Supplemental Table 1: The terms used to search relevant publications on the relation between ALA and risk of mortality

In PubMed, Scopus, and ISI Web of Science	**n**
1. “Fatty Acids, Omega-3”	
2. “Omega-3”	
3. “Omega 3”	
4. “n-3 PUFA”	
5. “n-3 Fatty Acids”	
6. “n-3 Fatty Acid”	
7. “n-3 Oils”	
8. “n-3 Oil”	
9. “Unsaturated Fatty Acid”	
10. “Polyunsaturated Fatty Acid”	
11. “alpha-Linolenic Acid”	
12. “α-Linolenic Acid”	
13. “Linolenate”	
14. “Linolenic Acid”	
15. (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14)	
16. mortality	
17. death	
18. fatal	
19. survive	
20. "Neoplasms"	
21. "Cancer Survivors"	
22. “cardiovascular disease”	
23. “coronary disease”	
24. "Myocardial Ischemia"	
25. “coronary artery disease”	
26. “myocardial infarction”	
27. stroke	
28. (16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27)	
(15 AND 28) **In PubMed**	5903
(15 AND 28) **In Scopus**	8023
(15 AND 28) **In ISI Web of Science**	4438
Duplicate	5991
In Google Scholar	500
“Linolenic acid” and mortality By searching the above combination in this engine, we screened the first 500 relevancy ranked papers to avoid missing any eligible studies.	
Total	12873

Supplemental Table 2: Characteristics of included studies on the association between ALA intake (or tissue biomarkers) and all-cause mortality in adults aged >18 years

Author	Country	Age*	Sample size	Follow up (years) ¥	Deaths	Exposure	Exposure assessment	Health status†	Median/cutoff point	RR (95%CI)	Adjustment
Lelli et al. 2019	Italy	>65	M/F: 927	9	318	Dietary intake	FFQ	Healthy	NR	1 0.83 (0.58-1.18) 0.87 (0.62-1.22) 0.84 (0.59-1.21)	Age, sex, education, BMI, estimated glomerular filtration rate (CKD-EPI), caloric intake/body weight, smoke, hypertension, diabetes, alcohol and oleic acid consumption.
						Total serum	GC		NR	1 0.77 (0.55-1.07) 0.74 (0.52-1.05) 0.75 (0.53-1.07)	
Zhuang et al. 2019	US	50-71	M/F: 521,120	16	129,328	Dietary intake	FFQ	Healthy	NR Per 1g	1 1.00 (0.98-1.02) 1.02 (1.00-1.04) 1.03 (1.01-1.06) 1.05 (1.02-1.08) 1.00 (0.97-1.04)	Age, gender, BMI, race, education, marital status, household income, smoking, alcohol drinking, physical activity, multi-vitamin use, aspirin use, history of hypertension, history of hypercholesterolemia, perceived health condition, history of heart disease, stroke, diabetes, and cancer at baseline, hormones use for women, intake of total energy, percentages of energy intake from protein, carbohydrates and remaining fatty acids.
Wang et al. 2016	US	40-75	M: 42884	26	12,990	Dietary intake	FFQ	Healthy	0.38 %E 0.45 %E 0.50 %E 0.56 %E 0.68 %E Per 1g	1 1.00 (0.94-1.06) 1.02 (0.96-1.08) 1.04 (0.98-1.10) 1.01 (0.94-1.08) 1.02 (0.98-1.06)	Age, Caucasian, marital status, BMI, physical activity, smoking status, alcohol consumption, multivitamin use, vitamin E supplementation use, current aspirin use, family history of myocardial infarction, family history of diabetes, family history of cancer, history of hypertension, history of hypercholesterolemia, intakes of total energy, dietary cholesterol and percentage of energy intake from dietary protein, and remaining fatty acids, and menopausal status and hormone use in women
Wang et al. 2016	US	30-55	F: 83,349	32	20,314	Dietary intake	FFQ	Healthy	0.41 %E 0.48 %E 0.53 %E 0.59 %E 0.70 %E Per 1g	1 1.00 (0.95-1.04) 1.05 (1.00-1.10) 1.02 (0.97-1.07) 0.98 (0.93-1.04) 1.01 (0.99-1.03)	Age, Caucasian, marital status, BMI, physical activity, smoking status, alcohol consumption, multivitamin use, vitamin E supplementation use, current aspirin use, family history of myocardial infarction, family history of diabetes, family history of cancer, history of hypertension, history of hypercholesterolemia, intakes of total energy, dietary cholesterol and percentage of energy intake from dietary protein, and remaining fatty acids, and menopausal status and hormone use in women
Jiao et al. 2019	US	30-75	M/F: 11264	11	2502	Dietary intake	FFQ	Unhealthy	0.40 %E 0.49 %E 0.58 %E 0.76 %E	1 0.98 (0.87-1.09) 0.80 (0.70-0.91) 0.88 (0.76-1.02)	Age, sex, survey period, ethnicity, BMI at diagnosis, physical activity, smoking status, smoking pack years, alcohol consumption, multivitamin use, current aspirin use, family history of myocardial infarction, family history of

									Per 1g	0.89 (0.81-0.98)	diabetes, history of hypercholesterolemia, history of hypertension, duration of diabetes, total energy intake, dietary cholesterol, and percentage of energy from dietary protein and remaining fatty acids.
Khankari et al. 2015	US	20-98	F: 1463	14.7	485	Dietary intake	FFQ	Unhealthy	. <0.38 g/d 0.38-0.68 g/d 0.68-1.10 g/d >1.10 g/d Per 1g	1 1.18 (0.91-1.52) 1.18 (0.90-1.55) 1.14 (0.83-1.57) 1.15 (0.89-1.49)	Age and total energy intake
Fretts et al. 2014	US	>65	M/F: 2709	12	1757	Dietary intake	FFQ	Healthy	0.42 %E 0.47 %E 0.51 %E 0.55 %E 0.63 %E Per 1g	1 0.98 (0.84-1.15) 0.88 (0·75-1·03) 0.86 (0.73-1.02) 0.73 (0·61-0·88) 0.88 (0.78-0.98)	Age, sex, total energy intake, race, enrolment site, education, smoking status, diabetes, BMI, alcohol consumption and treated hypertension.
						Phospholipids	GC		0.09 %FA 0.12 %FA 0.14 %FA 0.17 %FA 0.22 %FA Per 1-SD	1 1.09 0.93, 1.26) 1.09 (0.94-1.27) 0·95 (0.81-1.11) 0.93 (0.79-1.08) 0.97 (0.90-1.03)	
Zhuang et al. 2019	China	>20	M/F: 14,117	14	1007	Dietary intake	Food recall	Healthy	0-0.65 g/d 0.65-1.00 g/d 1.00-1.53 g/d >1.53 g/d Per 1g	1 0.93 (0.77-1.13) 0.93 (0.76-1.13) 1.23 (1.01-1.50) 0.93 (0.86-1.00)	Age, gender, BMI, education, marital status, residence, physical activity, smoking, alcohol drinking status, history of hypertension, history of diabetes, intake of total energy, vegetables, fruits, red meat and saturated fat.
Zhuang et al. 2019	US	>20	M/F: 36,032	9	4826	Dietary intake	Food recall	Healthy	0-0.70 g/d 0.70-1.15 g/d 1.15-1.80 g/d >1.80 g/d Per 1g	1 0.99 (0.89-1.10) 0.90 (0.78-1.04) 0.84 (0.70-1.00) 1.10 (0.98-1.22)	Age, gender, race-ethnicity, BMI, education, marital status, physical activity, smoking, alcohol drinking status, history of hypertension, history of diabetes, family history of cardiovascular disease, intake of total energy, vegetables, fruits, red meat and saturated fat.
Sala-Vila et al. 2016	Spanish	55-80	M/F: 7202	5.9	431	Dietary intake	FFQ	Healthy	<0.7 %E >0.7 %E	1 0.72 (0.55-0.93)	Age, sex, intervention group, body mass index, smoking status, physical activity, total energy intake, history of diabetes, history of hyperlipidemia, history of hypertension, alcohol intake, and dietary factors (fiber, vegetables, fruits, and red meat).
Fortes et al. 2000	Italy	>65	M/F: 162	5	53	Dietary intake	FFQ	Healthy	<1.1 g/d 1.1-1.5 g/d >1.5 g/d Per 1g	1 0.74 (0.37-1.50) 0.51 (0.23-1.13) 0.71 (0.45-1.10)	Age, sex, education, BMI, smoking, cognitive function, and chronic diseases.
Richman et al. 2013	US	40-75	M: 4577	8.4	1064	Dietary intake	FFQ	Unhealthy	0.36 %E 0.44 %E	1 0.94 (0.78, 1.13)	Age at diagnosis, energy, time since diagnosis, treatment, Gleason sum, clinical stage, diagnostic PSA, number of

									0.50 %E 0.58 %E 0.74 %E	0.81 (0.66, 1.00) 0.99 (0.80, 1.23) 0.87 (0.67-1.12)	PSA screening tests prior to diagnosis, body mass index, smoking, vigorous activity, and intake of calcium, alcohol, protein, saturated fat, monounsaturated fat, trans fat, linoleic acid, long-chain omega-3 fatty acids and pre-diagnostic intake of polyunsaturated fat based on the 1986 FFQ.
Dolecek et al. 1991	US	35-57	M: 12,866	8	439	Dietary intake	Food recall	Healthy	0.87 g/d 1.27 g/d 1.57 g/d 1.92 g/d 2.8 g/d Per 1g	1 0.94 (0.72-1.22) 0.68 (0.52-0.92) 0.86 (0.66-1.13) 0.67 (0.50-0.90) 0.84 (0.76-0.92)	Unadjusted
Gopinath et al. 2011	Australia	>49	M/F: 2514	15	214	Dietary intake	FFQ	Healthy	0-0.54 g/d 0.55-0.73 g/d 0.74-3.01 g/d Per 1g	1 0.95 (0.68-1.34) 0.74 (0.51-1.08) 0.84 (0.69-1.03)	Age, sex, total energy intake, for current smoking, alcohol consumption, poor self-rated health, BMI, presence of diabetes, total fiber, dietary glycemic index, use of corticosteroid drugs, and white blood cell count.
Marklund et al. 2019	Swedish	>60	M/F: 4232	14.5	456	Cholesteryl esters	GC	Healthy	0.68 %FA 0.81 %FA 0.93 %FA 1.01 %FA Per 1-SD	1 0.99 (0.75-1.30) 1.15 (0.88-1.49) 1.15 (0.89-1.50) 1.02 (0.97-1.07)	Sex, BMI, smoking, physical activity, education, alcohol intake, diabetes, drug-treated hypertension, and drug-treated hypercholesterolemia.
Erkkila et al. 2003	French	33-74	M/F: 398	5	35	Cholesteryl esters	GC	Unhealthy	<0.77 0.77-0.89 >0.89 Per 1-SD	1 0.76 (0.32-1.82) 0.33 (0.11-0.96) 0.93 (0.86-1.01)	Age, sex, diagnostic category, energy intake, serum cholesterol, serum triacylglycerol, diabetes (diagnosis or plasma glucose concentration>7 mmol/L), BMI, and education.
Lindberg et al. 2008	Norway	72.5–97.7	M/F: 254	3	NR	Phospholipids	GC	Unhealthy	<0.14 %FA 0.14-0.18 %FA 0.18-0.21 %FA >0.21 %FA Per 1-SD	1 1.00 (0.59-1.69) 0.83 (0.49-1.40) 0.91 (0.54-1.51) 0.96 (0.85-1.09)	Age, sex, assignment to Geriatric Evaluation and Management Unit treatment, Barthel Index, residence, current smoking status, history of cardiovascular disease, and HDL-cholesterol, LDL-cholesterol, prealbumin, and α-tocopherol concentrations.
Harris et al. 2017	US	65–80	F: 6501	15.9	1851	Erythrocyte	GC	Healthy	Per 1-SD	0.98 (0.91-1.05)	Age, race, HT assignment, BMI, highest education, smoking pack-year, physical activity, weekly alcohol intake, waist circumference, region, family history of cancer, family history of CVD, aspirin use, high cholesterol requiring pills (ever), and a history of hypertension, diabetes, cardiovascular disease and/or cancer.
Warensjö et al. 2008	Sweden	50	M: 1885	30.7	1012	Cholesteryl esters	GC	Healthy	Per 1-SD	1.03 (0.97, 1.10)	Total cholesterol, BMI, smoking, physical activity, and hypertension.
Miura et al. 2016	Australia	20–69	M/F: 1008	17	179	Phospholipids	GC	Healthy	NR Per 1-SD	1 0.97 (0.67-1.42) 0.90 (0.62-1.30) 0.86 (0.72-1.01)	Age, sex, smoking status, blood cholesterol, jaundice measure (proxy serum β-carotene level), and history of serious medical condition.

Pottala et al. 2010	US	>55	M/F: 956	5.9	237	Whole blood	GC	Unhealthy	Per 1%	0.90 (0.51–1.58)	Unadjusted
Iggman et al. 2016	Sweden	71	M: 853	14.8	605	Adipose tissue	GC	Healthy	Per 1-SD	0.96 (0.87-1.06)	Age, analysis occasion, smoking, body mass index, alcohol intake, physical activity, diabetes prevalence, systolic blood pressure, dyslipidemia, and hypertension treatment.
Kleber et al. 2016	Germany	62	M/F: 3259	9.9	975	Erythrocytes	GC	Unhealthy	0.10 %FA 11-13 %FA >13 %FA Per 1-SD	1 0.90 (0.77-1.05) 0.90 (0.76-1.06) 0.95 (0.88-1.02)	Age, gender, LDL-C, HDL-C, logTG, BMI, hypertension, diabetes mellitus, smoking, alcohol intake, physical exercise and lipid lowering therapy.
Harris et al. 2018	US	66	M/F: 2500	7.3	350	Erythrocytes	GC	Healthy	4.2 %FA 4.2-4.9 %FA 4.9-5.7 %FA 5.7-6.8 %FA >6.8 %FA	1 0.84 (0.58-1.21) 1.04 (0.72-1.50) 0.96 (0.67-1.39) 1.04 (0.73-1.47)	Age, sex, BMI, marital status, education, employment, health insurance status, regular aspirin use, alcohol consumption, smoking, METS, total to HDL cholesterol ratio, systolic BP, C-reactive protein, cholesterol medication use, history of diabetes.
Jayanama et al. 2020	US	>50	M/F: 4062	3	966	Dietary intake	Food recall	Healthy	Per 1 g	0.87 (0.79-0.95)	Sex, race, educational level, marital status, employment status, smoking, energy intake, body mass index, percent fatty acids intake, study cohort, nutrition index, and frailty index.
Lázaro et al. 2020	Spain	61	M/F: 944	3	108	Phospholipids	GC	Unhealthy	Per 1-SD	0.65 (0.44–0.96)	Age, sex, history of arterial hypertension, diabetes, cerebrovascular disease, heart failure and myocardial infarction, hemoglobin, estimated glomerular filtration rate, triglycerides, total cholesterol, Killip-Kimball Class III to IV, and left ventricular ejection fraction
Harris et al. 2013	US	59.5	M/F: 1144	2	135	Erythrocytes	GC	Unhealthy	>median vs. <median	1.02 (0.22-4.69)	Age, histories of myocardial infarction and heart failure, admission heart rate, systolic blood pressure, serum creatinine level, elevated initial serum cardiac biomarker level, ST-segment depression on presenting electrocardiogram, and percutaneous coronary intervention performed in hospital
Harris et al. 2021	12 countries	65	M/F: 39502	16	13989	Different tissues	GC	Healthy	NR	1 0.95 (0.87–1.04) 0.94 (0.89–0.99) 0.95 (0.90–1.01) 0.94 (0.89–0.99)	Age, sex, race, field center, body-mass index, education, occupation, marital status, smoking, physical activity, alcohol intake, prevalent diabetes, hypertension, and dyslipidemia, self-reported general health, and the sum of circulating n-6 PUFA

Abbreviation: ES: effect size- CI: confidence interval- M: male- F: female- FFQ: food frequency questionnaire- BMI: body mass index- US: United States- RR: risk ratio- GC: gas chromatography- GLC: gas-liquid chromatography- NR: not-reported

*Presented as mean or range

†Studies recruiting apparently healthy adults (without a prior diagnosis of cancer, CVD, or any other chronic diseases) were included in the healthy subgroup and studies that recruited individuals with at least one chronic disease were included in the unhealthy subgroup

Supplemental Table 3: Characteristics of included studies on the association between ALA intake (or tissue biomarkers) and CVD mortality in adults aged >18 years

Author	Country	Age*	Sample size	Follow up (years) ¥	Cases	Exposure	Exposure assessment	Health status†	Median/cutoff point	RR (95%CI)	Adjustment
Lelli et al. 2019	Italy	>65	M/F: 927	9	114	Dietary intake Total serum	FFQ GC	Healthy	NR	1 0.77 (0.41-1.45) 0.95 (0.54-1.69) 0.80 (0.43-1.50)	Age, sex, education, BMI, estimated glomerular filtration rate (CKD-EPI), caloric intake/body weight, smoke, hypertension, diabetes, alcohol and oleic acid consumption.
									NR	1 0.69 (0.40-1.22) 0.72 (0.40-1.30) 0.69 (0.39-1.23)	
Zhuang et al. 2019	US	50-71	M/F: 521,120	16	38,747	Dietary intake	FFQ	Healthy	NR Per 1g	1 0.99 (0.95-1.03) 1.01 (0.97-1.05) 1.02 (0.97-1.06) 1.02 (0.97-1.07) 0.98 (0.94-1.03)	Age, gender, BMI, race, education, marital status, household income, smoking, alcohol drinking, physical activity, multi-vitamin use, aspirin use, history of hypertension, history of hypercholesterolemia, perceived health condition, history of heart disease, stroke, diabetes, and cancer at baseline, hormones use for women, intake of total energy, percentages of energy intake from protein, carbohydrates and remaining fatty acids.
Wang et al. 2016	US	40-75	M: 42884	26	3,868	Dietary intake	FFQ	Healthy	0.38 %E 0.45 %E 0.50 %E 0.56 %E 0.68 %E Per 1g	1 0.99 (0.89, 1.11) 0.99 (0.89, 1.10) 1.00 (0.89, 1.12) 0.97 (0.86-1.10) 0.92 (0.84-1.00)	Age, Caucasian, marital status, BMI, physical activity, smoking status, alcohol consumption, multivitamin use, vitamin E supplementation use, current aspirin use, family history of myocardial infarction, family history of diabetes, family history of cancer, history of hypertension, history of hypercholesterolemia, intakes of total energy, dietary cholesterol and percentage of energy intake from dietary protein, and remaining fatty acids, and menopausal status and hormone use in women
Wang et al. 2016	US	30-55	F: 83,349	32	4000	Dietary intake	FFQ	Healthy	0.41 %E 0.48 %E 0.53%E 0.59%E 0.70%E Per 1g	1 0.89 (0.81, 0.99) 0.96 (0.86, 1.06) 0.92 (0.82, 1.03) 0.90 (0.80-1.02) 0.98 (0.92-1.06)	Age, Caucasian, marital status, BMI, physical activity, smoking status, alcohol consumption, multivitamin use, vitamin E supplementation use, current aspirin use, family history of myocardial infarction, family history of diabetes, family history of cancer, history of hypertension, history of hypercholesterolemia, intakes of total energy, dietary cholesterol and percentage of energy intake from dietary protein, and remaining fatty acids, and menopausal status and hormone use in women
Jiao et al. 2019	US	30-75	M/F: 11264	11	646	Dietary intake	FFQ	Unhealthy	0.40 %E 0.49 %E 0.58 %E 0.76 %E	1 1.06 (0.85-1.32) 0.98 (0.76-1.26) 1.13 (0.85-1.51)	Age, sex, survey period, ethnicity, BMI at diagnosis, physical activity, smoking status, smoking pack years, alcohol consumption, multivitamin use, current aspirin use, family history of myocardial infarction, family

									Per 1g	1.05 (0.87-1.27)	history of diabetes, history of hypercholesterolemia, history of hypertension, duration of diabetes, total energy intake, dietary cholesterol, and percentage of energy from dietary protein and remaining fatty acids.
Laaksonen et al. 2005	Finland	52	M: 1551	15	78	Dietary intake	Food record	Healthy	1.1 g/d 1.5 g/d 2 g/d Per 1g	1 1.16 (0.66-2.02) 0.63 (0.33-1.21) 0.90 (0.67-1.20)	Age, year of examination, smoking, alcohol consumption, adult socioeconomic status and moderate to vigorous leisure-time physical activity, plasma lipid-standardized α-tocopherol levels, plasma ascorbic acid, dietary total energy and energy-adjusted saturated fat and fiber intake, low-density lipoprotein cholesterol concentrations, systolic blood pressure, blood pressure medication, family history of ischemic heart disease, C-reactive protein concentrations, fasting concentrations of insulin and nonesterified fatty acids, and BMI.
						Total serum	GC		0.6 %FA 0.8 %FA 1 %FA	1 0.66 (0.34-1.28) 1.19 (0.63-2.26)	
Oomen et al. 2001	Netherlands	64–84	M: 667	10	49	Dietary intake	Cross-check dietary history	Healthy	<0.45 %E 0.45-0.58 %E >0.58 %E Per 1g	1 0.99 (0.43-2.28) 1.59 (0.62-4.08) 1.19 (0.69-2.05)	Age, BMI, ex-smoking, current smoking, alcohol intake, use of vitamin supplements, intake of saturated fatty acids, trans fatty acids, linoleic acid, eicosapentaenoic and docosahexaenoic acids, other cis unsaturated fatty acids, and protein (as a percentage of energy); and intake of energy, dietary cholesterol, fiber, vitamin E, vitamin C, and β-carotene
Fretts et al. 2014	US	>65	M/F: 2583	12	519	Dietary intake	FFQ	Healthy	0.42 %E 0.47 %E 0.51 %E 0.55 %E 0.63 %E Per 1g	1 0.93 (0.68-1.25) 0.83 (0.61-1.14) 0.97 (0.72-1.31) 0.96 (0.71-1.32) 0.94 (0.76-1.16)	Age, sex, total energy intake, race, enrolment site, education, smoking status, diabetes, BMI, alcohol consumption and treated hypertension.
						Phospholipids	GC		0.09 %FA 0.12 %FA 0.14 %FA 0.17 %FA 0.22 %FA Per 1-SD	1 1.15 (0.87-1.53) 1.08 (0.81-1.44) 1.05 (0.79-1.40) 1.02 (0.77-1.36) 1.01 (0.89-1.14)	
Zhuang et al. 2019	US	>20	M/F: 36,032	9	1299	Dietary intake	Food recall	Healthy	0-0.70 g/d 0.70-1.15 g/d 1.15-1.80 g/d >1.80 g/d Per 1g	1 1.07 (0.88, 1.30) 0.97 (0.78, 1.21) 0.87 (0.62-1.22) 0.96 (0.84, 1.09)	Age, gender, race-ethnicity, BMI, education, marital status, physical activity, smoking, alcohol drinking status, history of hypertension, history of diabetes, family history of cardiovascular disease, intake of total energy, vegetables, fruits, red meat and saturated fat.
Sala-Vila et al. 2016	Spanish	55-80	M/F: 7202	5.9	104	Dietary intake	FFQ	Healthy	<0.7 %E >0.7 %E	1 0.95 (0.57-1.56)	Age, sex, intervention group, body mass index, smoking status, physical activity, total energy intake, history of

											diabetes, history of hyperlipidemia, history of hypertension, alcohol intake, and dietary factors (fiber, vegetables, fruits, and red meat).
Pietinen et al.1997	Finnish	50-69	M/F: 21,930	6.1	635	Dietary intake	FFQ	Healthy	0.9 g/d 1.2 g/d 1.5 g/d 1.9 g/d 2.5 g/d Per 1g	1 0.94 (0.74-1.20) 0.98(0.77-1.25) 1.03(0.81-1.32) 0.99 (0.76-1.28) 1.00 (0.91-1.11)	Age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber, education, and physical activity.
Dolecek et al. 1991	US	35-57	M: 12,866	8	232	Dietary intake	Food recall	Healthy	0.87 g/d 1.27 g/d 1.57 g/d 1.92 g/d 2.8 g/d Per 1g	1 0.89 (0.62-1.29) 0.65 (0.43-0.97) 0.84 (0.58-1.22) 0.60 (0.39-0.91) 0.85 (0.74-0.97)	Unadjusted
Bork et al. 2016	Denmark	50–64	M/F: 25,782	17	417	Dietary intake	FFQ	Healthy	<1.67 g/d 1.67-1.94 g/d 1.94-2.19 g/d 2.19-2.54 g/d >2.54 g/d Per 1g	1 1.01 (0.72-1.42) 1.25 (0.90-1.76) 1.22 (0.86-1.73) 0.71 (0.47-1.08) 1.01 (0.89-1.14)	BMI, waist circumference, smoking, physical activity, alcohol consumption, length of education and, for women, menopausal status and use of hormone replacement therapy, self-reported history of hypercholesterolemia and/or use of lipid-lowering medication; self-reported history of hypertension and/or use of antihypertensive medication, and self-reported history of diabetes mellitus, total energy-intake, dietary intake of fiber; glycaemic load, dietary intake of monounsaturated fatty acids, linoleic acid, saturated fatty acids, and marine long-chain omega-3 fatty acids
						Adipose tissue	GC		0.31-0.73 %FA 0.73-0.82 %FA 0.82-0.90 %FA 0.90-1.00 %FA 1.00-1.81 %FA Per 1-SD	1 1.20 (0.76-1.91) 1.12 (0.69-1.82) 2.16 (1.29-3.62) 2.40 (1.35-4.28) 1.10 (1.02-1.18)	
Koh et al. 2013	China	45–74	M/F: 63,257	14	4780	Dietary intake	FFQ	Healthy	0.40 g/d 0.51 g/d 0.56 g/d 0.80 g/d Per 1g	1 0.94 (0.86–1.02) 0.87 (0.79–0.95) 0.81 (0.73–0.90) 0.79 (0.70-0.89)	Age, sex, dialect, year of interview, educational level, BMI, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, total energy, intakes of protein, dietary fibre, monounsaturated fat, saturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids.
Sadowa et al. 2014	US and European countries	37-67	M/F: 237,714	4-10	1,751	Dietary intake	FFQ	Healthy	<1.09 g/d >1.09 g/d Per 1g	1 0.99 (0.85-1.17) 0.88 (0.68-1.14)	Age, smoking habits, BMI, physical activity, educational level, history of hypertension, alcohol intake, total energy intake (where alcohol is excluded), fibre intake, monounsaturated fatty acid, saturated fatty acid, trans fatty acids, long-chain n-3 fatty acids, and linoleic acid intake.
Rhee et al. 2017	US	>45	F: 39,876	22	501	Dietary intake	FFQ	Healthy	0.74 %E 0.88 %E 0.99 %E 1.12 %E	1 0.86 (0.65–1.15) 0.86 (0.65–1.15) 0.83 (0.62–1.11)	randomized treatment, age, BMI, smoking, alcohol intake, physical activity, oral contraceptive use, hormone replacement therapy, multivitamin use, family history of myocardial infarction, and baseline history of

									1.36 %E Per 1g	0.88 (0.65-1.18) 0.94 (0.85-1.04)	hypertension, high cholesterol, and diabetes, intakes of dietary fiber, fruits and vegetables, trans fat, ratio of polyunsaturated to saturated fat, and sodium.
Erkkila et al. 2003	French	33-74	M/F: 398	5	18	Cholesteryl esters	GC	Unhealthy	<0.77 %FA 0.77-0.89 %FA >0.89 %FA Per 1-SD	1 1.12 (0.33-3.82) 0.44 (0.10-1.93) 0.97 (0.86-1.08)	Age, sex, diagnostic category, energy intake, serum cholesterol, serum triacylglycerol, diabetes (diagnosis or plasma glucose concentration>7 mmol/L), BMI, and education.
Harris et al. 2017	US	65–80	F: 6501	15.9	617	Erythrocytes	GC	Healthy	Per 1-SD	0.97 (0.84-1.12)	Age, race, HT assignment, BMI, highest education, smoking pack-year, physical activity, weekly alcohol intake, waist circumference, region, family history of cancer, family history of CVD, aspirin use, high cholesterol requiring pills (ever), and a history of hypertension, diabetes, cardiovascular disease and/or cancer.
Warensjö et al. 2008	Sweden	50	M: 1885	30.7	461	Cholesteryl esters	GC	Healthy	Per 1-SD	1.10 (1.00-1.21)	Total cholesterol, BMI, smoking, physical activity, and hypertension.
De Goede et al. 2013 (MORGEN)	Netherland	20–59	M/F: 444	12.5	222	Cholesteryl esters	GC	Healthy	Per 1-SD	0.93 (0.72-1.19)	Age, gender, smoking, BMI, education level, alcohol intake, systolic blood pressure, total cholesterol.
De Goede et al. 2013 (MP−CVDRF)	Netherland	20–65	M/F: 114	12.5	57	Cholesteryl esters	GC	Healthy	Per 1-SD	1.01 (0.61-1.70)	Age, gender, smoking, BMI, education level, alcohol intake, systolic blood pressure, total cholesterol.
Del Gobbo et al. 2016 (HPFS)	US	64	M: 1291	15	123	Total plasma	GC	Healthy	0.36 NR NR NR 0.88 Per 1-SD	1 NR NR NR 1.24 (0.46-3.32) 1.42 (0.37-5.46)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (KIHD)	Finland	52.4	M: 1837	27.8	168	Total plasma	GC	Healthy	0.47 NR NR NR 1.04 Per 1-SD	1 NR NR NR 0.50 (0.28-0.88) 0.75 (0.62-0.91)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (SCHS)	Singapore	66.2	M/F: 1555	14.4	292	Total plasma	GC	Healthy	0.18 NR NR NR 0.55 Per 1-SD	1 NR NR NR 0.72 (0.41-1.25) 0.70 (0.26-1.86)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.

Del Gobbo et al. 2016 (NHSI)	US	59.9	F: 603	16	57	Total plasma	GC	Healthy	0.16 NR NR NR 0.64 Per 1-SD	1 NR NR NR 0.21 (0.01-3.27) 0.75 (0.37-1.55)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (CHS)	US	74.4	M/F: 3491	21.6	516	Phospholipids	GC	Healthy	0.09 NR NR NR 0.22 Per 1-SD	1 NR NR NR 0.77 (0.56-1.06) 0.84 (0.76, 0.93)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (NSHDS II)	Sweden	53.6	M/F: 759	NR	80	Phospholipids	GC	Healthy	0.13 NR NR NR 0.31 Per 1-SD	1 NR NR NR 3.19 (0.63-16.24) 1.39 (0.87-2.22)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (PHS)	US	71	M: 832	NR	167	Phospholipids	GC	Healthy	0.12 NR NR NR 0.25 Per 1-SD	1 NR NR NR 2.51 (0.89-7.09) 1.21 (0.87-1.69)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (EPIC-Norfolk)	UK	62.7	M/F: 5105	16.1	507	Phospholipids	GC	Healthy	0.14 NR NR NR 0.34 Per 1-SD	1 NR NR NR 0.76 (0.55-1.06) 0.92 (0.83-1.02)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (MCCS)	Australia	56.1	M/F: 5278	16.2	391	Phospholipids	GC	Healthy	0.09 NR NR NR 0.27 Per 1-SD	1 NR NR NR 0.60 (0.37-0.97) 0.86 (0.72-1.02)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.

Del Gobbo et al. 2016 (MESA)	US	61.5	M/F: 2856	10.9	47	Phospholipids	GC	Healthy	0.10 NR NR NR 0.27 Per 1-SD	1 NR NR NR 0.23 (0.06-0.96) 0.85 (0.74-0.98)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (ULSAM 70)	Sweden	71	M: 763	20	74	Adipose tissue	GC	Healthy	0.76 NR NR NR 1.32 Per 1-SD	1 NR NR NR 1.08 (0.50-2.33) 1.03 (0.58-1.82)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (ULSAM 50)	Sweden	49.7	M: 1992	42	275	Cholesteryl esters	GC	Healthy	0.48 NR NR NR 0.87 Per 1-SD	1 NR NR NR 1.16 (0.83-1.62) 1.02 (0.92-1.13)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Iggman et al. 2016	Sweden	71	M: 853	14.8	251	Adipose tissue	GC	Healthy	Per 1-SD	0.99 (0.85-1.16)	Age, analysis occasion, smoking, body mass index, alcohol intake, physical activity, diabetes prevalence, systolic blood pressure, dyslipidemia, and hypertension treatment.
Kleber et al. 2016	Germany	62	M/F: 3259	9.9	614	Erythrocytes	GC	Unhealthy	0.10 %FA 11-13 %FA >13 %FA	1 0.89 (0.73-1.08) 0.95 (0.77-1.17)	Age, gender, LDL-C, HDL-C, logTG, BMI, hypertension, diabetes mellitus, smoking, alcohol intake, physical exercise and lipid lowering therapy.
Harris et al. 2018	US	66	2500	7.3	58	Erythrocytes	GC	Healthy	4.2 %FA 4.2-4.9 %FA 4.9-5.7 %FA 5.7-6.8 %FA >6.8 %FA	1 1.76 (0.62-4.93) 1.79 (0.59-5.44) 3.06 (1.09-8.60) 1.78 (0.62-5.06)	Age, sex, BMI, marital status, education, employment, health insurance status, regular aspirin use, alcohol consumption, smoking, METS, total to HDL cholesterol ratio, systolic BP, C-reactive protein, cholesterol medication use, history of diabetes.
Harris et al. 2021	12 countries	65	M/F: 38148	16	3963	Different tissues	GC	Healthy	NR	1 0.95 (0.87–1.04) 1.00 (0.91–1.10) 0.99 (0.91–1.09) 0.98 (0.89–1.08)	Age, sex, race, field center, body-mass index, education, occupation, marital status, smoking, physical activity, alcohol intake, prevalent diabetes, hypertension, and dyslipidemia, self-reported general health, and the sum of circulating n-6 PUFA

Abbreviation: ALA: α-linolenic acid- ES: effect size- CI: confidence interval- M: male- F: female- FFQ: food frequency questionnaire- BMI: body mass index- US: United States- RR: risk ratio- GC: gas chromatography- GLC: gas-liquid chromatography- NR: not-reported- CVD: cardiovascular disease

*Presented as mean or range

[†]Studies recruiting apparently healthy adults (without a prior diagnosis of cancer, CVD, or any other chronic diseases) were included in the healthy subgroup and studies that recruited individuals with at least one chronic disease were included in the unhealthy subgroup

Supplemental Table 4: Characteristics of included studies on the association between ALA intake (or tissue biomarkers) and CHD mortality in adults aged >18 years

Author	Country	Age*	Sample size	Follow up (years) ¥	Cases	Exposure	Exposure assessment	Health status†	Median/cutoff point	RR (95%CI)	Adjustment
Oomen et al. 2001	Netherlands	64–84	M: 667	10	49	Dietary intake	Cross-check dietary history	Healthy	<0.45 %E 0.45-0.58 %E >0.58 %E Per 1g	1 0.99 (0.43-2.28) 1.59 (0.62-4.08) 1.19 (0.69-2.05)	Age, BMI, ex-smoking, current smoking, alcohol intake, use of vitamin supplements, intake of saturated fatty acids, trans fatty acids, linoleic acid, eicosapentaenoic and docosahexaenoic acids, other cis unsaturated fatty acids, and protein (as a percentage of energy); and intake of energy, dietary cholesterol, fiber, vitamin E, vitamin C, and β-carotene
Zhuang et al. 2019	US	>20	M/F: 36,032	9	1299	Dietary intake	Food recall	Healthy	0-0.70 g/d 0.70-1.15 g/d 1.15-1.80 g/d >1.80 g/d Per 1g	1 1.10 (0.90, 1.33) 0.97 (0.77, 1.23) 0.98 (0.65, 1.46) 0.99 (0.86, 1.15)	Age, gender, race-ethnicity, BMI, education, marital status, physical activity, smoking, alcohol drinking status, history of hypertension, history of diabetes, family history of cardiovascular disease, intake of total energy, vegetables, fruits, red meat and saturated fat.
Sadowa et al. 2014	US and European countries	37-67	M/F: 237,714	4-10	1,751	Dietary intake	FFQ	Healthy	<1.09 g/d >1.09 g/d Per 1g	1 0.99 (0.85-1.17) 0.88 (0.68-1.14)	Age, smoking habits, BMI, physical activity, educational level, history of hypertension, alcohol intake, total energy intake (where alcohol is excluded), fibre intake, monounsaturated fatty acid, saturated fatty acid, trans fatty acids, long-chain n-3 fatty acids, and linoleic acid intake.
Sala-Vila et al. 2016	Spanish	55-80	M/F: 7202	5.9	104	Dietary intake	FFQ	Healthy	<0.7 %E >0.7 %E	1 0.75 (0.35-1.57)	Age, sex, intervention group, body mass index, smoking status, physical activity, total energy intake, history of diabetes, history of hyperlipidemia, history of hypertension, alcohol intake, and dietary factors (fiber, vegetables, fruits, and red meat).
Pietinen et al.1997	Finnish	50-69	M/F: 21,930	6.1	635	Dietary intake	FFQ	Healthy	0.9 g/d 1.2 g/d 1.5 g/d 1.9 g/d 2.5 g/d Per 1g	1 0.94 (0.74-1.20) 0.98(0.77-1.25) 1.03(0.81-1.32) 0.99 (0.76-1.28) 1.00 (0.91-1.10)	Age, treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber, education, and physical activity.
Dolecek et al. 1991	US	35-57	M: 12,866	8	232	Dietary intake	Food recall	Healthy	0.87 g/d 1.27 g/d 1.57 g/d 1.92 g/d 2.8 g/d Per 1g	1 0.92 (0.60-1.41) 0.55 (0.34-0.91) 0.93 (0.60-1.42) 0.65 (0.40-1.04) 0.87 (0.74-1.02)	Unadjusted

Bork et al. 2016	Denmark	50–64	M/F: 25,782	17	417	Dietary intake	FFQ	Healthy	<1.67 g/d 1.67-1.94 g/d 1.94-2.19 g/d 2.19-2.54 g/d >2.54 g/d Per 1g	1 1.01 (0.72-1.42) 1.25 (0.90-1.76) 1.22 (0.86-1.73) 0.71 (0.47-1.08) 1.01 (0.89-1.14)	BMI, waist circumference, smoking, physical activity, alcohol consumption, length of education and, for women, menopausal status and use of hormone replacement therapy, self-reported history of hypercholesterolemia and/or use of lipid-lowering medication; self-reported history of hypertension and/or use of antihypertensive medication, and self-reported history of diabetes mellitus, total energy-intake, dietary intake of fiber; glycaemic load, dietary intake of monounsaturated fatty acids, linoleic acid, saturated fatty acids, and marine long-chain omega-3 fatty acids
						Adipose tissue			0.31-0.73 %FA 0.73-0.82 %FA 0.82-0.90 %FA 0.90-1.00 %FA 1.00-1.81 %FA Per 1-SD	1 1.20 (0.76-1.91) 1.12 (0.69-1.82) 2.16 (1.29-3.62) 2.40 (1.35-4.28) 1.10 (1.02-1.18)	
Koh et al. 2013	China	45–74	M/F: 63,257	14	4780	Dietary intake	FFQ	Healthy	0.40 g/d 0.51 g/d 0.56 g/d 0.80 g/d Per 1g	1 1.01 (0.90–1.13) 0.90 (0.79–1.01) 0.82 (0.71–0.93) 0.82 (0.70-0.96)	Age, sex, dialect, year of interview, educational level, BMI, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, coronary heart disease, stroke, total energy, intakes of protein, dietary fibre, monounsaturated fat, saturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids.
Fretts et al. 2014	US	>65	M/F: 2583	12	429	Dietary intake	FFQ	Healthy	<1.67 g/d 1.67-1.94 g/d 1.94-2.19 g/d 2.19-2.54 g/d >2.54 g/d Per 1g	1 0·89 (0.62-1.29) 0.83 (0.57-1.21) 0.94 (0.65-1.36) 0.85 (0.58-1.26) 0.89 (0.69-1.15)	Age, sex, total energy intake, race, enrolment site, education, smoking status, diabetes, BMI, alcohol consumption and treated hypertension.
						Phospholipids	GC		0.31-0.73 %FA 0.73-0.82 %FA 0.82-0.90 %FA 0.90-1.00 %FA 1.00-1.81 %FA	1 1.06 (0.75-1.51) 1.16 (0.82-1.65) 1.02 (0.71-1.45) 1.03 (0.72-1.46)	
Ascherio et al. 1995	US	40-75	M: 43757	6	229	Dietary intake	FFQ	Healthy	0.80 g/d 0.90 g/d 1.10 g/d 1.20 g/d 1.50 g/d Per 1g	1 1.12 (0.72-1.72) 1.02 (0.66-1.58) 1.35 (0.90-2.03) 1.03 (0.66-1.59) 1.09 (0.83-1.42)	Age, BMI, smoking habits, alcohol consumption, physical activity, history of hypertension or high blood cholesterol, family history of myocardial infarction before age 60, profession, fibre and total energy intak.
Albert et al. 2016	US	30-55	F: 76763	18	206	Dietary intake	FFQ	Healthy	0.37 %E 0.45 %E 0.52 %E 0.60 %E 0.74 %E Per 1g	1 0.86 (0.57–1.29) 0.76 (0.50–1.16) 0.62 (0.39–0.98) 0.60 (0.37-0.96) 0.51 (0.29-0.89)	Age, total energy intake, smoking status, BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous to moderate activity, usual aspirin use, multivitamin use, vitamin E supplement use, history of hypertension, hypercholesterolemia, diabetes, family history of MI, and history of prior CVD, intakes of trans-

					641				0.37 %E 0.45 %E 0.52 %E 0.60 %E 0.74 %E Per 1g	1 1.13 (0.89–1.43) 0.92 (0.71–1.18) 0.96 (0.74–1.25) 1.01 (0.77-1.33) 0.97 (0.69-1.36)	unsaturated fat, ratio of polyunsaturated fat to saturated fat, and omega-3 fatty acids.
Erkkila et al. 2003	French	33-74	M/F: 398	5	18	Cholesteryl esters	GC	Unhealthy	<0.77 %FA 0.77-0.89 %FA >0.89 %FA Per 1-SD	1 1.12 (0.33-3.82) 0.44 (0.10-1.93) 0.97 (0.86-1.08)	Age, sex, diagnostic category, energy intake, serum cholesterol, serum triacylglycerol, diabetes (diagnosis or plasma glucose concentration>7 mmol/L), BMI, and education.
Del Gobbo et al. 2016 (HPFS)	US	64	M: 1291	15	123	Total plasma	GC	Healthy	0.36 NR NR NR 0.88 Per 1-SD	1 NR NR NR 1.24 (0.46-3.32) 1.42 (0.37-5.46)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (KIHD)	Finland	52.4	M: 1837	27.8	168	Total plasma	GC	Healthy	0.47 NR NR NR 1.04 Per 1-SD	1 NR NR NR 0.50 (0.28-0.88) 0.75 (0.62-0.91)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (SCHS)	Singapore	66.2	M/F: 1555	14.4	292	Total plasma	GC	Healthy	0.18 NR NR NR 0.55 Per 1-SD	1 NR NR NR 0.72 (0.41-1.25) 0.70 (0.26-1.86)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (NHSI)	US	59.9	F: 603	16	57	Total plasma	GC	Healthy	0.16 NR NR NR 0.64 Per 1-SD	1 NR NR NR 0.21 (0.01-3.27) 0.75 (0.37-1.55)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (CHS)	US	74.4	M/F: 3491	21.6	516	Phospholipids	GC	Healthy	0.09 NR NR NR 0.22 Per 1-SD	1 NR NR NR 0.77 (0.56-1.06) 0.84 (0.76-0.93)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (NSHDS II)	Sweden	53.6	M/F: 759	NR	80	Phospholipids	GC	Healthy	0.13 NR NR	1 NR NR	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular

									NR 0.31 Per 1-SD	NR 3.19 (0.63-16.24) 1.39 (0.87-2.22)	aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (PHS)	US	71	M: 832	NR	167	Phospholipids	GC	Healthy	0.12 NR NR NR 0.25 Per 1-SD	1 NR NR NR 2.51 (0.89-7.09) 1.21 (0.87-1.69)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (EPIC-Norfolk)	UK	62.7	M/F: 5105	16.1	507	Phospholipids	GC	Healthy	0.14 NR NR NR 0.34 Per 1-SD	1 NR NR NR 0.76 (0.55-1.06) 0.92 (0.83-1.02)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (MCCS)	Australia	56.1	M/F: 5278	16.2	391	Phospholipids	GC	Healthy	0.09 NR NR NR 0.27 Per 1-SD	1 NR NR NR 0.60 (0.37-0.97) 0.86 (0.72-1.02)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (MESA)	US	61.5	M/F: 2856	10.9	47	Phospholipids	GC	Healthy	0.10 NR NR NR 0.27 Per 1-SD	1 NR NR NR 0.23 (0.06-0.96) 0.85 (0.74-0.98)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (ULSAM 70)	Sweden	71	M: 763	20	74	Adipose tissue	GC	Healthy	0.76 NR NR NR 1.32 Per 1-SD	1 NR NR NR 1.08 (0.50-2.33) 1.03 (0.58-1.82)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
Del Gobbo et al. 2016 (ULSAM 50)	Sweden	49.7	M: 1992	42	275	Cholesteryl esters	GC	Healthy	0.48 NR NR NR 0.87 Per 1-SD	1 NR NR NR 1.16 (0.83-1.62) 1.02 (0.92-1.13)	Age, sex, race, clinical center, BMI, educational level, smoking, physical activity, alcohol intake, diabetes mellitus, treated hypertension, treated hypercholesterolemia, regular aspirin use, and biomarker concentrations of ω-6 PUFA linoleic acid (LA; 18:2ω-6), arachidonic acid (AA; 20:4ω-6), and total trans fatty acids.
De Goede et al. 2013 (MORGEN)	Netherland	20–59	M/F: 444	12.5	222	Cholesteryl esters	GC	Healthy	Per 1-SD	0.93 (0.72-1.19)	Age, gender, smoking, BMI, education level, alcohol intake, systolic blood pressure, total cholesterol.

De Goede et al. 2013 (MP−CVDRF)	Netherland	20–65	M/F: 114	12.5	57	Cholesteryl esters	GC	Healthy	Per 1-SD	1.01 (0.61-1.70)	Age, gender, smoking, BMI, education level, alcohol intake, systolic blood pressure, total cholesterol.

Abbreviation: ES: effect size- CI: confidence interval- M: male- F: female- FFQ: food frequency questionnaire- US: United States- UK: United Kingdom- Q: quintile or quartile- T: tertile- vs.: versus- HR: hazard ratio- OR: odds ratio- RR: risk ratio- GC: gas chromatography- NR: not-reported- CHD: coronary heart disease- ALA: α-linolenic acid

*Presented as mean or range.

†Studies recruiting apparently healthy adults (without a prior diagnosis of cancer, CVD, or any other chronic diseases) were included in the healthy subgroup and studies that recruited individuals with at least one chronic disease were included in the unhealthy subgroup

Supplemental Table 5: Characteristics of included studies on the association between ALA intake (or tissue biomarkers) and cancer mortality in adults aged >18 years

Author	Country	Age*	Sample size	Follow up (years) ¥	Cases	Exposure	Exposure assessment	Health status†	Median/cutoff point	RR (95%CI)	Adjustment
Zhuang et al. 2019	US	50-71	M/F: 521,120	16	45,783	Dietary intake	FFQ	Healthy	NR Per 1g	1 1.01 (0.98-1.04) 1.01 (0.97-1.05) 1.03 (0.99-1.08) 1.05 (1.00-1.10) 1.02 (0.98-1.05)	Age, gender, BMI, race, education, marital status, household income, smoking, alcohol drinking, physical activity, multi-vitamin use, aspirin use, history of hypertension, history of hypercholesterolemia, perceived health condition, history of heart disease, stroke, diabetes, and cancer at baseline, hormones use for women, intake of total energy, percentages of energy intake from protein, carbohydrates and remaining fatty acids.
Wang et al. 2016	US	40-75	M: 42884	26	4,192	Dietary intake	FFQ	Healthy	0.38 %E 0.45 %E 0.50 %E 0.56 %E 0.68 %E Per 1g	1 1.11 (1.00, 1.23) 1.10 (0.99, 1.22) 1.11 (0.99, 1.24) 1.15 (1.02-1.29) 1.09 (1.02-1.17)	Age, Caucasian, marital status, BMI, physical activity, smoking status, alcohol consumption, multivitamin use, vitamin E supplementation use, current aspirin use, family history of myocardial infarction, family history of diabetes, family history of cancer, history of hypertension, history of hypercholesterolemia, intakes of total energy, dietary cholesterol and percentage of energy intake from dietary protein, and remaining fatty acids, and menopausal status and hormone use in women
Wang et al. 2016	US	30-55	F: 83,349	32	7,919	Dietary intake	FFQ	Healthy	0.41 %E 0.48 %E 0.53%E 0.59%E 0.70%E Per 1g	1 1.05 (0.97-1.13) 1.12 (1.04-1.21) 1.11 (1.03-1.20) 1.10 (1.01-1.20) 1.10 (1.03-1.17)	Age, Caucasian, marital status, BMI, physical activity, smoking status, alcohol consumption, multivitamin use, vitamin E supplementation use, current aspirin use, family history of myocardial infarction, family history of diabetes, family history of cancer, history of hypertension, history of hypercholesterolemia, intakes of total energy, dietary cholesterol and percentage of energy intake from dietary protein, and remaining fatty acids, and menopausal status and hormone use in women
Jiao et al. 2019	US	30-75	M/F: 11264	11	451	Dietary intake	FFQ	Unhealthy	0.40 %E 0.49 %E 0.58 %E 0.76 %E Per 1g	1 1.00 (0.78, 1.29) 0.63 (0.46, 0.85) 0.75 (0.53-1.05) 0.80 (0.64-0.99)	Age, sex, survey period, ethnicity, BMI at diagnosis, physical activity, smoking status, smoking pack years, alcohol consumption, multivitamin use, current aspirin use, family history of myocardial infarction, family history of diabetes, history of hypercholesterolemia, history of hypertension, duration of diabetes, total energy intake, dietary cholesterol, and percentage of energy from dietary protein and remaining fatty acids.
Khankari et al. 2015	US	20-98	F: 1463	14.7	210	Dietary intake	FFQ	Unhealthy	<0.38 g/d 0.38-0.68 g/d 0.68-1.10 g/d >1.10 g/d Per 1g	1 1.06 (0.71-1.60) 1.17 (0.77-1.77) 1.03 (0.64-1.68) 1.09 (0.74-1.62)	Age and total energy intake
Epstein et al. 2012	Sweden	70.7	M: 525	20	222	Dietary intake	FFQ	Unhealthy	NR	1 1.18 (0.82-1.69) 0.83 (0.56-1.23)	Age at diagnosis, family history of prostate cancer, calendar year, alcohol intake, and BMI

									Per 1g	1.16 (0.79-1.69) 1.00 (0.86-1.17)	
Zhuang et al. 2019	US	>20	M/F: 36,032	9	1099	Dietary intake	Food recall	Healthy	0-0.70 g/d 0.70-1.15 g/d 1.15-1.80 g/d >1.80 g/d Per 1g	1 0.92 (0.73, 1.15) 0.96 (0.74, 1.25) 0.89 (0.66-1.19) 0.95 (0.84, 1.09)	Age, gender, race-ethnicity, BMI, education, marital status, physical activity, smoking, alcohol drinking status, history of hypertension, history of diabetes, family history of cardiovascular disease, intake of total energy, vegetables, fruits, red meat and saturated fat.
Richman et al. 2013	US	40-75	M: 4577	8.4	315	Dietary intake	FFQ	Unhealthy	0.36 %E 0.44 %E 0.50 %E 0.58 %E 0.74 %E	1 1.03 (0.71-1.48) 1.15 (0.80-1.67) 0.93 (0.61-1.41) 0.97 (0.61-1.55)	Age at diagnosis, energy, time since diagnosis, treatment, Gleason sum, clinical stage, diagnostic PSA, number of PSA screening tests prior to diagnosis, body mass index, smoking, vigorous activity, and intake of calcium, alcohol, protein, saturated fat, monounsaturated fat, trans fat, linoleic acid, long-chain omega-3 fatty acids and pre-diagnostic intake of polyunsaturated fat based on the 1986 FFQ.
Dolecek et al. 1991	US	35-57	M: 12,866	8	132	Dietary intake	Food recall	Healthy	0.87 g/d 1.27 g/d 1.57 g/d 1.92 g/d 2.8 g/d Per 1g	1 1.36 (0.81-2.26) 0.87 (0.49-1.55) 1.16 (0.68-1.96) 0.87 (0.49-1.55) 0.96 (0.79-1.16)	Unadjusted
Harris et al. 2017	US	65–80	F: 6501	15.9	462	Erythrocytes	GC	Healthy	Per 1-SD	0.98 (0.85-1.12)	Age, race, HT assignment, BMI, highest education, smoking pack-year, physical activity, weekly alcohol intake, waist circumference, region, family history of cancer, family history of CVD, aspirin use, high cholesterol requiring pills (ever), and a history of hypertension, diabetes, cardiovascular disease and/or cancer.
Simon et al. 1998	US	35-57	M: 323	6.9	108	Cholesteryl esters	GLC	Healthy	Per 1-SD	1.01 (0.79-1.29)	Age, smoking, alcohol intake, plasma cholesterol level, and diastolic blood pressure
Pelser et al. 2013	US	50–71	M: 288,268	9	725	Dietary intake	FFQ	Healthy	0.41 %E 0.52 %E 0.60 %E 0.70 %E 0.88 %E	1 1.09 (0.86–1.38) 0.91 (0.71–1.16) 1.00 (0.78–1.27) 1.13 (0.89-1.43)	Age, race, family history of prostate cancer, education, marital status, PSA testingin the past 3 years, physical activity, smoking, self-reported diabetes, BMI, total energy intake, alcohol and intake of tomatoes.
Harris et al. 2018	US	66	M/F: 2500	7.3	146	Erythrocytes	GC	Healthy	4.2 %FA 4.2-4.9 %FA 4.9-5.7 %FA 5.7-6.8 %FA >6.8 %FA	1 0.71 (0.41-1.21) 1.05 (0.65-1.71) 0.54 (0.28-1.03) 0.91 (0.54, 1.53)	Age, sex, BMI, marital status, education, employment, health insurance status, regular aspirin use, alcohol consumption, smoking, METS, total to HDL cholesterol ratio, systolic BP, C-reactive protein, cholesterol medication use, history of diabetes.
Perez-Cornago et al. 2020	European countries		M: 142,239	13.6	936	Dietary intake	FFQ and diet histories	Healthy	Per 1-SD	0.99 (0.90–1.09)	Age, educational level, smoking status, marital status, diabetes, physical activity, height, body mass index, and total energy intake
Harris et al. 2021	12 countries	65	M/F: 38148	16	3979	Different tissues	GC	Healthy	NR	1 0.98 (0.89–1.08) 0.96 (0.87–1.05) 0.99 (0.90–1.09)	Age, sex, race, field center, body-mass index, education, occupation, marital status, smoking, physical activity, alcohol intake, prevalent diabetes, hypertension, and dyslipidemia, self-reported general health, and the sum of circulating n-6 PUFA

										0.88 (0.80–0.98)	

Abbreviation: ES: effect size- CI: confidence interval- M: male- F: female- FFQ: food frequency questionnaire- BMI: body mass index- US: United States- RR: risk ratio- GC: gas chromatography- GLC: gas-liquid chromatography- NR: not-reported- ALA: α-linolenic acid

*Presented as mean or range

†Studies recruiting apparently healthy adults (without a prior diagnosis of cancer, CVD, or any other chronic diseases) were included in the healthy subgroup and studies that recruited individuals with at least one chronic disease were included in the unhealthy subgroup

Supplemental Table 6: Extracted and calculated data for the nonlinear dose-response analysis of dietary ALA and all-cause mortality

Author	Category	Participations	Deaths	Median of g/d from ALA intake	RR	LL	UL
Zhuang et al. 2019	1	130280	25,560	0.77	1	1	1
	2	130280	25,042	0.98	1.00	0.98	1.02
	3	130280	25,761	1.15	1.02	1	1.05
	4	130280	26,113	1.35	1.04	1.01	1.06
Wang et al. 2016	1	16,669	4274	0.7	1	1	1
	2	16670	3800	0.84	1.00	0.95	1.04
	3	16670	3831	0.93	1.05	1.00	1.10
	4	16670	3839	1.03	1.02	0.97	1.07
	5	16670	4570	1.2	0.98	0.93	1.04
Wang et al. 2016	1	8,576	2398	0.83	1	1	1
	2	8577	2431	0.99	1.00	0.94	1.06
	3	8577	2544	1.15	1.02	0.96	1.08
	4	8577	2700	1.24	1.04	0.98	1.10
	5	8577	2917	1.49	1.01	0.94	1.08
Jiao et al. 2019	1	2834	827	0.69	1	1	1
	2	2814	680	0.88	0.98	0.87	1.09
	3	2752	510	1.04	0.80	0.70	0.91
	4	2810	485	1.35	0.88	0.76	1.02
Khankari et al. 2015	1	365	114	0.38	1	1	1
	2	366	129	0.53	1.18	0.91	1.52
	3	366	121	0.89	1.18	0.90	1.55
	4	366	121	1.1	1.14	0.83	1.57
Fretts et al. 2014	1	516	328	0.94	1	1	1
	2	516	328	1.04	0.98	0.84	1.15
	3	517	301	1.12	0.88	0.75	1.03
	4	517	298	1.15	0.86	0.73	1.02
	5	517	262	1.23	0.73	0.61	0.88
Zhuang et al. 2019	1	9008	1784	0.35	1	1	1
	2	9008	1258	0.92	0.99	0.89	1.10
	3	9008	1082	1.47	0.90	0.78	1.04
	4	9008	702	2.12	0.84	0.70	1.00
Zhuang et al. 2019	1	3529	253	0.33	1	1	1
	2	3529	205	0.83	0.93	0.77	1.13
	3	3529	229	1.26	0.93	0.76	1.13
	4	3530	320	1.8	1.23	1.01	1.50
Fortes et al. 2000	1	40	21	0.9	1	1	1
	2	80	57	1.3	0.74	0.37	1.50

	3	40	29	1.7	0.51	0.23	1.13
Dolecek et al. 1991	1	1251	105	0.87	1	1	1
	2	1253	99	1.27	0.94	0.72	1.22
	3	1251	73	1.57	0.68	0.52	0.92
	4	1251	91	1.92	0.86	0.66	1.13
	5	1252	71	2.8	0.67	0.50	0.90
Gopinath et al. 2011	1	837	80	0.27	1	1	1
	2	838	78	0.64	0.95	0.68	1.34
	3	839	56	1.87	0.74	0.51	1.08

Abbreviations: RR: risk ratio- LL: lower limit- UL: upper limit- ALA: α-linolenic acid

Supplemental Table 7: Extracted and calculated data for the nonlinear dose-response analysis of dietary ALA and CVD mortality

Author	Category	Participations	Deaths	Median of g/d from ALA intake	RR	LL	UL
Wang et al. 2016	1	16,669	936	0.7	1	1	1
	2	16670	741	0.84	0.89	0.81	0.99
	3	16670	744	0.93	0.96	0.86	1.06
	4	16670	730	1.03	0.92	0.82	1.03
	5	16670	849	1.2	0.90	0.80	1.02
Wang et al. 2016	1	8,576	727	0.83	1	1	1
	2	8577	740	0.99	0.99	0.89	1.11
	3	8577	754	1.15	0.99	0.89	1.10
	4	8577	788	1.24	1.00	0.89	1.12
	5	8577	869	1.49	0.97	0.86	1.1
Jiao et al. 2019	1	2834	195	0.69	1	1	1
	2	2814	168	0.88	1.06	0.85	1.32
	3	2752	142	1.04	0.98	0.76	1.26
	4	2810	141	1.35	1.13	0.85	1.51
Fretts et al. 2014	1	516	89	0.94	1	1	1
	2	516	83	1.04	0.93	0.68	1.25
	3	517	76	1.12	0.83	0.61	1.14
	4	517	92	1.15	0.97	0.72	1.31
	5	517	89	1.23	0.96	0.71	1.32
Pietinen et al.1997	1	4,386	149	0.9	1	1	1
	2	4,386	127	1.2	0.94	0.74	1.20
	3	4,386	124	1.5	0.98	0.77	1.25
	4	4,386	122	1.9	1.03	0.81	1.32
	5	4,386	113	2.5	0.99	0.76	1.28
Oomen et al. 2001	1	222	12	0.96	1	1	1
	2	223	15	1.27	0.99	0.43	2.28
	3	222	22	1.61	1.59	0.62	4.08
Bork et al. 2016	1	5,156	70	1.53	1	1	1
	2	5,156	78	1.8	1.01	0.72	1.42
	3	5,156	100	2.06	1.25	0.90	1.76
	4	5,157	101	2.36	1.22	0.86	1.73
	5	5,157	68	2.71	0.71	0.47	1.08
Koh et al. 2013	1	15,814	1342	0.4	1	1	1
	2	15,814	1267	0.51	0.94	0.86	1.02
	3	15,814	1156	0.56	0.87	0.79	0.95
	4	15,814	1015	0.8	0.81	0.73	0.90
Dolecek et al. 1991	1	1251	58	0.87	1	1	1
	2	1253	52	1.27	0.89	0.62	1.29
	3	1251	38	1.57	0.65	0.43	0.97

	4	1251	49	1.92	0.84	0.58	1.22
	5	1252	35	2.8	0.60	0.39	0.91
Rhee et al. 2017	1	7,426	100	1.26	1	1	1
	2	7,836	89	1.5	0.86	0.65	1.15
	3	7,856	96	1.87	0.86	0.65	1.15
	4	7,470	99	2.24	0.83	0.62	1.11
	5	7,804	117	2.9	0.88	0.65	1.18
Zhuang et al. 2019	1	9008	325	0.35	1	1	1
	2	9008	325	0.92	1.07	0.88	1.30
	3	9008	325	1.47	0.97	0.78	1.21
	4	9008	324	2.12	0.87	0.63	1.22
Laaksonen et al. 2005	1	517	26	1.1	1	1	1
	2	517	26	1.5	1.16	0.66	2.02
	3	517	26	2	0.63	0.33	1.21

Abbreviations: RR: risk ratio- LL: lower limit- UL: upper limit- ALA: α-linolenic acid- CVD: cardiovascular disease

Supplemental Table 8: Extracted and calculated data for the nonlinear dose-response analysis of dietary ALA and CHD mortality

Author	Category	Participations	Deaths	Median of g/d from ALA intake	RR	LL	UL
Pietinen et al.1997	1	4,386	149	0.9	1	1	1
	2	4,386	127	1.2	0.94	0.74	1.20
	3	4,386	124	1.5	0.98	0.77	1.25
	4	4,386	122	1.9	1.03	0.81	1.32
	5	4,386	113	2.5	0.99	0.76	1.28
Oomen et al. 2001	1	222	12	0.96	1	1	1
	2	223	15	1.27	0.99	0.43	2.28
	3	222	22	1.61	1.59	0.62	4.08
Bork et al. 2016	1	5,156	70	1.53	1	1	1
	2	5,156	78	1.8	1.01	0.72	1.42
	3	5,156	100	2.06	1.25	0.90	1.76
	4	5,157	101	2.36	1.22	0.86	1.73
	5	5,157	68	2.71	0.71	0.47	1.08
Dolecek et al. 1991	1	1251	43	0.87	1	1	1
	2	1253	40	1.27	0.92	0.60	1.41
	3	1251	24	1.57	0.55	0.34	0.91
	4	1251	40	1.92	0.93	0.6	1.42
	5	1252	28	2.8	0.65	0.40	1.04
Ascherio et al. 1995	1	8,751	40	0.8	1	1	1
	2	8,751	44	0.9	1.12	0.72	1.72
	3	8,751	42	1.1	1.02	0.66	1.58
	4	8,751	59	1.2	1.35	0.90	2.03
	5	8,751	44	1.5	1.03	0.66	1.59
Albert et al. 2016	1	15,352	54	0.71	1	1	1
	2	15,352	44	0.86	0.86	0.57	1.29
	3	15,352	40	0.98	0.76	0.50	1.16
	4	15,352	32	1.12	0.62	0.39	0.98
	5	15,352	36	1.36	0.6	0.37	0.96
Albert et al. 2016	1	15,352	146	0.71	1	1	1
	2	15,352	144	0.86	1.13	0.89	1.43
	3	15,352	116	0.98	0.92	0.71	1.18
	4	15,352	112	1.12	0.96	0.74	1.25
	5	15,352	123	1.36	1.01	0.77	1.33
Fretts et al. 2014	1	516	0.61	0.94	1	1	1
	2	516	55	1.04	0.89	0.62	1.29
	3	517	50	1.12	0.83	0.57	1.21
	4	517	62	1.15	0.94	0.65	1.36
	5	517	52	1.23	0.85	0.58	1.26
Koh et al. 2013	1	15,814	730	0.4	1	1	1

	2	15,814	733	0.51	1.01	0.90	1.13
	3	15,814	651	0.56	0.90	0.79	1.01
	4	15,814	583	0.8	0.82	0.71	0.93
Zhuang et al. 2019	1	9008	244	0.35	1	1	1
	2	9008	245	0.92	1.10	0.90	1.33
	3	9008	245	1.47	0.97	0.77	1.23
	4	9008	244	2.12	0.98	0.65	1.46

Abbreviations: RR: risk ratio- LL: lower limit- UL: upper limit- ALA: α-linolenic acid- CHD: coronary heart disease

Supplemental Table 9: Extracted and calculated data for the nonlinear dose-response analysis of dietary ALA and cancer mortality

Author	Category	Participations	Deaths	Median of g/d from ALA intake	RR	LL	UL
Jiao et al. 2019	1	2834	149	0.69	1	1	1
	2	2814	130	0.88	1.00	0.78	1.29
	3	2752	79	1.04	0.63	0.46	0.85
	4	2810	93	1.35	0.75	0.53	1.05
Wang et al. 2016	1	16,669	1558	0.7	1	1	1
	2	16670	1517	0.84	1.05	0.97	1.13
	3	16670	1559	0.93	1.12	1.04	1.21
	4	16670	1556	1.03	1.11	1.03	1.20
	5	16670	1729	1.2	1.1	1.01	1.20
Wang et al. 2016	1	8,576	723	0.83	1	1	1
	2	8577	821	0.99	1.11	1.00	1.23
	3	8577	830	1.15	1.10	0.99	1.22
	4	8577	864	1.24	1.11	0.99	1.24
	5	8577	954	1.49	1.15	1.02	1.29
Khankari et al. 2015	1	365	46	0.38	1	1	1
	2	366	50	0.53	1.06	0.71	1.60
	3	366	57	0.89	1.17	0.77	1.77
	4	366	57	1.1	1.03	0.64	1.68
Dolecek et al. 1991	1	1251	25	0.87	1	1	1
	2	1253	34	1.27	1.36	0.81	2.26
	3	1251	22	1.57	0.87	0.49	1.55
	4	1251	29	1.92	1.16	0.68	1.96
	5	1252	22	2.8	0.87	0.49	1.55
Pelser et al. 2013	1	57,653	136	0.82	1	1	1
	2	57,653	152	1.04	1.09	0.86	1.38
	3	57,653	129	1.2	0.91	0.71	1.16
	4	57,653	144	1.4	1.00	0.78	1.27
	5	57,653	164	1.76	1.13	0.89	1.43
Zhuang et al. 2019	1	9008	275	0.35	1	1	1
	2	9008	275	0.92	0.92	0.73	1.15
	3	9008	275	1.47	0.96	0.74	1.25
	4	9008	275	2.12	0.89	0.66	1.19

Abbreviations: RR: risk ratio- LL: lower limit- UL: upper limit- ALA: α-linolenic acid

Online Supporting Material

Supplemental Table 10: Results of risk of bias assessment based on the ROBINS-E tool

Author	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of exposures	Bias due to departures from intended exposures	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall judgment
Lelli et al. 2019	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Zhuang et al. 2019	Low	Low	Low	Low	Low	Low	Low	Low
Wang et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Jiao et al. 2019	Low	Low	Low	Low	Low	Low	Low	Low
Khankari et al. 2015	Serious	Low	Low	Low	Low	Low	Low	Serious
Fretts et al. 2014	Low	Low	Low	Low	Low	Low	Low	Low
Zhuang et al. 2019	Low	Low	Moderate	Low	Low	Low	Low	Moderate
Sala-Vila et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Fortes et al. 2000	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Richman et al. 2013	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Dolecek et al. 1991	Critical	Low	Moderate	Low	Low	Low	Low	Critical
Gopinath et al. 2011	Low	Low	Low	Low	Low	Low	Low	Low
Marklund et al. 2019	Low	Low	Low	Low	Low	Low	Low	Low
Lindberg et al. 2008	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Harris et al. 2017	Low	Low	Low	Low	Low	Low	Low	Low
Warensjö et al. 2008	Low	Low	Low	Low	Low	Low	Low	Low
Miura et al. 2016	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Rhee et al. 2017	Low	Low	Low	Low	Low	Low	Low	Low
Pottala et al. 2010	Critical	Moderate	Low	Low	Low	Low	Low	Critical
Laaksonen et al. 2005	Low	Low	Low	Low	Low	Low	Low	Low
Oomen et al. 2001	Low	Moderate	Low	Low	Low	Low	Low	Low
Pietinen et al.1997	Low	Low	Low	Low	Low	Low	Low	Low
Bork et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Koh et al. 2013	Low	Low	Low	Low	Low	Low	Low	Low
Sadowa et al. 2014	Low	Low	Low	Low	Low	Low	Low	Low
Ascherio et al. 1995	Low	Low	Low	Low	Low	Low	Low	Low
Albert et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Erkkila et al. 2003	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Epstein et al. 2012	Low	Moderate	Low	Low	Low	Low	Low	Moderate
De Goede et al. 2013	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Lázaro et al. 2020	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Harris et al. 2013	Serious	Low	Low	Low	Low	Low	Low	Serious
Iggman et al. 2016	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Del Gobbo et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Del Gobbo et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Del Gobbo et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Del Gobbo et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Del Gobbo et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Del Gobbo et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Del Gobbo et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Del Gobbo et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Del Gobbo et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Del Gobbo et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low

Del Gobbo et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Jayanama et al. 2020	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Simon et al. 1998	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Pelser et al. 2013	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Harris et al. 2018	Low	Low	Low	Low	Low	Low	Low	Low
Kleber et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Perez-Cornago et al. 2020	Low	Low	Moderate	Low	Low	Low	Low	Moderate
Harris et al. 2021	Low	Low	Low	Low	Low	Low	Low	Low

Abbreviation: ROBINS-E: risk of bias in non-randomized studies of exposures

The risk of bias in non-randomized studies of exposures (ROBINS-E) tool comprises 7 domains through which bias might be introduced. The questions of these domains include: (1) bias due to confounding, (2) bias in selection of participants into study, (3) bias in the classification of exposures, (4) bias due to departure from intended exposures, (5) bias due to missing data, (6) bias in the measurement of outcomes, and (7) bias in the selection of reported results. Studies were categorized as low risk, moderate risk, serious risk, and critical risk of bias under each domain.

Supplemental Table 11: Summary risk estimates for the association between ALA and risk of mortality in adults aged ≥18 years[1]

	#RR[2]	Pooled RR (95% CI)	Baseline Risk per 10,000 Person-years[3]	AR per 10,000 person-years (95% CI)	I^2 (%)[4]	P-heterogeneity[5]
ALA and all-cause mortality						
The highest vs. lowest comparison						
Dietary ALA intake						
Random	15	0.90 (0.83-0.97)	1130	-113 (-192 to -34)	77.8	<0.001
Fixed	15	1.01 (0.99-1.03)	1130	11 (-11 to 34)	77.8	<0.001
Tissue ALA levels						
Random	15	0.95 (0.90-0.99)	1130	-57 (-113 to -11)	8.2	0.36
Fixed	15	0.94 (0.91-0.98)	1130	-68 (-102 to -23)	8.2	0.36
Linear dose-response association						
Dietary ALA intake						
Random	12	0.95 (0.91-0.99)	1130	-57 (-102 to -11)	76.2	<0.001
Fixed	12	0.99 (0.98-1.01)	1130	-11 (-23 to 11)	76.2	<0.001
Tissue ALA levels						
Random	11	0.97 (0.94-1.01)	1130	-34 (-68 to 11)	29.5	0.16
Fixed	11	0.98 (0.96-1.01)	1130	-23 (-45 to 11)	29.5	0.16
ALA and CVD mortality						
The highest vs. lowest comparison						
Dietary ALA intake						
Random	16	0.92 (0.86-0.99)	410	-33 (-57 to -4)	48.2	0.01
Fixed	16	0.96 (0.93-0.99)	410	-16 (-29 to -4)	48.2	0.01
Tissue ALA levels						
Random	21	0.98 (0.86-1.11)	410	-8 (-57 to 45)	45.6	0.01
Fixed	21	0.99 (0.92-1.06)	410	-4 (-33 to 25)	45.6	0.01
Linear dose-response association						
Dietary ALA intake						
Random	14	0.95 (0.91-0.98)	410	-21 (-37 to -8)	30.7	0.13
Fixed	14	0.96 (0.93-0.98)	410	-16 (-29 to -8)	30.7	0.13
Tissue ALA levels						
Random	17	0.97 (0.91-1.03)	410	-12 (-37 to 12)	54.2	0.004
Fixed	17	0.96 (0.90-1.03)	410	-16 (-41 to 12)	54.2	0.004
ALA and CHD mortality						
The highest vs. lowest comparison						
Dietary ALA intake						
Random	9	0.89 (0.81-0.97)	210	-23 (-40 to -6)	5.6	0.38
Fixed	9	0.88 (0.81-0.96)	210	-25 (-40 to -8)	5.6	0.38
Tissue ALA levels						
Random	16	0.90 (0.70-1.15)	210	-21 (-63 to 32)	57	0.003
Fixed	16	0.88 (0.76-1.01)	210	-25 (-50 to 2)	57	0.003
Linear dose-response association						
Dietary ALA intake						
Random	10	0.95 (0.90-1.01)	210	-11 (-21 to 2)	10.8	0.34
Fixed	10	0.95 (0.90-1.00)	210	-11 (-21 to 0)	10.8	0.34
Tissue ALA levels						
Random	16	0.94 (0.87-1.01)	210	-13 (-27 to 2)	61.1	0.001
Fixed	16	0.96 (0.93-1.00)	210	-8 (-15 to 0)	61.1	0.001
ALA and cancer mortality						

The highest vs. lowest comparison						
Dietary ALA intake						
Random	10	1.06 (1.02-1.11)	1050	63 (21 to 116)	3.8	0.40
Fixed	10	1.06 (1.02-1.10)	1050	63 (21 to 105)	3.8	0.40
Tissue ALA levels						
Random	4	0.93 (0.86-1.01)	1050	-74 (-147 to 11)	0	0.39
Fixed	4	0.93 (0.86-1.01)	1050	-74 (-147 to 11)	0	0.39
Linear dose-response association						
Dietary ALA intake						
Random	8	1.03 (0.98-1.08)	1050	32 (-21 to 84)	51	0.04
Fixed	8	1.04 (1.01-1.06)	1050	42 (11 to 63)	51	0.04
Tissue ALA levels						
Random	2	0.99 (0.88-1.11)	1050	-11 (-126 to 116)	0	0.83
Fixed	2	0.99 (0.88-1.11)	1050	-11 (-126 to 116)	0	0.83

[1]Abbreviation: ALA, α-linolenic acid; BMI, body mass index; CI, confidence interval; RR, relative risk; CVD, cardiovascular disease; AR, absolute risk

[2]Number of effect sizes

[3]Baseline risks for all-cause, CVD, and CHD mortality were obtained from the Emerging Risk Factors Collaboration that contained data from 102 international cohorts. For cancer mortality, baseline risk was based on the GLOBOCAN that described cancer incidence and mortality from 20 large areas of the world

[4]Inconsistency- the percentage of variation across studies due to heterogeneity

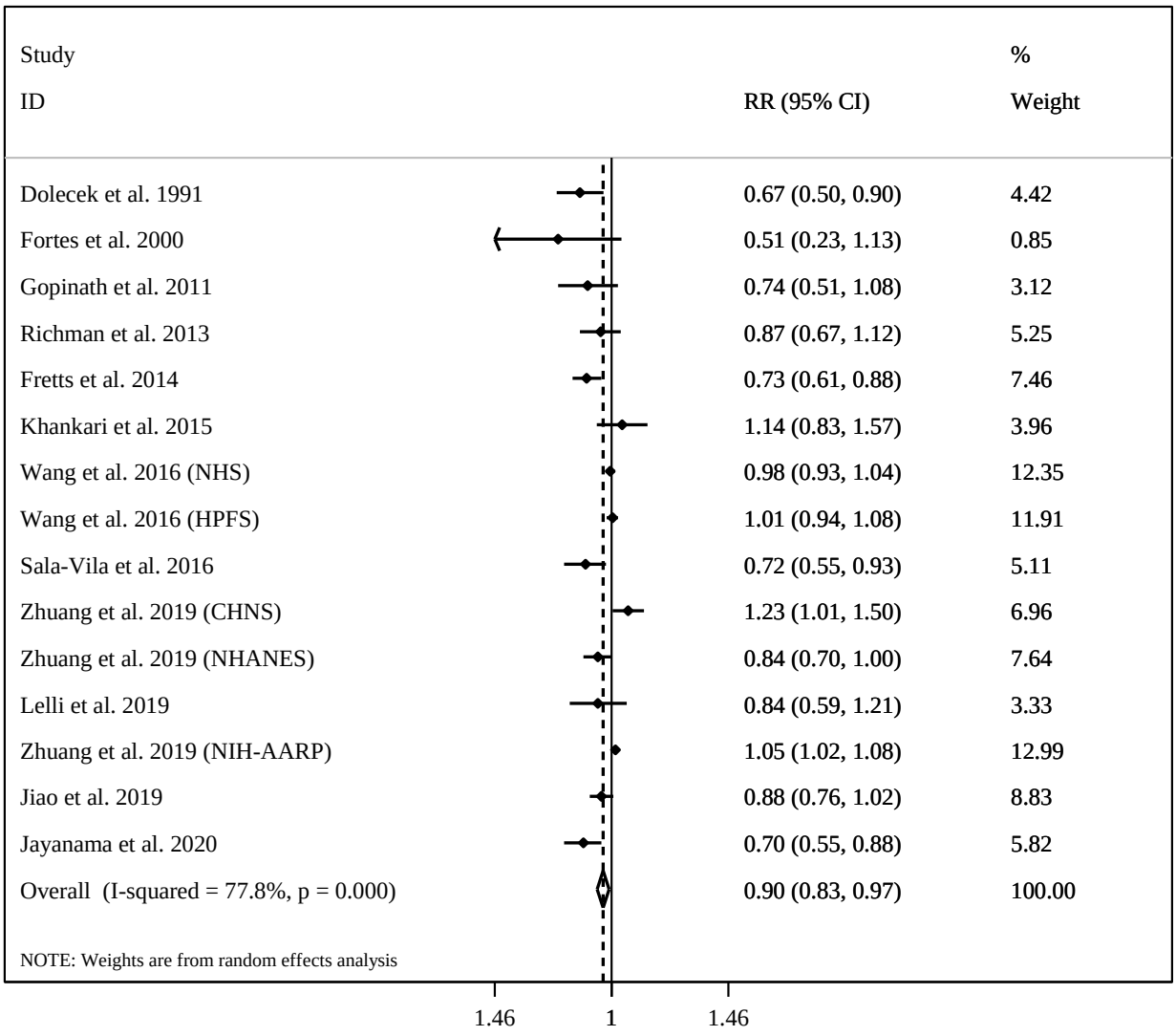
[5]Obtained from the Q-test

Supplemental Table 12: Relative risks and 95% CIs of mortality in different doses of ALA based on the nonlinear dose-response analysis

ALA (g/d)	All-cause mortality			CVD mortality	CHD mortality	Cancer mortality
	Total	Male	Female			
0.27-0.40	1.00 (0.27 g/d)	1.00 (0.35)	1.00 (0.35)	1.00 (0.35 g/d)	1.00 (0.40 g/d)	1.00 (0.35 g/d)
0.50	0.99 (0.97-1.02)	0.98 (0.94-1.03)	1.01 (0.99-1.04)	0.98 (0.95-1.01)	0.93 (0.88-0.98)	1.01 (0.96-1.07)
0.75	0.98 (0.92-1.04)	0.95 (0.84-1.08)	1.03 (0.96-1.11)	0.94 (0.87-1.02)	0.89 (0.80-1.00)	1.03 (0.89-1.20)
1.00	0.96 (0.88-1.05)	0.92 (0.75-1.13)	1.04 (0.95-1.14)	0.91 (0.81-1.03)	0.82 (0.68-0.99)	1.05 (0.83-1.32)
1.25	0.94 (0.85-1.03)	0.90 (0.69-1.18)	1.02 (0.94-1.11)	0.88 (0.75-1.04)	0.78 (0.61-0.99)	1.05 (0.81-1.36)
1.50	0.91 (0.80-1.02)	0.90 (0.66-1.23)	1.00 (0.92-1.09)	0.86 (0.72-1.03)	0.75 (0.57-0.98)	1.05 (0.82-1.35)
1.75	0.87 (0.74-1.03)	0.91 (0.63-1.30)	0.98 (0.88-1.09)	0.84 (0.70-1.02)	0.74 (0.56-0.97)	1.05 (0.83-1.33)
2.00	0.84 (0.66-1.06)	0.91 (0.60-1.39)	0.96 (0.84-1.10)	0.83 (0.68-1.00)	0.73 (0.55-0.97)	1.04 (0.83-1.32)
2.25	0.80 (0.59-1.09)	0.92 (0.56-1.49)	0.94 (0.79-1.12)	0.81 (0.67-0.99)	0.73 (0.54-0.98)	1.04 (0.82-1.31)
2.50	0.78 (0.53-1.13)	0.92 (0.53-1.61)	0.92 (0.75-1.14)	0.80 (0.65-0.98)	0.72 (0.53-0.99)	1.03 (0.81-1.32)
2.75	0.74 (0.48-1.16)	0.93 (0.50-1.74)	0.90 (0.70-1.16)	0.79 (0.64-0.98)	0.72 (0.52-1.01)	1.03 (0.79-1.34)
3.00	0.71 (0.42-1.20)	-	-	0.77 (0.62-0.98)	0.72 (0.50-1.03)	1.03 (0.77-1.37)
$P_{nonlinearity}$	0.58	0.44	0.31	0.56	0.13	0.72

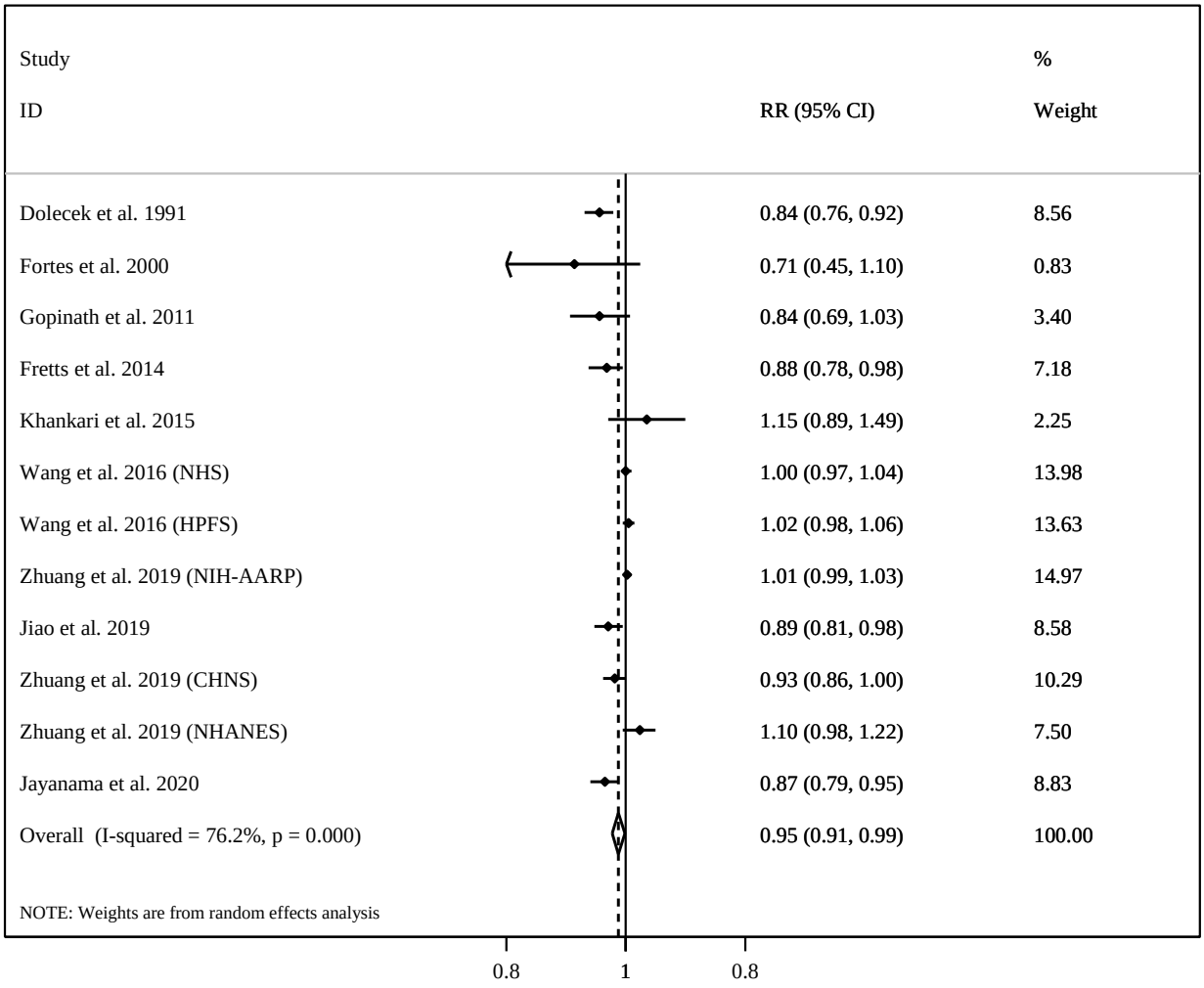
Abbreviations: CHD: coronary heart disease- CVD: cardiovascular disease- ALA: α-linolenic acid

Online Supporting Material
Supplemental Figure 1



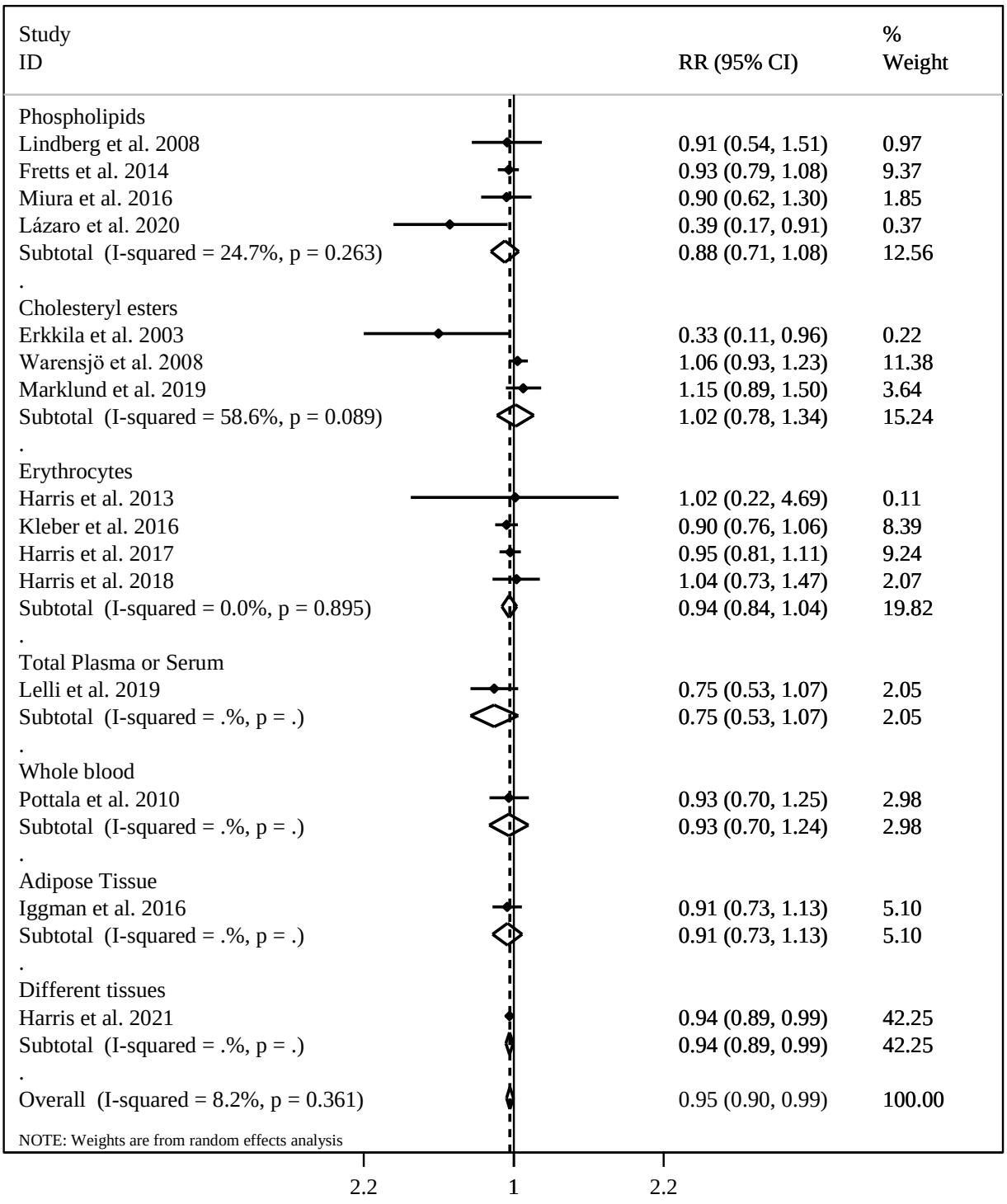
Forest plot for the association between dietary ALA intake and all-cause mortality by considering the highest and lowest intakes of ALA

Online Supporting Material
Supplemental Figure 2



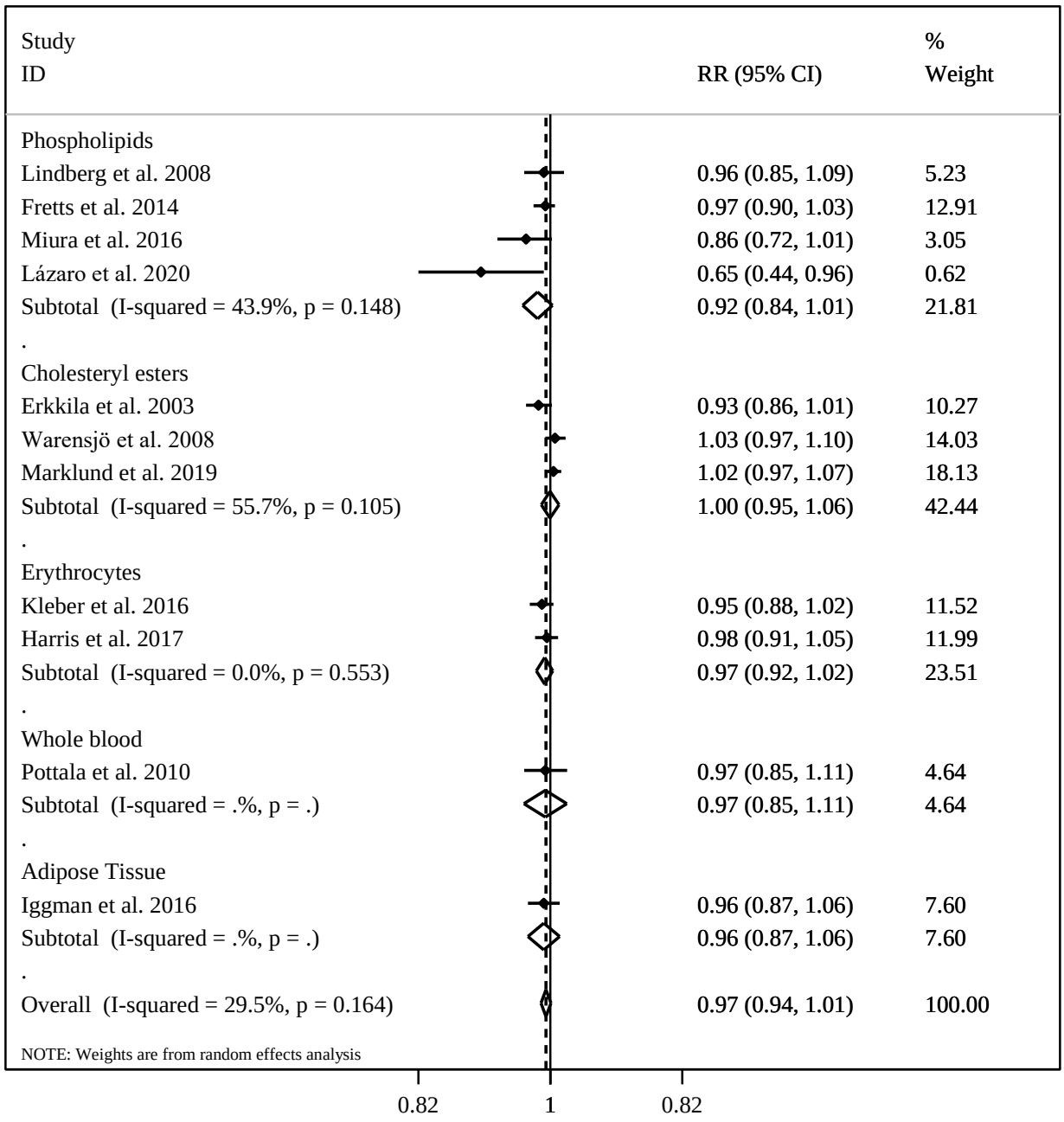
Forest plot for the association between dietary ALA intake and all-cause mortality based on a 1-g/d increase in dietary ALA intake

Online Supporting Material
Supplemental Figure 3



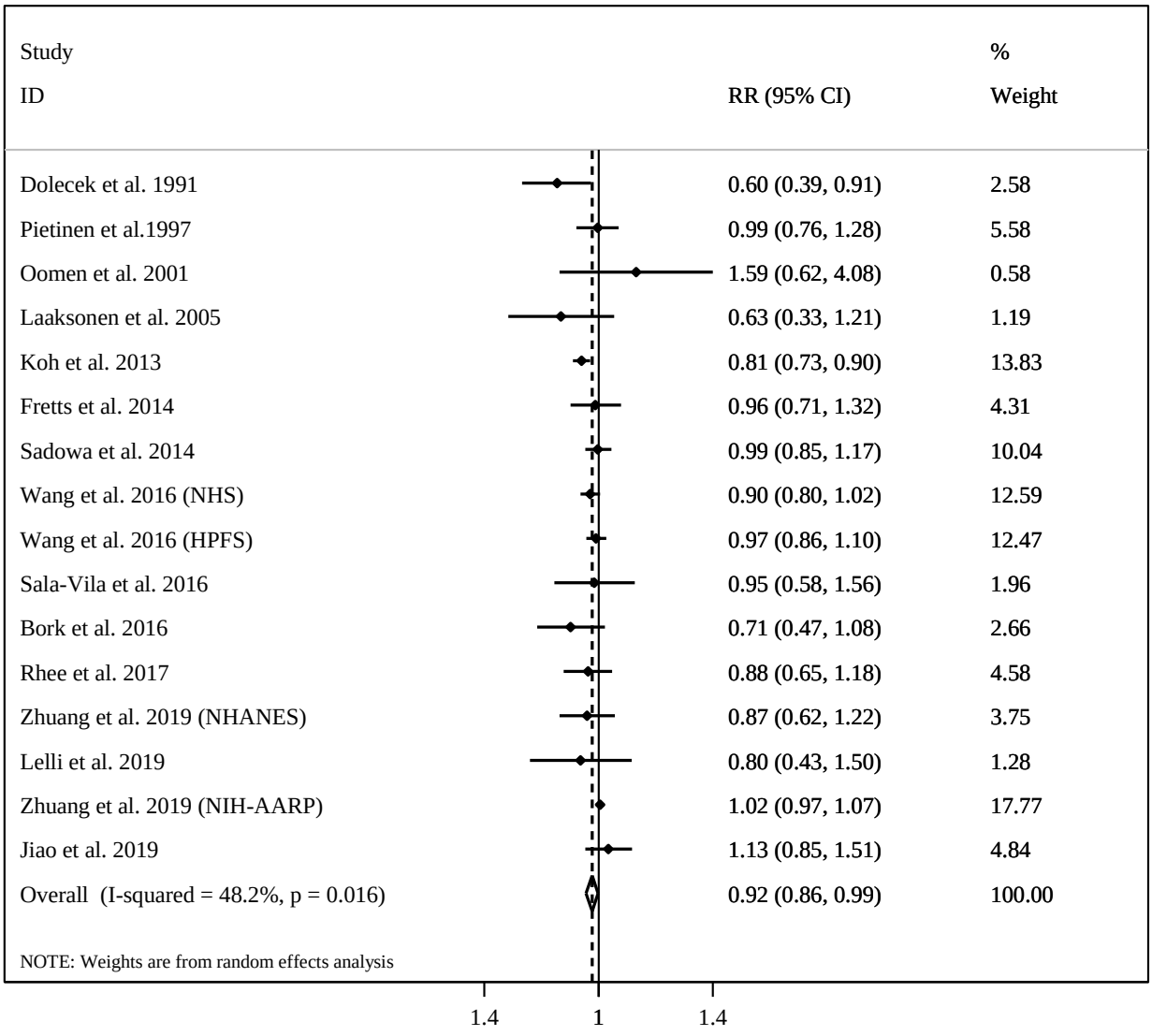
Forest plot for the association between tissue ALA levels and all-cause mortality by comparing the highest and lowest levels of ALA

Online Supporting Material
Supplemental Figure 4



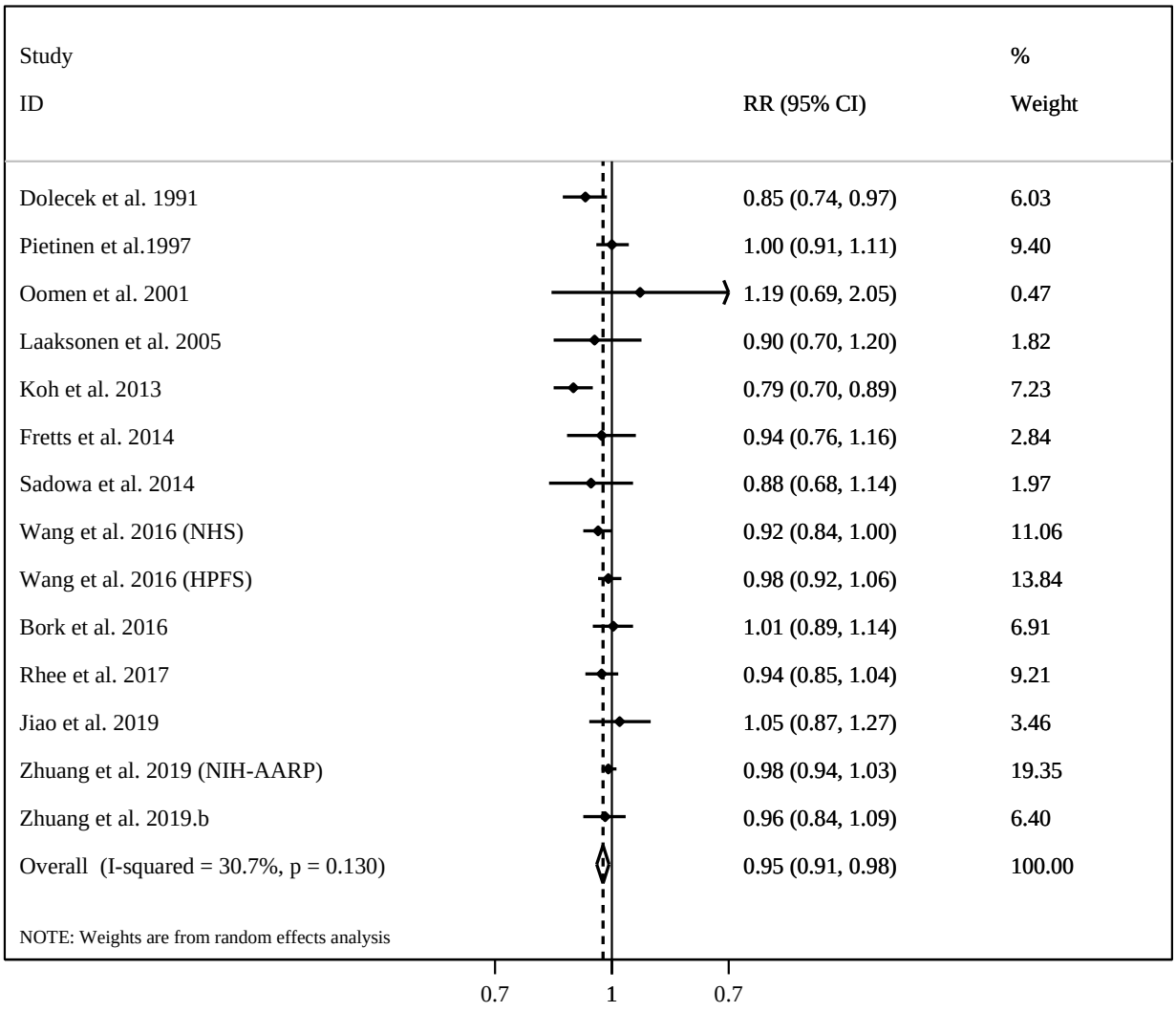
Forest plot for the association between tissue ALA levels and all-cause mortality according to a 1-SD increase in ALA levels

Online Supporting Material
Supplemental Figure 5



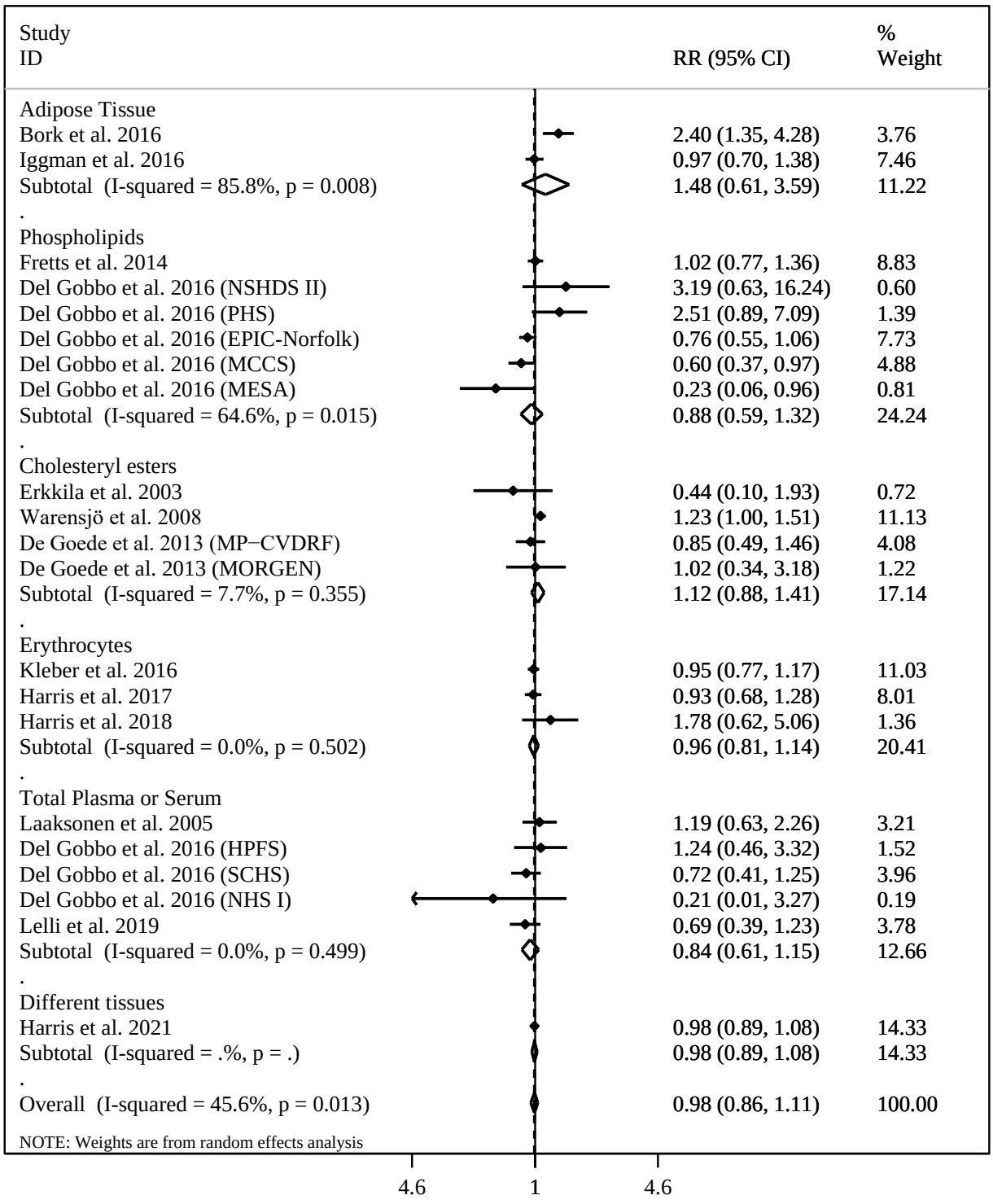
Forest plot for the association between dietary ALA intake and CVD mortality by comparing the highest and lowest intakes of ALA

Online Supporting Material
Supplemental Figure 6



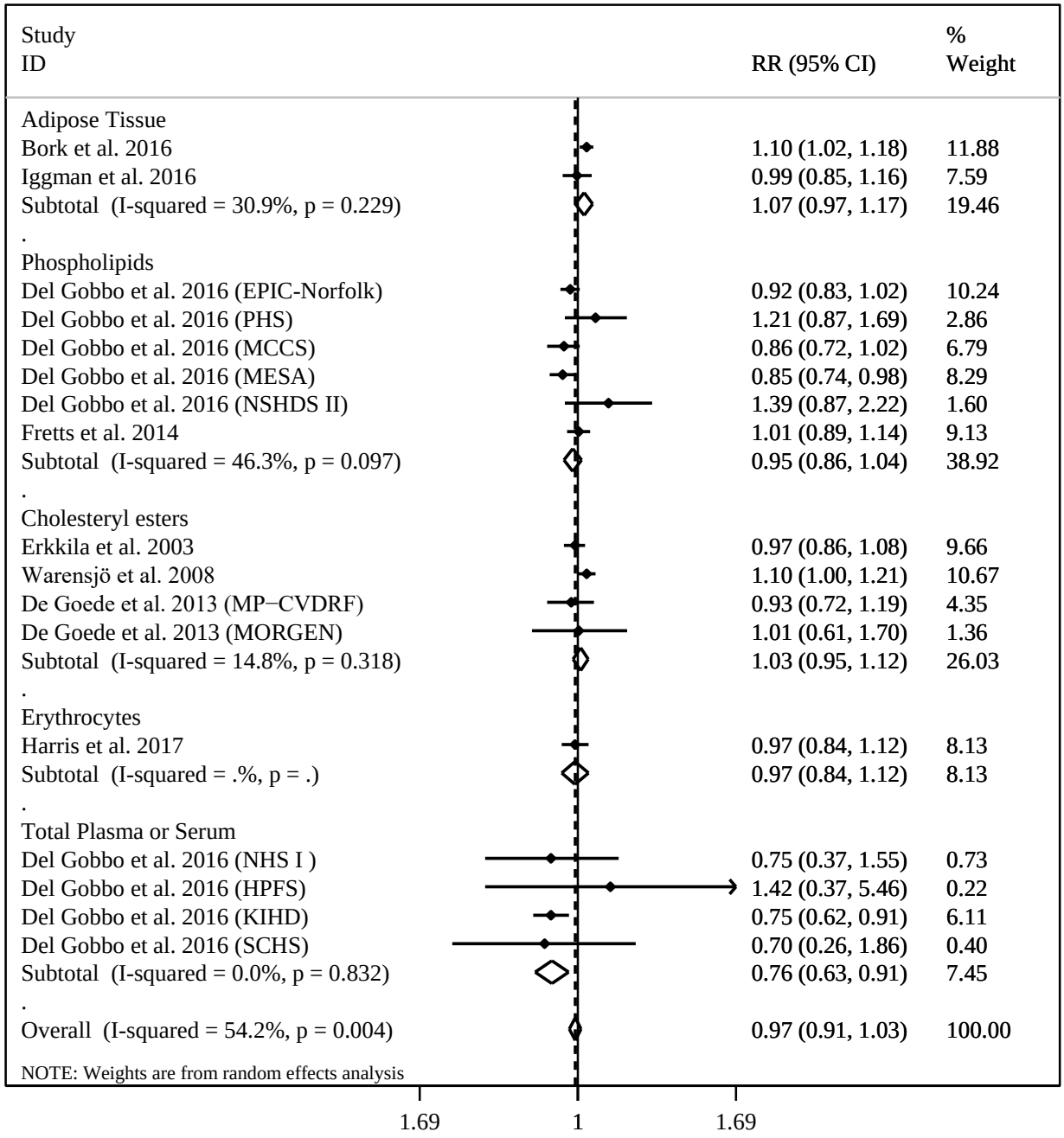
Forest plot for the association between dietary ALA intake and CVD mortality based on a 1-g/d increase in dietary ALA

Online Supporting Material
Supplemental Figure 7



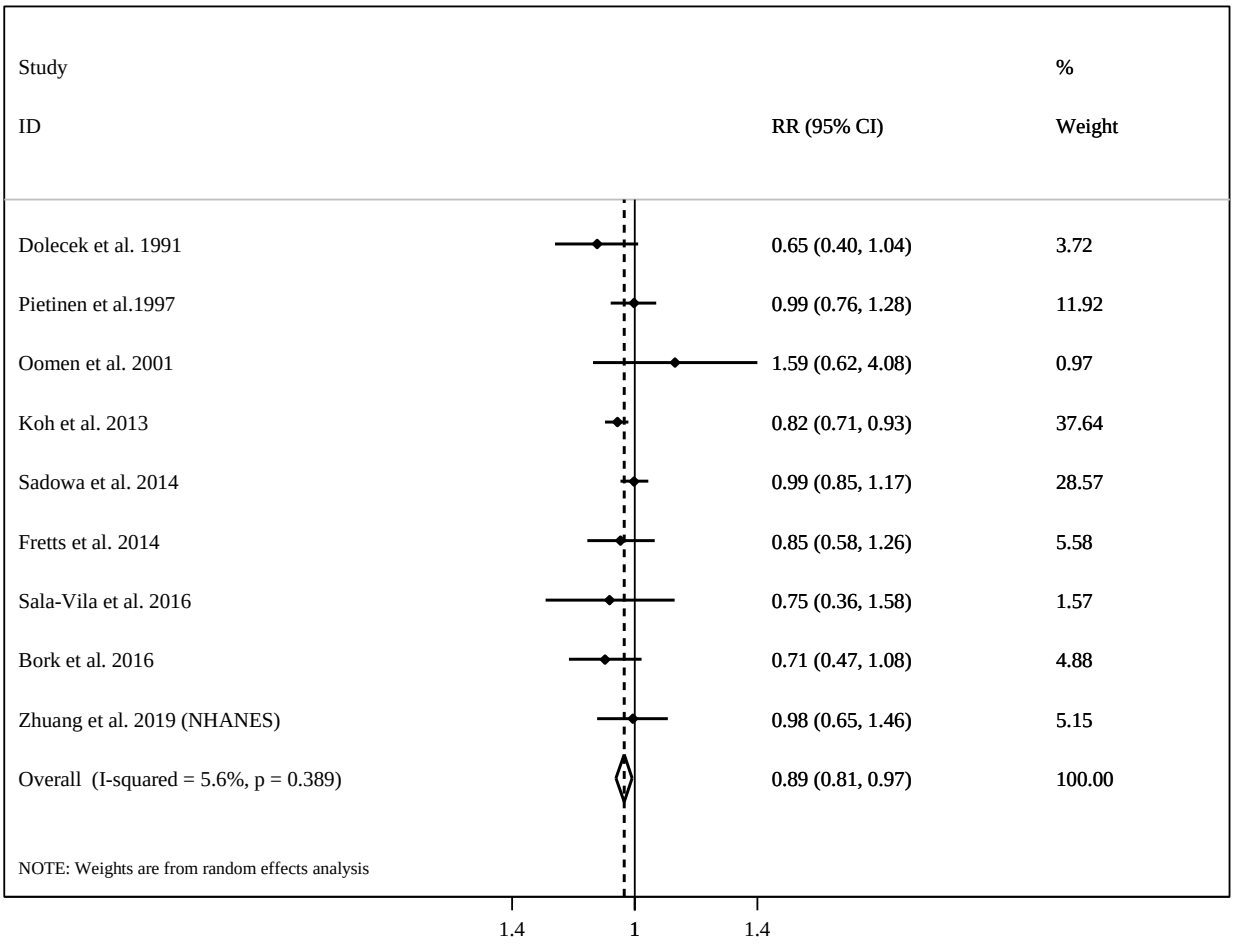
Forest plot for the association between tissue ALA levels and CVD mortality by comparing the highest and lowest levels of ALA

Online Supporting Material
Supplemental Figure 8



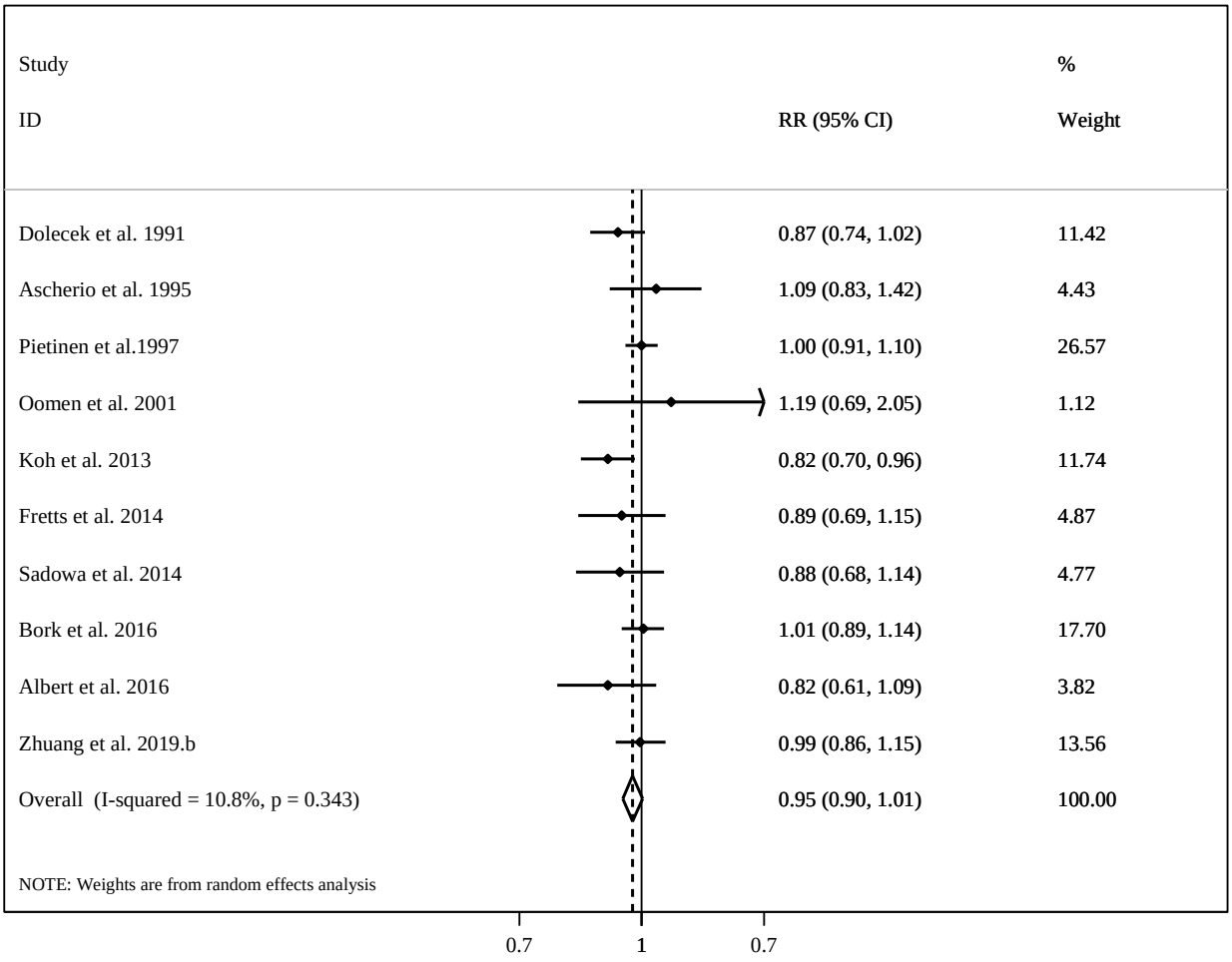
Forest plot for the association between tissue ALA levels and CVD mortality based on a 1-SD increase in ALA levels

Online Supporting Material
Supplemental Figure 9



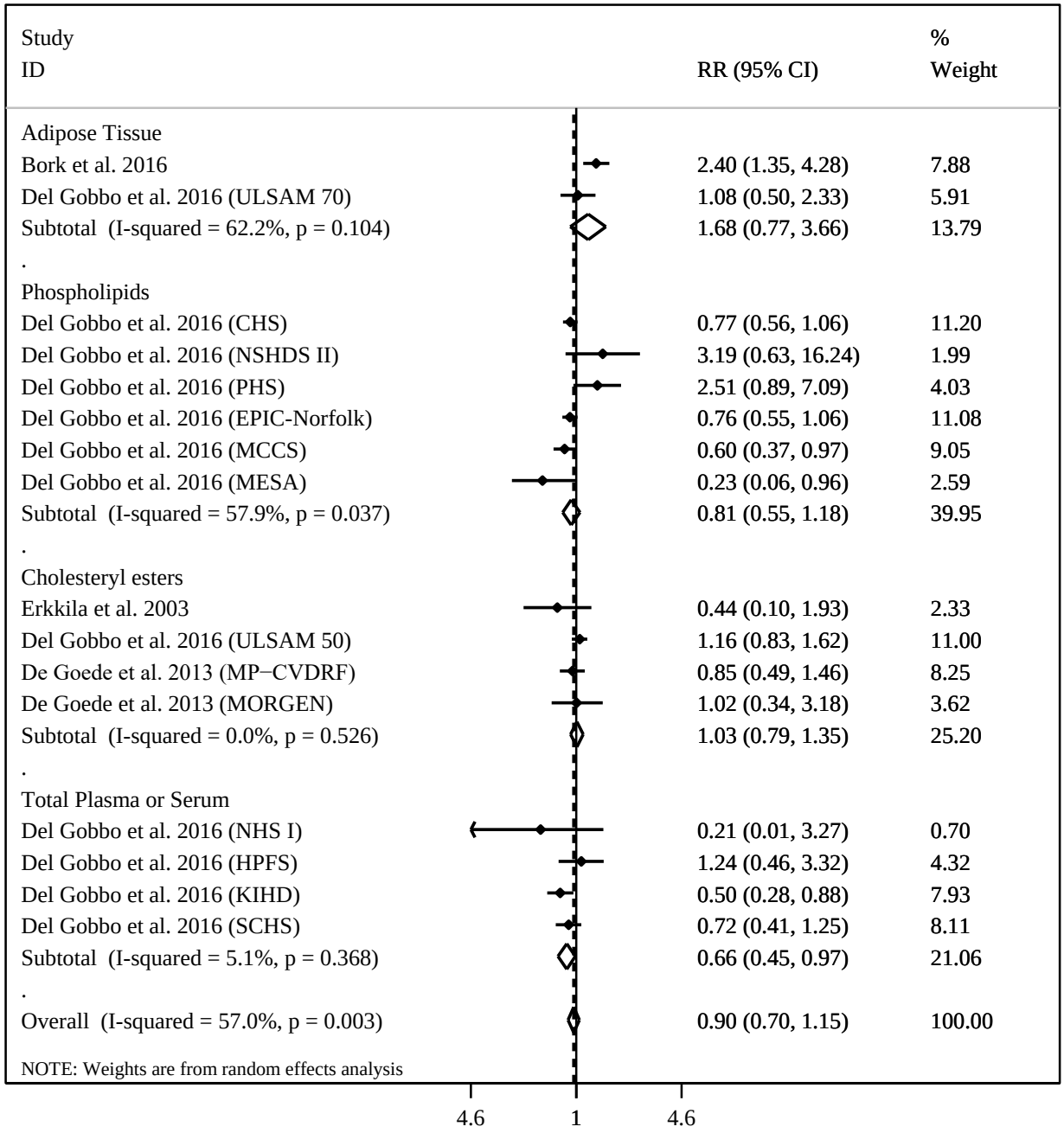
Forest plot for the association between dietary ALA intake and CHD mortality by comparing the highest and lowest intakes of ALA

Online Supporting Material
Supplemental Figure 10



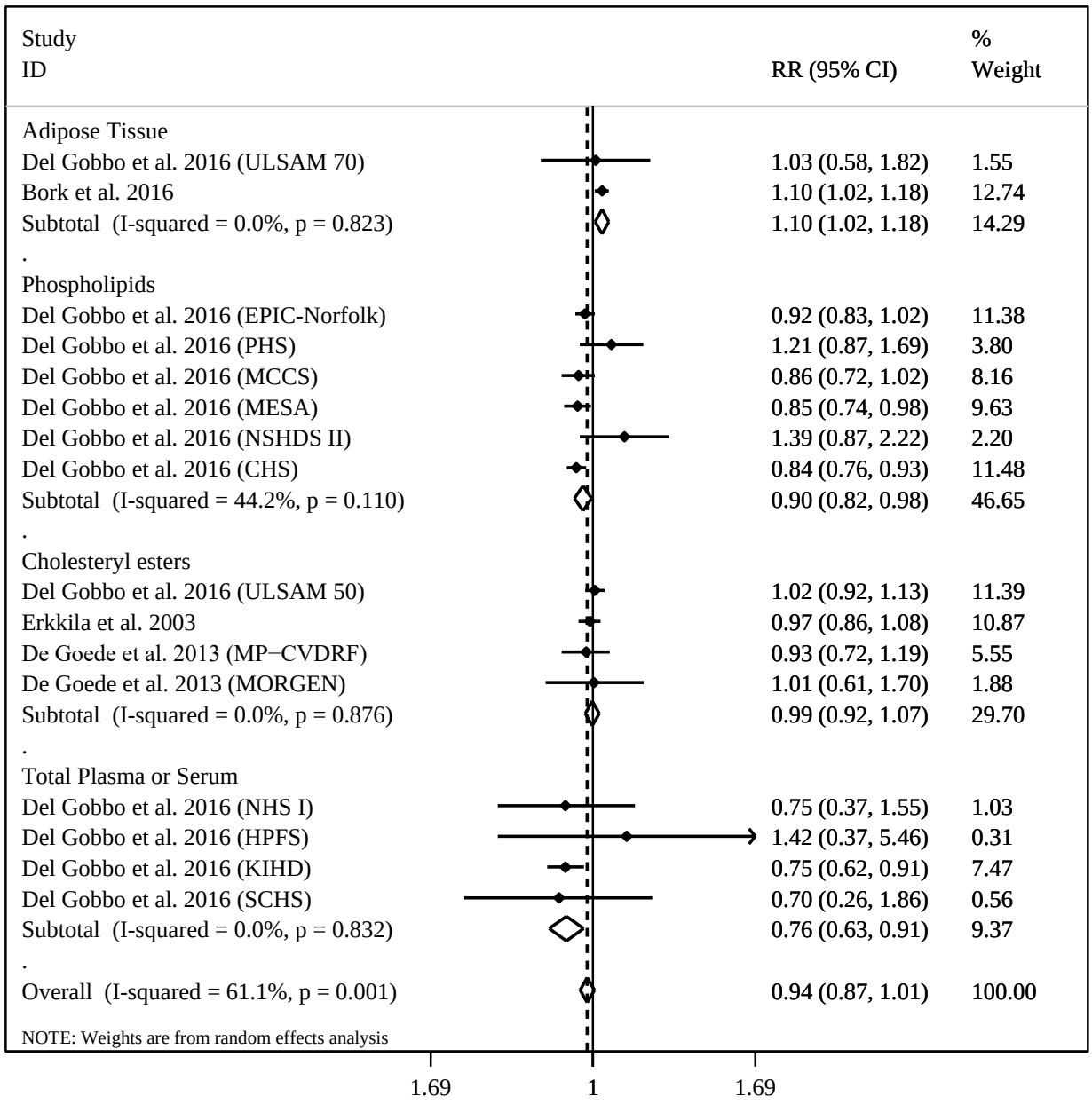
Forest plot for the association between dietary ALA intake and CHD mortality according to a 1-g/d increase in dietary ALA

Online Supporting Material
Supplemental Figure 11



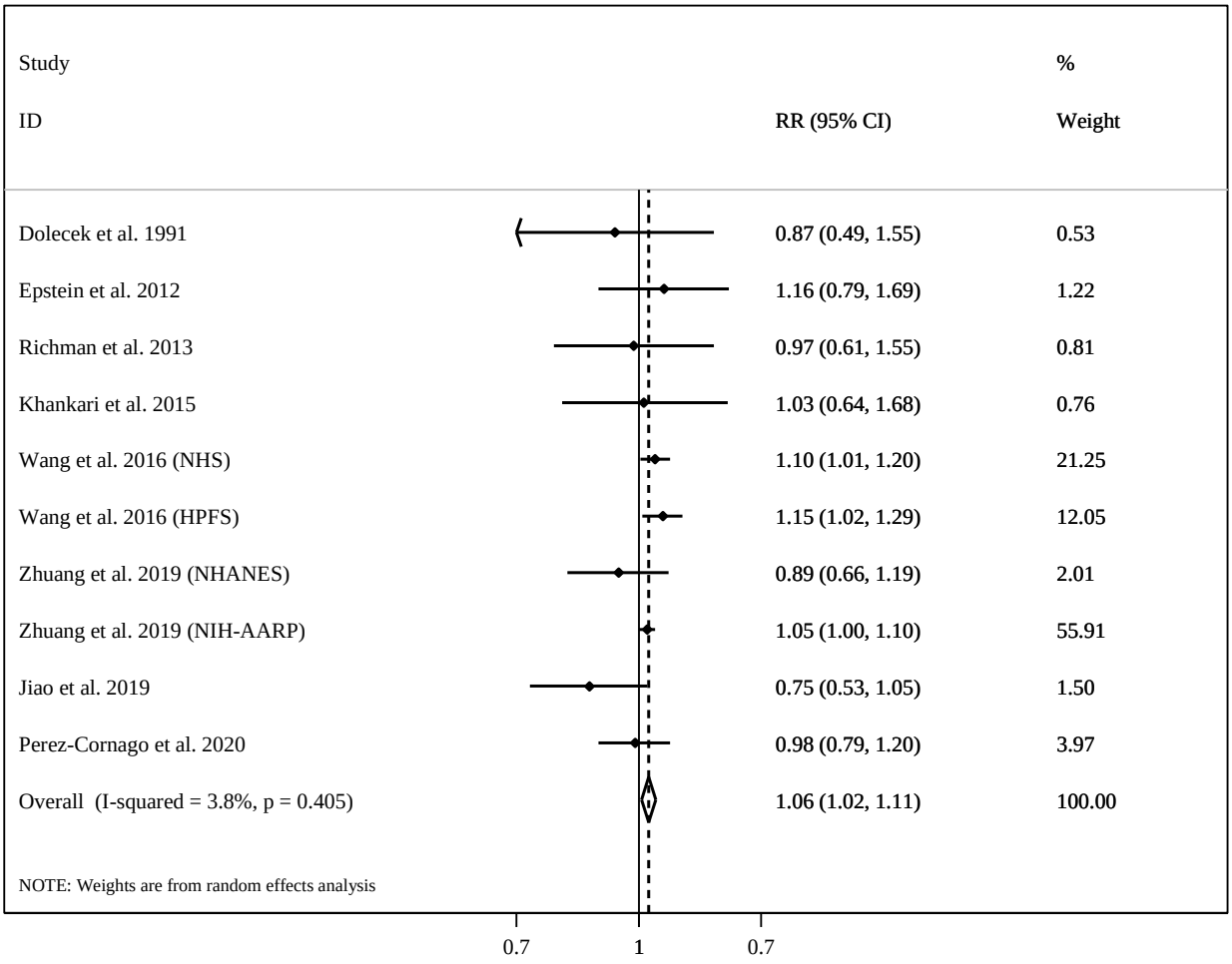
Forest plot for the association between tissue ALA levels and CHD mortality by comparing the highest and lowest levels of ALA

Online Supporting Material
Supplemental Figure 12



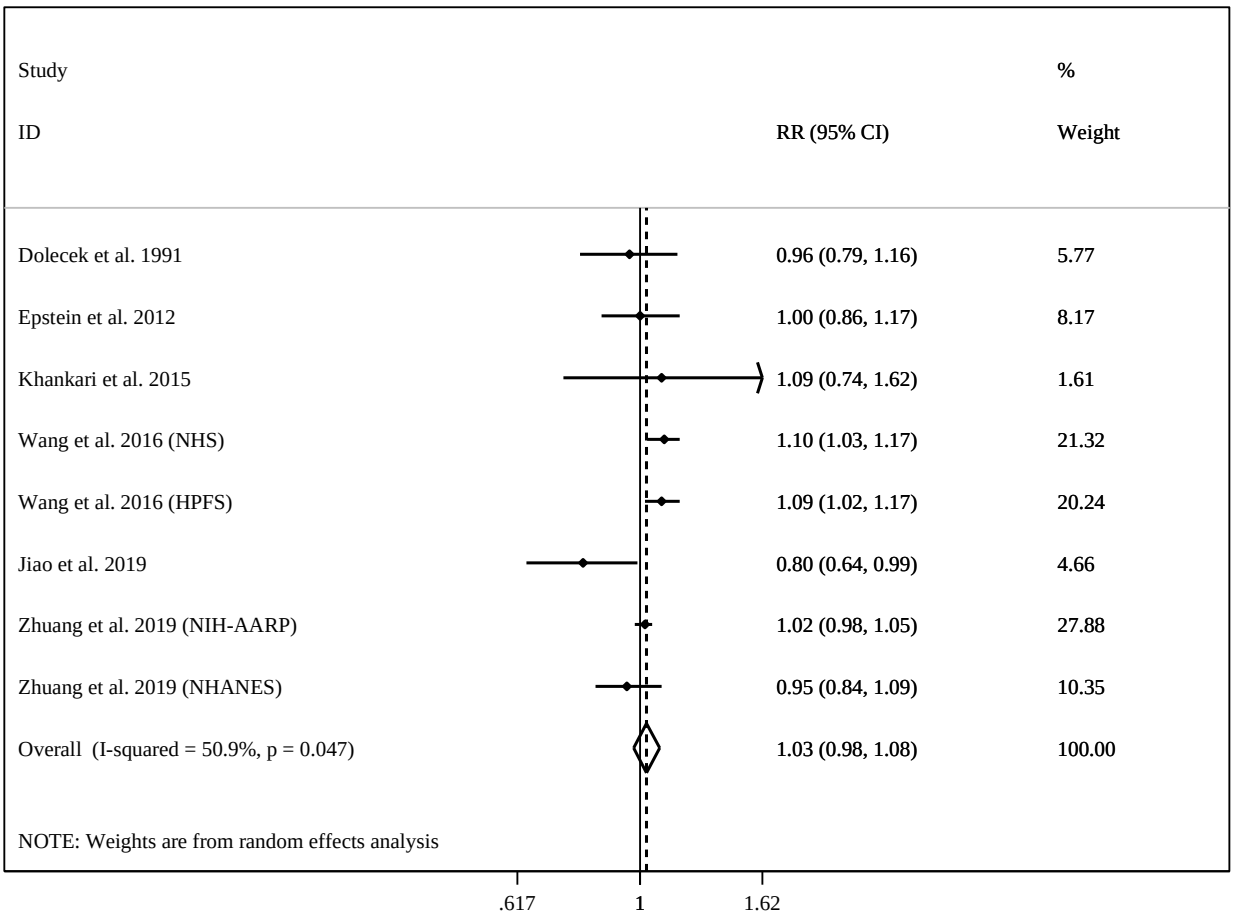
Forest plot for the association between tissue ALA levels and CHD mortality according to a 1-SD increase in the levels of ALA

Online Supporting Material
Supplemental Figure 13



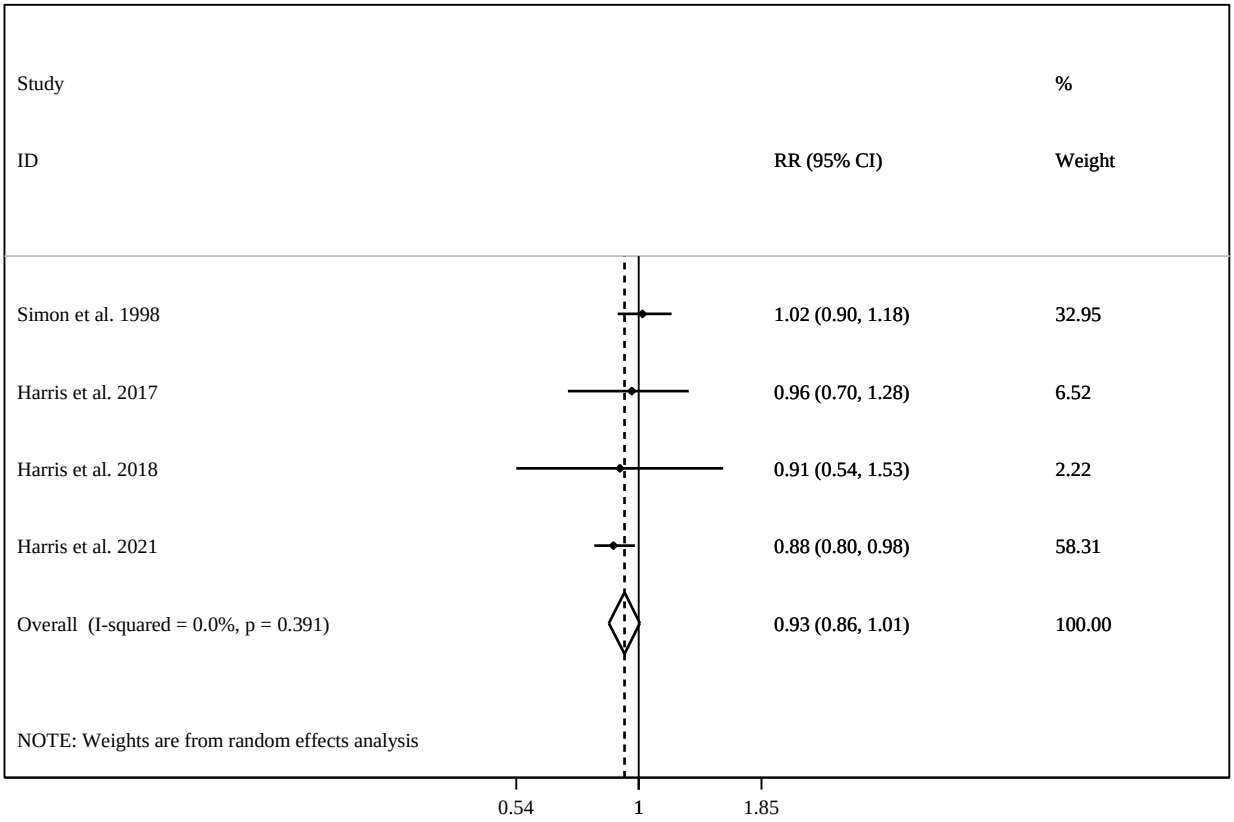
Forest plot for the association between dietary ALA intake and cancer mortality by comparing the highest and lowest intakes of ALA

Online Supporting Material
Supplemental Figure 14



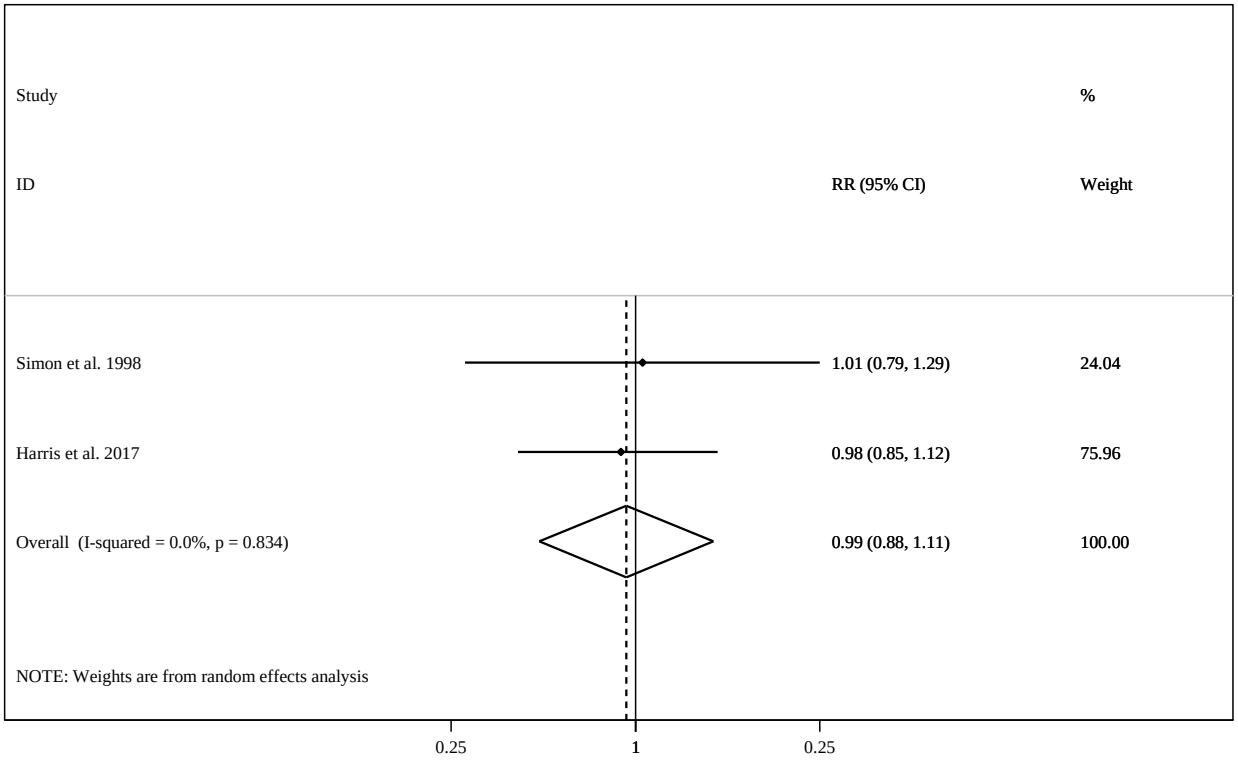
Forest plot for the association between dietary ALA intake and cancer mortality according to a 1-g/d increase in dietary ALA

Online Supporting Material
Supplemental Figure 15



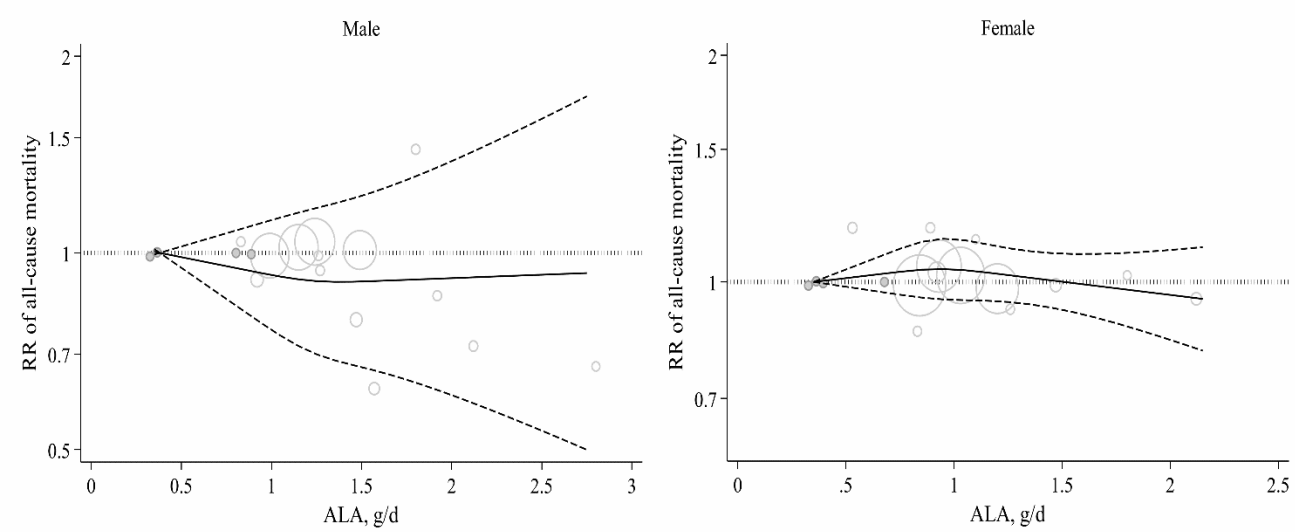
Forest plot for the association between tissue ALA levels and cancer mortality by comparing the highest and lowest levels of ALA

Online Supporting Material
Supplemental Figure 16



Forest plot for the association between tissue ALA levels and cancer mortality based on a 1-SD increase in ALA levels

Online Supporting Material
Supplemental Figure 17



Non-linear dose-response association of α-linolenic acid intake (based on g/day) with risk of mortality from all-cause in men and women aged ≥18 years. Solid line indicates the spline model. Dashed line presents the 95% CI. RR: relative risk, CI: confidence interval