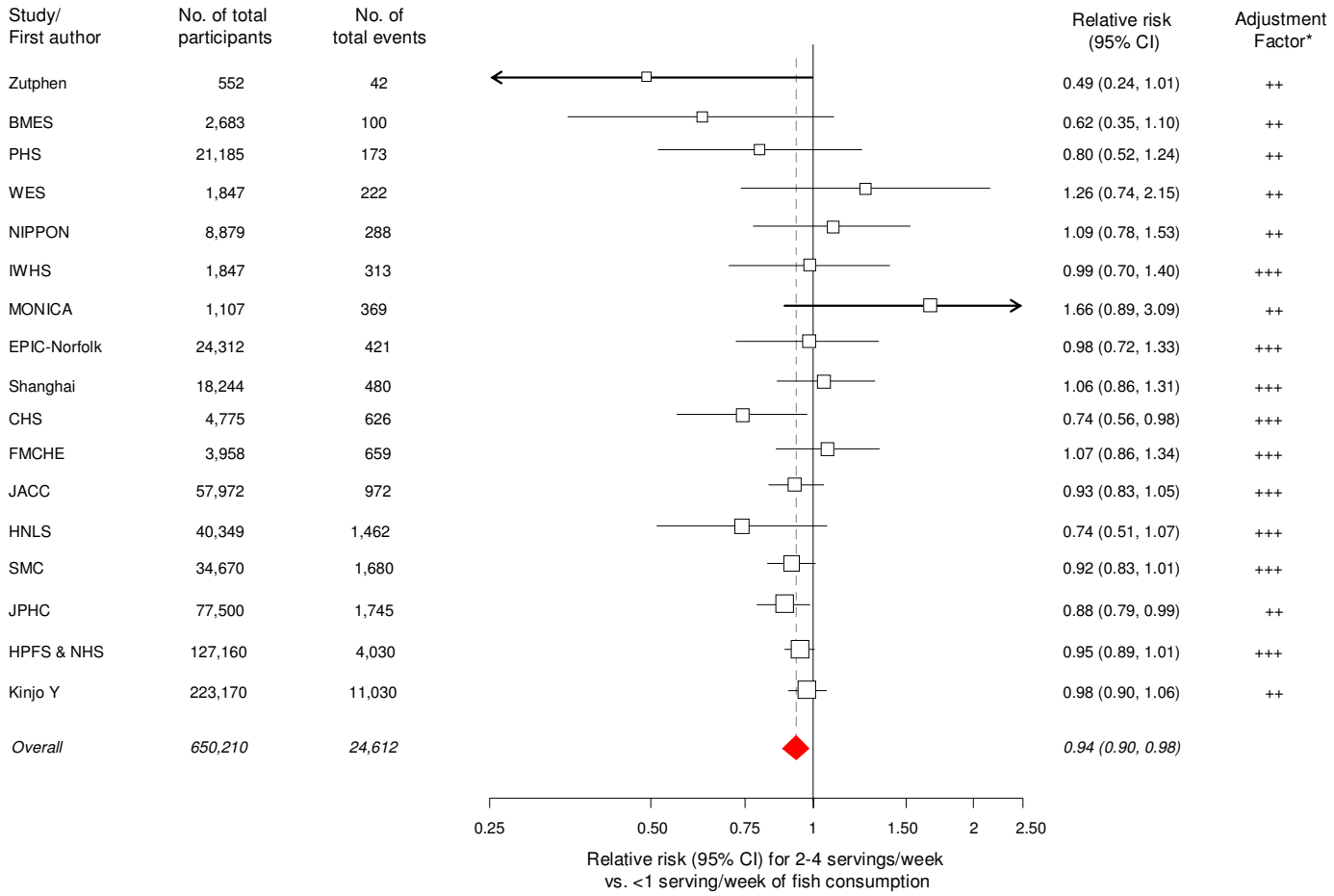
Supplementary Figures

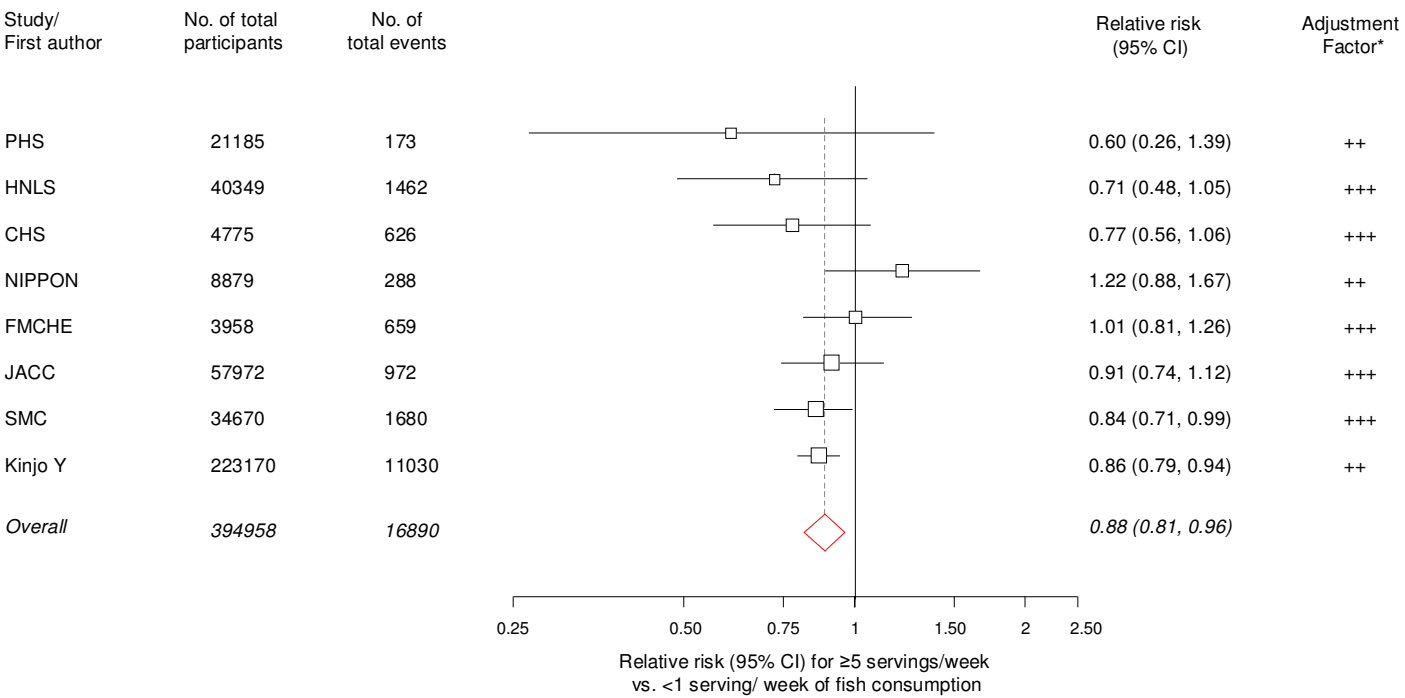
eFigure 1. Relative risk for 2-4 servings per week compared to <1 serving per week categories of total fish consumption derived from prospective cohort studies



From random-effects metaanalysis. I^2 statistic (95% CI) for heterogeneity = 22% (4%, 48%), P = 0.20

* '+', RRs adjusted for age and sex only, '++', further adjusted for conventional CVD risk factors, '+++', further adjusted for other additional variables

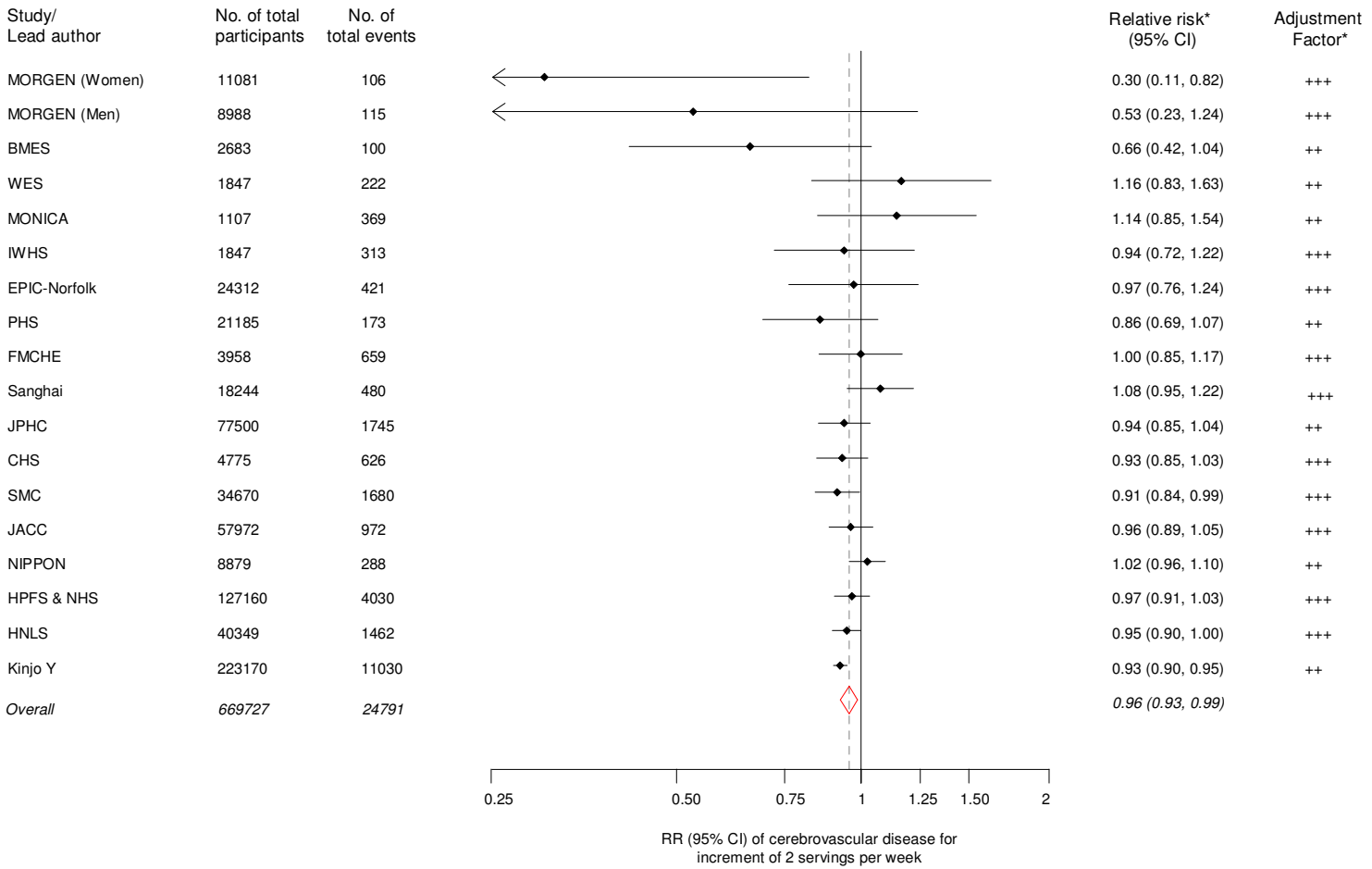
eFigure 2. Relative risk for ≥5 servings per week compared to <1 serving per week categories of total fish consumption derived from prospective cohort studies



From random-effects metaanalysis. I^2 statistic (95% CI) for heterogeneity = 20% (3%, 50%), P = 0.28

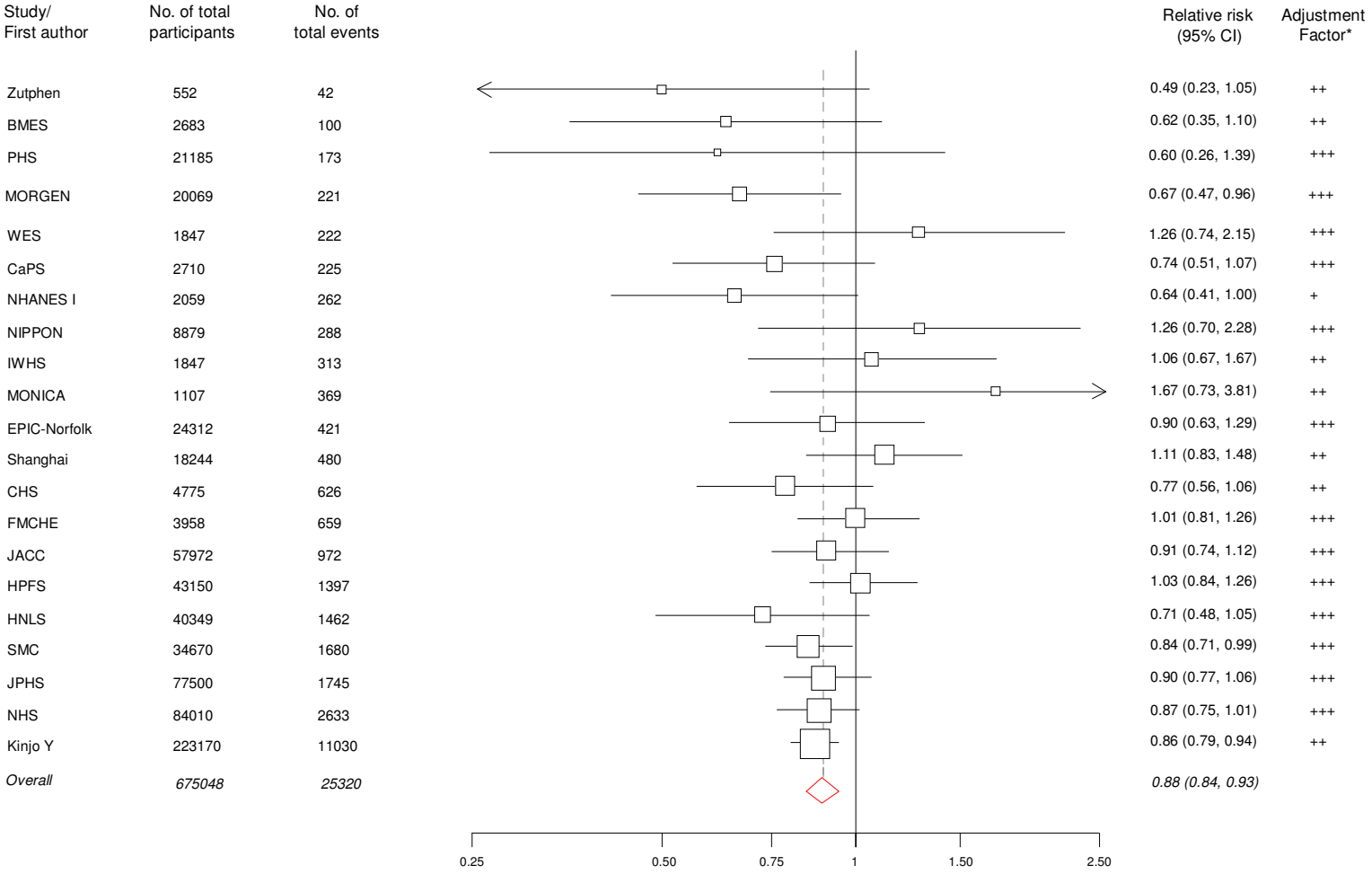
* '+', RRs adjusted for age and sex only, '++', further adjusted for conventional CVD risk factors, '+++', further adjusted for other additional variables

eFigure 3. Relative risk for cerebrovascular disease for increment of two servings of fish intake per week, derived from prospective cohort studies



*From random-effects meta-analysis; I-squared = 37%, p = 0.06

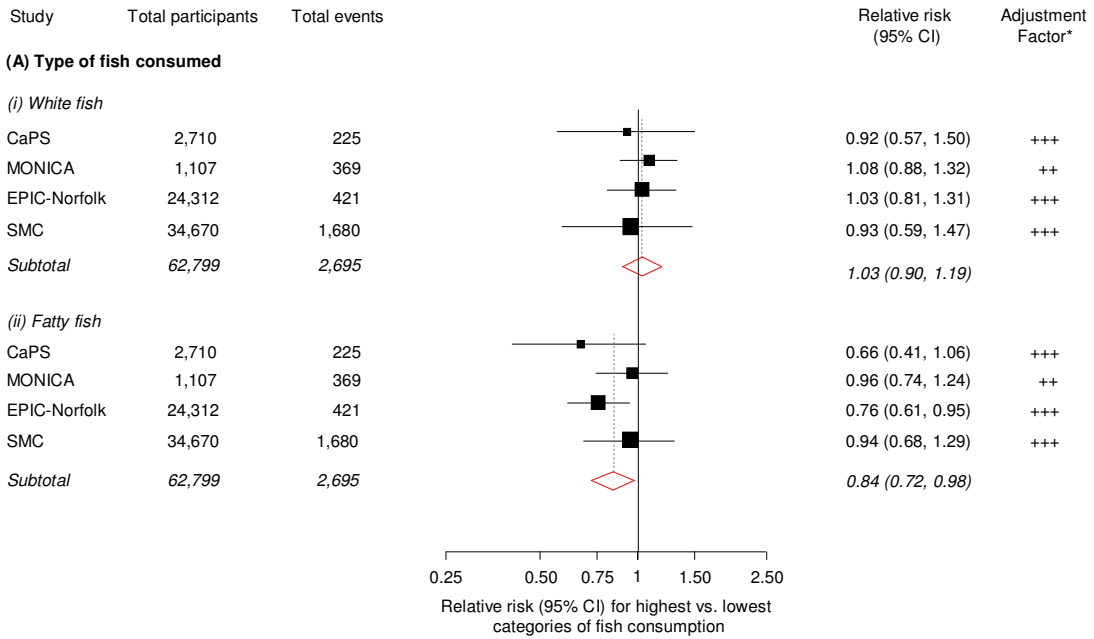
eFigure 4. Relative risk for cerebrovascular disease comparing highest vs. lowest categories of fish consumption derived from 21 available prospective cohort studies



From random-effects metaanalysis. I^2 statistic (95% CI) for heterogeneity = 18.5% (0%, 52%), P = 0.22

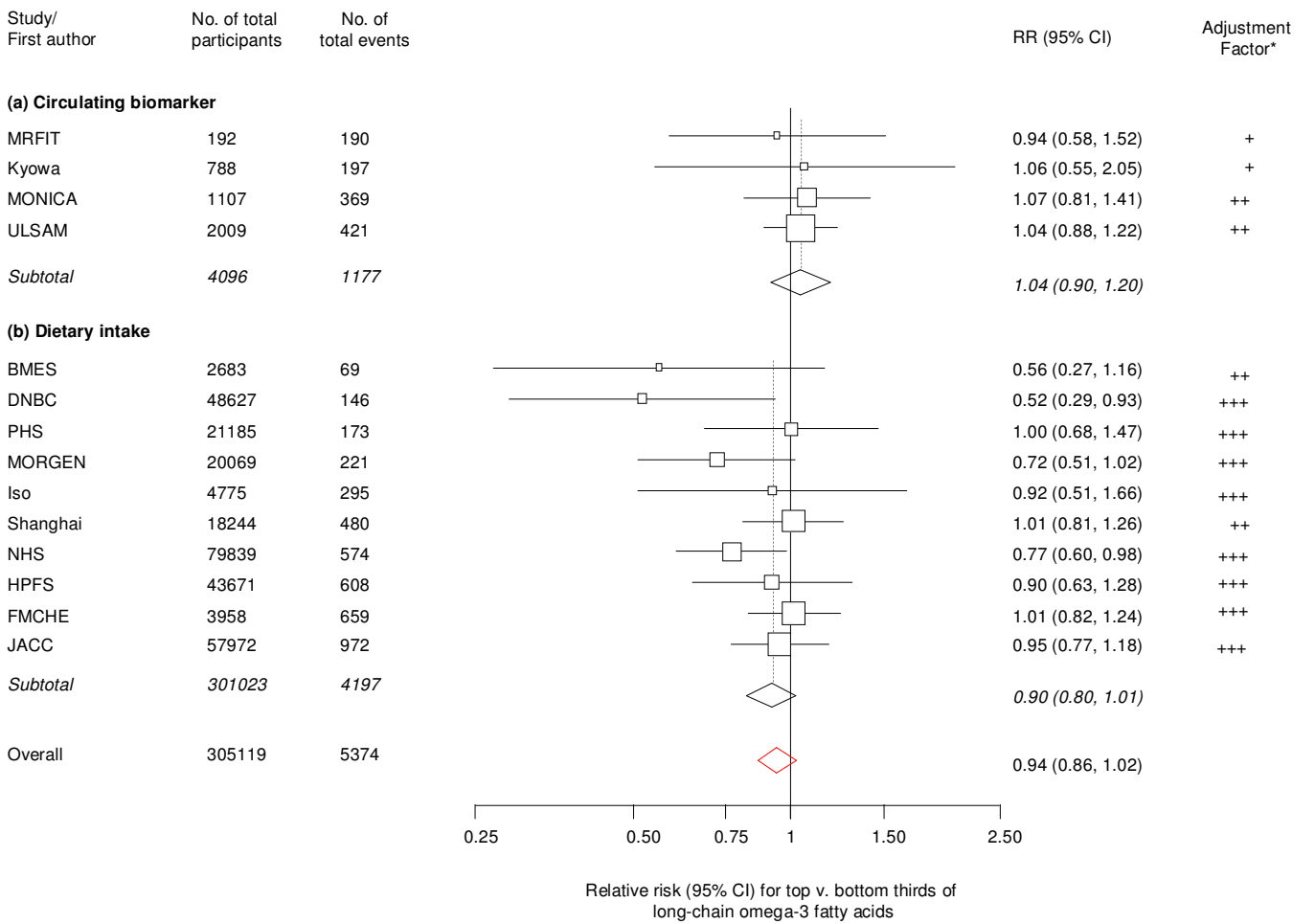
* '+', RRs adjusted for age and sex only, '++', further adjusted for conventional CVD risk factors, '+++', further adjusted for other additional variables

eFigure 5. Relative risk of cerebrovascular disease for types of fish consumed based on prospective cohort studies



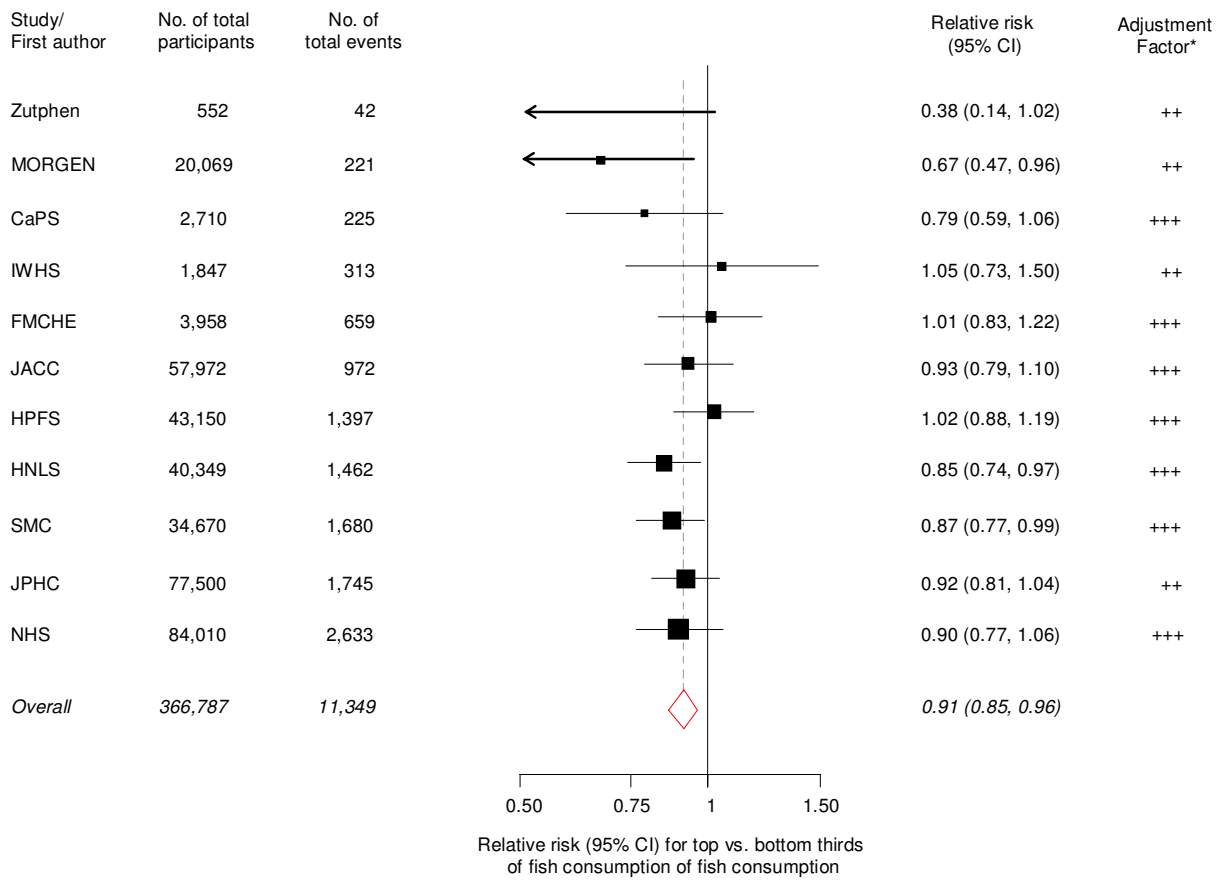
I^2 statistics for heterogeneity were 0.0% for white fish, and 10.1% for fatty fish (P >0.05 for both); * '+', RRs adjusted for age and sex only, '++', further adjusted for conventional CVD risk factors, '+++', further adjusted for other additional variables

eFigure 6. Relative risk for cerebrovascular disease comparing top vs. bottom thirds of long-chain omega-3 fatty acids derived from 14 available prospective cohort studies, based on circulating biomarker and dietary intake studies



From random-effects metaanalysis. I^2 statistic for heterogeneity: 18%, P = 0.27 for Dietary studies; 0%, P = 0.97 for Biomarkers studies; and 9%, P = 0.35 for all studies.
* '+', RRs adjusted for age and sex only, '++', further adjusted for conventional CVD risk factors, '+++', further adjusted for other additional variables

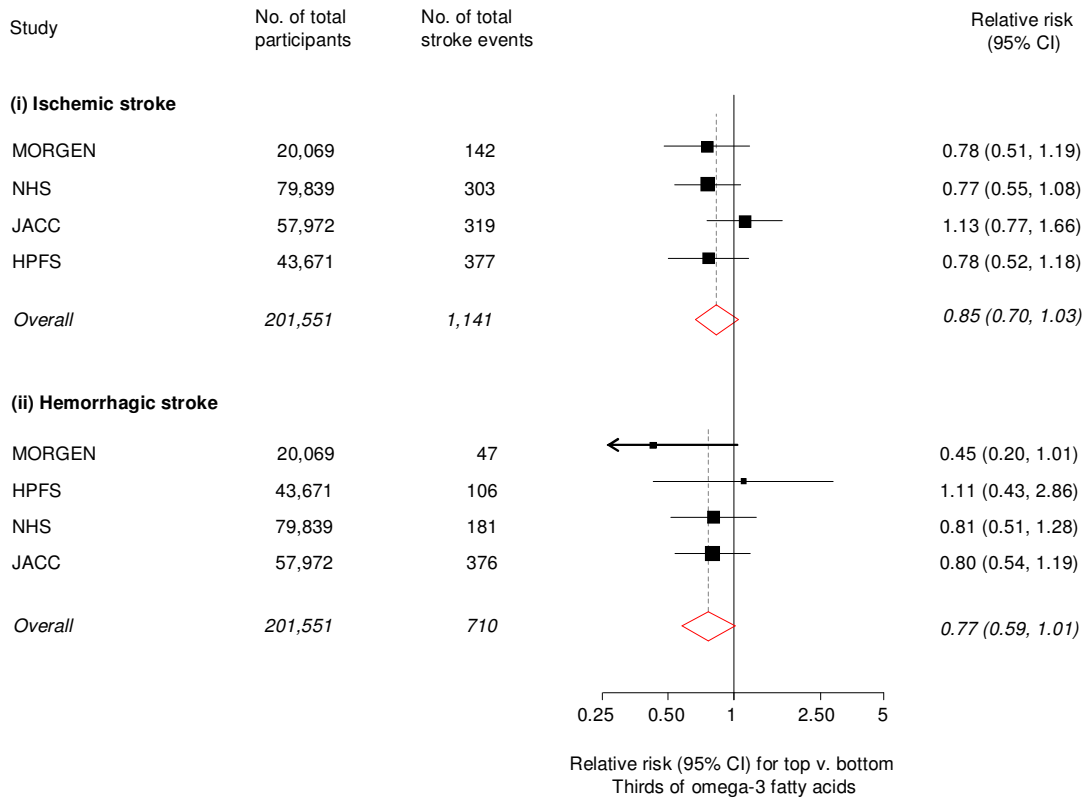
eFigure 7. Relative risk for cerebrovascular disease comparing top vs. bottom thirds of fish consumption derived from 11 prospective cohort studies with the available information



From random-effects metaanalysis. I^2 statistic for heterogeneity = 17.8; P = 0.28

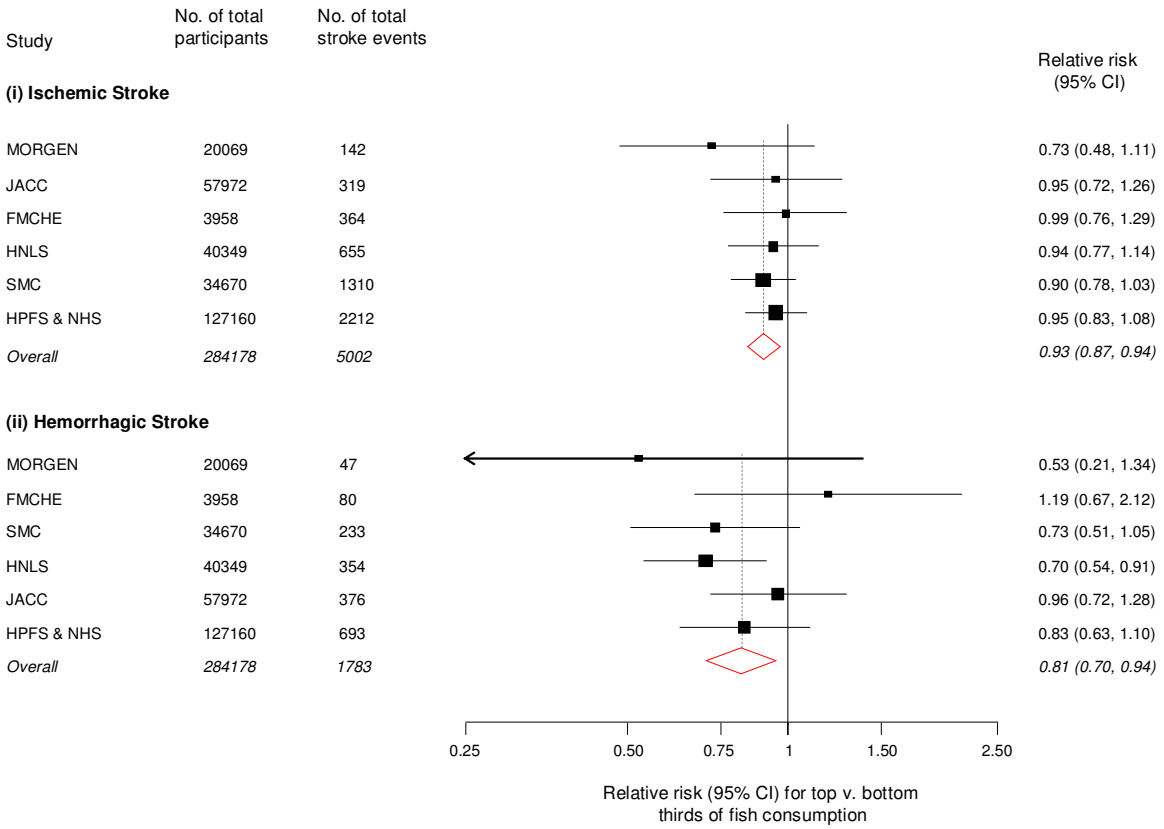
* '+', RRs adjusted for age and sex only, '++', further adjusted for conventional CVD risk factors, '+++', further adjusted for other additional variables

eFigure 8. Relative risks for (i) ischemic and (ii) hemorrhagic strokes comparing top vs. bottom thirds of total long-chain omega-3 fatty acids derived from available prospective cohort studies



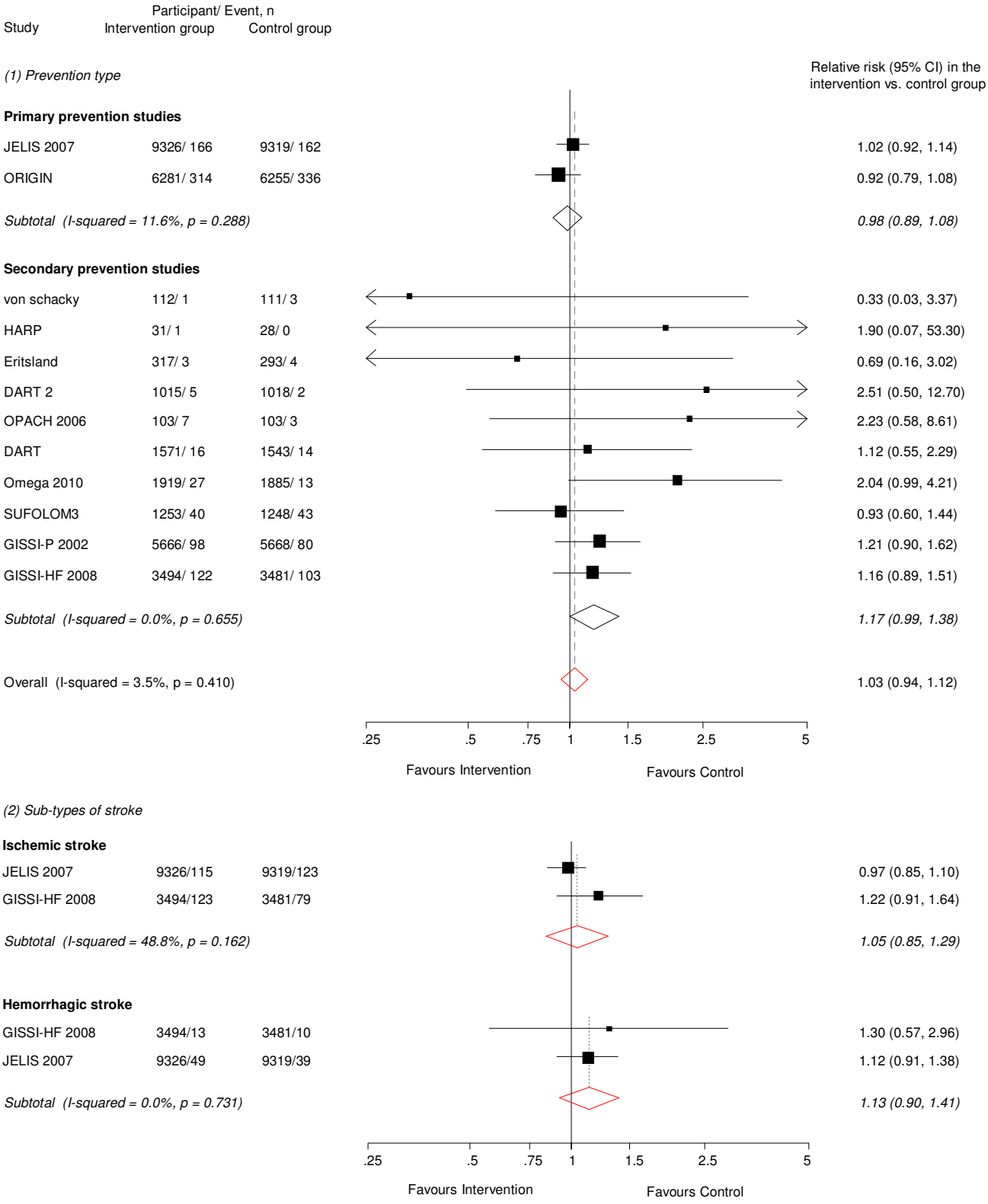
From random-effects metaanalysis. I^2 statistic (95% CI) for heterogeneity was 0% (0%, 82%), P = 0.42 for ischemic stroke and 0% (0%, 78%), P = 0.50 for hemorrhagic stroke

eFigure 9. Relative risks for (i) ischemic and (ii) hemorrhagic strokes comparing top vs. bottom thirds of fish consumption derived from available prospective cohort studies



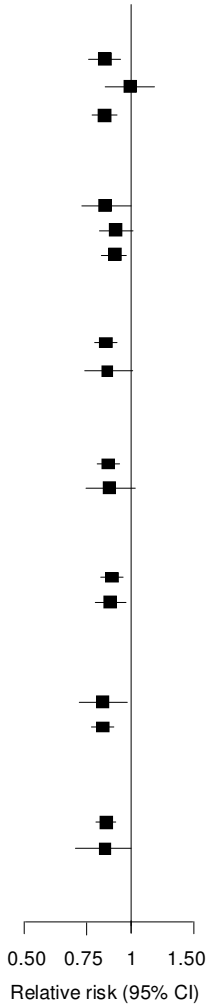
From random-effects metaanalysis. I^2 statistic (95% CI) for heterogeneity was 0% P = 0.87 for ischemic stroke and 6%, P = 0.38 for hemorrhagic stroke

eFigure 10. Effects of long-chain omega 3 fatty acid supplementations on cerebrovascular disease, derived from 12 available randomised control trials



eFigure 11. Association between fish consumption and risk of cerebrovascular disease in prospective cohort studies for different characteristics

Subgroup*	No. of studies	No. of participants	No. of events	Relative risk (95% CI)
Sex§				
Women	9	184445	6355	0.86 (0.79, 0.93)
Men	12	135307	4606	1.01 (0.89, 1.15)
Not reported separately	6	357356	15251	0.86 (0.80, 0.92)
Location				
Europe	7	87378	3617	0.86 (0.75, 1.00)
North America	7	158873	5626	0.89 (0.78, 1.02)
Asia-Pacific	7	428797	16077	0.88 (0.83, 0.94)
Average intake, g/ wk				
≥200	9	419270	17311	0.87 (0.82, 0.92)
<200	12	255778	8009	0.89 (0.78, 1.01)
Average follow up, yr				
≥10	18	552051	22981	0.89 (0.83, 0.98)
<10	3	122997	2339	0.89 (0.77, 1.03)
Risk comparison approach				
Highest v. lowest tertiles	11	366787	11349	0.91 (0.86, 0.97)
Highest v. lowest intake categories	10	308261	13971	0.90 (0.79, 0.99)
No. of events				
≥1000	6	502849	19947	0.88 (0.79, 1.00)
<1000	15	172199	5373	0.88 (0.83, 0.92)
Levels of adjustment‡				
+++	13	420611	12098	0.90 (0.84, 0.94)
++	8	254437	13222	0.86 (0.72, 1.01)



Metaregression P>0.05 for all subgroups. §Several studies reported risk estimates on both gender separately and therefore total number of studies exceeds 21. ‡ "++", adjusted for conventional CVD risk factors; and '+++' when further adjusted for other additional variables.

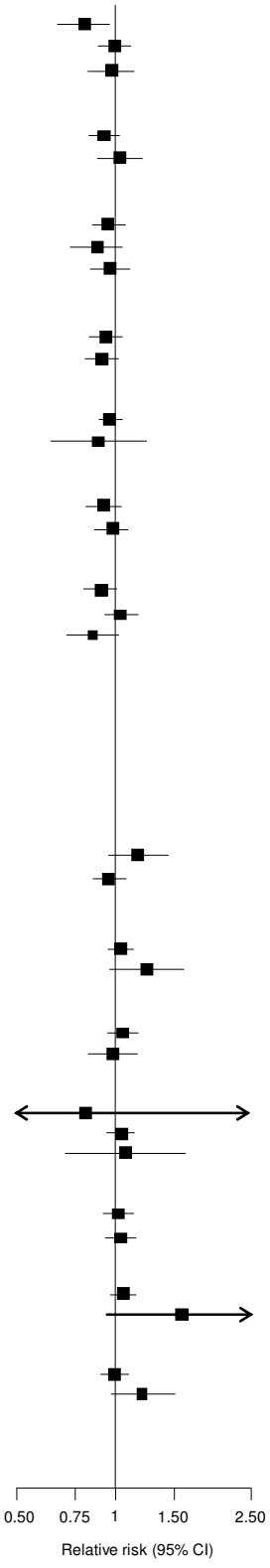
eFigure 12. Relative risks of cerebrovascular disease in (a) prospective cohort studies and (b) randomised clinical trials of total long-chain omega-3 fatty acids for different characteristics

(a) Prospective cohort studies

	No. of studies	Total participants	Total events	Relative risk (95% CI)*
Sex‡				
Women	5	175080	1968	0.78 (0.64, 0.97)
Men	8	117836	3406	1.00 (0.92, 1.09)
Not reported separately	4	12204	1220	0.97 (0.81, 1.16)
Study design				
Prospective cohort	11	303032	4618	0.91 (0.83, 1.01)
Nested case-control	3	2087	756	1.04 (0.83, 1.30)
Location				
Europe	5	75770	1816	0.93 (0.78, 1.11)
North America	4	144887	1545	0.88 (0.70, 1.05)
Asia-Pacific	5	84462	2013	0.96 (0.83, 1.10)
Average consumption, g/wk§				
≥2	5	159003	2680	0.93 (0.81, 1.07)
<2	5	142020	1517	0.85 (0.72, 1.01)
Follow up, yr				
≥10	10	234327	4668	0.95 (0.87, 1.04)
<10	4	70792	706	0.90 (0.63, 1.11)
Events, n				
≥500	4	185440	2813	0.92 (0.82, 1.04)
<500	10	119679	2561	0.95 (0.84, 1.07)
Level of adjustment¶				
+++	8	280096	3648	0.88 (0.78, 1.00)
++	4	24043	1339	1.04 (0.92, 1.17)
+	2	980	387	0.87 (0.77, 1.01)

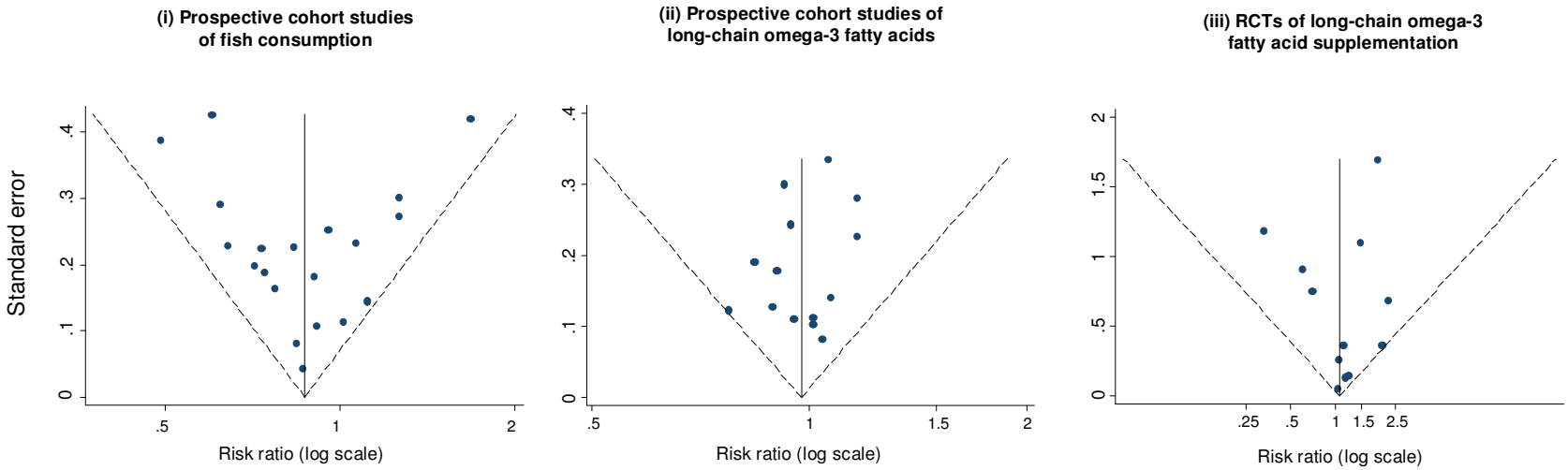
(b) Randomised clinical trials

	No. of studies	*Intervention group* No. of subjects/ events	*Control group* No. of subjects/ events	
Location				
Europe	9	15450/ 319	15350/ 265	1.15 (0.97, 1.35)
Other$^{\phi}$	3	15638/ 481	15602/ 498	0.98 (0.90, 1.08)
Participants, n				
≥5000	4	24764/ 700	24723/ 681	1.02 (0.94, 1.10)
<5000	8	6321/ 100	6229/ 82	1.23 (0.88, 1.72)
Blinding of subjects				
No	5	19497/ 312	19433/ 271	1.06 (0.95, 1.17)
Yes	7	11591/ 488	11519/ 492	0.98 (0.86, 1.10)
Daily dose, g				
>2	2	348/ 4	321/ 4	0.82 (0.21, 3.17)
1-2	7	26901/ 735	26822/ 700	1.02 (0.94, 1.11)
<1	3	3839/ 61	3809/ 59	1.07 (0.70, 1.63)
Type of supplement				
EPA only	3	11912/ 187	11880/ 178	1.02 (0.92, 1.14)
EPA+DHA	9	19176/ 613	19072/ 585	1.03 (0.92, 1.15)
Follow up, yr				
>2	7	27622/ 757	27542/ 738	1.02 (0.94, 1.10)
≤2 years	5	3466/ 43	3410/ 25	1.66 (0.97, 2.84)
Events, n				
≥200	3	19101/ 602	19055/ 601	1.00 (0.92, 1.10)
<200	9	11987/ 198	11897/ 162	1.22 (0.98, 1.52)
Overall	*12*	*31088/ 800*	*30952/ 763*	*1.03 (0.95, 1.12)*



P>0.05 from meta-regression analyses on each of the covariates. * For prospective cohorts: denotes association with top vs. bottom thirds of baseline long-chain omega-3 fatty acids; randomised trials: denotes effect of omega-3 supplementation compared to the control group. ‡ Several studies reported risk estimates on both gender separately and therefore total number of studies exceeds 14. § limited to prospective dietary omega-3 studies. ¶ Defined as '+' when RRs were adjusted for age and sex, '++' following further adjustment for conventional CVD risk factors, and '+++' when further adjusted for other additional variables; ϕ includes 1 multi-centre RCT and 1 trial each from the US and Japan, repectively.

eFigure 13. Funnel plots showing associations with cerebrovascular disease in (i) cohort studies of fish consumption, (ii) cohort studies of long-chain omega-3 fatty acid and (iii) randomised controlled trials (RCTs) of long-chain omega-3 fatty acid supplementation



The dotted lines show 95% confidence intervals around the overall summary estimate; Egger's asymmetry test of associations for cohort studies of fish consumption, P=0.91; omega-3 fatty acids, P=0.62; and randomised controlled trials, P=0.35