

# INPLASY PROTOCOL

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**Corresponding author:**  
I-Chen Tsai

sillyduck.radiology@gmail.com

**Author Affiliation:**  
新思惟國際

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**Conflicts of interest:**  
None declared.

## Effectiveness of Coenzyme Q10 for Reducing Fatigue: a Systematic Review and Meta-analysis of Randomized Controlled Trials

Tsai, IC<sup>1</sup>; Chang, KV<sup>2</sup>.

**Review question / Objective:** To investigate the treatment effect of CoQ10 on fatigue syndromes.

**Eligibility criteria:** To generate a recruited study list, the following inclusion criteria will be used: (1) randomized controlled trials (RCTs) enrolling human participants, (2) RCTs investigating the quantitative evaluation of fatigue symptoms before and after CoQ10 supplement, (3) placebo-controlled trials (without limitation of age and treatment duration ) and (4) trials with available data of pre- and post-intervention fatigue assessment or changes in fatigue scores. In this meta-analysis, open-label studies were also included since recent studies found that the open-label placebo had similar efficacy as the double-blind one.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 January 2022 and was last updated on 23 January 2022 (registration number INPLASY202210113).

### INTRODUCTION

**Review question / Objective:** To investigate the treatment effect of CoQ10 on fatigue syndromes.

**Rationale:** Coenzyme Q10 (CoQ10), an antioxidant, is an essential component of the mitochondrial electron transport chain.

It has been suggested to reduce fatigue in some clinical studies. However, the clinical effectiveness was inconclusive. Therefore, we would like to perform a systematic review and meta-analysis to investigate the treatment effect of CoQ10 on fatigue syndromes.

**Condition being studied:** The PICO (population, intervention, comparison, outcome) setting of the current meta-analysis included: (1) P: human participants; (2) I: CoQ10 supplement; (3) C: placebo; and (4) O: changes in the scores of fatigue symptoms.

## METHODS

**Search strategy:** Two authors (I.-C.T. and K.-V.C.) made independent electronic searches in the PubMed, Embase, Cochrane CENTRAL, Web of Science and ClinicalTrials.gov with keyword of ('Q10' OR 'Q 10' OR 'CoQ10' OR 'Coenzyme Q10' OR 'ubiquinol-10' OR 'ubiquinol' OR 'ubiquinone') AND ('fatigue' OR 'chronic fatigue syndrome' OR 'tiredness') through the earliest record to Jan 16,2022.

**Participant or population:** P: human participants.

**Intervention:** CoQ10 supplement.

**Comparator:** Placebo.

**Study designs to be included:** Randomized controlled trials.

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'ubiquinol-10' OR 'ubiquinol' OR 'ubiquinone') AND ('fatigue' OR 'chronic fatigue syndrome' OR 'tiredness') through the earliest record to Jan 16, 2022.

**Main outcome(s):** The primary outcomes were the changes in the fatigue scores following CoQ10 supplements or placebo regimens. The validity and appropriateness of the fatigue scale used in each trial were also examined by checking the pertinent references. If there were more than one scoring system for fatigue evaluation in a single trial, the index test included for meta-analysis was decided by the consensus of two authors (I.-C.T. and K.-V.C.).

**Additional outcome(s):** The secondary outcome was treatment-related adverse event rates. The aforementioned outcomes were quantified by odds ratios.

**Data management:** Two independent authors (I.-C.T. and K.-V.C.) extracted data from the recruited studies, encompassing demographic data, study design, details of CoQ10 and placebo regimens, and values of the primary and secondary outcomes. The evaluators paid special attention to the effect direction of the scale used in each trial to avoid mis-interpretation. In situations where the data was unavailable in the published articles, we contacted the corresponding authors to obtain the original data. The secondary outcome was treatment-related adverse event rates. The aforementioned outcomes were quantified by odds ratios. The secondary outcome was treatment-related adverse event rates. The aforementioned outcomes were quantified by odds ratios. The secondary outcome was treatment-related adverse event rates. The aforementioned outcomes were quantified by odds ratios.

**Quality assessment / Risk of bias analysis:** To investigate the methodological quality of recruited studies, we used the Cochrane risk-of-bias tool for randomized trials, version 2 (RoB 2), which consisted of 6 main items: randomization process, intervention adherence, missing outcome data, outcome measurement, selective

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reporting, and overall risk of bias. In the intervention adherence section of RoB 2, there are two options for literature assessment: intention-to-treat (intervention assignment) or per-protocol (intervention adherence). In this meta-analysis, we chose the per-protocol evaluation, since it fits the design of our included studies.

**Strategy of data synthesis:** Because of the heterogeneity of the target populations in the enrolled studies, the current meta-analysis was conducted with a random-effects model, using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ). A two-tailed p value less than 0.05 was considered statistically significant. We chose Hedges' g and 95% confidence intervals (CIs) to quantify the primary outcomes (changes in fatigue scores). A Hedges' g of 0.2, 0.5, and 0.8 is considered a small, moderate, and large effect size, respectively. We chose odds ratios and their 95% CIs to investigate the secondary outcome (treatment-related adverse event rates). The I<sup>2</sup> and Cochran's Q statistics were used to evaluate the degree of heterogeneity among studies. An I<sup>2</sup> value of 25%, 50%, and 75% was considered low, moderate, and high heterogeneity, respectively.

**Subgroup analysis:** Subgroup analyses based on the disease and CoQ10 formulations were performed. Meta-regressions of the treatment effects on daily CoQ10 doses and treatment durations were conducted to see if the fatigue relieving effect of CoQ10 correlated with the aforementioned parameters.

**Sensitivity analysis:** To confirm the robustness of the meta-analysis, the sensitivity analyses were performed using one-study removal method to see if there was a significant change in the summary effect size after removing a particular trial from the analysis.

**Language:** No language limit.

**Country(ies) involved:** Taiwan.

**Keywords:** coenzyme Q10, fatigue, clinical trials, meta-analysis, systematic review.

**Contributions of each author:**

Author 1 - I-Chen Tsai.

Email: [sillyduck.radiology@gmail.com](mailto:sillyduck.radiology@gmail.com)

Author 2 - Ke-Vin Chang.

Email: [kvchang011@gmail.com](mailto:kvchang011@gmail.com)