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Acute clinical events and trajectories of frailty after age 60: A population-based cohort study

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Abstract. Tazzeo C, Gregorio C, Rizzuto D, Fratiglioni L, Innocenti F, Bjurgert J. et al., Acute clinical events and trajectories of frailty after age 60: A population-based cohort study. *J Intern Med*. 2026;1–12.

Background. We aimed to examine the relationship between acute events and frailty trajectories of community-dwelling adults aged 60 and older.

Methods. We included 3146 participants, aged 60+, from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K). We considered all myocardial infarctions (MIs), lower respiratory tract infections (LRTIs) and falls that resulted in a hospitalization 5 years before to 12 years after SNAC-K baseline (2001–2004). Frailty was operationalized using a data-driven frailty index (FI), scored from 0 to 1. Linear quantile mixed models were used to examine the relationship between number and type of acute events and FI trajectories over a median follow-up of 11 years.

Results. Falls (n = 690) were most common, followed by LRTIs (n = 353) and MIs (n = 205). Those with more acute events showed significantly higher frailty levels over time from age 75 to 95. The greatest differences in frailty trajectories by event count were observed at age 80, with increases between zero to one, one to two and two to three or more events of 0.04 (95% confidence interval [CI] = 0.03–0.05), 0.08 (95% CI = 0.05–0.11) and 0.09 (95% CI = 0.05–0.13) FI units, respectively. Falls emerged as most deleterious, but there were also clear differences by MI and LRTI count after imputing frailty at death.

Conclusion. Older adults who experience falls, LRTIs and MIs are more likely to sustain unfavourable frailty trajectories, with increasingly higher frailty levels with each additional acute event. Prevention, before age 75, should be optimized to avoid a vicious cycle of acute events and frailty progression as well as reduced lifespan.

Keywords: falls, frailty, hospitalization, lower respiratory tract infections, myocardial infarction, prevention

Abbreviations: BMI, body mass index; CI, confidence interval; FI, frailty index; HAT, Health Assessment Tool; LRTI, lower respiratory tract infection; MI, myocardial infarction; m/s, metres per second; SNAC-K, Swedish National Study on Aging and Care in Kungsholmen

Introduction

As we age, our health becomes less stable [1]. Many diseases and negative health events occur more frequently and are often accompanied by greater consequences, with age [2]. Frailty contributes to this lack of stability in health, being a geriatric syndrome marked by reduced homeostatic func-

tion and accelerated biological ageing [2]. Frail individuals encounter everyday stressors (e.g., infections and medical procedures) with less resilience than expected for those of the same chronological age [2]. As a result, frail individuals can face negative health-related consequences that are disproportionately severe in relation to the stressor, putting them at greater risk of death [3], disability [4] and lower quality of life [2].

Myocardial infarctions (MIs), injurious falls and lower respiratory tract infections (LRTIs) are three acute clinical events that become more common with age and pose as considerable stressors for older adults [5–7]. Oftentimes, these events require hospitalization, which is a traumatic and debilitating event, itself [8, 9]. Not only are those with frailty more likely to experience MIs, LRTIs and falls than those without [10–12], but in the wake of such events, frail individuals also face increased risk of adverse outcomes, including mortality [13–15], 30-day readmission [15, 16], longer treatments [13, 17] and higher care needs post-discharge [13].

MIs, LRTIs and falls have major consequences and can recur many times in older ages [2, 14–16, 18]. However, frailty progression in relation to the individual and cumulative burden of such events has not been studied. Most investigations have considered acute events as an outcome [11, 19, 20] or single transitions in frailty states [21, 22], limiting the possibility of really understanding the complex interplay between exposure to different patterns of acute events and the multidimensional trajectories of frailty in older age.

We have previously shown that compared with earlier generations, more recent cohorts of older Swedish adults live longer with frailty before death [23]. In light of these trends [23], understanding the role of MIs, LRTIs and falls in frailty development is of great interest from both a clinical and a public health perspective. Although these events can have devastating consequences, they are also largely preventable through vaccinations, lifestyle interventions and clinical monitoring [18, 24, 25]. Consequently, determining whether an association exists between specific acute events and frailty progression could inform prevention efforts and resource allocation prioritization [26]. Accordingly, this study aims to examine the relationship between acute clinical events (MIs, LRTIs and injurious falls) and frailty trajectories and to investigate whether this association differs by event type.

Methods

Study population

Data from the first five waves (2001–2004 to 2013–2016) of the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K; https://www.snac-k.se/) were included. SNAC-K is a population-based cohort of older adults who were invited through age-stratified (60, 66, 72, 78, 81, 84, 87, 90, 93, 96, 99+ years) random sampling of Kungsholmen (Stockholm) residents. At baseline, 3363 participants (response rate: 73% [baseline], 87% [wave 2], 90% [wave 3], 93% [wave 4], 92% [wave 5]) enrolled and have since been followed every 3 (age $\geq$ 78) to 6 (age $<$ 78) years. After excluding 195 participants institutionalized at baseline and 22 without frailty measurements, 3146 were included (Fig. S1). Those excluded due to missing frailty status were, on average, older, less educated, taking more medications and slower walkers, with a greater proportion being female, disabled and exhibiting chronic diseases (Table S1). Ethical approval for SNAC-K was received from the Ethics Committee at Karolinska Institutet and the Regional Ethical Review Board in Stockholm (approval numbers: KI 01-114, 04-929/3, Ö26-2007, 2009/595-32, 2010/447-31/2, 2013/828-31/3, 2016/730-31/1, 2019/02528, 2020/02497, 2021/01069, 022/03091/02, 022/03078/02, 2023/02375-02). All participants or substitute decision-makers, where applicable, provided informed consent.

Data collection

Acute events. MIs, LRTIs (pneumonia, bronchitis and influenza) and injurious falls (arising from low force) leading to at least a one-night hospitalization were retrieved from the Swedish National Patient Register [27], which was linked to the SNAC-K data (Supporting Information Appendix 1). Hospitalizations occurring 5 years before baseline, up to the fifth SNAC-K wave (2013–2016), were considered. Acute events were operationalized as a cumulative count occurring in the time period leading to the SNAC-K visits. Accordingly, hospitalizations prior to baseline were also considered, as they could influence the baseline frailty measurement. Hospitalizations for the same type of event had to be at least 10 days apart to be considered distinct events.

Frailty measure. A 40-deficit frailty index (FI), operationalized previously [23, 28], was implemented. A genetic algorithm was used to select the optimal number and type of FI deficits to predict death in the baseline SNAC-K population [28]. The resulting FI contained 40 deficits, which were operationalized based on data collected by trained SNAC-K health professionals during a physical examination and social interview conducted by a nurse; a medical examination, laboratory test and interview regarding medical and clinical history carried out by a physician; and a neuropsychological assessment performed by a psychologist [29]. The deficits included 19 chronic diseases; 13 physical function/performance measures; four socioeconomic variables; one cognitive measure; one health problem; one sign; and a history of unplanned hospitalizations in the last year, which was identified using the Swedish National Patient Register and modified to exclude hospitalizations for MIs, LRTIs and falls (Table S2). We calculated FI scores for each participant, when possible, for the first five SNAC-K waves. FI scores were calculated as the number of deficits with which a participant presented divided by the number of non-missing (maximum 40) deficits considered, with potential scores between 0 and 1. Participants needed to have complete data for at least 36 deficits (no more than 10% missing) to receive a frailty score. We employed a continuous measure of frailty in the statistical models but also contextualize our findings in categories—robust (FI $\leq$ 0.125), mild frailty (0.125 $<$ FI $\leq$ 0.25) and moderate to severe frailty (FI $>$ 0.25)—in line with our previous study [23].

We used the Health Assessment Tool (HAT) [30], an externally validated composite indicator that combines cognitive and physical function, disability and morbidity burden into a score from 0 to 10, with higher values reflecting better health, in place of the FI in a sensitivity analysis. The construction and validation of the HAT have been described elsewhere [30, 31].

Covariates. Several variables from the physician and nurse SNAC-K visits were included in the descriptive analyses. Date of birth, sex, primary education, basic and instrumental activities of daily living and walking speed in metres per second (m/s) were collected during the nurse's interview and assessment. Height (cm) and weight (kg) were also measured by the nurse to calculate body mass index (BMI), which was then categorized into underweight (BMI $<$ 18.5 kg/m^2), normal weight (18.5 kg/m^2 $\leq$ BMI $<$ 25 kg/m^2), overweight (25 kg/m^2 $\leq$ BMI kg/m^2 $<$ 30 kg/m^2) and obese (BMI $\geq$ 30 kg/m^2). Mini-Mental State Examination score, as a measure of global cognition, and the number of medications were ascertained during the SNAC-K physician visit. The number of diseases was measured as described above through the SNAC-K physician examination, lab tests, medication use and clinical records.

Statistical analyses

Descriptive statistics by frailty status at baseline were compared across groups using chi-square tests and one-way analyses of variance. In light of the right-skewed nature of the FI scores (Fig. S2), we used linear quantile mixed models, implemented through the 'lqmm' package in R [32], to model the median frailty trajectory by age and acute event count, as these models do not make assumptions about the underlying distribution of the response variable and are robust to outliers. Age was the time scale, and participants were followed from 5 years before the SNAC-K baseline until whatever came first: dropout, death (Swedish Cause of Death Register or SNAC-K records), 1 day after their first SNAC-K visit where they were reported as institutionalized, or the date of their wave five SNAC-K study visit. In the main analysis, the relationship between the number of acute events (0, 1, 2, 3+) and frailty trajectories was estimated through a model adjusted for sex, and an interaction between age (non-linear, cubic spline with two degrees of freedom) and number of acute events was included as a time-dependent covariate. In the event-specific analysis, the model was adjusted for sex, as well as three separate interactions between age (non-linear, cubic with two degrees of freedom) and (1) MIs, (2) LRTIs and (3) falls, with each event categorized into 0, 1, 2+ as time-varying covariates. Based on the models, frailty trajectories were predicted for all combinations of events (number and type) and ages (60–100 at 1-year intervals), with 100 bootstrap repetitions to obtain 95% confidence intervals (CIs) for the trajectories. Changes in FI scores and 95% CIs by event were presented for the most common event occurrences (number and type) over the follow-up at the median age at which they occurred. All analyses were conducted in R version 4.2.1 and Stata/SE 17.0.

Table 1. Participant characteristics by frailty status at baseline.

	Robust ($n = 2447$; 77.8%)	Mild frailty ($n = 439$; 14.0%)	Moderate–severe frailty ($n = 258$; 8.2%)	Total ($n = 3146$)
Age	70.4 ± 8.9	83.8 ± 7.6	88.4 ± 7.3	73.7 ± 10.7*
Sex (female)	1483 (60.6)	314 (71.5)	200 (77.5)	1998 (63.5)*
Elementary education	259 (10.6)	138 (31.6)	123 (48.2)	520 (16.6)*
Walking speed <0.8 m/s	254 (10.5)	348 (81.3)	225 (96.2)	829 (26.8)*
MMSE score <27	99 (4.1)	138 (31.4)	188 (73.2)	426 (13.6)*
1+ impaired ADLs	18 (0.7)	36 (8.2)	106 (41.4)	160 (5.1)*
1+ impaired IADLs	99 (4.1)	244 (58.0)	243 (98.8)	586 (19.1)*
Body mass index[a]				
Underweight	31 (1.3)	27 (7.0)	22 (13.8)	80 (2.7)*
Normal weight	1032 (42.5)	195 (50.4)	95 (59.4)	1322 (44.5)*
Overweight	1034 (42.6)	121 (31.3)	30 (18.8)	1185 (39.9)*
Obese	329 (13.6)	44 (11.4)	13 (8.1)	386 (13.0)
Number of medications	3.2 ± 2.9	5.7 ± 3.7	6.6 ± 3.8	3.9 ± 3.3*
Number of chronic diseases	3.3 ± 1.9	5.9 ± 2.4	7.0 ± 2.8	4.0 ± 2.4*
Chronic diseases				
Atrial fibrillation	125 (5.1)	94 (21.4)	64 (24.8)	283 (9.0)*
COPD	74 (3.0)	47 (10.7)	31 (12.0)	152 (4.8)*
Dementia	10 (0.4)	41 (9.3)	108 (41.9)	160 (5.1)*
Depression	175 (7.2)	55 (12.5)	42 (16.3)	272 (8.7)*
Heart failure	71 (2.9)	116 (26.4)	107 (41.5)	294 (9.4)*
Ischemic heart dis.	250 (10.2)	128 (29.2)	81 (31.4)	459 (14.6)*
Stroke	78 (3.2)	70 (16.0)	69 (26.7)	217 (6.9)*

Notes: Missing variables: baseline frailty status ($n = 2$); elementary education ($n = 6$); walking speed ($n = 56$); MMSE ($n = 8$); ADLs ($n = 7$); IADLs ($n = 85$); BMI ($n = 173$); number of drugs ($n = 7$).
Abbreviations: ADLs, activities of daily living; BMI, body mass index; COPD, chronic obstructive pulmonary disease; dis., disease; IADLs, instrumental activities of daily living; MMSE, Mini-Mental State Examination.
[a]BMI categories are based on the World Health Organization cut-offs: underweight (BMI < 18.5 kg/m^2), normal weight (18.5 kg/m^2 ≤ BMI < 25 kg/m^2), overweight (25 kg/m^2 ≤ BMI kg/m^2 < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2). Values are presented as absolute number and column percentage (%) or mean ± standard deviation.
*$p < 0.001$.

Sensitivity analyses

To address death, the models were re-run after imputing FI scores to 0.4 (the median FI score at SNAC-K visits occurring within 6 months of death) for the dates of death occurring during follow-up ($n = 1065$). In addition, the analyses were re-run (1) adjusting for a binary variable that indicated whether a participant had experienced an acute event in the 5 years before baseline, (2) excluding individuals ($n = 388$) who had experienced an event during those 5 years and (3) replacing the FI with the HAT [30]. We also repeated the main analysis, stratified by sex.

Results

Among the 3146 participants at baseline, the mean age was 74 years, and 64% were female. Most participants were robust (78%), followed by 14% with mild frailty and 8% with moderate to severe frailty. Those with a higher degree of frailty were, on average, older, less educated, taking more medications, slower walkers and exhibiting lower cognitive function (Table 1). Moreover, a higher proportion of frailer participants were female, had impaired activities of daily living and exhibited chronic diseases (Table 1).

Table 2. Median change in frailty index score following acute events by age and count of acute events occurring since 5 years before Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) baseline.

	From 0 to 1 event Difference (95% CI)	From 1 to 2 events Difference (95% CI)	From 2 to 3+ events Difference (95% CI)
Age 65	0.01 (0.00, 0.03)	0.04 (−0.04, 0.12)	−0.01 (−0.14, 0.12)
Age 70	**0.03 (0.01, 0.04)**	**0.06 (0.00, 0.11)**	0.03 (−0.05, 0.12)
Age 75	**0.04 (0.03, 0.05)**	**0.07 (0.03, 0.11)**	**0.07 (0.01, 0.12)**
Age 80	**0.04 (0.03, 0.05)**	**0.08 (0.05, 0.11)**	**0.09 (0.05, 0.13)**
Age 85	**0.05 (0.04, 0.06)**	**0.08 (0.05, 0.10)**	**0.09 (0.06, 0.13)**
Age 90	**0.06 (0.04, 0.07)**	**0.07 (0.04, 0.09)**	**0.08 (0.05, 0.11)**
Age 95	**0.06 (0.04, 0.09)**	**0.05 (0.02, 0.08)**	**0.05 (0.02, 0.09)**

Notes: The results in the table are derived from a linear quantile mixed model adjusted for an interaction between age and acute events and sex. Significant results are presented in bold.
Abbreviation: CI, confidence interval.

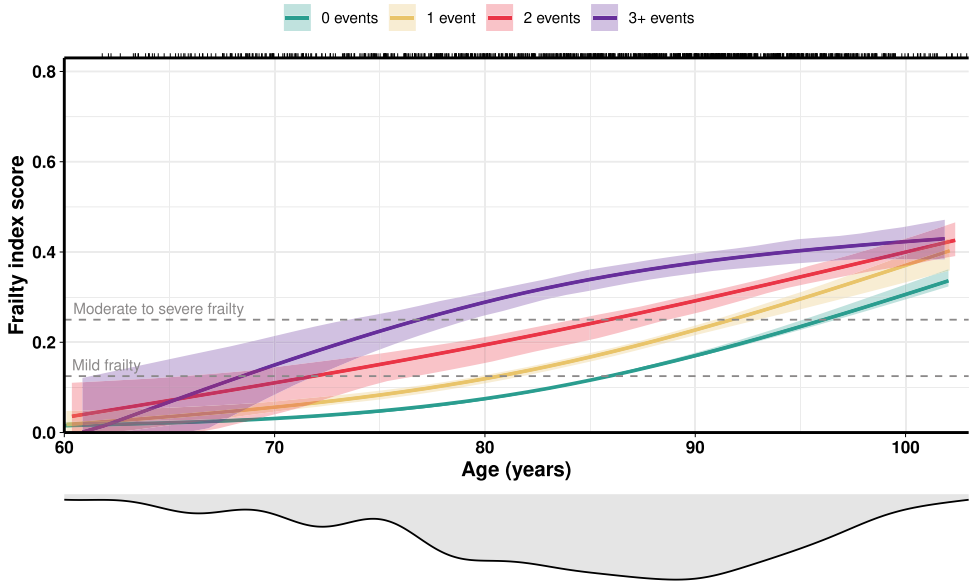

Fig. 1 *Median frailty trajectories by number of acute clinical events occurring since 5 years before Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) baseline. The results in the figure are derived from a linear quantile mixed model adjusted for an interaction between age and acute events and sex. Shaded areas represent 95% confidence intervals. The horizontal dashed lines outline frailty levels. The grey density curve at the bottom of the figure represents the density of acute events by age and the ticks at the top of the figure represent deaths that occurred during the follow-up.*

Over the follow-up (median 11 years, interquartile range 6 years), 880 participants experienced at least one acute event, 1065 died, 675 dropped out, and 209 were institutionalized. Most events were falls (n = 690), followed by LRTIs (n = 353) and MIs (n = 205) (Fig. S3). With age, the average FI score and proportion of participants who had experienced at least one acute event increased (Figs. S4 and S5).

Statistically significant differences in the frailty trajectories by acute event count were observed between ages 75 and 95 (Table 2, Fig. S6), with more events being associated with higher frailty levels over time (Fig. 1). For instance, at age 80, the median frailty level for individuals who had experienced one acute event was 0.04 (95% CI = 0.03–0.05) FI units higher than that of those who had not experienced any events, with additional median

increases of 0.08 (95% CI = 0.05–0.11) and 0.09 (95% CI = 0.05–0.13) FI units among individuals who had encountered two and three or more events, respectively.

The event-specific analyses (Fig. 2, Table S3) showed a clear difference in frailty trajectory by number of falls, with more falls being associated with higher frailty levels after age 80. There was a similar but less pronounced pattern for LRTIs, with significantly higher frailty levels between ages 70 and 85 by LRTI count. The median frailty levels between ages 75 and 90 were also significantly higher among those who had experienced one MI after age 60 compared with those with no events. There were clear increases in the median frailty levels following the four most common event scenarios (Fig. 3, Table S4). Experiencing a fall ($n = 381$; median age = 84) was most likely, leading to a predicted median increase of 0.06 (95% CI = 0.04, 0.08) FI units at age 84. Many participants ($n = 119$) experienced a second fall (median age = 90), which was expected to further increase frailty by a median of 0.11 (95% CI = 0.06, 0.16) FI units when it occurred at age 90. It was also common to experience an LRTI (median age 84) or MI (median age 79), which were associated with median FI increases of 0.06 (95% CI = 0.04, 0.09) and 0.05 (95% CI = 0.03, 0.07) units, at ages 84 and 79, respectively.

Results of the sensitivity analyses

After imputing FI scores to 0.4 at death, there was a marked change in the frailty trajectories characterized by two and three or more acute events, as they overlapped more and tended towards a FI score of 0.4 across the included ages (Fig. S7). Similarly, the frailty trajectories for one or more events were higher across the event-specific analyses (Fig. S8). There was a clear difference between the frailty trajectories by number of LRTIs, which was less apparent in the unimputed analysis (Fig. S8). Moreover, the frailty trajectories by MI count were more distinct, albeit remaining statistically non-significant, compared with the unimputed analysis (Fig. S8). The results of the sensitivity analyses that excluded and adjusted for the occurrence of an event 5 years before baseline were comparable to the main analyses, but less precise (data not shown). Results obtained using the HAT (Figs. S9 and S10) were comparable to those based on the FI (Figs. 1 and 3), although the patterns appeared reversed due to the opposite scaling of the two indicators. The sensitivity analyses stratified by sex showed similar results as the main analysis, with men having a slightly steeper initial trajectory and then levelling off for the trajectory characterized by two or more events.

Discussion

Employing comprehensive data and robust statistical analyses, our novel investigation into the associations between MIs, LRTIs and falls with frailty trajectories led to several key findings. We found a direct relationship between acute events and frailty trajectories, with each additional event being associated with progressively higher frailty levels over time. This association was most apparent between ages 75 and 95, coinciding with the ages at which most events occurred. Falls were associated with the clearest increases in frailty after age 80. Although there was a similar but weaker relationship between LRTIs and frailty trajectories, MIs only demonstrated differences between zero and one events. The sensitivity analyses revealed that our findings were influenced by deaths over the follow-up, highlighting that public health effort to manage MIs, LRTIs and falls could be important targets in preventing frailty progression and postponing death.

In line with others [11, 19–22], our findings demonstrate that even one acute event is associated with higher levels of frailty between ages 75 and 95. Notably, our study goes beyond previous research in showing that there are additional increases in frailty levels corresponding to the second and third events and that the magnitude of these increases grows with the number of events. Our study design does not facilitate causal conclusions regarding the relationship between acute events and frailty; however, we believe that these major acute events can shape one's frailty trajectory and that this relationship is bidirectional to some degree, whereby acute events incite deficits that constitute frailty, and in turn, higher frailty levels increase the risk and consequences of future events. In line with the deficit accumulation model, acute MIs, LRTIs, falls—and arguably their immediate and delayed sequelae—lead to buildup of damage, diminishing the body's ability to overcome stress [33]. Moreover, hospitalization, itself, isolates patients, reduces mobility, involves many environmental disturbances and has been linked with adverse outcomes like delirium and deconditioning, effectively serving as a springboard to frailty [8, 9]. However, frailty also

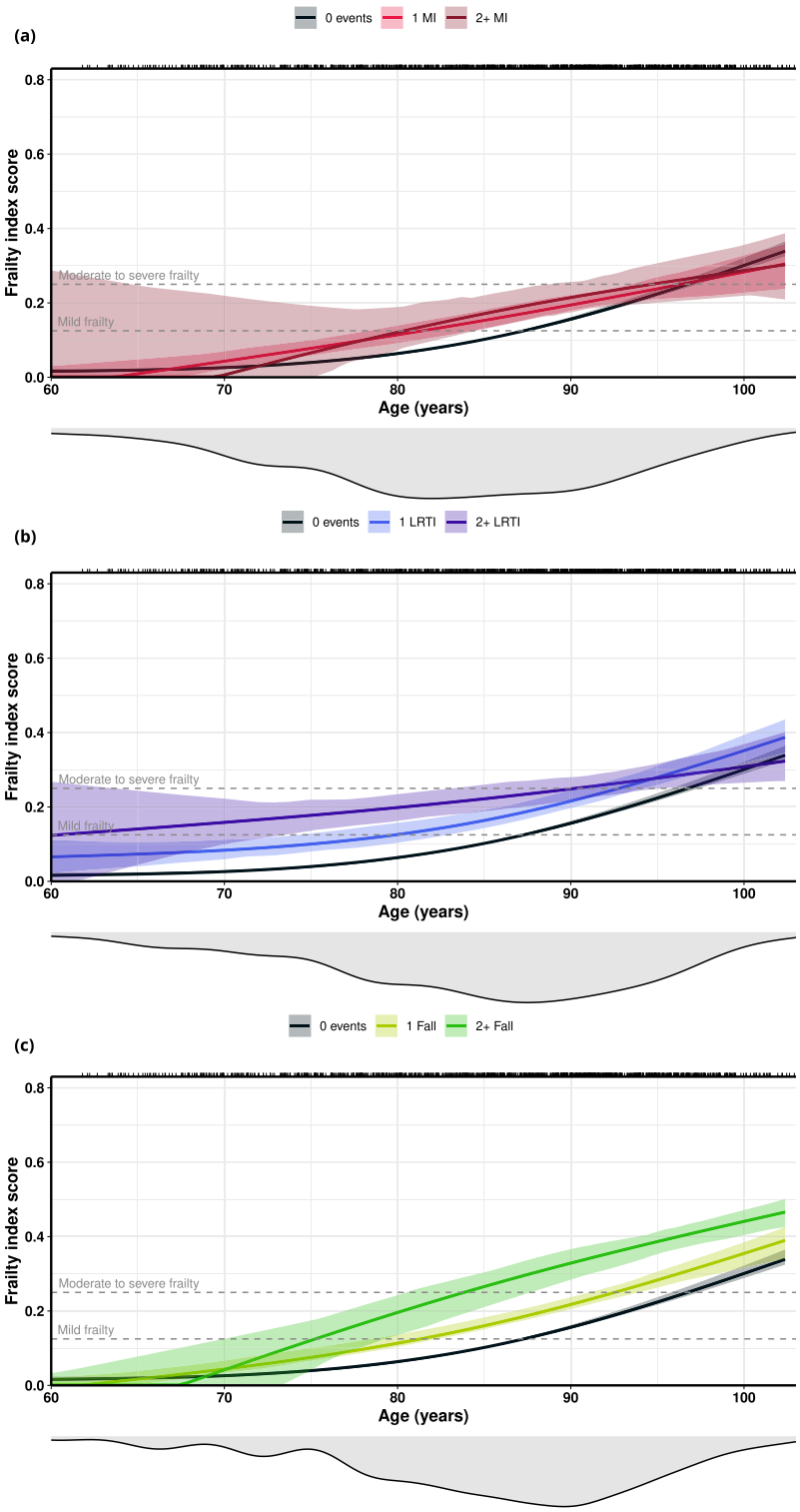

Fig. 2 *Median frailty trajectories by number of (a) myocardial infarctions (MIs), (b) lower respiratory tract infections (LRTIs) and (c) falls occurring since five years before Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) baseline. The results in the figure are derived from a linear quantile mixed model adjusted for sex as well as interactions between age and MIs, age and LRTIs, and age and falls. Part (a) displays the results for 0, 1 and 2+ MIs (and no other events), Part (b) displays the results for 0, 1 and 2+ LRTIs (and no other events), and Part (c) displays the results for 0, 1 and 2+ falls (and no other events). Shaded areas represent 95% confidence intervals. The horizontal dashed lines outline frailty levels. The grey density curves at the bottom of the figure represent the density of acute events by age and the ticks at the top of the figure represent deaths that occurred during the follow-up.*

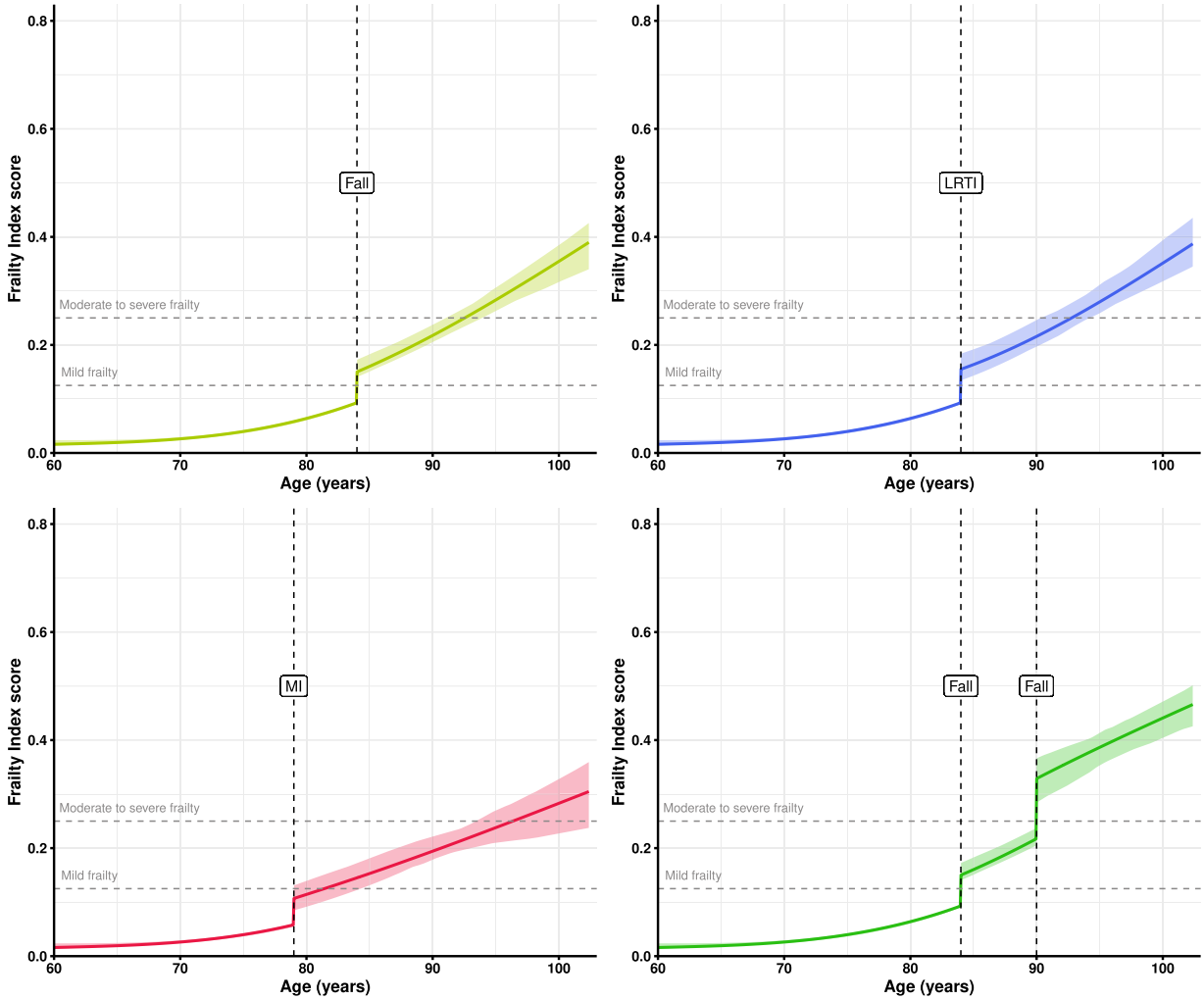

Fig. 3 *Individual predictions of frailty trajectories for the most common event occurrences at the median age that they occurred. The results in the figure are derived from a linear quantile mixed model adjusted for sex as well as interactions between age and myocardial infarctions (MIs), age and lower respiratory tract infections (LRTIs), and age and falls. Changes in frailty index (FI) scores were predicted for the most common event occurrences (number and type) and the median ages at which they occurred. Shaded areas represent 95% confidence intervals. The vertical dashed lines mark the ages of event occurrence, and the horizontal dashed lines outline frailty levels.*

entails reduced functional reserves that might dispose one to falls, MIs and LRTIs, or impede recovery [33]. Evidence also indicates that people with frailty are more likely to encounter ageist attitudes in healthcare provision, which could lead to suboptimal outpatient and hospital care, perhaps promoting further events or deterioration [34, 35].

Our study was also novel in comparing how frailty trajectories differ depending on the type of acute event. We found that falls exhibited the greatest differences in frailty trajectories, particularly after age 80. Of note, other studies have reported greater odds of falls among those with frailty progression [19, 20]. Injurious falls often entail fractures, head trauma and joint dislocation; these could induce disability, institutionalization, mobility limitations and activity restriction related to fear of falling, each of which would manifest as deficits in the FI [18, 36, 37]. In line with the bidirectional relationship proposed in the previous paragraph, frailty is also associated with slow gait speed, fatigue and

reduced homeostatic reserves, which may indicate a greater fall risk [2]. Those already progressing in frailty may have been more susceptible to experiencing a fall and more vulnerable to greater frailty progression. In addition, there might be a selective impairment of specific deficits depending on the acute event at play. For example, we can expect falls to mostly act on deficits reflecting functional impairment, even if it is known that more systemic consequences can be triggered by falls, especially when accompanied by fractures, such as cardiovascular events, bleeding and infections. Along with this, those who progressed in frailty after a fall might be at risk for a recurrent fall. In fact, experiencing two falls was one of the most common combinations of acute events, occurring at median ages of 84 and 90. Falls are likely less deadly than MIs and LRTIs, which might allow participants to live long enough to develop frailty and encounter multiple falls, as evidenced by the high median age of these events. However, these years of life following falls might also extend and increase their burden on the healthcare system [38].

Our sensitivity analysis imputing frailty at death supported the possibility of selection bias, revealing minimal changes in the trajectories by number of falls with the emergence of clear differences by LRTI count, particularly before age 80. We were not surprised by this, given the well-established relation between LRTIs and shortened survival [7]. Moreover, there is a strong physiological rationale underlying the association between LRTIs and frailty, whereby LRTIs trigger an inflammatory response in systems across the body, which can increase frailty risk [24]. Our findings are supported by another study that found evidence of physical decline following LRTIs, particularly among those with pre-existing frailty [39]. LRTIs might also induce subsequent acute events and further frailty progression, or a cycle of the two [40]; others have posited a strong relationship between acute respiratory infections and MI, likely stemming from the infection and related physiological response [41]. As with MIs and falls, underlying frailty might lead LRTI infections to progress in severity, resulting in hospitalization or morbidity.

Frailty levels were also higher over time for those who experienced an MI. Although the association with frailty was stronger for falls and LRTIs, one must interpret the results critically. MIs were the least common event type and are deadly [5], particularly if one is frail [13, 42]. However, the approach to treating frail individuals is sometimes governed by comfort care measures rather than evidence-based treatment [34, 42, 43]. Perhaps too few people are living long enough to receive a follow-up frailty measure, as per the SNAC-K follow-up scheme, or even to experience a second MI. Alternatively, the rarity of recurrent MIs could be explained by successful pharmacological or revascularization therapies [43]. Another study reported a higher risk of cardiovascular diseases among those progressing in frailty [11], and notably, others suggest that this association is bidirectional [11, 44]. This is plausible, as both share common risk factors (physical inactivity, malnutrition and comorbidities) [25, 28, 33] and are associated with elevated inflammatory biomarkers, potentially signalling shared biological pathways [44, 45].

Frailty and hospitalizations for MIs, LRTIs and falls may be a troublesome reality faced by many older adults and healthcare systems, but these events are all largely avoidable [18, 24, 25]. Often, acute events are not sufficiently accounted for or prevented in chronically ill or frail individuals [34, 35]. Our study stresses this important deficiency in the traditional healthcare system. Primary care clinicians and public health officials are key figures who could incite meaningful change in the prevention and early treatment of these acute events and frailty, whether it be through comprehensive geriatric assessments, public health campaigns for vaccinations or proactive integrated person-centred primary care [24, 33]. Most participants in this study experienced an injurious fall; public health campaigns to enhance fall prevention through psychological interventions addressing fall-related anxiety, strength and balance exercise (e.g., Tai Chi), or routine multifactorial falls risk assessment and interventions in primary care [6, 18] could mean improved quality of life for many people. Likewise, population-level promotion of vaccines for respiratory vaccine-preventable diseases (e.g., pneumonia, influenza and COVID-19) could greatly reduce LRTI risk [24]. Preventive efforts require resources; however, these would likely be lower than the costs of treating such conditions when they reach a level of severity requiring hospitalization.

This study is strengthened by its novel research questions, comprehensive data and long follow-up. However, there are limitations to consider. Selection bias due to missing frailty status might have underestimated our findings, as those excluded for

this reason were less healthy than the included participants. Imputing frailty at death allowed us to investigate this among those whose frailty status was missing due to death. Selection bias due to non-entry in the study and loss-to-follow-up may have also influenced our results, likely through underestimation. Fortunately, the response rates across the first five waves of SNAC-K were quite high, and participants were still able to contribute if they had one frailty assessment. Furthermore, we could only assess frailty during SNAC-K visits, and deficits for chronic diseases included in the FI were considered permanent after the first occurrence, potentially limiting our ability to capture subtler nuances in the trajectories. Despite this, another study employing the same FI demonstrated increases and reductions in frailty across SNAC-K waves [23], giving us confidence in our FI to capture dynamic changes. Acute events occurring before SNAC-K could have also influenced our estimates; however, analyses where events that occurred in the 5 years before baseline were included, excluded and adjusted for showed similar results. Although some degree of circularity may exist between the FI and the specific acute events, replication of the analyses using the HAT, which emphasizes functional components, yielded consistent results, reinforcing the robustness of the findings. Institutionalized individuals represent an important contribution to the frailty trajectory of the population, especially in the context of this study, as acute events could result in institutionalization. However, hospitalization rates and frailty prevalence among those living in nursing homes differ from those of community-dwelling people [46, 47], which could have biased our findings. As such, we excluded individuals who were institutionalized at baseline and censored them at their last SNAC-K visit after being institutionalized, allowing us to measure frailty following acute events while they were living in the community. Lastly, the SNAC-K participants are from a relatively prosperous area of Stockholm, potentially limiting the external validity of the results; further examination of this association in diverse populations is warranted.

In conclusion, those who encounter MIs, LRTIs and falls experience higher levels of frailty between ages 75 and 95, with progressive increases in frailty levels corresponding to each additional event incurred. The difference in frailty progression by falls was most evident, but we found that death likely followed MIs and LRTIs before frailty could be measured. Moving forward, enhanced prevention and management of both frailty and acute clinical events, preferably before age 75, are necessary to prevent a vicious cycle of frailty progression, acute events and shortened survival.

Author contributions

Laura Fratiglioni: Supervision; writing—review and editing; funding acquisition. **Clare Tazzeo**: Conceptualization; formal analysis; visualization; writing—original draft; methodology; investigation; writing—review and editing. **Caterina Gregorio**: Formal analysis; methodology; writing—review and editing. **Anna-Karin Welmer**: Writing—review and editing. **Alberto Zucchelli**: Writing—review and editing. **Amaia Calderón-Larrañaga**: Supervision; writing—review and editing; funding acquisition. **Francesco Innocenti**: Formal analysis; visualization; writing—review and editing. **Stefania Maggi**: Writing—review and editing. **Jonas Bjurgert**: Writing—review and editing. **Debora Rizzuto**: Supervision; writing—review and editing. **Davide L. Vetrano**: Conceptualization; supervision; project administration; writing—review and editing; funding acquisition; resources.

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Conflict of interest statement

The authors declare no conflicts of interest.

Data availability statement

Data are from the SNAC-K project, a population-based study on ageing and dementia (http://www.snac-k.se/). Access to these original data is available to the research community upon approval by the SNAC-K data management and maintenance committee. Applications for accessing these data can be submitted at http://www.snac-k.se/.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 Flowchart of study participation.

Fig. S2 Density curve of frailty index scores in the SNAC-K population at baseline.

Fig. S3 Mean cumulative count of acute events by age and type of event.

Fig. S4 Mean frailty index score by age.

Fig. S5 Percentage of participants that experienced acute clinical events by age.

Fig. S6 Change in frailty index score following acute event by age and number of acute events.

Fig. S7 Frailty trajectories by number of previous acute clinical events with imputation of frailty score (FI = 0.4) at age of death.

Fig. S8 Frailty trajectories by number of previous MIs, LRTIs and falls with imputation of frailty score (FI = 0.4) at age of death.

Fig. S9 Median HAT trajectories by number of acute clinical events occurring since five years before SNAC-K baseline.

Fig. S10 Individual predictions of HAT trajectories for the most common event occurrences at the median age that they occurred.

Table S1. Baseline characteristics of individuals included versus excluded due to missing data.

Table S2. Deficits included in the frailty index.

Table S3. Change in FI score following acute event by age and event type.

Table S4. Frequency and median age of most common event combinations.

Supporting Information Appendix 1 ICD-10 codes included in operationalization of acute clinical events.