



# Selenium supplementation and autoantibody titers in Graves' disease

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## Abstract

**Objectives:** To evaluate the efficacy of Se supplementation in patients with GD and GO in terms of changes in ocular and systemic signs and symptoms, health-related quality of life (HRQoL), and selenoprotein, thyrotropin, thyroid hormone, and autoantibody levels.

**Methods:** RCTs evaluating the efficacy of Se supplementation in adult patients with GD and active GO, versus placebo or an alternative drug, and on top of standard therapy, were included. A literature search was performed by two independent authors with eligible studies undergoing a validity screen. Data extraction of selected studies was done using a data extraction form, with statistical analysis using RevMan 5.1 software. Results were presented as mean differences, standard errors, and 95% confidence intervals, and graphically presented as forest plots. Estimates were calculated using the inverse variance method for continuous variables and pooled using the fixed effects model.  $I^2$  and  $\chi^2$  tests were used to assess heterogeneity.

**Results:** Fourteen studies were initially retrieved for consideration, but only two trials were ultimately included. Both had good methodological quality and totaled 197 patients with GD and non-severe GO. The only available common outcomes of interest were changes in TRAB and TPOAB titers. No statistically significant difference was found in TRAB (95% CI, -1.38 [-3.19, 0.44],  $p=0.14$ ) as well as in TPOAB (95% CI, 36.66 [-32.56, 105.88],  $p=0.3$ ) titers on follow up among those given Se supplementation as compared to placebo. No significant heterogeneity was found in either the TRAB ( $I^2=36\%$ ) or TPOAB ( $I^2=0\%$ ) analysis.

**Conclusions:** This is the first meta-analysis summarizing the current available data on the efficacy of Se supplementation in patients with GD and active non-severe GO. Se supplementation in these patients was not associated with statistically significant differences in both TRAB and TPOAB titers on follow up. Larger studies are recommended to strengthen these findings.

## Background

Selenium (Se), a trace mineral with anti-oxidative properties, has been proposed by studies to be potentially beneficial in patients with Graves' disease (GD), especially those with active Graves' ophthalmopathy (GO).

## Objectives

**General:** To evaluate efficacy of Se supplementation in patients with GD and GO  
**Specific:** To evaluate changes in:

1. Ocular and systemic signs and symptoms
2. Health-related quality of life
3. Selenoprotein, thyrotropin, thyroid hormone, and autoantibody levels

## Methods

### Databases

- MEDLINE, Embase, ClinicalTrials.gov, Google Scholar, Cochrane Central Register of Controlled Trials
- References of articles and individual authors

### Keywords

- "selenium", "selenite", "selenoprotein"
- "thyroid", "orbitopathy", "ophthalmopathy", "hyperthyroidism", "Graves' disease", "thyrotoxicosis", "thyroid-related eye disease", "Basedow disease"

### Inclusion Criteria

- RCTs evaluating efficacy of Se supplementation on top of standard therapy in adult GD patients with active GO
- Versus either placebo or alternative controller
- Outcomes: clinical activity of GO as measured via objective examination or symptom scores; levels of selenium or selenoproteins, TSH, thyroid hormones, TRAB and TPOAB, HRQoL
- No restrictions on language, ethnicity or gender

### Exclusion Criteria

- Pregnancy
- Comorbid systemic or ocular disease
- Severe GO requiring steroid use at outset
- Previous or ongoing use of Se supplements

## Flowchart

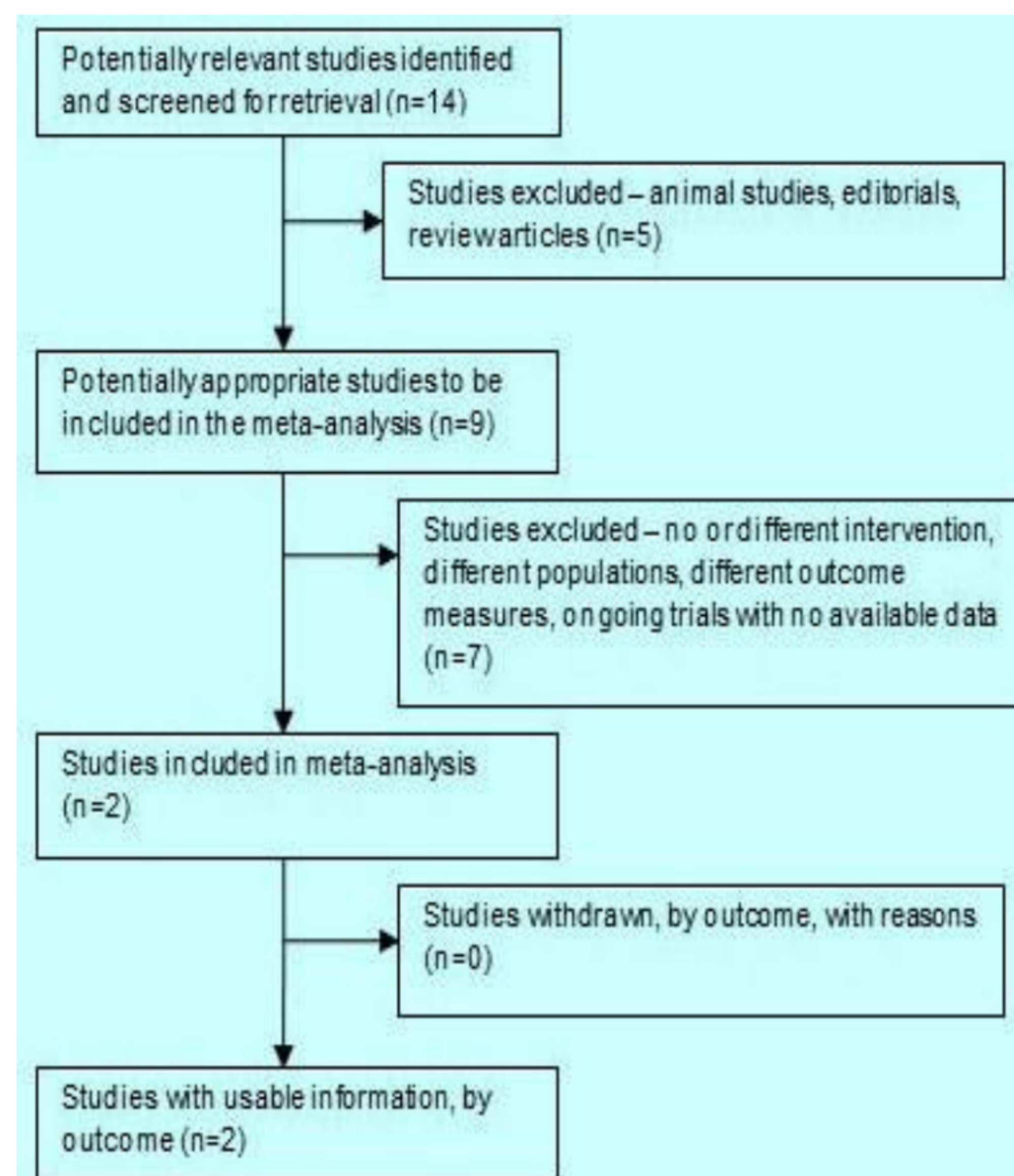


Figure 1. Flowchart of methodology used to arrive at the studies included in the analysis.

## Results

Study	Marcocci et al (EuGOGO Trial) 2011	Calissendorff et al 2015
Randomization	Adequate	Adequate
Allocation Concealment	Yes	Yes
Baseline Characteristics	No significant difference	No significant difference
Blinding	Double blind	Double blind
Follow-up Rates	Adequate	Adequate

Table 1. Methodological assessment of the quality of studies included in the review.

Study	Marcocci et al (EuGOGO Trial) 2011	Calissendorff et al 2015
Title	Selenium and the course of mild Graves' ophthalmopathy	A prospective investigation of Graves' disease and selenium: thyroid hormones, auto-antibodies, and self-rated symptoms
Design	RCT	RCT
Therapy Duration	6 months	9 months
Sample Size	159	38
Population	Adult GD patients aged 18-70 with mild GO <18 mo duration	Adult GD patients aged 18-55 without severe GO
Outcomes	Eye evaluation, GO-QoL score, clinical activity score, diplopia score, TRAB, TPOAB	Selenoprotein concentration, self-rated symptom score, anxiety and depression score, TSH, ft4, ft3, TRAB, TPOAB
Intervention	Se 200 ug/day	Se 200 ug/day
Comparator	Placebo, Pentoxifylline	Placebo

Table 2. Characteristics of the studies included in the review.

Study	Reason for Exclusion
Watt 2013	Ongoing trial, no data yet available
Werthenbruch 2007	Case control design, no intervention
Khong 2014	Case control design, no intervention
Pedersen 2013	Cross-sectional design, no intervention
Vrca 2003	Different intervention and outcome measures
Smith 2011	Review article
Duntas 2011	Review article
Dharmasena 2014	Review article
Sturmiolo 2013	Editorial
Toulis 2010	Different disease population
Fan 2014	Different disease population
Xu 2011	Animal study

Table 3. List of excluded studies and reasons for exclusion.

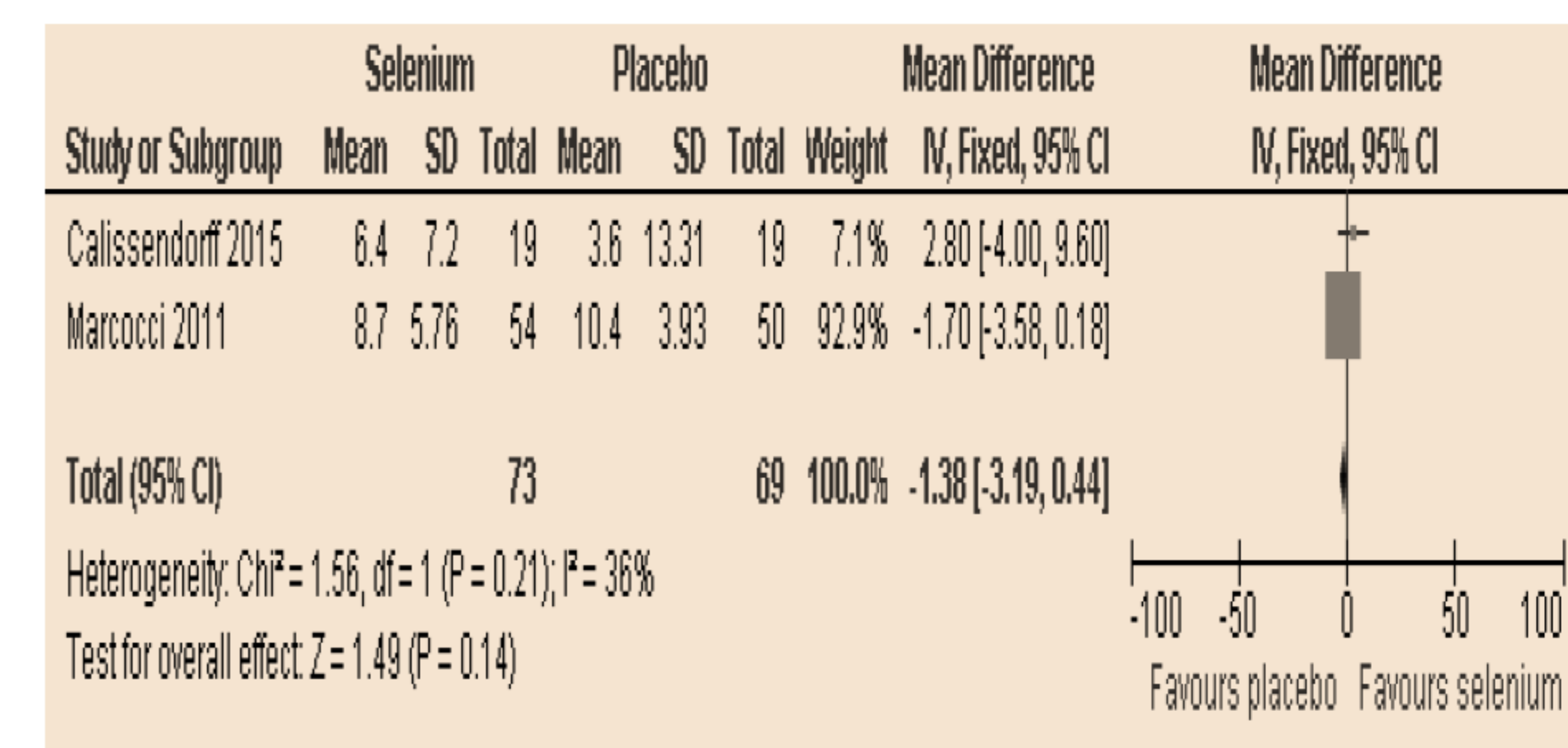


Figure 2. Mean difference in TRAB titers between the Se and placebo groups.

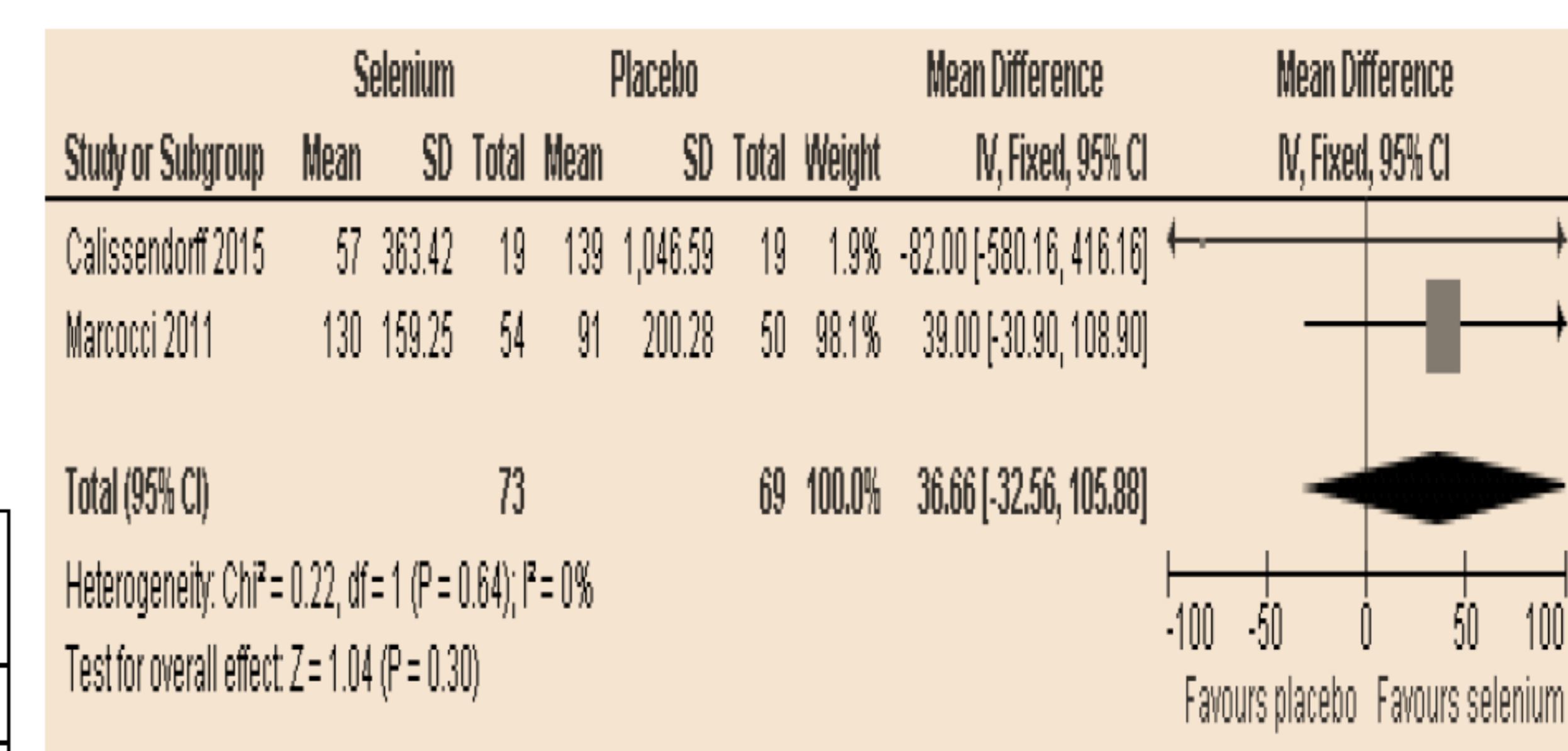


Figure 3. Mean difference in TPOAB titers between the Se and placebo groups.

## Conclusions

- Se supplementation in patients with GD and non-severe GO was not associated with significant differences in TRAB and TPOAB titers.
- More studies with larger populations and more clinical outcomes are recommended.