

Social network and ikigai are interconnected pathways to frailty, with physical activity as an independent parallel input, among community-dwelling older Japanese adults in the Kyotango longevity area

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Abstract

The Kyotango Declaration of Healthy Aging formulated at the First World Longevity Summit proposes four interconnected pillars as the foundation of healthy longevity: dietary diversity, life-long physical activity (PA), strong social ties, and ikigai. Nonetheless, the mutual quantitative relationships among these pillars have not yet been formally investigated. This cross-sectional study aimed to quantify pathways linking the Lubben Social Network Scale-6, an ikigai composite (WHO-5 well-being + life-satisfaction score), and total PA to the Mitnitski–Rockwood frailty index in 751 community-dwelling older adults (mean age: 72.9 ± 5.8 years; women, 59.4%) from the Kyotango Multipurpose Cohort. In a serial-mediation model, the indirect pathway through ikigai alone accounted for 95.3% of the total indirect effect ($\beta = -0.00845$, 95% bootstrap confidence interval: $[-0.01101, -0.00610]$), whereas the *a priori* three-step serial chain was statistically null ($\beta = -0.00005$ $[-0.00023, +0.00008]$). PA operated as an independent parallel pathway ($\beta = -0.006$, $p = 0.002$), uncoupled from ikigai ($d = +0.025$, $p = 0.485$). Findings were robust across four prespecified versions of the frailty index and remained unchanged after adjustment for dietary fiber intake, indicating independence from the diet–microbiota pathway previously reported in the same cohort. Integrating these results with our previously reported paradoxical observation of significantly higher plasma interleukin (IL)-6 concentrations in non-frail individuals than in frail participants from the same cohort and with the recent Kashiwa cohort finding of increased plasma IL-6 concentrations in ikigai-positive women who did not develop frailty, we propose a unified interpretation in which IL-6 acts as a muscle-derived exerkine rather than a canonical inflammaging marker and may constitute a biological signature of successful aging in this population. These findings, along with the results of our concurrent food–microbiota–frailty analysis, provide the first quantitative empirical support for a parallel-pillar architecture of healthy longevity and highlight ikigai as a substantive, biologically plausible, and intervenable mediator of frailty prevention.

Introduction

Population aging represents a defining global demographic transition in the twenty-first century. In Japan, nearly 30% of the population is aged ≥ 65 years¹. Consequently, the imperative is no longer to extend lifespan but to compress the gap between lifespan and healthspan. Frailty, defined as a state of decreased physiological reserve and increased vulnerability to stressors, can predict falls, hospitalization, disability, and mortality and is now recognized as a central operational endpoint of healthspan science². Two operational frameworks dominate the field: the physical phenotype defined by Fried et al.³ and the deficit-accumulation model proposed by Rockwood et al.⁴, which expresses frailty as the proportion of accumulated age-related deficits and provides a continuous risk gradient that complements categorical phenotyping. Building on this framework, Searle et al.⁵ subsequently formulated a standard procedure for constructing the frailty index (FI) in individual studies. Owing to the multifactorial nature of frailty, identifying modifiable upstream social, psychological, behavioral, and nutritional determinants has become a priority for preventive geriatrics.

In November 2025, the First World Longevity Summit was convened in Kyotango, Japan, and produced the Kyotango Declaration of Healthy Aging⁶, which proposes four interconnected pillars as the pragmatic foundation of healthy longevity in a designated longevity area: dietary diversity, life-long physical activity (PA), strong social ties, and ikigai (a Japanese concept broadly translated as “a sense of life worth living”). Independent supporting evidence has been accumulated for each pillar: dietary patterns and gut microbiota jointly stratify frailty in the Kyotango cohort⁷; the Lubben Social Network Scale-6 (LSNS-6)⁸ and comparable social engagement measures predict incident frailty in Japanese⁹ and Western¹⁰ cohorts; ikigai and purpose in life are associated with reduced all-cause and cardiovascular mortality in the Ohsaki study¹¹, with reduced dementia and functional disability in the JAGES cohort¹² and with a substantially lower 5-year incidence of frailty among Japanese women in the Kashiwa cohort (adjusted hazard ratio [aHR]: 0.24, 95% confidence interval [CI]: 0.08–0.73), a protection accompanied by a paradoxical increase in plasma interleukin (IL)-6 levels that the authors interpreted as evidence of muscle-derived exerkine action¹³; and PA indexed by domain-specific metabolic equivalents¹⁴ remains a well-established protective factor against frailty in older Japanese adults¹⁵. Nonetheless, whether the three nondietary pillars operate independently, jointly, or sequentially through a common causal chain has not been quantitatively investigated in a single cohort.

The Kyotango region, a coastal area with more than 200 centenarians per 100,000 residents in northern Kyoto Prefecture, has been the setting of our group’s ongoing efforts to characterize the biological and environmental correlates of healthy longevity. Our previous work revealed an enrichment of butyrate-producing gut microbial taxa in older Kyotango residents compared with urban Kyoto residents¹⁶; a graded relationship among nutrient intake, gut microbial composition, and frailty in the Kyotango Multipurpose Cohort¹⁷; and a joint stratification of frailty by dietary patterns and gut microbial clusters in a companion cross-sectional analysis of 785 Kyotango residents, with partial mediation of the fiber–frailty association through a butyrate-producer-rich microbial axis⁷. In the Kyotango Multipurpose Cohort, plasma IL-6 levels were significantly higher in non-frail individuals than in frail participants (2.1 ± 5.2 vs. 1.9 ± 1.5 pg/mL, $p < 0.001$) even as high-sensitivity C-reactive protein (hs-CRP) followed the conventional inflammaging direction (higher in the frail group, $p < 0.05$)¹⁷, an observation that could not be adequately explained under the classical inflammaging framework at that time. The Kashiwa cohort finding of ikigai-associated increase in IL-6 levels among women who resisted frailty¹³ now provides a coherent biological framework for reinterpreting our earlier Kyotango observation.

Building on the Kyotango research program and complementing our concurrent food–microbiota–frailty analysis⁷, the present study aimed to investigate the pathways linking social network, ikigai, and PA to the FI in 786 community-dwelling Kyotango residents. A serial-mediation hypothesis was prespecified as “LSNS-6 → ikigai → PA → FI” based on conventional intuition that social ties promote ikigai, which motivates PA, which in turn prevents frailty. Prespecified sex-stratified analyses were further conducted because a striking female-specific protective effect of ikigai on incident frailty was observed in the recent Kashiwa study¹³. Four versions of the FI (namely, FI-32, FI-29, FI-26, and FI-23) were prespecified

to address the potential circular relationship between FI items and psychosocial exposures. For the present study, three objectives were prespecified: (i) to explore whether the ikigai-mediated pathway or three-step serial chain accounts for the greater share of the LSNS-6 → frailty association in simple- and serial-mediation models; (ii) to investigate whether the findings are robust across the four prespecified FI versions and after adjustment for dietary fiber intake, establishing independence from the previously reported diet–microbiota pathway⁷; and (iii) to characterize sex differences in the mediation architecture, extending the Kashiwa findings¹³ to a longevity-area cohort.

Results

Participant characteristics

A total of 786 participants from the Kyotango Multipurpose Cohort were recruited from June 2017 to March 2020. Following the exclusion of 35 (4.5%) individuals with one or more missing primary variables (LSNS-6 [$n = 23$], ikigai composite [$n = 5$], log(total PA) [$n = 2$], and covariates [$n = 5$]), 751 participants (95.5%) were included in the final analytic sample (Supplementary Fig. 1). The 786 vs. 785 difference from our companion food–microbiota analysis⁷ reflected an alternative exclusion path centered on complete psychosocial and PA data rather than on complete dietary-questionnaire data. The mean age was 72.9 ± 5.8 (range: 65–96) years, with women accounting for 59.4% ($n = 446$). The mean LSNS-6 total score was 18.3 ± 5.9 , with 100 (13.3%) participants meeting the criterion for social isolation (< 12). The ikigai composite was 63.5 ± 16.4 , with 417 (55.5%) participants self-reporting ikigai on the single-item binary measure. The mean FI-29 score was 0.136 ± 0.077 , with 109 (14.5%) participants being classified as frail (FI-29 score ≥ 0.21). The characteristics of participants stratified by self-reported ikigai are summarized in Table 1.

[Insert Table 1 (Participant characteristics stratified by ikigai) approximately here]

Participants reporting ikigai showed a substantially higher LSNS-6 score (19.4 vs. 16.8, $p < 0.001$), lower prevalence of social isolation (8.6% vs. 19.2%, $p < 0.001$), 47% higher sport-related PA (10.9 vs. 7.4 MET-h/week, $p = 0.002$), lower sedentary time (35.1 vs. 40.0 h/week, $p = 0.010$), higher dietary fiber intake (7.4 vs. 6.9 g/1,000 kcal, $p = 0.004$), lower FI-29 score (0.124 vs. 0.151, $p < 0.001$), and approximately half the prevalence of frailty (9.6% vs. 20.7%, $p < 0.001$). Total PA did not differ between the groups (155.9 vs. 157.7 MET-h/week, $p = 0.84$), indicating the dominance of occupational activity in this rural cohort—a pattern-level nuance that we return to below.

Bivariate associations among the primary variables

Pearson correlation analysis among the four primary variables (Supplementary Table 1) revealed a coherent pattern: LSNS-6 was moderately correlated with the ikigai composite ($r = +0.32$, $p < 0.001$),

weakly correlated with log(total PA) ($r = +0.09, p = 0.012$), and inversely correlated with FI-29 ($r = -0.18, p < 0.001$). The ikigai composite exhibited the strongest inverse correlation with FI-29 ($r = -0.41, p < 0.001$, visualized in Fig. 1) but only showed a weak and nonsignificant association with log(total PA) ($r = +0.06, p = 0.13$). Log(total PA) was inversely correlated with FI-29 ($r = -0.234, p < 0.001$). These patterns confirmed that each of the three exposures was independently associated with frailty (Supplementary Fig. 2). Furthermore, the negligible ikigai-PA correlation pre-shadowed that PA may not lie on a serial causal pathway between ikigai and frailty.

[Insert Fig. (IKIGAI composite × FI-29 scatter with regression line) approximately here]

Simple mediation: PA does not explain the ikigai-frailty link

In the simple-mediation model with the ikigai composite as X, log(total PA) as M, and FI-29 as Y (Fig. 2), the *a*-path (ikigai → PA) was weak and nonsignificant (standardized $\beta = +0.053, p = 0.115$), whereas the *b*-path (PA → FI-29 adjusted for ikigai) was significant ($\beta = -0.007, p = 0.01$). Ikigai exerted a substantial direct effect on FI-29 ($c' = -0.029, p < 0.001$). The bootstrap-estimated indirect effect $a \times b$ was -0.00028 (95% CI: $[-0.00102, +0.00001]$), accounting for only 1.0% of the total effect ($c = -0.030$). Thus, PA did not significantly mediate the ikigai-frailty association, motivating an expanded serial-mediation framework anchored by social network.

[Insert Fig. 2 (Simple mediation diagram: IKIGAI → PA → FI-29) approximately here]

Serial mediation: LSNS-6 → ikigai → PA → FI

In the serial-mediation model with LSNS-6 as X, ikigai composite as M_1 , log(total PA) as M_2 , and FI-29 as Y (Fig. 3 and Table 2), the upper-pathway coefficients were strong, with $a_1 = +0.301 (p < 0.001)$ for LSNS-6 → ikigai and $b_1 = -0.028 (p < 0.001)$ for ikigai → FI-29. The lower-pathway PA effect was smaller but significant ($b_2 = -0.006, p = 0.002$). Both the ikigai → PA link ($d = +0.025, p = 0.485$) and LSNS-6 → PA link ($a_2 = +0.061, p = 0.091$) were nonsignificant. The small residual direct effect of LSNS-6 on FI-29 remained after accounting for all mediators ($c' = -0.0040, p = 0.049$).

Decomposition of the total indirect effect into three component pathways (Table 2) showed that the indirect effect through ikigai alone (ind1: LSNS-6 → ikigai → FI-29) dominated (-0.00845 , 95% CI: $[-0.01101, -0.00610]$), accounting for 95.3% of the total indirect effect. The indirect effect through PA alone (ind2: LSNS-6 → PA → FI-29) was small and nonsignificant (-0.00038 , 95% CI: $[-0.00137, +0.00008]$). The full three-step serial pathway (ind3: LSNS-6 → ikigai → PA → FI-29) was essentially zero

(-0.00005 , 95% CI: [-0.00023 , $+0.00008$]), refuting the *a priori* hypothesis of a true serial causal chain. The total indirect effect was -0.00887 (95% CI: [-0.01170 , -0.00636]), representing 69.1% of the total LSNS-6 score $\rightarrow$ FI-29 effect ($c = -0.0128$, $p < 0.001$).

[Insert Fig. 3 (Serial mediation diagram: LSNS-6 $\rightarrow$ IKIGAI $\rightarrow$ PA $\rightarrow$ FI-29 with path coefficients) approximately here]

[Insert Table 2 (Bootstrap decomposition of indirect effects: ind1, ind2, ind3) approximately here]

Sensitivity to FI composition

The ikigai-mediated pathway (ind1) remained dominant across all four FI versions (Fig. 4), with point estimates ranging from -0.00412 (FI-23) to -0.00903 (FI-32). The three-step serial pathway (ind3) was statistically null across all FI versions, with point estimates ranging from -0.00005 to -0.00007 . In all four versions, the total indirect effect remained significant (95% CI excluding zero), with proportion-mediated values of 65.2% for FI-32, 69.1% for FI-29, 59.6% for FI-26, and 54.7% for FI-23. These results indicated that the principal findings were not driven by item overlap between FI and psychosocial exposures.

[Insert Fig. 4 (Sensitivity to FI composition across 4 pre-specified versions) approximately here]

Independence from the diet–microbiota pathway and additional sensitivity analyses

Four additional prespecified sensitivity analyses were conducted to confirm robustness. First, the dominant ind1 pathway remained essentially unchanged (from -0.00845 to -0.00839 , 95% CI: [-0.01094 , -0.00599]) after further adjustment for dietary fiber intake (per 1,000 kcal), which was the key exposure in our companion food–microbiota analysis in the same cohort⁷. The total indirect effect changed from -0.00887 to -0.00881 , with the proportion mediating 69.1–68.8% (Supplementary Table 2). These results indicated that the psychosocial mediation pathway operated statistically independently of the diet–microbiota pathway, supporting a parallel-pillar architecture across the two pathways. Second, sex-stratified analyses revealed that the dominant ind1 pathway was preserved across sexes but was substantially stronger in men (ind1 = -0.00988 [-0.01413 , -0.00622], proportion mediated: 79.3%) than in women (ind1 = -0.00768 [-0.01076 , -0.00510], proportion mediated: 62.7%) (Supplementary Table 3). Additionally, the residual direct effect c' was fundamentally zero in men ($p = 0.77$) but was significant in women ($p = 0.040$). Third, age-stratified analyses revealed that ind1 was dominant across strata (Supplementary Table 4). Fourth, replacing the ikigai composite with the single-item binary ikigai measure, which was the operationalization applied in the Ohsaki¹¹, JAGES¹², and

Kashiwa¹³ cohorts, reproduced the qualitative pattern (ind1, dominant; ind3, null) with attenuated magnitude (proportion mediated: 21.3%), consistent with information loss from dichotomization (Supplementary Table 5).

Discussion

This study involving 751 community-dwelling older adults from the Kyotango longevity area yielded three principal findings that refine the conceptual map linking social engagement, psychological purpose, and PA to frailty. First, in the simple-mediation model, only 1.2% of the ikigai–frailty association was attributable to PA, refuting the conventional assumption that ikigai protects against frailty primarily via movement promotion. Second, in the serial-mediation model anchored by social network, the indirect pathway through ikigai alone was dominant at 95.3% of the total indirect effect, whereas the three-step serial chain hypothesized *a priori* was statistically null. Third, PA was a significant and independent protective factor against frailty but operated as a parallel pathway uncoupled from ikigai in this rural cohort. All three findings were robust across four pre-specified FI versions— constructed following the Rockwood-Mitnitski deficit-accumulation framework⁴ via the Searle standard procedure⁵ with three question-tailored modifications— and remained essentially unchanged after adjustment for dietary fiber intake, indicating statistical independence between the psychosocial and dietary–microbial pathways.

Our findings extend a rapidly growing evidence base regarding ikigai and healthy longevity

The Ohsaki study by Sone et al.¹¹ showed that self-reported ikigai was associated with reduced 7-year all-cause and cardiovascular mortality among 43,391 Japanese adults. The JAGES longitudinal outcome-wide analysis conducted by Okuzono et al.¹² revealed that ikigai was associated with 31% and 36% lower risks of incident functional disability and dementia, respectively, over 3 years. Alimujiang et al.¹⁸ reported that a strong sense of purpose in life was associated with reduced all-cause and cardiovascular mortality among US adults. Meta-analytic evidence across ten prospective studies further supports the association with reduced mortality¹⁹. A more recent Kashiwa cohort finding ($n = 832$) by Son et al.¹³, which is the most relevant to the present analysis, indicated that ikigai was associated with a 76% decrease in the incidence of Fried-phenotype frailty over 5 years among women (aHR: 0.24, 95% CI: 0.08–0.73). Our cross-sectional analysis complements this longitudinal finding by identifying the upstream pathway that produces the protective ikigai signal: strong social networks appear to sustain ikigai ($a_1 = +0.301, p < 0.001$), which in turn protects against frailty ($b_1 = -0.028, p < 0.001$).

An unexpected sex-modulation pattern

The present analysis both replicates and refines the emerging sex-specific structure of the ikigai–frailty relationship. Son et al.¹³ reported the existence of the total (unmediated) protective association between ikigai and new-onset frailty in women; however, such an association was not statistically significant in men. Our sex-stratified serial-mediation analysis revealed a complementary but distinct pattern: the

ikigai-mediated pathway was present in both sexes; however, its architecture differed. In men, the absolute magnitude of ind1 was larger (-0.00988 vs. -0.00768), ind1 accounted for a greater share of the total effect (79.3% vs. 62.7%), and the residual direct effect c' was essentially zero ($p = 0.77$). In women, the significant direct effect of social network on frailty remained after full mediation adjustment ($c' = -0.005$, $p = 0.040$). One interpretation is that the social ties of men in this rural longevity cohort protect against frailty almost entirely through their psychological function (sustaining ikigai), whereas the social ties of women additionally protect against frailty through pathways not captured by our mediator set. The apparent divergence with the Kashiwa cohort finding¹², which indicated stronger total ikigai–frailty association in women, reflects the distinction between the total protective effect of ikigai (which the Kashiwa longitudinal design quantifies) and the proportion of the LSNS → frailty pathway mediated by ikigai (which our serial-mediation design quantifies). Both interpretations are compatible with a broader picture in which ikigai carries a substantial biological weight among older Japanese adults, but with different architectural roles by sex.

Biological mechanisms: an integrated re-interpretation of IL-6 as a muscle-derived exerkinase across Kyotango and Kashiwa cohorts

Neuroendocrine, autonomic and inflammatory pathways

The protective effect of ikigai on frailty appears to be biologically plausible. Sustained purpose in life is associated with diminished hypothalamic–pituitary–adrenal (HPA) axis reactivity, lower diurnal cortisol slopes, and reduced allostatic load²⁰; lower circulating IL-6, CRP, and tumor necrosis factor- α levels²¹; and greater heart rate variability and reduced sympathetic tone²²—pathways that could plausibly slow the deficit-accumulation process indexed by the FI without measurable changes in volitional PA.

A paradoxical IL-6 signature: from the Kyotango 2024 observation to the Kashiwa 2025 interpretation

A particularly striking convergence emerges when the present psychosocial findings are read alongside two prior blood-biomarker observations from independent Japanese cohorts. In our earlier cross-sectional analysis of the same Kyotango Multipurpose Cohort¹⁷, plasma IL-6 was, unexpectedly and against the classical inflammaging framework, significantly higher in the non-frail ($n = 667$; 2.1 ± 5.2 pg/mL) than in the frail participants ($n = 119$; 1.9 ± 1.5 pg/mL, $p < 0.001$), even as hs-CRP followed the conventional inflammaging pattern in the same subjects (higher in the frail group: 0.10 ± 0.11 vs. 0.08 ± 0.15 mg/dl, $p < 0.05$). At the time of that report, the IL-6 finding was cautiously interpreted as measurement noise (large SD in the non-frail group) and no biological mechanism was proposed. The Kashiwa cohort study by Son et al.¹³ has since documented a strikingly parallel observation: in 5-year longitudinal follow-up, women with ikigai who did not develop frailty had significantly higher baseline plasma IL-6 concentrations than women without ikigai who did develop frailty. Based on the muscle-secretory-organ framework of Pedersen²³—in which contracting skeletal muscle releases IL-6 as an

exerkine with paracrine and autocrine anti-inflammatory actions—the Kashiwa authors proposed that IL-6 in that context reflects muscle-derived exerkine activity rather than canonical inflammaging.

A unified interpretation: IL-6 as a biological signature of successful aging

Collectively, the two independent observations in the two independent Japanese cohorts—namely, the paradoxically increased IL-6 levels in Kyotango non-frail participants¹⁷ and the paradoxically increased IL-6 levels in Kashiwa ikigai-positive frailty-resistant women¹³—converge on a coherent biological hypothesis: in older Japanese adults, non-frail individuals (in Kyotango) and ikigai holders who resist frailty (in Kashiwa) may share a common biological substrate in which preserved skeletal-muscle activity produces IL-6 as an exerkine with anti-inflammatory rather than pro-inflammatory action²³. Under this framework, circulating IL-6 in older adults should not be treated as a unitary inflammaging marker but decomposed by biological source and signaling context: hepatocyte-derived IL-6 downstream of chronic systemic inflammation (represented by hs-CRP) would track the classical inflammaging axis and be increased in frailty, whereas skeletal-muscle-derived exerkine IL-6 would reflect preserved musculoskeletal activity and be increased in successful aging²³. Recent conceptual work on the anti-inflammatory versus pro-inflammatory duality of IL-6—determined by inductive signals, source cell type, receptor context (classical versus trans-signaling), and downstream activation/inhibition ratios²⁴—provides a mechanistic framework in which these two apparently contradictory patterns can coexist in the same blood measurement.

Integration with the present psychosocial pathway

The IL-6 exerkine hypothesis integrates directly with the psychosocial architecture reported here. Ikigai-positive participants in the present analysis showed 47% higher sport-related PA than ikigai-negative participants (10.9 vs. 7.4 MET-h/week, $p = 0.002$; Table 1) despite essentially identical total PA, indicating that ikigai selectively drives volitional muscle-contracting exercise rather than structural occupational activity. Volitional muscle contraction is precisely the physiological context in which skeletal muscle releases IL-6 as an exerkine²³. Together with the direct neuroendocrine, autonomic and inflammatory pathways described above, we therefore propose a two-route mechanism by which ikigai may protect against frailty: (i) direct psychoneuroimmunological modulation of the deficit-accumulation process (HPA axis, autonomic tone, systemic inflammatory tone) and (ii) motivation of volitional sport activity that generates muscle-derived exerkine IL-6, sustaining anti-inflammatory tone and musculoskeletal integrity. This two-route model is compatible with both our finding that PA operated as an independent parallel pathway in the serial-mediation architecture (because the biological consequence of exercise operates through IL-6 signaling rather than through additional psychological uplift) and the Kashiwa observation that the ikigai-associated increase in IL-6 levels is specifically linked to frailty resistance among women¹³.

Complementary pathways: gut microbiota and SCFA

A fourth complementary biological mechanism deserves mention. Our companion analysis⁷ identified a butyrate-producer-rich microbial axis (Microbe PC2) that partially mediated the fiber–frailty association. Whether ikigai independently shapes the gut microbiota—through sleep, stress-buffering, or lifestyle-driven dietary choices—and whether short-chain fatty acids (SCFA) from butyrate-producing gut microbiota converge on skeletal-muscle IL-6 exerkine signaling represents a promising target for future longitudinal investigation. Direct measurement of muscle-specific IL-6 markers (soluble IL-6 receptor, sIL-6R:gp130 ratio) alongside fecal and plasma SCFA concentrations would allow decomposition of the total IL-6 signal into its exerkine, inflammatory, and gut-microbiota-linked components.

Why PA is an independent parallel pathway in Kyotango

The observation that PA operated as an independent parallel pathway, uncoupled from ikigai in this cohort, warrants further comment. In Kyotango, total PA is dominated by occupational and lifestyle activity (farming, household work, walking), with sport-related activity accounting for only approximately 6% of total MET-h/week. This may explain the striking observation that ikigai-yes and ikigai-no groups had essentially identical total PA (155.9 vs. 157.7 MET-h/week, $p = 0.84$) despite a 47% higher sport-related PA in the ikigai-yes group ($p = 0.002$): ikigai appears to motivate discretionary exercise but not the structural occupational activity that constitutes most movement in this rural setting. In urban Japanese cohorts, where discretionary exercise contributes proportionally more of total activity, the ikigai–PA relationship may be stronger, and the three-step serial pathway may carry more weight—a hypothesis directly testable in urban comparisons such as JAGES¹² and Kashiwa¹³. Under the IL-6-exerkine interpretation, the 47% ikigai-associated increase in sport-related activity may be biologically the most relevant PA component, because volitional muscle contraction—not occupational activity performed at lower intensity—is the physiological context that maximally stimulates muscle-derived IL-6 exerkine release²³.

Empirical validation of the Kyotango Declaration

Together with our companion food–microbiota analysis⁷, the present study provides the first quantitative empirical support for a refined interpretation of the Kyotango Declaration⁶: rather than a linear chain in which the four pillars operate sequentially, the data support a parallel-pillar architecture in which each pillar contributes to frailty resilience through partially overlapping but functionally distinct routes. The independence of the fiber–microbiota pathway from the LSNS-6 → ikigai pathway—established statistically by the essentially unchanged mediation estimates after fiber adjustment—provides a strong methodological anchor for this refined interpretation. Clinically, our findings suggest that frailty-prevention strategies focused exclusively on PA are likely to be incomplete; combined interventions strengthening social networks and psychological purpose alongside diet and activity are likely to yield additive protective effects, consistent with multi-domain-intervention frameworks validated for cognitive decline²⁵. At the community level, the LSNS-6 → ikigai pathway identifies social engagement as an actionable upstream lever for population-level ikigai promotion; community-based interventions such as

kayoi-no-ba (community gathering places), intergenerational programs and locally organized PA, all of which have long been supported in Japan²⁶, now carry mechanistic rationale from the present findings.

Strengths and limitations

The strengths of this study lie in the inclusion of a large community-dwelling Japanese cohort and the performance of data collection supported one-on-one by trained local public health nurses (hokenshi), yielding item-level missingness < 3%. Second, our FI construction rigorously followed the Rockwood-Mitnitski deficit-accumulation framework⁴ via the Searle standard procedure⁵, with three pre-specified Rockwood-style modifications appropriate to the psychosocial research question: (i) four-level ordinal grading of graded deficits, (ii) question-tailored pre-specification of three modified FI versions (FI-29, FI-26, FI-23) to remove item overlap with the psychosocial exposures, and (iii) the ≥ 0.21 clinical threshold recommended by Rockwood and Mitnitski⁴. The consistent direction and magnitude of effects across all four FI versions substantially strengthens causal inference. Third, we used both continuous (WHO-5 well-being + life satisfaction) and binary (single-item) operationalizations of ikigai with congruent qualitative findings. Fourth, bootstrap percentile CIs with nine-covariate adjustment. Fifth, five orthogonal sensitivity analyses that collectively support the robustness of the principal findings. An additional strength emerges from the integration of the present psychosocial pathway analysis with the biomarker observations of our previous cohort report¹⁷ and the independently-conducted Kashiwa study¹³, which together support a coherent IL-6-exerkine interpretation across two independent Japanese longevity/community cohorts.

This study has some limitations. First (and most importantly), the cross-sectional design precludes causal inference. Second, all exposures were self-reported; nevertheless, support from public health nurses markedly mitigated typical concerns regarding recall bias in older participants. Third, the cohort was geographically confined to one Japanese longevity area. Fourth, the ikigai composite combines well-being (WHO-5) and life satisfaction, which are two related but conceptually distinct constructs. Fifth, the small sample in the ≥ 85 -year stratum ($n = 32$) limits stratified inference. Sixth, the observed sex-modulation pattern was based on a single cohort and requires independent replication. Seventh (and directly relevant to the IL-6 interpretation above), IL-6 or other biological mediators in the present dataset were not directly measured; thus, the IL-6 exerkine interpretation should be read as a hypothesis-generating framework that unifies our prior 2024 Kyotango observation¹⁷ with the recent Kashiwa longitudinal finding¹² and awaits direct testing in our ongoing Phase 2 data collection, in which sIL-6R, sIL-6R:gp130 ratios, plasma and fecal SCFA, and accelerometer-derived sport-related PA are planned measurements.

Conclusion

This analysis of 751 community-dwelling older adults from the Kyotango longevity area revealed that social network protected against frailty primarily through ikigai and that PA operated as an independent parallel pathway. Along with the concurrent food–microbiota–frailty analysis in the same cohort⁶ and

the longitudinal ikigai–frailty evidence from Kashiwa¹³, these findings support a parallel-pillar architecture of healthy longevity and identify ikigai as a substantive, biologically plausible, and intervenable mediator of frailty prevention. The convergent IL-6 observations across our Kyotango cohort¹⁷ and the Kashiwa cohort¹³ further suggest that muscle-derived IL-6 exerkine, rather than canonical inflammaging, may constitute a biological signature of successful aging in older Japanese adults—a hypothesis that requires direct biomarker testing in prospective studies. As the global community grapples with rapidly aging populations, the ikigai construct may be an essential and actionable component of healthy-aging science and should be incorporated into cross-cultural cohort consortia and multi-domain intervention trials.

Methods

Study design and participants

A cross-sectional analysis was conducted using data from the Kyotango Multipurpose Cohort Study, which was organized by the Department of Longevity and Community Epidemiology, Kyoto Prefectural University of Medicine, and recruited community-dwelling adults aged ≥ 65 years residing in the Kyotango region in northern Kyoto Prefecture^{16,17}. The Kyotango region consists of two cities and two towns and has a combined population of approximately 100,000; more than 38% of Kyotango residents are aged ≥ 65 years, making Kyotango one of the regions with the highest proportion of centenarians in Japan (> 200 centenarians per 100,000 residents)^{6,16}. The cohort comprised 786 participants who were recruited from June 2017 to March 2020; the recruitment procedures and deficit-accumulation FI have been previously described in detail^{7,17}. For the present analysis, participants with complete data on all primary variables and nine covariates were retained. A total of 751 (95.5%) participants were included in the final analytic sample (Supplementary Fig. 1).

This study was conducted in accordance with the principles embodied in the Declaration of Helsinki and was approved by the Ethics and Conflict-of-Interest Committees of Kyoto Prefectural University of Medicine (approval no. ERB-C-885-4). Written informed consent was obtained from all participants.

Data collection supported by public health nurses

All baseline questionnaires were administered with one-on-one support from trained local public health nurses (hokenshi). Each participant met individually with a nurse for approximately 60–90 min. The nurse explained each item, clarified the terminology, and recorded responses for participants experiencing difficulty in completing their written self-reports. This procedure substantially reduced item-level missingness ($< 3\%$ across all primary variables).

Social network

Social network was evaluated using the validated Japanese version of the LSNS-6^{8,27}. The LSNS-6 scores ranged from 0 to 30, with scores < 12 indicating social isolation.

Ikigai measurement

Ikigai was operationalized as a continuous composite of the WHO-5 Well-being Index²⁸ and life-satisfaction score, each rescaled to 0–100. A single-item binary ikigai measure (as applied in the Ohsaki¹¹, JAGES¹², and Kashiwa¹³ cohorts) was used as a sensitivity analysis (Supplementary Table 5).

PA

PA was quantified using MET values from the 2011 Compendium of Physical Activities¹⁴ across sport, occupational, and lifestyle domains. Total PA was log-transformed ($\log(1 + \text{MET-h/week})$) for regression.

FI and prespecified modified versions

The FI was constructed following the deficit-accumulation framework originally proposed by Mitnitski, Mogilner and Rockwood²⁹ and formalised into a standard procedure for individual-study implementation by Searle and colleagues⁵, identically to our previous reports from this cohort^{7,17}. Under this framework, FI is defined as the unweighted proportion of accumulated age-related deficits present out of the total items assessed, providing a continuous 0–1 scale that captures the multi-system nature of frailty. In the present study, we implemented this framework with three pre-specified Rockwood-style modifications appropriate to the psychosocial research question:

- (i) Four-level ordinal grading. Graded deficits were assigned intermediate values on a four-level scale (0, 0.33, 0.67, 1.0) rather than the simple 0/0.5/1 mapping of the original Searle procedure⁵, following the more granular scoring approach subsequently refined by Rockwood and Mitnitski⁴.
- (ii) Question-tailored item pre-specification. In addition to the original 32-item FI (FI-32), three modified versions were pre-specified to exclude items conceptually overlapping with the psychosocial exposures examined here — FI-29 (excluding "feel happy", "feel lonely", "walk outside"), FI-26 (further excluding grip strength, walking speed, rapid pace), and FI-23 (further excluding three IADL items). This extends the Rockwood principle that FI item selection should be tailored to the research question⁴ while retaining direct comparability with our previous Kyotango reports^{7,17}. FI-29 was pre-specified as the primary outcome.
- (iii) Clinical frailty cut-off. The ≥ 0.21 threshold for binary categorisation follows the Rockwood-recommended clinical cut-off validated across multiple cohorts^{2,4}, rather than the more conservative ≥ 0.25 used in some earlier Searle-only implementations.

These three Rockwood-style modifications — four-level ordinal grading, question-tailored item pre-specification, and the ≥ 0.21 clinical threshold — align our FI construction with contemporary Rockwood-

Mitnitski best practice⁴ while preserving comparability with our earlier reports from this cohort^{7,17} and with the companion analysis of dietary patterns and gut microbial clusters⁷.

Statistical analyses

Mediation analyses were conducted following Hayes' framework³⁰ using PROCESS Models 4 (simple) and 6 (serial), with bootstrap percentile 95% CIs from 2,000 resamples (seed = 42)³¹. All continuous predictors were z-standardized, with the FI outcome retained on a 0–1 scale. Adjustment was made for age, sex, body mass index, education, smoking, drinking, chronic-disease count, energy intake, and dietary fiber intake. Five prespecified sensitivity analyses (FI composition, sex, age, ikigai definition, covariate adjustment level) were performed. This study was reported in accordance with the STROBE statement³².

Declarations

Competing Interests

Yuji Naito received scholarship funds from Taiyo Kagaku Co. Ltd., Morinaga Co. Ltd., Miyarisan Pharma Co. Ltd, Morishita-Jintan Co. Ltd., Fujikko Co. Ltd., Mizkan Co. Ltd., Mykinso Co. Ltd. and KINS Co. Ltd.; a collaboration research fund from TOTO Ltd., Takeda Pharma. Co. Ltd. and Taiyo Kagaku Co., Ltd.; and received lecture fees by Takeda Pharma. Co. Ltd., Biofermin. Co. Ltd., and Miyarisan Pharma. Co. Ltd. Tomohisa Takagi received a collaboration research funds from PreMedica Inc., and lecture fees from Mochida Pharma. Co. Ltd., Yanssen Pharmaceutical K.K., EA Pharma. Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co. Ltd, AbbVie GK, Bristol-Myers Squibb, and Pfizer Japan Inc.

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Author Contribution

Conceptualization, Y.N. and T.T.; validation and formal analysis, T.Y., H.K., K.M.; and R.I.; human cohort study management, N.O., A.A., Tadaaki Kamitani, J.N., Tomoya Kitani and S.M.; writing-original draft preparation, Y.N.; writing-review and editing, K.M., R.I., and T.T.; funding acquisition, Y.N. and S.M.. All authors have read and agreed to be published version of the manuscript.

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Data Availability

De-identified individual participant data will be made available upon reasonable request to the corresponding author, subject to institutional data-sharing agreements.

Code availability

Python analytic scripts used to produce all results reported in this paper will be released at the project's GitHub repository upon acceptance.

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Tables

Table 1 & 2 are available in the Supplementary Files section.

Figures

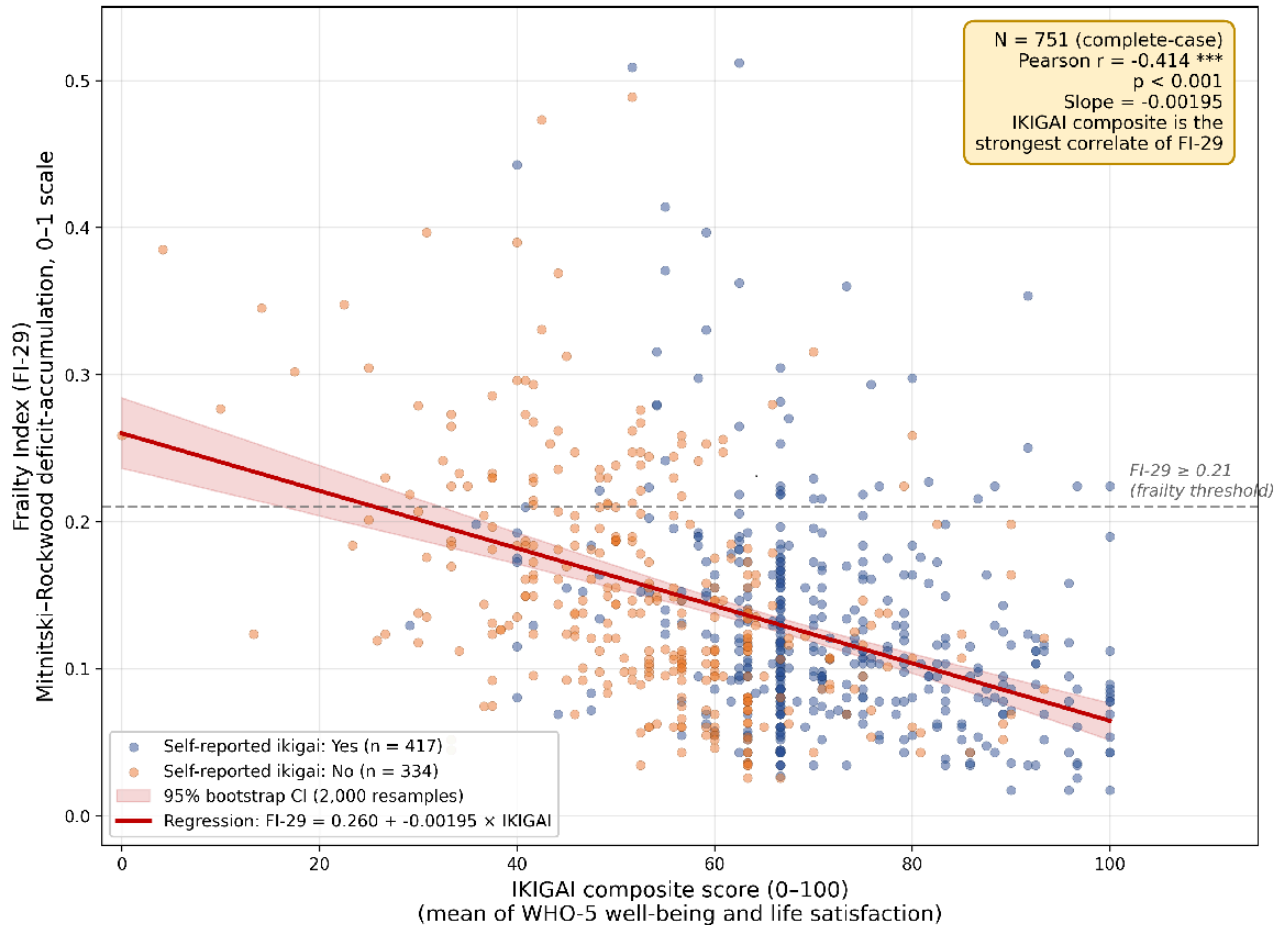


Figure 1

Cross-sectional association between the IKIGAI composite and the Frailty Index (FI-29).

Scatter plot of individual-participant IKIGAI composite scores (x-axis; 0–100, mean of WHO-5 well-being percentage and life-satisfaction percentage) against FI-29 values (y-axis; Mitnitski–Rockwood deficit-accumulation, 0–1 scale). Data points are colour-coded by the binary single-item ikigai self-report (blue: 'Yes, I have ikigai', $n = 417$; orange: 'No, I do not', $n = 334$). The solid red line shows the ordinary least-squares regression line ($FI-29 = 0.260 - 0.00195 \times IKIGAI$); the shaded band shows the bootstrap percentile 95% confidence interval (2,000 resamples). The horizontal dashed line at $FI-29 = 0.21$ indicates the Rockwood-recommended clinical frailty threshold. The IKIGAI composite is the strongest bivariate correlate of FI-29 in the cohort (Pearson $r = -0.414$, $p < 0.001$), with each 10-point increase in IKIGAI associated with a 0.020 decrease in FI-29 on the raw scale. Statistics inset shows N , correlation coefficient, slope and interpretation. $n = 751$ community-dwelling older adults from the Kyotango Multipurpose Cohort (mean age 72.9 years, 59.4% women).

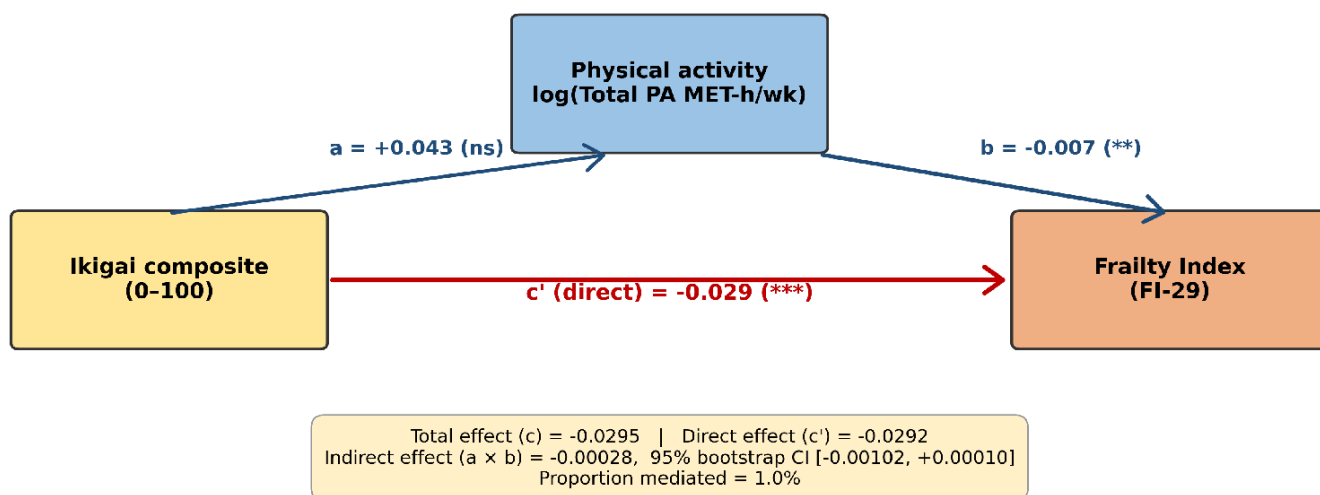


Figure 2

Simple mediation: Ikigai → Physical activity → Frailty Index (FI-29).

Path diagram of the single-mediator model with the ikigai composite (0–100, mean of WHO-5 well-being percentage and life-satisfaction percentage) as the independent variable, log-transformed total physical activity (MET-h/week) as the mediator, and the 29-item modified Frailty Index (FI-29) as the outcome. Standardized regression coefficients are shown for the $X \rightarrow M$ path (a) and the $M \rightarrow Y$ path (b, adjusted for X). The direct effect (c') is shown as a red arrow. Significance stars: *** $p < 0.001$; ** $p < 0.01$; ns $p \geq 0.05$. The bootstrap-estimated indirect effect ($a \times b$) accounted for only 1.0% of the total effect, refuting the assumption that ikigai protects against frailty primarily by promoting physical activity. $n = 751$ (complete-case). Adjusted for all nine covariates (age, sex, BMI, education, smoking, drinking, chronic-disease count, energy intake, dietary fiber). Bootstrap percentile 95% CIs from 2,000 resamples.

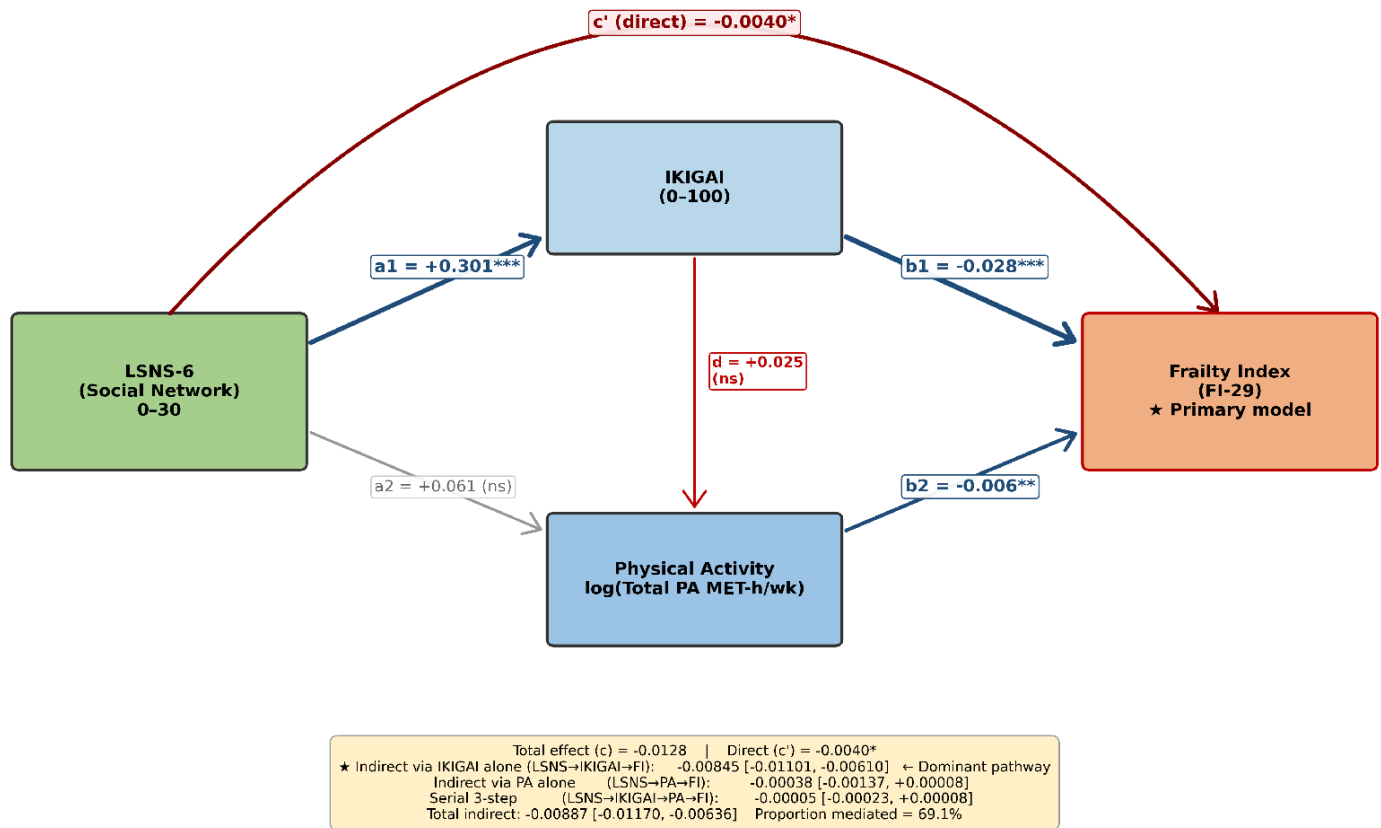


Figure 3

Serial mediation model: LSNS-6 → IKIGAI → Physical activity → Frailty Index (FI-29).

Path diagram of the serial two-mediator model (Hayes PROCESS Model 6) with LSNS-6 total score (0–30) as the independent variable, ikigai composite as the first mediator (M_1), log(total physical activity) as the second mediator (M_2), and FI-29 as the outcome. Standardized regression coefficients are shown for all six structural paths (a_1 , a_2 , d , b_1 , b_2 , c'). The ikigai-mediated pathway ($a_1 \times b_1$; blue arrows through IKIGAI) is dominant, whereas the IKIGAI → PA link (d) is not significant and the direct effect (c' ; red top arc) is small. Bottom box reports the decomposition of the total indirect effect into three component pathways (ind1: LSNS → IKIGAI → FI; ind2: LSNS → PA → FI; ind3: three-step serial LSNS → IKIGAI → PA → FI) with bootstrap percentile 95% CIs. The IKIGAI-only pathway (ind1) accounts for 95.3% of the total indirect effect, and the three-step serial chain (ind3) is statistically null. Total proportion mediated = 69.1%. N = 751 (complete-case). Adjusted for all nine covariates (age, sex, BMI, education, smoking, drinking, chronic-disease count, energy intake, dietary fiber).

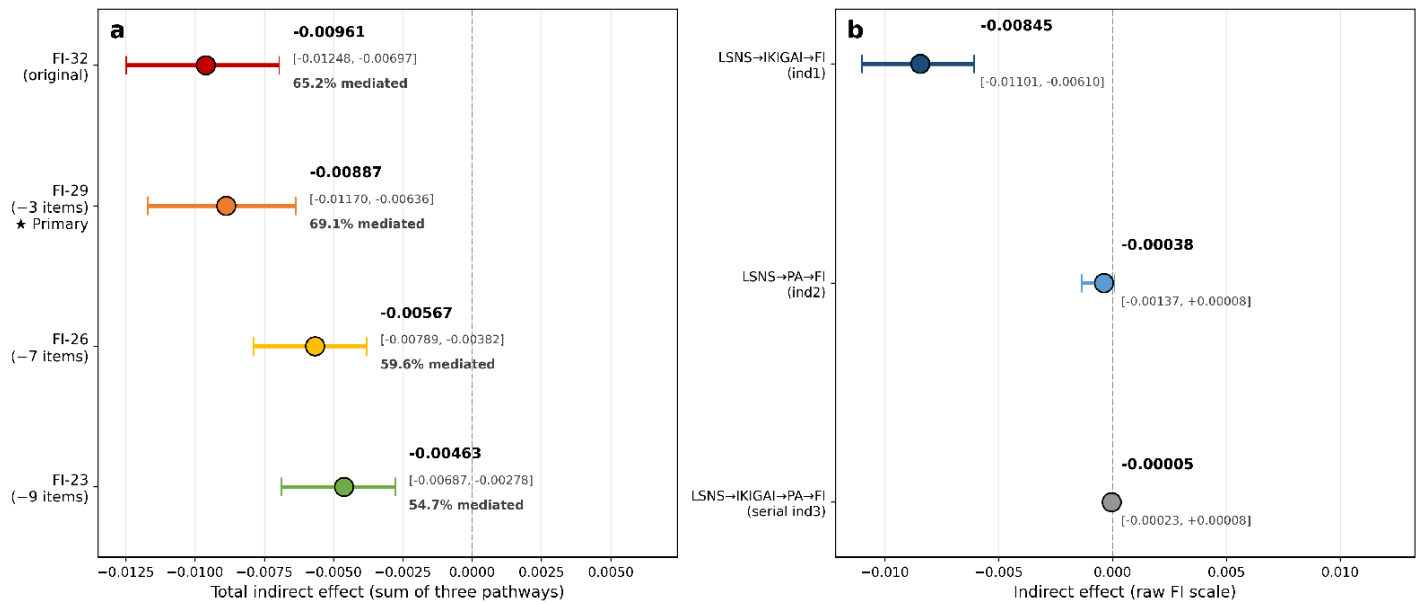


Figure 4

Sensitivity analyses: robustness of the ikigai-mediated pathway across four pre-specified FI versions and decomposition of the three indirect pathways.

a, Total indirect effect (sum of three pathways) estimated from the serial-mediation model using each of the four pre-specified Frailty Index versions: FI-32 (original 32 items, red), FI-29 (excluding three items conceptually overlapping with the psychosocial exposures — 'feel happy', 'feel lonely', 'walk outside'; orange; primary outcome), FI-26 (further excluding grip strength, walking speed, rapid pace; yellow) and FI-23 (further excluding three IADL items; green). Point estimates and bootstrap percentile 95% CIs are shown for each version, together with the proportion of the total effect mediated. All four versions yield statistically significant total indirect effects (95% CI excluding zero), with proportion-mediated values within the narrow band of 54.7–69.1%, demonstrating that the principal findings are not driven by item overlap between FI and the psychosocial exposures.

b, Decomposition of the total indirect effect in the FI-29 primary model into the three component pathways: ind1 (LSNS → IKIGAI → FI, dark blue), ind2 (LSNS → PA → FI, light blue) and ind3 (three-step serial LSNS → IKIGAI → PA → FI, grey). The IKIGAI-mediated pathway (ind1) is clearly separated from zero and dominates the total indirect effect (95.3%), whereas the three-step serial pathway (ind3) is statistically null (95% CI crossing zero). $n = 751$ (complete-case). Error bars: bootstrap percentile 95% CI from 2,000 resamples with random seed = 42.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.xlsx](#)
- [Table2.xlsx](#)
- [SupplementaryFigureTable.pdf](#)