cell expressed and secreted, *SWLS* satisfaction with life scale, *TEMRA* terminally differentiated effector memory T cells, *TNF-α* tumor necrosis factor-alpha, *WHOQOL-AGE* World Health Organization Quality of Life AGE.

Table 5 | Mean biological age residuals based on lifestyle variables and health outcomes in centenarians

Variable	Mean	SD	*p*-Value
Current tobacco consumption			0.34
No	0.012	0.964	
Yes	−0.438	1.223	
Previous tobacco consumption			**0.01**
No	−0.230	0.999	
Yes	0.230	0.885	
Current alcohol consumption			0.54
No	0.019	0.961	
Yes	−0.161	1.056	
Previous alcohol consumption			0.93
No	−0.006	0.910	
Yes	0.009	1.058	
Regular exercise			0.06
No activity or once a week	0.094	0.894	
2 to 3 times per week	−0.701	1.178	
4 or more times per week	−0.038	1.238	
Insomnia			0.76
No	0.011	0.988	
Yes	−0.065	0.867	
Life satisfaction			0.08
Extremely satisfied	−0.160	0.918	
Satisfied	0.099	0.812	
Somewhat satisfied	0.185	1.077	
Neutral	−0.332	1.613	
Somewhat dissatisfied	0.386	0.795	
Dissatisfied	−1.296	0	
Extremely dissatisfied	2.371	0	
COVID-19 history			0.88
No	−0.005	0.977	
Yes	0.032	0.942	
Frailty			0.90
No	-0.005	0.920	
Pre-frail	-0.077	0.948	
Yes	0.024	0.985	
Sarcopenia			0.37
No	0.132	0.819	
Yes	−0.050	1.019	
Nutritional status			0.41
Malnutrition	0.060	1.057	
Nutritional risk	-0.112	0.905	
Good nutrition	0.200	0.981	
Risk falls			0.63
Low	0.046	0.933	
Risk	−0.041	1.004	
CDR-SB Scale category			0.57
No dementia	0.080	0.714	
Questionable dementia	0.119	0.936	
Mild dementia	−0.074	0.956	
Moderate dementia	0.083	1.182	
Severe dementia	−0.317	1.096	
MMSE category			0.29
Normal	0.050	1.198	

Table 5 (continued) | Mean biological age residuals based on lifestyle variables and health outcomes in centenarians

Variable	Mean	SD	*p*-Value
Mild impairment	0.187	0.792	
Moderate impairment	0.037	0.936	
Severe impairment	−0.217	1.108	
Yesavage scale categories			**0.03**
Normal	0.035	0.902	
Moderate depression	−0.212	1.236	
Severe depression	2.371	0	
Immune Health Grade			0.72
I	−0.084	0.997	
II	0.260	1.001	
IV	0.041	0.942	

diversity. This mixed picture illustrates the paradox of immunosenescence: classical features of aging coexist with preserved or adapted subsets that may contribute to immune resilience[11]. Such heterogeneity reinforces the idea that extreme longevity does not simply reflect a slower rate of immune decline, but rather a reorganization of the immune repertoire that balances vulnerability with compensation[9,11].

A new categorization of centenarians based on patient-reported outcomes is presented (Fig. 2). Previously, three centenarians' categories have been defined by Evert et al.[28]: (1) Escapers (individuals who reach and continue beyond the age of 100 without age-related chronic diseases); (2) Delayers (those who develop these diseases late in life after becoming centenarians), and (3) Survivors (those who reach and continue beyond 100 years while living with age-related chronic diseases). Among these, the Escaper phenotype is considered the most prevalent in Colombians[29].

The primary difference between our classification of centenarians and the classification by Evert et al.[28] lies in the criteria and methodology used for categorization. Our classification gives a snapshot of the centenarian's current clinical status, while Evert et al.[28] offer a perspective on their lifetime disease trajectory. Both classifications provide valuable insights into longevity, but they address different aspects of the centenarian experience.

As mentioned, not all centenarians evaluated showed signs of immunosenescence. A substantial proportion exhibited immune parameters comparable to those described in younger elderly or even midlife populations, echoing observations in semi-supercentenarians and supercentenarians who maintain favorable immune cell ratios and preserved adaptive responses[30,31]. Having high levels of memory T cells, including subtypes like CD4+ TEMRA, CD3+ KLRG1+ CD57+, among others (Table 4), observed in vigorous centenarians indicates several important aspects of an individual's immune status including previous infections or vaccination and a balanced memory response capable of mounting a rapid response to previously encountered antigens[32,33]. KLRG1+ CD57+ is considered a more terminally differentiated, potentially senescent state with reduced or exhausted function as compared with KLRG1+ CD57− cells[32,33].

Contrary to the classic paradigm that positions immunosenescence as an inherent hallmark of longevity[6,7], our findings support a more selective model: while certain centenarians indeed exhibit signs of immune system exhaustion, others maintain relatively youthful immune signatures. The subset of centenarians with preserved immune profiles in our cohort also had lower biological-age residuals and better QoL, suggesting a clustering of favorable biological trajectories.

Centenarians with higher biological age residuals not only exhibited worse inflammatory profiles but also reported lower QoL and well-being scores. These associations remained consistent across different domains of life satisfaction and psychological health[34]. The direction of the association between biological age and physical activity is consistent with previous reports that indicate a positive association between physical capacity and biological aging[35]. On the contrary, centenarians with a history of previous tobacco consumption and severe depression exhibited significantly higher biological-age residuals, confirming previous reports showing that these two conditions represent an important accelerator of the aging process[36,37].

Vigorous centenarians exhibited elevated levels of vitamin B12 in comparison to other groups (Table 4). However, in all groups, the levels of Vitamin B12 fall within the normal range. Vitamin B12 is essential for various bodily functions, including red blood cell formation, neurological function, and deoxyribonucleic acid synthesis[38]. Some research suggests that adequate levels of vitamin B12 may play a role in promoting longevity and overall health, primarily through its impact on cellular health and brain function[38].

Beyond the absolute level of biological age, our findings may also reflect inter-individual differences in the pace of aging, a dynamic concept that captures the rate at which biological decline occurs over time[39]. In our cohort, the combination of lower biological age residuals, better QoL, and preserved immune markers in a subset of individuals might reflect a slower pace of aging, possibly due to lifelong resilience mechanisms or late-life deceleration[40]. This opens a new avenue for geroscientific inquiry, as centenarians may not only represent survivors of mortality risks, but also individuals with inherently slower biological deterioration over time.

This study presents some limitations that warrant consideration. The cross-sectional design precludes causal inferences regarding the directionality of associations between biological age, immunosenescence, and age-related clinical variables, including QoL. Also, the cross-sectional nature of our biological age estimation, which precludes direct assessment of the pace of aging over time. Future research should explore dynamic metrics, such as epigenetic clocks, to better understand biological aging trajectories in centenarians. The sample size for immunological profiling was limited, which may have reduced statistical power to detect associations with certain markers. However, data from centenarians, regardless the sample size, provides valuable insights into the understanding of extreme longevity[41]. Utilizing these unique data sets can yield valuable insights that may influence aging science, public health, and personalized approaches to healthy longevity. The absence of alkaline phosphatase measurements required imputation for phenotypic age estimation, potentially introducing measurement bias. We did not assess cytomegalovirus serostatus, which is a known driver of CD8+ differentiation, clonal expansion, and TEMRA enrichment in advanced age. Therefore, our CD4+/CD8+ and CD8+ subset patterns must be interpreted cautiously, as underlying latent infection could not be determined. Finally, the generalizability of the findings may be constrained by the sociocultural and geographic specificity of the centenarian cohort.

In summary, by the integration of phenotypic age estimation with clinical and immunological profiling, it was observed that better QoL, and well-being were significantly associated with lower biological age, while depressive symptoms, prior tobacco, elevated levels of RANTES and G-CSF as well as a distinct CD8+ T cell phenotype were linked to higher biological age. These findings confirm that biological age, rather than chronological age, serves as a more accurate indicator of aging heterogeneity in extreme longevity and underscore the importance of incorporating biological and clinical measures (i.e., translational research) in geroscience.

From a clinical standpoint, the use of biological age estimation and immune-inflammatory profiling may contribute to the identification of individuals at greater risk of functional decline, supporting more precise approaches in geriatric care. In the research context, the need for longitudinal studies is underscored to better understand causal relationships and validate biological aging metrics across diverse populations. At the policy level, the integration of age-related clinical variables and biological aging markers into aging-related programs may enhance intervention design, promote equitable health outcomes, and foster dignified aging.

Methods

Study design

Cross-sectional study as part of the Colombian Centenarians Project[29].

Setting and participants

Participant data came from the Colombian Centenarians Project, a nationwide study involving centenarians in Colombia, starting in October 2023[29]. This study applied simple random sampling to select subjects aged 100 years or older, whose ages were verified by identification documents or state records, and who provided written informed consent. No exclusion criteria were determined. The centenarians were assessed at a geriatric outpatient clinic or at their home and were recruited from five provinces of Colombia (Atlántico, Bogotá D.C., Bolívar, Sucre, and Valle del Cauca).

Variables

The outcomes, whether categorical or quantitative, were the QoL, biological age and immune profile. Independent variables were sociodemographic, lifestyle, psychological, and biochemical characteristics.

Data measurement

Data were collected through a semi-structured questionnaire administered during a medical interview with the centenarian and their caregiver, as reported elsewhere[42]. The WHOQOL-AGE scale was utilized to assess QoL[42].

All psychological and cognitive measures used were standardized instruments validated in Spanish and culturally adapted for Colombia. The CDR-SB evaluates the degree of functional impairment due to cognitive decline[43], whereas the MMSE quantifies current cognitive performance[44]. The Geriatric Depression Scale-15 (GDS-15, Yesavage) measures depressive symptoms[45], while the Satisfaction With Life Scale (SWLS) assesses subjective well-being and global life satisfaction[46]. Although these domains may be inter-related, they represent conceptually distinct constructs and have demonstrated adequate discriminant validity previously[42].

Additionally, other standardized clinical scales were used to evaluate specific geriatric domains. Anxiety was assessed using the Geriatric Anxiety Inventory-Short Form (GAI-SF)[47], a brief instrument validated in older adults and culturally adapted into Spanish to capture subclinical and clinical anxiety symptoms[48]. Frailty was operationalized according to Fried's phenotype criteria[49], encompassing unintentional weight loss, exhaustion, weakness, slow gait speed, and low physical activity, widely applied in epidemiologic aging cohorts[49]. Sarcopenia was screened with the SARC-F questionnaire[49], which reflects muscle strength and functional capacity and has demonstrated predictive validity in community-dwelling older persons[49].

Nutritional status was evaluated through the Mini Nutritional Assessment (MNA)[50], the international gold standard for identifying malnutrition risk in older persons[50]. Risk of falls was determined by the Downton scale[51], which integrates medication use, sensory deficits, gait instability, and previous falls[51]. Sleep quality was examined using the Insomnia Severity Index (ISI)[52], validated for Spanish-speaking older adults as a measure of perceived insomnia burden[52]. Physical performance was quantified with the Short Physical Performance Battery (SPPB)[53], combining balance, gait speed, and chair-stand tests to estimate functional reserve[53]. Each instrument captures a distinct physiological or psychosocial construct; together they provide a multidimensional view of functional, emotional, and biological aging. All have validated Spanish versions and established reliability in Latin American contexts, minimizing redundancy and ensuring domain-specific assessment[48]. Finally, immune health was characterized by the IHG[54], a framework that categorizes an individual's immune resilience based on the balance of CD4 and CD8 T-cell counts[54].

We used Levine's equation to calculate biological age (PhenoAge)[55]. Levine's biological age measure is based on nine biochemical parameters (albumin (g/L), creatinine (μmol/L), serum glucose (mmol/L), C-reactive protein (mg/dL), lymphocyte percentage, mean cell volume (fL), red cell distribution width (%), white blood cell count (1000 cells/μL), and alkaline phosphatase (U/L) along with chronological age[55]. Because we did not measure alkaline phosphatase in the present study, we imputed a value of 86 U/L for all participants based on the estimated average among older persons[56].

To be eligible for the application of this questionnaire, participants did not need to be fully cognitively intact but able to reliably respond to questions about themselves. In some cases, caregivers or relatives helped them comprehend and respond to the questions

Centenarians' classification

We developed a new classification of centenarians based on patient-reported outcomes, including QoL[42], MNA[50], Barthel Index[48], Lawton & Brody scale[48], SPPB[48], and the MMSE[48]. Dynamometry was also included as a covariate in this analysis[57]. We used the mixed-cluster methodology proposed by Lebart et al.[58] First, principal component analysis of the data was conducted. Next, the number of clusters was determined using hierarchical clustering, and finally, a consolidation step using k-means clustering was performed. Then, we evaluated the clinical and laboratory characteristics that differentiated every cluster by the Kruskal-Wallis test or the chi-squared test.

Cytokine assay and lymphocytes immunophenotype

Venous blood samples were collected between 08:00 and 12:00 in serum separator and ethylenediaminetetraacetic acid (EDTA) tubes using standard phlebotomy procedures[59]. Serum was obtained after clotting (30–60 min, room temperature) and centrifugation (1500–2000×*g*, 10–15 min), aliquoted to avoid repeated freeze-thaw cycles and stored at −80 °C until analysis[60]. Whole blood collected in EDTA tubes was processed on the day of collection for flow cytometry and complete blood counts[59].

Serum concentration of 20 cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p70, IL-13, IL-17A, TNF-α, G-CSF, granulocyte-macrophage CSF [GM-CSF], RANTES, monocyte chemoattractant protein [MCP]-1, monokine induced by gamma interferon-gamma (MIG), IFN-γ, IFN-α) was assessed by Cytometric Bead Array [CBA], Becton Dickinson Biosciences, San Diego, CA) in 114 centenarians. The test was done according to the manufacturer's protocols. Concentration of the cytokines was calculated using the FCAP Array Software (BD Bioscience) as reported elsewhere[59].

Eleven lymphocyte markers were also assessed in 42 participants, allowing for the determination of multiple cellular phenotypes. Immunophenotyping was performed on fresh EDTA blood using a Navios EX flow cytometer (Beckman Coulter)[60]. A minimum of 100,000 lymphocyte events per sample were acquired. Compensation was set with single-stained controls; instrument performance was verified daily with manufacturer's QC beads. Data were analyzed in FlowJo v9 (BD Biosciences) and Kaluza (Beckman Coulter).

Panel markers included anti-human IgD (Beckman Coulter), KLRG1 (Rochem Biocare), CD95 (Rochem Biocare), CD45RA (Beckman Coulter), CD28 (Beckman Coulter), CD27 (Beckman Coulter), CD8 (Beckman Coulter), CD19 (Beckman Coulter), CD4 (Beckman Coulter), CD57 (Beckman Coulter), and CD3 (Beckman Coulter); additional reagents included OptiLyse C and Flow-Count Fluorospheres (both Beckman Coulter).

Gating was performed as follows: singlets → lymphocytes (FSC/SSC) → CD3 + T cells and CD19 + B cells. CD3+ cells were subdivided into CD4+ and CD8+ subsets, then into (CD45RA + /CD27 +) central memory (CD45RA−/CD27 +) effector memory (CD45RA−/CD27−) and TEMRA (CD45RA + /CD27−). Senescence/exhaustion-associated phenotypes were identified by KLRG1 and CD57 co-expression and by CD95 were indicated. The CD4 + /CD8+ ratio was computed from absolute counts. CD28 marker was used as an indicator of aging in the human immune system. CD19 + B cells were classified into naïve, unswitched memory, switched memory, and double-negative subsets using CD27 and IgD expression (Fig. S1).

Relative frequencies are reported as % of the parent population. Absolute counts for major T- and B-cell subsets were derived by multiplying flow cytometric frequencies by absolute lymphocyte counts from the clinical hematology panel (dual-platform approach)[60]. When volumetric

acquisition was used, Flow-Count Fluorospheres enabled single-platform absolute quantification.

Samples were rejected if acquisition fell below 100,000 lymphocyte events, showed unstable fluidics, or had evident debris/hemolysis. Replicate staining and internal controls were included per run. Analysts were blinded to clinical data.

Statistical methods

Descriptive statistics were used to summarize the sociodemographic, clinical, and immunological characteristics of the centenarians. Continuous variables were expressed as means and standard deviations, while categorical variables were reported as frequencies and percentages.

For the analysis of biological aging, we used Levine's phenotypic age algorithm[55] as mentioned above. To our knowledge, this is the first time that Levine's phenotypic age algorithm has been used in Colombian centenarians. To adjust for chronological age and sex, the estimated biological age was regressed on these two variables, and the resulting residuals were inverse-normal transformed to generate a standardized variable with a mean of zero and a standard deviation of one. These adjusted residuals were used in subsequent analyses and are referred to as biological-age residuals.

We explored associations between biological-age residuals and various clinical, psychological, and immunological variables. Pearson's correlation coefficient was used to assess the relationship between biological-age residuals and continuous variables such as QoL scores, well-being, depression scores, cytokine concentrations, and immune cell counts (Supplementary Data 1 and 2 describe in detail the cell populations studied). For categorical variables, including health-related behaviors, frailty status, cognitive categories, and centenarian phenotypes, ANOVA was used to test differences in biological-age residuals across groups.

All analyses were exploratory in nature and aimed at identifying potential associations between biological aging, markers of immunosenescence and age-related clinical variables in Colombian centenarians. All statistical analyses were conducted using SPSS v.29 or R version 4.0.1. (for clustering analyses). Statistical significance was set at a two-tailed p-value < 0.05.

This study complied with Act 008430/1993 of the Ministry of Health of the Republic of Colombia, which classified it as minimal-risk research. Also, this research has been performed in accordance with the Declaration of Helsinki. The institutional and ethical committee of Universidad de la Costa approved the study design. Informed consent was obtained from all centenarians or their legal representatives.

Data availability

Individual-level data cannot be stored in public repositories or otherwise made publicly available due to ethical and data protection restrictions. However, data are available upon request for researchers who meet the criteria for access to confidential data.

Received: 1 October 2025; Accepted: 27 January 2026;
Published online: 16 February 2026

References

1. Cohen, A. A. et al. A complex systems approach to aging biology. *Nat. Aging* **2**, 580–591 (2022).
2. Giuliani, C. et al. Centenarians as extreme phenotypes: An ecological perspective to get insight into the relationship between the genetics of longevity and age-associated diseases. *Mech. Ageing Dev.* **165**, 195–201 (2017).
3. Mak, J. et al. Clinical biomarker-based biological aging and risk of cancer in the UK Biobank. *Br. J. Cancer* **129**, 94–103 (2023).
4. Bortz, J. et al. Biological age estimation using circulating blood biomarkers. *Commun. Biol.* **6**, 1089 (2023).
5. Terekhova, M., Bohacova, P. & Artyomov, M. N. Human immune aging. *Immunity* **58**, 2646–2669 (2025).
6. Barbé-Tuana, F., Funchal, G., Schmitz, C. R. R., Maurmann, R. M. & Bauer, M. E. The interplay between immunosenescence and age-related diseases. *Semin. Immunopathol.* **42**, 545–557 (2020).
7. Franceschi, C. et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann. N. Y. Acad. Sci.* **908**, 244–254 (2000).
8. Rodriguez, I. J. et al. Immunosenescence study of T cells: a systematic review. *Front. Immunol.* **11**, 604591 (2021).
9. Anaya, J. M., Lozada-Martinez, I. D., Torres, I. & Shoenfeld, Y. Autoimmunity in centenarians. A paradox. *J. Transl. Autoimmun.* **8**, 100237 (2024).
10. Marzo, R. R. et al. *Front. Public Health* **11**, 1193789 (2023).
11. Ahuja, S. K. et al. Immune resilience despite inflammatory stress promotes longevity and favorable health outcomes including resistance to infection. *Nat. Commun.* **14**, 3286 (2023).
12. Vitlic, A., Lord, J. M. & Phillips, A. C. Stress, ageing and their influence on functional, cellular and molecular aspects of the immune system. *Age* **36**, 9631 (2014).
13. Lozada-Martinez, I. D., Diazgranados-Garcia, M. C., Castelblanco-Toro, S. & Anaya, J. M. Global research on centenarians: a historical and comprehensive bibliometric analysis from 1887 to 2023. *Ann. Geriatr. Med. Res.* **28**, 144–155 (2024).
14. Fundación Saldarriaga Concha, Fedesarrollo, PROESA & DANE. Misión Colombia Envejece—Una Investigación Viva. (Bogotá, D.C., Colombia, 2023). https://www.saldarriagaconcha.org/wp-content/uploads/2023/11/MCE-00-1-Completo-Octubre12-2023.pdf.
15. von Elm, E. et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J. Clin. Epidemiol.* **61**, 344–349 (2008).
16. Daunay, A. et al. Centenarians consistently present a younger epigenetic age than their chronological age with four epigenetic clocks based on a small number of CpG sites. *Aging (Albany NY)* **14**, 7718–7733 (2022).
17. Vacinova, G. et al. Regulated upon activation, normal T cell expressed and secreted (RANTES) levels in the peripheral blood of patients with Alzheimer's disease. *Neural Regen. Res.* **16**, 796–800 (2021).
18. Guo, Y. et al. Elevated RANTES levels are associated with increased risk of cerebral atherosclerotic stenosis. *BMC Neurol.* **23**, 39 (2023).
19. Link, H. Current state and future opportunities in granulocyte colony-stimulating factor (G-CSF). *Support. Care Cancer* **30**, 7067–7077 (2022).
20. Galván, S. T. et al. Plasma concentrations of granulocyte colony-stimulating factor (G-CSF) in patients with substance use disorders and comorbid major depressive disorder. *Sci. Rep.* **11**, 13629 (2021).
21. Chen, Y. & Rudolph, K. L. Granulocyte colony-stimulating factor acts on lymphoid-biased, short-term hematopoietic stem cells. *Haematologica* **106**, 1516–1518 (2021).
22. Ju, Z. et al. Telomere dysfunction induces environmental alterations limiting hematopoietic stem cell function and engraftment. *Nat. Med.* **13**, 742–747 (2007).
23. He, Z. et al. Declining neutrophil production despite increasing G-CSF levels is associated with chronic inflammation in elderly rhesus macaques. *J. Leukoc. Biol.* **109**, 1033–1043 (2021).
24. Van Avondt, K. et al. Neutrophils in aging and aging-related pathologies. *Immunol. Rev.* **314**, 357–375 (2023).
25. Alonso-Fernández, P., Puerto, M., Maté, I., Ribera, J. M. & De la Fuente, M. Neutrophils of centenarians show function levels similar to those of young adults. *J. Am. Geriatr. Soc.* **56**, 2244–2251 (2008).
26. Duchowny, K. A. et al. The aging immune system and all-cause mortality in older Americans: differences across sex and race/ethnicity. *Immun. Ageing* **22**, 25 (2025).
27. Chang, S. T. et al. Age-dependent immune profile in healthy individuals: an original study, systematic review and meta-analysis. *Immun. Ageing* **21**, 75 (2024).

28. Evert, J., Lawler, E., Bogan, H. & Perls, T. Morbidity profiles of centenarians: survivors, delayers, and escapers. *J. Gerontol. A Biol. Sci. Med. Sci.* **58**, M232–M237 (2003).
29. Lozada-Martinez, I. D. et al. *Arch. Gerontol. Geriatr. Plus* **1**, 100006 (2024).
30. Conte, M. et al. Human aging and longevity are characterized by high levels of mitokines. *J. Gerontol. A Biol. Sci. Med. Sci.* **74**, 600–607 (2019).
31. Accardi, G. et al. The Phenotypic Characterization of the Oldest Italian Man from December 28, 2020, to September 23, 2021, A.T., strengthens the idea that the immune system can play a key role in the attainment of extreme longevity. *J. Clin. Med.* **12**, 7591 (2023).
32. Wherry, E. J. & Kurachi, M. Molecular and cellular insights into T cell exhaustion. *Nat. Rev. Immunol.* **15**, 486–499 (2015).
33. Slaets, H., Veeningen, N., de Keizer, P. L. J., Hellings, N. & Hendrix, S. Are immunosenescent T cells really senescent? *Aging Cell* **23**, e14300 (2024).
34. Ng, T. P. et al. Socio-Environmental, Lifestyle, Behavioural, and Psychological Determinants of Biological Ageing: The Singapore Longitudinal Ageing Study. *Gerontology* **66**, 603–613 (2020).
35. Tzemah-Shahar, R., Hochner, H., Iktilat, K. & Agmon, M. What can we learn from physical capacity about biological age? A systematic review. *Ageing Res. Rev.* **77**, 101609 (2022).
36. Nicita-Mauro, V. et al. Smoking, aging and the centenarians. *Exp. Gerontol.* **43**, 95–101 (2008).
37. Gao, S., Deng, H., Wen, S. & Wang, Y. Effects of accelerated biological age on depressive symptoms in a causal reasoning framework. *J. Affect. Disord.* **339**, 732–741 (2023).
38. Zhu, M., Lv, T., Peng, M., Sun, H. & Li, Y. PTP-3 regulated by VB12 is important for ageing health in *C. elegans*. *NPJ Aging* **11**, 10 (2025).
39. Elliott, M. L. et al. Disparities in the pace of biological aging among midlife adults of the same chronological age have implications for future frailty risk and policy. *Nat. Aging* **1**, 295–308 (2021).
40. Balachandran, A. et al. Pace of Aging analysis of healthspan and lifespan in older adults in the US and UK. *Nat. Aging* **5**, 1132–1142 (2025).
41. Santos-Pujol, E. et al. The multiomics blueprint of the individual with the most extreme lifespan. *Cell Rep. Med.* **6**, 102368 (2025).
42. Anaya, J. M., Alpi, S. V., Castelblanco-Toro, S. M., Lozada-Martˌnez, I. D. & Salazar-Uribe, J. C. Quality of life and well-being in Colombian centenarians. *Sci. Rep* **15**, 32071 (2025).
43. O'bryant, S. E. et al. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. *Arch. Neurol.* **65**, 1091–1095 (2008).
44. Feng, L. et al. Malnutrition is positively associated with cognitive decline in centenarians and oldest-old adults: a cross-sectional study. *EClinicalMedicine* **47**, 101336 (2022).
45. Cheng, A., Leung, Y., Harrison, F. & Brodaty, H. The prevalence and predictors of anxiety and depression in near-centenarians and centenarians: a systematic review. *Int. Psychogeriatr* **31**, 1539–1558 (2019).
46. Ruiz, F. J. et al. Validity of the Satisfaction with Life Scale in Colombia and factorial equivalence with Spanish data. *Rev. Latinoam Psicol* **51**, 58–65 (2019).
47. Ribeiro, O., Teixeira, L., Ara£jo, L., Afonso, R. M. & Pachana, N. Predictors of anxiety in centenarians: health, economic factors, and loneliness. *Int. Psychogeriatr* **27**, 1167–1176 (2015).
48. Chavarro Carvajal, D. A. et al. Scales frequently used in geriatrics [Escalas de uso frecuente en geriatría] [Internet]. 1st ed. (Pontificia Universidad Javeriana, Bogotá, 2020) [cited 2025 Sep 7]. 1–80 p. https://apidspace.javeriana.edu.co/server/api/core/bitstreams/ec7f3b83-0fc3-48a5-890d-bb6b2a9d10a8/content.
49. Croize-Pourcelet, C. et al. Geriatric syndromes in a centenarians population. *Aging Clin. Exp. Res.* **34**, 3131–3136 (2022).
50. Lozada-Martinez, I. D., Vindas-Meza, L., Castelblanco-Toro, S., Salazar-Uribe, J. C. & Anaya, J. M. The impact of nutritional status on centenarians' physical, mental, and functional health. *Clin. Nutr. Open Sci.* **60**, 10–20 (2025).
51. Chen, T. Y. et al. Prevalence and correlates of falls among centenarians: results from the Five-Country Oldest Old Project (5-COOP). *J. Gerontol. A Biol. Sci. Med. Sci.* **75**, 974–979 (2020).
52. Zhong, B.L., Li, H.J., Xu, Y.M. & Jiang, X.F. *Front. Public Health* **10**, 1026034 (2022).
53. Cress, M. E. et al. Assessing physical performance in centenarians: norms and an extended scale from the Georgia Centenarian Study. *Curr. Gerontol. Geriatr. Res.* **2010**, 1–6 (2010).
54. Lee, G. C. et al. Immunologic resilience and COVID-19 survival advantage. *J. Allergy Clin. Immunol.* **148**, 1176–1191 (2021).
55. Levine, M. E. et al. An epigenetic biomarker of aging for lifespan and healthspan. *Aging (Albany NY)* **10**, 573–591 (2018).
56. Wu, J. et al. Age differences in associations of serum alkaline phosphatase and mortality among peritoneal dialysis patients. *Chin. Med. J.* **132**, 232–236 (2019).
57. Vieira, F. T. et al. Hip muscle strength, dynamic balance and functional capacity of community-dwelling older adults aged 60 and older: a cross-sectional study. *J. Biomech.* **129**, 110753 (2021).
58. Lebart, L., Morineau, A., Piron, M. *Statistique Exploratoire Multidimensionnelle*. (Dunod Paris, 1995).
59. Acosta-Ampudia, Y. et al. Persistent autoimmune activation and proinflammatory state in post-coronavirus disease 2019 syndrome. *J. Infect. Dis.* **225**, 2155–2162 (2022).
60. Di Mitri, D. et al. Reversible senescence in human CD4+CD45RA +CD27- memory T cells. *J. Immunol.* **187**, 2093–2100 (2011).

Acknowledgements

We extend our special thanks to the members of the Colombian Centenarians Alliance who made the design and maintenance of this national study possible. To the University EIA, Soluciones Moleculares SAS, the Office for the Older Persons of the Bogotá Health Secretary, and particularly to the commitment of the centenarians for their desire to contribute to the study, understanding, and promotion of extreme longevity. This work was supported by the Colombian Centenarians Alliance, Clínica de la Costa (Barranquilla, Colombia) and Universidad del Rosario (Bogotá, Colombia).

Author contributions

J.M.A., E.A.R.N., I.D.L.M., and M.R. conceived and designed the study. J.M.A., E.A.R.N., I.D.L.M., M.R., Y.A.A., D.M.M. and J.A.A.A. contributed to methodology and data analysis. J.M.A., I.D.L.M., M.J.D.G., O.P., and B.G. collected and curated the data. J.E.G., I.T. and C.R.S. contributed to biological sample management for formal analysis and interpretation. A.A.C.B. supported clinical and laboratory work. J.M.A., I.D.L.M., and E.A.R.N. wrote the first draft of the paper. All authors contributed to data interpretation and revised the paper for intellectual content. J.M.A. supervised the study. All authors have read and approved the paper.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41514-026-00340-6.

Correspondence and requests for materials should be addressed to Juan-Manuel Anaya.