SUPPLEMENTAL MATERIAL

Supplemental Methods. Literature search strategy in Pubmed.

#1 Search "Fatty Acids, Omega-6"[Mesh] OR "n-6 fatty acid*"[tiab] OR "omega-6 fatty acid*"[tiab] OR "essential fatty acid*"[tiab] OR "polyunsaturated fatty acid*"[tiab] OR “fatty acid” [tiab] OR "linoleic acid"[tiab] OR "corn oil"[tiab] OR “sunflower oil” [tiab]

#2 Search "Cerebrovascular Disorders"[Mesh] OR "stroke*"[tiab] OR "cerebrovascular accident*"[tiab]

#3 Search "Cardiovascular diseases"[Mesh] OR "cardiovascular"[tiab] OR "heart"[tiab] OR "myocardial infarction*"[tiab] OR "sudden death*"[tiab] OR “coronary heart disease” OR “CHD”

#4 Search “Mortality”[Mesh] OR “Death”[Mesh] OR “mortality”[tiab] OR “death”[tiab] OR

“fatal”[tiab]

#5 Search "Epidemiology "[MESH] OR "Epidemiologic Studies"[MESH] OR “Intervention Studies” [MESH] OR "cohort*"[tiab] OR "incident*"[tiab] OR "incidence*"[tiab] OR "prospective"[tiab] OR "follow-up" [tiab] OR "predict*”[tiab] OR "prognos*"[tiab] OR "case-control"[tiab] OR "cross-sectional"[tiab] OR "intervention*”[tiab] OR "clinical trial*"[tiab] OR "randomized*"[tiab]

#6 Search #2 OR #3 OR #4

#7 Search #1 AND #5

#8 Search #6 AND #7

Table S1. Extracted and calculated data for the included studies for dietary linoleic acid and coronary heart disease events.

Study name	Category	RR	LL	UL	Median of E% from LA intake	Number of cases	person/year
MONICA –in women, total CHD events (24)							
	1	1	1	1	2.57 [1]	54	513 [2]
	2	0.67	0.43	1.03	4.13	51	606
	3	0.65	0.33	1.21	6.58	54	524
MONICA –in men, total CHD events (24)							
	1	1	1	1	2.56 [1]	105	553 [2]
	2	1.00	0.74	1.34	3.98	102	565
	3	1.03	0.73	1.46	6.10	105	516
MORGEN-in men and women, total CHD events (25)							
	1	1	1	1	3.7	61	4013 [2]
	2	0.90	0.61	1.33	4.7	50	4014
	3	0.83	0.56	1.24	5.4	46	4014
	4	1.00	0.68	1.47	6.2	61	4014
	5	0.90	0.60	1.36	7.7	62	4014
NHS, in women, total CHD events (26) [3]							
	1	1	1	1	2.94	1099	465,643
	2	0.86	0.77	0.94	3.95	729	467,525
	3	0.87	0.78	0.97	4.60	680	467,975
	4	0.80	0.71	0.90	5.26	621	467,906
	5	0.75	0.65	0.85	6.38	647	467,547
HPFS, in men, total CHD events (27) [3]							
	1	1	1	1	3.58	842	182,079
	2	1.00	0.90	1.11	4.37	776	182,779
	3	1.02	0.91	1.15	4.95	758	182,970
	4	1.02	0.90	1.15	5.60	731	182,931
	5	0.98	0.86	1.13	6.73	735	182,930
ATBC study, in men, total CHD events (28) [3]							
	1	1	1	1	1.50	307	23,825
	2	0.86	0.70	1.05	1.88	251	24,409
	3	0.92	0.72	1.19	2.34	261	24,269
	4	0.83	0.62	1.11	3.26	235	24,702
	5	0.86	0.58	1.27	6.01	285	24,608
ARIC Study, in women, total CHD events (4) [4]							
	1	1	1	1	2.96	47	19,078
	2	0.59	0.33	1.06	4.08	35	19,925
	3	0.64	0.33	1.25	5.54	41	19,196
ARIC Study, in men, total CHD events (4) [4]							
	1	1	1	1	2.92	62	9183
	2	0.72	0.46	1.12	3.73	46	9193
	3	1.01	0.65	1.56	4.37	63	9074
	4	0.64	0.39	1.04	5.06	46	9246
	5	0.76	0.45	1.27	6.23	52	9165
FMC study, in women, total CHD events (4) [4]							
	1	1	1	1	1.14	60	7762
	2	0.61	0.34	1.09	1.47	52	8096
	3	0.57	0.23	1.40	2.22	50	7785
FMC study, in men, total CHD events (4) [4]							
	1	1	1	1	1.11	81	4777

	2	0.66	0.44	1.00	1.32	58	4982
	3	0.57	0.35	0.92	1.49	55	4984
	4	0.62	0.35	1.08	1.76	72	4911
	5	0.40	0.18	0.87	2.64	56	4945
WHS study, in women, total CHD events (4) [4]							
	1	1	1	1	3.34	29	37,506
	2	0.93	0.53	1.63	4.15	27	38,010
	3	0.94	0.51	1.72	4.76	26	38,151
	4	1.14	0.59	2.20	5.45	29	38,444
	5	1.46	0.70	3.04	6.61	41	38,644
VIP study, in women, total CHD events (4) [4]							
	1	1	1	1	2.72	6	14,496
	2	1.27	0.35	4.67	3.26	14	14,975
	3	0.54	0.06	4.85	4.10	3	14,401
VIP study, in men, total CHD events (4) [4]							
	1	1	1	1	2.74	54	12,920
	2	1.08	0.63	1.85	3.37	42	13,411
	3	1.57	0.71	3.45	4.26	38	12,899

[1] Calculated E% of LA by means of calorie intake.
[2] Number of person, not person-years
[3] Updated published data
[4] Data from unpublished cohort studies
ARIC, Atherosclerosis Risk in Communities Study; ATBC, Alpha-Tocopherol and Beta-Carotene Cancer Prevention; CHD, coronary heart disease; FMC, Finnish Mobile Clinic Health Study; HPFS, Health Professional s' Follow-up Study; IWHS, Iowa Women's Health Study; LA, linoleic acid; MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases; MORGEN, Monitoring Project on Risk Factors for Chronic Diseases; NHS, Nurses' Health Study; VIP, Västerbotten Intervention Program; WHS, Women's Health Study.

Table S2. Extracted and calculated data for the included studies for dietary linoleic acid and coronary heart disease deaths.

Study name	Category	RR	LL	UL	Median of E% from LA intake	Number of cases	person/year
NHS, in women, CHD deaths (26) [1]							
	1	1	1	1	2.94	388	471,210
	2	0.84	0.70	1.01	3.95	214	473,125
	3	0.78	0.63	0.95	4.59	172	473,581
	4	0.78	0.62	0.97	5.25	165	473,507
	5	0.69	0.54	0.88	6.38	172	473,110
HPFS, in men, CHD deaths (27) [1]							
	1	1	1	1	3.58	476	187,389
	2	0.99	0.86	1.15	4.37	408	188,150
	3	0.95	0.81	1.11	4.95	369	188,444
	4	0.97	0.82	1.15	5.60	359	188,364
	5	0.90	0.74	1.09	6.73	359	188,368
ATBC study, in men, CHD deaths (28) [1]							
	1	1	1	1	1.50	122	24,343
	2	0.91	0.66	1.24	1.88	97	24,884
	3	1.19	0.81	1.75	2.34	106	24,752
	4	1.00	0.64	1.58	3.26	83	25,122
	5	1.29	0.70	2.36	6.01	126	25,093
ARIC Study, in men, CHD deaths (4) [2]							
	1	1	1	1	2.92	9	9202
	2	0.91	0.21	3.87	3.73	6	9205
	3	1.55	0.47	5.10	4.37	16	9077
	4	0.89	0.22	3.52	5.06	15	9252
	5	0.54	0.10	3.00	6.23	5	9176
FMC study, in women, CHD deaths (4) [2]							
	1	1	1	1	1.14	17	7923
	2	0.46	0.12	1.80	1.47	13	8226
	3	0.69	0.09	5.11	2.22	18	7933
FMC study, in men, CHD deaths (4) [2]							
	1	1	1	1	1.11	36	4976
	2	0.55	0.28	1.10	1.32	18	5157
	3	0.94	0.46	1.93	1.49	30	5088
	4	1.07	0.45	2.54	1.76	36	5085
	5	0.73	0.23	2.32	2.64	27	5088
WHS study, in women, CHD deaths (4) [2]							
	1	1	1	1	3.65	3	62,234
	2	0.68	0.07	6.26	4.76	2	65,082
	3	4.28	0.34	54.42	6.11	5	63,738
VIP study, in men, CHD deaths (4) [2]							
	1	1	1	1	2.75	16	12,996
	2	1.20	0.39	3.68	3.37	11	13,472
	3	1.50	0.28	7.93	4.26	11	12,942
IWHS study, in women, CHD deaths (4) [2]							
	1	1	1	1	3.65	69	58,800
	2	0.64	0.43	0.95	4.58	42	59,003
	3	0.82	0.55	1.23	5.28	54	58,865
	4	0.87	0.56	1.34	6.04	61	59,033
	5	0.95	0.57	1.56	7.31	68	58,919

IIHD study, in men, CHD deaths (4) [2]							
	1	1	1	1	3.59	34	15,890
	2	1.05	0.64	1.73	5.21	31	16,141
	3	1.07	0.65	1.76	6.42	32	16,071
	4	1.31	0.80	2.14	7.72	38	16,117
	5	0.97	0.56	1.67	9.52	30	16,255
MRFIT study, in men, CHD deaths (29)							
	1	1	1	1	3.30	NA	1251[3]
	2	0.69	NA	NA	4.54	NA	1252
	3	0.86	NA	NA	5.43	NA	1252
	4	0.80	NA	NA	6.48	NA	1252
	5	0.58	NA	SE for Q5 vs Q1 =0.2362	8.84	NA	1251

[1] Updated published data

[2] Data from unpublished cohort studies

[3] Number of person, not person-years

ARIC, Atherosclerosis Risk in Communities Study; ATBC, Alpha-Tocopherol and Beta-Carotene Cancer Prevention; CHD, coronary heart disease; FMC, Finnish Mobile Clinic Health Study; HPFS, Health Professional s' Follow-up Study; IIHD, Israeli Ischemic Heart Disease Study; IWHS, Iowa Women's Health Study; LA, linoleic acid; MRFIT, Multiple Risk Factor Intervention Trial; NHS, Nurses' Health Study; VIP, Västerbotten Intervention Program; WHS, Women's Health Study.

Table S3. Extracted and calculated data for the included studies for substituting dietary linoleic acid for saturated fat and coronary heart disease events.

Study name	Category	RR	LL	UL	Median of E% from LA intake	Number of cases	person/year
NHS, in women, total CHD events (26) [3]							
	1	1	1	1	2.94	1099	465,643
	2	0.86	0.78	0.95	3.95	729	467,525
	3	0.88	0.79	0.98	4.60	680	467,975
	4	0.81	0.72	0.91	5.26	621	467,906
	5	0.76	0.67	0.86	6.38	647	467,547
HPFS, in men, total CHD events (27) [3]							
	1	1	1	1	3.58	842	182,079
	2	0.99	0.89	1.10	4.37	776	182,779
	3	1.01	0.90	1.13	4.95	758	182,970
	4	1.00	0.88	1.12	5.60	731	182,931
	5	0.96	0.84	1.10	6.73	735	182,930
ATBC study, in men, total CHD events (28) [3]							
	1	1	1	1	1.50	307	23,825
	2	0.85	0.69	1.04	1.88	251	24,409
	3	0.91	0.71	1.16	2.34	261	24,269
	4	0.81	0.62	1.06	3.26	235	24,702
	5	0.83	0.58	1.19	6.01	285	24,608
ARIC Study, in women, total CHD events (4) [4]							
	1	1	1	1	2.96	47	19,078
	2	0.62	0.35	1.10	4.08	35	19,925
	3	0.72	0.38	1.38	5.54	41	19,196
ARIC Study, in men, total CHD events (4) [4]							
	1	1	1	1	2.92	62	9,183
	2	0.74	0.47	1.16	3.73	46	9,193
	3	1.07	0.70	1.65	4.37	63	9,074
	4	0.70	0.43	1.13	5.06	46	9,246
	5	0.89	0.54	1.48	6.23	52	9,165
FMC study, in women, total CHD events (4) [4]							
	1	1	1	1	1.14	60	7,762
	2	0.60	0.34	1.08	1.47	52	8,096
	3	0.56	0.23	1.34	2.22	50	7,785
FMC study, in men, total CHD events (4) [4]							
	1	1	1	1	1.11	81	4,777
	2	0.67	0.44	1.00	1.32	58	4,982
	3	0.58	0.36	0.93	1.49	55	4,984
	4	0.63	0.36	1.11	1.76	72	4,911
	5	0.42	0.20	0.90	2.64	56	4,945
WHS study, in women, total CHD events (4) [4]							
	1	1	1	1	3.34	29	37,506
	2	0.96	0.55	1.66	4.15	27	38,010
	3	0.98	0.54	1.76	4.76	26	38,151
	4	1.20	0.64	2.25	5.45	29	38,444
	5	1.60	0.81	3.18	6.61	41	38,644
VIP study, in women, total CHD events (4) [4]							
	1	1	1	1	2.72	6	14,496
	2	1.18	0.33	4.19	3.26	14	14,975
	3	0.44	0.05	3.91	4.10	3	14,401

VIP study, in men, total CHD events (4) [4]							
	1	1	1	1	2.75	54	12,920
	2	1.03	0.60	1.74	3.37	42	13,411
	3	1.40	0.64	3.05	4.26	38	12,899

[1] Calculated E% of LA by means of calorie intake.
[2] Number of person not person-years
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ARIC, Atherosclerosis Risk in Communities Study; ATBC, Alpha-Tocopherol and Beta-Carotene Cancer Prevention; CHD, coronary heart disease; FMC, Finnish Mobile Clinic Health Study; HPFS, Health Professional s' Follow-up Study; IWHS, Iowa Women's Health Study; LA, linoleic acid; NHS, Nurses' Health Study; VIP, Västerbotten Intervention Program; WHS, Women's Health Study.

Table S4. Extracted and calculated data for the included studies for substituting dietary linoleic acid for saturated fat and coronary heart disease deaths.

Study name	Category	RR	LL	UL	Median of E% from LA intake	Number of cases	person/year
NHS, in women, CHD deaths (26) [1]							
	1	1	1	1	2.94	388	471,210
	2	0.86	0.72	1.03	3.95	214	473,125
	3	0.80	0.65	0.98	4.59	172	473,581
	4	0.81	0.66	1.01	5.25	165	473,507
	5	0.74	0.58	0.92	6.38	172	473,110
HPFS, in men, CHD deaths (27) [1]							
	1	1	1	1	3.58	476	187,389
	2	0.98	0.85	1.14	4.37	408	188,150
	3	0.94	0.80	1.10	4.95	369	188,444
	4	0.96	0.81	1.13	5.60	359	188,364
	5	0.89	0.74	1.07	6.73	359	188,368
ATBC study, in men, CHD deaths (28) [1]							
	1	1	1	1	1.50	122	24,343
	2	0.91	0.66	1.25	1.88	97	24,884
	3	1.21	0.83	1.76	2.34	106	24,752
	4	1.03	0.67	1.59	3.26	83	25,122
	5	1.38	0.80	2.37	6.01	126	25,093
ARIC Study, in men, CHD deaths (4) [2]							
	1	1	1	1	2.92	9	9,202
	2	1.04	0.24	4.44	3.73	6	9,205
	3	1.69	0.52	5.51	4.37	16	9,077
	4	1.09	0.28	4.23	5.06	15	9,252
	5	0.90	0.17	4.83	6.23	5	9,176
FMC study, in women, CHD deaths (4) [2]							
	1	1	1	1	1.14	17	7,923
	2	0.46	0.12	1.80	1.47	13	8,226
	3	0.70	0.10	4.98	2.22	18	7,933
FMC study, in men, CHD deaths (4) [2]							
	1	1	1	1	1.11	36	4,976
	2	0.55	0.28	1.10	1.32	18	5,157
	3	0.94	0.46	1.91	1.49	30	5,088
	4	1.06	0.45	2.50	1.76	36	5,085
	5	0.72	0.24	2.23	2.64	27	5,088
WHS study, in women, CHD deaths (4) [2]							
	1	1	1	1	3.65	3	62,234
	2	0.62	0.07	5.46	4.76	2	65,082
	3	2.17	0.22	21.49	6.11	5	63,738
VIP study, in men, CHD deaths (4) [2]							
	1	1	1	1	2.75	16	12,996
	2	1.07	0.36	3.17	3.37	11	13,472
	3	1.27	0.25	6.42	4.26	11	12,942
IWHS study, in women, CHD deaths (4) [2]							
	1	1	1	1	3.65	69	58,800
	2	0.61	0.41	0.91	4.58	42	59,003
	3	0.78	0.53	1.14	5.28	54	58,865
	4	0.80	0.53	1.20	6.04	61	59,033
	5	0.83	0.53	1.31	7.31	68	58,919

IIHD study, in men, CHD deaths (4) [2]							
	1	1	1	1	3.59	34	15,890
	2	0.97	0.58	1.61	5.21	31	16,141
	3	0.93	0.55	1.58	6.42	32	16,071
	4	1.07	0.62	1.84	7.72	38	16,117
	5	0.71	0.37	1.36	9.52	30	16,255

[1] Updated published data

[2] Data from unpublished cohort studies

[3] Number of person not person-years

ARIC, Atherosclerosis Risk in Communities Study; ATBC, Alpha-Tocopherol and Beta-Carotene Cancer Prevention; CHD, coronary heart disease; FMC, Finnish Mobile Clinic Health Study; HPFS, Health Professional s' Follow-up Study; IIHD, Israeli Ischemic Heart Disease Study; IWHS, Iowa Women's Health Study; LA, linoleic acid; NHS, Nurses' Health Study; VIP, Västerbotten Intervention Program; WHS, Women's Health Study.

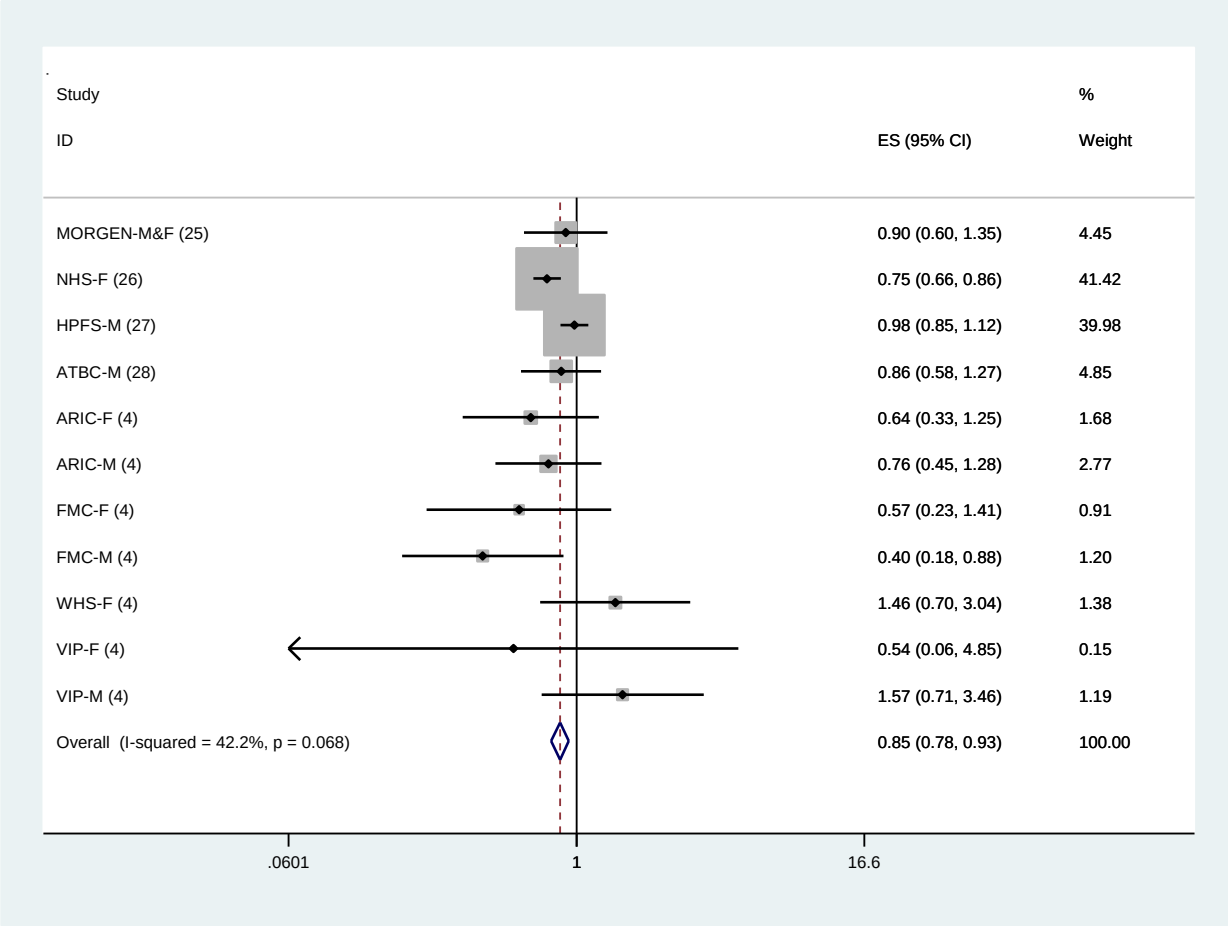

Figure S1. Substituting linoleic acid for carbohydrate and relative risk of total coronary heart disease events (highest category versus lowest category). The relative risks were pooled by using fixed effects meta-analysis.

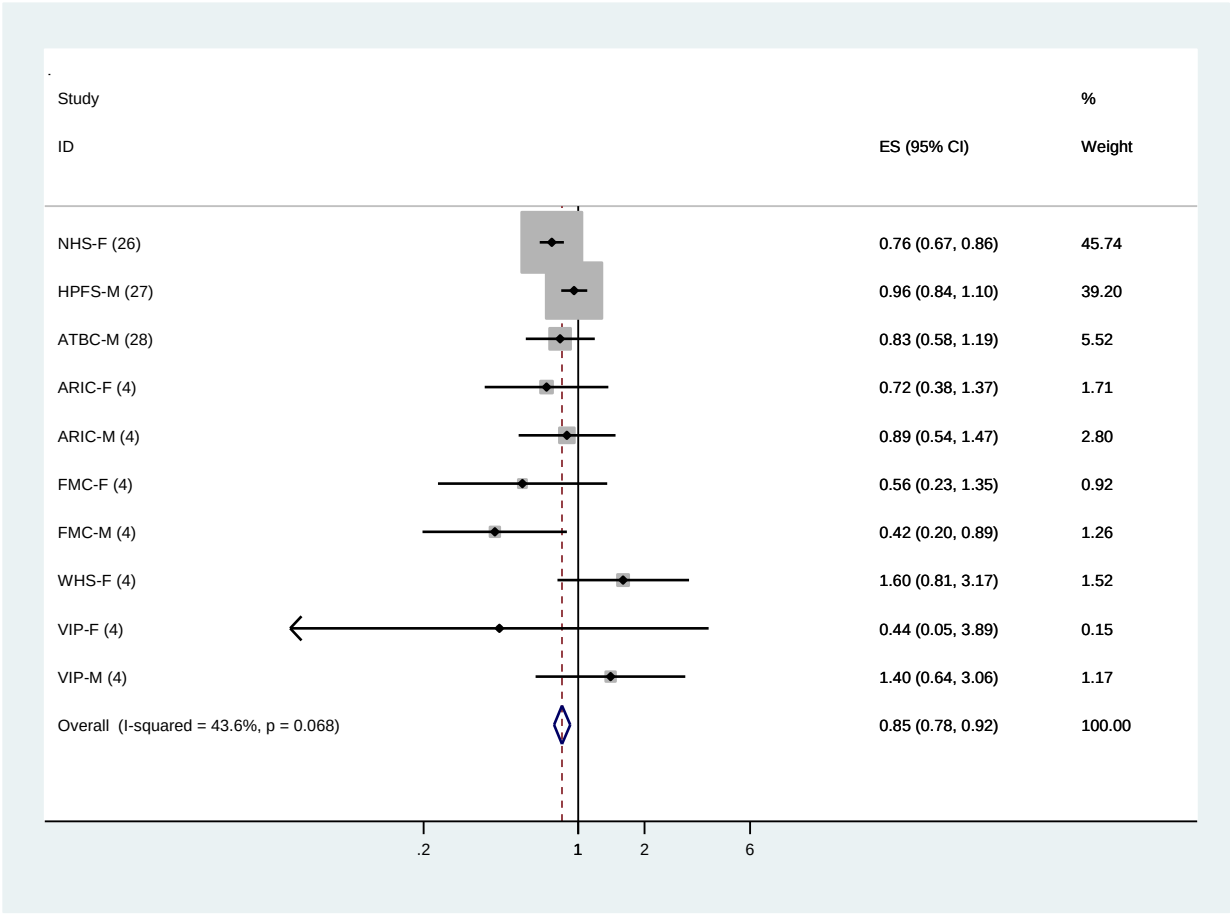

Figure S2. Substituting linoleic acid for saturated fat and relative risk of total coronary heart disease events (highest category versus lowest category). The relative risks were pooled by using fixed effects meta-analysis.

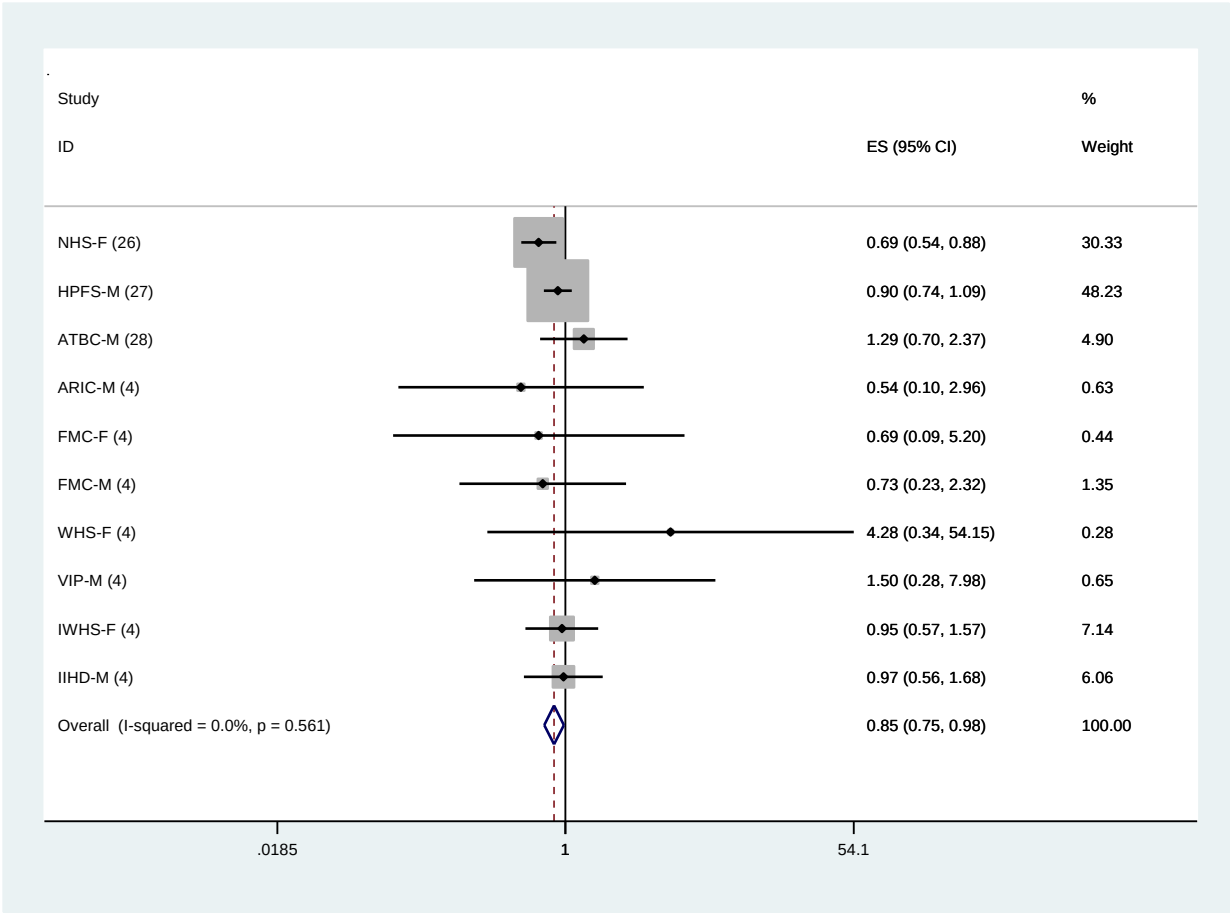

Figure S3. Substituting linoleic acid for carbohydrate and relative risk of coronary heart disease deaths (highest category versus lowest category). The relative risks were pooled by using fixed effects meta-analysis.

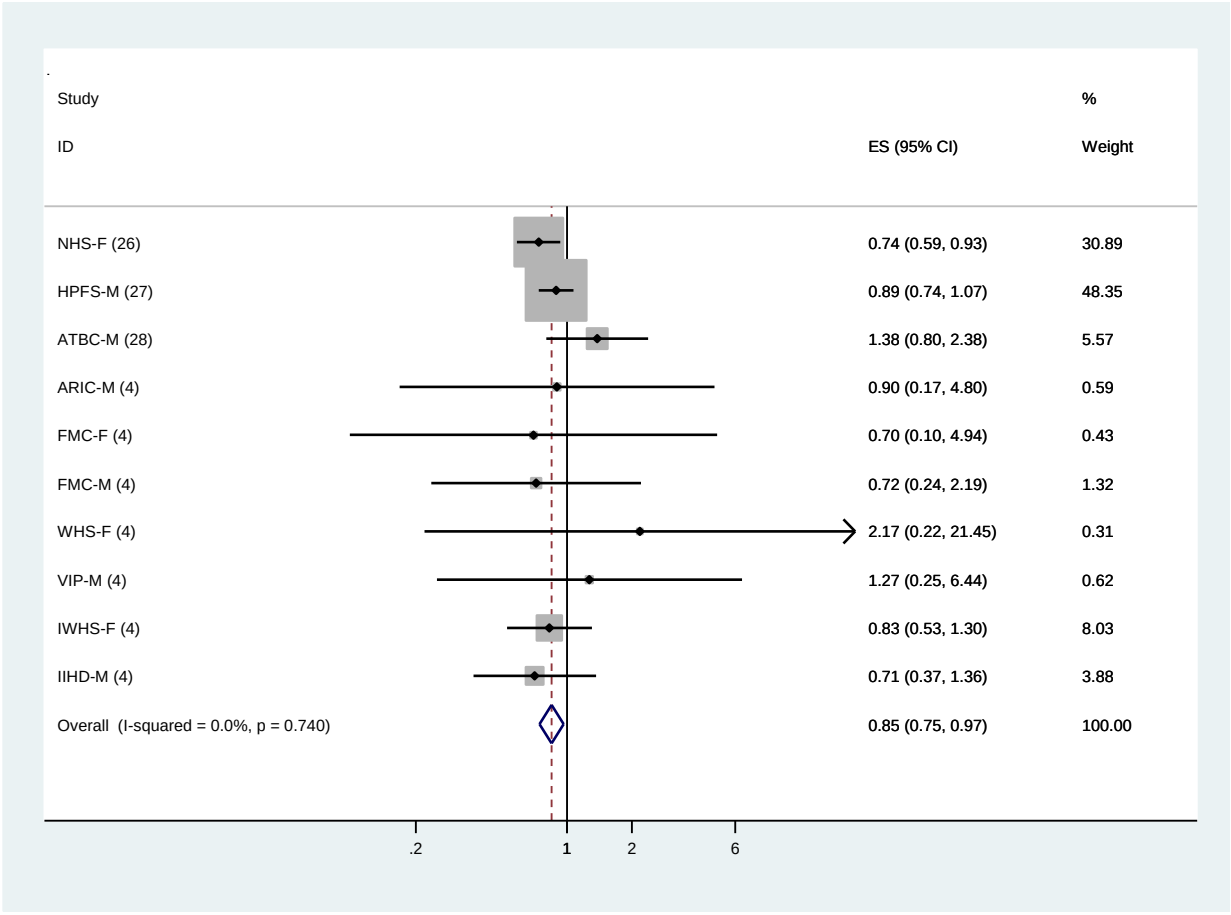

Figure S4. Substituting linoleic acid for saturated fat and relative risk of coronary heart disease deaths (highest category versus lowest category). The relative risks were pooled by using fixed effects meta-analysis.

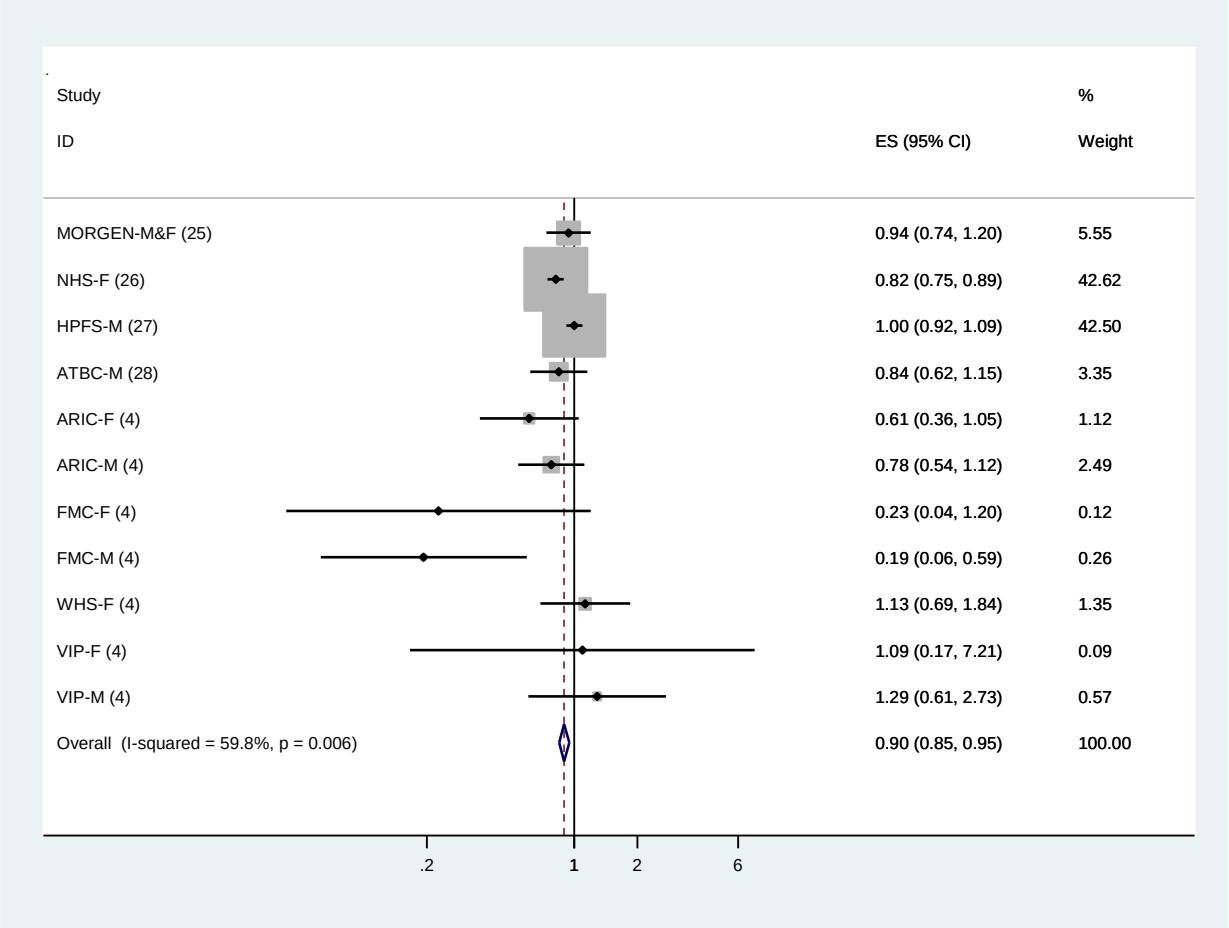

Figure S5. Two-stage dose-response meta-analysis of substituting each 5 E% of dietary intake from linoleic acid for 5 E% of dietary intake from carbohydrate and relative risk of total coronary heart disease events. The relative risks were pooled by using fixed effects meta-analysis.

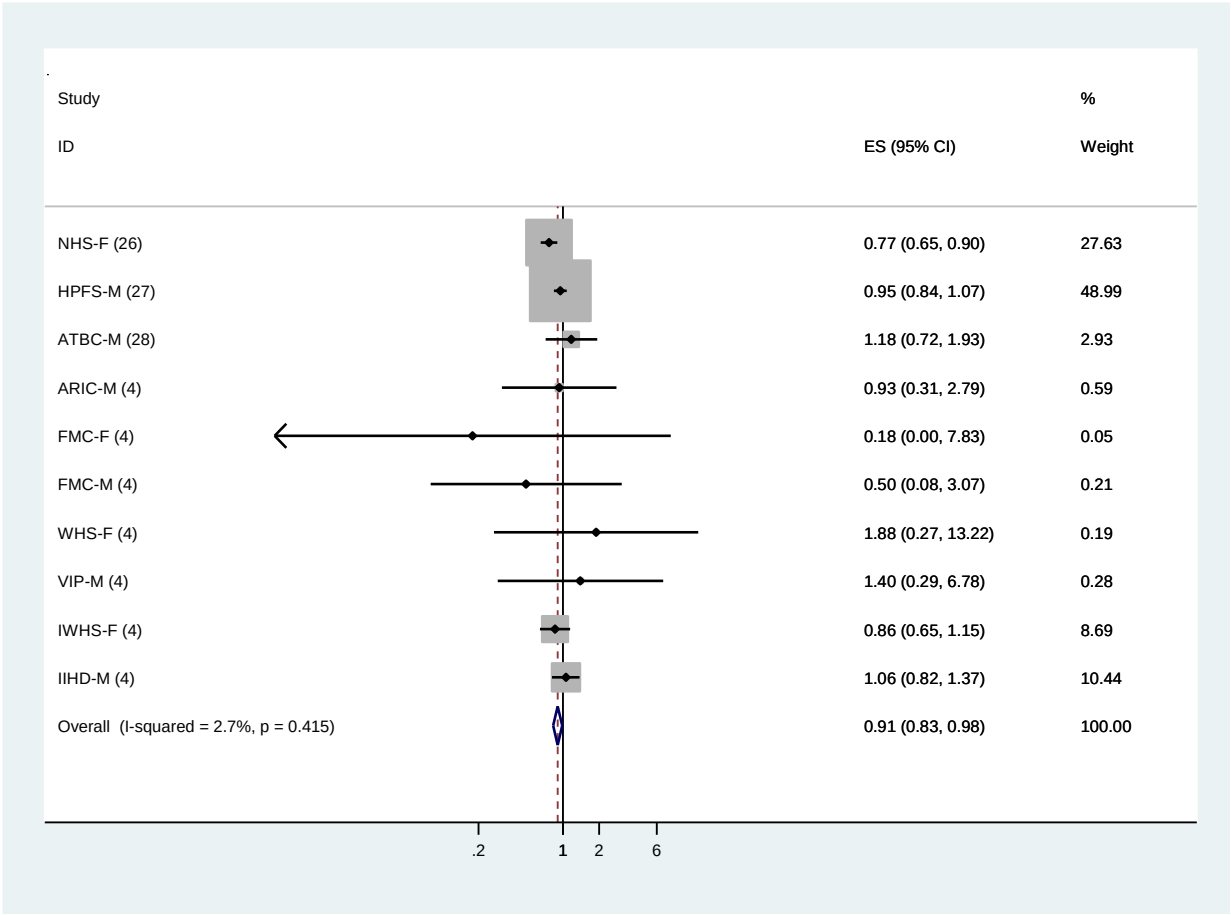

Figure S6. Two-stage dose-response meta-analysis of substituting each 5 E% of dietary intake from linoleic acid for 5 E% of dietary intake from carbohydrate and relative risk of coronary heart disease deaths. The relative risks were pooled by using fixed effects meta-analysis.

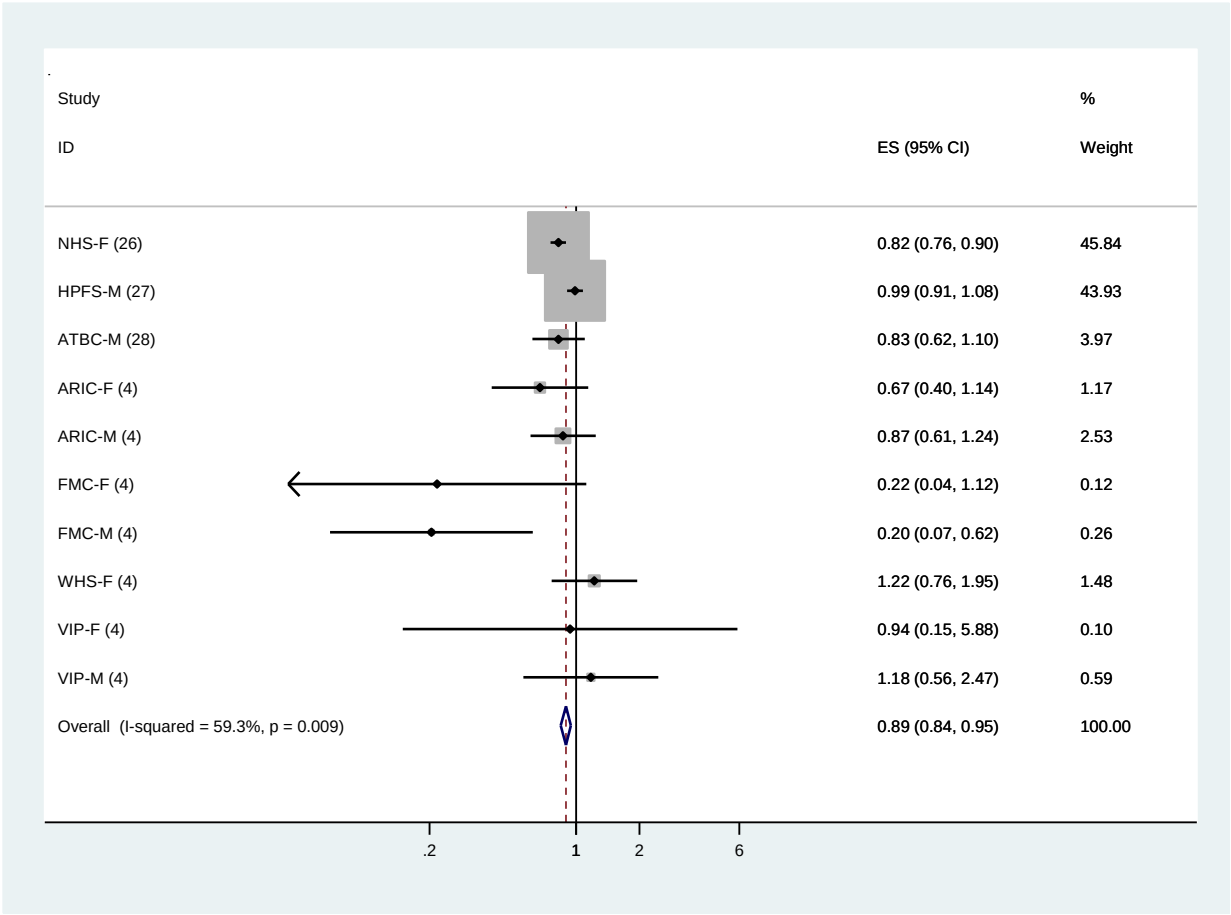

Figure S7. Two-stage dose-response meta-analysis of substituting each 5 E% of dietary intake from linoleic acid for 5 E% of dietary intake from saturated fat and relative risk of total coronary heart disease events. The relative risks were pooled by using fixed effects meta-analysis.

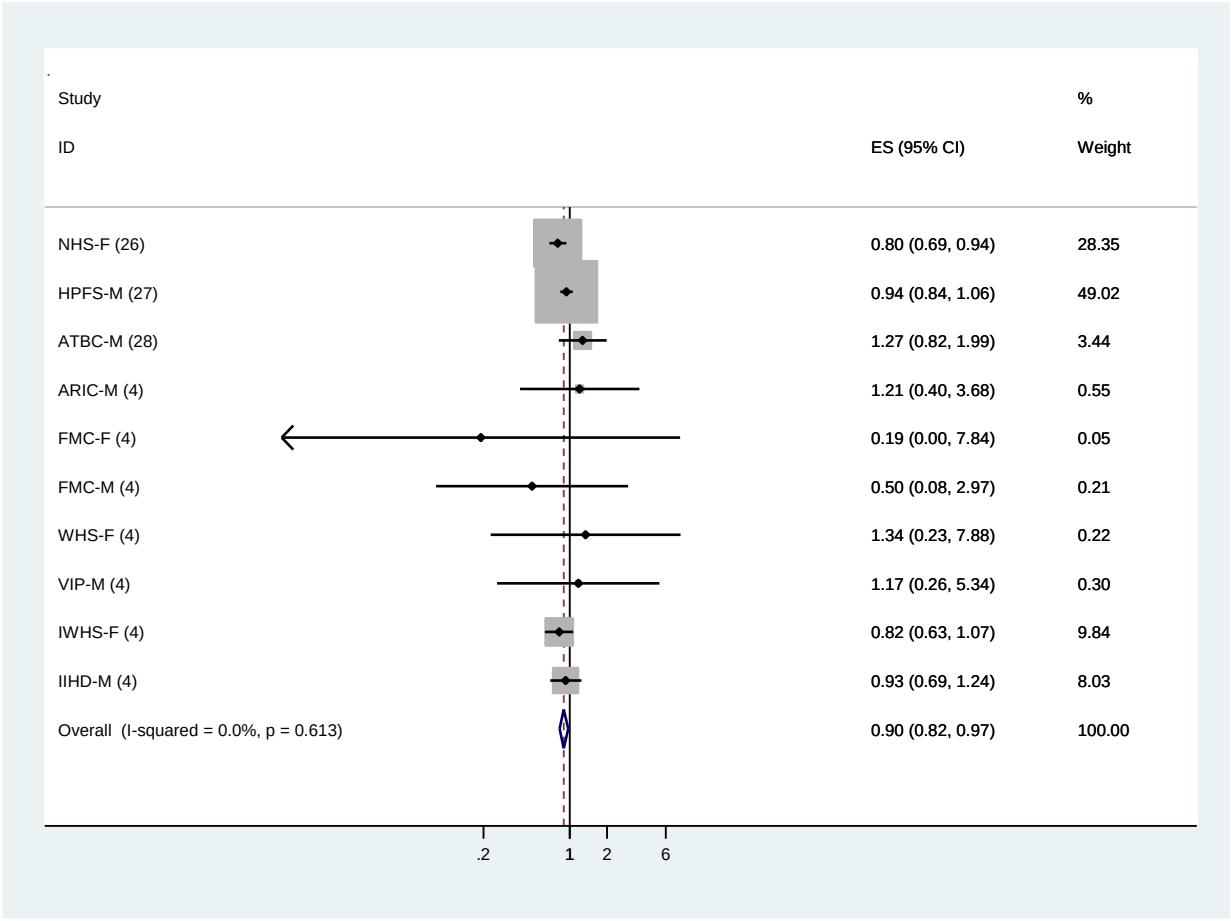

Figure S8. Two-stage dose-response meta-analysis of substituting each 5 E% of dietary intake from linoleic acid for 5 E% of dietary intake from saturated fat and relative risk of coronary heart disease deaths. The relative risks were pooled by using fixed effects meta-analysis.

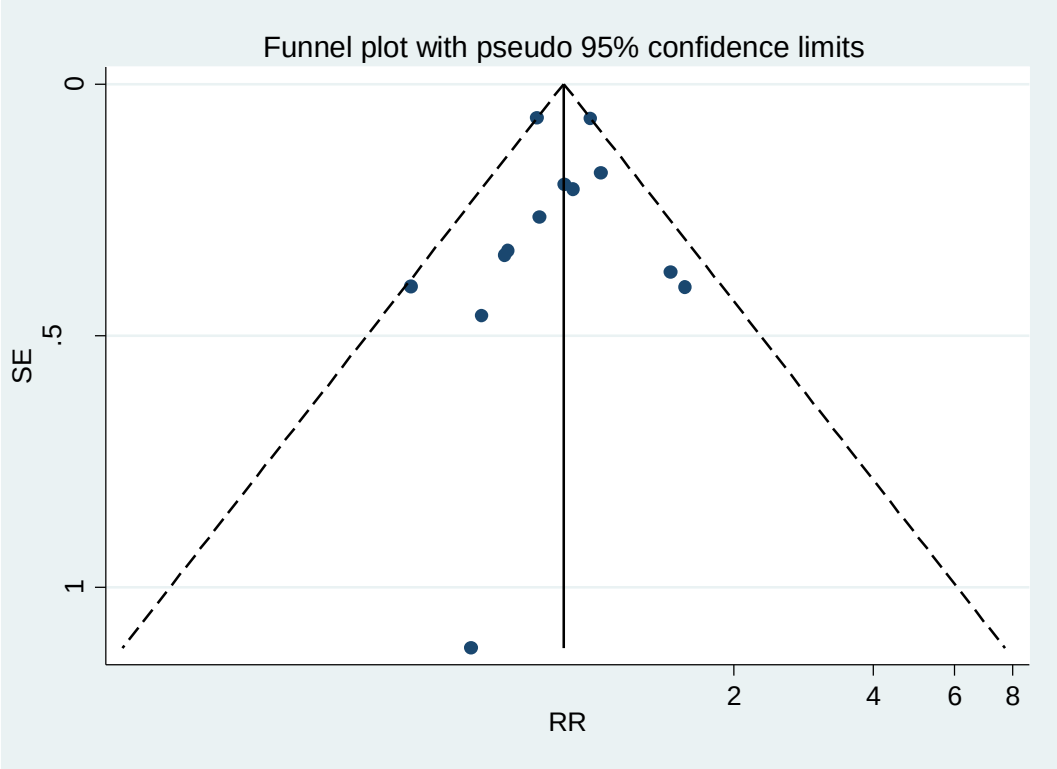

Figure S9. Funnel Plots for Detection of Publication Bias for dietary linoleic acid intake and risk of total coronary heart disease.

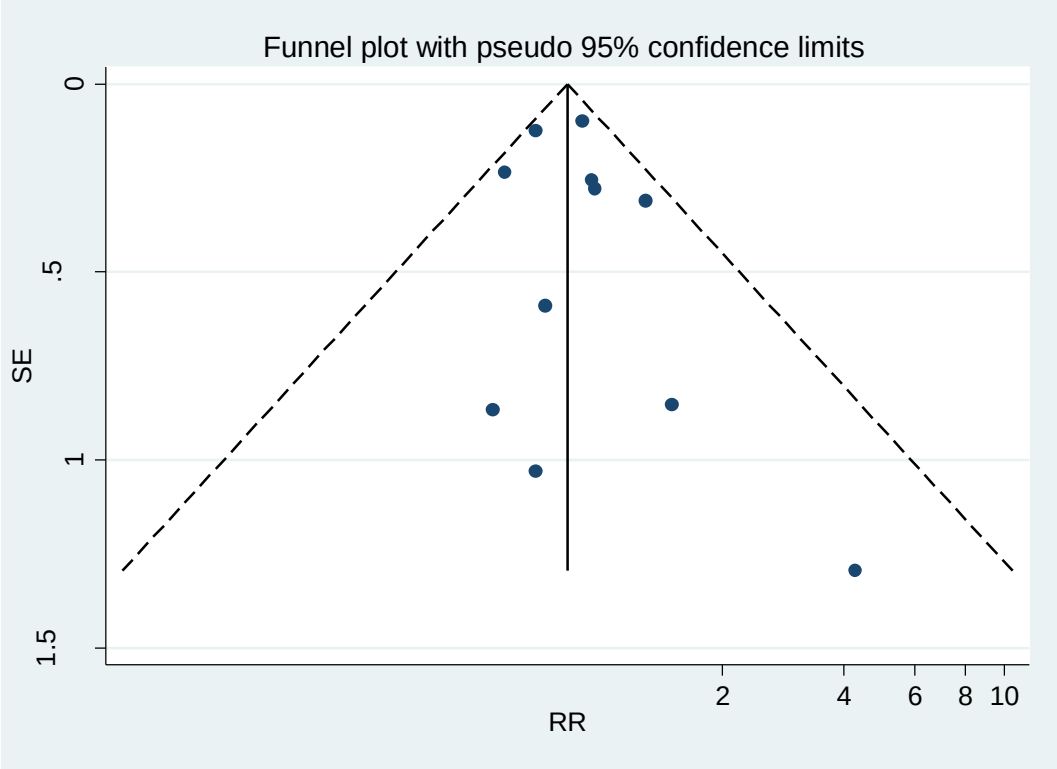

Figure S10. Funnel Plots for Detection of Publication Bias for dietary linoleic acid intake and risk of coronary heart disease deaths.