Exercise Intervention Effects on Depression in Older Adults with Cancer: A Multi-Center Analysis

1. Introduction

The primary objective is to determine whether exercise interventions of any type reduce depression severity compared to control conditions, and further examined by whether this effect is moderated by patient age, intervention duration, or geographic location.

Main Research Question:

1. Does exercise intervention significantly reduce depression severity at follow-up compared to control?

Sub Research Questions

1. Does patient age moderate the effect of exercise intervention on depression?
2. Does intervention duration moderate the effect of exercise intervention on depression?
3. Does the country where the study was conducted moderate the effect of exercise intervention on depression?

2. Methods

2.1 Study Design and Participants

Data from 1,912 older adults with cancer were analyzed from a multi-center randomized controlled trial across 27 research centers in 5 countries (Australia, Canada, Germany, United Kingdom, United States). Participants were randomized to either exercise intervention (n = 952) or control group (n = 960). Depression was assessed at baseline and follow-up using standardized depression scales (reported as standardized scores).

2.2 Data Preparation

Before analysis, treatment and country variables were converted to factors for categorical analysis. Age was centered at the sample mean (69.78 years) to facilitate interpretation of model intercepts as effects for average-aged patients rather than the zero-age baseline.

2.3 Statistical Analysis

Linear mixed-effects models were used to account for the hierarchical clusters of data with patients nested within research centers. Mixed models can handle within-center correlation

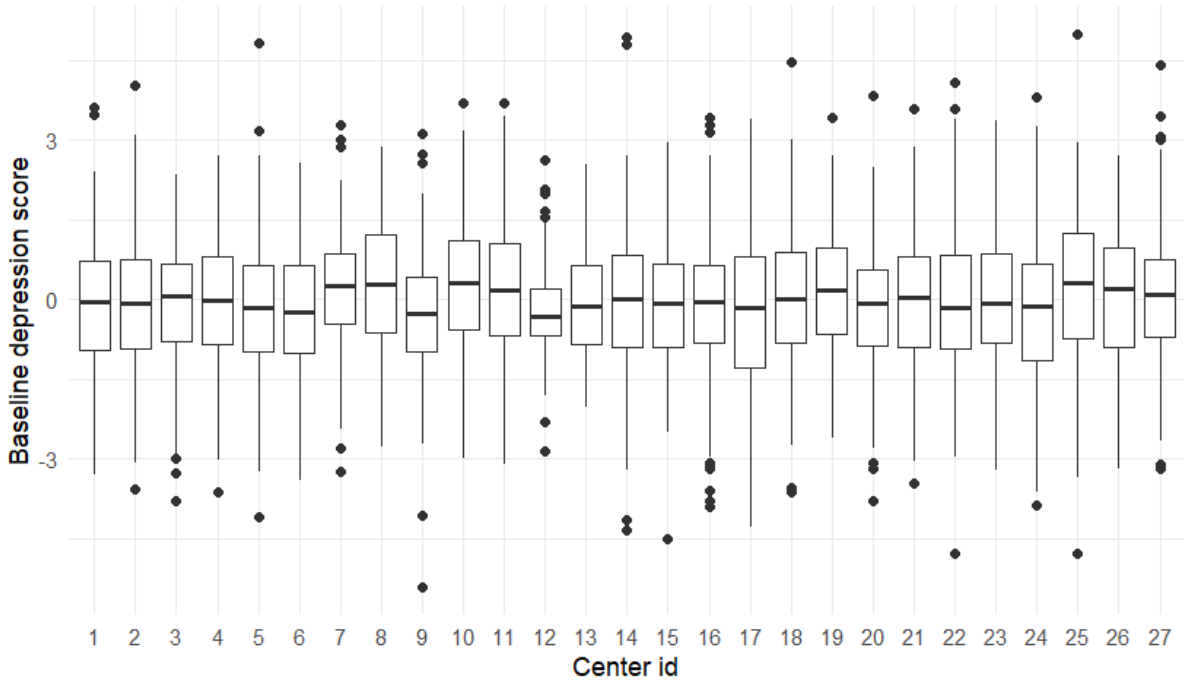
that would be ignored in standard regression approaches. This aims to help prevent underestimation of standard errors.

Descriptive statistics: Descriptive statistics were computed to get an insight in participant characteristics and to assess whether the intervention and control group were balanced at baseline. Two boxplots were made to compare changes in depression scores between the two treatment groups.

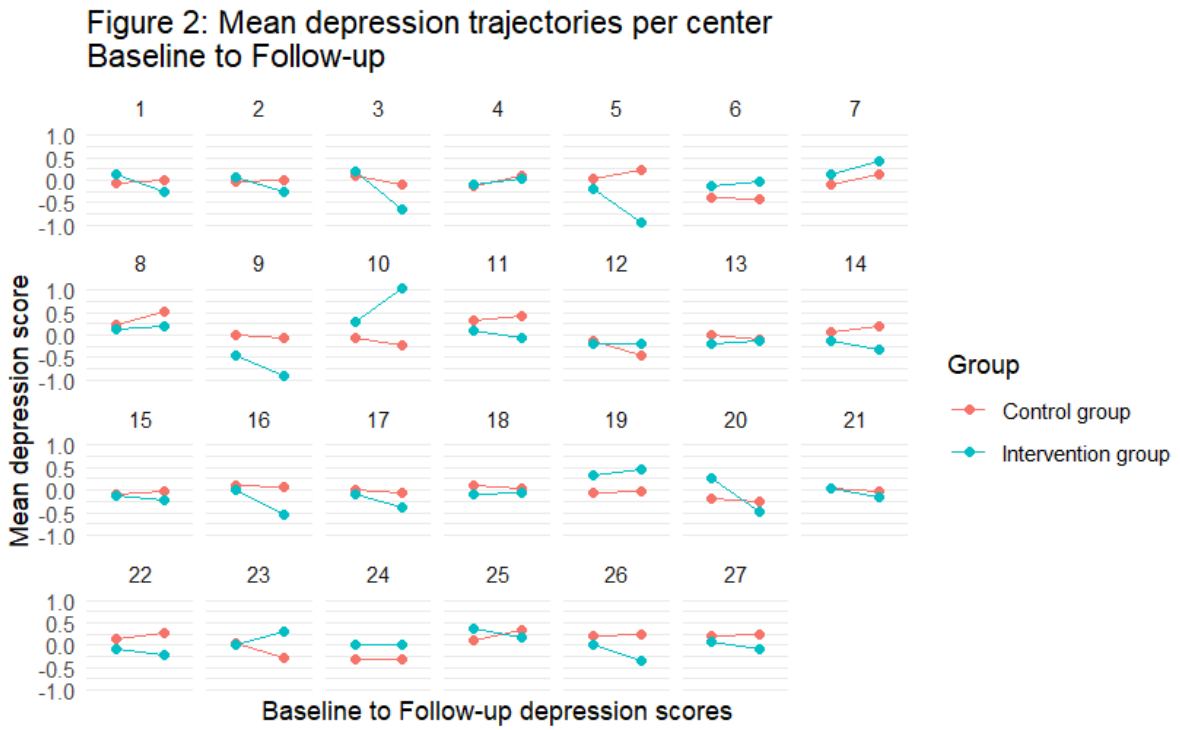
Random Effects Structure: The choice of random effects was determined through theoretical considerations, inspecting visualisations, and testing.

Random intercepts were included to account for differences in the mean baseline depression levels across centers due to varying populations and local characteristics. These differences are shown in Figure 1.

Figure 1: Distribution of baseline depression scores per center



Random slopes for treatment were also tested as it would be plausible that the treatment effect differs between centers. The likelihood ratio test indicated that treatment effect varied significantly across centers ($p < .001$), justifying the inclusion of a random slope for treatment in all the models. The different effects of treatment between centers is shown in Figure 2.



Correlation structures for repeated measures were not used as the data contained only two time points (baseline and follow-up).

Model Building Strategy: A systematic hierarchical approach was used for model building. The base model included baseline depression as a covariate and treatment as a fixed effect with random intercepts and slopes for treatment by center. For the sub research questions, potential moderators (age, duration, country) were first tested as main effects, then as interactions with treatment. All model comparisons used maximum likelihood (ML) estimation, with final parameter estimates obtained via restricted maximum likelihood (REML) for unbiased variance estimation. Likelihood ratio tests assessed model improvements with $\alpha = .05$.

2.4 Model Diagnostics

Model assumptions were checked through the visuals of diagnostic plots. Q-Q plots of residuals showed approximate normality, and residual versus fitted value plots showed no systematic patterns suggesting heteroscedasticity. While some potential outliers were identified, they did not substantially impact our conclusions.

3. Results

3.1 Descriptive Statistics

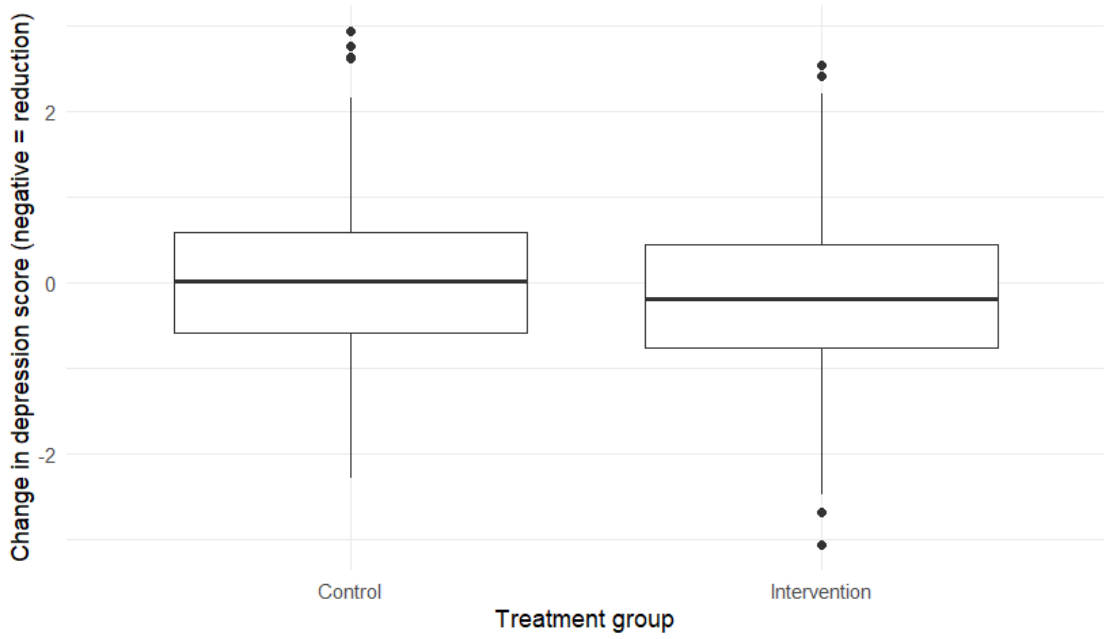
The intervention and control group were well-balanced as shown in table 1.

Table 1. Population Characteristics by Treatment Group

Characteristic	Control (n = 960)	Intervention (n = 952)	Total (N = 1,912)
Age, M (SD)	69.6 (8.7)	70.0 (8.9)	69.8 (8.8)
Female, n (%)	592 (61.7%)	587 (61.8%)	1,179 (61.7%)
Baseline Depression, M (SD)	0.01 (1.01)	0.03 (1.02)	0.02 (1.02)
Follow-up Depression, M (SD)	0.03 (1.50)	-0.14 (1.55)	-0.05 (1.53)

A first visual look at the data, Figure 3, shows a reduction in depression scores for the intervention group , which is not observed in the control group. This shows a positive effect of the intervention.

Figure 3: Change in depression score by treatment group



3.2 Primary Analysis: Treatment Effect (RQ1)

The exercise intervention had a significant positive effect on depression outcomes. Patients in the intervention group reported significantly lower depression scores at follow-up compared to the control group (p = .023*). This represents an average reduction of 0.17 units in depression score due to exercise intervention.

3.3 Moderation Analyses

Table 2 summarizes the hierarchical model comparisons examining potential moderators of treatment effect.

Table 2. Hierarchical Model Comparisons for Moderation Analyses

Research Question	Model Specification	Comparison	p-value	Conclusion
Treatment Effect				
Base model	depression_baseline + treatment	-	.023*	Treatment significant
Age Moderation				
Add age main effect	Base + age_centered	vs. Base	.013*	Age significant
Add age interaction	+ treatment × age_centered	vs. + age	<.001***	Interaction significant
Duration Moderation				
Add duration main effect	Base + duration_weeks	vs. Base	.048*	Duration significant
Add duration interaction	+ treatment × duration_weeks	vs. + duration	.81	No significant interaction
Country Moderation				
Add country main effect	Base + country	vs. Base	.59	No country effect
Add country interaction	+ treatment × country	vs. + country	.06	No significant interaction

*Note: All models include random intercepts and random slopes for treatment by study center. Comparisons use maximum likelihood estimation. * p < .05, ** p < .01, *** p < .001*

Age Moderation: Age as a main effect significantly improved the base model (p = .013*). The treatment × age interaction was highly significant (p < .001***). The positive interaction coefficient indicates that the intervention becomes less beneficial by about 0.016 units for every additional unit above the sample mean. Meaning that younger patients benefit more from treatment than older patients.

Duration Moderation: Duration as a main effect significantly improved the base model (p = .048*), but the treatment × duration interaction was not significant (p = .81). While depression trajectories differ by intervention length, treatment effectiveness remains consistent regardless of program duration.

Country Moderation: Neither the main effect of country (p = .59) nor the treatment × country interaction (p = .06) was significant. The intervention effect appears generalizable across the five countries, though the marginally non-significant interaction suggests potential subtle differences warranting investigation in larger samples.

4. Conclusions

Exercise interventions significantly reduce depression severity in older adults with cancer, with effectiveness strongly moderated by patient age. Treatment effectiveness remains

consistent across intervention durations and geographic locations, supporting the broad applicability of exercise as a therapeutic intervention for this population.