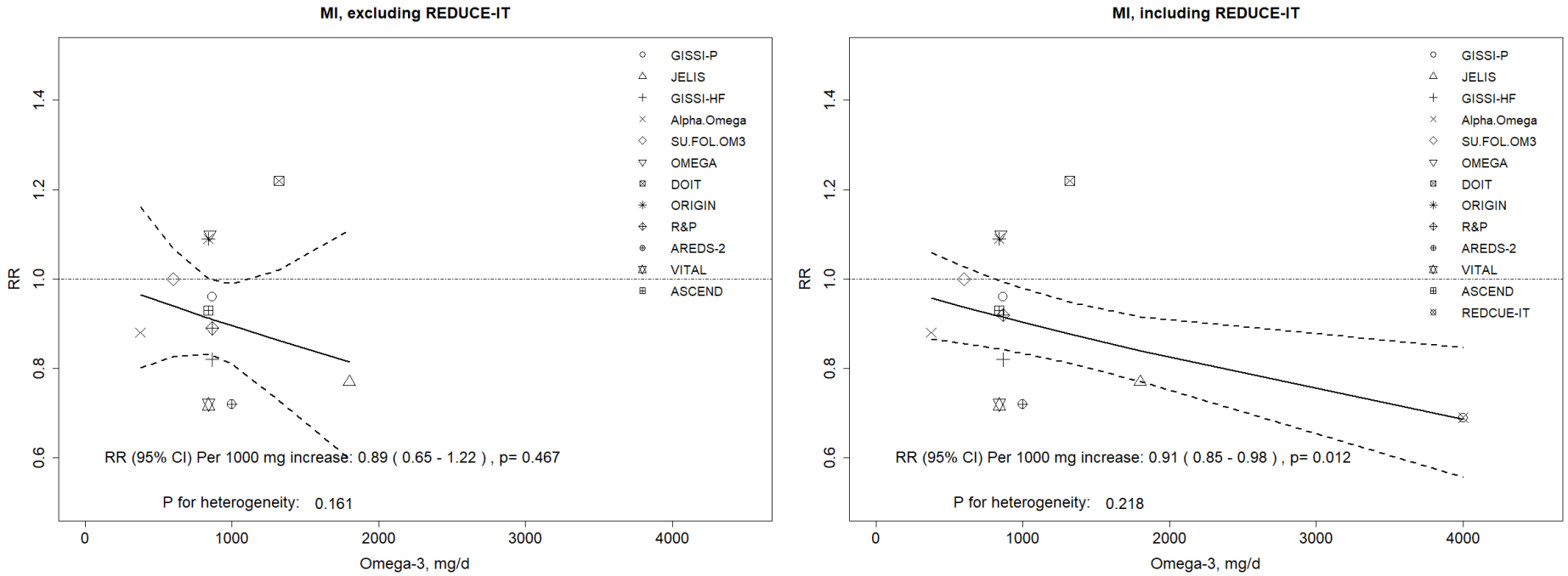
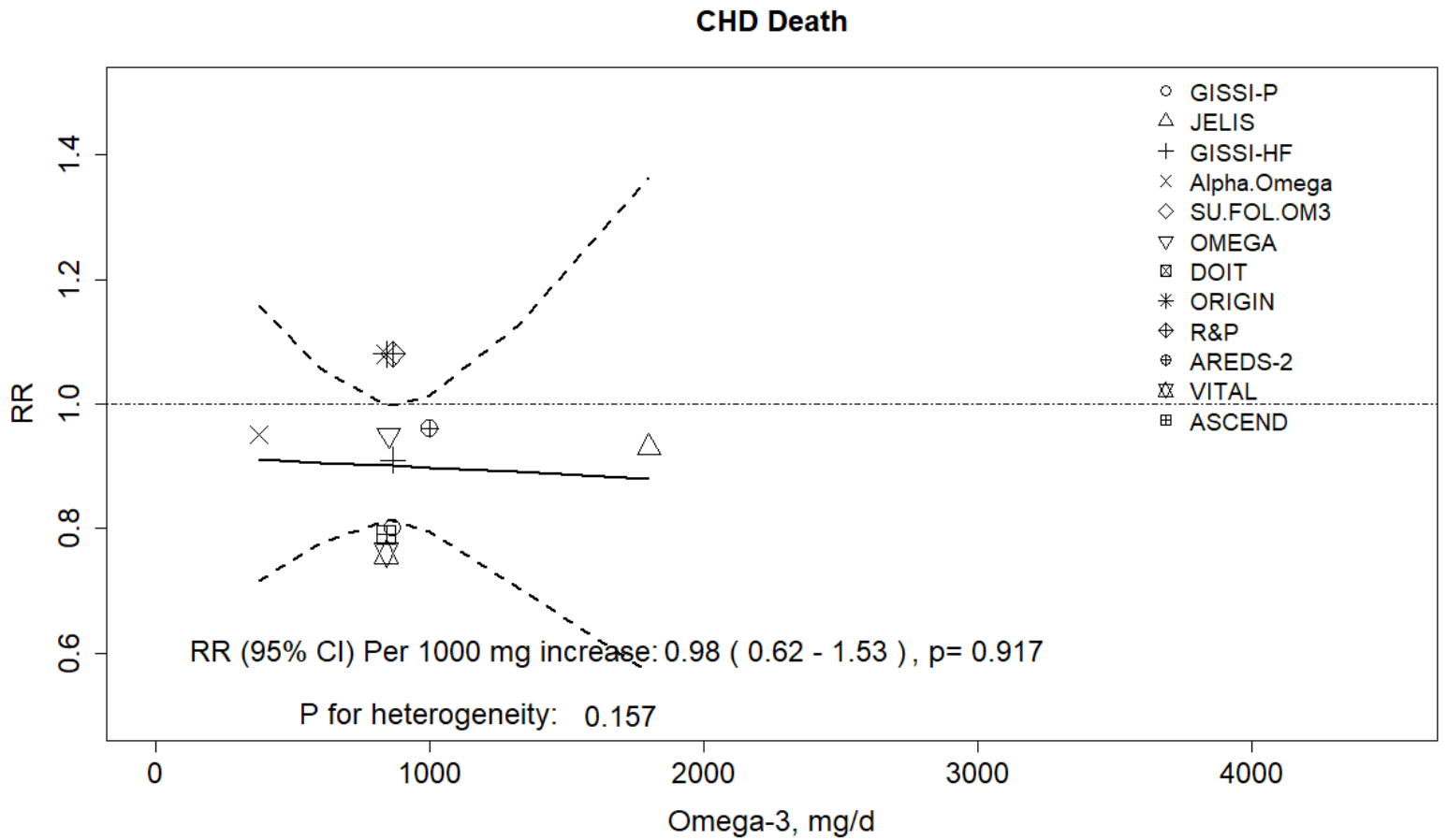
SUPPLEMENTAL MATERIAL

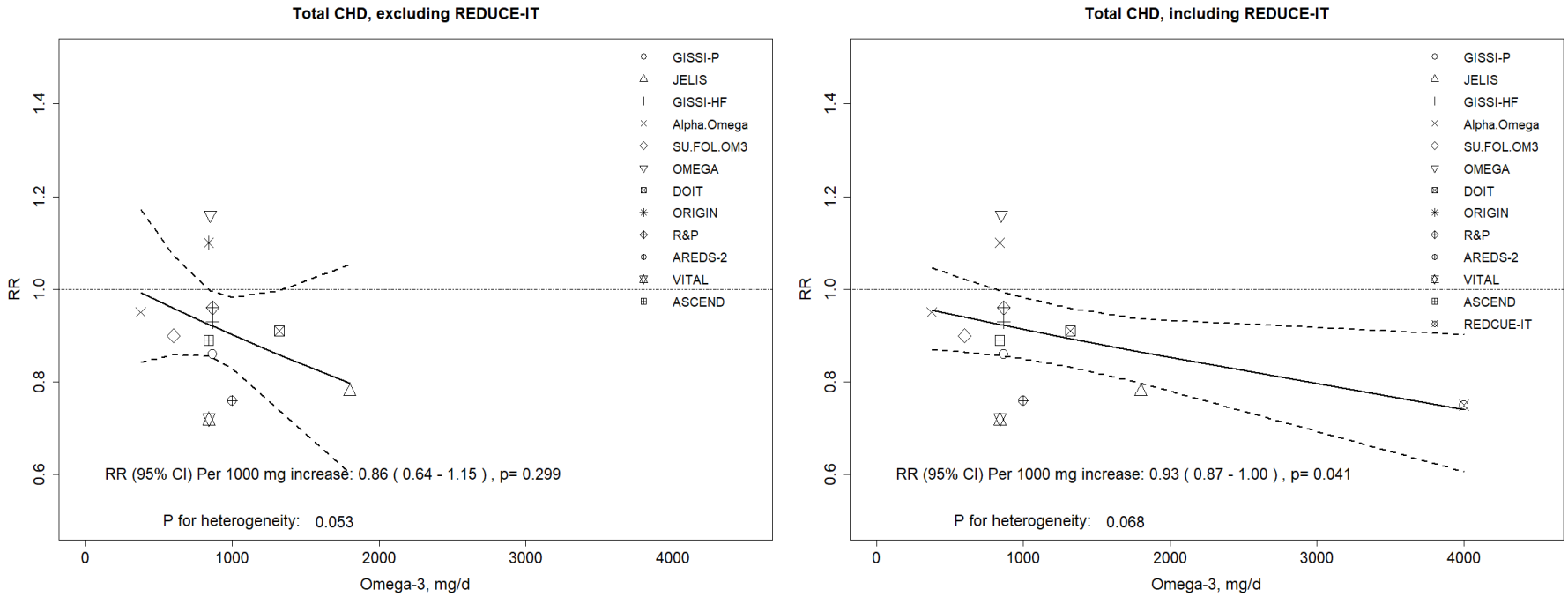
Figure S1. Dose-response relationship between marine omega-3 supplementation and risk of coronary heart disease endpoints.



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

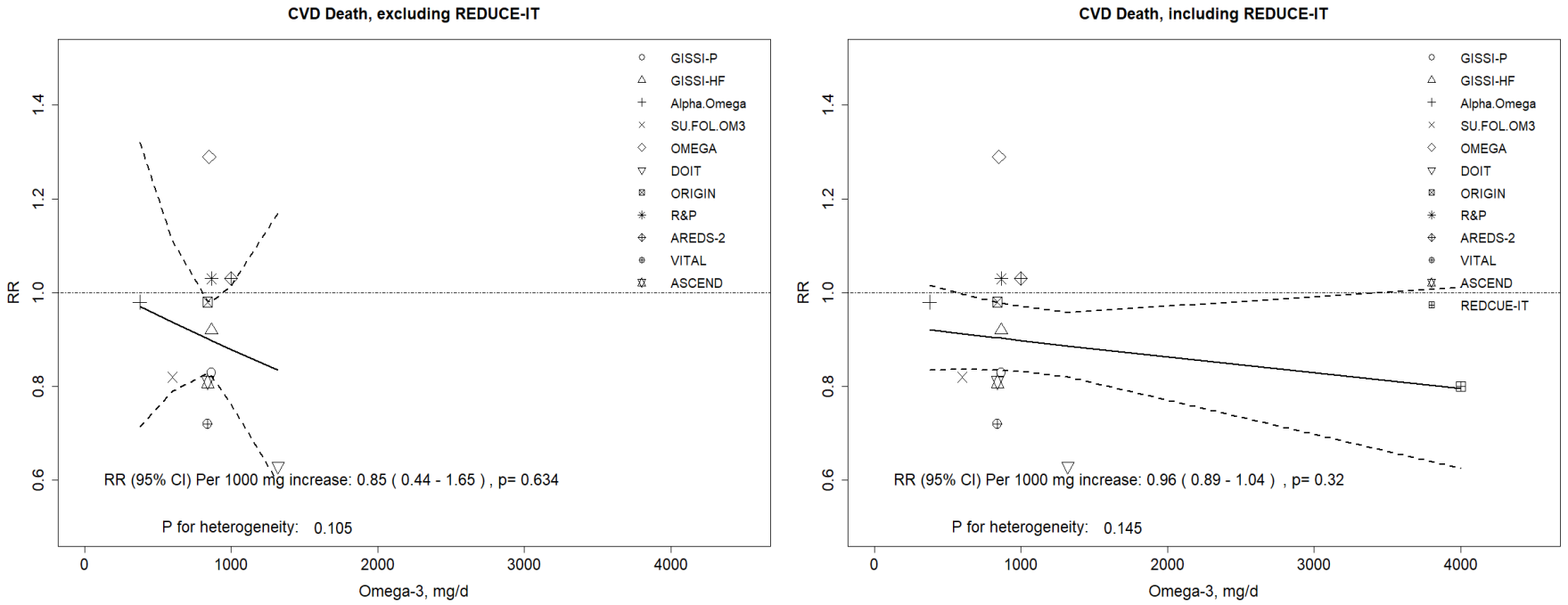


Panel B: Dose-response relationship between marine omega-3 supplementation and risk of CHD death.
Data not available in REDUCE-IT.
The RRs for SU.FOL.OM3 and DOIT were 0.41 and 0.39 which were too small to be captured in the figure.

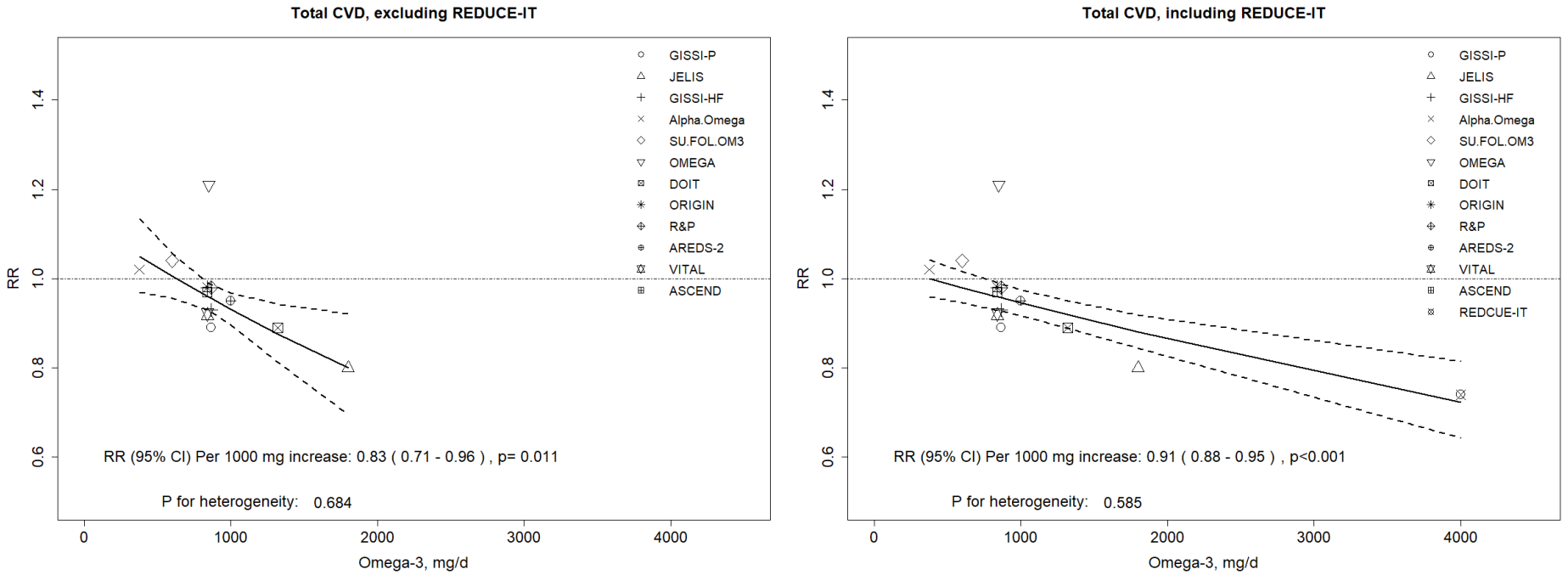


Panel C: Dose-response relationship between marine omega-3 supplementation and risk of total CHD, which includes MI, death from CHD, or coronary revascularization.

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

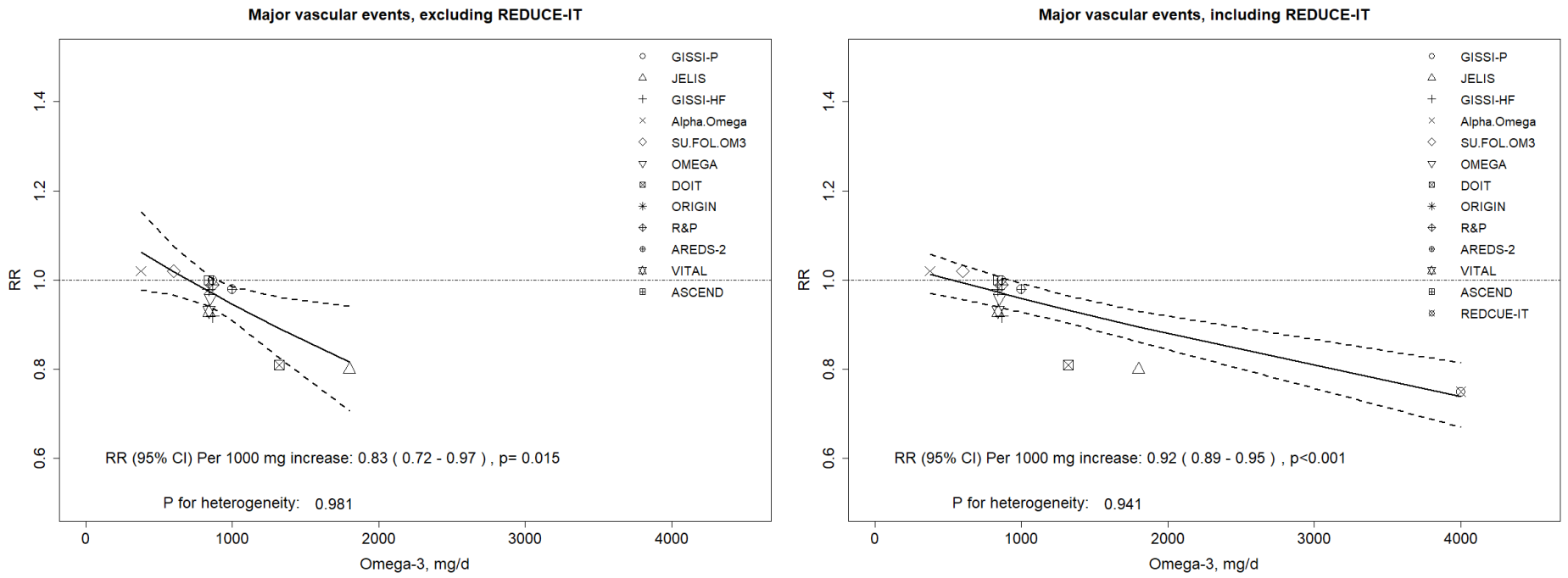


Panel A: Dose-response relationship between marine omega-3 supplementation and risk of CVD death.



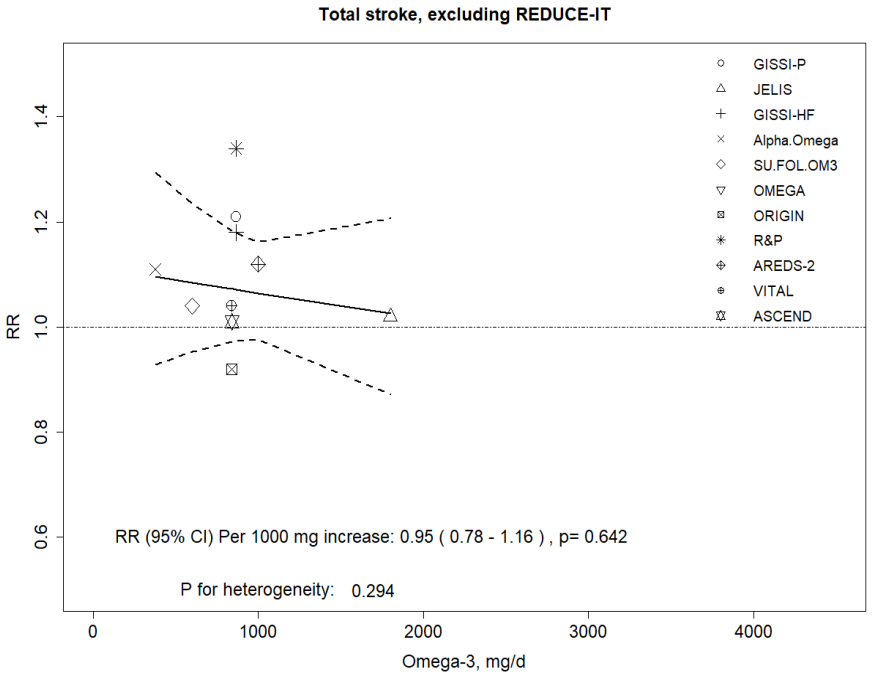
Panel B: Dose-response relationship between marine omega-3 supplementation and risk of total CVD, which includes nonfatal MI, nonfatal stroke, death from CVD, or hospitalization due to a cardiovascular cause (except for JELIS and ALPHA Omega which include revascularization).

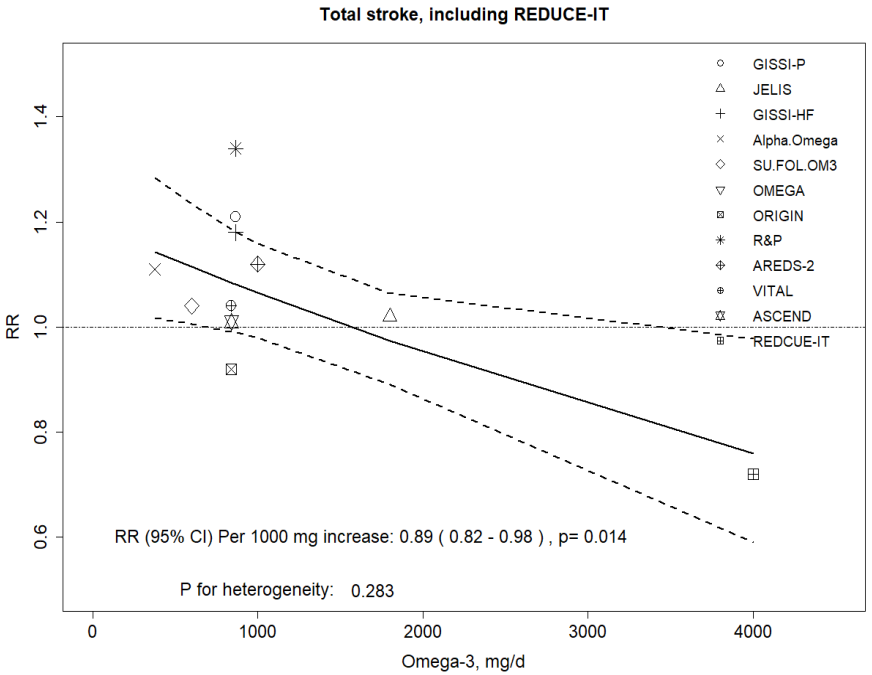
Removing JELIS and ALPHA OMEGA resulted in RR (95% CI) per 1,000 mg/d increase 0.75 (0.47, 1.18), p=0.207 without including REDUCE-IT, and 0.92 (0.88, 0.96), p<0.001 with REDUCE-IT.



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.

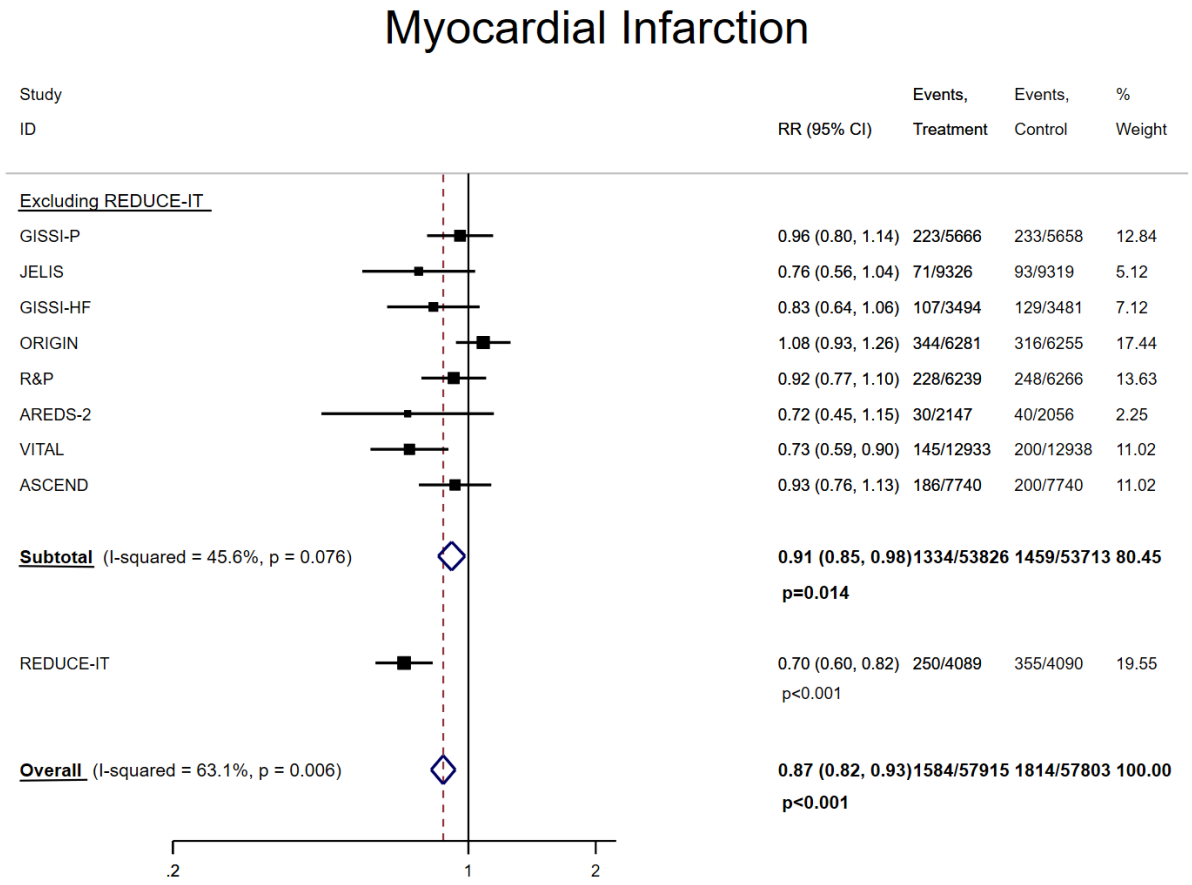
Figure S3. Dose-response relationship between marine omega-3 supplementation and risk of stroke.



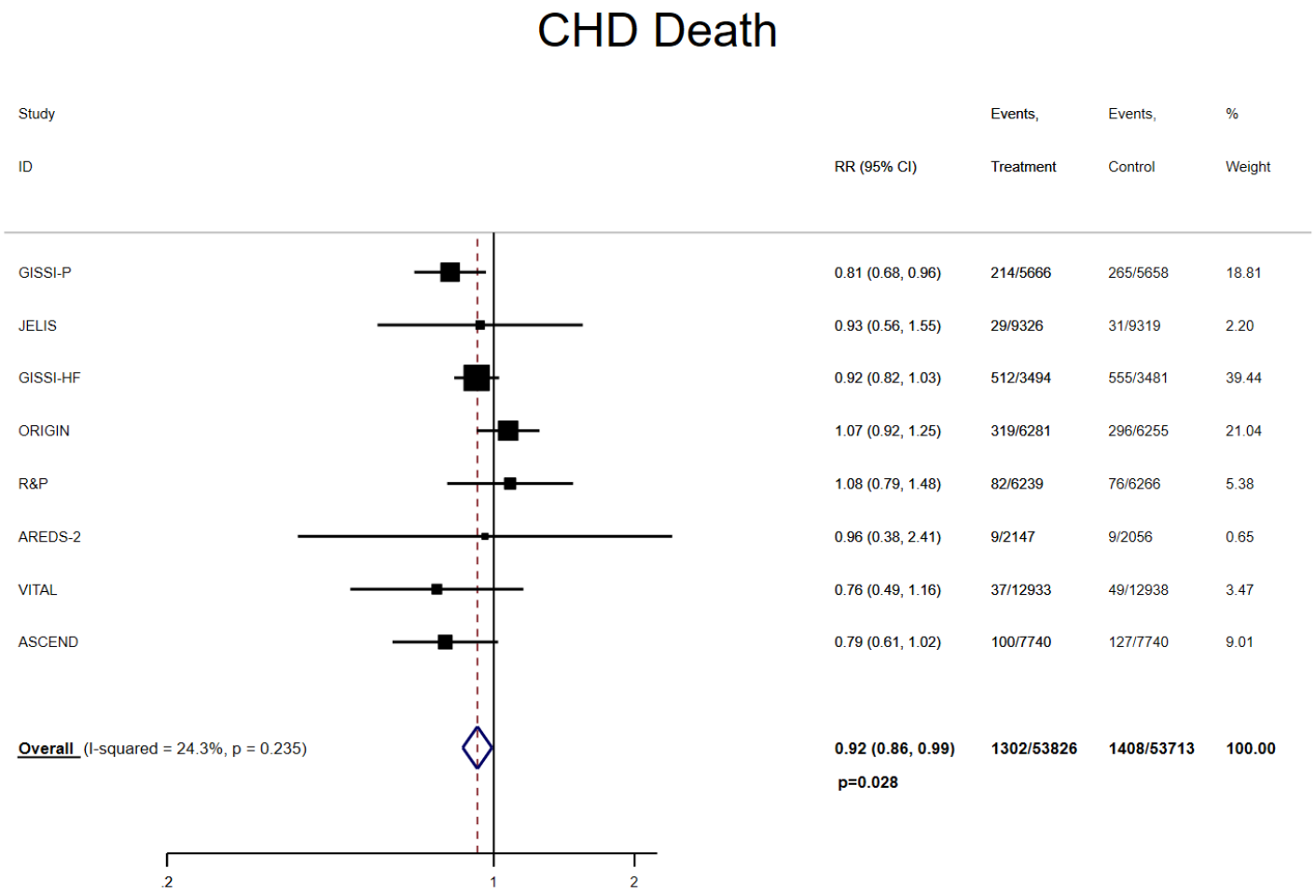


Total stroke includes fatal and/or nonfatal stroke

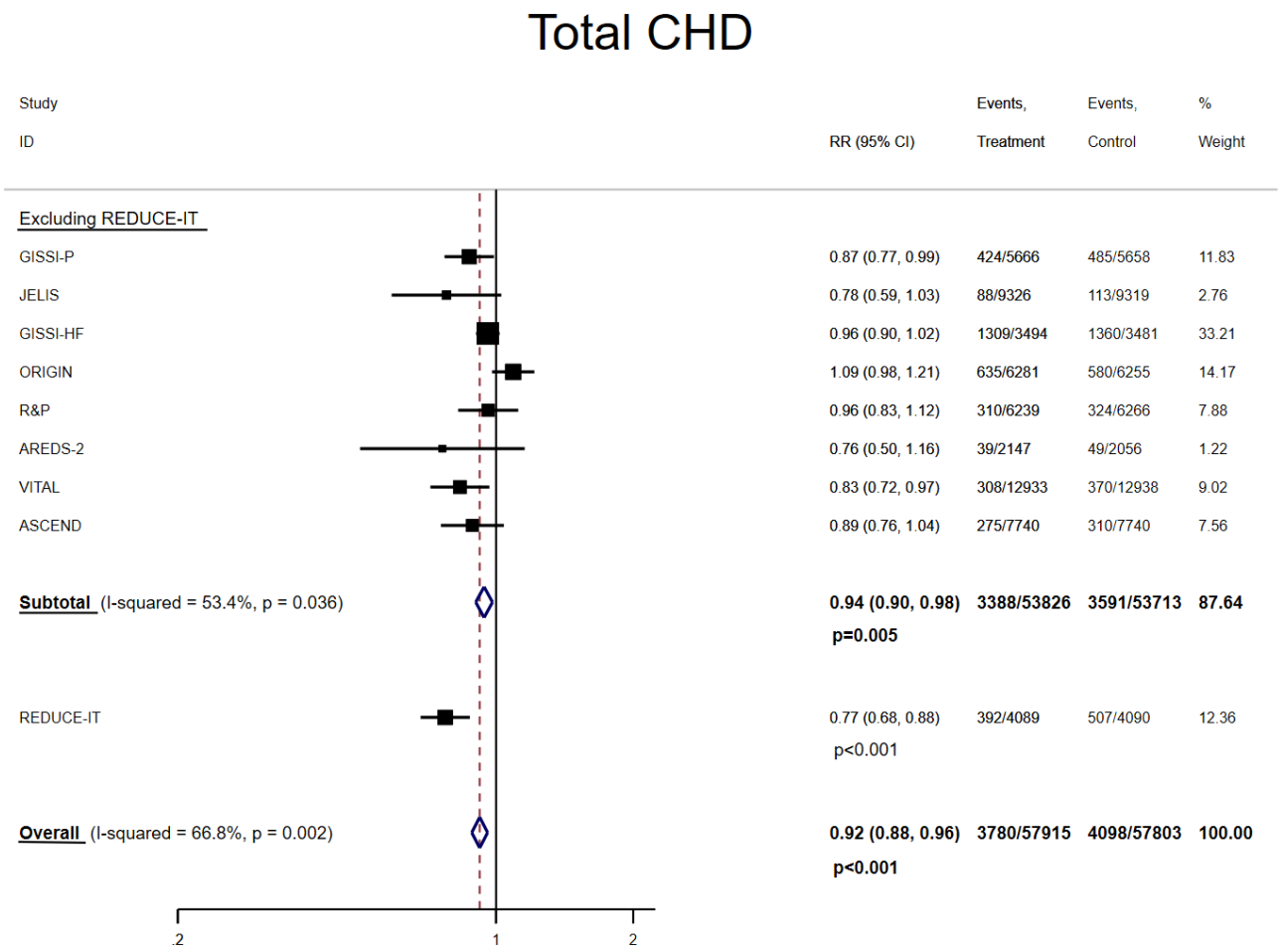
Figure S4. Pooled associations between marine omega-3 supplementation and risk of cardiovascular disease endpoints excluding DOIT, SU.FOL.OM3, Alpha.Omega, and OMEGA due to lower dose, shorter follow-up duration, or smaller sample size than the rest of included studies.



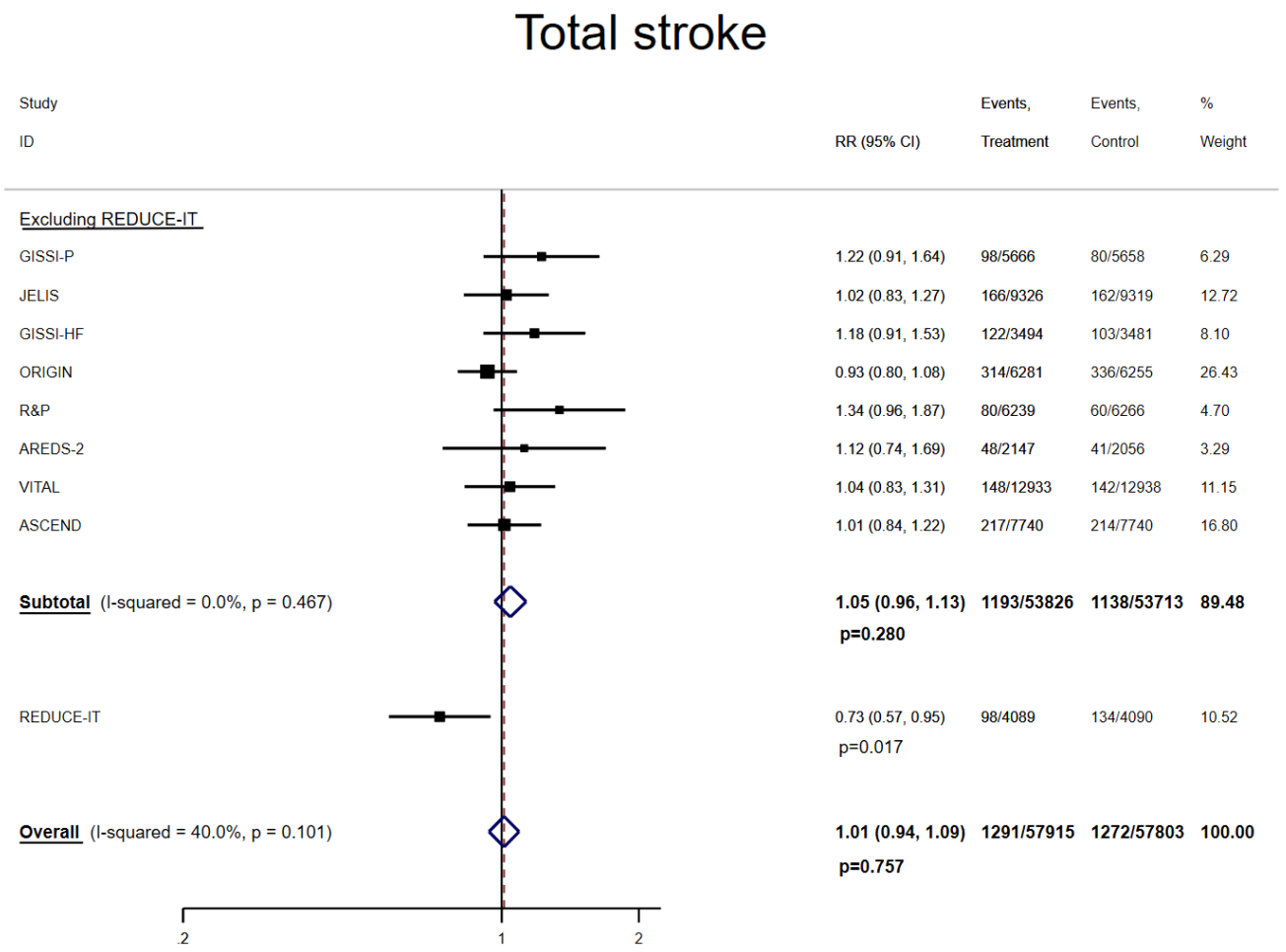
Panel A: Marine omega-3 supplementation and risk of myocardial infarction, which includes fatal and/or nonfatal MI.



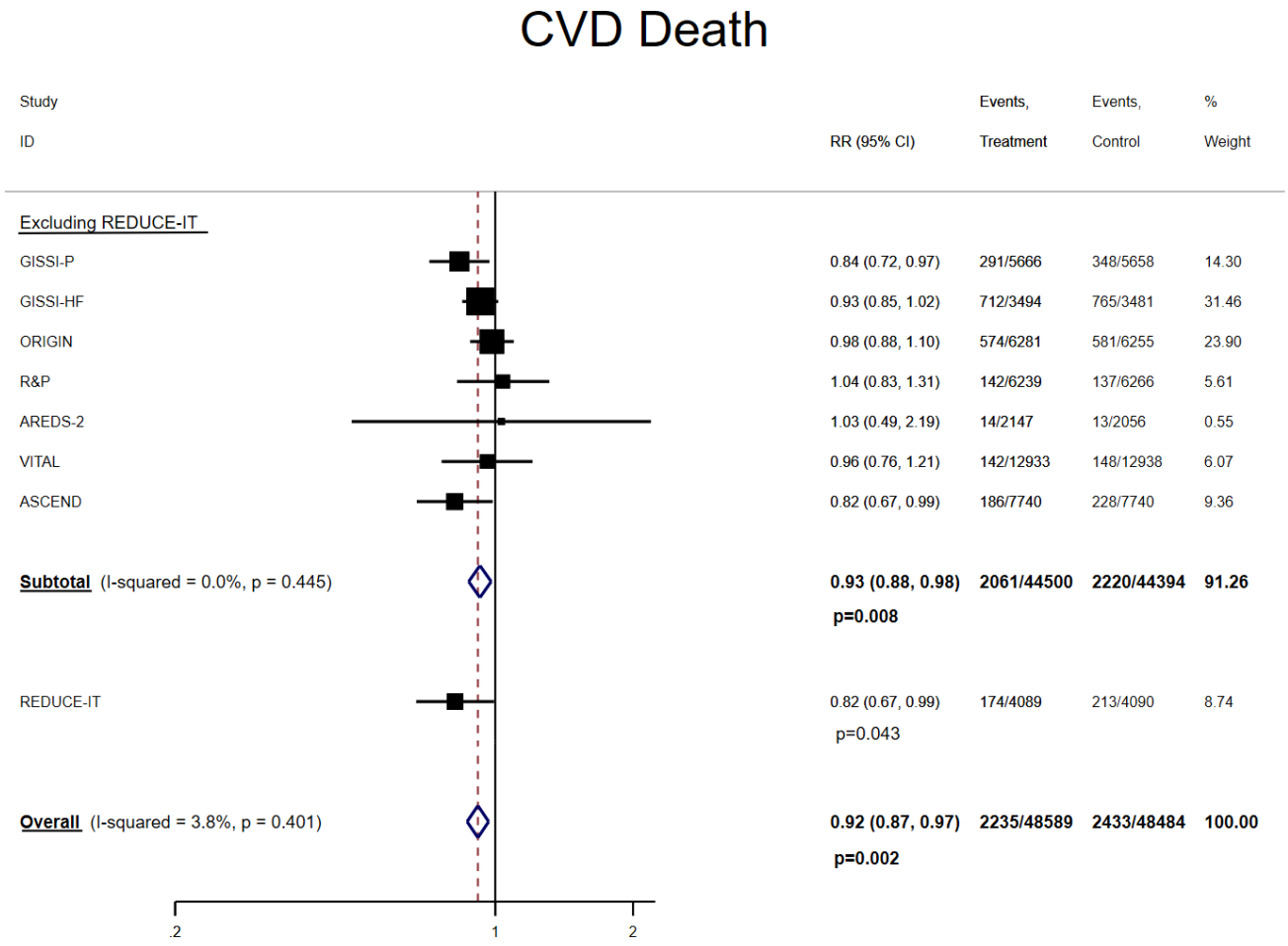
Panel B: Marine omega-3 supplementation and risk of CHD death.



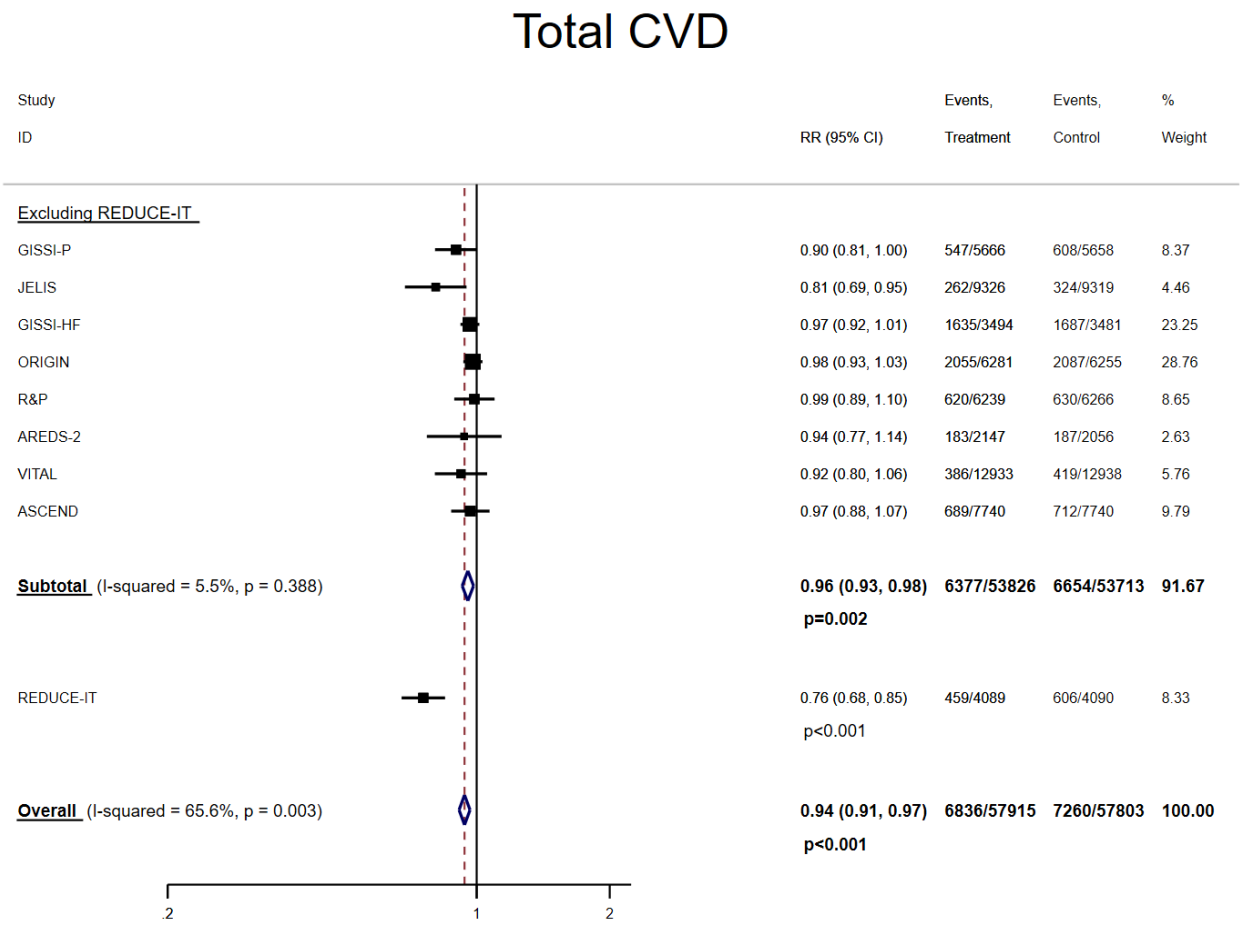
Panel C: Marine omega-3 supplementation and risk of total CHD, which includes MI, death from CHD, or coronary revascularization.



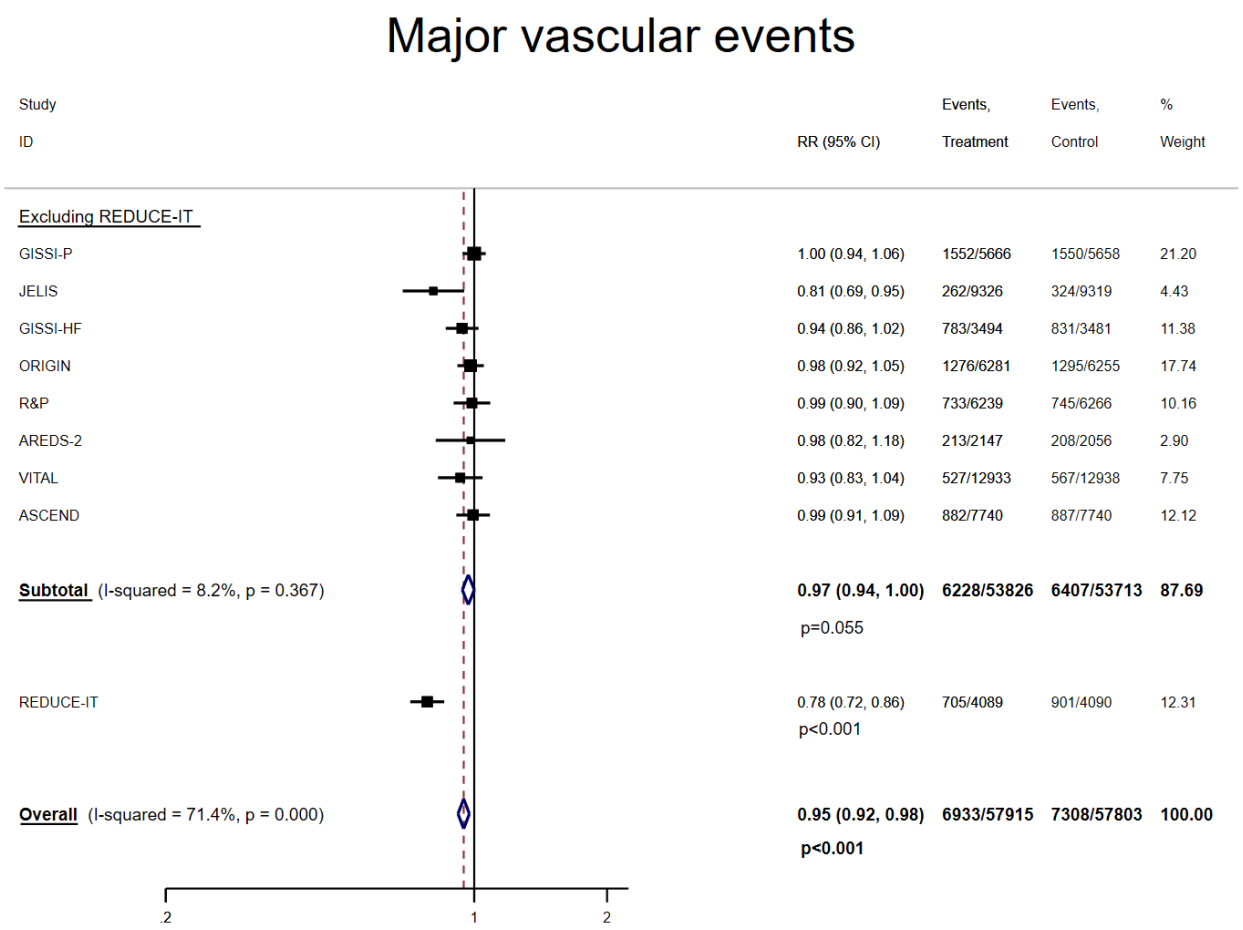
Panel D: Marine omega-3 supplementation and risk of total stroke, which includes fatal and/or nonfatal stroke.



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

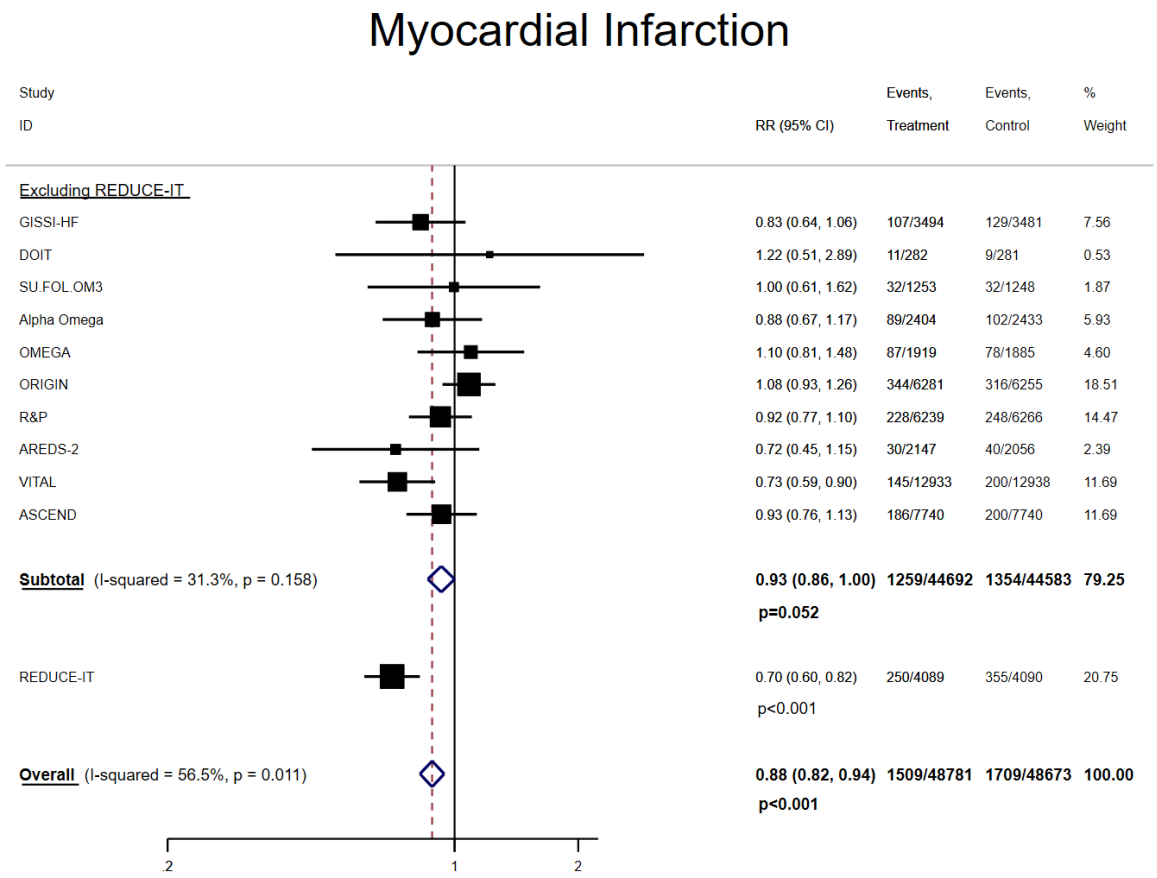


Panel F: Marine omega-3 supplementation and risk of total CVD, which includes nonfatal MI, nonfatal stroke, death from CVD, or hospitalization due to a cardiovascular cause (except for JELIS and ALPHA Omega which include revascularization).

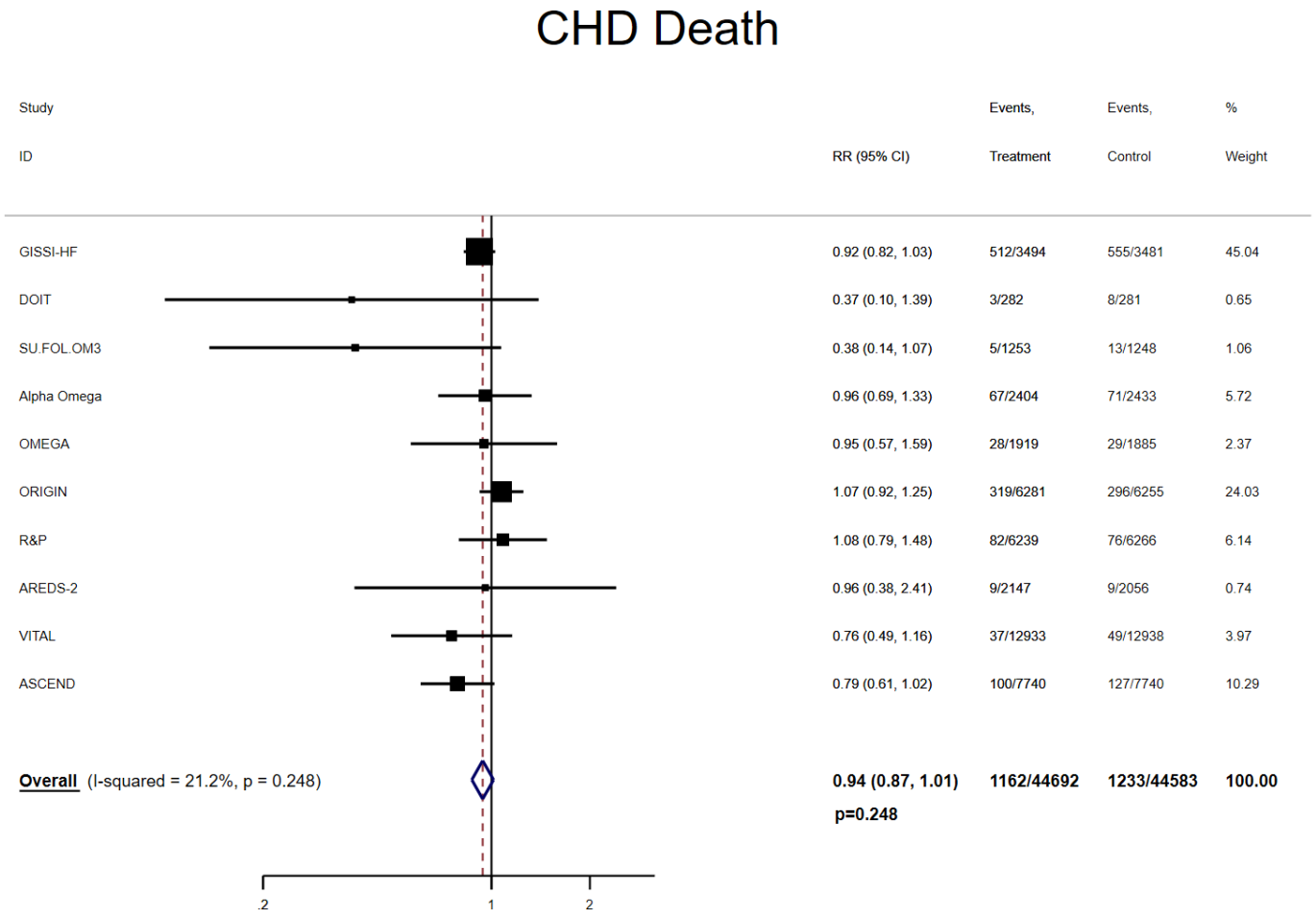


Panel G: Marine omega-3 supplementation and risk of major vascular events, which include nonfatal MI, nonfatal stroke, death from CVD, or revascularization.

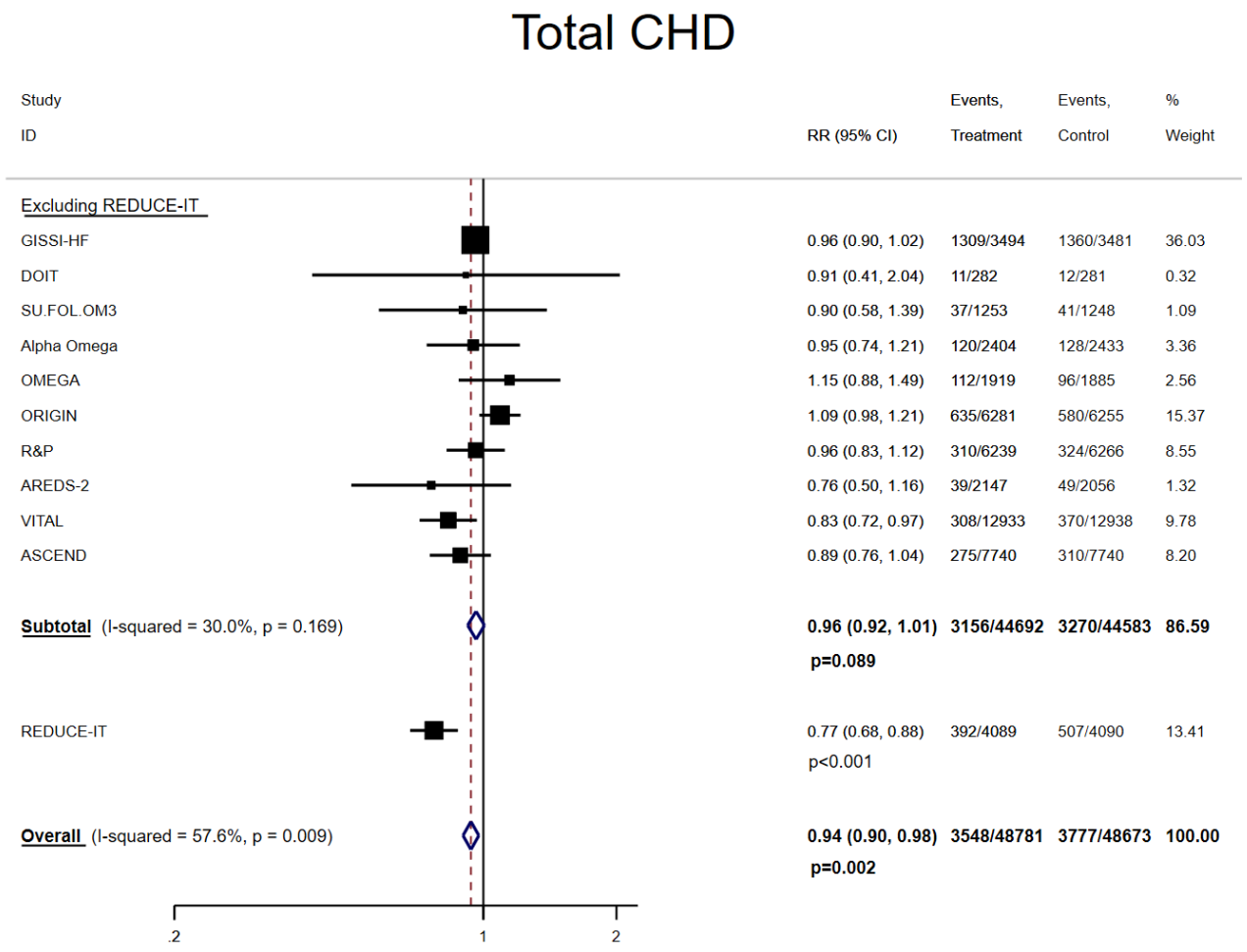
Figure S5. Pooled associations between marine omega-3 supplementation and risk of cardiovascular disease endpoints excluding two open-label trials, GISSI-P and JELIS.



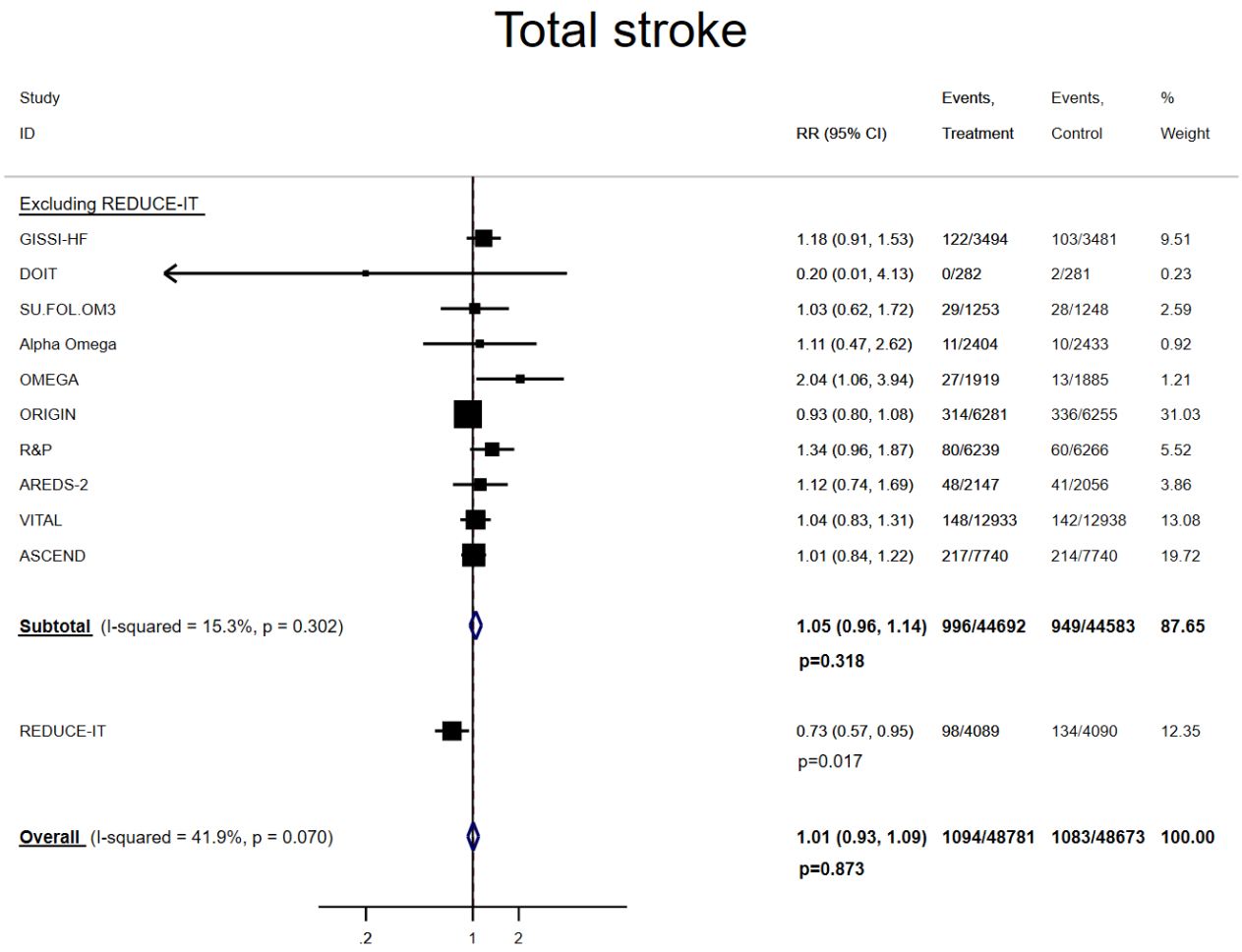
Panel A: Marine omega-3 supplementation and risk of myocardial infarction, which includes fatal and/or nonfatal MI.



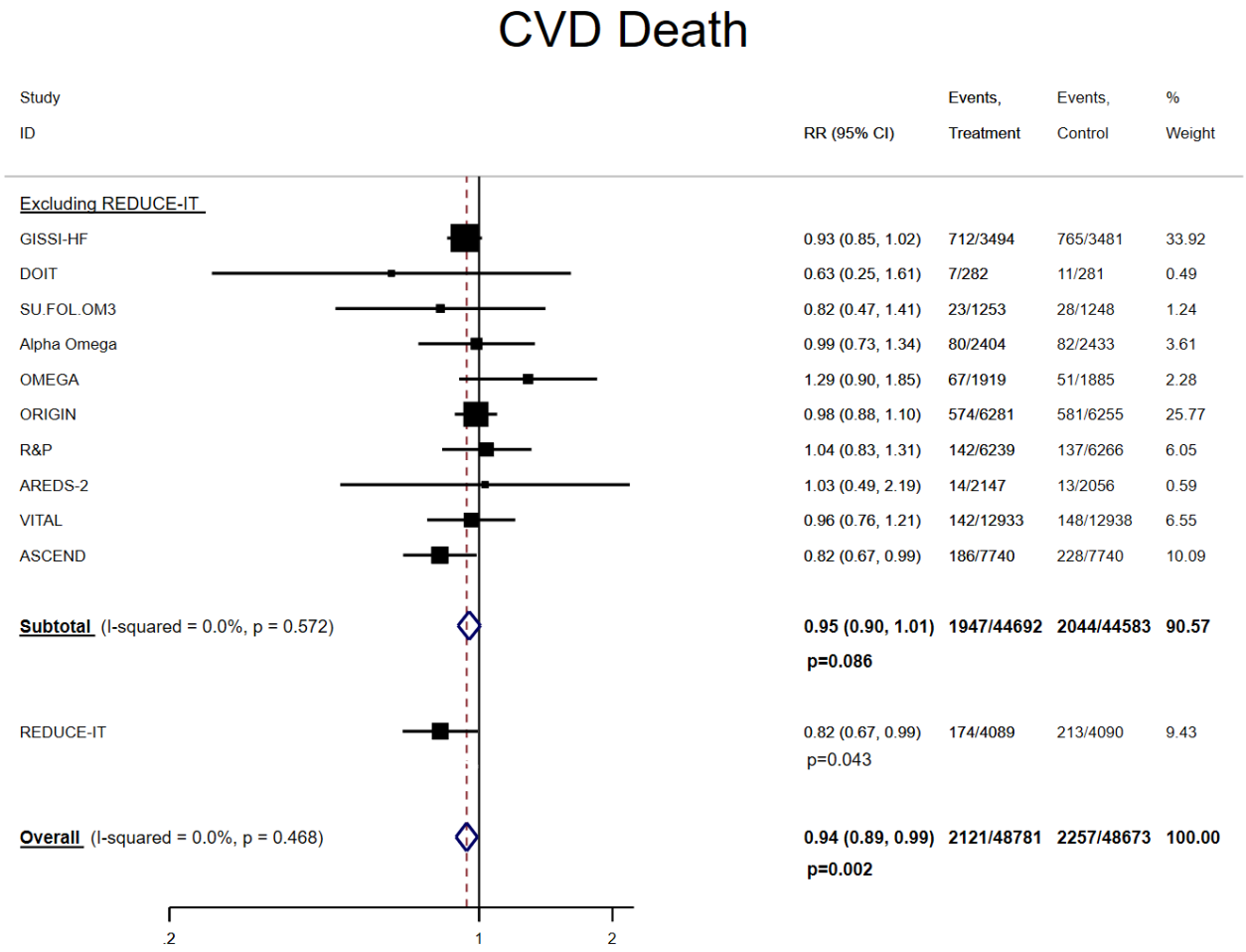
Panel B: Marine omega-3 supplementation and risk of CHD death.



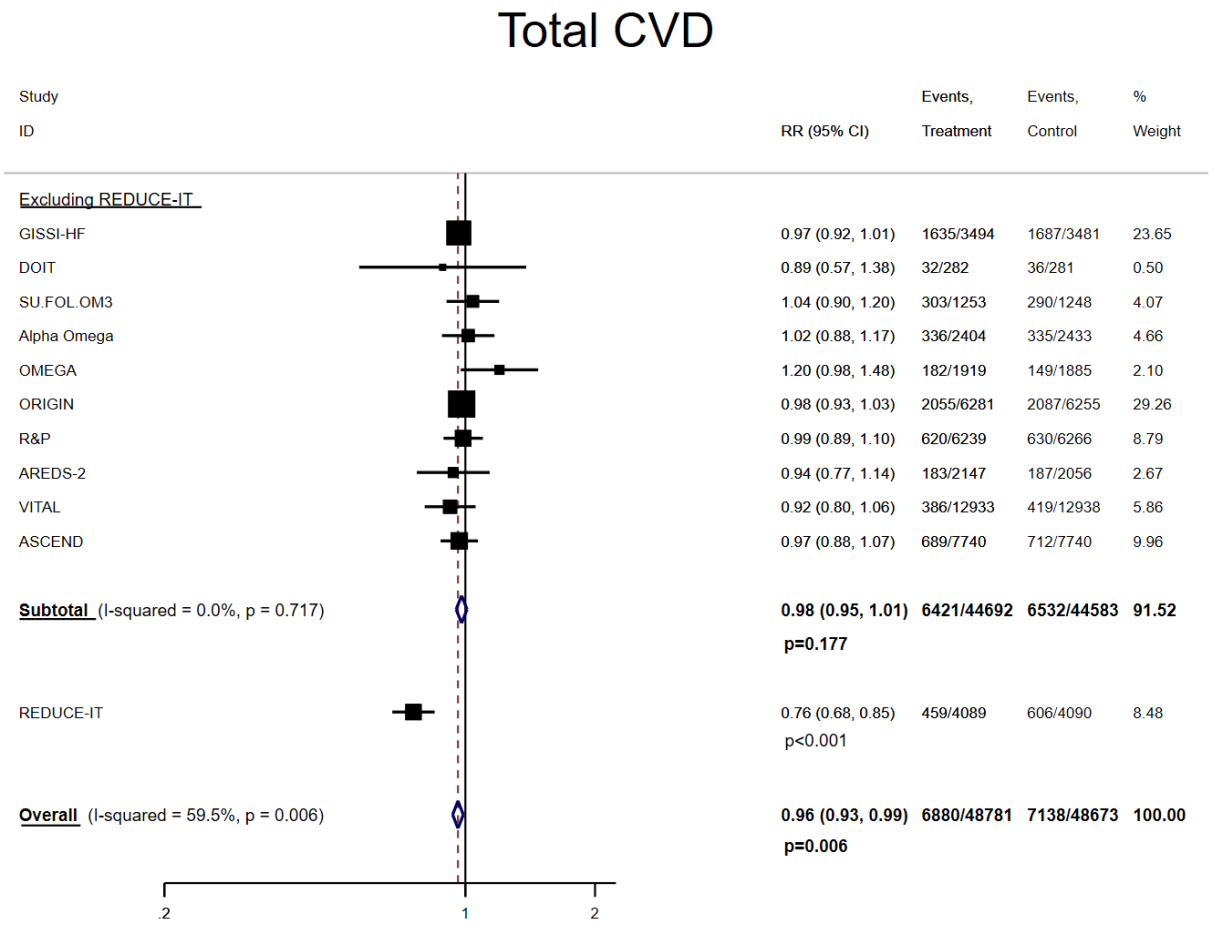
Panel C: Marine omega-3 supplementation and risk of total CHD, which includes MI, death from CHD, or coronary revascularization.



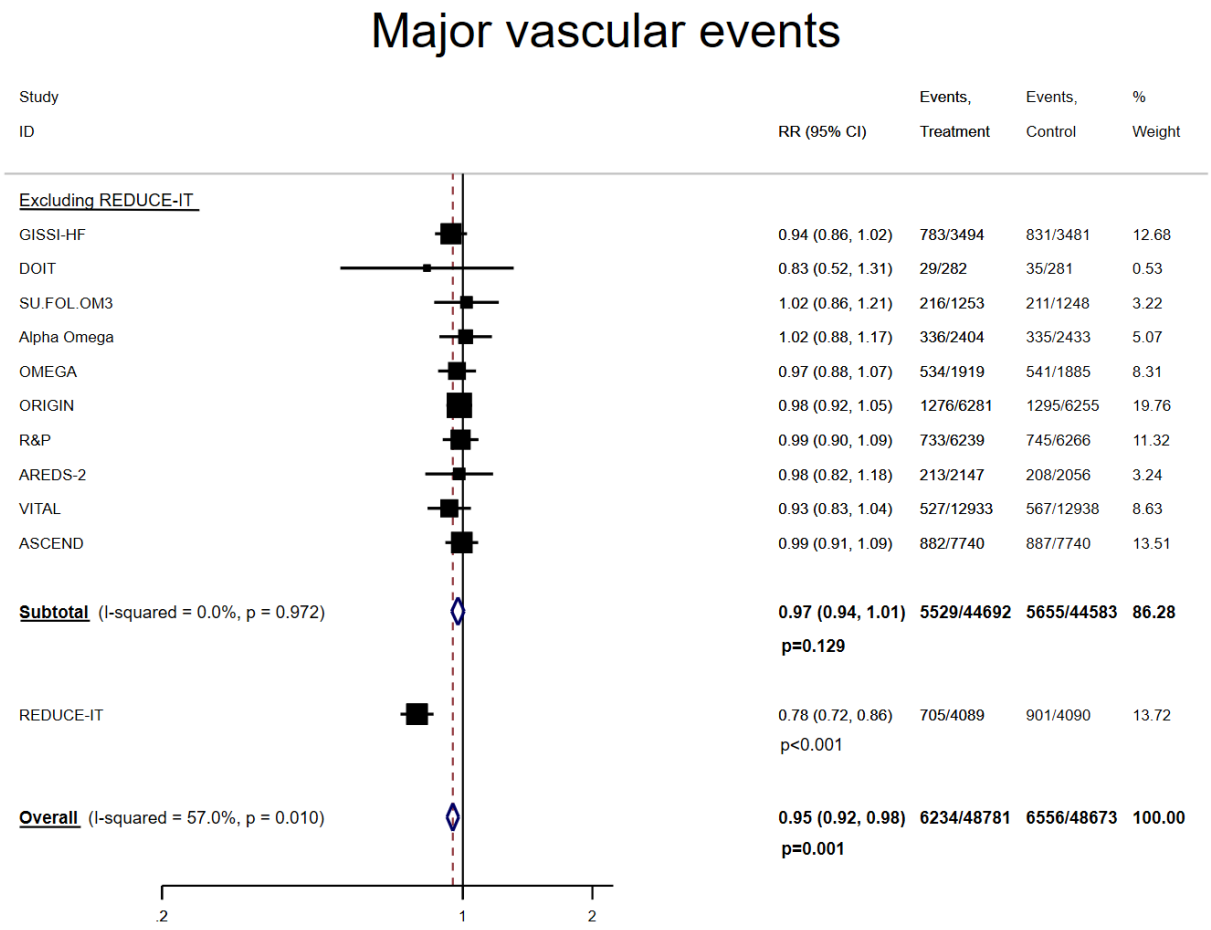
Panel D: Marine omega-3 supplementation and risk of total stroke, which includes fatal and/or nonfatal stroke.



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



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).



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.