

Longitudinal Trajectories of Functional Dependency and Depressive Symptoms Among Middle-Aged and Older Adult Cancer Survivors: A Linear Mixed-Effects Analysis from the China Health and Retirement Longitudinal Study

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Research Article

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Abstract

Purpose

Cancer survivors face substantial physical and psychological sequelae, but large-scale longitudinal evidence on functional and depressive trajectories remains limited, particularly in China. This study quantified differences in activities of daily living (ADL), instrumental ADL (IADL), and depressive symptom trajectories between cancer survivors and controls, and tested sex differences.

Methods

Waves 2–5 (2013–2020) of the China Health and Retirement Longitudinal Study were analyzed using random-intercept linear mixed-effects models for ADL, IADL, and CES-D 10 scores among 815 cancer survivors and 22,131 controls (22,946 participants; 67,647 observations), adjusted for sex and baseline age. Multiplicity was controlled with the Holm procedure; sensitivity analyses comprised covariate adjustment, age ≥ 45 restriction, and binary-outcome models.

Results

Cancer survivors had higher baseline ADL (0.44 vs. 0.28), IADL (0.60 vs. 0.41), and CES-D (8.92 vs. 7.66). Time $\times$ cancer interactions were significant for ADL (beta = 0.019/year, $p < 0.001$), IADL (beta = 0.014, $p = 0.020$), and CES-D (beta = 0.082, $p = 0.021$); all survived Holm correction, indicating 1.7-, 1.8-, and 1.5-fold faster deterioration, with robust sensitivity analyses. Three-way time $\times$ cancer $\times$ sex tests were non-significant (all $p > 0.14$).

Conclusion

Chinese middle-aged and older cancer survivors show accelerated deterioration in both functional dependency and depressive symptoms, alongside a persistently higher depression burden. These findings support integrated long-term survivorship care combining functional monitoring with sustained psychological support.

What does this article add?

- In a nationally representative Chinese cohort of 22,946 middle-aged and older adults (815 cancer survivors) followed over seven years, cancer survivors experienced significantly faster annual deterioration in both physical function (ADL 1.7-fold; IADL 1.8-fold) and depressive symptoms (CES-D 1.5-fold) than peers without cancer.
- Beyond a persistently higher depression burden, the depressive gap widened over time, while formal interaction testing showed no significant sex differences—supporting integrated, long-term survivorship care that combines routine functional monitoring with sustained psychological support for all survivors.

1. Background

Cancer survival rates have improved considerably over recent decades, and in the United States alone, nearly 17 million people are living with a history of cancer.[1] In China, cancer incidence ranks highest worldwide and the number of survivors continues to grow.[2, 3] Yet surviving cancer does not simply mean returning to a pre-diagnosis state of health. Surgery, chemotherapy, radiotherapy, and newer targeted therapies can all leave lasting physical and psychological sequelae that accumulate over time.[4] Understanding the scope and trajectory of these long-term effects, and whether they differ between men and women, is central to building effective survivorship care.

Functional decline is among the most consequential of these sequelae. Activities of daily living (ADL) and instrumental activities of daily living (IADL) are standard measures of independence in older adults.[5] Population-based studies show that cancer survivors report more functional limitations than peers without a cancer history,[6] and longitudinal work on frailty trajectories documents a substantial subgroup with progressive deterioration.[7] Biological explanations include treatment-related sarcopenia, peripheral neuropathy, cardiopulmonary toxicity, and chronic inflammation (elevated IL-6 and CRP).[8] Most prior evidence, however, comes from single cancer types, small Western samples, or cross-sectional designs; large-scale longitudinal data from Chinese populations are lacking.

Depression represents a parallel and possibly intertwined burden. Clinically significant depressive symptoms affect cancer populations at roughly twice the general-population prevalence,[9] and are associated with poorer adherence, lower quality of life, and increased mortality.[10] Longitudinal evidence from breast cancer cohorts indicates that some survivors experience chronic or worsening symptoms rather than recovery,[11] and death anxiety partly mediates the link between symptom burden and psychological distress.[12] Physical-activity interventions can improve physical function, quality of life, and fatigue together in survivors,[13] suggesting the two domains share modifiable determinants.

Indeed, depression and functional decline may be bidirectionally linked: depression promotes inactivity and social withdrawal, which accelerate functional loss, while functional limitations may deepen helplessness; inflammatory pathways and the cancer-related accelerated-ageing framework provide a unifying biological context.[8, 14] Whether this “dual deterioration” is amplified in cancer survivors has not been well characterized longitudinally.

Sex adds further complexity. Women generally report more functional limitations but draw on stronger social support and more adaptive emotion-focused coping,[15] whereas men may experience heightened psychological impact from disrupted provider roles.[16] Sex-stratified longitudinal data on cancer survivors are scarce, particularly in non-Western settings, and formal tests of sex differences in trajectory slopes are rarely reported.

The China Health and Retirement Longitudinal Study (CHARLS) offers a valuable data resource for addressing these gaps: a nationally representative cohort of adults aged 45 and older with repeated assessments of health, function, and psychological wellbeing from 2011 to 2020.[17] Using CHARLS data from 2013 to 2020 (Waves 2–5), this study aimed to: (1) quantify longitudinal trajectory differences in ADL, IADL, and CES-D depressive symptoms between cancer survivors and non-cancer controls; (2) assess the independent effect of cancer history on functional and psychological deterioration; and (3) formally test sex differences in cancer-related trajectories through sex-stratified analyses and three-way interaction models.

2. Methods

2.1. Data source and study population

CHARLS employs a multistage stratified probability sampling strategy, covering 150 county-level units and 450 village-level units across China, representing adults aged ≥ 45 years nationwide.[17] The baseline survey was conducted in 2011 (Wave 1), with follow-up waves in 2013 (Wave 2), 2015 (Wave 3), 2018 (Wave 4), and 2020 (Wave 5).

This study used Waves 2–5 (2013–2020). Wave 1 was excluded because the IADL module had unacceptably high missingness ($> 50\%$), which would have compromised the completeness of outcome assessment. Inclusion criteria were: (1) participation in at least one wave with complete ADL, IADL, and CES-D assessments; and (2) determinable cancer status. The final analytical sample comprised 22,946 participants contributing 67,647 person-wave observations (2,445 from cancer survivors and 65,202 from non-cancer controls).

2.2. Measures

Cancer status. Cancer status was defined using the CHARLS harmonized cancer history indicator (variable *cancre*), which identifies respondents who reported having been diagnosed with cancer or a malignant tumor. Participants who reported a cancer diagnosis at any of Waves 2–5 were classified as cancer survivors (*cancer* = 1); those who never reported cancer across all waves were classified as non-cancer controls (*cancer* = 0).

Outcome variables. Three outcomes were examined: (1) ADL score (0–6), comprising six basic self-care activities (dressing, bathing, eating, getting in/out of bed, toileting, and continence), each scored 0 = no difficulty or 1 = difficulty; (2) IADL score (0–5), comprising five instrumental activities (housework, cooking, shopping, telephone use, and managing money), scored identically; and (3) CES-D 10 score (0–30), a 10-item depression scale. Higher scores indicate greater functional impairment or more severe depressive symptoms.

Covariates. Sex (male/female) and baseline age (age at first observation) were included as covariates in the primary models. For sensitivity analyses, education level (*raeduc1*: three categories reflecting low/medium/high education) and urban/rural classification (*hrural*: 0 = urban, 1 = rural) were additionally included.

Time variable. Time was defined as years since the individual's first observation; participants entering at Wave 2 (2013) had time = 0, with subsequent observations at 2, 5, and 7 years (Waves 3–5).

2.3. Statistical analysis

Linear mixed-effects models (LMMs) with random intercepts for individuals were employed to analyze longitudinal changes in each outcome. The model specification was:

$$Y_{ij} = \beta_0 + \beta_1 time_{ij} + \beta_2 cancer_i + \beta_3 (time_{ij} \times cancer_i) + \beta_4 sex_i + \beta_5 age_i + u_i + \epsilon_{ij}$$

where Y_{ij} represents the outcome for individual i at wave j ; β_3 (the time $\times$ cancer interaction) is the primary parameter of interest, representing the additional annual change in cancer survivors relative to non-cancer controls; u_i is the individual-specific random intercept accounting for within-person correlation; and ϵ_{ij} is the residual error term.

Separate models were fitted with ADL, IADL, and CES-D as the dependent variable. The Satterthwaite approximation was used for denominator degrees of freedom and p-value computation. Restricted maximum likelihood (REML) estimation was applied.

Robustness was assessed through: (1) sequential addition of education and urban/rural classification as covariates; (2) restriction to participants aged ≥ 45 years at baseline; and (3) generalized linear mixed models (GLMMs) with binary outcomes (any ADL difficulty, any IADL difficulty, CES-D ≥ 10), using a logit link. Sex-stratified models (adjusted for age) and formal three-way interaction models (time x cancer x sex) tested whether trajectory differences differed between sexes.

Analyses used R version 4.3.3 (lme4, lmerTest). Significance was set at $\alpha = 0.05$ (two-sided); for the three primary outcomes, multiplicity was controlled with the Holm stepwise procedure, with unadjusted p-values reported alongside. The repeated-measures approach is consistent with prior longitudinal work capturing dynamic psychological changes in chronic disease populations.[18] The study is reported following the STROBE guideline for observational research.

3. Results

3.1. Sample characteristics

The final analytical sample included 22,946 participants (815 cancer survivors and 22,131 non-cancer controls), contributing 67,647 person-wave observations (2,445 from cancer survivors and 65,202 from controls).

Baseline characteristics are summarized in Table 1. Cancer survivors were slightly older (58.75 ± 9.71 vs. 57.65 ± 10.14 years) and more often female (63.1% vs. 51.6%), and had significantly worse outcomes across all three domains: ADL scores were 1.6 times higher (0.44 ± 1.03 vs. 0.28 ± 0.84), IADL scores 1.5 times higher (0.60 ± 1.12 vs. 0.41 ± 0.97), and CES-D scores higher by 1.26 points (8.92 ± 6.36 vs. 7.66 ± 5.86 ; all $p < 0.001$ in models adjusted for sex and baseline age).

Table 1
Baseline characteristics of cancer survivors and non-cancer controls

Characteristic	Cancer survivors (n = 815)	Non-cancer controls (n = 22,131)
Age, years, mean +/- SD	58.75 +/- 9.71	57.65 +/- 10.14
Male, n (%)	301 (36.9%)	10,701 (48.4%)
Female, n (%)	514 (63.1%)	11,430 (51.6%)
Education - Low, n (%)	709 (87.0%)	19,165 (86.6%)
Education - Middle, n (%)	87 (10.7%)	2,392 (10.8%)
Education - High, n (%)	19 (2.3%)	570 (2.6%)
Urban, n (%)	366 (44.9%)	9,401 (42.5%)
Rural, n (%)	449 (55.1%)	12,730 (57.5%)
Waves completed, mean +/- SD	3.00 +/- 1.04	2.95 +/- 1.07
ADL score (0–6), mean +/- SD	0.44 +/- 1.03	0.28 +/- 0.84
IADL score (0–5), mean +/- SD	0.60 +/- 1.12	0.41 +/- 0.97
CES-D 10 score (0–30), mean +/- SD	8.92 +/- 6.36	7.66 +/- 5.86
Note: Values are from each participant's first observation (baseline). SD = standard deviation; ADL = Activities of Daily Living; IADL = Instrumental ADL; CES-D = Center for Epidemiologic Studies Depression Scale. Between-group differences in ADL, IADL, and CES-D were all significant at $p < 0.001$ in mixed models adjusted for sex and baseline age.		

3.2. Mixed-effects model results

Table 2 presents the time x cancer interaction effects for all three outcomes.

For ADL, the time x cancer interaction was $\beta = 0.019$ ($SE = 0.006$, $t = 3.53$, $p < 0.001$): survivors' ADL score rose 0.046 points/year versus 0.027 in controls (~ 1.7-fold). For IADL, $\beta = 0.014$ ($SE = 0.006$, $t = 2.32$, $p = 0.020$; 0.032 vs. 0.018 points/year, 1.8-fold). For CES-D, $\beta = 0.082$ ($SE = 0.036$, $t = 2.30$, $p = 0.021$; 0.248 vs. 0.166 points/year, 1.5-fold), adding 0.58 points over 7 years to an adjusted baseline gap of 1.04 points. All three interactions survived Holm correction (all adjusted $p < 0.05$); cancer main effects were also significant (baseline ADL + 0.107, IADL + 0.142, CES-D + 1.043; all $p < 0.001$).

Table 2
Time x cancer interaction effects from linear mixed-effects models

Outcome / Model	beta	SE	t	p	95% CI
ADL - Base	0.0195	0.0055	3.53	< 0.001	[0.0087, 0.0303]
ADL - + Education	0.0195	0.0055	3.53	< 0.001	[0.0087, 0.0303]
ADL - + Urban/rural	0.0196	0.0055	3.56	< 0.001	[0.0088, 0.0304]
IADL - Base	0.0136	0.0059	2.32	0.020	[0.0021, 0.0252]
IADL - + Education	0.0136	0.0059	2.32	0.020	[0.0021, 0.0251]
IADL - + Urban/rural	0.0138	0.0059	2.36	0.019	[0.0023, 0.0254]
CES-D - Base	0.0823	0.0357	2.30	0.021	[0.0123, 0.1523]
CES-D - + Education	0.0821	0.0357	2.30	0.021	[0.0121, 0.1520]
CES-D - + Urban/rural	0.0839	0.0357	2.35	0.019	[0.0140, 0.1539]

Note: beta = time x cancer interaction coefficient (additional annual change in survivors vs. controls); SE = standard error; CI = confidence interval. Satterthwaite denominator degrees of freedom ranged approximately 48,300 – 49,400. Models include random intercepts and adjust for sex and baseline age (n = 67,647 observations, 22,946 participants, 815 survivors). All Base-model interactions remain significant after Holm correction.

3.3. Longitudinal trajectories

Figure 3. Trajectories of CES-D depressive symptoms by cancer status. Predicted values from random-intercept linear mixed-effects models adjusted for sex and baseline age. Solid line/blue circles, non-cancer participants; dashed line/red circles, cancer survivors; error bars, +/- 1 standard error of observed group means.

3.4. Sensitivity analyses

Sensitivity analyses supported the primary findings (Online Resource 2). Adding education or urban/rural classification did not materially alter interaction estimates (all $p < 0.05$; ADL beta ~ 0.0195, IADL beta ~ 0.0136, CES-D beta 0.082–0.084).

Restriction to participants aged ≥ 45 (21,609 participants; 64,324 observations) yielded comparable estimates: ADL beta = 0.020 ($p < 0.001$), IADL beta = 0.014 ($p = 0.025$), CES-D beta = 0.097 ($p = 0.008$).

Binary-outcome GLMMs (any ADL difficulty: 17.9%; any IADL: 22.5%; CES-D ≥ 10 : 34.6% of observations) gave interaction odds ratios in the same direction (ADL OR = 1.02/year; IADL OR = 1.04; CES-D OR = 1.02) but non-significant ($p = 0.38, 0.09, 0.25$), as expected given lost severity information and reduced power.

Rural residence was associated with higher ADL and CES-D levels, but adjustment did not attenuate the cancer-specific trajectory differences.

3.5. Sex-stratified analysis (exploratory)

Sex-stratified results appear in Fig. 4 and Online Resource 1. In age-adjusted models, the ADL interaction was significant in females (beta = 0.022, $p = 0.003$) but not males (beta = 0.011, $p = 0.196$); the IADL interaction was

significant in males (beta = 0.025, p = 0.004) but not females (beta = 0.007, p = 0.360); and the CES-D interaction was significant in males (beta = 0.144, p = 0.011) but not females (beta = 0.036, p = 0.442).

Crucially, formal three-way interaction tests (time x cancer x sex) were not significant for any outcome (ADL p = 0.329; IADL p = 0.158; CES-D p = 0.149). The apparent sex-specific patterns in the stratified analyses therefore do not constitute statistically significant sex differences: a significant effect in one stratum and a non-significant effect in the other does not establish that the two effects differ. All sex-stratified findings are accordingly presented as exploratory and hypothesis-generating only.

4. Discussion

This study followed over 22,000 middle-aged and older Chinese adults across four waves spanning seven years, comparing cancer survivors with non-cancer controls. Three findings stand out. First, cancer survivors experienced approximately 1.5- to 1.8-fold accelerated deterioration across ADL, IADL, and CES-D trajectories; all three time x cancer interactions remained significant after Holm correction, although the absolute cumulative differences over 7 years (approximately 0.14 ADL, 0.10 IADL, and 0.58 CES-D points) remain modest and should be interpreted with corresponding restraint. Second, cancer survivors carried a persistently higher depression burden (an adjusted baseline gap of approximately 1 CES-D point) that did not converge over follow-up, while the depressive symptom gap also widened modestly over time. Third, formal three-way interaction tests provided no statistically significant evidence of sex differences in any trajectory; sex-stratified patterns are exploratory only.

4.1. Cancer and accelerated functional decline

The approximately 1.7- to 1.8-fold acceleration in ADL and IADL decline observed in our study corroborates prior Western research documenting greater functional limitations among cancer survivors[6] and aligns with evidence of heterogeneous frailty trajectories with a substantial deteriorating subgroup.[7] Our findings confirm these patterns in a Chinese population and demonstrate that excess decline persists after adjusting for sex, age, education, and urban-rural residence.

The biological mechanisms driving this acceleration are likely multifactorial: treatment-related sarcopenia, peripheral neuropathy, and cardiopulmonary toxicity directly impair physical capacity, while the chronic inflammatory milieu associated with cancer (elevated IL-6, CRP) accelerates age-related physiological deterioration.[8, 14] Metabolic reprogramming in cancer, including altered glutamine utilization and lactate-mediated immune suppression, may further compound functional decline by depleting substrates needed for muscle maintenance.[19] These mechanisms likely act in concert with normal ageing processes, producing the multiplicative effect observed here.

4.2. Cancer and depression: persistent burden with modest trajectory acceleration

The CES-D results indicate both a persistent burden and a modestly accelerated trajectory. Cancer survivors entered follow-up with CES-D scores approximately 1 point higher than controls after adjustment for sex and age, a gap that remained stable rather than converging; the significant time x cancer interaction (beta = 0.082 per year) indicates that this gap additionally widened by approximately 0.58 points over 7 years. The annual rate difference is small in absolute terms, but its consistency across model specifications-including strengthening

after restriction to participants aged ≥ 45 years—supports the conclusion that depressive symptoms deteriorate faster in cancer survivors.

This pattern aligns with longitudinal evidence from older breast cancer cohorts, where a substantial subset follows an emerging depressive trajectory, worsening rather than resolving after therapy.[11] The persistent baseline gap likely reflects the cumulative psychological toll of cancer, treatment-related side effects (including endocrine therapy-induced mood changes and chemotherapy-associated cognitive impairment), fear of recurrence, financial toxicity, and social role disruption.[12]

4.3. Sex differences: exploratory findings without formal significance

Although the sex-stratified analyses appeared to suggest differing patterns—ADL acceleration significant only in females, IADL and CES-D acceleration significant only in males—formal three-way interaction tests were not significant for any outcome (all $p > 0.14$). We therefore make no claim of sex differences. The stratified estimates are best regarded as hypotheses for future research with larger survivor samples.

Should future studies confirm sex differences, candidate explanations include coping differences—women tend to maintain larger social networks and use more adaptive emotion-focused strategies[15]—and Chinese cultural role dynamics, in which male patients who can no longer fulfil provider roles may experience profound psychological loss.[16, 20] These explanations require direct testing in formally powered studies.

4.4. The depression-functional decline nexus

Cancer survivors showed parallel deterioration in both domains, raising the question of whether these trajectories are independent consequences of cancer or interact causally. Our design does not permit testing bidirectionality: both outcomes are modeled separately as functions of cancer status. However, the co-occurrence of accelerated decline is consistent with a common-cause model in which cancer drives simultaneous deterioration across physical and psychological systems.

A complementary interpretation is a self-reinforcing cycle: depression promotes inactivity and social withdrawal, accelerating functional loss,[13, 21] while functional decline may deepen hopelessness; treatment side effects, pain, and fatigue could amplify both components, consistent with evidence that autonomic dysfunction accompanies cancer-related fatigue and pain.[22]

5. Clinical and Research Implications

Several implications emerge. Functional assessment using standardized ADL/IADL measures should be considered for routine incorporation into long-term cancer survivorship follow-up, alongside repeat depression screening, so that early deterioration can trigger referral to rehabilitation and psychosocial services. Integrated rehabilitation programs addressing physical function and psychological wellbeing together merit evaluation in Chinese cancer survivors.

6. Limitations

Several limitations warrant discussion. Cancer status was self-reported without pathological confirmation or staging, so the survivor group is heterogeneous in cancer type, stage, and treatment; non-differential misclassification would bias estimates toward the null, though differential reporting could inflate associations. The timing of diagnosis was uncertain, treatment information was unavailable, and residual confounding by treatment intensity cannot be excluded; Wave 1 was excluded due to high IADL missingness.

ADL and IADL are bounded, right-skewed count outcomes with floor effects; linear mixed models assume approximately normal residuals, but directionally consistent binary GLMMs and the large sample mitigate this concern. Despite these limitations, this study draws on nationally representative longitudinal data (22,946 participants; 67,647 observations), with multiple sensitivity analyses consistently supporting the robustness of the core findings.

7. Conclusions

Drawing on four waves of the CHARLS national longitudinal cohort, this study demonstrates that middle-aged and older adult Chinese cancer survivors face accelerated deterioration in both functional dependency (approximately 1.7-1.8 times the rate of non-cancer peers) and depressive symptoms (approximately 1.5 times the rate), together with a persistently higher depression burden that does not diminish over time. Formal interaction testing did not establish significant sex differences. These findings underscore the need for integrated cancer survivorship care that combines routine functional monitoring with sustained psychological support.

Declarations

Disclosures

Ethics approval and consent to participate: The CHARLS baseline and follow-up surveys were approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and all participants provided written informed consent. The present secondary analyses used publicly available, de-identified CHARLS data and required no additional ethical approval.

Author contributions (CRediT): Bochang Zhu: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. Yan Huang: Validation, Investigation, Writing - review & editing. Junqiao Zhao: Validation, Investigation, Writing - review & editing. Chen Zhao: Supervision, Writing - review & editing.

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Data Availability Statement: The CHARLS dataset is publicly available at <http://charls.pku.edu.cn/>.

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Figures

Figure 1. Trajectory of ADL score (0-6) by cancer status

Interaction (time x cancer): $\beta = 0.019$, $P < 0.001$

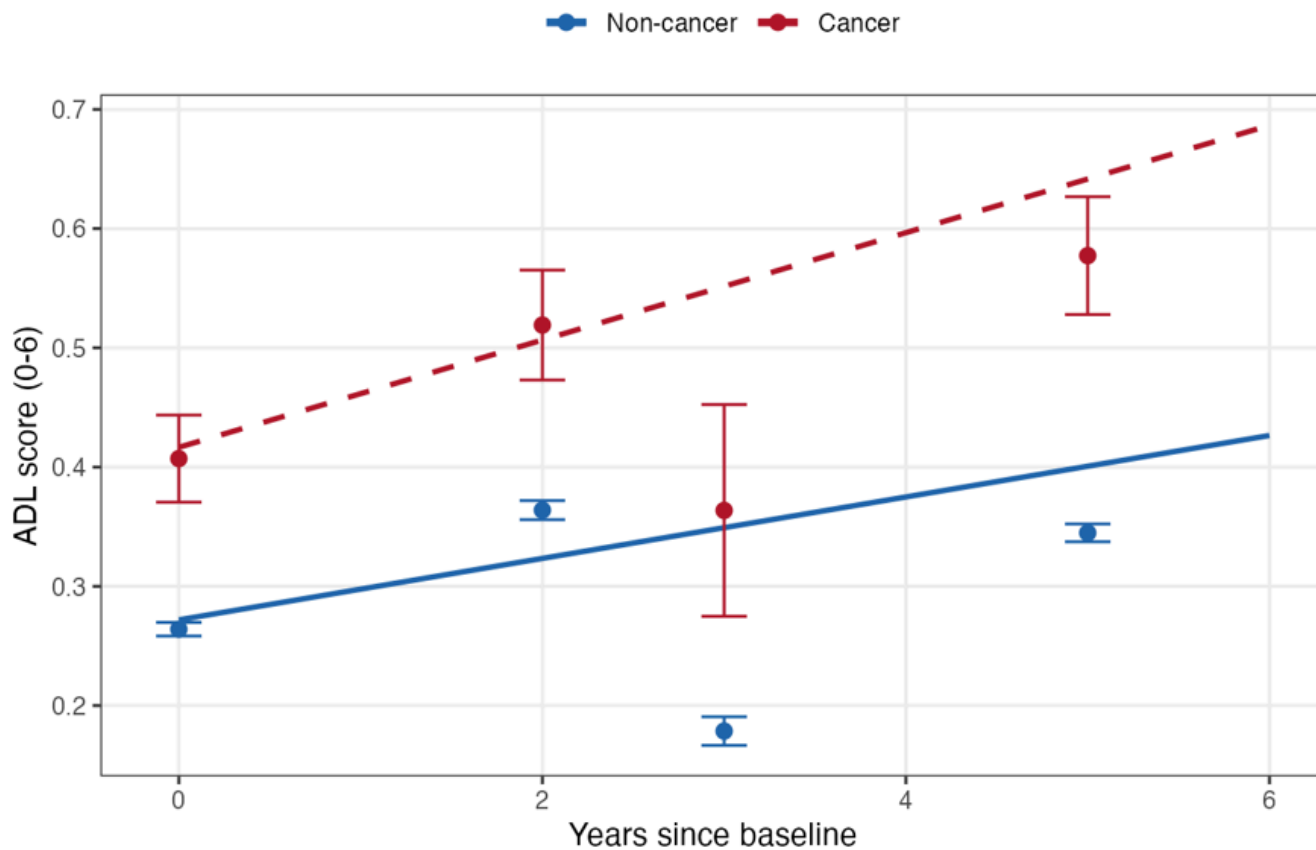


Figure 1

Trajectories of ADL disability by cancer status. Predicted values from random-intercept linear mixed-effects models adjusted for sex and baseline age (cancer group $n = 815$, controls $n = 22,131$). Solid line/blue circles, non-cancer participants; dashed line/red circles, cancer survivors; error bars, ± 1 standard error of observed group means.

Figure 2. Trajectory of IADL score (0-5) by cancer status

Interaction (time x cancer): $\beta = 0.013$, $P = 0.025$

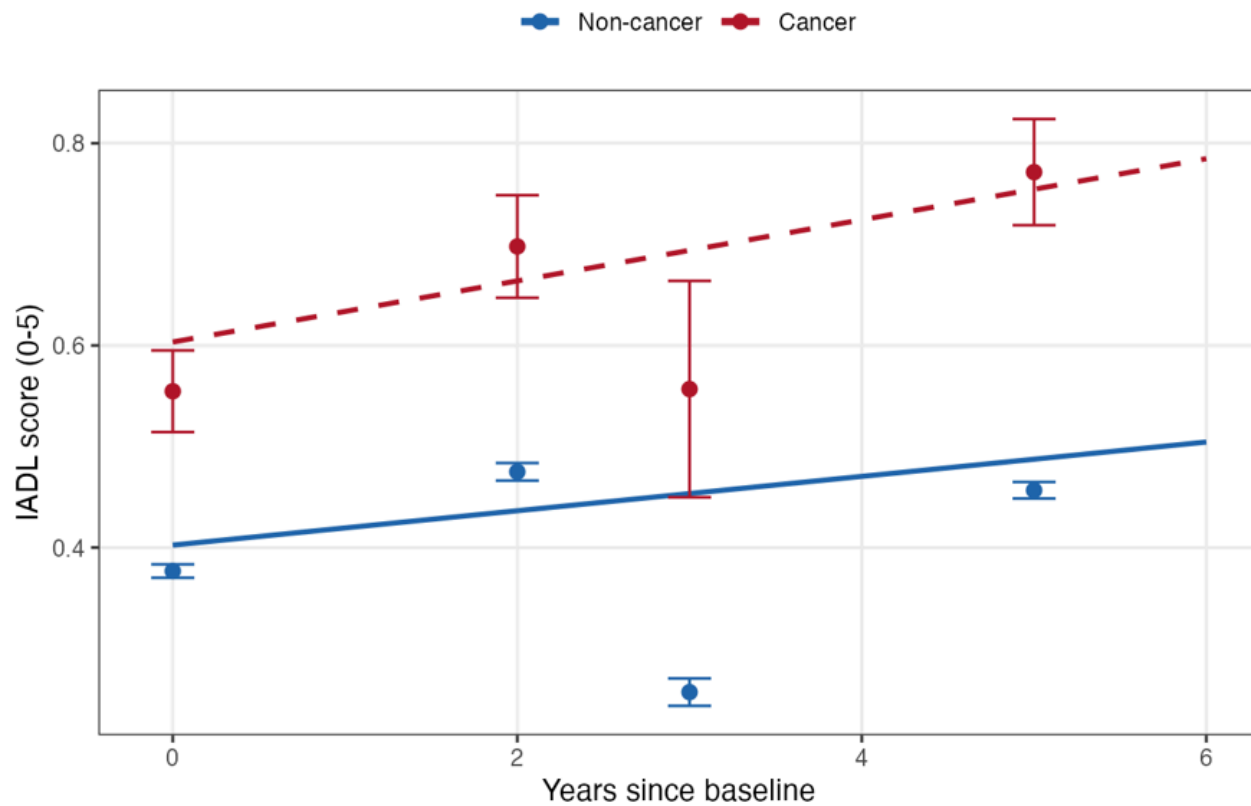


Figure 2

Trajectories of IADL disability by cancer status. Predicted values from random-intercept linear mixed-effects models adjusted for sex and baseline age. Solid line/blue circles, non-cancer participants; dashed line/red circles, cancer survivors; error bars, +/- 1 standard error of observed group means.

Figure 3. Trajectory of CES-D 10 score (0-30) by cancer status

Interaction (time x cancer): $\beta = 0.083$, $P = 0.021$

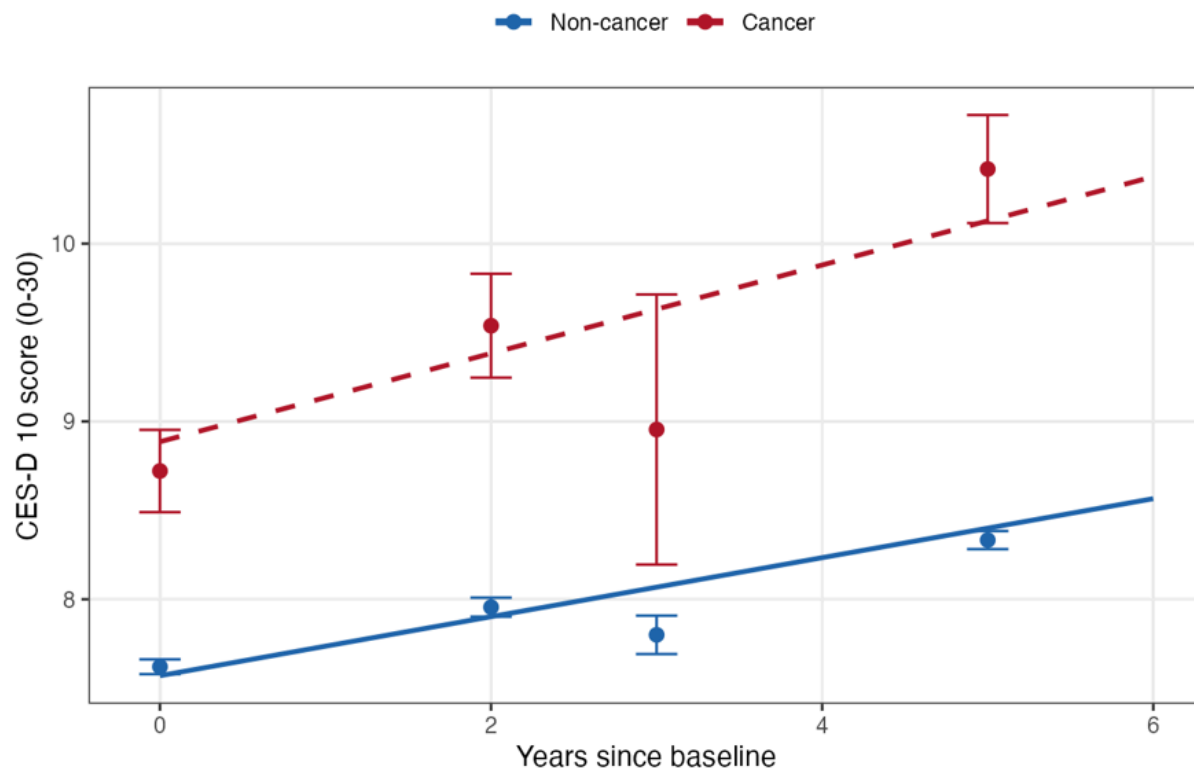


Figure 3

Trajectories of CES-D depressive symptoms by cancer status. Predicted values from random-intercept linear mixed-effects models adjusted for sex and baseline age. Solid line/blue circles, non-cancer participants; dashed line/red circles, cancer survivors; error bars, +/- 1 standard error of observed group means.

Figure 4. Sensitivity analysis: time x cancer interaction across subgroups

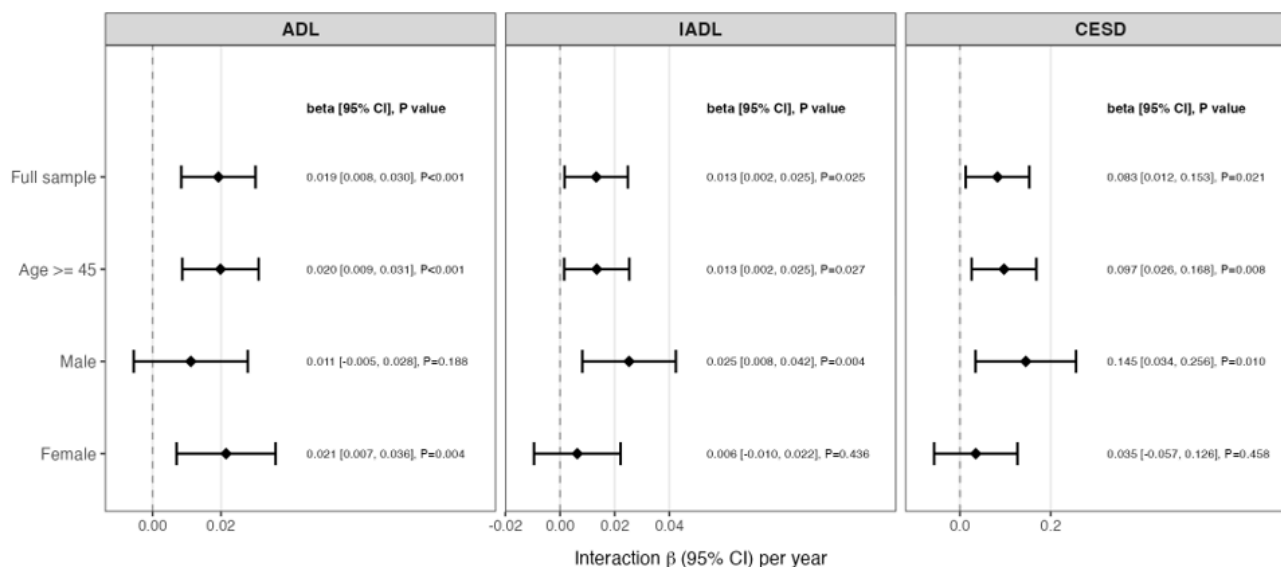


Figure 4

Forest plot of time x cancer interaction effects for the full sample, the age ≥ 45 restricted sample, and sex-stratified subsamples. P-values are unadjusted for multiple comparisons; formal three-way interaction tests for sex differences were non-significant for all outcomes (ADL $p = 0.329$; IADL $p = 0.158$; CES-D $p = 0.149$).

Supplementary Files

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

- [SupplementarymaterialOnlineResource20260908.docx](#)