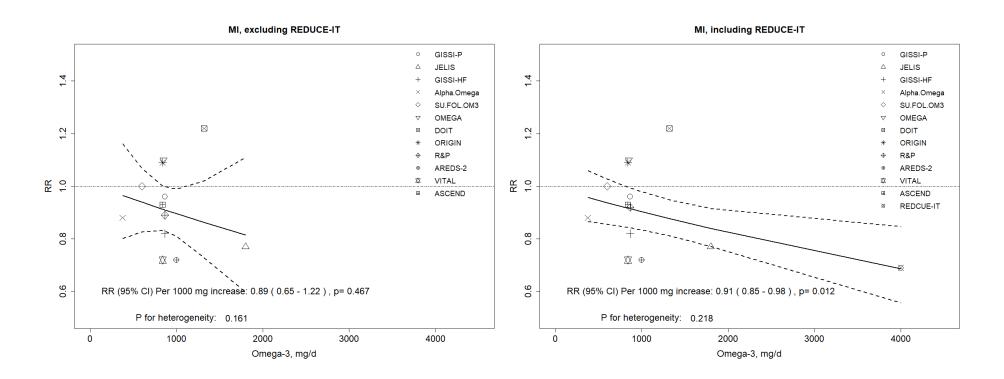
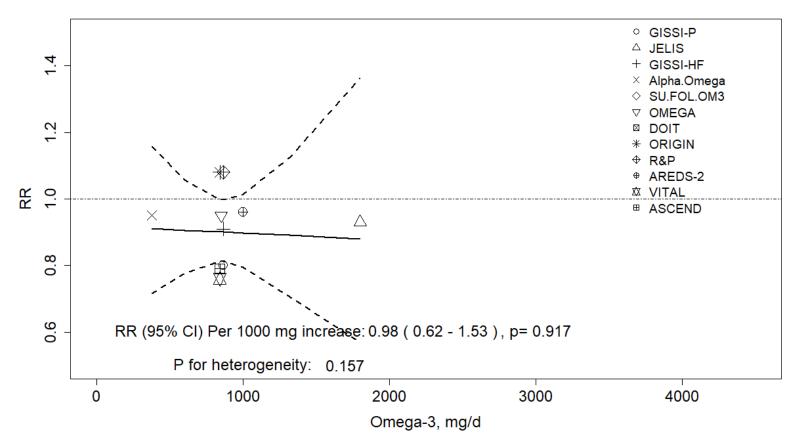


Figure S1. Dose-response relationship between marine omega-3 supplementation and risk of coronary heart disease endpoints.



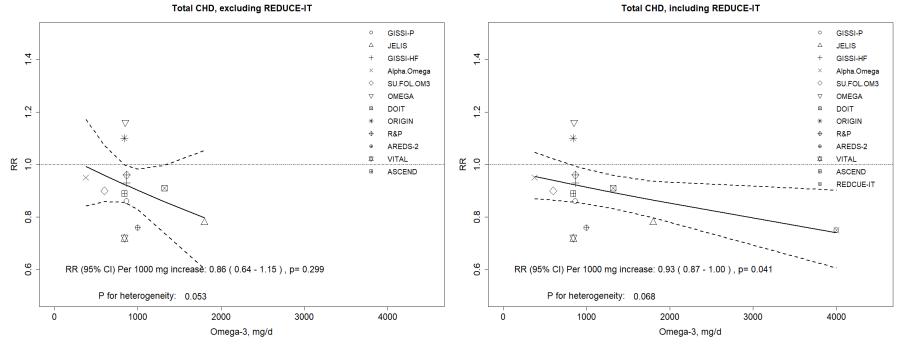
Panel A: Dose-response relationship between marine omega-3 supplementation and risk of myocardial infarction, which includes fatal and/or nonfatal MI.

CHD Death



Panel B: Dose-response relationship between marine omega-3 supplementation and risk of CHD death. Data not available in REDUCE-IT.

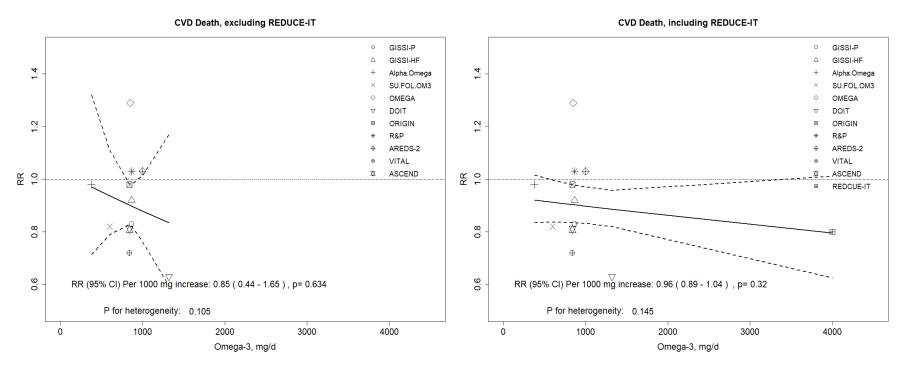
The RRs for SU.FOL.OM3 and DOIT were 0.41 and 0.39 which were too small to be captured in the figure.



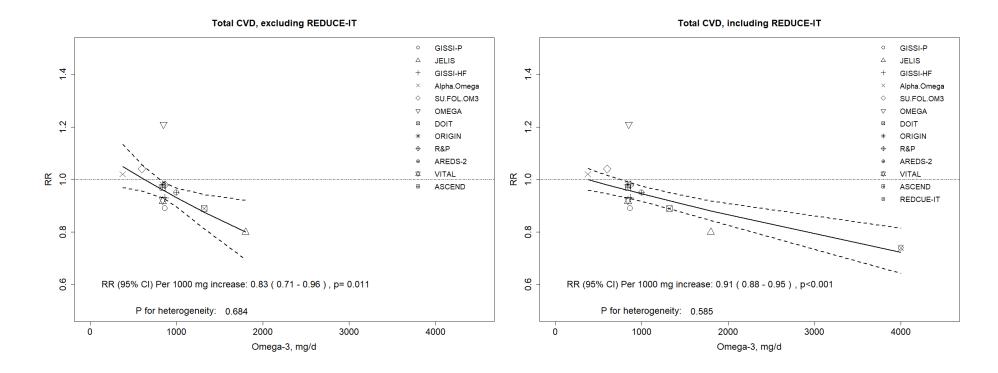
Panel C: Dose-response relationship between marine omega-3 supplementation and risk of total CHD, which includes MI, death from CHD, or coronary

revascularization.

Figure S2. Dose-response relationships between marine omega-3 supplementation and risk of other CVD subtypes.

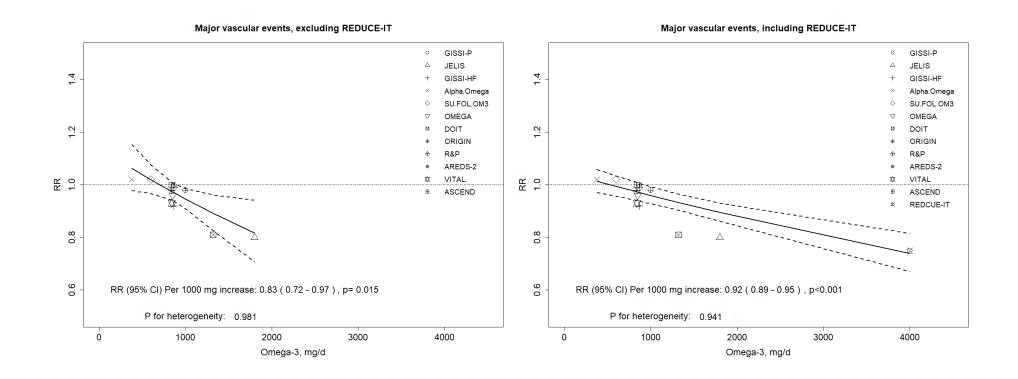


Panel A: Dose-response relationship between marine omega-3 supplementation and risk of CVD death.



Panel B: Dose-response relationship between marine omega-3 supplementation and risk of total CVD, which includes nonfatal MI, nonfatal stroke, death from CVD, or hospitalization due to a cardiovascular cause (except for JELIS and ALPHA Omega which include revascularization).

Removing JELIS and ALPHA OMEGA resulted in RR (95% CI) per 1,000 mg/d increase 0.75 (0.47, 1.18), p=0.207 without including REDUCE-IT, and 0.92 (0.88, 0.96), p<0.001 with REDUCE-IT.



Panel C: Dose-response relationship between marine omega-3 supplementation and risk of major vascular events, which include nonfatal MI, nonfatal stroke, death from CVD, or revascularization.

Figure S3. Dose-response relationship between marine omega-3 supplementation and risk of stroke.

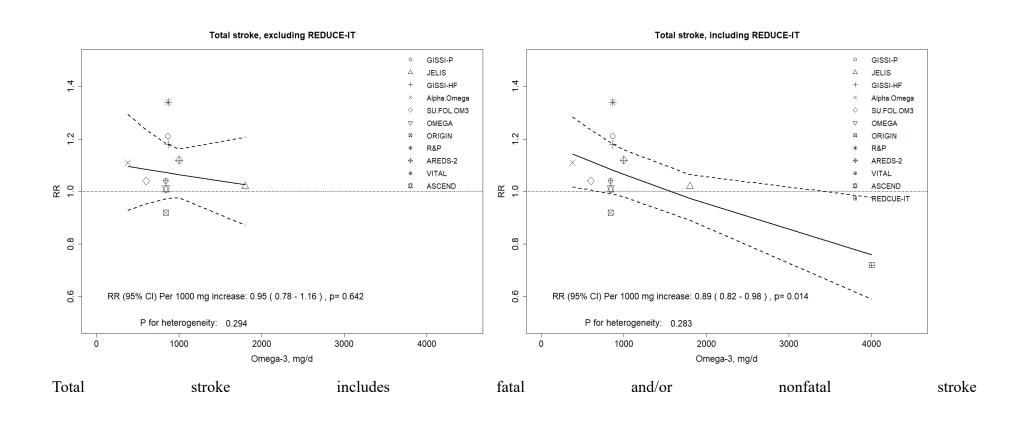
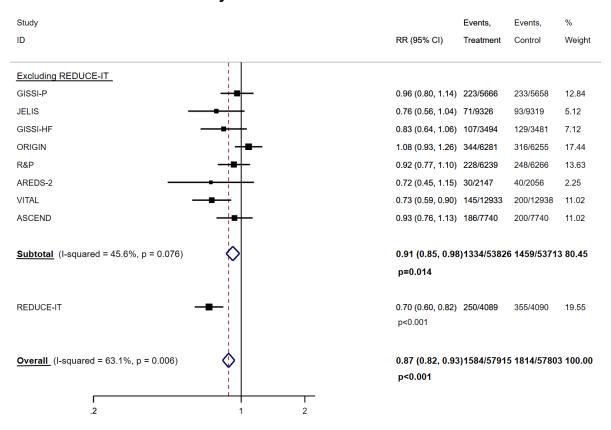


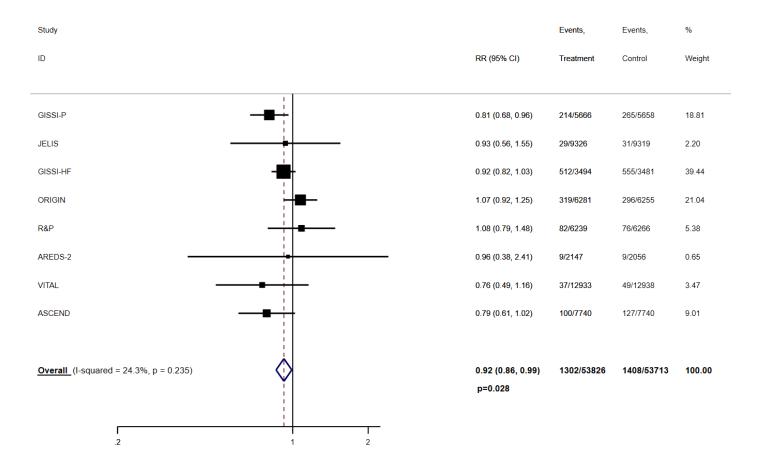
Figure S4. Pooled associations between marine omega-3 supplementation and risk of cardiovascular disease endpoints excluding DOIT, SU.FOL.OM3, Alpha.Omega, and OMEGA due to lower dose, shorter follow-up duration, or smaller sample size than the rest of included studies.

Myocardial Infarction



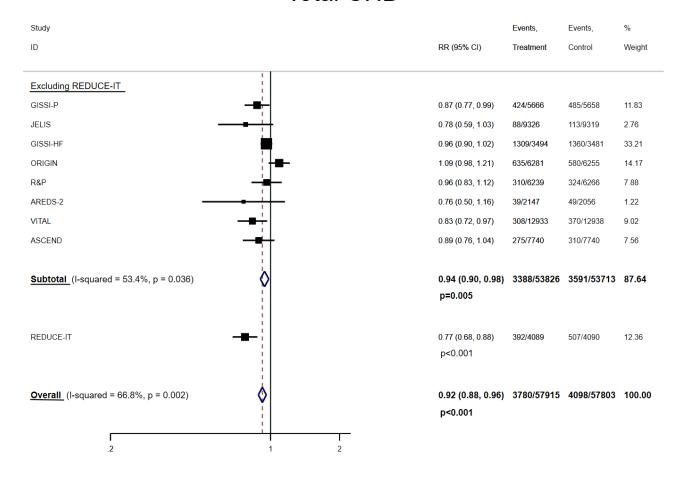
Panel A: Marine omega-3 supplementation and risk of myocardial infarction, which includes fatal and/or nonfatal MI.

CHD Death



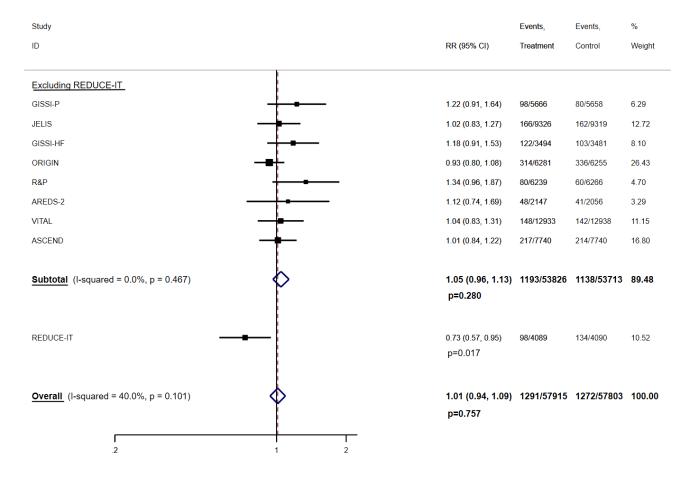
Panel B: Marine omega-3 supplementation and risk of CHD death.

Total CHD



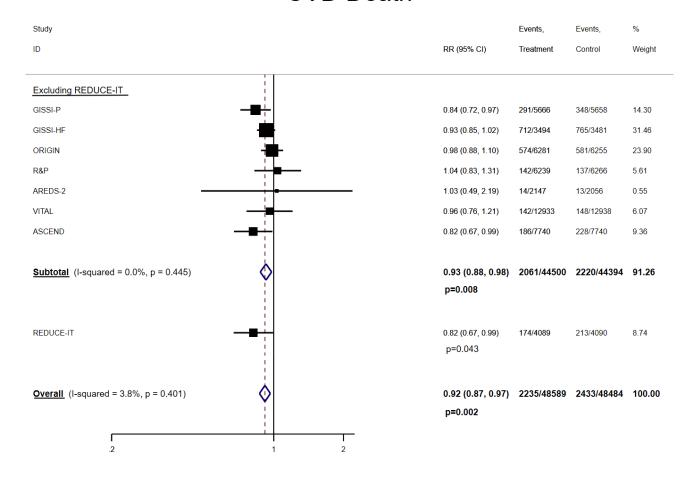
Panel C: Marine omega-3 supplementation and risk of total CHD, which includes MI, death from CHD, or coronary revascularization.

Total stroke



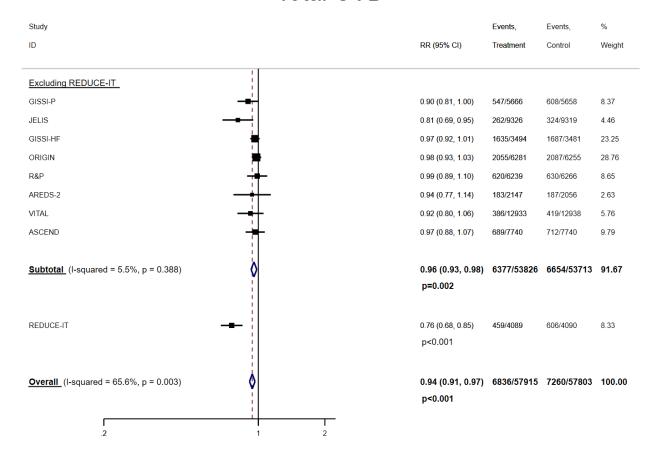
Panel D: Marine omega-3 supplementation and risk of total stroke, which includes fatal and/or nonfatal stroke.

CVD Death



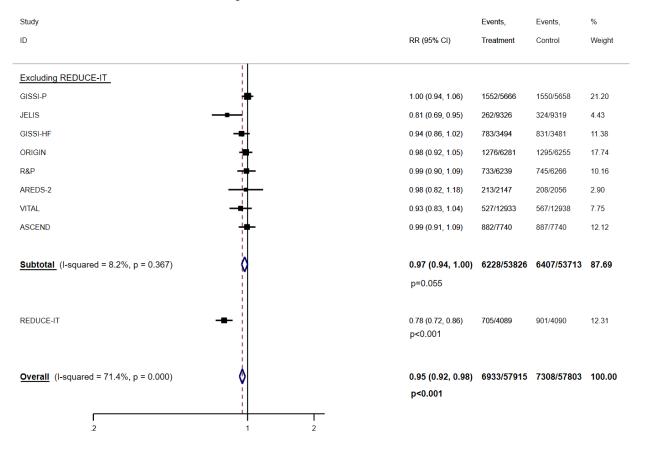
Panel E: Marine omega-3 supplementation and risk of CVD death.

Total CVD



Panel F: Marine omega-3 supplementation and risk of total CVD, which includes nonfatal MI, nonfatal stroke, death from CVD, or hospitalization due to a cardiovascular cause (except for JELIS and ALPHA Omega which include revascularization).

Major vascular events



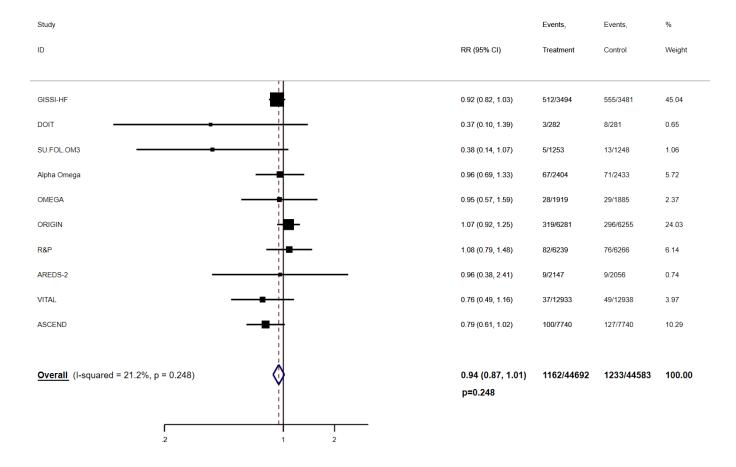
Panel G: Marine omega-3 supplementation and risk of major vascular events, which include nonfatal MI, nonfatal stroke, death from CVD, or revascularization.

Figure S5. Pooled associations between marine omega-3 supplementation and risk of cardiovascular disease endpoints excluding two open-label trials, GISSI-P and JELIS.

Myocardial Infarction Study ID RR (95% CI) Weight Control Excluding REDUCE-IT GISSI-HF 0.83 (0.64, 1.06) 107/3494 129/3481 7.56 0.53 DOIT 11/282 9/281 1.22 (0.51, 2.89) SU.FOL.OM3 1.00 (0.61, 1.62) 32/1253 32/1248 1.87 Alpha Omega 0.88 (0.67, 1.17) 89/2404 102/2433 5.93 OMEGA 1.10 (0.81, 1.48) 87/1919 78/1885 4.60 ORIGIN 1.08 (0.93, 1.26) 344/6281 316/6255 R&P 0.92 (0.77, 1.10) 228/6239 248/6266 14.47 AREDS-2 0.72 (0.45, 1.15) 30/2147 40/2056 2.39 VITAL 0.73 (0.59, 0.90) 145/12933 11.69 200/12938 **ASCEND** 0.93 (0.76, 1.13) 186/7740 200/7740 11.69 **Subtotal** (I-squared = 31.3%, p = 0.158) 0.93 (0.86, 1.00) 1259/44692 1354/44583 79.25 p=0.052 REDUCE-IT 0.70 (0.60, 0.82) 250/4089 355/4090 20.75 p<0.001 **Overall** (I-squared = 56.5%, p = 0.011) 0.88 (0.82, 0.94) 1509/48781 1709/48673 100.00 p<0.001

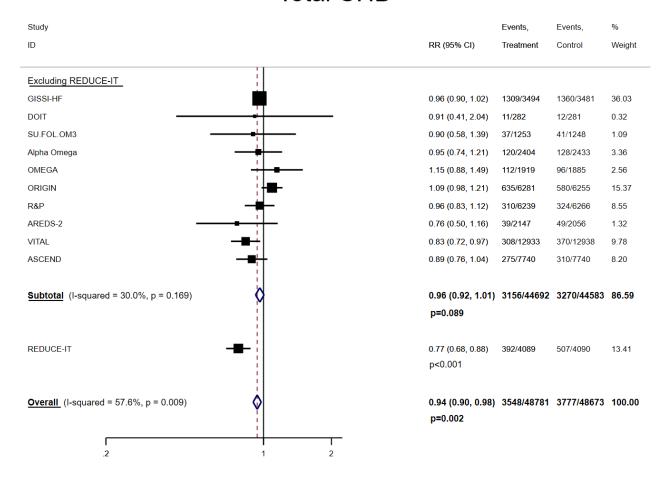
Panel A: Marine omega-3 supplementation and risk of myocardial infarction, which includes fatal and/or nonfatal MI.

CHD Death



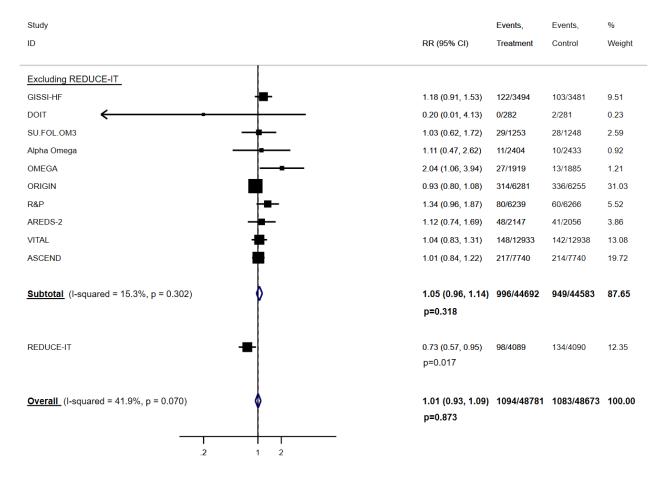
Panel B: Marine omega-3 supplementation and risk of CHD death.

Total CHD



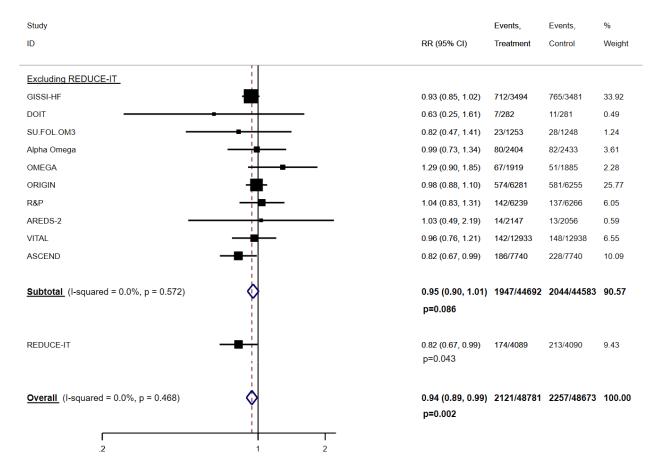
Panel C: Marine omega-3 supplementation and risk of total CHD, which includes MI, death from CHD, or coronary revascularization.

Total stroke



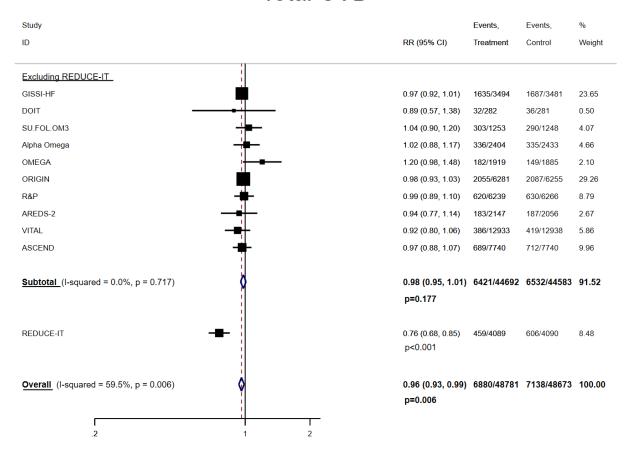
Panel D: Marine omega-3 supplementation and risk of total stroke, which includes fatal and/or nonfatal stroke.

CVD Death



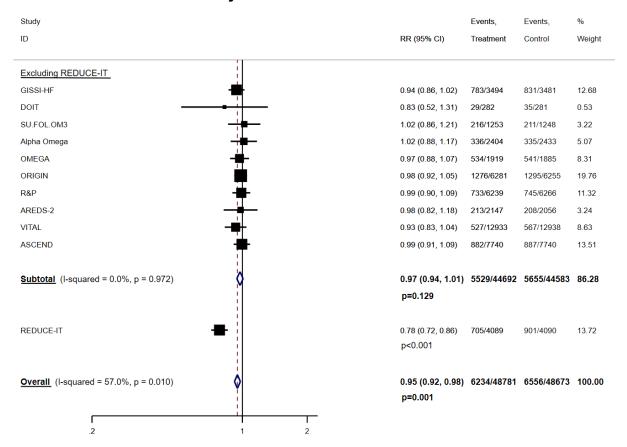
Panel E: Marine omega-3 supplementation and risk of CVD death.

Total CVD



Panel F: Marine omega-3 supplementation and risk of total CVD, which includes nonfatal MI, nonfatal stroke, death from CVD, or hospitalization due to a cardiovascular cause (except for JELIS and ALPHA Omega which include revascularization).

Major vascular events



Panel G: Marine omega-3 supplementation and risk of major vascular events, which include nonfatal MI, nonfatal stroke, death from CVD, or revascularization.

Table S1. Sensitivity analysis that excluded open-label trials and trials with smaller sample size, lower dose, and shorter follow-up duration.

	Main analysis (n=13 trials)*		Sensitivity analysis (n=7 trials) [†]	
	RR (95% CI)			
Endpoints	Excluding REDUCE-IT	Including REDUCE-IT	Excluding REDUCE-IT	Including REDUCE-IT
Myocardial infarction	0.92 (0.86, 0.99)	0.88 (0.83, 0.94)	0.92 (0.84, 0.99)	0.87 (0.80, 0.93)
CHD death	0.91 (0.85, 0.98)	NA	0.95 (0.88, 1.03)	NA
Total CHD	0.95 (0.91, 0.99)	0.93 (0.89, 0.96)	0.96 (0.92, 1.00)	0.93 (0.89, 0.97)
Total stroke	1.05 (0.98, 1.14)	1.02 (0.95, 1.10)	1.03 (0.94, 1.13)	0.99 (0.91, 1.08)
CVD death	0.93 (0.88, 0.99)	0.92 (0.88, 0.97)	0.94 (0.89, 1.00)	0.93 (0.88, 0.99)
Total CVD	0.97 (0.94, 0.99)	0.95 (0.92, 0.98)	0.97 (0.94, 1.00)	0.95 (0.92, 0.98)
Major vascular events	0.97 (0.94, 1.00)	0.95 (0.93, 0.98)	0.97 (0.93, 1.01)	0.94 (0.91, 0.97)

^{*}n referred to the number of included studies.

[†] DOIT, SU.FOL.OM3, Alpha.Omega, OMEGA, GISSI-P, and JELIS are excluded.