Supplemental Material

Effect of long-term marine Omega-3 fatty acids supplementation on the risk of atrial fibrillation in randomized controlled trials of cardiovascular outcomes: a systematic review and meta-analysis.

Table of Contents

Abbreviation List:

AF: atrial fibrillation.

ASCEND: A Study of Cardiovascular Events in Diabetes.

GISSI-HF: Gruppo Italiano per lo Studio della Sopravvi- venza nell'Insufficienza Cardiaca.

OMEMI: Omega-3 fatty acids in Elderly with Myocardial Infarction.

REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial.

RP: The Risk and Prevention Study.

STRENGTH: Long-Term Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh Cardiovascular Risk PatienTs With Hypertriglyceridemia.

VITAL: The Vitamin D and Omega-3 Trial.

Supplementary Methods

Research Algorithm

Potential trials were identified from MEDLINE and Embase. The following algorithms were used in MEDLINE: *(("Fatty Acids"[MeSH] OR "Fatty Acids"[tiab] OR "omega-3"[tiab] OR "fish oil"[tiab]) AND ("random*"[Text Word] OR "trial"[tiab]) AND ("Cardiovascular diseases"[MeSH Terms] OR "Cardiovascular diseases"[tiab] OR "Myocardial Infarction"[MeSH] OR "Myocardial Infarction"[tiab] OR "stroke"[MeSH] OR "stroke"[tiab] OR "death"[MeSH] OR "death"[tiab] OR "MACE"[tiab] OR "major adverse cardiovascular events"[tiab] OR "major adverse cardiac events"[tiab] OR "atrial fibrillation"[MeSH] OR "atrial fibrillation"[tiab]) AND 2012/01/01:2020/12/31[Date - Publication])* and in Embase: *('fatty acid'/exp OR 'fatty acid' OR 'omega 3'/exp OR 'omega 3' OR 'fish oil'/exp OR 'fish oil') AND ('cardiovascular disease'/exp OR 'cardiovascular disease') AND [randomized controlled trial]/lim AND [article]/lim AND [embase]/lim AND [2012-2020]/py.*

Results were supplemented from the reference files of all authors and from references lists of original articles, reviews, and meta-analyses. To qualify trials had to be a controlled randomized dedicated cardiovascular outcomes trial of marine omega-3 fatty acids supplements of at least 500 participants with a median follow-up of at least 1 year. Baseline characteristics (sample size, gender, race age, population), marine omega-3 fatty acids supplementation dosage, and AF outcomes for each relevant trial were extracted and reviewed by 2 authors. Captured AF outcomes in each trials were reported as a pre-specified outcome, as an adverse event or as a cause for hospitalization. Four trials reported new-onset AF outcomes (GISSI-HF, VITAL, OMEMI, STRENGTH), whereas three trial did not specifically exclude preexisting AF (REDUCE-IT, ASCEND and RP).

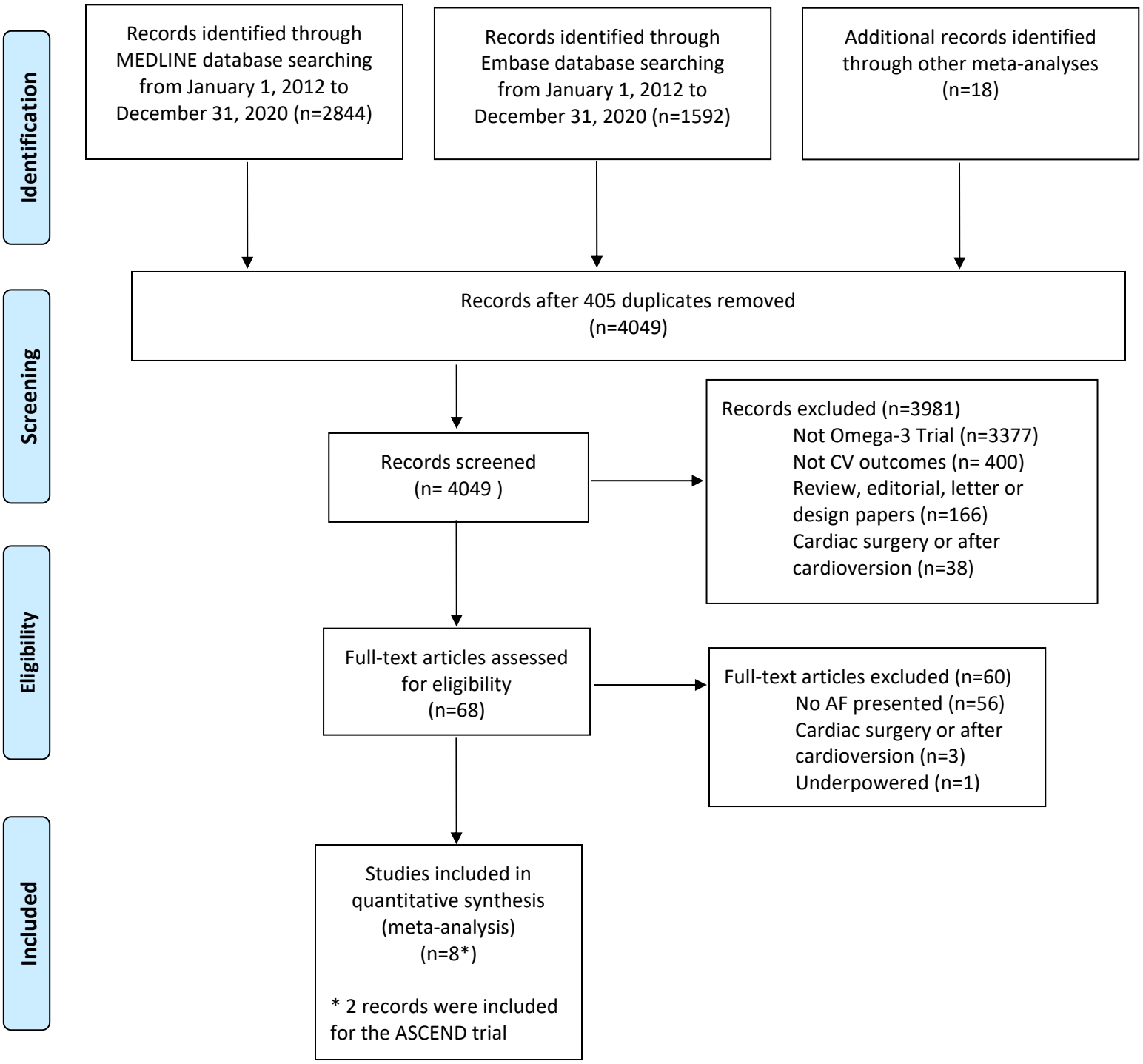
In the GISSI-HF (*Eur J Heart Fail*. 2013;15:1289-95), the analysis reporting AF endpoints was a post-hoc analysis in an ancillary manuscript. In the VITAL, the AF endpoint was reported in dedicated original article published after the publication of the main results. In the ASCEND trial, the original publication of the main trial presented patient-reported AF adverse events in the overall population (RR 1.23, 95%CI 0.98-1.54)., whereas a post-hoc research letter (*Circulation*. 2020;141:331-333) reported the relative treatment effect of AF using a more comprehensive review of electronic health records in patients without known AF (N=15374, 99% of the population) but without proceeding with an independent adjudication. The number of AF cases per treatment arm was not reported, only the proportion 7.7% (experimental) vs. 7.6% (placebo) in both arms and the rate ratio 1.02 (95%CI 0.91-1.15). The treatment effect reported in the original article was used for the primary analysis, whereas the post-hoc research letter was used for the sensitivity analysis.

The 2018 Cochrane review (Cochrane Database Syst Rev. 2018 Nov 30;11(11):CD003177) on Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease reported a RR of 0.97 (95%CI 0.90-1.05) on the risk of arrythmia including studies performed in the secondary prevention setteing of AF. The arrythmia endpoint was defined as fatal or nonfatal, new or re- current arrhythmia, including AF, ventricular tachycardia and ventricular fibrillation. Since the definition was not specific for AF, we haven't included the results of this review in our meta-analysis.

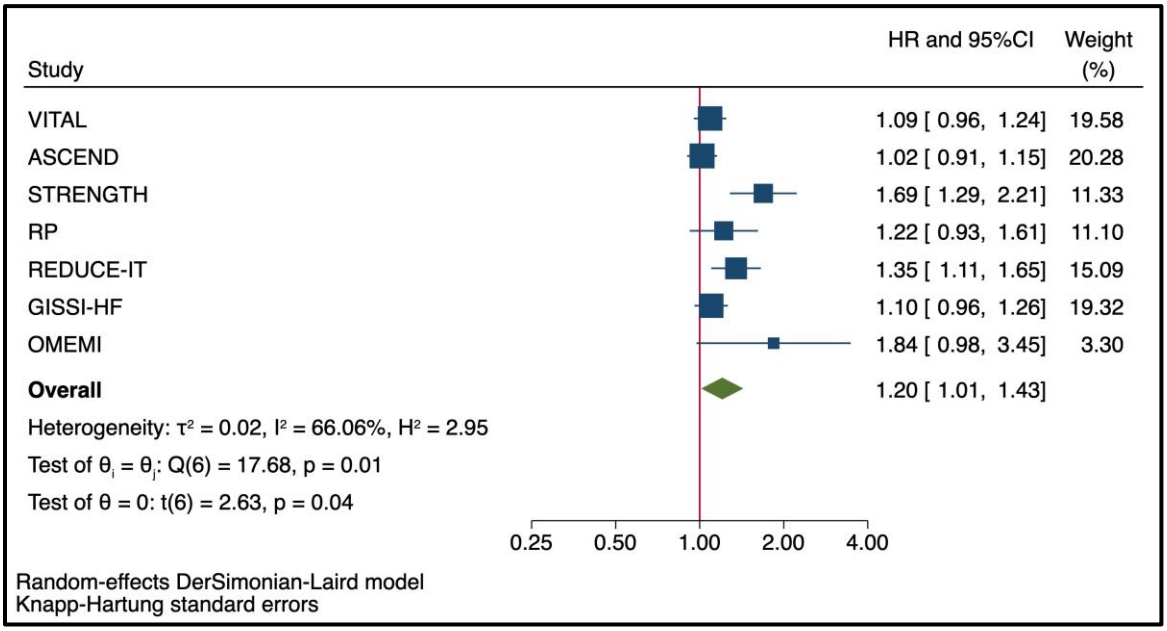
Supplemental Table I: Risk of Bias Summary

	Random Sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personal (performance bias)	Blinding of outcome assessment (detection-bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)
VITAL	Low	Low	Low	Low	Low	Low
ASCEND	Low	Low	Low	Low	Low	Low
STRENGTH	Low	Low	Low	Low	Low	Low
RP	Low	Low	Low	Low	Low	Low
REDUCE-IT	Low	Low	Low	Low	Low	Low
GISSI-HF	Low	Low	Low	Low	Low	Low
OMEMI	Low	Low	Low	Low	Low	Low

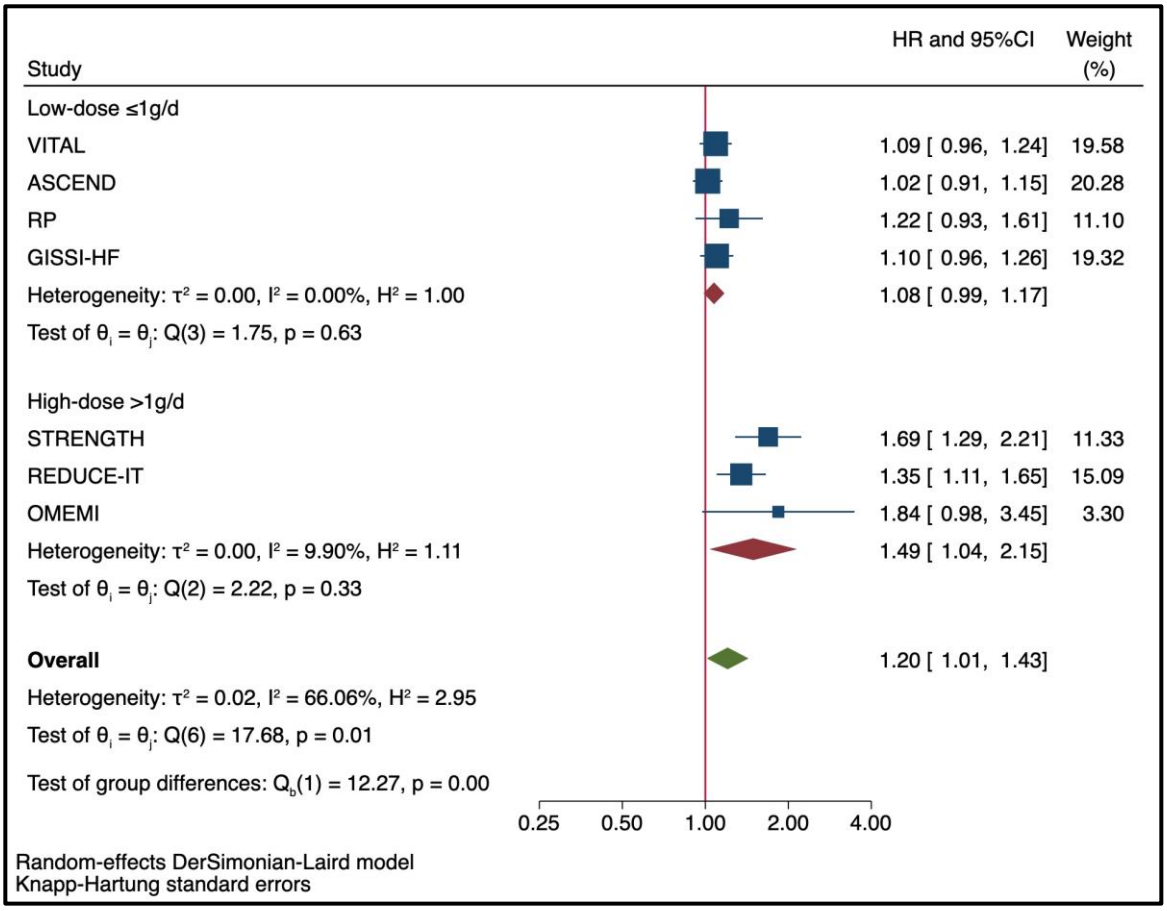
Supplemental Figure I: PRISMA Flow Diagram for Study Selection



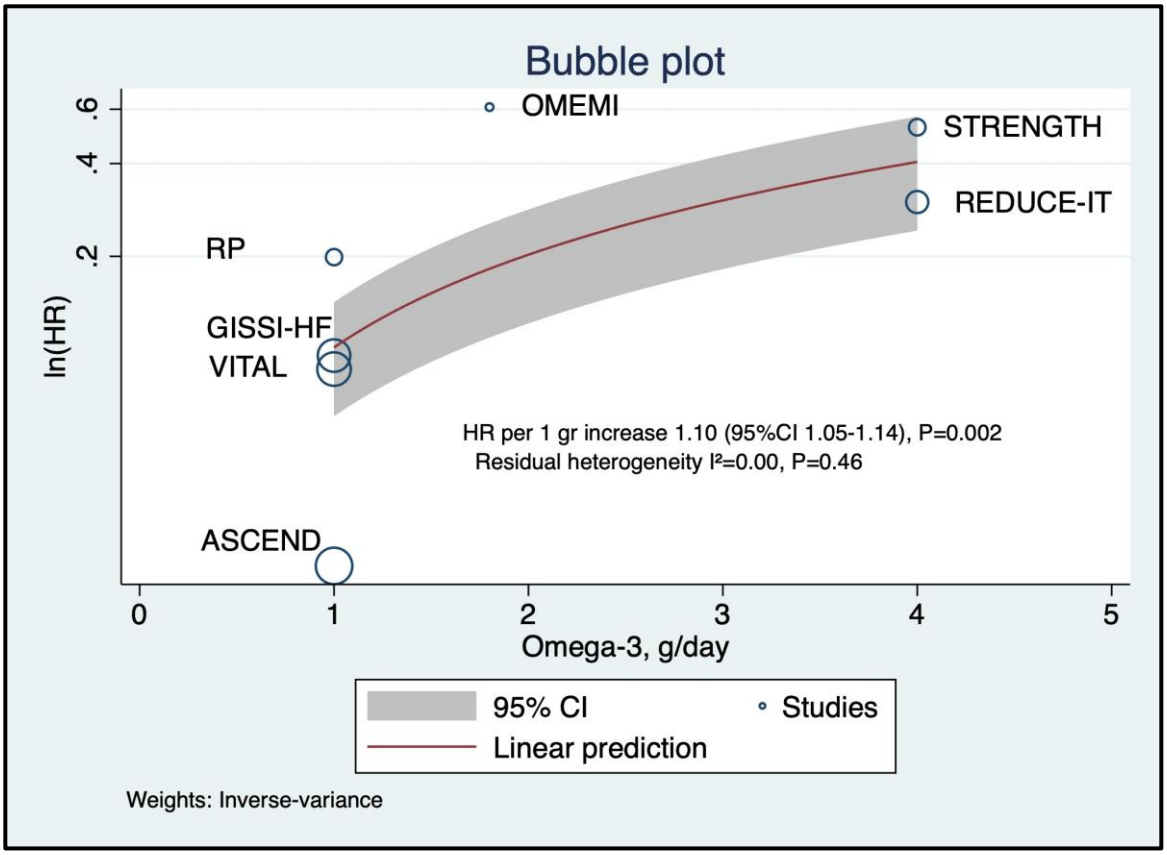
Supplemental Figure II: Effect of marine omega-3 fatty acids supplements on the risk of AF events using data from the post-hoc publication of the ASCEND trial



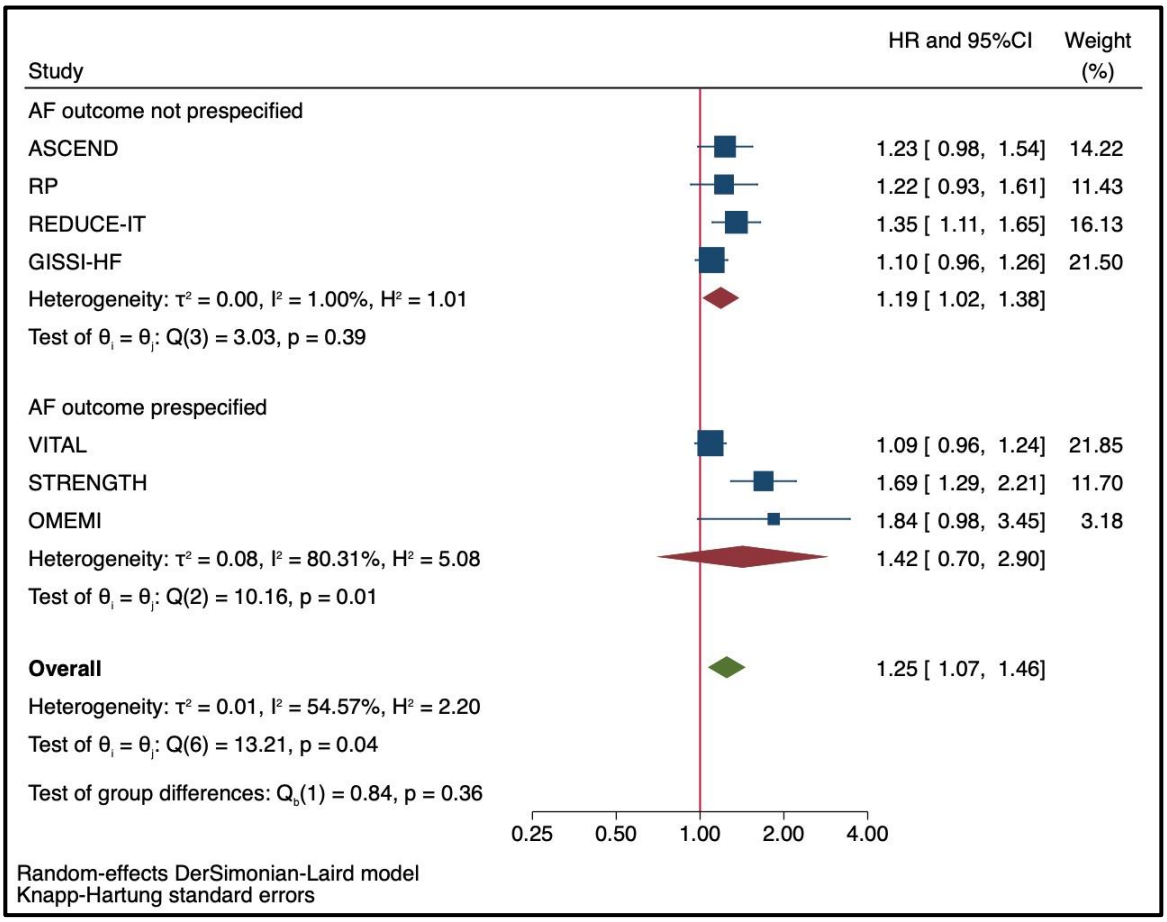
Supplemental Figure III: Effect of marine omega-3 fatty acids supplements on the risk of AF events stratified by low dose (≤1 gr per day) vs. high dose (>1 gr per day) and using data from the post-hoc publication of the ASCEND trial



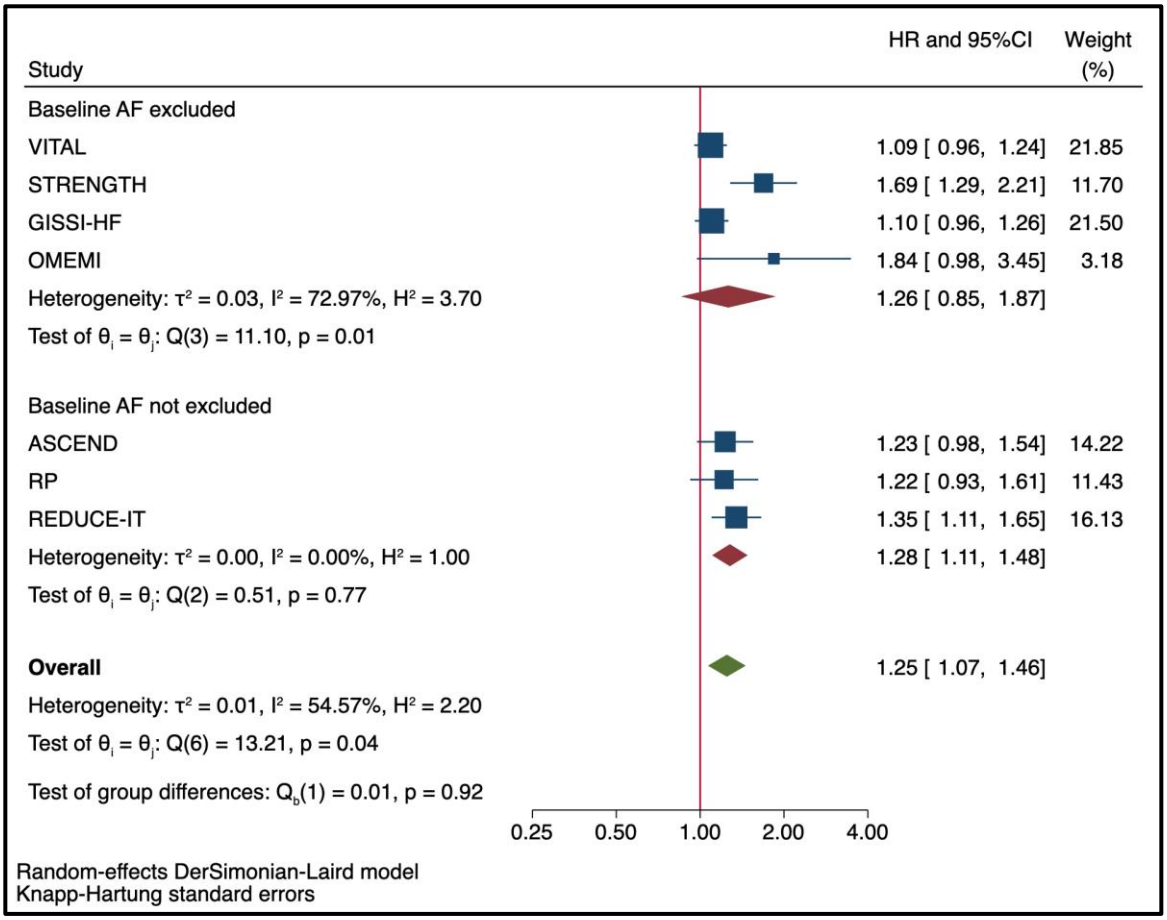
Supplemental Figure IV: Regression of omega-3 fatty acids dosage and risk for AF events in 7 randomized controlled trials using data from the post-hoc publication of the ASCEND trial[22]



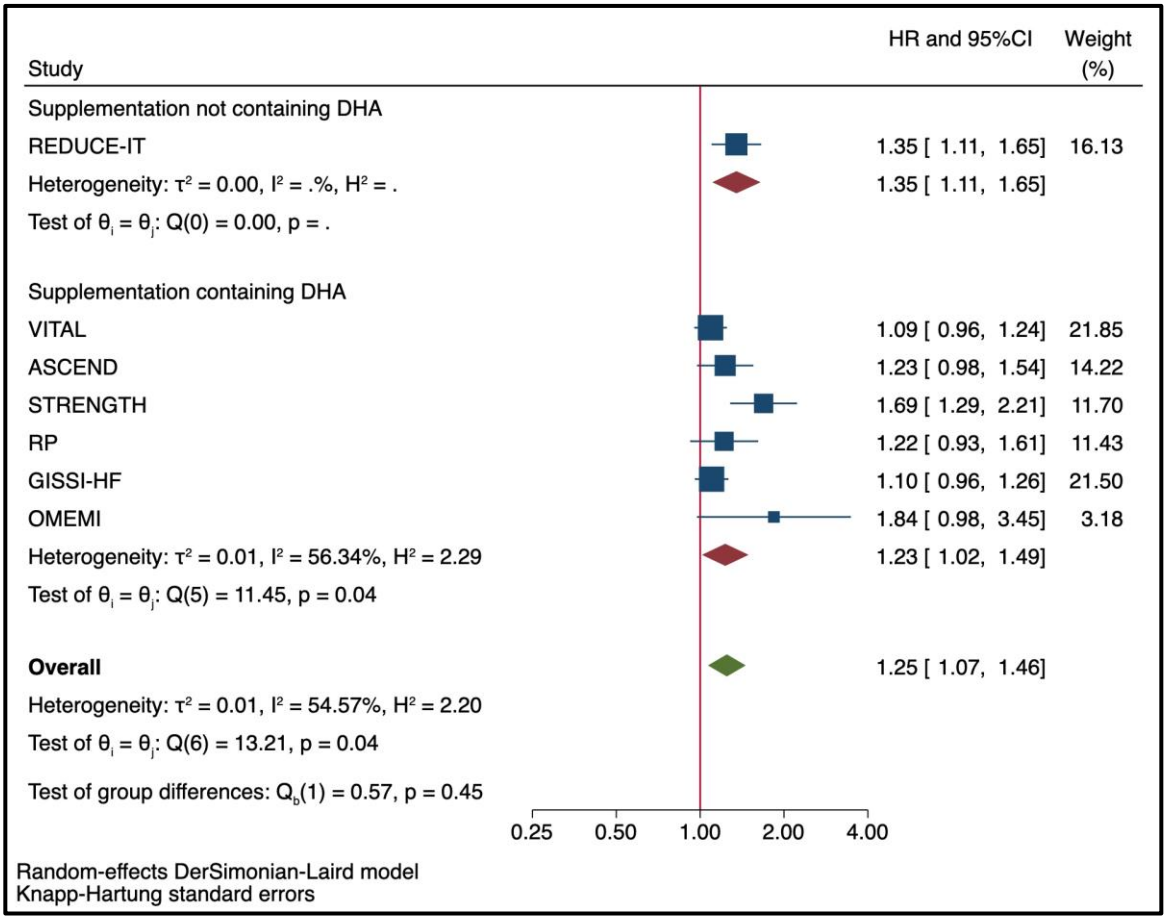
Supplemental Figure V: Effect of marine omega-3 fatty acids supplements on the risk of AF events by studies that prespecified AF outcomes vs. not



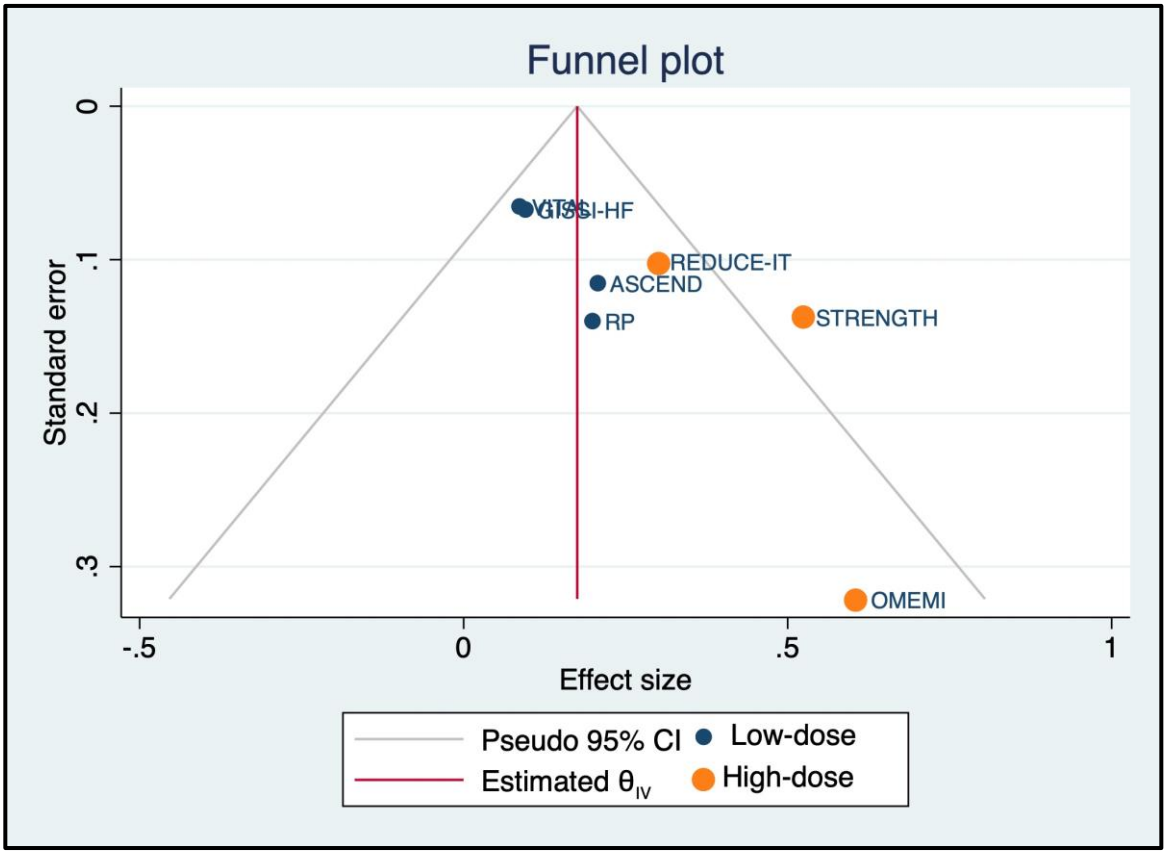
Supplemental Figure VI: Effect of marine omega-3 fatty acids supplements on the risk of AF events by studies that excluded baseline AF (or qualified AF events as new-onset) vs. those that did not exclude baseline AF



Supplemental Figure VII: Effect of marine omega-3 fatty acids supplements on the risk of AF events after excluding the REDUCE-IT trial



Supplemental Figure VIII: Publication bias assessment with funnel plot



Supplemental Figure IX: Trim-and-fill analysis of publication bias