Supplementary Table 1: Human studies exploring the association between SASP factors and frailty or frailty-related parameters

SASP factor	Population *	Study design **	Sample size	Age (years) §	Assessment tools	Association with frailty-related parameters	Ref.
Activin A	USA community dwelling (Mayo Clinic Biobank)	Retrospective cross-sectional	115	≥60	FI	Positive association with prevalent frailty	1
	USA sedentary older adults (LIFE)	Cross-sectional	1377	70-89	SPPB, 400m walk	Positive association with poor physical function	2
CCL1	USA sedentary older adults (LIFE)	Cross-sectional	1377	70-89	SPPB, 400m walk	Positive association with poor physical function	2
CCL4	USA patients w/ovarian cancer or aortic stenosis	Cross-sectional/ Longitudinal (1y)	133	>60	FI	Positive association with prevalent frailty	1
GDF-15	Australian non demented older adults (MAS)	Cross sectional/ Longitudinal (2y)	888 585	78.5(4.7) 78.2(4.7)	Various cognitive tests	Positive association with lower global cognition and with cognitive decline	3
	USA community dwelling (Mayo Clinic Biobank)	Retrospective cross-sectional	115	≥60	FI	Positive association with prevalent frailty	1
	USA patients w/ovarian cancer or aortic stenosis	Cross-sectional/ Longitudinal (1y)	133	≥60	FI	Positive association with prevalent frailty	1
	Italian community dwelling older adults (InCHIANTI)	Longitudinal (8.5y)	660	71.9(6.0)	400 m walk	Predictor of mobility disability onset	4
	USA Community dwelling older adults (ARIC)	Cross-sectional/ Longitudinal (6y)	3838 1725	≥65	FP	Positive association with prevalent pre-frailty and frailty; positive association with incident frailty	5
	USA Community dwelling older adults (CHS)	Cross-sectional	2570	≥65	FP	Positive association with prevalent frailty	5
	French community dwelling older adults (MAPT)	Longitudinal (3y)	1083	≥70	Body weight, PA	Positive association with past lower physical activity levels and faster future body weight loss	6
	Acutely admitted Danish older patients (PROTECT)	Cross-sectional	1036	78.9(7.8)	HGS, CFS, muscle mass	Positive association with prevalent frailty or sarcopenia	7

	European community dwelling (MARK-AGE)	Cross-sectional	1666	≥55	GCF, SDS	Positive association with prevalent cognitive frailty and depression	8
	USA sedentary older adults (LIFE)	Longitudinal (2y)	1377	70-89	SPPB	Predictor of physical function deterioration	9
	French community dwelling older adults (MAPT)	Longitudinal (2y)	1089	≥70	Various cognitive tests	Positive association with cognitive decline	10
	UK community dwelling (UK Biobank)	Cross-sectional/ Longitudinal (10y)	43895	56.8(8.2)	FP	Positive association with prevalent frailty; predictor of death among pre-frail and frail	11
	Spanish older adults (Seniors-ENRICA-2)	Cross-sectional/ Longitudinal (2.2y)	2481	≥65	FI, SPPB, HGS, agility, mobility	Positive association with prevalent/ incident frailty and impaired physical function	12
sICAM-1	Taiwanese community dwelling adults	Cross-sectional	946	65.5(9.4)	FP	Positive association with prevalent frailty	13
IGFBP-2	USA community dwelling older adults (ARIC)	Cross-sectional/ Longitudinal (6y)	3838 1725	≥65	FP	Positive association with prevalent pre-frailty and frailty; positive association with incident frailty	5
	USA community dwelling older adults (CHS)	Cross-sectional	2570	≥65	FP	Positive association with prevalent pre-frailty and frailty	5
IL-6	Northeast England (Newcastle 85+)	Cross-sectional	552 811	85	FP FI	Positive association with prevalent frailty	14
	USA community dwelling (Framingham Offspring)	Cross-sectional	1919	>60	FP	Positive association with prevalent frailty and slower gait speed	15
	Non-demented community dwelling adults	Meta-analysis of 8 prospective studies	15828	55.7(6.0) - 75.4(6.6)	Various cognitive tests	Predictor of future global cognitive decline	16
	Australian community dwelling men	Cross-sectional/ Longitudinal (3y)	901	81.3	FP, FI	Positive association with prevalent frailty	17
	USA community dwelling (Mayo Clinic Biobank)	Retrospective Cross-sectional	115	≥60	FI	Positive association with prevalent frailty	1
	Australian community dwelling men	Cross-sectional/ Longitudinal (3y)	901	81.3	FP, FI	Positive association with prevalent frailty	17

IL-15	USA community dwelling (Mayo Clinic Biobank)	Retrospective cross-sectional	115	≥60	FI	Positive association with prevalent frailty	[1]
MMP-7	USA sedentary older adults (LIFE)	Cross-sectional	1377	70-89	SPPB, 400m walk	Positive association with poor physical function	[2]
	USA sedentary older adults (LIFE)	Longitudinal (2y)	1377	70-89	400m walk	Predictor of mobility disability onset	[9]
OPN	USA community dwelling (Mayo Clinic Biobank)	Retrospective cross-sectional	115	≥60	FI	Positive association with prevalent frailty	[1]
	USA patients w/ovarian cancer or aortic stenosis	Cross-sectional/ Longitudinal (1y)	133	≥60	FI	Positive association with prevalent frailty	[1]
	USA sedentary older adults (LIFE)	Longitudinal (2y)	1377	70-89	SPPB	Predictor of physical function deterioration	[9]
THBS-2	Italian community dwelling older adults (InCHIANTI)	Longitudinal (8.5y)	660	71.9(6.0)	400 m walk	Predictor of mobility disability onset	[4]
TNF-α	Northeast England (Newcastle 85+)	Cross-sectional	552 811	85	FP FI	Positive association with prevalent frailty	[14]
	USA patients w/ovarian cancer or aortic stenosis	Cross-sectional/ Longitudinal (1y)	133	>60	FI	Positive association with prevalent frailty	[1]
sTNFR-1	USA community dwelling (Mayo Clinic Biobank)	Retrospective cross-sectional	115	≥60	FI	Positive association with prevalent frailty	[1]
	USA patients w/ovarian cancer or aortic stenosis	Cross-sectional/ Longitudinal (1y)	133	≥60	FI	Positive association with prevalent frailty	[1]
	USA sedentary older adults (LIFE)	Longitudinal (2y)	1377	70-89	SPPB, 400 m walk	Predictor of mobility disability onset and physical function deterioration	[9]
	French community dwelling older adults (MAPT)	Longitudinal (2y)	1089	≥70	Various cognitive tests	Positive association with cognitive decline	[10]
sTNFR-2	Spanish older adults	Cross-sectional	259	65-102	FP	Positive association with prevalent frailty	[18]
VEGF-A	USA sedentary older adults (LIFE)	Cross-sectional	1377	70-89	SPPB 400m walk	Positive association with poor physical function	[2]

USA sedentary older adults (LIFE)	Longitudinal (2y)	1377	70-89	400 m walk SPPB	Predictor of mobility disability onset and physical function deterioration	9

* When available the name of the study or cohort is given in brackets.

** In longitudinal studies the length of follow up is given in months (m) or years (y).

§ Age is indicated as range, median or mean (SD).

Abbreviations: CCL1: C-C motif chemokine ligand 1; CCL4: C-C motif chemokine ligand 4;CFS: 9-point clinical frailty scale;[19] FI: frailty index;[20] FP: frailty phenotype;[21] GCF: global cognitive functioning score;[22] GDF-15: growth differentiation factor 15; HGS: hand grip strength; sICAM-1: soluble intercellular adhesion molecule 1; IGFBP-2: insulin like growth factor binding protein 2; IL-6: interleukin 6; IL-15: interleukin 15; MMP-7: matrix metallopeptidase 7; OPN: osteopontin; PA: physical activity level; SASP: senescence-associated secretory phenotype; SDS: self-rating depression scale;[23] SPPB: short physical performance battery (gait speed, balance, chair rise time); THBS-2: thrombospondin-2; TNF-α: tumour necrosis factor α; sTNFR-1: soluble tumour necrosis factor receptor 1; sTNFR-2: soluble tumour necrosis factor receptor 2; VEGF-A: vascular endothelial growth factor A.

References

1. Schafer MJ, Zhang X, Kumar A, et al. The senescence-associated secretome as an indicator of age and medical risk. JCI Insight 2020;5:e133668. https://doi.org/10.1172/jci.insight.133668; PMID: 32554926.
2. Fielding RA, Atkinson EJ, Aversa Z, et al. Associations between biomarkers of cellular senescence and physical function in humans: observations from the lifestyle interventions for elders (LIFE) study. GeroScience 2022;44:2757–70. https://doi.org/10.1007/s11357-022-00685-2; PMID: 36367600.
3. Fuchs T, Trollor JN, Crawford J, et al. Macrophage inhibitory cytokine-1 is associated with cognitive impairment and predicts cognitive decline - the Sydney Memory and Aging Study. Aging Cell 2013;12:882–9. https://doi.org/10.1111/acel.12116; PMID: 23758647.
4. Osawa Y, Semba RD, Fantoni G, et al. Plasma proteomic signature of the risk of developing mobility disability: a 9-year follow-up. Aging Cell 2020;19:e13132. https://doi.org/10.1111/acel.13132; PMID: 32157804.
5. Liu F, Austin TR, Schrack JA, et al. Late-life plasma proteins associated with prevalent and incident frailty: a proteomic analysis. Aging Cell 2023;22:e13975. https://doi.org/10.1111/acel.13975; PMID: 37697678.
6. Raffin J, Rolland Y, Parini A, et al. Association between physical activity, growth differentiation factor 15 and bodyweight in older adults: a longitudinal mediation analysis. J Cachexia Sarcopenia Muscle 2023;14:771–80. https://doi.org/10.1002/jcsm.13152; PMID: 36999490.
7. Kamper RS, Nygaard H, Praeger-Jahnsen L, et al. GDF-15 is associated with sarcopenia and frailty in acutely admitted older medical patients. J Cachexia Sarcopenia Muscle 2024;15:1549–57. https://doi.org/10.1002/jcsm.13513; PMID: 38890783.
8. Kochlik B, Herpich C, Moreno-Villanueva M, et al. Associations of circulating GDF15 with combined cognitive frailty and depression in older adults of the MARK-AGE study. GeroScience 2024;46:1657–69. https://doi.org/10.1007/s11357-023-00902-6; PMID: 37715843.
9. Fielding RA, Atkinson EJ, Aversa Z, et al. Biomarkers of cellular senescence predict the onset of mobility disability and are reduced by physical activity in older adults. J Gerontol A Biol Sci Med Sci 2024;79:glad257. https://doi.org/10.1093/gerona/glad257; PMID: 37948612.
10. Gonzalez-Bautista E, Soto M, Abellan van Kan G, Delrieu J. Association between inflammatory biomarkers and the cognitive response to a multidomain intervention: secondary longitudinal analyses from the MAPT study. GeroScience 2025;47:5365–76. https://doi.org/10.1007/s11357-024-01497-2; PMID: 39825168.
11. Xu J, Liu J, Tang J, et al. Plasma proteomic signature of risk and prognosis of frailty in the UK Biobank. GeroScience 2025;47:2365–81. https://doi.org/10.1007/s11357-024-01415-6; PMID: 39535692.
12. Ferreira de Campos K, García-Esquinas E, Buño-Soto A, et al. Growth differentiation factor 15 predicts physical function impairment in Spanish older adults: a real-world prospective study. GeroScience 2025. https://doi.org/10.1007/s11357-025-01779-3; PMID: 40601215.

13. Lee WJ, Chen LK, Liang CK, et al. Soluble ICAM-1, independent of IL-6, is associated with prevalent frailty in community-dwelling elderly Taiwanese people. PLOS One 2016;11:e0157877. https://doi.org/10.1371/journal.pone.0157877; PMID: 27310835.
14. Collerton J, Martin-Ruiz C, Davies K, et al. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: cross-sectional findings from the Newcastle 85+ Study. Mech Ageing Dev 2012;133:456–66. https://doi.org/10.1016/j.mad.2012.05.005; PMID: 22663935.
15. Liu CK, Lyass A, Larson MG, et al. Biomarkers of oxidative stress are associated with frailty: the Framingham Offspring Study. Age (Dordr) 2016;38:1. https://doi.org/10.1007/s11357-015-9864-z; PMID: 26695510.
16. Bradburn S, Sarginson J, Murgatroyd CA. Association of peripheral interleukin-6 with global cognitive decline in non-demented adults: A meta-analysis of prospective studies. Front Aging Neurosci 2017;9:438. https://doi.org/10.3389/fnagi.2017.00438; PMID: 29358917.
17. Hsu B, Hirani V, Cumming RG, et al. Cross-sectional and longitudinal relationships between inflammatory biomarkers and frailty in community-dwelling older men: the concord health and ageing in men project. J Gerontol A Biol Sci Med Sci 2019;74:835–41. https://doi.org/10.1093/gerona/glx142; PMID: 28977375.
18. Marcos-Pérez D, Sánchez-Flores M, Maseda A, et al. Frailty in older adults is associated with plasma concentrations of inflammatory mediators but not with lymphocyte subpopulations. Front Immunol 2018;9:1056. https://doi.org/10.3389/fimmu.2018.01056; PMID: 29868017.
19. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–95. https://doi.org/10.1503/cmaj.050051; PMID: 16129869.
20. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci 2007;62:722–7. https://doi.org/10.1093/gerona/62.7.722; PMID: 17634318.
21. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–56. https://doi.org/10.1093/gerona/56.3.m146; PMID: 11253156.
22. Rietman ML, Spijkerman AMW, Wong A, et al. Antioxidants linked with physical, cognitive and psychological frailty: analysis of candidate biomarkers and markers derived from the MARK-AGE study. Mech Ageing Dev 2019;177:135–43. https://doi.org/10.1016/j.mad.2018.04.007; PMID: 29719199.
23. Zung WW. A Self-Rating Depression Scale. Arch Gen Psychiatry 1965;12:63–70. https://doi.org/10.1001/archpsyc.1965.01720310065008; PMID: 14221692.