# Mental health outcomes in older breast cancer survivors: five-year follow-up from the CLIMB study

Lemij, A.A.; Glas, N.A.D.; Derks, M.G.M.; Linthorst-Niers, E.M.H.; Guicherit, O.R.; Pol, C.C.V.; ... ; Portielje, J.E.A.

**Citation**

Lemij, A. A., Glas, N. A. D., Derks, M. G. M., Linthorst-Niers, E. M. H., Guicherit, O. R., Pol, C. C. V., ... Portielje, J. E. A. (2023). Mental health outcomes in older breast cancer survivors: five-year follow-up from the CLIMB study. *European Journal Of Cancer*, *187*, 87-95. doi:10.1016/j.ejca.2023.04.001

European Journal of Cancer 187 (2023) 87–95

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

# Mental health outcomes in older breast cancer survivors: Five-year follow-up from the CLIMB study

Annelieke A. Lemij [a,b], Nienke A. de Glas [a], Marloes G.M. Derks [a], Eugenie M.H. Linthorst-Niers [c], Onno R. Guicherit [d], Carmen C. van der Pol [e], Titia E. Lans [f], Thijs van Dalen [g], Annelie J.E. Vulink [h], Jos W.S. Merkus [i], Leander van Gerven [j], Frederiek van den Bos [k], Nathaly Rius Ottenheim [l], Gerrit-Jan Liefers [b,*], Johanneke E.A. Portielje [a]

[a] *Department of Medical Oncology, Leiden University Medical Center, Leiden, the Netherlands*
[b] *Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands*
[c] *Department of Surgery, Groene Hart Hospital, Gouda, the Netherlands*
[d] *Department of Surgery, Haaglanden Medical Center, The Hague, the Netherlands*
[e] *Department of Surgery, Alrijne Hospital, Leiden and Leiderdorp, the Netherlands*
[f] *Department of Surgery, Admiraal de Ruyter Hospital, Goes, the Netherlands*
[g] *Department of Surgery, Diakonessenhuis, Utrecht, the Netherlands*
[h] *Department of Medical Oncology, Reinier de Graaf Gasthuis, Delft, the Netherlands*
[i] *Department of Surgery, Haga Hospital, The Hague, the Netherlands*
[j] *Department of Internal Medicine, LangeLand Hospital, Zoetermeer, the Netherlands*
[k] *Department of Gerontology & Geriatrics, Leiden University Medical Center, Leiden, the Netherlands*
[l] *Department of Psychiatry, Leiden University Medical Center, Leiden, the Netherlands*

Received 19 February 2023; Received in revised form 28 March 2023; Accepted 1 April 2023
Available online 5 April 2023

**KEYWORDS**
Breast cancer;
Older patients;
Mental health outcomes;
Frailty

**Abstract** ***Background:*** There is a lack of information on mental health outcomes for the increasing older population. Therefore, the aim of the current study is to assess depressive symptoms, loneliness, and apathy in older patients with breast cancer within the first 5 years after diagnosis.

***Methods:*** Women aged ≥70 years with early-stage breast cancer were included. Multivariate linear mixed models were used to assess longitudinal changes in symptoms of depression (according to the 15-item Geriatric Depression Scale), loneliness (according to the De Jong

---

* *Corresponding author*: Leiden University Medical Center, Department of Surgery, P.O. Box 9600, 2300 RC Leiden, the Netherlands.
*E-mail address:* g.j.liefers@lumc.nl (G.-J. Liefers).

https://doi.org/10.1016/j.ejca.2023.04.001

Gierveld Loneliness Scale) and apathy (according to the Starkstein Apathy Scale) over time at 3, 9, 15, 27 and 60 months follow-up.

***Results:*** In total, 299 patients were included (mean [standard deviation (SD)] age: 75.8 [5.2] years). At 3 months follow-up, shortly after the acute treatment, 10% of patients had significant depressive symptoms, while loneliness and apathy were present in 31% and 41% of all patients, respectively. Depression, loneliness and apathy scores showed no clinically relevant changes over time in the whole cohort. Patients who received adjuvant systemic therapies (i.e. endocrine therapy and/or chemotherapy and/or targeted therapy (trastuzumab)) had similar mental health outcomes as those who did not. However, frail patients had more symptoms ($p < 0.001$) and were more prone to develop depressive symptoms over time than non-frail patients ($p = 0.002$).

***Discussion:*** Depression, loneliness and apathy were frequently observed in older women with breast cancer and did not change over time. Patients who received adjuvant systemic therapies had similar mental health outcomes as those who did not. However, frail patients were at higher risk to experience these symptoms.

## 1. Introduction

Breast cancer is the most frequently diagnosed malignancy in women, and more than 30% of patients are over the age of 70 years at the time of diagnosis [1]. Older patients form a heterogeneous group with disparities in fitness and frailty. Frailty is a condition in which a person's physiological reserve has deteriorated due to the accumulation of ageing processes in multiple organ systems, making them more susceptible to side effects and complications of treatment [2]. Consequently, older patients are often excluded from participating in large randomised controlled trials, making it challenging to guide individualised, evidence-based treatment for older patients. As the proportion of older patients with breast cancer is expected to increase due to ageing populations, more research in this group is needed.

Although prolongation of life has always been the key aim of cancer treatment, a more comprehensive approach is often required, especially in the older population. An important, perhaps sometimes underestimated, aspect of breast cancer care is the impact of breast cancer diagnosis and treatment on mental health and social functioning [3–8]. Mental health is associated with quality of life and may even have implications for treatment adherence and survival [9,10].

Several studies have investigated mental health outcomes in patients with breast cancer [11–14]. However, few studies have focused on older patients and most studies have a short follow-up, while for the majority of patients the processing and acceptance of their diagnosis and disease begins once the acute symptoms of the disease and its treatment have resolved. Therefore, the aim of the current study was to assess depressive symptoms, loneliness and apathy in older women with early-stage breast cancer in the first 5 years after diagnosis.

## 2. Methods

The Climb Every Mountain study prospectively included women aged 70 years and older with primary, in situ or stage I-III breast cancer from nine Dutch hospitals between 2013 and 2018. Patients were excluded if they had a previous breast cancer history, stage IV disease, were unable to read Dutch, or had advanced dementia. For the current analysis, only patients who completed at least two questionnaires for either depression, loneliness or apathy were included. All patients gave written informed consent, and the study was approved by the medical ethics committee of Leiden University Medical Centre.

### *2.1. Data collection*

Details of this longitudinal cohort study have been extensively described in previous publications [15,16]. In short, a geriatric assessment was performed at baseline, using validated questionnaires on nutritional status (using the Malnutrition Universal Screening Tool (MUST)) [17], cognition (using the Mini-Mental State Examination (MMSE)) [18], functional status (using the Groningen Activity Restriction Scale (GARS)) [19], and mobility (using the Timed Up and Go test (TUG)) [20]. Age, comorbidities (using the Charlson Comorbidity Index, without adjustment for age and breast cancer diagnosis) [21], medication use (categorised as less than five or five or more types of medication), and tumour- and treatment characteristics were also collected at baseline.

Patients were followed up at 3, 9, 15, 27 and 60 months after surgery (Supplemental Fig. 1). Follow-up consisted of multiple assessments and questionnaires, including depression, loneliness and apathy questionnaires. Depressive symptoms were assessed by the 15-item Geriatric Depression Scale (GDS) [22,23]. The

15-item GDS is a shortened screening questionnaire to assess depressive symptoms in older adults. The total score ranges from 0 to 15 and a score of 5 or higher indicates clinically relevant depressive symptoms [23]. De Jong Gierveld Loneliness Scale was used to assess loneliness [24,25]. The 11 items add up to a score between 0 and 11 with a cut-off of 3 for moderate loneliness and a cut-off of 9 for severe loneliness [26]. Apathy was evaluated with the Starkstein Apathy Scale [27]. This questionnaire consists of 14 questions with a maximum score of 42. A score of at least 14 is considered indicative for the presence of clinically relevant apathy [28]. If 10% was missing in any of these three questionnaires, the average of the other questions was taken. If more than 10% of a single questionnaire was missing, that questionnaire was scored as 'unknown'. Recurrences were assessed until 27 months after treatment initiation.

Frailty was defined as impairments in two or more domains: cognitive (MMSE < 24), physical (timed up and go > 12 s), somatic (Charlson Comorbidity Index ≥ 2 or polypharmacy) or nutrition (high risk on the Malnutrition Universal Screening Tool). Patients with a GARS score of ≥29 were also considered frail [29].

### 2.2. *Statistical analysis*

The chi-square test was used to assess differences between patients who had completed questionnaires on at least two time points and those who had not. Least square means were estimated to evaluate average longitudinal trajectories in depressive symptoms, loneliness and apathy during the first 5 years after diagnosis, using linear mixed models. All three outcome measures were separately analysed as dependent variable, with a random intercept and time as a fixed parameter. To adjust for predefined confounders, baseline characteristics age, tumour stage, Charlson Comorbidity Index, type of surgery, and adjuvant systemic therapy were added as fixed parameters to the models [30,31]. Longitudinal trajectories were evaluated for minimal clinically important changes. According to previous studies, any change of two points on the 15-item GDS questionnaire represents a clinically relevant change [32]. As no thresholds exist for the loneliness and apathy questionnaires, clinical relevance was assessed according to Norman's rule-of-thumb [33]. Norman and his colleagues determined that changes of at least half the standard deviation of the baseline mean are considered clinically relevant.

Second, additional analyses were conducted to assess whether the use of adjuvant systemic therapy (yes or no endocrine therapy and/or chemotherapy and/or targeted therapy (trastuzumab)) affected the longitudinal behaviour of depressive symptoms, loneliness and apathy using linear mixed models. An interaction term between time and adjuvant systemic therapy was added to the model to analyse whether longitudinal changes in depressive symptoms, loneliness and apathy differed between patients who were treated with adjuvant systemic therapy and those who were not. This model was repeated with adjustment for age, tumour stage, Charlson Comorbidity Index, and type of surgery. Of note, the median time between start of endocrine therapy and return of the first questionnaire was 2.5 months (interquartile range (IQR): 1–3 months).

Third, differences in outcomes between frail and non-frail patients were studied using linear mixed models. Interaction terms between time and frailty were used to estimate the difference in longitudinal change between frail and non-frail patients. This model was additionally adjusted for age, tumour stage, Charlson Comorbidity Index, type of surgery, and adjuvant systemic therapy.

Fourth, previous studies showed that patients with vascular diseases are at higher risk of developing apathy [34,35]. Therefore, a sensitivity analysis was performed to assess whether the presence of vascular diseases (i.e. myocardial infarction, angina pectoris, myocardial ischaemia, intermittent claudication, arterial surgery, or stroke) was associated with a higher risk of apathy, using linear mixed models.

The results of all linear mixed models were presented as beta coefficients (ß), 95% confidence intervals (CI) and *p*-values. The threshold for a two-sided, statistically significant *p*-value was 0.050. All analyses were performed in SPSS® version 25.0 (IBM, Armonk, New York, USA).

## 3. Results

A total of 299 patients completed questionnaires on at least two different time points and were included in the current analysis (Supplemental Fig. 1). Compared to patients who were excluded, included patients were younger, had less comorbidities and polypharmacy, were less dependent, had more breast (conserving) surgery, and received more radiotherapy (Supplemental Table 1). In the current analysis, half of all patients were 75 years and older and 123 patients (41.1%) had a Charlson Comorbidity Index of 1 or more (Table 1). Very few patients (2.0%) had cognitive deficits (i.e. MMSE < 24) at baseline. Hundred fifty-eight patients (52.9%) were not completely independent in their activities of daily living and instrumental activities of daily living (i.e. GARS ≥ 19). Approximately half of all patients (50.8%) had stage I breast cancer and 246 (82.3%) had oestrogen receptor (ER)-positive tumours. Almost all patients underwent breast surgery (96.3%), of whom 170 patients (56.8%) had breast-conserving surgery and 118 patients (39.5%) a mastectomy. The majority underwent a sentinel lymph node procedure (74.6%). Over half of all patients (51.2%) were not treated with any form of adjuvant systemic treatment, whereas 127

Table 1
Patients-, tumour-, and treatment characteristics at baseline

| | |
|---|---|
| **Age** | |
| 70–74 | 154 (51.5) |
| 75–79 | 67 (22.4) |
| 80–84 | 54 (18.1) |
| ≥85 | 24 (8.0) |
| **TNM stage** | |
| 0 | 11 (3.7) |
| I | 152 (50.8) |
| II | 100 (33.5) |
| III | 18 (6.0) |
| Unknown | 18 (6.0) |
| **Grade** | |
| I | 70 (23.4) |
| II | 122 (40.8) |
| III | 91 (30.4) |
| Unknown | 16 (5.4) |
| **ER-status** | |
| Negative | 33 (11.0) |
| Positive | 246 (82.3) |
| Unknown | 20 (6.7) |
| **PR-status** | |
| Negative | 86 (28.8) |
| Positive | 191 (63.9) |
| Unknown | 22 (7.3) |
| **HER2-status** | |
| Negative | 217 (72.6) |
| Positive | 27 (9.0) |
| Unknown | 55 (18.4) |
| **Charlson Comorbidity Index (CCI)** | |
| 0 | 176 (58.9) |
| 1 | 67 (22.4) |
| ≥2 | 56 (18.7) |
| **Polypharmacy** | |
| No | 177 (59.2) |
| Yes | 108 (36.1) |
| Unknown | 14 (4.7) |
| **BMI** | |
| < 20 | 12 (4.0) |
| 20–25 | 102 (34.2) |
| 25–30 | 116 (38.8) |
| > 30 | 68 (22.7) |
| Unknown | 1 (0.3) |
| **Mental status (MMSE)** | |
| Normal (≥24) | 276 (92.3) |
| Impaired (< 24) | 6 (2.0) |
| Unknown | 17 (5.7) |
| **Functional status (GARS)** | |
| No dependency (< 19) | 138 (46.2) |
| Some dependency (19–28) | 133 (44.5) |
| Disabled (≥ 29) | 25 (8.4) |
| Unknown | 3 (0.9) |
| **Highest education level** | |
| Low | 185 (61.9) |
| Middle | 39 (13.0) |
| High | 52 (17.4) |
| Unknown | 23 (7.7) |
| **Employment status during working life** | |
| Full time | 70 (23.4) |
| Part time | 84 (28.1) |
| Housewife | 104 (34.8) |
| Other/Unknown | 41 (13.7) |
| **Marital status** | |
| Married/living with partner | 143 (47.8) |
| Divorced/widowed | 113 (37.8) |
| Never married | 13 (4.3) |
| Unknown | 30 (10.0) |
| **Living situation** | |
| Independent | 293 (98.0) |
| Assisted living | 5 (1.7) |
| Unknown | 1 (0.3) |
| **Neo-adjuvant systemic treatment** | |
| None | 257 (85.9) |
| Chemotherapy (CT) | 5 (1.7) |
| Endocrine therapy (ET) | 19 (6.4) |
| Unknown | 18 (6.0) |
| **Most extensive breast surgery** | |
| No surgery | 11 (3.7) |
| Breast conserving | 170 (56.8) |
| Mastectomy | 118 (39.5) |
| **Most extensive axillary surgery** | |
| No axillary surgery | 21 (7.0) |
| Sentinel lymph node procedure | 223 (74.6) |
| Axillary lymph node dissection | 52 (17.4) |
| Unknown | 3 (1.0) |
| **Adjuvant systemic treatment** | |
| None | 153 (51.2) |
| Chemotherapy (CT) | 10 (3.3) |
| Endocrine therapy (ET) | 127 (42.5) |
| Combination of ET and CT | 9 (3.0) |
| **Adjuvant radiotherapy** | |
| No | 116 (38.8) |
| Yes | 183 (61.2) |
| **Adjuvant Herceptin (trastuzumab)** | |
| No | 288 (96.3) |
| Yes | 11 (3.7) |

Abbreviations: ER, oestrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CCI, Charlson Comorbidity Index; BMI, body mass index; MMSE, mini-mental state examination; GARS, Groningen Activity Restriction Scale; CT, chemotherapy; ET, endocrine therapy; TNM, primary tumour, lymph node and metastasis, according to the eighth edition of TNM criteria from the cancer staging manual of the American Joint Committee on Cancer.

patients (42.5%) received endocrine therapy, 10 patients (3.3%) chemotherapy and 9 patients (3.0%) both. Of note, 10 out of 299 (3.3%) patients had a recurrence within 27 months after treatment initiation. Six of them continued to complete questionnaires afterwards, three died soon after and one was lost to follow-up.

### 3.1. Depression

Thirty-one patients (10.4%) had depressive symptoms three months after diagnosis. After adjustment for predefined confounders, depressive scores barely increased over time ($ß = 0.01$; 95% CI = 0.01–0.02; $p < 0.001$) (Fig. 1). Patients who received adjuvant systemic therapies had similar rates of depression as those who did not ($ß = -0.02$; 95% CI = −0.61 to 0.57; $p = 0.95$) and the longitudinal trajectories of depressive symptoms were also equal for both groups ($p = 0.73$) (Fig. 2).

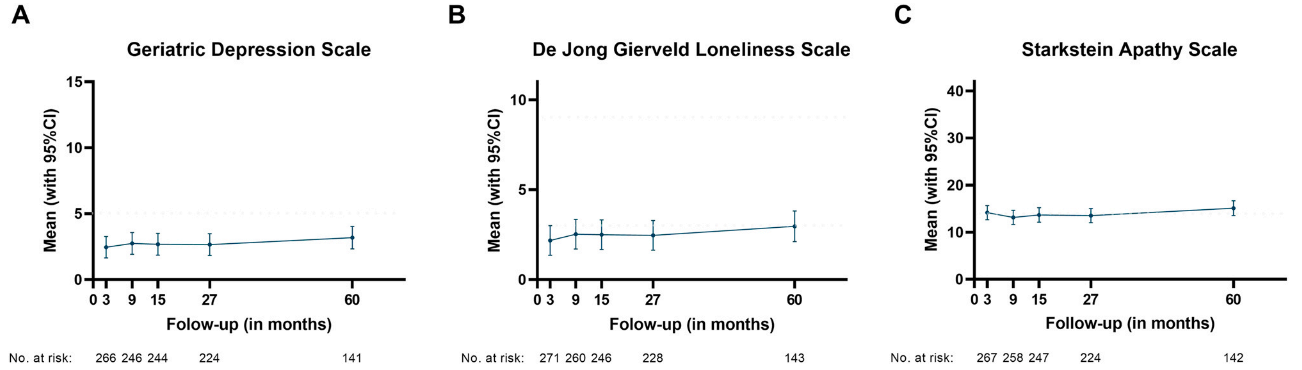

Fig. 1. Depressive symptoms (A), loneliness (B) and apathy (C) over a 5-year follow-up period. All graphs are adjusted for age, tumour stage, Charlson Comorbidity Index, type of breast surgery, and adjuvant systemic therapy. The horizontal dashed lines indicate cut-off values. The number of completed questionnaires are described below the graphs.

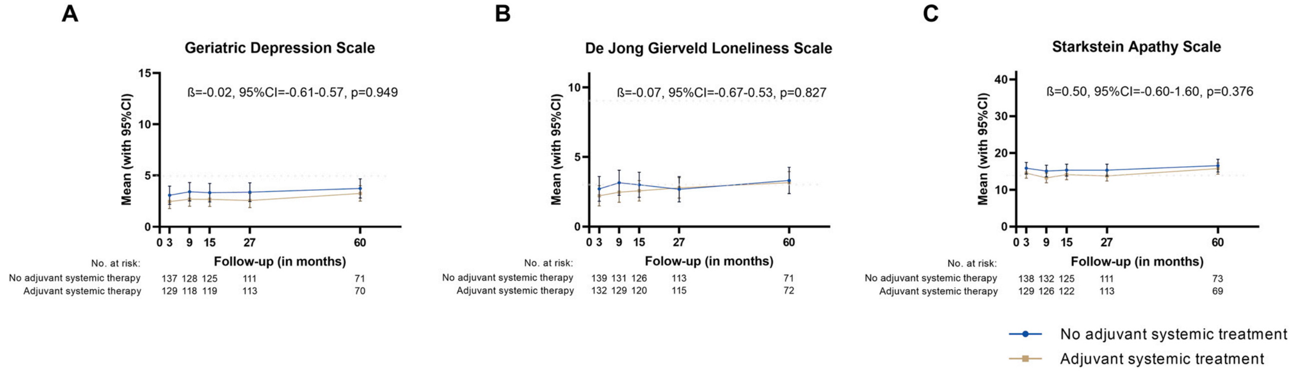

Fig. 2. Depressive symptoms (A), loneliness (B) and apathy (C) stratified for adjuvant systemic therapy over a five-year follow-up period. All graphs are adjusted for age, tumour stage, Charlson Comorbidity Index, and type of breast surgery. The horizontal dashed lines indicate cut-off values. The number of completed questionnaires is described below the graphs.

Patients who were classified as frail at baseline experienced more depressive symptoms over the entire study period than non-frail patients (ß = 2.13; 95% CI = 1.25–3.01; $p < 0.001$) (Fig. 3). Moreover, according to the statistically significant interaction term between frailty and time ($p = 0.002$), frail patients developed (clinically significantly) more depressive symptoms during follow-up than non-frail patients.

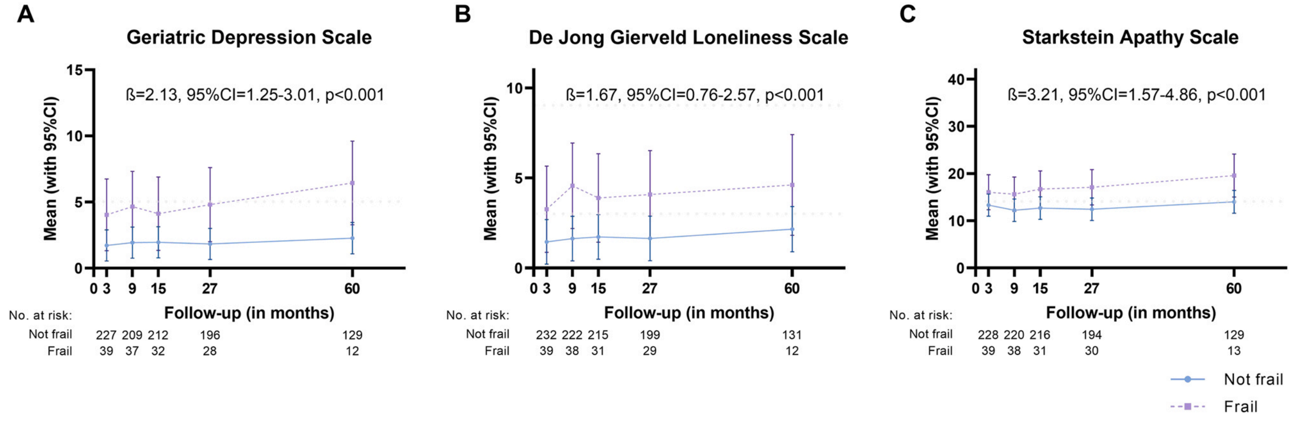

Fig. 3. Depressive symptoms (A), loneliness (B) and apathy (C) stratified for frailty over a five-year follow-up period. All graphs are adjusted for age, tumour stage, Charlson Comorbidity Index, type of breast surgery, and adjuvant systemic therapy. The horizontal dashed lines indicate cut-off values. The number of completed questionnaires are described below the graphs.

### 3.2. Loneliness

Ninety-two patients (30.8%) experienced loneliness at three months follow-up, of whom 83 (27.8%) had moderate and 9 (3.0%) severe loneliness. Linear mixed models showed a very small increase in symptoms over time (ß = 0.01; 95% CI = 0.01–0.02; $p < 0.001$) (Fig. 1). Patients treated with adjuvant systemic therapy were not lonelier than patients not treated with adjuvant systemic therapy (ß = −0.07; 95% CI = −0.67 to 0.53; $p = 0.83$) and their longitudinal trajectories were similar ($p = 0.05$) (Fig. 2). Patients who were classified as frail at baseline were lonelier than non-frail patients (ß = 1.67; 95% CI = 0.76–2.57; $p < 0.001$). Moreover, frail patients had mean scores above the clinically relevant threshold for moderate loneliness over the entire study period, while non-frail patients did not (Fig. 3). The longitudinal changes were the same for frail and non-frail patients ($p = 0.52$).

### 3.3. Apathy

Apathy was prevalent in 121 patients (40.5%) at 3 months after diagnosis and the average apathy score grew marginally each month (ß = 0.02; 95% CI = 0.01–0.04; $p = 0.002$) (Fig. 1). Patients who were treated with adjuvant systemic therapy had similar apathy scores (ß = 0.50; 95% CI = −0.60 to 1.60; $p = 0.38$) and similar longitudinal trajectories over time ($p = 0.31$) than patients without adjuvant systemic therapy (Fig. 2). Frail patients scored worse on the apathy questionnaire than non-frail patients during follow-up (ß = 3.21; 95% CI = 1.57–4.86; $p < 0.001$), exceeding the threshold for clinically relevant apathy (Fig. 3). Moreover, frail patients developed more apathy during follow-up than non-frail patients ($p = 0.03$). Vascular diseases at baseline were not associated with a higher occurrence of apathy over the entire study period (ß = 0.26; 95% CI = −1.44 to 1.95; $p = 0.77$) and were not associated with an increased risk of developing apathy over time ($p = 0.69$).

## 4. Discussion

This real-world multicentre cohort study of older women with early-stage breast cancer showed that shortly after surgery, 10%, 31% and 41% of patients had depressive symptoms, loneliness and apathy, respectively. Longitudinal trajectories of these outcomes did not change clinically significantly in the first 5 years of follow-up for the whole group. Importantly, patients who received adjuvant systemic therapies had similar mental health outcomes as those who did not. Frail patients had more symptoms after surgery and were more prone to developing clinically relevant depression over time.

A recent systematic review showed that single (divorced or widowed) women who have a low income, an advanced diagnosis, functional limitations, comorbidities, and low social support are at higher risk of emotional distress, which are all factors inherent in many older patients with breast cancer [30]. Our study showed that around a third of older patients experienced loneliness after the acute phase of treatment and that frail patients were more likely to be lonely than non-frail patients. The prevalence of loneliness is consistent with previous reports. Deckx and colleagues found that 22% of around one hundred older patients with early-stage breast or colorectal cancer were lonely at the time of diagnosis and 35% at 1-year follow-up [6]. De Boer et al. demonstrated that one-third of older patients with metastasised breast cancer (N = 80) experienced loneliness at baseline and throughout a 6-month follow-up period [36]. To put the high prevalence of loneliness among breast cancer survivors into perspective, a previous study found that 39% of older adults from the general population without cancer experienced loneliness [6]. Nevertheless, extensive research has shown that loneliness is a major health concern as it is associated with unhealthy behaviours, impaired physical functioning, worse quality of life, and increased morbidity and mortality [37,38]. Therefore, this high prevalence still requires further attention. Effective loneliness interventions already exist, but sample sizes are small and no studies have specifically focused on older patients with breast cancer [39–42].

Depression is generally quite common in breast cancer survivors, with a prevalence ranging from 8% to 66% [12,13,43,44]. The occurrence of clinically relevant depression in the current study is similar to what has been previously reported in the general older population (5–15%) and much lower than has been found in the advanced setting (46%) [36,43,45]. This relatively low percentage of depressive symptoms in older breast cancer survivors may reflect different treatment allocation and an increased psychological resilience in this age group due to their life stage, while the latter is probably less in frail older patients. Moreover, the majority of patients in the current analysis had hormone receptor-positive disease in which recurrences rarely occur within the first 5 years. According to a study at longer follow-up (cross sectional at 5–16 years post-diagnosis), older breast cancer survivors without recurrences had similar depression rates as controls with no history of breast cancer [46]. However, patients aged 80 years and younger with a recurrence had considerably higher rates of depression than their controls, but not when they were 80–89 years old.

A less frequently reported mental health outcome in patients with breast cancer is apathy [47]. Apathy is characterised by diminished goal-directed behaviour, cognition and emotion, leading to reduced daily functioning [48]. Apathy can be present as a symptom of depression, but can also occur on its own [49]. A previous study of over 1100 Dutch community-dwelling older adults aged 75 years and older found that 11% of them experienced apathy [28]. This percentage is much lower than was found in our study of older patients with breast cancer and than what has been previously reported in the advanced setting [36]. Apathy is often overlooked by physicians as it is usually not perceived as a nuisance by patients themselves. Moreover, patients with apathy typically have low degrees of suffering and tend to be indifferent, which can result in neglect and caregiver distress [50]. As apathy also interferes with poor treatment adherence and outcome, it requires further attention [51]. There are currently no specific interventions available for this population.

Although it is difficult to identify an aetiological association between systemic therapy and mental health outcomes, endocrine therapy and chemotherapy are believed to exacerbate it, especially depressive symptoms. Fear of these side effects may be a reason for withholding therapy. Nevertheless, the current study showed no difference in apathy, loneliness and depression in patients treated with adjuvant systemic therapy and those not. The results suggest that adjuvant systemic therapy in older patients should not be withheld in fear of worse mental health outcomes, although it must be noted that in this observational cohort, patients with pre-existing mental health problems may have been more reluctant to start adjuvant treatment.

Previous research has shown that patients are reluctant to ask for psychological help [52]. Also, healthcare professionals are not always familiar with all psychological care facilities, do not know how to discuss these topics or simply lack time to do so [52]. Nevertheless, it is important for patients, caregivers and physicians to be aware of the potential impact of cancer and its treatment on mental health outcomes, as well as the possibility of psychosocial support. Psychological care should therefore be given more prominence in breast cancer care to ensure timely detection of patients with a wish for referral to psychological care. Training in communication skills for physicians proved useful in integrating the discussion on mental health outcomes into daily clinical practice [53].

The most important strength of this study is its longitudinal design with extensive information on older women with breast cancer. The study also has limitations. Although the intention was to include all women aged 70 years and older with breast cancer into our study, a relatively fit older population was included. Since frailty exacerbates depressive symptoms, loneliness and apathy, the current study may underestimate the prevalence of these outcomes. Nevertheless, the current study revealed that depressive symptoms, loneliness and apathy are common and frailty probably warrants more attention by physicians. Another limitation of the study is that patients that experienced disease recurrence were not excluded from follow-up, which may have impacted the outcome. However, the number of recurrences was very small, so the impact of this factor is likely to be limited. Furthermore, the first questionnaires on depression, loneliness and apathy were completed at a median time of three months after surgery (IQR: 3–4 months). It is therefore difficult to draw conclusions about the direct effect of surgery on these mental health outcomes. However, baseline questionnaires on mental health outcomes may be burdensome for patients at the time of diagnosis (as the questionnaires are quite time-consuming) and the results at that time may also be biased because of the large mental stress the cancer diagnosis already brings.

In conclusion, depression, loneliness and apathy are common in older women with breast cancer, especially in frail patients. Although depressive symptoms and loneliness do not appear to be more prevalent than in the general older population, apathy is. Importantly, adjuvant systemic therapy does not seem to exacerbate these symptoms. As mental health outcomes may interfere with adherence to therapy, survival and quality of life, it is important to address the potential impact of cancer on mental health outcomes and to inform patients about the possibility of psychosocial support.

## Funding

This work was supported by KWF Kankerbestrijding with grant reference number: UL 2011-5263. The funder did not play a role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

## CRediT authorship contribution statement

Conceptualization; GJL, NAdG, JEAP, Data curation; NAdG, MGMD, AAL, Formal analysis; NAdG, EB, AAL, Funding acquisition; GJL, NAdG, JEAP, Investigation; JEAP, GJL, NAdG, AAL, Methodology; JEAP, GJL, NAdG, AAL, MGMD, NRO, Project administration; NAdG, MGMD, AAL, Resources; JEAP, Software; AAL, NAdG, MGMD, Supervision; JEAP, GJL, NAdG, MGMD, NRO, Validation; NAdG, MGMD, Visualization; AAL, Roles/Writing—original draft; AAL, NAdG, MGMD, JEAP, GJL, Writing—review & editing; all authors.

## Data availability

The dataset generated during and analysed during the current study are not publicly available due to participant privacy but are available from the corresponding author on reasonable request.

## Declaration of Competing Interest

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

## Acknowledgements

The authors thank Wil Planje and Elma Meershoek-Klein Kranenbarg from the Datacenter Heelkunde for data collection and preparation of the datasets.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.04.001.

## References

[1] DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, et al. Breast cancer statistics, 2019. CA Cancer J Clin 2019;69(6):438–51.

[2] Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. Lancet 2019;394(10206):1365–75.

[3] Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol 2011;12(2):160–74.

[4] Pilevarzadeh M, Amirshahi M, Afsargharehbagh R, Rafiemanesh H, Hashemi SM, Balouchi A. Global prevalence of depression among breast cancer patients: a systematic review and meta-analysis. Breast Cancer Res Treat 2019;176(3):519–33.

[5] Hashemi SM, Rafiemanesh H, Aghamohammadi T, Badakhsh M, Amirshahi M, Sari M, et al. Prevalence of anxiety among breast cancer patients: a systematic review and meta-analysis. Breast Cancer 2020;27(2):166–78.

[6] Deckx L, van den Akker M, van Driel M, Bulens P, van Abbema D, Tjan-Heijnen V, et al. Loneliness in patients with cancer: the first year after cancer diagnosis. Psycho-Oncol 2015;24(11):1521–8.

[7] Lemij AA, de Glas NA, Derks MGM, Bastiaannet E, Merkus JWS, Lans TE, et al. Discontinuation of adjuvant endocrine therapy and impact on quality of life and functional status in older patients with breast cancer. Breast Cancer Res Treat 2022;193(3):567–77.

[8] Vaz-Luis I, Masiero M, Cavaletti G, Cervantes A, Chlebowski RT, Curigliano G, et al. ESMO expert consensus statements on cancer survivorship: promoting high-quality survivorship care and research in Europe. Ann Oncol 2022;33(11):1119–33.

[9] Colleoni M, Mandala M, Peruzzotti G, Robertson C, Bredart A, Goldhirsch A. Depression and degree of acceptance of adjuvant cytotoxic drugs. The Lancet 2000;356(9238):1326–7.

[10] Wang X, Wang N, Zhong L, Wang S, Zheng Y, Yang B, et al. Prognostic value of depression and anxiety on breast cancer recurrence and mortality: a systematic review and meta-analysis of 282,203 patients. Mol Psychiatry 2020;25(12):3186–97.

[11] Maass SWMC, Boerman LM, Verhaak PFM, Du J, de Bock GH, Berendsen AJ. Long-term psychological distress in breast cancer survivors and their matched controls: a cross-sectional study. Maturitas 2019;130:6–12.

[12] Pilevarzadeh M, Amirshahi M, Afsargharehbagh R, Rafiemanesh H, Hashemi S-M, Balouchi A. Global prevalence of depression among breast cancer patients: a systematic review and meta-analysis. Breast Cancer Res Treat 2019;176(3):519–33.

[13] Maass SW, Roorda C, Berendsen AJ, Verhaak PF, de Bock GH. The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. Maturitas 2015;82(1):100–8.

[14] Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. BMJ 2005;330(7493):702.

[15] Lemij AA, van der Plas-Krijgsman WG, Bastiaannet E, Merkus JWS, van Dalen T, Vulink AJE, et al. Predicting postoperative complications and their impact on quality of life and functional status in older patients with breast cancer. Br J Surg 2022;109(7):595–602.

[16] van der Plas-Krijgsman WG, Morgan JL, de Glas NA, de Boer AZ, Martin CL, Holmes GR, et al. Differences in treatment and survival of older patients with operable breast cancer between the United Kingdom and the Netherlands - a comparison of two national prospective longitudinal multi-centre cohort studies. Eur J Cancer 2022;163:189–99.

[17] Boléo-Tomé C, Monteiro-Grillo I, Camilo M, Ravasco P. Validation of the Malnutrition Universal Screening Tool (MUST) in cancer. Br J Nutr 2012;108(2):343–8.

[18] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189–98.

[19] Kempen GI, Suurmeijer TP. The development of a hierarchical polychotomous ADL-IADL scale for noninstitutionalized elders. Gerontologist 1990;30(4):497–502.

[20] Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991;39(2):142–8.

[21] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–83.

[22] Korner A, Lauritzen L, Abelskov K, Gulmann N, Marie Brodersen A, Wedervang-Jensen T, et al. The geriatric depression scale and the cornell scale for depression in dementia. A validity study. Nord J Psychiatry 2006;60(5):360–4.

[23] D'Ath P, Katona P, Mullan E, Evans S, Katona C. Screening, detection and management of depression in elderly primary care attenders. I: The acceptability and performance of the 15 Item Geriatric Depression Scale (GDS15) and the development of short versions. Family Pract 1994;11(3):260–6.

[24] De Jong Gierveld J, Van Tilburg T. The De Jong Gierveld short scales for emotional and social loneliness: tested on data from 7 countries in the UN generations and gender surveys. Eur J Ageing 2010;7(2):121–30.

[25] de Jong-Gierveld J, Kamphuls F. The development of a Rasch-type loneliness scale. Appl Psychol Measurement 1985;9(3):289–99.

[26] van Tilburg T, de Jong-Gierveld J. Cesuurbepaling van de eenzaamheidsschaal. Tijdschr voor Gerontol en Geriatr 1999;30:158–63.

[27] Starkstein SE, Petracca G, Chemerinski E, Kremer J. Syndromic validity of apathy in Alzheimer's disease. Am J Psychiatry 2001;158(6):872–7.

[28] Groeneweg-Koolhoven I, de Waal MWM, van der Weele GM, Gussekloo J, van der Mast RC. Quality of life in community-dwelling older persons with apathy. Am J Geriatr Psychiatry 2014;22(2):186–94.

[29] Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Ann Oncol 2015;26(6):1091–101.

[30] Silva S, Bártolo A, Santos IM, Pereira A, Monteiro S. Towards a better understanding of the factors associated with distress in elderly cancer patients: a systematic review. Int J Environ Res Public Health 2022;19(6):3424.

[31] Steptoe A, Deaton A, Stone AA. Subjective wellbeing, health, and ageing. Lancet 2015;385(9968):640–8.

[32] Vinkers DJ, Gussekloo J, Stek ML, Westendorp RG, Van Der Mast RC. The 15-item Geriatric Depression Scale (GDS-15) detects changes in depressive symptoms after a major negative life event. The Leiden 85-plus Study. Int J Geriatr Psychiatry 2004;19(1):80–4.

[33] Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41(5):582–92.

[34] van der Mast RC, Vinkers DJ, Stek ML, Bek MC, Westendorp RG, Gussekloo J, et al. Vascular disease and apathy in old age. The Leiden 85-Plus Study. Int J Geriatr Psychiatry 2008;23(3): 266–71.

[35] Dalen JWv, Charante EPMv, Nederkoorn PJ, Gool WAv, Richard E. Poststroke apathy. Stroke 2013;44(3):851–60.

[36] de Boer AZ, Derks MGM, de Glas NA, Bastiaannet E, Liefers GJ, Stiggelbout AM, et al. Metastatic breast cancer in older patients: a longitudinal assessment of geriatric outcomes. J Geriatr Oncol 2020;11(6):969–75.

[37] Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. Perspect Psychol Sci 2015;10(2):227–37.

[38] Musich S, Wang SS, Hawkins K, Yeh CS. The impact of loneliness on quality of life and patient satisfaction among older, sicker adults. Gerontol Geriatr Med 2015;1:2333721415582119.

[39] Nelson CJ, Saracino RM, Roth AJ, Harvey E, Martin A, Moore M, et al. Cancer and Aging: Reflections for Elders (CARE): a pilot randomized controlled trial of a psychotherapy intervention for older adults with cancer. Psychooncology 2019;28(1):39–47.

[40] Samarel N, Tulman L, Fawcett J. Effects of two types of social support and education on adaptation to early-stage breast cancer. Res Nurs Health 2002;25(6):459–70.

[41] Tabrizi FM, Radfar M, Taei Z. Effects of supportive-expressive discussion groups on loneliness, hope and quality of life in breast cancer survivors: a randomized control trial. Psychooncology 2016;25(9):1057–63.

[42] McElfresh JJ, Skiba MB, Segrin CG, Badger TA, Crane TE, Crist JD, et al. Interventions for loneliness among adult cancer survivors: a systematic review and meta-analysis. J Psychosoc Oncol 2021;39(4):509–33.

[43] Deckx L, van Abbema DL, van den Akker M, van den Broeke C, van Driel M, Bulens P, et al. A cohort study on the evolution of psychosocial problems in older patients with breast or colorectal cancer: comparison with younger cancer patients and older primary care patients without cancer. BMC Geriatr 2015;15:79.

[44] Charles C, Bardet A, Larive A, Gorwood P, Ramoz N, Thomas E, et al. Characterization of depressive symptoms trajectories after breast cancer diagnosis in women in France. JAMA Netw Open [Internet] 2022;5(4):e225118https://doi.org/10.1001/jamanetworkopen.2022.5118 Available from: http://europepmc.org/abstract/MED/35420663 〈https://europepmc.org/articles/PMC9011125〉.

[45] Fiske A, Wetherell JL, Gatz M. Depression in older adults. Annu Rev Clin Psychol 2009;5:363–89.

[46] Doege D, Thong MSY, Koch-Gallenkamp L, Jansen L, Bertram H, Eberle A, et al. Age-specific prevalence and determinants of depression in long-term breast cancer survivors compared to female population controls. Cancer Med 2020;9(22):8713–21.

[47] Carreira H, Williams R, Müller M, Harewood R, Stanway S, Bhaskaran K. Associations between breast cancer survivorship and adverse mental health outcomes: a systematic review. J Natl Cancer Inst 2018;110(12):1311–27.

[48] Maris R. Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci 1991;3(3):243–54.

[49] Ishii S, Weintraub N, Mervis JR. Apathy: a common psychiatric syndrome in the elderly. J Am Med Dir Assoc 2009;10(6):381–93.

[50] Pinyopornpanish K, Soontornpun A, Wongpakaran T, Wongpakaran N, Tanprawate S, Pinyopornpanish K, et al. Impact of behavioral and psychological symptoms of Alzheimer's disease on caregiver outcomes. Sci Rep 2022;12(1):14138.

[51] van der Linde RM, Matthews FE, Dening T, Brayne C. Patterns and persistence of behavioural and psychological symptoms in those with cognitive impairment: the importance of apathy. Int J Geriatr Psychiatry 2017;32(3):306–15.

[52] Schuit AS, Holtmaat K, van Zwieten V, Aukema EJ, Gransier L, Cuijpers P, et al. Organizing psycho-oncological care for cancer patients: the patient's perspective. Front Psychol 2021;12.

[53] Moore PM, Rivera S, Bravo-Soto GA, Olivares C, Lawrie TA. Communication skills training for healthcare professionals working with people who have cancer. Cochrane Database Syst Rev 2018;7(7):Cd003751.