Exercise Intervention Effects on Depression in Older Adults with Cancer: A Two-Stage Individual Participant Data Meta-Analysis

1. Introduction

The primary objective of this analysis is to determine whether exercise interventions of any type reduce depression severity compared to control conditions, and to examine whether this effect is moderated by patient age, intervention duration, or geographic location using individual participant data meta-analysis (IPDMA) methods.

Main Research Question:

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

Sub Research Questions:

- Does patient age modify the effect of exercise intervention on depression?
- Does intervention duration moderate the treatment effect across studies?
- Does the country where the study was conducted moderate the treatment effect across studies?

2. Methods

2.1 Study Design and Data Source

Data from 1,929 older adults with cancer were analyzed from 27 independent studies conducted across 5 countries (Australia, Canada, Germany, United Kingdom, United States). Participants were randomized to either exercise intervention (n = 965) or control group (n = 964). Depression was assessed at baseline and follow-up using standardized depression scales. Each study implemented different exercise intervention programs (aerobic, resistance training, combined programs, or mind-body exercises) with varying durations.

2.2 Data Preparation

Treatment and country variables were converted to factors for categorical analysis. Age was centered within each study (at study-specific means) to separate within-study individual-level effects from between-study differences in mean age. This centering is essential for IPDMA to correctly interpret age as an individual-level effect modifier. Duration and country were identified as study-level characteristics (no within-study variation) and were examined as study-level moderators rather than individual-level covariates.

2.3 Statistical Analysis

A two-stage individual participant data meta-analysis approach was used, treating the dataset as 27 separate studies combined through meta-analysis. This approach preserves study-level randomization, accounts for clustering by study, and allows flexible modeling of effect modification while avoiding convergence issues common in one-stage models with limited studies.

Stage 1 - Study-Specific Analyses: Linear regression models were fit separately within each study to estimate study-specific treatment effects. The base model included follow-up depression as the outcome, treatment and baseline depression as predictors. For age moderation, the model included a treatment × age interaction. Treatment effects and standard errors were extracted from each study-specific model.

Stage 2 - Meta-Analysis: Study-specific treatment effects were pooled using random-effects meta-analysis with restricted maximum likelihood (REML) estimation. Random-effects models were chosen to account for anticipated heterogeneity in treatment effects across different study populations, interventions, and settings.

For duration and country (study-level variables), meta-regression was performed in Stage 2 to test whether these study characteristics predicted treatment effect magnitude. Baseline depression was included as a covariate in all Stage 1 models to improve precision and account for regression to the mean.

Heterogeneity Assessment: Between-study heterogeneity was quantified using τ^2 (between-study variance), I^2 (percentage of total variation due to heterogeneity), and Q-tests. For meta-regression models, R^2 indicated the proportion of heterogeneity explained by the moderator.

3. Results

3.1 Descriptive Statistics

The descriptive statistics of the data is represented in Table 1:

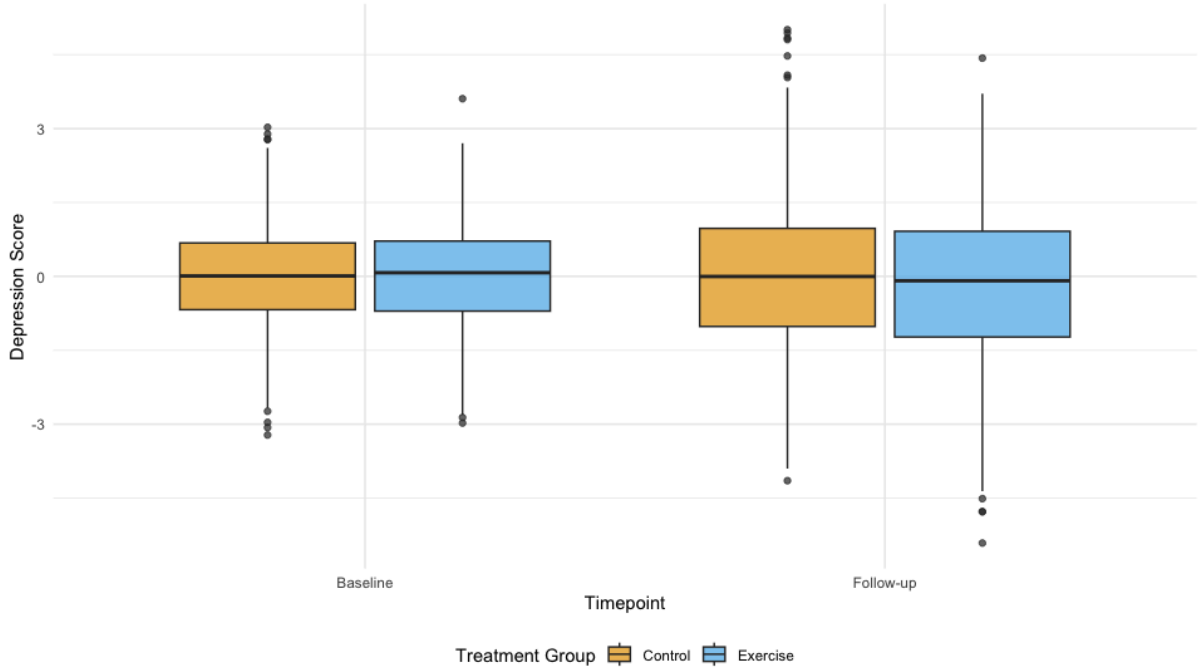
Table 1: Participant Characteristics by Treatment Group

Treatment	N	Age Mean	Age SD	Female N	Female %	Baseline Mean	Baseline SD	Follow-up Mean	Follow-up SD	Group
0	960	69.6	8.7	592	61.7	0.01	1.01	0.03	1.50	Control
1	952	70.0	8.9	588	61.8	0.03	1.02	-0.14	1.55	Exercise

Study characteristics varied: sample sizes ranged from 40 to 100 participants per study, intervention durations ranged from 6 to 24 weeks, and studies were distributed across Australia (n = 8), Canada (n = 5), Germany (n = 4), United Kingdom (n = 6), and United States (n = 4).

Visual inspection of depression scores by treatment group and timepoint suggested beneficial effects of exercise intervention (Figure 1).

Figure 1: Depression Scores by Treatment Group and Timepoint

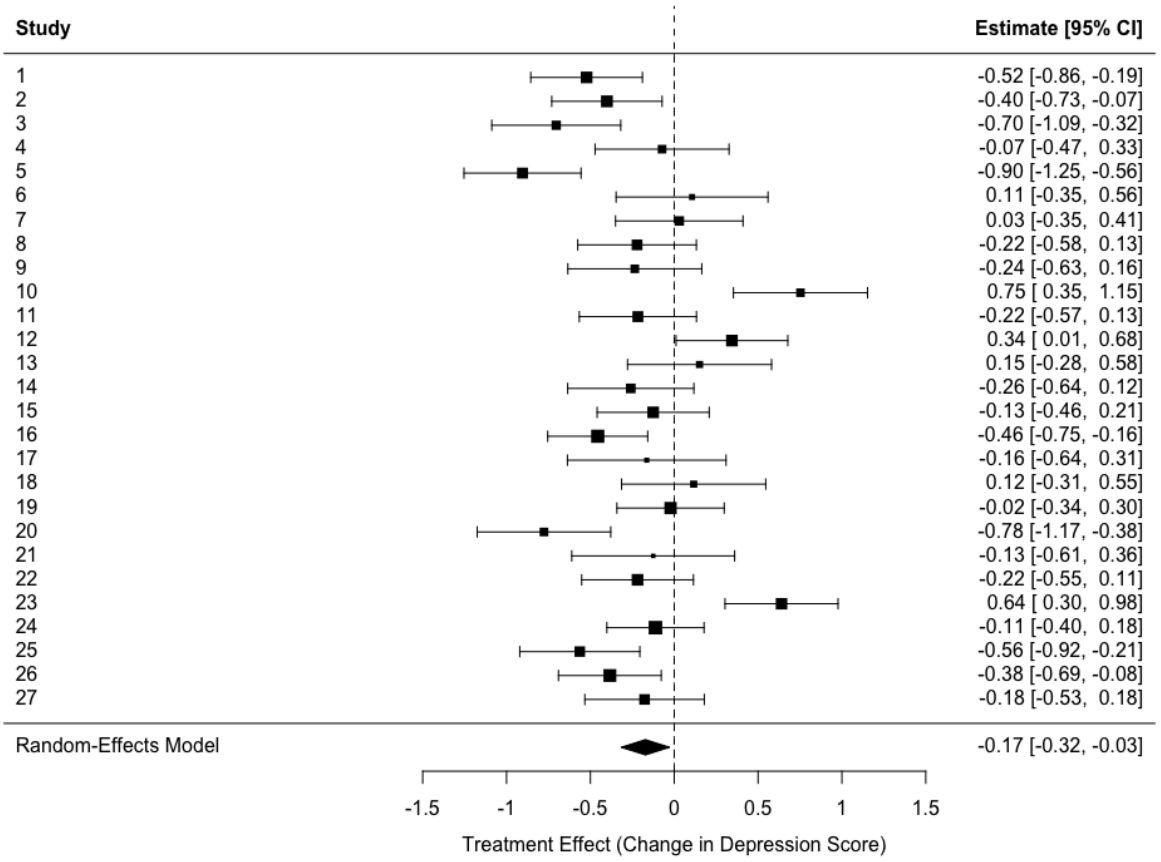


3.2 Primary Analysis: Overall Treatment Effect (RQ1)

Random-effects meta-analysis of 27 studies showed a significant benefit of exercise intervention (pooled estimate = -0.172, SE = 0.074, p = 0.020). Exercise reduced depression scores by approximately 0.17 units versus control conditions.

Substantial heterogeneity was observed ($\tau^2 = 0.111$, $I^2 = 76.5\%$, Q-test: $p < .001$), with ~77% of variation due to true differences between studies rather than sampling error. This high heterogeneity warranted moderation analyses. Figure 2 displays study-specific effects and the pooled estimate.

Figure 5: Forest Plot - Overall Treatment Effect on Depression



3.3 Moderation Analyses

Age Moderation (Individual-Level Effect Modification):

We first tested age as a main effect (without interaction), then tested the treatment × age interaction. First, the main treatment effect at mean age was -0.192 (SE = 0.072, p = 0.008). Second, the treatment × age interaction was significant (β = 0.019, SE = 0.005, p < .001). Treatment benefits decreased by approximately 0.02 depression units per year above mean age, meaning younger participants benefited more than older participants.

The interaction effect showed minimal variation across studies (τ^2 =0.000, I^2 = 0.2%, Q-test: p = 0.329), indicating that age consistently moderated the treatment-outcome relationship.

Duration Moderation (Study-Level Meta-Regression):

Meta-regression found no significant association between study duration and treatment effect (p = 0.86). Duration explained none of the between-study heterogeneity (τ^2 =0.116, R^2 = 0.0%, residual I^2 = 77.4%). Intervention duration (6-24 weeks) did not account for variability in treatment effects.

Country Moderation (Study-Level Meta-Regression):

Meta-regression tested whether the country predicted treatment effects. The overall test approached but did not reach significance ($p = 0.453$). Country accounted for 19.3% of between-study heterogeneity ($\tau^2 = 0.089$, $R^2 = 19.3\%$, residual $I^2 = 72.3\%$), suggesting geographic location may play a modest role, though most heterogeneity remained unexplained.

Table 2 summarizes the meta-analysis results across all models, including heterogeneity statistics and variance explained by each moderator.

Table 2: Comparison of Meta-Analysis Models

Model	Estimate 95% CI	SE	P-value	τ^2	I^2 (%)
Base (Overall Effect)	-0.172 (-0.316, -0.028)	0.074	0.0195	0.1105	76.5
Age Main Effect	-0.192 (-0.332, -0.051)	0.072	0.0075	0.1031	75.2
Age Interaction	0.019 (0.009, 0.028)	0.005	0.0001	0.0000	0.2
Duration Meta-Regression	-0.124 (-0.681, 0.432)	0.284	0.6618	0.1161	77.4
Country Meta-Regression	-0.094 (-0.341, 0.152)	0.126	0.4531	0.0892	72.3

4. Conclusions

Exercise interventions significantly reduce depression severity in older adults with cancer. Treatment effectiveness is strongly modified by age, with younger participants benefiting more.

Study-level characteristics showed different patterns: intervention duration (6-24 weeks) did not moderate effects, while geographic location showed a trend toward moderation, explaining 19% of heterogeneity.