Frailty and affective disorders throughout adult life: a 5-year follow-up of the Lifelines Cohort Study

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Abstract

Background: Frailty is an important concept for risk stratification in clinical practice, but it is hardly acknowledged at all in mental healthcare settings. This paper aims to assess the impact of frailty on the course of depression and anxiety, and the impact of these affective disorders on the course of frailty.

Methods: Lifelines, a prospective population-based cohort study, evaluated 167,729 people living in the northern Netherlands. Frailty was based on the deficit accumulation model, which resulted in a 60-item frailty index (FI) at baseline and a 35-item FI at baseline and 5-year follow-up. Current depressive and anxiety disorders were assessed with the Mini International Neuropsychiatric Interview according to DSM-IV criteria. Bidirectional associations between frailty and affective disorders were investigated using separate multivariable regression analyses in younger (<60 years) and older adults (≥60 years).

Results: The FI was associated with the onset of a depressive disorder (younger adults: odds ratio [OR] = 1.12; 95% confidence interval [CI] 1.11–1.13; older adults: OR = 1.13; 95% CI 1.09–1.16) as well as any anxiety disorder (younger adults: OR = 1.10; 95% CI 1.09–1.10; older adults: OR = 1.07; 95% CI 1.04–1.09). The other way around, depressive disorder and anxiety disorders were associated with an accelerated increase of frailty over time (depressive disorder: younger adults: beta [β] = 0.03, p < 0.001; older adults: β = 0.04, p < 0.001; and any anxiety disorder: younger adults: β = 0.02, p < 0.001; older adults: β = 0.01, p < 0.142), although the effect of anxiety disorders was less equivocal among older adults.

Conclusions: Affective disorders are reciprocally related to frailty. Results with respect to the impact of anxiety disorders on frailty suggest most impact at lower levels of frailty. Our results might imply that interventions to slow biological aging should be broadened towards younger and middle-aged people.
INTRODUCTION

Frailty is recognized as an important concept to stratify risk and measure accelerated aging at a population level. Frailty is defined as a vulnerability state characterized by poor resolution of homeostasis after a stressor, placing an individual at risk of developing several adverse events such as hospitalization, disability or death. In the deficit accumulation model of frailty, multiple deficits may contribute to the onset and progression of frailty, and in clinical practice, identification of frailty is crucial to prevent further decline and adverse health outcomes. In spite of knowledge of the course of frailty in the general population, and for clinical purposes, potential interactions with mental disorders need to be better explored.

Epidemiological studies have consistently shown a strong and reciprocal relationship between depression and physical frailty. Biological explanations for this relationship include an unhealthy lifestyle and overlapping pathophysiological mechanisms, for example, inflammation. However, this association may also be explained partly by the overlapping diagnostic criteria for depressive disorders and physical frailty based on the frailty phenotype model. In addition, most studies have been based on self-reported depressive symptoms scales that are not meant to approximate psychiatric diagnosis according to DSM-criteria. Depressive symptom scales may yield high scores due to overlapping diagnostic criteria between the frailty phenotype and depression, such as fatigue and weight loss. In clinical practice, overlapping criteria require clinical judgment to prevent misdiagnosis or even inappropriate treatment for older adults. Falsely classifying depressed older people as being frail will result in undertreatment with antidepressants or psychotherapy, whereas falsely classifying frail older people as depressed may result in overtreatment with antidepressants and iatrogenic damage. In summary, to better understand the reciprocal relationship between frailty and depression, it may be relevant to include other frailty models such as the frailty index, and to assess depression according to DSM-criteria, and preferably broadening the assessment to the full spectrum of affective disorders.

Key points
- Affective disorders, including both depressive disorder as well as anxiety disorders, are positively associated with higher frailty over time.
- Frailty is associated with an increased risk on the onset of either depressive or anxiety disorders.
- The reciprocal relationship between frailty and affective disorders is present in both younger and older people.

Why does this paper matter?
Frailty is largely neglected in mental healthcare settings even though frailty and psychopathology mutually reinforce each other. Geriatric care models could make it easier to recognize and manage frailty and deserve more attention in mental healthcare institutions.

From the perspective of prevention, if our findings are proven to be causal in randomized controlled trials, it will provide an opportunity to slow the progression of frailty by improving mental health treatment and also to prevent the initial onset of affective disorders by targeting frailty.

The frailty index is based on the deficit accumulation model and operationalized as the proportion of deficits present in an individual out of the total number of age-related health variables considered. Measuring frailty with the frailty index may overcome some of these limitations described above. First, overlap with depression can be further minimized by excluding depression-related health deficits, as long as the frailty index still includes over 30 health deficits covering different (physiological) systems. Secondly, deficit accumulation is considered to be a stochastic process that occurs across the lifespan. This means that the FI could also be relevant in younger people, as included in recent aging cohorts.
Furthermore, there is limited data available on the association between frailty and depressive disorder according to DSM-criteria, let alone other clusters of affective disorders. Thus far, only one study has examined the association between frailty and medically unexplained somatic symptoms, one clinical study with combined depressive and anxiety symptoms, and no studies on the association with anxiety disorders alone. This is surprising because pure affective disorders are rare: the coexistence of anxiety and depressive disorders is high (40%–70%), and diagnostic stability over time is limited. Furthermore, coexistence of affective disorders increases the burden of disease and could also accelerate the aging process more than can be explained by the sum of the individual psychiatric disorders. The presence of an affective disorder is also associated with lower life expectancy, which means that frailty may become relevant earlier in life in psychiatric populations. However, limited data on the longitudinal association between frailty and other clusters of affective disorders, might also be one of the explanations of why mental health care hardly acknowledges the potential importance of frailty.

We hypothesize that frailty is reciprocally associated with depressive and anxiety disorders in both younger (<60 years) and older adults (≥60 years). There were therefore two main objectives of this study: (1) to assess the impact of frailty on the course of depressive and anxiety disorders prospectively, and (2) to assess the impact of these affective disorders on the course of frailty.

METHODS

Lifelines Cohort Study

Lifelines is a multi-disciplinary prospective population-based cohort study with a unique three-generation design to investigate the health conditions and lifestyle-related aspects of 167,729 people living in the northern Netherlands. It uses a wide range of investigative procedures to assess biomedical, behavioral, physical, and psychological factors that contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. Recruitment and baseline assessments started in 2006 and were completed in 2013. Follow-up visits are scheduled every 5 years and conducted by research assistants blinded for previous findings. All participants also receive follow-up questionnaires in between and at 5 years.

The Lifelines Cohort Study is conducted according to the principles of the Declaration of Helsinki and in accordance with the research code of the University Medical Center Groningen (UMCG). All participants signed informed consent prior to participation and the Lifelines study is approved by the medical ethical committee of the UMCG, The Netherlands. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Sample

People living in the northern Netherlands were either invited by their general practitioners (GP; if between 25 and 50 years of age) or self-registered at the Lifelines website (if ≥18 years of age). People with limited life expectancy due to severe illness (clinical judgment), and who had insufficient knowledge of the Dutch language were excluded. After signing informed consent, participants received a baseline questionnaire and were invited for a physical examination and a blood test after fasting at one of the Lifelines research sites. During these visits, participants were asked whether their family members would also be willing to participate. Overall, 49% of the participants (n = 81,652) were invited by their GP, 38% (n = 64,489), by participating family members, and 13% (n = 21,588) self-registered via the Lifelines website.

For this study, a priori participants below 18 years of age (n = 15,001) and those with Mini Mental State Examination (MMSE) scores below 26 points were excluded and therefore received a lower assessment (n = 2,215), resulting in an eligible sample of 150,187 people at baseline.

Measures

Frailty index (FI)

Frailty was assessed at baseline (two versions, i.e., FI-64 and FI-39) as well as at 5-year follow-up (FI-39). As described previously, we initially constructed the Lifelines-FI based on items regarding chronic somatic diseases, physical measures, disabilities, subjective health measures, sensory function, mental health indicators, neuropsychological markers, and blood biomarkers, following a standard procedure. In short, health deficit variables were included in the Lifelines-FI if they (a) were biologically meaningful in representing several organ systems, (b) accumulated with age, but not too prevalent at younger age, and (c) had less than 5% missing values. Each deficit was coded as 0 (absence) or 1 (presence), or when clinically relevant as any number between 0 and 1. In general, an FI ≥ 0.25 is considered to indicate frailty.
This procedure resulted in a baseline Lifelines-FI consisting of 64 items (age-related deficits), the FI-64. To prevent confounding with depressive or anxiety disorders, we excluded all mental health variables, that is, (a) feeling depressed in the past 2 weeks, (b) loss of interest/anhedonia in the past 2 weeks, (c) feeling happy, and (d) feeling nervous, which resulted in a 60-item FI (see Appendix S1).

Since some key-variables were not available at the 5-year follow-up (e.g., the MMSE and the Ruff Figural Fluency Test since cognitive measures have been replaced by the Cogstate), we also constructed a 39-item Lifelines-FI to have similar FIs at baseline and 5-year follow-up to allow longitudinal monitoring of frailty severity and transitions. From this latter index, we again excluded the four mental health variables, resulting in the FI-35. At baseline, the FI-60 and FI-35 had a Pearson’s correlation coefficient of 0.88 \( (p < 0.001) \).

**Depression and anxiety assessments**

Current depressive and anxiety disorders according to criteria of the Diagnostic and Statistical Manual of Mental disorders—fourth version (DSM-IV) were assessed with the Mini International Neuropsychiatric Interview (MINI) at baseline and 5-year follow-up. The MINI is a semi-structured psychiatric interview with good sensitivity and positive predictive value. The MINI is much more accurate than assessing depression based on self-report screening instruments as often used in community-based studies. Lifelines participants were interviewed by trained medical professionals during their visit to a research facility, where the MINI sections on generalized anxiety disorder (GAD), panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia, and depressive disorder were administered.

When referring to the presence of either a depressive disorder or any anxiety disorders, we will use the term affective disorder.

**Covariates**

Demographic and lifestyle variables, all measured at baseline, were included as covariates. The demographic variables of age, sex, level of education, and living situation (living alone vs other) were included. To adjust for lifestyle, we included body mass index (BMI), alcohol use, smoking (never, former, current) and physical activity which could contribute independently to the accumulation of health deficits. BMI was calculated by dividing body weight (kg) by the squared body length in meters (m\(^2\)). Alcohol use was classified as drinking no alcohol at all (abstainer), using moderate levels of alcohol (social), or using excessive levels of alcohol (\( \geq 21 \) drinks a week). Physical activity was measured with the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) questionnaire which measures physical activity by the metabolic equivalent of takes per minute (MET-minutes) based on light, moderate and intense activity in leisure time, community activities, household activities, and activity at work and school. Participants were classified as having or not having sufficient physical activity according to the current Dutch norms regarding physical activity, that is, more than 30 min of moderate physical activity at least 5 days a week.

**Statistical analysis**

Participants who completed the study and those with missing value at either baseline or 5-year follow-up were compared by Student t-tests for continuous normally distributed variables and Chi-square test for categorical variables. We a priori stratified our sample by age (<60 years; \( \geq 60 \) years) to facilitate the comparison of our results with previous population-based frailty studies including older people only. We also explored differential effects by age by conducting the analyses below in the whole sample and including an interaction term with non-dichotomized age.

For objective 1, we applied logistic regression analyses to investigate whether the Lifelines-FI (independent variable) was associated with the onset of an affective disorder at 5-year follow-up (dependent variable) among patients without that affective disorder at baseline. The Lifelines-FI was included as a continuous variable and multiplied by 100 for better interpretation of the odds ratio. Similarly, among persons with specific affective disorders at baseline, we investigated whether the Lifelines-FI was associated with persistence of that disorder at follow-up. All analyses were adjusted for age, sex, level of education, living situation, and lifestyle characteristics (smoking, alcohol use, physical activity, and BMI).

For objective 2, we applied linear regression analyses on the association between affective disorders and the FI (as continuous outcome) at 5-year follow-up. These analyses were adjusted for the FI at baseline in addition to the same covariates as described above.

For this second objective, we performed sensitivity analyses applying logistic regression analyses to examine whether the presence of any affective disorder was associated with the onset of frailty according to the Lifelines-FI-35 \( \geq 0.25 \) at follow-up among non-frail persons at baseline (i.e., FI-35 at baseline <0.25).
All analyses were performed using SPSS version 25.0. The threshold for statistical significance was $p < 0.05$.

**RESULTS**

Figure 1 shows the selection of participants stratified by age group. Of the eligible sample of 150,187 people, a total of 77,036 (51.3%) could be analyzed for objective 1 and a total of 89,667 (59.7%) for objective 2.

Table 1 shows the baseline characteristics of the sample. Although participants with complete data differed significantly from those who dropped out due to missing data at either baseline or follow-up, potentially clinically relevant differences were only found with respect to psychopathology (more among dropouts) and smoking (more current smokers among dropouts).

Tables S1 and S2 present these results stratified by age group. The dropout rate significantly differed between both age groups. A significantly lower number of younger people dropped out regarding objective 1 (62,217/129,865 [47.9%] vs 10,934/20,322 [53.8%], $\chi^2 = 244.4$, df = 1, $p < 0.001$), whereas regarding objective 2 a significantly higher number of younger people dropped out (54,588/129,865 [42.1%] vs 5832/20,322 [28.7%], $\chi^2 = 1314.1$, df = 1, $p < 0.001$).

Frailty as a determinant for a depressive and/or anxiety disorder

Of the 77,036 people available for the analysis of onset and persistence of affective disorders, at baseline, a total of 1384 had a depressive disorder and 5647 an anxiety disorder. Of the 75,652 non-depressed participants at baseline, 1852 (2.4%) were depressed at follow-up (2.6% younger adults vs 1.0% older adults; $\chi^2 = 91.2$, df = 1, $p < 0.001$). Of the 1384 depressed people at baseline, 1003 had no depressive disorder at follow-up (72.2% younger adults vs 75.9% older adults; $\chi^2 = 0.7$, df = 1, $p = 0.403$). As shown in Table 2 and Figure 2A, the score on the Lifelines Frailty Index-60 (multiplied by 100) was associated with respectively the onset and persistence of a depressive disorder in both younger adults and older adults. Combining both age groups, the interaction terms between the FI and age as a continuous variable was significant for the association with the onset of depression ($p < 0.001$) showing that the impact of frailty increased with age. The interaction between the FI and age was not significant for the association with the persistence of depression.

Of the 71,389 people without anxiety at baseline, 4366 (6.1%) had anxiety at follow-up (6.6% younger adults vs 2.6% older adults; $\chi^2 = 219.8$, df = 1, $p < 0.001$). Of the 5647 people with anxiety at baseline, 3636 had no anxiety disorder at follow-up (63.5% younger adults vs 74.1% older adults; $\chi^2 = 21.8$, df = 1, $p < 0.001$). The FI was associated with respectively the onset and persistence of any anxiety disorder in both younger and older adults (see Table 2 and Figure 2A). Combining both age groups, the interaction terms between the FI and age as a continuous variable was significant for the association with the onset of any anxiety disorder ($p < 0.001$) showing that the impact of frailty decreased with age. The interaction between the FI and age was not significant for the association with the persistence of any anxiety disorder.

Depressive and anxiety disorders as determinants for the course of frailty

Of the 89,667 people that were available for the analysis of the course of frailty, linear regression analyses showed that in younger people depressive disorder and all anxiety disorders except social phobia were significantly associated with higher levels of frailty after adjustment (Table 3). Among older adults, only depressive disorder and social phobia were associated with an accelerated increase in frailty (Table 3). The interaction term between each specific affective disorder and age as a continuous variable was only statistically significant for

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**FIGURE 1** Flowchart of the study
social phobia \( (p = 0.002) \) indicating a stronger impact on the course of frailty among older persons.

For the sensitivity analyses, we excluded 4450 (5.0%) were already classified as frail at baseline (4.0% younger adults vs 10.0% older adults, \( \chi^2 = 942.5, df = 1, p < 0.001 \). Of the 85,217 non-frail people at baseline, 4883 (5.7%) were frail at 5-year follow-up (4.6% younger adults vs 11.8% older adults, \( \chi^2 = 1065.1, df = 1, p < 0.001 \). Figure 2 presents the odds ratio (OR) with 95% confidence intervals for depressive disorder and for any anxiety disorder at baseline as determinant for the onset of frailty among non-frail persons stratified by age.

Among younger adults, the presence a depressive disorder and each specific anxiety disorder was associated with the onset of frailty at 5-year follow-up (see Table S3), although depressive disorder and social phobia lost significance when all disorders were combined in one model. Among older adults, all specific anxiety disorders were associated with the onset of frailty at 5-year follow-up, while depressive disorder was not significant (Table S3).

### TABLE 1  Main characteristics of study participants for objective 1 (course of affective disorders, \( n = 77,036 \)) and for objective 2 (course of frailty, \( n = 89,667 \)) compared to study dropouts

<table>
<thead>
<tr>
<th>Characteristics:</th>
<th>Course of affective disorders(^a)</th>
<th>Course of frailty(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participants ((n = 77,036))</td>
<td>Dropouts ((n = 73,151))</td>
</tr>
<tr>
<td>Demographics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>44.5 (12.0)</td>
</tr>
<tr>
<td>Female</td>
<td>(n) (%)</td>
<td>45,602 (59.2%)</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>(n) (%)</td>
<td>20,132 (26.2%)</td>
</tr>
<tr>
<td>Middle</td>
<td>(n) (%)</td>
<td>32,297 (42.0%)</td>
</tr>
<tr>
<td>Higher</td>
<td>(n) (%)</td>
<td>24,466 (31.8%)</td>
</tr>
<tr>
<td>Living alone</td>
<td>(n) (%)</td>
<td>7658 (10.1%)</td>
</tr>
<tr>
<td>Psychiatric diagnoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>(n) (%)</td>
<td>1384 (1.8%)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>(n) (%)</td>
<td>3019 (3.9%)</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>(n) (%)</td>
<td>179 (0.3%)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>(n) (%)</td>
<td>694 (1.0%)</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>(n) (%)</td>
<td>2799 (3.6%)</td>
</tr>
<tr>
<td>Lifestyle characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>(n) (%)</td>
<td>27,649 (36.0%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>(n) (%)</td>
<td>14,993 (19.5%)</td>
</tr>
<tr>
<td>Sufficient physical activity</td>
<td>(n) (%)</td>
<td>33,386 (53.9%)</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>Mean (SD)</td>
<td>25.9 (4.2)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>(n) (%)</td>
<td>14,990 (19.4%)</td>
</tr>
<tr>
<td>Social</td>
<td>(n) (%)</td>
<td>54,072 (70.2%)</td>
</tr>
<tr>
<td>Excessive</td>
<td>(n) (%)</td>
<td>7974 (10.4%)</td>
</tr>
<tr>
<td>Frailty Index—60 deficits version</td>
<td>Mean (SD)</td>
<td>0.15 (0.05)</td>
</tr>
<tr>
<td>Frailty Index—39 deficits version</td>
<td>Mean (SD)</td>
<td>0.16 (0.05)</td>
</tr>
</tbody>
</table>

\(^a\)Except for panic disorder \( (p = 0.236) \), all baseline characteristics were significantly different \( (p < 0.001) \) between study participants with complete data and those who had either missing data at baseline and/or 5-year follow-up with respect to objective 1.

\(^b\)Except for sex \( (p = 0.017) \) and panic disorder \( (p = 0.004) \), all baseline characteristics were significantly different \( (p < 0.001) \) between study participants with complete data and those who had either missing data at baseline and/or 5-year follow-up with respect to objective 2.
### TABLE 2  Score on the Lifelines Frailty Index-60 at baseline as determinant for the onset and persistence of a depressive and/or specific anxiety disorder by multivariable logistic regression

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Younger persons (≤59 years)</th>
<th>Older persons (≥60 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N&lt;sup&gt;a&lt;/sup&gt;</td>
<td>OR [95% C.I.]</td>
</tr>
<tr>
<td>Onset of affective disorders&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>1758/66,372</td>
<td>1.12 [1.11–1.13]</td>
</tr>
<tr>
<td>Any AD</td>
<td>4135/62,484</td>
<td>1.10 [1.09–1.10]</td>
</tr>
<tr>
<td>GAD</td>
<td>3453/64,785</td>
<td>1.10 [1.10–1.11]</td>
</tr>
<tr>
<td>PD</td>
<td>147/67,478</td>
<td>1.13 [1.11–1.16]</td>
</tr>
<tr>
<td>SPH</td>
<td>171/67,049</td>
<td>1.11 [1.10–1.13]</td>
</tr>
<tr>
<td>AGO</td>
<td>1212/65,183</td>
<td>1.10 [1.09–1.11]</td>
</tr>
<tr>
<td>Persistence of affective disorders&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>355/1276</td>
<td>1.06 [1.04–1.08]</td>
</tr>
<tr>
<td>Any AD</td>
<td>1886/5164</td>
<td>1.06 [1.05–1.08]</td>
</tr>
<tr>
<td>GAD</td>
<td>913/2863</td>
<td>1.06 [1.04–1.07]</td>
</tr>
<tr>
<td>PD</td>
<td>24/170</td>
<td>1.07 [0.99–1.15]</td>
</tr>
<tr>
<td>SPH</td>
<td>163/599</td>
<td>1.01 [0.98–1.04]</td>
</tr>
<tr>
<td>AGO</td>
<td>687/2465</td>
<td>1.05 [1.03–1.07]</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; DD, depressive disorder; any AD, any anxiety disorder; GAD, generalized anxiety disorder; PD, panic disorder; SPH, social phobia; AGO, agoraphobia.

<sup>a</sup>The Lifelines Frailty Index-60 was included as a dimensional measure multiplied by 100.

<sup>b</sup>Adjusted for age, sex, level of education, living alone, physical activity, BMI, alcohol use and smoking.

<sup>c</sup>n = number of events; N = eligible population for that analysis.

<sup>d</sup>Sample restricted to persons with no depressive and/or a specific anxiety disorder at baseline.

<sup>e</sup>Sample restricted to persons with a depressive and/or a specific anxiety disorder at baseline.

(A) Onset of affective disorders at 5-year follow-up  
(B) Onset of frailty (FI-35 ≥0.25) at 5-year follow-up

**FIGURE 2** Odds ratios (and 95% confidence intervals) for the onset of either depressive disorder (A, left), any anxiety disorder (A, right) or frailty (B) stratified by age and adjusted for covariates using logistic regression analyses.  
<sup>a</sup>Sample restricted to non-depressed persons at baseline (n = 75,652) to predict onset of depressive disorder at 5-year follow-up.  
<sup>b</sup>Sample restricted to non-anxious persons at baseline (n = 71,389) to predict onset of any anxiety disorder at 5-year follow-up.  
<sup>c</sup>Sample restricted to non-frail persons at baseline (n = 85,217) to predict onset of frailty at 5-year follow-up.
DISCUSSION

Based on a cohort study of 150,187 eligible community participants over a 5-year follow-up, we have shown that depressive disorder as well as anxiety disorders accelerate the accumulation of health deficits and vice versa. The impact of frailty on the onset of depressive disorder is slightly more pronounced with increasing age, while the impact on the onset of anxiety disorders is slightly more pronounced at lower age. The other way around, findings did hardly differ between younger and middle-aged adults compared to older adults regarding the impact of depressive and anxiety disorders on the course of frailty. Only social phobia had a significantly stronger impact on the course of frailty in older compared to younger persons.

To our knowledge, this study is the first one to apply the FI as a useful tool to evaluate the onset of frailty in younger adults, as well as to assess depression and anxiety according to DSM criteria using a psychiatric interview at baseline and 5-year follow-up.

The bidirectional association between mental health and frailty

Systematic reviews and meta-analyses have reported a bidirectional association of depression and frailty over time in older adults.\(^5,13\) Our results confirm these previous findings and extend these findings to younger and middle-aged people. One of the main strengths of our study was the use of DSM-based psychiatric diagnoses, while previous studies on the association between frailty and depression are based mostly on the physical frailty phenotype and self-reported depressive symptoms scales.\(^26,27\) Self-report depression scales are prone to confounding with frailty.\(^28\) Furthermore, prospective studies including both younger and older people have been lacking. Since most aging-related health deficits develop or emerge already in midlife,\(^4\) modern population-based aging studies, like the UK Biobank and the Canadian Longitudinal Study on Aging (CLSA) have included middle-aged people.\(^11,12\) As previously reported, most studies in this field of research have assessed frailty according to the physical frailty phenotype or any of its variations,\(^29\) which is a syndrome-based approach (i.e., three out of five criteria have to be met). The alternative dimensional approach of the continuous FI has, however, been shown to have some clear advantages. First, the FI has better predictive power for adverse health outcomes.\(^30\) Second, the dimensional nature of the FI enables it to assess small changes in frailty severity over time.\(^31\) Third, the FI has been validated as a proxy of accelerated aging in both humans and other species such as dogs and mice.\(^32\) Finally, to avoid confounding due to overlapping components between affective disorders and frailty, one may—as we did—exclude all mental health variables when composing the frailty index.

To our knowledge, only cross-sectional data has demonstrated evidence that (self-reported) anxiety symptoms

| TABLE 3 | Depressive and anxiety disorders as determinants for change in frailty over time by multivariable linear regression\(^a\) |
|----------|---------------------------------------------------------------------------------|----------|---------------------------------------------------------------------------------|----------|
| Frailty at follow-up associated with | Younger adults (\(\leq 59\) years) \((n = 77,036)\) | Older adults (\(60+\) years) \((n = 14,490)\) |
| Psychopathology at baseline (separate models) | | |
| Depressive disorder | 0.03 | \(<0.001\) | 0.04 | \(<0.001\) |
| Any anxiety disorder | 0.02 | \(<0.001\) | 0.01 | 0.142 |
| Generalized anxiety disorder | 0.01 | \(<0.001\) | \(<0.01\) | 0.674 |
| Panic disorder | 0.01 | 0.007 | \(<0.01\) | 0.499 |
| Agoraphobia | 0.02 | \(<0.001\) | 0.01 | 0.150 |
| Social phobia | \(<0.01\) | 0.167 | 0.02 | \(<0.001\) |
| Psychopathology at baseline (combined model) | | |
| Depressive disorder | 0.04 | \(<0.001\) | 0.04 | \(<0.001\) |
| Generalized anxiety disorder | 0.02 | \(<0.001\) | \(<0.01\) | 0.788 |
| Panic disorder | 0.01 | 0.075 | \(<0.01\) | 0.797 |
| Agoraphobia | 0.02 | \(<0.001\) | 0.01 | 0.154 |
| Social phobia | \(<0.01\) | 0.352 | 0.03 | \(<0.001\) |

\(^a\)Dependent variable was the FI-35 at follow-up and the FI-35 at baseline was included as a covariate (so significance points to independent determinants of change of frailty over time).
are associated with frailty.\textsuperscript{11,33} Our findings suggest that this association is also bidirectional over time, although interpretation of these findings is not straightforward.

In our study, frailty is associated with the onset as well as persistence of anxiety disorders in both age groups. These findings confirm a recent study among a selected sample of COVID-19 patients among which frailty was associated with the onset of clinically relevant self-report anxiety levels 1 year after hospitalization.\textsuperscript{34} In our study, the impact of frailty on anxiety seems to be driven by general anxiety disorder (in both age groups) and social phobia (in younger adults only), although the null-result for the other anxiety disorders may be due to limited statistical power.

The other way around, anxiety disorders were consistently associated with an accelerated increase of frailty in younger age group, but not in the older age group. Since the interaction between most anxiety disorders and age were not significant, the non-significant findings in de older age group may again result from a lack of statistical power in this age group. On the other hand, some theoretical explanations can also be put forward to explain these differential results.

Focusing on the positive association in the younger age group, it might be explained by stronger physiological consequences of affective disorders in younger age groups, as it is known that with increasing age the physiological reactivity to stress is reduced and coping skills are enhanced due to maturity and higher level of resilience.\textsuperscript{35,36} Second, pathways linking frailty to mental health might involve specific mechanisms that particularly affect mental health in middle-age, such as hormonal alterations or inflammation,\textsuperscript{37} while in later life, these physiological systems become less active and therefore interfere less with mental health.\textsuperscript{38}

Focusing on the absence of an association in the older age group, it may be explained by more competing pathways for the development of frailty in later life. Furthermore, anxiety disorders and chronic somatic diseases are also associated prospectively in a bidirectional manner.\textsuperscript{39} Diagnostic accuracy of anxiety disorders may be reduced with increasing age, as it can be challenging to determine whether a symptom arises from an anxiety disorder or from a chronic somatic disease.\textsuperscript{40} Interestingly, however, the sensitivity analyses showed that anxiety disorders were associated with the onset of frailty among non-frail older persons. This might be explained by avoidance behavior, which is a core component of anxiety disorders and a determinant of chronicity.\textsuperscript{41} In otherwise healthy older people, avoidance behavior results in a less active and healthy lifestyle which increases the risk of frailty. When persons become frail, avoidance behavior will no longer be a decisive factor on the course of frailty, as frailty itself also limits their activity level. In other words, avoidance behavior may become less relevant in disabled, older persons.

### Underlying pathways

The reciprocal associations found in our study could be explained by several mechanisms.\textsuperscript{5,6} These include both biological mechanisms such as metabolic, inflammatory, cellular, hypothalamic–pituitary–adrenal (HPA) axis dysregulation and cerebrovascular disease\textsuperscript{42} as well as lifestyle characteristics such as smoking, excessive alcohol use, less physical activity and unhealthy diet.\textsuperscript{43–46} Since our analyses were adjusted for lifestyle characteristics, avoidance behavior and biological aging mechanisms seem to be involved. All pathways may be involved in both directions and thus mental health and frailty may be considered as mutually reinforcing conditions.

### Limitations

However, some limitations of our study should be considered. We only assessed current disorders, while most epidemiological studies are based on a past-year or lifetime diagnosis of either anxiety or depressive disorders. Also, anxiety disorders (except panic disorder) are based on 6-month periods, but depressive episodes require only 2 weeks. While this may have underestimated the effect of current disorders, bias might be minor because depressive episodes in the general population have a median duration of 6 months.\textsuperscript{47} Nonetheless, we have no information on the impact of during of illness prior to the study or on the mental status during the five-year follow-up period, and such episodes of mental illness may therefore have just been missed. This latter limitation for example hampers our definition of persistence by also including people with recurrent disorders. Secondly, people with an MMSE score lower than 26 points were excluded. Therefore, results cannot be generalized to older people with mild cognitive impairment or dementia.

One final important limitation of our study is the high dropout rate, which differed between age groups. These age-differences suggest that for older people the MINI might be burdensome, whereas for younger people an additional visit for blood collection might be burdensome. While the baseline population of the Lifelines study cohort is representative of the general population, study dropout was related to the presence of any affective disorder but not to frailty. This could have led to an underestimation of the impact of these affective disorders on the course of frailty.
CONCLUSIONS

In conclusion, our results show a bidirectional dose–response interaction between affective disorders and frailty in younger and older people. Results with respect to the impact of anxiety disorders on frailty suggest most impact at lower levels of frailty. Future clinical and epidemiologic studies should focus on the underlying pathways because this could guide the development of targeted treatment. Nonetheless, even in the absence of more detailed knowledge, interventions targeted at frailty will likely stimulate healthy aging in older adults with affective disorders. Just as these interventions have impact in somatic health care, they could also reduce the number of adverse health outcomes associated with psychiatric disorders and their treatment.

AUTHOR CONTRIBUTIONS
All authors (Marcus K. Borges, Hans W. Jeuring, Radboud M. Marijnissen, Barbara C. van Munster, Ivan Aprahamian, Rob H. S. van den Brink, Emiel O. Hoogendijk, Richard C. Oude Voshaar) satisfy the four conditions of the ICMJE for an authorship by having contributed substantially to the concept of the study, interpretation of the data, critical revision of the article, approval of the final version, and have agreed to be accountable for all aspects of the work. Marcus K. Borges, Richard C. Oude Voshaar, and Rob H. S. van den Brink analyzed the data. Marcus K. Borges drafted the first version under supervision of Ivan Aprahamian. Richard C. Oude Voshaar supervised all of the research.

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CONFLICT OF INTEREST
None of the authors has a conflict of interest.

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REFERENCES


**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**Table S1** Main characteristics of study participants for objective 1 (course of affective disorders, \( n = 77,036 \)) compared to study dropouts stratified by age group.

**Table S2** Main characteristics of study participants for objective 2 (course of frailty, \( n = 89,667 \)) compared to study dropouts stratified by age group.

**Table S3** Depressive and anxiety disorders as predictors of the onset of frailty (i.e., FI-35 at follow-up \( \geq 0.25 \)) among non-frail people at baseline (\( n = 85,217 \)) by multivariable logistic regression.a

**Figure S1** Distribution of the frailty among younger (left) and older people (right).

**Appendix S1** Items included in the frailty index (FI-60 and FI-39) of the LifeLines Cohort Study.