Statistical Approach to the Efficacy of Individual Cognitive Stimulation in Alzheimer's Disease: The Added Value of Meta-Regression and Subgroup Analysis

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Outline

Alzheimer's Disease (AD)

Definition

AD is a neurodegenerative disorder characterized by progressive loss of cognitive functions, associated with behavioral changes and functional impairment (American Psychiatric Association, 2022).

Epidemiology

- It affects more women than men from the age of 60 onwards
- The prevalence of AD is expected to **double** by 2050 (Alzheimer's Association, 2022) reaching over **half a million in Portugal** (Alves et al., 2024).

The burden of AD ...

on health

AD is the most common cause of dementia, accounting for 60-70% of cases worldwide.

on the economy

The global cost of dementia was estimated at more than €1.2 billion (World Alzheimer Report,2023).

on public health

In 2023, 55 million people lived with dementia, projected to reach 139 million by 2050 (WHO).

Social Burden

Emotional and psychological stress for caregivers with high rates of burnout, depression, and anxiety.

Diagnosis of AD

Currently, with high degree of confidence

in vivo diagnosis

- Detailed clinical assessment (cognitive, functional, and behavioral);
- Complementary tests;
- Biomarkers.

Definitive diagnosis (100% certainty)

post-mortem

- Histopathological confirmation

Normal

Alzheimer

source: https://www.saudebemestar.pt

Treatments

- Treatments for AD can vary and broadly include pharmacologic and **non-pharmacologic** options.
- One common non-pharmacologic treatment for AD is **individual Cognitive Stimulation (iCS)**[1].

[1] iCS includes activities and discussions aimed at enhancing cognitive and social functioning through therapies such as reminiscence therapy and reality orientation (Woods et al., 2012)

Aim of the study

The aim is to answer the question:

At what level of AD severity was iCS most effective?

Study design

- A **multicenter RCT** was conducted with **68** older adults with AD in Portugal (from 6th March to 26th May 2023).
- Two **groups** were considered: **iCS** (n=30) and Treatment As Usual-**TAU** (n=38).
- **Three** time points were considered: before the intervention (baseline, T0), immediately after its completion (T1), and 12 weeks later (follow-up, T2).
- Alzheimer's Disease Severity (ADS) was categorised into **two levels**: moderately severe and moderate.

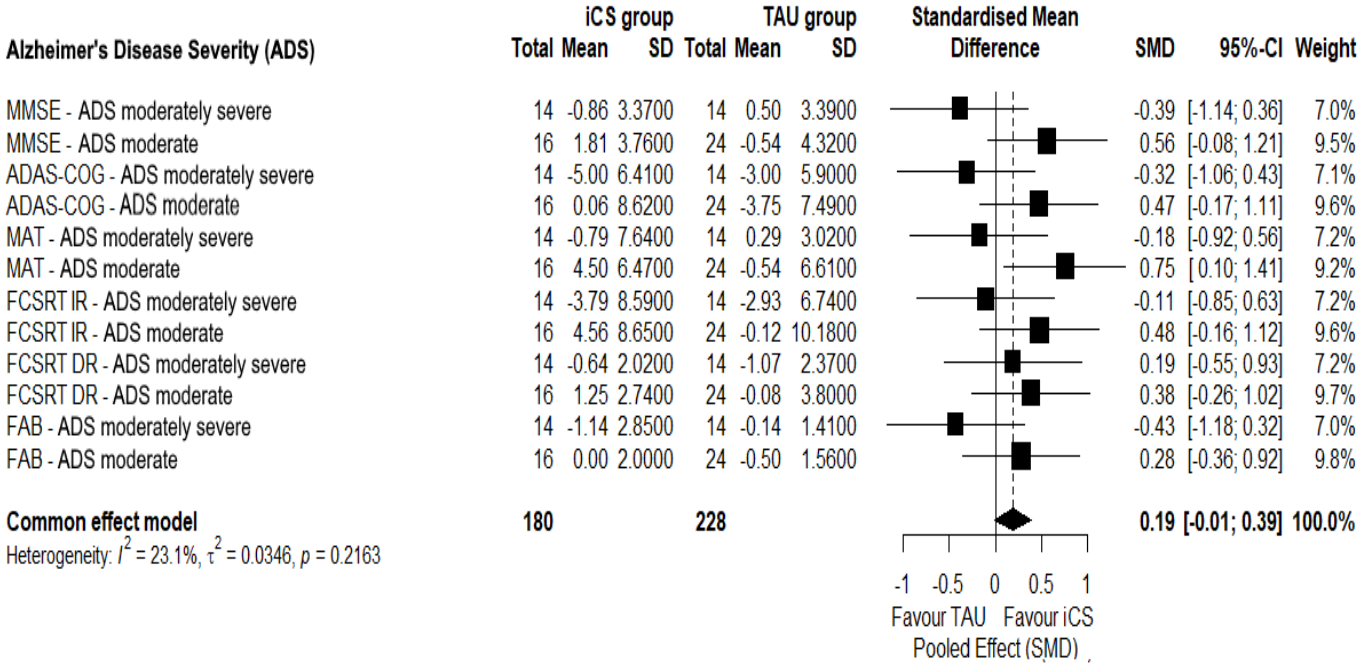
The significance level set was 5%. Statistical analyses were conducted using R.

Methodology

- **Six standardised instruments** (MMSE, ADAS-Cog, MAT, FCSRT IR/DR, and FAB)[1] **were used** to assess global cognitive functioning, memory, and executive function.
- The Standardized Mean Difference **(SMD)**, adjusted using **Hedges'g method**, was calculated to estimate the direction and magnitude of the effect between the iCS and TAU groups.
- Effects were presented using **forest plots**. **Heterogeneity** across outcomes (instruments) was assessed using the I^2, τ^2 **and Q-test** statistics.
- In cases of low heterogeneity, the analysis was complemented with **meta-regression models** and **subgroup** analyses.

[1] Abbreviations: MMSE Mini-Mental State Examination; ADAS-COG Alzheimer's Disease Assessment Scale-Cognitive; MAT Memory Alteration Test; FCSRT IR/ Free and Cued Selective Reminding Test Immediate Recall/Delayed Recall, FAB Frontal Assessment Battery

Results - forest plot

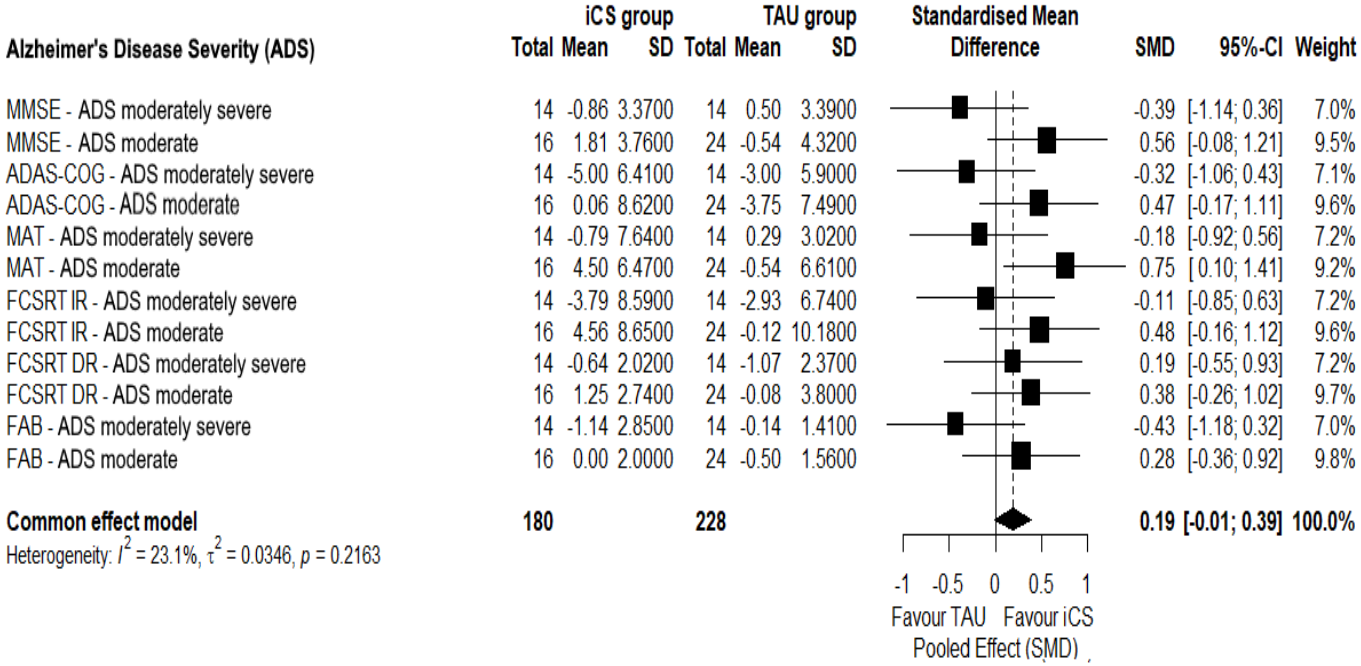


Alzheimer's Disease Severity (ADS)	iCS group Total	Mean	SD	TAU group Total	Mean	SD	SMD	95%-CI	Weight
MMSE - ADS moderately severe	14	-0.86	3.3700	14	0.50	3.3900	-0.39	[-1.14; 0.36]	7.0%
MMSE - ADS moderate	16	1.81	3.7600	24	-0.54	4.3200	0.56	[-0.08; 1.21]	9.5%
ADAS-COG - ADS moderately severe	14	-5.00	6.4100	14	-3.00	5.9000	-0.32	[-1.06; 0.43]	7.1%
ADAS-COG - ADS moderate	16	0.06	8.6200	24	-3.75	7.4900	0.47	[-0.17; 1.11]	9.6%
MAT - ADS moderately severe	14	-0.79	7.6400	14	0.29	3.0200	-0.18	[-0.92; 0.56]	7.2%
MAT - ADS moderate	16	4.50	6.4700	24	-0.54	6.6100	0.75	[0.10; 1.41]	9.2%
FCSRT IR - ADS moderately severe	14	-3.79	8.5900	14	-2.93	6.7400	-0.11	[-0.85; 0.63]	7.2%
FCSRT IR - ADS moderate	16	4.56	8.6500	24	-0.12	10.1800	0.48	[-0.16; 1.12]	9.6%
FCSRT DR - ADS moderately severe	14	-0.64	2.0200	14	-1.07	2.3700	0.19	[-0.55; 0.93]	7.2%
FCSRT DR - ADS moderate	16	1.25	2.7400	24	-0.08	3.8000	0.38	[-0.26; 1.02]	9.7%
FAB - ADS moderately severe	14	-1.14	2.8500	14	-0.14	1.4100	-0.43	[-1.18; 0.32]	7.0%
FAB - ADS moderate	16	0.00	2.0000	24	-0.50	1.5600	0.28	[-0.36; 0.92]	9.8%
Common effect model	**180**			**228**			**0.19**	**[-0.01; 0.39]**	**100.0%**

Heterogeneity: $I^2 = 23.1\%$, $\tau^2 = 0.0346$, $p = 0.2163$

- Reading SMD values: > 0: favors iCS; < 0: favors TAU; $= 0$: identical.
- The diamond represents the pooled effect of the SMD. Its value, 0.19 means that, on average, the iCS group shows a positive effect (thus more beneficial) but without significance (touches the line at SMD $= 0$).
- Significant positive effect of iCS on the MAT instrument at the Moderate level.

Results - forest plot



- The I^2, expressed in %, quantifies heterogeneity among instruments and is interpreted as follows: [0;25[: low; [25;50[: moderate; [50;75[: high; $\geq$75: very high. We have **low** heterogeneity ($I^2 = 23.1\%$) between instruments.
- The τ^2 quantifies the real variability between instruments not explained by groups (iCS vs TAU). $\tau^2 \approx 0.035$ indicates **residual variability** among instruments.
- p-value= 0.216 from the heterogeneity test (Q-test) **supports** the results.

Results: subgroup analysis and meta-regression

Based on the previous results, we do not have an **explicit breakdown by levels** of ADS; therefore, we cannot determine whether one level shows a significantly different effect from the other.

We have two approaches to deal with this:

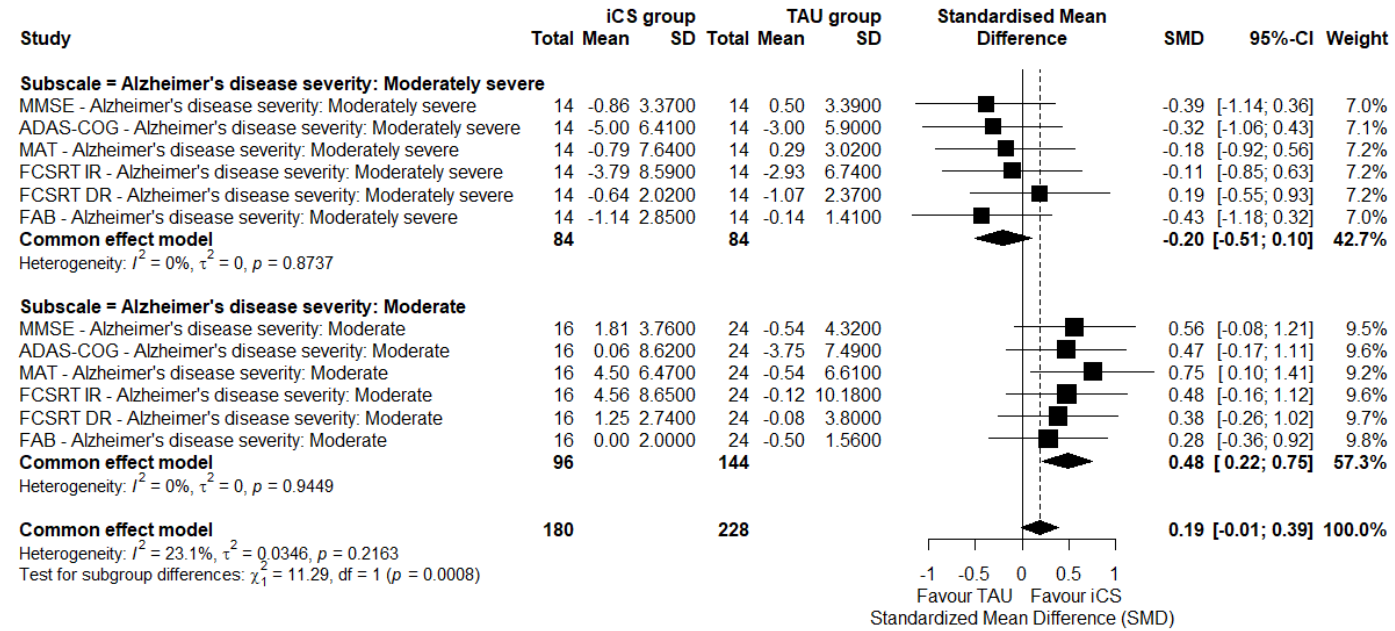
subgroup analysis

and

meta-regression.

Results - Subgroup Analysis

Explicit breakdown by levels of ADS



Note: in ADAS-Cog, higher scores reflect lower performance.

The Q-test = 11.29 (p-value = 0.0008) indicates a statistically significant difference between levels. The Moderate ADS showed a positive (Favour iCS) and significant effect, whereas the Moderately Severe ADS showed a negative effect (Favour TAU) without significance.

Results: Meta-Regression

- In this model, the **explanatory variables** are the **levels**, while the **outcome variable** is the **SMD** adjusted using Hedges' g method.
- intercept=0.4848, which represents the SMD mean for the reference level (Moderate AD).
- The model coefficient/slope of -0.6891 (95% CI [-1.0911; -0.2872], p-value = 0.0008) indicates that shifting from the Moderate AD level to the Moderately Severe AD level leads to a reduction of 0.6891 units in the mean SMD value, **meaning that the level significantly influences the results**
- Since the levels are the only moderator in the meta-regression model and the R^2 value is 100%, this suggests that the **level is a strong and relevant moderating factor for the assessments considered**.

Conclusions & clinical implications

- This study demonstrated a significant difference between the two severity levels, suggesting that the iCS treatment may be more beneficial in the earlier stages of AD, but may have reduced or no benefit in the more advanced stages.
- These findings may have clinical relevance for evaluating the effectiveness of non-pharmacological interventions.
- This statistical approach may offers an alternative to standard models (ANOVA and MLM) in studies involving two or more experimental groups.

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Presence, Participation and Attention.

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