The Journal of Frailty & Aging 15 (2026) 100132

Contents lists available at ScienceDirect

The Journal of Frailty & Aging

journal homepage: www.elsevier.com/locate/tjfa

Original Research

Association of allostatic load with frailty trajectories and the mediating role of depressive symptoms

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ARTICLE INFO

Key words:
Frailty
Allostatic load
Depressive symptoms
Mediation analysis

ABSTRACT

Background: Frailty is a dynamic, age-related condition marked by progressive loss of resilience. Its risk factors include socioeconomic status and physiological stress burden, such as allostatic load score (ALS), remain unclear. This study aims to examine the role of depression in the association between ALS and frailty trajectories.
Methods: We analyzed data from 5885 LEAD cohort participants aged 25–82 years at baseline and from 3564 participants with follow-up data. Frailty status (robust, pre-frail, frail) was defined using the Fried phenotype, and transitions between visits were assessed. ALS was calculated from 14 parameters spanning cardiovascular, metabolic, and body composition measures. Associations of ALS with frailty status at baseline and with frailty transitions at follow-up were examined, and depressive symptoms were tested as a mediator.
Results: At baseline, 62.3% of participants were robust, 36.2% pre-frail, and 1.5% frail. Between visits, 16.3% transitioned to a worse frailty stage, while 17.7% improved. Higher ALS was linked to increased odds of being pre-frail/frail at baseline (OR 1.11; 95% CI: 1.08–1.15), and to a higher risk of transitioning from robust to pre-frail/frail (RRR 1.06; 95% CI: 1.02–1.09). Depressive symptoms mediated 35% (95% CI: 25–47%) of the cross-sectional and 17% (95% CI: 6.6–43%) of the longitudinal association between ALS and frailty.
Conclusions: Socioeconomic factors influenced frailty onset but not its progression, whereas depressive symptoms mediated approximately 17% of the effect of ALS on frailty development over time. These findings highlight the importance of exploring the effect of interventions for depression on frailty progression.

1. Introduction

Frailty is a complex, age-related clinical condition that involves multiple contributing factors and raises the risk of adverse outcomes in older people [1]. This progressive loss of resilience is often driven by the lifelong accumulation of chronic diseases, functional impairments, and environmental noxes [2]. Its prevalence among older adults is rising in parallel with demographic shifts [3]. Importantly, frailty is not a static condition—individuals may move between stages of being robust, prefrail, and frail [4]. Longitudinal studies show that transitions occur between stages of frailty: some individuals deteriorate from robust to prefrail or frail, while others improve toward robustness [5]. This

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https://doi.org/10.1016/j.tjfa.2026.100132
Received 7 November 2025; Received in revised form 22 December 2025; Accepted 29 December 2025
Available online 29 January 2026

bidirectional movement suggests that frailty reflects an ongoing balance between physiological stressors and adaptive reserves. Understanding which modifiable factors can tip this balance toward recovery rather than decline is therefore of particular interest. One factor receiving increasing attention is allostatic load (AL), a composite measure reflecting the cumulative physiological burden imposed by chronic life stressors [6]. AL represents the aggregated physiological strain on multiple systems arising from repeated or chronic activation of the body's stress response, particularly the hypothalamic–pituitary–adrenal axis and autonomic nervous system, ultimately diminishing systemic resilience [7]. Higher AL was significantly associated with elevated frailty levels in former investigations [8], an intuitively plausible yet not surprising finding. However, this relationship is not consistently observed across studies: although AL generally increases with age, individuals with similar levels may differ markedly in their vulnerability to frailty. For example, in one recent community-based investigation, age, sex, and place of residence—but not AL—were significantly associated with frailty [9]. Such heterogeneous findings indicate that additional factors—beyond allostatic load itself—may mediate or modify its influence on frailty. There are many different conceptual definitions of frailty in circulation: physical frailty involves motor and functional impairments such as low grip strength and exhaustion, whereas other concepts encompass other domains such as psychological functioning, cognitive decline, mood symptoms, and reduced psychological resilience ([10,11]).

These domains interact bidirectionally, with physical decline exacerbating psychological vulnerability and vice versa [12]. Understanding these multidimensional interactions is crucial for clarifying how individuals transition from robustness to prefrailty and frailty, and which factors might accelerate or reverse these trajectories.

Prior research has suggested a link between allostatic load and depressive symptoms albeit with varying degrees of robustness and consistency ([13,14]).

Current evidence indicates that depression and allostatic load contribute to frailty through converging mechanisms of systemic physiological dysregulation [10]. Over the last fifteen years, research has identified physiological changes associated with depressive disorders that are consistent with biological aging. Biological substrates of depression in frailty include disturbances in immune, neuroendocrine, and autonomic stress-response systems, alongside broader proteomic and metabolomic alterations [15]. AL on the other hand, reflects the cumulative biological burden of chronic stress, resulting in measurable multisystem impairment—including immune dysfunction, metabolic and cardiovascular dysregulation, and neurostructural vulnerability—that progressively reduces physiological resilience [16].

Several specific mechanisms appear particularly relevant for the development of frailty within the context of AL and depression: chronic low-grade inflammation, characterized by elevated IL-6, TNF-α, and CRP levels, is associated with both depressive symptoms and increased frailty risk, in part through its catabolic effects on muscle tissue [17]. Mitochondrial dysfunction is another central mechanism: reduced ATP generation and impaired respiratory capacity are linked to lower mobility and increased fatigability, and muscle biopsies in depressed adults demonstrate decreased ATP production, reinforcing a self-perpetuating cycle of reduced activity, energy availability, and physical performance [17]. Dopaminergic decline contributes further, as age-related reductions in striatal dopamine levels are associated with psychomotor slowing and cognitive impairment, both of which intensify vulnerability to frailty [17]. Similarly, slow gait and fatigue in the context of depression are associated with higher mortality and increased cardiovascular risk in later life.

Longitudinal studies demonstrate bidirectional relationships: frail individuals are more likely to develop depression, and depressive symptoms are linked with accelerated physical and cognitive decline and higher risk of becoming frail ([15,18–20],).

Investigating depression as a potential mediating factor in the relationship between physiological stress burden and frailty, depending on age and across longitudinal trajectories, could yield important insights for the development of targeted therapeutic interventions.

This study aims to examine the mediating role of depressive symptoms in the longitudinal relationship between allostatic load, presence of frailty and frailty trajectories within a large, population-based cohort, highlighting depression as a potentially modifiable factor in temporal dynamics of frailty.

2. Methods

2.1. Study population

The data were collected from the Austrian LEAD study (NCT01727518; http://clinicaltrials.gov), a longitudinal, observational, population-based cohort. The study design and methodological details have been previously published [21]. In summary, the LEAD study examines the respiratory, metabolic, and cardiovascular health. Furthermore, psychological well-being, mental health, health related quality of life, habits, lifestyle, and medical history are assessed by using questionnaires. At baseline, more than 15,000 participants aged 6–82 years, from Vienna (urban population) and six villages in Lower Austria (rural population), were recruited between 2012–2022 and completed the measurements of the first visit. Participants attended visit 1 are invited to take part in following visits every four years. Measurements at the following visits are the same as visit 1.

All the measurements are conducted in the local language and administered by trained staff at the LEAD study centre of the Ludwig Boltzmann Institute for Lung Health at the site Penzing of Clinic Ottakring, Vienna, Austria. The LEAD study has been approved by the local ethics committee of Vienna (protocol number: EK-11–117–0711). All participants signed an informed consent.

2.2. Subject selection

In this study, participants aged $\geq$ 25 years at visit 1 with complete data for the calculation of the Fried frailty phenotype were included in the cross-sectional analysis. Among them, those who also participated in visit 2 were included in the longitudinal analysis.

2.3. Measures

2.3.1. Fried frailty phenotype

The Fried frailty phenotype was assessed based on five criteria: weak handgrip strength, physical exhaustion, slowness, low physical activity, and unintentional weight loss of $\geq$ 5 kg in the preceding year [22]. The operationalization of these criteria was adapted according to data availability within our cohort and aligned with validated approaches reported in the literature.

Handgrip strength was measured for all participants using an electronic hand dynamometer (Camry, H101). Participants performed three attempts with their dominant hand, and the highest value was recorded. Weak handgrip strength was defined as a measurement below the sex-specific threshold adjusted for body mass index (BMI) [4]. The detailed criteria used to define weak handgrip strength are presented in the online supplement (Online Method S1).

Physical exhaustion was assessed using item 10 of the Short Form-12 (SF-12) questionnaire: *"How many times have you had a lot of energy in the past week?"* Participants who reported experiencing high energy *none of the time, a little of the time, or some of the time* were classified as experiencing physical exhaustion.

Slowness was assessed using item 4 of the Hospital Anxiety and Depression Scale - Depression subscale (HADS-D): *"I feel as if I am slowed down."* Participants who scored $\geq$2 (*most of the time or almost always*) were classified as experiencing slowness.

Low physical activity was determined based on the physical

component score of the SF-12 ([22,23]). The SF-12 physical component score ranges from 0 to 100, with higher scores indicating better physical health. A score of 25 or less was considered indicative of low physical activity.

Unintentional weight loss of $\geq$ 5 kg in the past year was assessed through self-report during the study visit. If participants answered "yes," the amount of weight lost was also recorded.

Frailty status was categorized at each visit as follows [24].

1. **Robust:** No criteria met.
2. **Prefrail:** One or two criteria met, regardless of which.
3. **Frail:** Three or more criteria met.

2.3.2. Allostatic load score

Allostatic load has been calculated using different sets of biomarkers and various scoring algorithms in previous studies [25]. Based on the availability of our data, we included biomarkers from multiple physiological systems and applied a common scoring approach; therefore, the allostatic load score (ALS) was calculated based on 14 parameters representing multiple physiological systems. These included systolic blood pressure (SBP) and diastolic blood pressure (DBP) as cardiovascular indicators; hemoglobin A1c (HbA1c), total cholesterol (TC), high-density lipoprotein (HDL), triglycerides (TG), and glomerular filtration rate (GFR, estimated using the CKD-EPI equation) as metabolic markers; high-sensitivity C-reactive protein (hs-CRP) as an inflammatory marker; z-scores of appendicular lean mass index (ALMI, defined as appendicular lean mass in kilograms divided by height in meters squared), fat mass index (FMI, defined as fat mass in kilograms divided by height in meters squared), visceral adipose tissue (VAT), and total body bone mineral density (BMD) as body composition and bone health indicators; and z-scores of pre-bronchodilator forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) as lung function parameters. Using data from the first study visit, the 25th and 75th percentiles for each parameter were determined (Supplemental Table S1). The at-risk range was defined as values above the 75th percentile for SBP, DBP, HbA1c, TC, TG, hs-CRP, z-scores of FMI, and VAT, and below the 25th percentile for HDL, GFR, z-score of FEV1, FVC, ALMI, and total body BMD. For each biomarker, participants received a score of 1 if the value fell within the at-risk range and 0 otherwise. Additionally, participants were assigned 1 point for the use of antihypertensive, antidiabetic, and lipid-lowering medications, respectively. The sum of these points constituted the ALS.

2.3.3. Covariates

Demographic data, including age and sex, were obtained from the study database. Smoking status was categorized as never smoker or ever smoker, with smoking defined as having smoked at least 20 packs of cigarettes in total, or at least 1 cigarette per day for 1 year, or at least 2 cigarettes per day for 6 months. Living area was recorded as a categorical variable, distinguishing between urban (Vienna) and rural (Lower Austria) residence. Education level was initially recorded in six categories: no formal education, primary school, completed apprenticeship, professional school, upper secondary education (general qualification for university entrance, high school diploma), and tertiary education (university degree). For analysis, education level was dichotomized into 'low' and 'intermediate to high,' with individuals classified as having a 'low' education level if they had not completed upper secondary or tertiary education. Household income was categorized as 'low' or 'intermediate to high,' with 'low' income defined as an equivalised monthly income of less than 1100 Euros. Equivalised income was calculated by dividing the total household income by the sum of person-specific weighting factors: 1.0 for the first adult, 0.5 for each additional adult, and 0.3 for each child. This approach accounts for household size and composition and follows the EU-Scala definition provided by Statistics Austria [26].

Symptoms of depression were assessed using the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D), which consists of seven items. Each item was rated by participants on a four-point Likert scale ranging from 0 to 3, resulting in a possible total score ranging from 0 to 21. Higher scores indicate more pronounced depressive symptoms.

2.4. Statistical analysis

Due to the small number of frail individuals at both visit 1 and visit 2, prefrail and frail individuals were combined into a single group for all analyses. Participants' characteristics for the robust and prefrail/frail groups at visit 1 were described as mean $\pm$ standard deviation (SD) or median (interquartile range) for continuous variables and as frequencies with percentages for categorical variables.

Binary logistic regression was used to evaluate the cross-sectional association between ALS and the likelihood of being classified as prefrail/frail at visit 1. Results are presented as odds ratios (OR) with corresponding 95 % confidence intervals (CI).

For the longitudinal analysis, multivariable Poisson regression with robust error variance was applied to assess the association between AL score at visit 1 and the risk of transitioning from a robust to a prefrail/frail status by visit 2. This approach provides relative risk (RR) estimates with 95 % CI, offering an interpretable measure of risk.

In addition, mediation analyses were performed for both cross-sectional and longitudinal settings to investigate whether depressive symptoms, assessed by the HADS-D, mediated the association between AL score and frailty status. The mediate function from the mediation package in R was used to estimate the average causal mediation effect (ACME), average direct effect (ADE), total effect, and the proportion of the total effect of AL score on frailty status mediated by depressive symptoms. Non-parametric bootstrapping with 500 simulations was conducted to generate 95 % confidence intervals for all mediation estimates. Since HADS-D item 4 contributes to both the depression scale and frailty scoring, we performed a sensitivity analysis by excluding HADS-D item 4 from the depression scale to account for potential bias in mediation analysis.

All models were adjusted for potential confounders, including age, sex, smoking status, household income, educational level, and living area (rural vs. urban). All statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria; https://cran.r-project.org). A two-sided p-value of <0.05 was considered statistically significant.

3. Results

A total of 5885 participants from the first visit of the LEAD study, aged 25–82 years and with complete data for the calculation of the Fried frailty phenotype were included in the cross-sectional analysis. Handgrip strength was the most frequently missing variable and the main reason for exclusion. Among the included participants, 3664 (62.3 %) were robust, 2130 (36.2 %), were prefrail, and 91 (1.5 %) categorised as frail. The characteristics of the included participants according to their frailty status (robust vs. prefrail/frail) are presented in Table 1.

Among the participants included in the cross-sectional analysis, 2321 did not attend the follow-up visit, of whom six died. Of these, 1311 (56.5 %) were robust, 954 (41.1 %) were prefrail, and 56 (2.4 %) were frail. The distribution of characteristics in this subgroup (robust vs. prefrail/frail) was comparable to that of the full cross-sectional sample (Supplemental Table S2). Therefore, 3564 participants who completed both the first and second visits (mean $\pm$ SD assessment interval: 4.1 $\pm$ 0.5 years) were included in the longitudinal analysis.

3.1. Association of ALS with frailty status (cross-sectional analysis)

Controlling for the effects of age, sex, smoking status, educational level, income level and living area, ALS at visit 1 showed a significant

Table 1
Characteristics of robust, prefrail/frail participants at visit 1.

	Robust (n = 3664)	Prefrail/frail (n = 2221)	P-value
Age (years, mean±SD)	47.0 ± 14.7	48.2 ± 15.9	0.004
Age categories			
25–40	1390 (62.2 %)	844 (37.8 %)	<0.001
40–60	1495 (65.9 %)	773 (34.1 %)	
≥60	815 (57.4 %)	604 (42.6 %)	
Gender (female, n (%))	1865 (50.9 %)	1212 (54.6 %)	0.006
BMI (kg/m^{2,} mean±SD)	25.7 ± 4.6	26.5 ± 5.2	<0.001
SF_12_Q10(exhaustion, median (Q1-Q3))	4 [3–4]	2 [1–2]	<0.001
SF_12 (PCS, median (Q1-Q3))	54.78 (51.48–55.92)	51.93 (44.74–54.78)	<0.001
Weight loss (≥5 kg, (n (%))	0 (0 %)	147 (6.6 %)	<0.001
Handgrip strength (Kg, mean±SD)	39.8 ± 12.6	36.7 ± 13.0	<0.001
HADS-D_Q4 (slowness, median (Q1-Q3))	1 (0–1)	1 [1–2]	<0.001
HADS-D Sum score (median (Q1-Q3))	2 [1–3]	4 [2–7]	<0.001
Living area (rural, n (%))	754 (20.6 %)	308 (13.9 %)	<0.001
Smoking status (ever smoker, n (%))	1994 (54.4 %)	1248 (56.2 %)	0.19
Education (Low, n (%))	940 (25.7 %)	750 (33.8 %)	<0.001
Income (Low, n (%))	307 (10.4 %)	325 (18.4 %)	<0.001
Allostatic load score (mean±SD)	3.2 ± 2.5	4.0 ± 2.8	<0.001

Note: SD: Standard deviation; Q1: First quartile; Q3: Third quartile; BMI: Body mass index; SF12: Short-form 12; Q10: Question number 10; PCS: Physical component score; HADS: Hospital anxiety depression scale; Q4: Question number 4.

association with risk of being prefrail/frail (OR= 1.11; 95 %CI: 1.08-1.15) at the same visit. Furthermore, female participants and those with low education or low income have a significantly higher risk of being prefrail/frail. In contrast, participants living in rural areas have a lower risk of being prefrail or frail (Fig.1).

Mediation analysis showed that depressive symptoms, assessed by the HADS-D, partially mediated the association between ALS and frailty status. The OR (95 % CI) for the direct, indirect, and total effect were 1.015 (1.010–1.020), 1.007 (1.005–1.01), and 1.023 (1.018–1.028), respectively. The proportion of the effect of ALS on frailty which is mediated via depression was 35 % (95 %CI: 25–47 %). Sensitivity analysis using the modified depression scale (HADS-D excluding item 4) yielded similar results, with depression still significantly mediating the ALS–frailty association ($p < 0.001$). In this model, 24 % of the ALS effect on frailty was mediated via depression (95 % CI: 15–35 %).

3.2. Longitudinal analysis

3.2.1. Transition pattern of frailty status

Among the 3564 participants who participated in both visits and included in the longitudinal analysis, 2353 (66.0 %) were classified as robust, 1176 (33.0 %) as prefrail, and 35 (1.0 %) as frail at visit 1. Transition pattern of frailty status from visit 1 to visit 2 is shown in Fig. 2. In visit 2, 581 (16.3 %) participants had deteriorated from robust to prefrail/frail or from prefrail to frail, and 631 (17.7 %) participants improved from prefrail/frail to robust/prefrail.

3.2.2. Association of ALS at visit 1 on development of frailty

Controlling for the effects of age, sex, smoking status, educational level, Income level and living area, ALS at visit 1 showed a significant association with risk of transitioning from robust to prefrail/frail status at visit 2 (relative risk ratio (RRR)= 1.06; 95 %CI: 1.02–1.09; Fig. 3).

Mediation analysis revealed that depressive symptoms, assessed using the HADS-D, partially mediated the association between ALS and the development of prefrail or frail status. The relative risk ratios (RRR) with 95 % confidence intervals (CI) for the direct, indirect, and total effects were 1.002 (1.001–1.002), 1.010 (1.003–1.020), and 1.012 (1.005–1.020), respectively. Overall, 17 % of the effect of ALS on frailty was mediated through depressive symptoms (95 % CI: 6.6–43 %). Sensitivity analysis using the modified depression scale (HADS-D excluding item 4) showed comparable results, with 13 % (95 % CI: 4.0–38 %) of the ALS effect on frailty mediated via depression.

3.3. Subgroup analysis

In participants aged ≥ 60 years, the results of the cross-sectional analysis were consistent with those observed in the overall cohort. ALS at visit 1 showed a significant association with the risk of being prefrail/frail at the same visit (OR = 1.15; 95 % CI: 1.09–1.21; Supplemental Fig. S1). Mediation analysis indicated that depressive symptoms, assessed using the HADS-D (24 % [95 %CI: 12–39 %]) and the

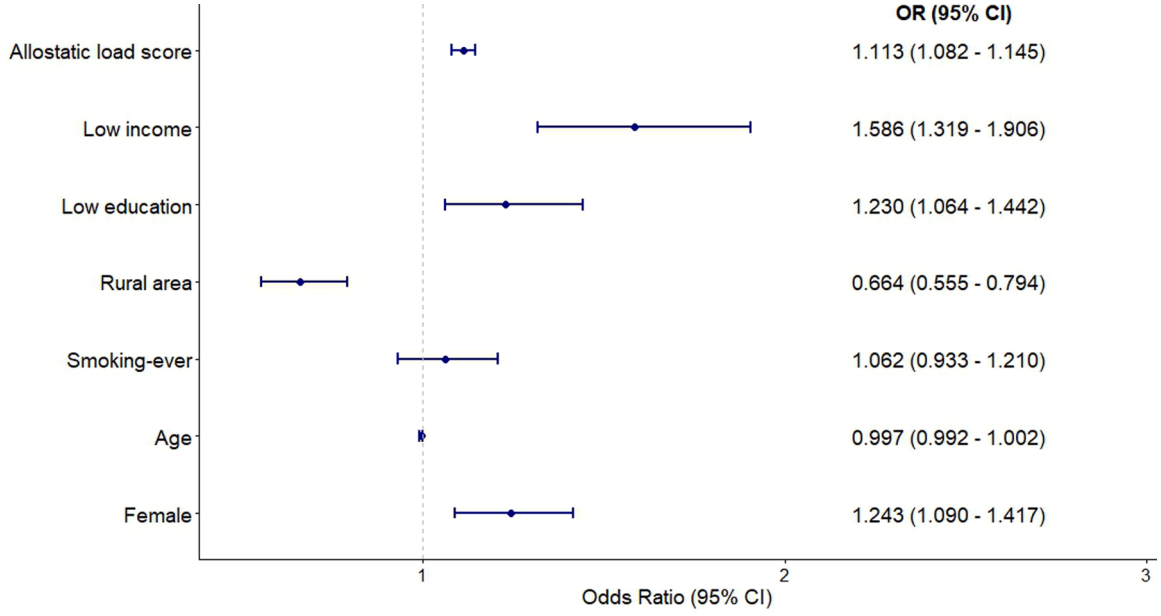

Fig. 1. Forest plot showing the association of ALS and sociodemographic characteristics at visit 1 and risk of being prefrail/frail at the same visit.

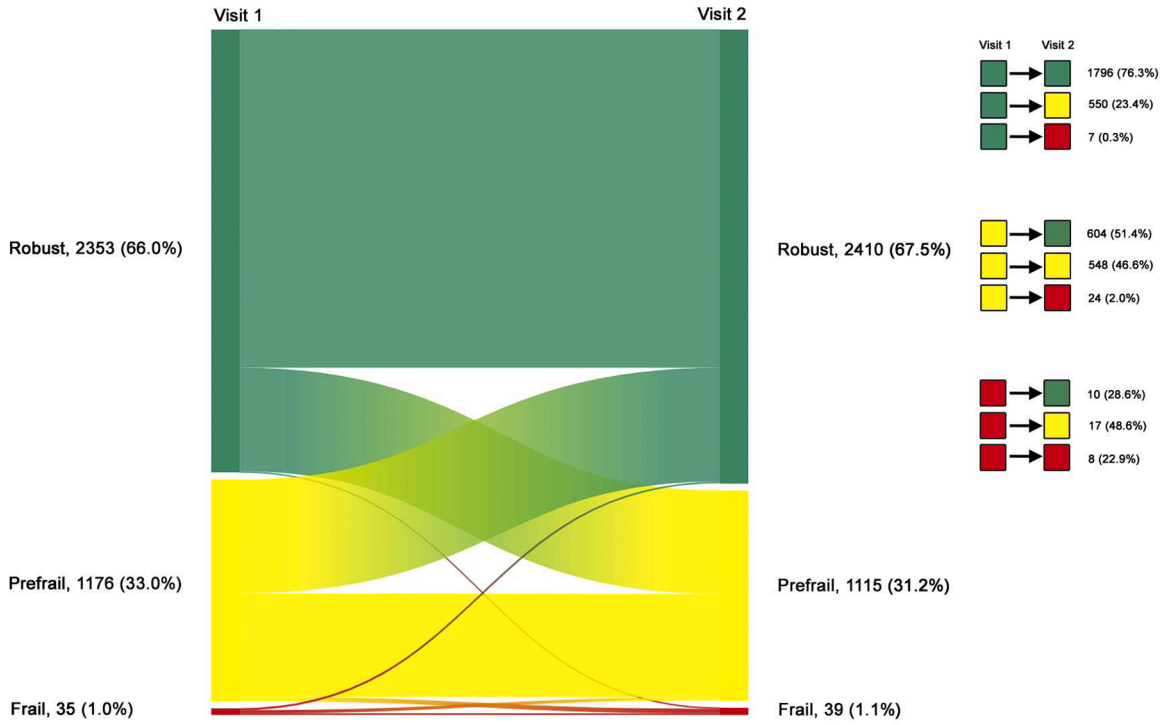

Fig. 2. Alluvial plot showing the transition pattern of frailty status from visit 1 to visit 2.

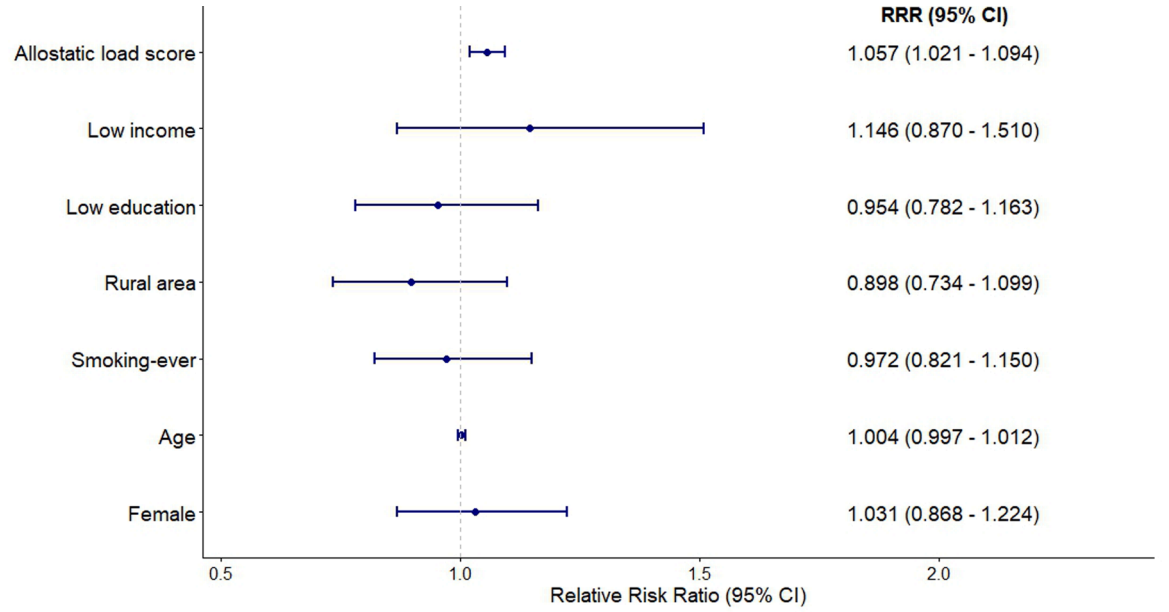

Fig. 3. Forest plot showing the association of ALS and sociodemographic characteristics at visit 1 and risk of transitioning from robust to prefrail/frail status at visit 2.

HADS-D excluding item 4 (15 % [95 %CI: 7–28 %]), partially mediated the association between ALS and frailty status.

Regarding the longitudinal analysis, ALS at visit 1 was significantly associated with the risk of transitioning from robust to prefrail/frail status (RRR = 1.08; 95 % CI: 1.02–1.15; Supplemental Fig. S2). However, mediation analysis revealed that depressive symptoms, assessed with the HADS-D (10 % [95 %CI: −3–29 %]) and the HADS-D excluding item 4 (6 % [95 %CI: −4–28 %]), did not significantly mediate the association between ALS and the development of prefrail/frail status.

4. Discussion

In this cohort of adults aged 25–82 years, 62.3 % were robust, 36.2 % prefrail, and 1.5 % frail at baseline. Low income and low education were associated with baseline frailty. Frailty trajectories were dynamic, with 16.3 % worsening and 17.7 % improving over time. Notably, 17 % of the effect of allostatic load (AL) on frailty trajectories was mediated by depression, an effect that was no longer observed in adults over 60 years, suggesting that depression represents an early and potentially modifiable pathway to frailty in midlife.

Prevalence of frailty in our cohort was lower than in other studies [27], likely reflecting the inclusion of younger adults from age 25. Contrary to common perceptions, frailty is increasingly recognized in younger and middle-aged adults [28]. For example, in community-based cohorts aged 50–65 years, pre-frailty prevalence ranged from 22 % to 66.8 %, with 2–5 % classified as frail [29]. In very young adults, large cross-sectional analyses indicate that approximately 10 % of individuals aged ≤55 exhibit frailty [28]. Risk factors differ by age: younger frail adults exhibit poorer mental well-being and altered immunological profiles, whereas older frail adults are more affected by cardiometabolic, cancer-related, musculoskeletal, and sensory impairments. In younger adults, elevated AL predicts poorer physical performance in men and differential psychological outcomes in women [30]. Our data further suggests that the mediating effect of depression on the development of frailty is more pronounced during the first half of the lifespan.

AL has been associated with frailty in some cohorts, such as the US MacArthur Study of Successful Aging [31] but not consistently [9], suggesting additional factors—including mental health, income, or social environment—modulate its impact. In our longitudinal analyses, depressive symptoms mediated approximately 17 % of the effect of AL on frailty trajectories. Depression and AL share common underlying mechanisms, particularly chronic physiological and psychological stress [32]. In depression, negative cognitive schemas impair executive control and goal-directed behavior interacting with physiological stress systems [32]. AL may induce dysregulation of primary stress mediators (e.g., HPA axis, cortisol, norepinephrine) and inflammatory markers, reflecting physiological adaptation of the body to chronic stress. Conversely, chronic stress itself constitutes an etiological risk factor for neuroinflammation and depression potentially sustaining depressive symptoms over time ([33,34]). A possible interplay between AL and depression is suggested by longitudinal evidence, showing that AL was associated with depression within the same year, but the effect attenuated over three years and, with age emerging the only significant predictor of depressive symptoms over six years [35].

Depression has been linked to both cognitive frailty [19] and also physical frailty [36] in older adults emphasizing its potential role in mediating the translation of cumulative physiological stress into longitudinal frailty trajectories. The mediating role of depression is particularly relevant because AL accumulates over the life course through largely non-modifiable exposures, while depressive symptoms can be targeted via various pharmacological and non-pharmacological interventions [37–39]. Psychosocial determinants such as loneliness, social isolation, and low social support exacerbate depressive symptoms and may amplify physiological stress, accelerating frailty and even mortality [40]. Although depression was associated with frailty also in the subgroup aged >60 years, its effect on the longitudinal course of frailty (frailty trajectories) was no longer evident in this age group. This suggests that depression exerts a stronger influence on the development of frailty in younger and middle-aged individuals, and that the window of opportunity for preventive interventions may therefore be greatest before the age of 60.

This pattern is consistent with prior findings showing that the association between depressive symptoms and frailty tends to weaken with advancing age and is strongest among “young-old” adults [41]. Depression occurring in early or midlife may reflect a more persistent vulnerability within stress-response systems, such as immune, endocrine, or autonomic pathways, which could accelerate physiological decline and increase the long-term risk of developing frailty. Late-life depression may be more reactive to cumulative comorbidities, functional impairments, or social adversity, functioning not only as a potential contributing factor but also as a correlate of frailty in older age. Depressive symptoms emerging in late life also demonstrate a dose-dependent association with frailty, with prevalence increasing alongside the severity of depressive symptoms [42]. Baseline depressive symptoms are conceptualized as a proxy for longer-term psychological vulnerability in our investigation, rather than transient mood state. This assumption underpins their use as a mediator of frailty trajectories over the follow-up period. Importantly, previous longitudinal research supports this strategy: for example, a recent study in a large middle-aged and older cohort found that depressive symptoms assessed at baseline predicted incident frailty over 2–4 years [43].

Addressing depression may help to interrupt the feedback loop between inflammation, neuroendocrine dysregulation, and frailty, potentially improving overall resilience ([44,45]). However, our findings indicate that the mediating effect of depressive symptoms may differ by age, suggesting that other mechanisms—such as comorbidities, chronic inflammation, or social determinants—could play a more prominent role in older subgroups. This underscores the heterogeneity of frailty transitions in later life, which has important clinical implications for individualized assessment and management. Moreover, these findings suggest that interventions targeting depressive symptoms may be particularly relevant in younger adults although longitudinal and experimental studies are needed to confirm such potential effects.

Education was linked to baseline frailty but not to frailty transitions in our cohort, consistent with previous studies showing that while higher education predicts better initial health, it does not strongly influence changes in frailty over time [46]. This may reflect education as a stable, early-life factor that shapes baseline health without necessarily predicting improvements or worsening in frailty status during follow-up. Similarly, older adults with low income show higher odds of frailty, independent of age, comorbidities, or health behaviors ([29,47–49]). These findings suggest that socioeconomic factors may predispose individuals to frailty onset but exert limited influence on its longitudinal course. In our study, these factors did not emerge as relevant modifiable determinants of frailty trajectories, whereas depression was identified as a potentially modifiable factor shaping frailty progression over time.

From a clinical perspective, integrated strategies including screening for depression, reducing social isolation, and enhancing community support may improve functional outcomes and attenuate frailty progression [50]. Importantly, symptoms of frailty and depression may overlap, as fatigue, weight loss, reduced activity, and psychomotor slowing are characteristic of both syndromes, which complicates their differentiation in clinical practice ([51,52]). While some overlap between frailty and depression cannot be excluded in our study, existing evidence indicates that both syndromes frequently co-occur in later life [52]. However, our operationalization of frailty also included grip strength, which provides a more distinct indicator of physical vulnerability. Interventions such as cognitive-behavioral therapy, exercise programs with social components, and community engagement have demonstrated efficacy in reducing depressive symptoms and improving resilience in older adults ([50,53.54]).

Several limitations should be acknowledged. Although the longitudinal design strengthens causal inference, the analyses remain correlational rather than causal, residual confounding cannot be ruled out, and the mediating effect of depression may be influenced by unmeasured variables such as socioeconomic status or medication use. Although the distribution of baseline characteristics among robust and prefrail/frail participants who were lost to follow-up was comparable to that of those who completed both visits, attrition may still have been non-random and may have influenced the longitudinal results. Additionally, since only two waves were available in our cohort, ALS as the exposure and depression as the mediator were both recorded at visit 1. Consequently, our mediation analyses cannot fully establish temporal ordering. Furthermore, depressive symptoms were assessed only at baseline and not repeatedly over the follow-up period; therefore, we cannot determine how depression and frailty may have co-evolved over time or whether dynamic changes in depressive symptoms might have influenced transitions between frailty states. Moreover, depressive symptoms were assessed via self-report measures, which, although validated, are subject to reporting biases. The operationalization of allostatic load included 14 biomarkers covering multiple physiological systems, but it remains possible that relevant biological processes or disease states were

not captured by this selection. Frailty was measured using the Fried phenotype, which primarily reflects physical frailty; nevertheless, the observed associations with depressive symptoms underscore the relevance of psychological factors even within a predominantly physical frailty framework. Finally, due to statistical constraints arising from a small number of frail individuals, prefrail and frail categories were combined. Although this approach increased statistical power, it limited differentiation between early and advanced frailty states. Future studies employing clinical diagnostic interviews and incorporating biomarkers of neuroendocrine and inflammatory activity could provide more nuanced insights into the biopsychosocial pathways linking AL, depression, and frailty.

Funding

The Austrian LEAD Study is financially unrestrictedly supported by Ludwig Boltzmann Gesellschaft, Sigmund Freud Private University Faculty of Medicine, Vienna Healthcare Group, the Lower Austrian Health and Social Fund, AstraZeneca, Chiesi Farmaceutics, GlaxoSmithKline, and Menarini Pharma. These funding bodies have no role in the writing of this manuscript or the decision to submit for publication. The authors have not been paid to write this article by a pharmaceutical company or any other agency.

Declaration of generative AI and AI-assisted technologies in the writing process

ChatGPT-4.0 were used during manuscript preparation to support translation and improve linguistic clarity. The authors carefully reviewed and edited the output to ensure accuracy and scientific integrity, and take full responsibility for the content of the submitted manuscript.

Data availability

The datasets used and/or analysed for the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Mohammad Azizzadeh: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Agnes Pirker-Kees:** Writing – review & editing, Writing – original draft, Conceptualization. **Emiel F.M. Wouters:** Writing – review & editing, Supervision. **Daisy J.A. Janssen:** Writing – review & editing, Supervision. **Bart Spaetgens:** Writing – review & editing, Supervision. **Robab Breyer-Kohansal:** Writing – review & editing, Supervision, Resources, Project administration. **Marie-Kathrin Breyer:** Writing – review & editing, Supervision, Resources, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors express their gratitude to all participants for their valuable contribution to advancing medical science through the LEAD study. Special appreciation is extended to the entire LEAD study team for their dedicated daily efforts in ensuring the highest quality of data collection.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjfa.2026.100132.

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