Dietary and Biomarkers of Linoleic Acid and Mortality: Systematic Review and Meta-analysis of Prospective Cohort Studies

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Supplementary information - Search terms

In the PubMed (fatty acid[MeSH] OR linoleic OR α-linoleic) AND (death[MeSH] OR mortality[MeSH]) AND (humans[Mesh]) AND (English[lang])

In the Embase "human'/exp AND ('fatty acid'/exp OR 'linoleic acid'/exp OR 'α-linoleic':ab,ti) AND ('mortality'/exp OR death:ab,ti) AND ([embase]/lim OR [medline]/lim) AND [english]/lim

Supplementary Table 1 Quality of the studies included in the meta-analyses, according to the Newcastle-Ottawa Scale.

Cohort	Study	Total score	Selection				Comparability		Outcome		
			(1) Exposed cohort	(2) Non-exposed cohort	(3) Ascertain-ment of exposure	(4) Outcome not present at start	(1) Basic factors	(2) Additional factors	(1) Assessment of outcome	(2) Follow-up length	(3) Follow-up adequacy
Studies reported dietary LA intake and mortality											
MRFIT	Dolecek 1991 (1)	6	0	1	1	1	1	0	1	1	0
MRFIT	Dolecek 1992 (2)	7	0	1	1	1	1	1	1	1	0
Italian elderly	Fortes 2000 (3)	5	0	1	1	0	1	0	1	1	0
CSPOC-BC patients	McEligot 2006 (4)	7	0	1	1	0	1	1	1	1	1
NHS, HPFS	Wang 2016 (5)	8	0	1	1	1	1	1	1	1	1
NHS, HPFS	Jiao 2019 (6)	7	0	1	0	1	1	1	1	1	1
HPFS	Richman 2013 (7)	7	0	1	1	0	1	1	1	1	1
NHS	Holmes 1999 (8)	7	0	1	1	0	1	1	1	1	1
LIBCSP	Khankari 2015 (9)	6	0	1	1	0	1	0	1	1	1
ATBC	Pietinen 1997 (10)	8	0	1	1	1	1	1	1	1	1
IWHS	Farvid 2014 (11)	8	1	1	1	1	1	1	1	1	0
ARIC	Farvid 2014 (11)	8	1	1	1	1	1	1	1	1	0
FMC	Farvid 2014 (11)	8	1	1	1	1	1	1	1	1	0
VIP	Farvid 2014 (11)	8	1	1	1	1	1	1	1	1	0
IIHD	Farvid 2014 (11)	8	1	1	1	1	1	1	1	1	0
MDC	Farvid 2014 (11)	9	1	1	1	1	1	1	1	1	1
Canada-BC	Goodwin 2003 (12)	6	0	1	0	0	1	1	1	1	1
NBSS	Jain 1994 (13)	6	0	1	0	0	1	1	1	1	1
AARP-DHS	Zhuang 2019a (14)	7	1	1	0	0	1	1	1	1	1
Örebro-PC	Epstein 2012 (15)	6	0	1	0	0	1	1	1	1	1
CHNS	Zhuang 2019b (16)	6	1	1	0	1	1	1	0	1	0
NHANES	Zhuang 2019b (16)	8	1	1	0	1	1	1	1	1	1
Studies reported dietary intake and biomarkers of LA and mortality											
KIHD	Laaksonen 2005 (17)	9	1	1	1	1	1	1	1	1	1
InCHIANTI	Lelli 2019 (18)	8	1	1	1	0	1	1	1	1	1
Studies reported biomarkers of LA and mortality											
KIHD	Virtanen 2018 (19)	9	1	1	1	1	1	1	1	1	1
60YO	Marklund 2015 (20)	9	1	1	1	1	1	1	1	1	1
60YO	Marklund 2019 (21)	9	1	1	1	1	1	1	1	1	1
CHS	Wu 2014 (22)	9	1	1	1	1	1	1	1	1	1
CHS	Marklund 2019 (21)	9	1	1	1	1	1	1	1	1	1
MP-1 & MP-2	de Goede 2013 (23)	9	1	1	1	1	1	1	1	1	1
EUROASPIRE	Erkkila 2003 (24)	6	0	1	1	0	1	1	1	1	0
ULSAM-50	Warensjö 2008 (25)	8	1	1	1	0	1	1	1	1	1
ULSAM-50	Kilander 2001 (26)	7	1	1	1	0	1	0	1	1	1
ULSAM-70	Iggman 2016 (27)	8	1	1	1	0	1	1	1	1	1
TRIUMP	Harris 2013 (28)	5	0	1	1	0	1	0	1	1	0
WHIMS	Harris 2017 (29)	7	0	1	1	0	1	1	1	1	1

Swedish dialysis patients	Huang 2012 (30)	5	0	1	1	0	1	0	1	0	1
HSS	Pottala 2010 (31)	5	0	1	1	0	0	0	1	1	1
LURIC	Delgado 2017 (32)	7	0	1	1	0	1	1	1	1	1
Norway old patients	Lindberg 2008 (33)	7	0	1	1	0	1	1	1	1	1
NSCS	Miura 2016 (34)	7	1	1	1	0	1	1	1	1	0
FHS	Harris 2018 (35)	8	1	1	1	1	1	1	1	1	0
3C [1]	Satizabal 2018 (36)	7	1	1	1	0	1	1	1	1	0
EPIC-Norfolk	Marklund 2019 (21)	8	1	1	1	1	1	1	1	1	0
MCCS	Marklund 2019 (21)	8	1	1	1	1	1	1	1	1	0
MESA	Marklund 2019 (21)	9	1	1	1	1	1	1	1	1	1
CCCC	Marklund 2019 (21)	7	0	1	1	1	1	1	1	1	0
SHHEC	Marklund 2019 (21)	8	1	1	1	1	1	1	1	1	0
ARIC	Marklund 2019 (21)	8	1	1	1	1	1	1	1	1	0
AGES	Marklund 2019 (21)	7	0	1	1	1	1	1	1	1	0
HS	Marklund 2019 (21)	8	1	1	1	1	1	1	1	1	0
PPSII	Zureik 1995 (37)	7	0	1	1	0	1	1	1	1	1
MRFIT	Simon 1998 (38)	7	0	1	1	1	1	1	1	1	0

Scoring criteria: Selection-(1), representativeness of the exposed cohort: if the study truly or somewhat representative of the average of a population in the community then score 1; selection-(2), if the non-exposed cohort was drawn from the same community as the exposed cohort then score 1; selection-(3), if the exposure is ascertained from secure record or structured interview then score 1; selection-(4), if the authors demonstrated that outcome of interest (in this case, prevalent of CVD for CVD mortality, or prevalent cancer for cancer mortality) was not present at the start of the study, then score 1. Comparability-(1), if the study is age and gender adjusted, then score 1; comparability-(2), if the study further adjusted for BMI, smoking, alcohol intake, disease-related risk factors (for populations at high risk for certain disease), and energy intake and other dietary factors (dietary linoleic acid intake as exposure), then score 1. Outcome-(1), if the outcome is assessed based on independent blink adjudication or record linkage, then score 1; outcome-(2), if the follow-up time ≥5 years for general populations and ≥2 years for populations with existing diseases, then score 1; outcome-(3), if it is stated in the paper that the follow-up is complete for all subjects or follow-up rate is ≥90% for included participants, then score 1. Note for [1]: this study investigated both the FHS and 3C study; because data from FHS has been reported in detail in other publications, in this study we only evaluated data for the 3C study.

Supplementary Table 2 Stratified meta-analysis for dietary linoleic acid intake in relation to mortality from all-causes, CVD, and cancer.

Strata	All-cause mortality					CVD mortality					Cancer mortality				
	RR (95%CI) [1]	*P* [2]	*P*-het [3]	Study N [4]	*P*meta-reg [5]	RR (95%CI) [1]	*P* [2]	*P*-het [3]	Study N [4]	*P*meta-reg [5]	RR (95%CI) [1]	*P* [2]	*P*-het [3]	Study N [4]	*P*meta-reg [5]
Baseline Population #															
General population	0.85 (0.80, 0.90)	<0.001	0.02	8	[ref]	0.86 (0.80, 0.92)	<0.001	0.34	14	[ref]	0.88 (0.85, 0.92)	<0.001	0.58	4	[ref]
CVD/high risk for CVD	0.82 (0.72, 0.94)	0.003	0.80	2 [6]	0.77	0.79 (0.63, 0.99)	0.04	0.59	2 [6]	0.62	1.02 (0.78, 1.34)	0.86	0.84	2 [5]	0.32
Cancer	1.15 (0.82, 1.62)	0.41	0.02	4 [6]	0.11	-	-	-	-	-	0.98 (0.76, 1.26)	0.86	0.55	4	0.46
Study location															
North American	0.87 (0.81, 0.93)	<0.001	0.002	7	[ref]	0.84 (0.77, 0.93)	<0.001	0.12	7	[ref]	0.89 (0.85, 0.93)	<0.001	0.62	8	[ref]
European	0.72 (0.54, 0.95)	0.02	0.25	3	0.38	0.86 (0.71, 1.04)	0.11	0.64	7	0.94	0.91 (0.63, 1.32)	0.62	-	1	0.90
Asian	1.16 (0.91, 1.48)	0.24	-	1	0.18	0.87 (0.82, 0.92)	0.91	-	1	0.64	-	-	-	0	-
NOS score															
<8	1.02 (0.82, 1.27)	0.88	0.001	6	[ref]	0.92 (0.87, 0.97)	0.004	0.67	2	[ref]	0.88 (0.83, 0.92)	<0.001	0.60	6	[ref]
≥8	0.82 (0.79, 0.86)	<0.001	0.56	5	0.07	0.80 (0.74, 0.87)	<0.001	0.83	13	0.17	0.91 (0.85, 0.98)	0.01	0.62	3	0.91
Dietary assessment															
Baseline EEQ/record	0.94 (0.80, 1.11)	0.45	0.001	8	[ref]	0.91 (0.86, 0.97)	0.001	0.89	12	[ref]	0.87 (0.83, 0.92)	<0.001	0.71	6	[ref]
Repeated FFQ/record	0.83 (0.79, 0.86)	<0.001	0.60	3	0.42	0.78 (0.72, 0.86)	<0.001	0.65	3	**0.02**	0.92 (0.85, 0.99)	0.03	0.52	3	0.32
Age															
<60 years	0.87 (0.79, 0.96)	0.006	0.008	7	[ref]	0.80 (0.74, 0.87)	<0.001	0.85	12	[ref]	0.92 (0.86, 0.99)	0.02	0.70	7	[ref]
≥60 years	0.94 (0.66, 1.35)	0.75	0.02	4	0.83	0.92 (0.87, 0.98)	0.006	0.90	3	**0.01**	0.87 (0.83, 0.92)	<0.001	0.82	2	0.26
Gender															
Male%<50	0.98 (0.81, 1.19)	0.83	0.001	7	[ref]	0.84 (0.76, 0.94)	0.002	0.94	6	[ref]	0.90 (0.82, 0.98)	0.02	0.62	5	[ref]
Male%≥50	0.83 (0.76, 0.91)	<0.001	0.04	4	0.17	0.83 (0.73, 0.95)	0.006	0.13	9	0.53	0.88 (0.84, 0.93)	<0.001	0.46	4	0.67
Follow-up period															
<10 years	0.93 (0.62, 1.39)	0.73	0.02	4	[ref]	0.91 (0.69, 1.20)	0.49	0.78	4	[ref]	0.86 (0.66, 1.11)	0.25	0.97	3	[ref]
≥10 years	0.87 (0.81, 0.94)	<0.001	0.002	7	0.96	0.84 (0.78, 0.92)	<0.001	0.20	11	0.64	0.89 (0.85, 0.93)	<0.001	0.39	6	0.78

[1] Relative risks (RRs) and 95% confidence intervals (CIs) from an inverse variance-weighted random-effects meta-analysis.
[2] *P* values for the association between linoleic acid intake and mortality.
[3] *P* values for the heterogeneity test from the random-effects meta-analysis within each subgroup.
[4] Studies that were input as 2 records, mostly due to separated data records for man and women, were counts as 2 studies in this table.
[5] The potential modification effect of the stratification factor (i.e., test of difference between subgroups) was examined using univariate meta-regression, with log RRs as dependent variable, and each stratification factors as independent variable.
[6] Three additional papers (Holmes, 1999; Richman, 2013; and Jiao, 2019) that did not include in the main analysis (because they were conducted in subsamples of individuals with cancers while results in the whole cohorts were reported in Wang, 2016) were included in the stratification analysis.
NOS: Newcastle-Ottawa Scale.

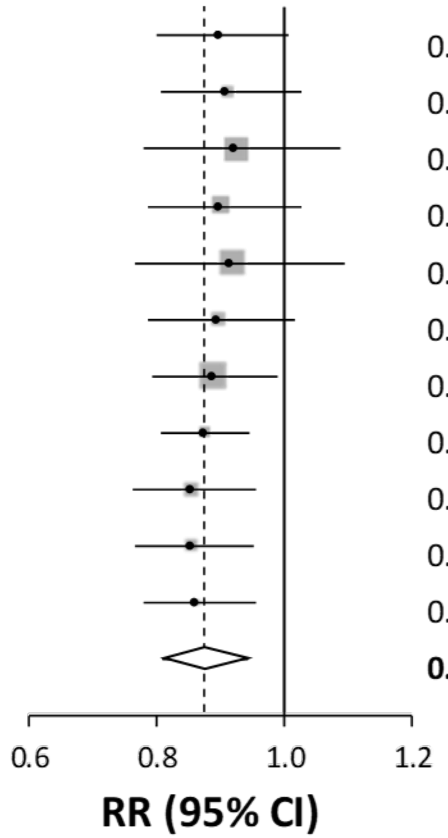
Supplementary Table 3 Stratified meta-analysis for biomarkers of linoleic acid in relation to mortality from all-causes, CVD, and cancer.

Strata	All-cause mortality					CVD mortality					Cancer mortality				
	RR (95%CI) [1]	*P* [2]	*P*-het [3]	Study N	*P*meta-reg [4]	RR (95%CI) [1]	*P* [2]	*P*-het [3]	Study N	*P*meta-reg [4]	RR (95%CI) [1]	*P* [2]	*P*-het [3]	Study N [5]	*P*meta-reg [4]
Tissue types															
Adipose tissue	0.90 (0.82, 0.98)	0.02	-	1	[ref]	0.83 (0.67, 1.04)	0.11	0.09	2	[ref]	-	-	-	0	-
Erythrocytes	0.96 (0.92, 1.00)	0.05	0.28	4	0.48	0.94 (0.89, 1.00)	0.06	0.87	3	0.20	0.94 (0.84, 1.05)	0.28	0.97	2	[ref]
Cholesteryl esters	0.84 (0.75, 0.95)	0.004	0.06	4	0.47	0.86 (0.80, 0.94)	<0.001	0.41	5	0.99	0.82 (0.60, 1.13)	0.22	0.03	3	0.46
Whole blood	1.28 (0.79, 2.07)	0.32	-	1	0.23	-	-	-	0	-	-	-	-	0	-
Phospholipids	0.93 (0.84, 1.04)	0.20	0.15	5	0.66	0.94 (0.87, 1.01)	0.08	0.72	6	0.26	0.96 (0.85, 1.08)	0.49	0.44	2	0.87
Total serum or plasma	0.86 (0.76, 0.97)	0.01	0.18	3	0.56	0.78 (0.67, 0.91)	0.002	0.21	4	0.32	0.90 (0.78, 1.03)	0.14	-	1	0.75
Baseline conditions															
General population	0.89 (0.84, 0.94)	<0.001	0.005	11	[ref]	0.87 (0.83, 0.92)	<0.001	0.20	17	[ref]	0.88 (0.79, 0.97)	0.01	0.19	5	[ref]
CVD/high risk for CVD	0.93 (0.88, 0.98)	0.006	0.41	4	0.34	0.95 (0.80, 1.14)	0.61	0.29	2	0.29	1.05 (0.81, 1.36)	0.71	-	1	0.37
Other disease conditions	0.95 (0.80, 1.13)	0.56	0.08	3	0.21	0.96 (0.88, 1.05)	0.37	-	1	0.20	0.94 (0.83, 1.07)	0.34	-	1	0.54
Study location															
North American	0.97 (0.94, 1.01)	0.10	0.66	5	[ref]	0.92 (0.82, 1.04)	0.19	0.06	6	[ref]	0.95 (0.87, 1.03)	0.21	0.88	4	[ref]
European	0.88 (0.83, 0.92)	<0.001	0.02	13	**0.02**	0.88 (0.84, 0.92)	<0.001	0.42	13	0.15	0.83 (0.69, 0.99)	0.03	0.10	3	0.17
Asian	-	-	-	-	-	0.86 (0.57, 1.31)	0.48	-	1	0.71	-	-	-	0	-
NOS score															
<8	0.95 (0.90, 1.00)	0.05	0.16	10	[ref]	0.89 (0.79, 1.01)	0.07	0.03	5	[ref]	0.88 (0.75, 1.04)	0.14	0.05	4	[ref]
≥8	0.88 (0.83, 0.94)	<0.001	0.002	8	0.18	0.88 (0.84, 0.92)	<0.001	0.44	15	0.23	0.92 (0.84, 1.01)	0.07	0.92	3	0.76
Study Design															
Cohort analysis	0.91 (0.87, 0.95)	<0.001	<0.001	18	-	0.89 (0.85, 0.94)	<0.001	0.07	18	[ref]	0.89 (0.83, 0.97)	0.006	0.24	6	[ref]
Nested case-control	-	-	-	-	-	0.94 (0.77, 1.15)	0.55	0.55	2	0.66	1.05 (0.81, 1.36)	0.71	-	1	0.37
Age															
<60 years	0.85 (0.79, 0.91)	<0.001	0.16	5	[ref]	0.84 (0.79, 0.89)	<0.001	0.55	6	[ref]	0.87 (0.74, 1.02)	0.09	0.07	4	[ref]
≥60 years	0.93 (0.89, 0.98)	0.003	0.02	13	0.07	0.92 (0.88, 0.97)	0.002	0.30	14	**0.02**	0.94 (0.86, 1.02)	0.14	1.00	3	0.40
Sex															
Male%<50	0.97 (0.94, 1.01)	0.14	0.88	8	[ref]	0.94 (0.89, 0.99)	0.02	0.83	11	[ref]	0.94 (0.86, 1.02)	0.14	1.00	3	[ref]
Male%≥50	0.86 (0.81, 0.92)	<0.001	0.006	10	**0.008**	0.86 (0.79, 0.93)	<0.001	0.03	9	0.08	0.87 (0.74, 1.02)	0.09	0.07	4	0.41
Follow-up period															
<10 years	0.95 (0.91, 0.99)	0.03	0.55	9	[ref]	0.92 (0.79, 1.07)	0.28	0.84	5	[ref]	0.91 (0.76, 1.10)	0.33	0.11	4	[ref]
≥10 years	0.89 (0.83, 0.95)	<0.001	<0.001	9	0.14	0.89 (0.84, 0.94)	<0.001	0.03	15	0.17	0.89 (0.83, 0.96)	0.004	0.43	3	0.43

[1] Relative risks (RRs) and 95% confidence intervals (CIs) from an inverse variance-weighted random-effects meta-analysis.
[2] *P* values for the association between linoleic acid intake and mortality.
[3] *P* values for the heterogeneity test from the random-effects meta-analysis.
[4] The potential modification effect of the stratification factor (i.e., test of difference between subgroups) was examined using univariate meta-regression, with log RRs as dependent variable, and each stratification factors as independent variable.
[5] The MRFIT study (Simon, 1998) provided data of LA in phospholipid and cholesteryl ester for the same population. We used both data for meta-analysis by tissue types but chose to use LA in phospholipid in the overall meta-analysis.
NOS: Newcastle-Ottawa Scale.

Supplement Figure 1 Meta-analysis of dietary linoleic acid intake and total mortality in prospective cohorts, after excluding one study at a time. Relative risks (RRs) correspond to comparison between extreme categories. RRs from different studies were pooled using an inverse variance-weighted random-effects meta-analysis. Squares denote the weight of the excluded studies in the meta-analysis.

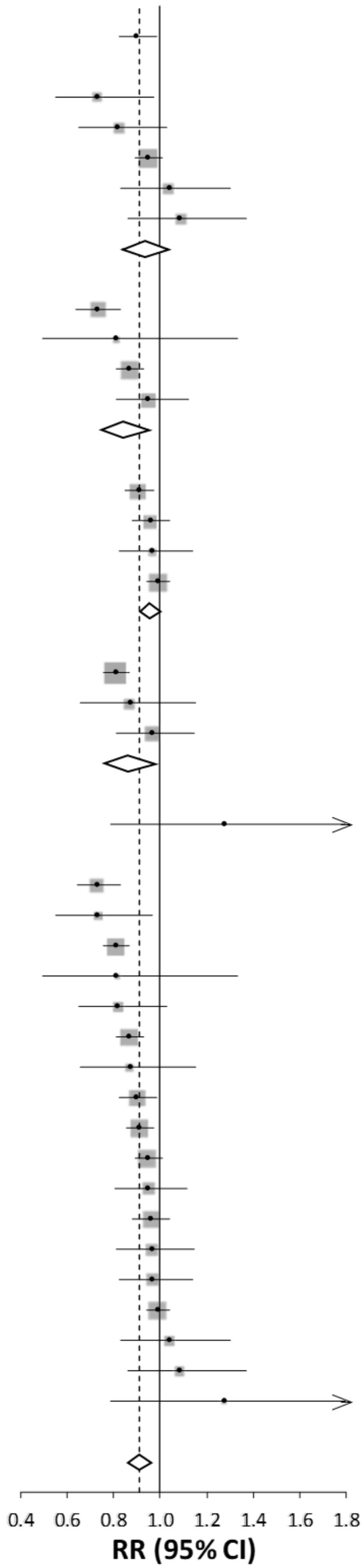
Reference	Cohort Name	Total N	Case N	HR (95%CI)	I^2	*P* -het	%Weight
Exclude							
Fortes 2000 (3)	Italian elderly	162	53	0.90 (0.80, 1.01)	68.6%	0.001	1.08
Laaksonen 2005 (17)	KIHD	1,551	220	0.91 (0.81, 1.03)	68.3%	0.001	4.41
Wang 2016 (5)	HPFS	42,884	12,990	0.92 (0.78, 1.09)	65.6%	0.002	19.16
Zhuang 2019b (16)	NHANES	36,032	4,826	0.90 (0.79, 1.03)	70.9%	<0.001	9.75
Wang 2016 (5)	NHS	83,349	20,314	0.91 (0.77, 1.09)	69.8%	<0.001	20.6
Dolecek 1991 (1)	MRFIT	6,258	439	0.89 (0.79, 1.02)	71.1%	<0.001	6.27
Zhuang 2019a (14)	AARP-DHS	521,120	129,328	0.89 (0.79, 0.99)	67.8%	0.001	22.86
Lelli 2019 (18)	InCHIANTI	927	318	0.87 (0.81, 0.95)	71.1%	<0.001	3.56
Zhuang 2019b (16)	CHNS	14,117	1,007	0.85 (0.76, 0.95)	65.1%	0.002	6.75
Khankari 2015 (9)	LIBCSP	1,463	485	0.85 (0.77, 0.95)	64.1%	0.003	4.49
McEligot 2006 (4)	CSPOC-BC	516	96	0.86 (0.78, 0.95)	61.6%	0.005	1.07
Include all studies		**708,379**	**170,076**	**0.87 (0.81, 0.94)**	67.9%	**0.001**	



Supplement Figure 2 Meta-analysis of the association between LA biomarkers and mortality from all-causes (A), CVD (B), and cancer (C). Relative risks (RRs) were for each standard deviation increment in linoleic acid biomarkers. The area of each blue square is proportional to the weight of the study, which is the inverse of the variance of the log RRs. Dots and horizontal lines represent RRs and 95% confidence interval (CI). Diamonds depict pooled estimates from a random-effects inverse variance-weighted meta-analysis. Abbreviations: 3C: the Three-City study; 60YO: Stockholm old men and women; AGES-Reykjavik: Age, gene/environment susceptibility – Reykjavik Study; ARIC: Atherosclerosis Risk in Communities; CCCC: Chin-Shan Community Cardiovascular Cohort Study; CHS: Cardiovascular Health Study; CVD: Cardiovascular disease; CVD: Cardiovascular disease; DIA Patient: A small cohort of dialysis patients in Sweden; EPIC: European Prospective Investigation of Cancer; EUROASPIRE-Finnish: European Action on Secondary and Primary Prevention by Intervention to Reduce Events – Finnish; Framingham: Framingham Heart Study; HS: Hisayama Study; HSS: The Heart and Soul Study; InCHIANTI, the longitudinal InCHIANTI study; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; LA: Linoleic acid; LURIC: The Ludwigshafen Risk and Cardiovascular Health study; MCCS: Melbourne Collaborative Cohort Study; MESA: Multi-Ethnic Study of Atherosclerosis; MP-1 & 2: Monitoring Project on Cardiovascular Disease Risk Factors; MRFIT: The Multiple Risk Factor Intervention Trial.; NSCS: The Nambour Skin Cancer Study; Old patients: A small cohort of old patients, frail, old patients in Norway; PPSII: Paris prospective study II; SHHEC: Scottish Heart Health Extended Cohort; TRIUMPH: The Translational Research Investigating Underlying disparities in acute Myocardial Infarction Patients' Health status study; ULSAM 50: Uppsala Longitudinal Study of Adult Men investigations, recruitment at 50 years old; ULSAM 70: Uppsala Longitudinal Study of Adult Men investigations, recruitment at 70 years old; WHIMS: Women's Health Initiative Memory Study.

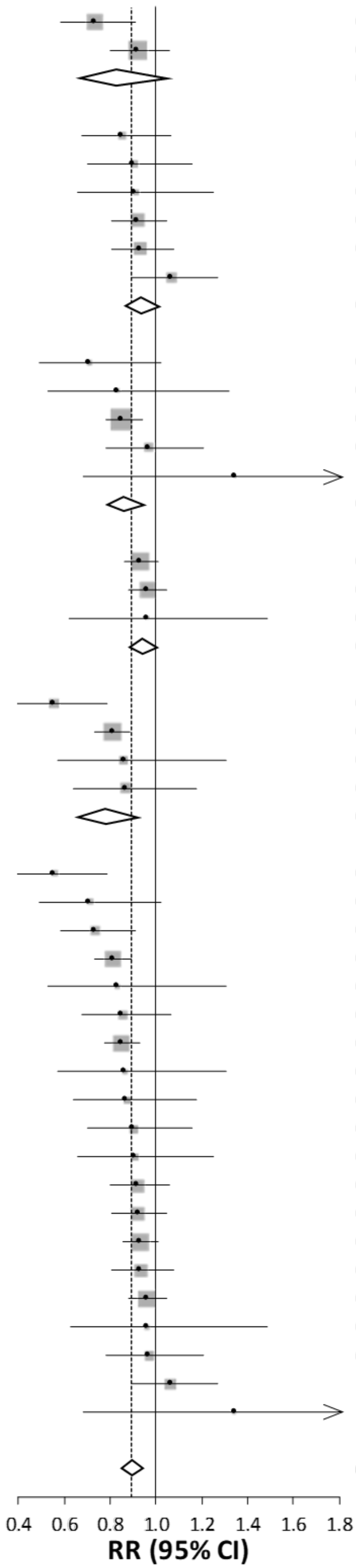
A All-cause mortality

Reference	Cohort Name	Total N	Case N	HR (95%CI)	% Weight
Adipose Tissue					
Iggman 2016 (27)	ULSAM 70	853	605	0.90 (0.82, 0.98)	***P* =0.02**
Phospholipids					
Huang 2012 (30)	DIA Patient	222	61	0.73 (0.55, 0.97)	11.09
Miura 2016 (34)	NSCS-Men	444	98	0.82 (0.65, 1.03)	15.13
Wu 2014 (22)	CHS	2,792	1,994	0.95 (0.89, 1.01)	43.10
Miura 2016 (34)	NSCS-Women	564	81	1.04 (0.83, 1.30)	15.68
Lindberg 2008 (33)	Old patients	254	156	1.09 (0.86, 1.37)	15.01
Summary (I^2 =40.6%; *P* =0.15)		4,276	2,390	0.93 (0.84, 1.04)	***P* =0.201**
Cholesterol esters					
Marklund 2015 (20)	60YO-Men	1,733	265	0.73 (0.64, 0.83)	29.80
Erkkila 2003 (24)	EUROASPIRE-Fin	398	35	0.81 (0.50, 1.33)	5.06
Warensjö 2008 (25)	ULSAM 50	2,009	1,012	0.87 (0.81, 0.93)	40.33
Marklund 2015 (20)	60YO-Women	1,938	191	0.95 (0.81, 1.12)	24.81
Summary (I^2 =60.2%; *P* =0.06)		6,078	1,503	0.84 (0.75, 0.95)	***P* =0.004**
Erythrocytes					
Delgado 2017 (32)	LURIC	3,259	975	0.91 (0.85, 0.97)	30.36
Harris 2013 (28)	TRIUMPH	1,144	135	0.96 (0.88, 1.04)	21.23
Harris 2018 (35)	Framingham	2,500	350	0.97 (0.82, 1.14)	6.60
Harris 2017 (29)	WHIMS	6,501	1,851	0.99 (0.94, 1.04)	41.81
Summary (I^2 =22.7%; *P* =0.28)		13,404	3,311	0.96 (0.92, 1.00)	***P* =0.047**
Total Serum or Plasma					
Virtanen 2018 (19)	KIHD	2,480	1,143	0.81 (0.76, 0.87)	58.43
Satizabal 2018 (36)	3C	1,406	251	0.87 (0.66, 1.16)	13.77
Lelli 2019 (18)	InCHIANTI	927	318	0.96 (0.81, 1.15)	27.80
Summary (I^2 =42.4%; *P* =0.18)		4,813	1,712	0.86 (0.76, 0.97)	***P* =0.01**
Whole blood					
Pottala 2010 (31)	HSS	956	237	1.28 (0.79, 2.07)	***P* =0.32**
All Tissue types combined					
Marklund 2015 (20)	60YO-Men	1,733	265	0.73 (0.64, 0.83)	6.13
Huang 2012 (30)	DIA Patient	222	61	0.73 (0.55, 0.97)	2.21
Virtanen 2018 (19)	KIHD	2,480	1,143	0.81 (0.76, 0.87)	9.32
Erkkila 2003 (24)	EUROASPIRE-Fin	398	35	0.81 (0.50, 1.33)	0.84
Miura 2016 (34)	NSCS-Men	444	98	0.82 (0.65, 1.03)	3.06
Warensjö 2008 (25)	ULSAM 50	2,009	1,012	0.87 (0.81, 0.93)	9.24
Satizabal 2018 (36)	3C	1,406	251	0.87 (0.66, 1.16)	2.22
Iggman 2016 (27)	ULSAM 70	853	605	0.90 (0.82, 0.98)	8.16
Delgado 2017 (32)	LURIC	3,259	975	0.91 (0.85, 0.97)	9.4
Wu 2014 (22)	CHS	2,792	1,994	0.95 (0.89, 1.01)	9.58
Marklund 2015 (20)	60YO-Women	1,938	191	0.95 (0.81, 1.12)	4.86
Harris 2013 (28)	TRIUMPH	1,144	135	0.96 (0.88, 1.04)	8.46
Lelli 2019 (18)	InCHIANTI	927	318	0.96 (0.81, 1.15)	4.47
Harris 2018 (35)	Framingham	2,500	350	0.97 (0.82, 1.14)	4.86
Harris 2017 (29)	WHIMS	6,501	1,851	0.99 (0.94, 1.04)	10.12
Miura 2016 (34)	NSCS-Women	564	81	1.04 (0.83, 1.30)	3.17
Lindberg 2008 (33)	Old patients	254	156	1.09 (0.86, 1.37)	3.03
Pottala 2010 (31)	HSS	956	237	1.28 (0.79, 2.07)	0.86
Total: Cohorts=16		**30,380**	**9,758**		
Overall (I^2 =64.1%, *P* <0.001)		**Random effect**		**0.91 (0.87, 0.95)**	***P* <0.001**



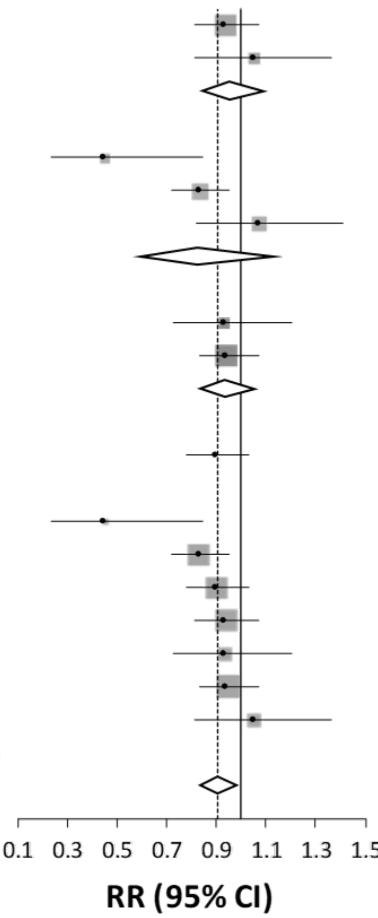
B CVD mortality

Reference	Cohort Name	Total N	Case N	HR (95%CI)	% Weight
Adipose Tissue					
Marklund 2019 (21)	SHHEC	4,391	308	0.73 (0.58, 0.91)	42.54
Iggman 2016 (27)	ULSAM 70	853	251	0.92 (0.80, 1.06)	57.46
Summary (I^2 =65.6%; *P* =0.09)		5,244	559	0.83 (0.67, 1.04)	***P* =0.11**
Phospholipids					
Marklund 2019 (21)	AGES-Reykjavik	1,195	162	0.85 (0.68, 1.07)	10.47
Marklund 2019 (21)	MCCS	6,265	282	0.90 (0.70, 1.16)	8.64
Marklund 2019 (21)	MESA	2,722	208	0.91 (0.66, 1.25)	5.3
Marklund 2019 (21)	EPIC-Norfolk	7,016	951	0.92 (0.81, 1.05)	31.43
Marklund 2019 (21)	CHS	2,907	832	0.93 (0.81, 1.08)	26.88
Marklund 2019 (21)	ARIC	3,749	289	1.06 (0.89, 1.27)	17.28
Summary (I^2 =0%; *P* =0.72)		23,854	2,724	0.94 (0.87, 1.01)	***P* =0.084**
Cholesterol esters					
Marklund 2019 (21)	60YO	4,150	69	0.71 (0.49, 1.03)	4.89
de Goede 2013 (23)	MP-2	114	57	0.83 (0.53, 1.32)	3.2
Warensjö 2008 (25)	ULSAM 50	2,009	461	0.85 (0.78, 0.94)	76.61
de Goede 2013 (23)	MP-1	444	222	0.97 (0.78, 1.21)	13.83
Erkkila 2003 (24)	EUROASPIRE-Finla	398	18	1.34 (0.68, 2.64)	1.47
Summary (I^2 =0%; *P* =0.41)		7,115	827	0.86 (0.80, 0.94)	***P* < 0.001**
Erythrocytes					
Delgado 2017 (32)	LURIC	3,259	614	0.93 (0.86, 1.01)	54.31
Harris 2017 (29)	WHIMS	6,501	617	0.96 (0.88, 1.05)	43.83
Harris 2018 (35)	Framingham	2,500	58	0.96 (0.62, 1.49)	1.85
Summary (I^2 =0%; *P* =0.87)		12,260	1,289	0.94 (0.89, 1.00)	***P* =0.055**
Total Serum or Plasma					
Marklund 2019 (21)	CCCC	1,838	306	0.55 (0.39, 0.79)	15.34
Virtanen 2018 (19)	KIHD	2,480	575	0.81 (0.73, 0.89)	53.38
Marklund 2019 (21)	HS	3,103	98	0.86 (0.57, 1.30)	12
Lelli 2019 (18)	InCHIANTI	927	114	0.87 (0.64, 1.18)	19.27
Summary (I^2 =34.5%; *P* =0.21)		8,348	1,093	0.78 (0.67, 0.91)	***P* =0.002**
All Tissue types combined					
Marklund 2019 (21)	CCCC	1,838	306	0.55 (0.39, 0.79)	1.63
Marklund 2019 (21)	60YO	4,150	69	0.71 (0.49, 1.03)	1.51
Marklund 2019 (21)	SHHEC	4,391	308	0.73 (0.58, 0.91)	3.66
Virtanen 2018 (19)	KIHD	2,480	575	0.81 (0.73, 0.89)	10.85
de Goede 2013 (23)	MP-2	114	57	0.83 (0.53, 1.31)	1.02
Marklund 2019 (21)	AGES-Reykjavik	1,195	162	0.85 (0.68, 1.07)	3.55
Warensjö 2008 (25)	ULSAM 50	2,009	461	0.85 (0.77, 0.93)	11.48
Marklund 2019 (21)	HS	3,103	98	0.86 (0.57, 1.31)	1.22
Lelli 2019 (18)	InCHIANTI	927	114	0.87 (0.64, 1.18)	2.15
Marklund 2019 (21)	MCCS	6,265	282	0.90 (0.70, 1.16)	3.02
Marklund 2019 (21)	MESA	2,722	208	0.91 (0.66, 1.25)	1.96
Iggman 2016 (27)	ULSAM 70	853	251	0.92 (0.80, 1.06)	7.3
Marklund 2019 (21)	EPIC-Norfolk	7,016	951	0.92 (0.81, 1.05)	7.95
Delgado 2017 (32)	LURIC	3,259	614	0.93 (0.86, 1.01)	12.98
Marklund 2019 (21)	CHS	2,907	832	0.93 (0.81, 1.08)	7.19
Harris 2017 (29)	WHIMS	6,501	617	0.96 (0.88, 1.05)	11.91
Harris 2018 (35)	Framingham	2,500	58	0.96 (0.62, 1.49)	1.11
de Goede 2013 (23)	MP-1	444	222	0.97 (0.78, 1.21)	3.78
Marklund 2019 (21)	ARIC	3,749	289	1.06 (0.89, 1.27)	5.27
Erkkila 2003 (24)	EUROASPIRE-Finla	398	18	1.34 (0.68, 2.64)	0.48
Total: Cohorts=20		**56,821**	**6,492**		
Overall (I^2 =28.9%, *P* =0.11)		**Random effect**		**0.89 (0.85, 0.94)**	***P* <0.001**

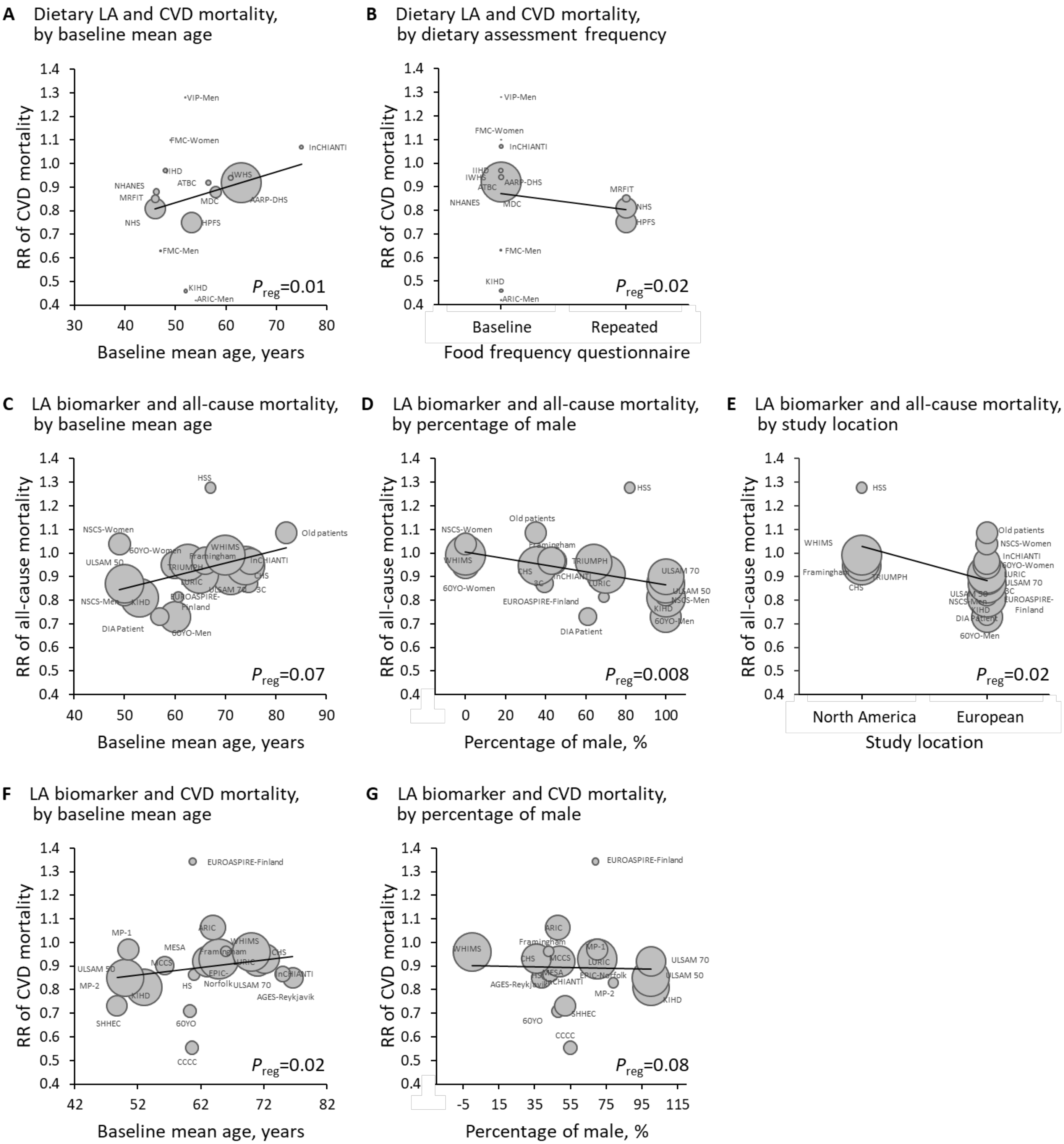


C Cancer mortality

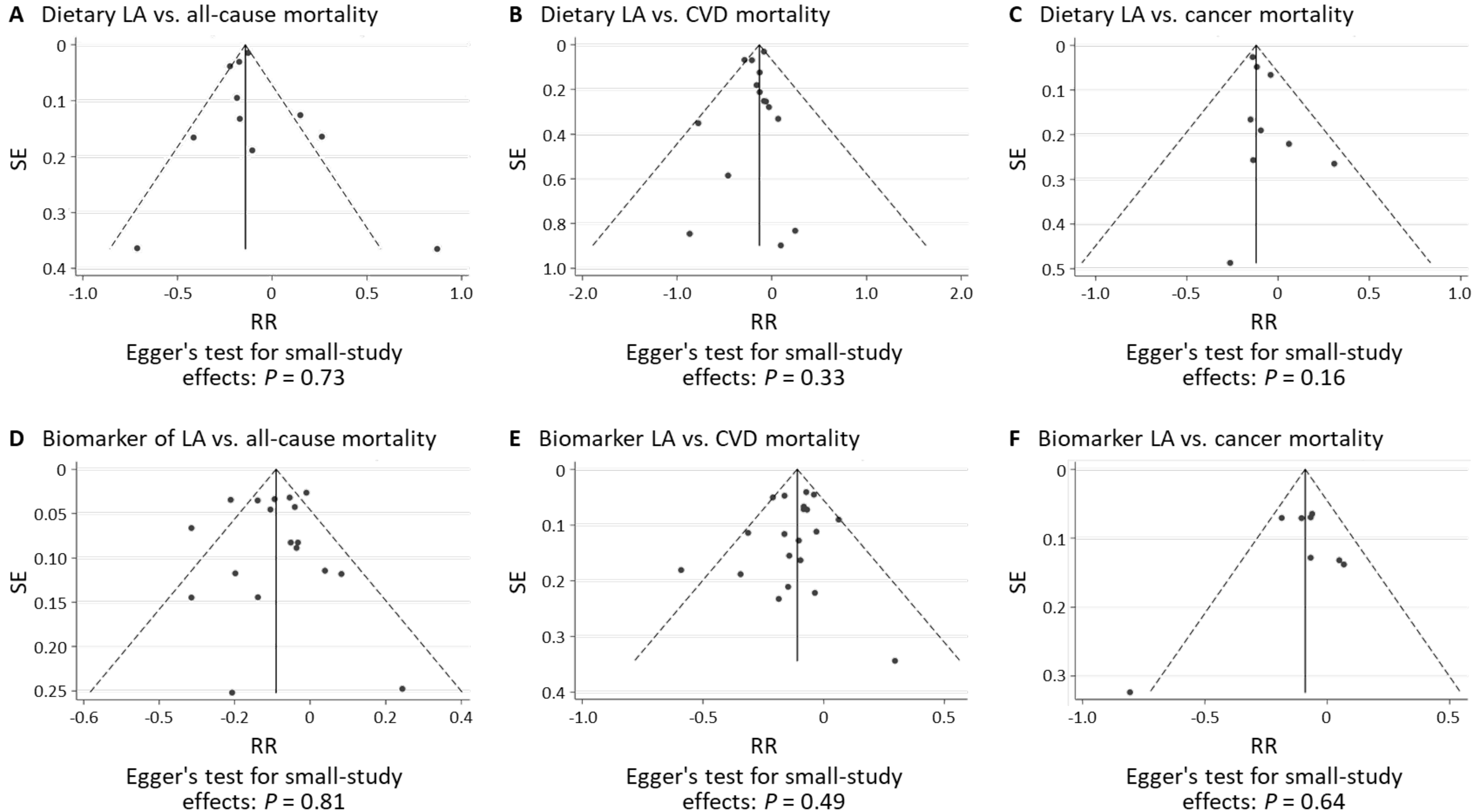
Reference	Cohort Name	Total N	Case N	HR (95%CI)	% Weight
Phospholipids					
Wu 2014 (22)	CHS	2,792	411	0.93 (0.81, 1.07)	78.19
Simon 1998 (38)	MRFIT	323	108	1.05 (0.81, 1.36)	21.81
Summary (*I*^{2} =0%; *P* =0.44)		3,115	519	0.96 (0.85, 1.08)	***P* =0.49**
Cholesterol esters					
Zureik 1995 (37)	PPSII	3,277	59	0.45 (0.24, 0.84)	16.4
Kilander 2001 (26)	ULSAM 50	1,990	216	0.83 (0.72, 0.95)	46.62
Simon 1998 (38)	MRFIT	323	108	1.07 (0.82, 1.41)	36.98
Summary (*I*^{2} =70.7%; *P* =0.03)		5,590	383	0.82 (0.60, 1.13)	***P*= 0.22**
Erythrocytes					
Harris 2018 (35)	Framingham	2,500	146	0.93 (0.73, 1.20)	20.27
Harris 2017 (29)	WHIMS	6,501	462	0.94 (0.83, 1.07)	79.73
Summary (*I*^{2} =0%; *P* =0.0.97)		9,001	608	0.94 (0.84, 1.05)	***P* =0.28**
Total Serum or Plasma					
Virtanen 2018 (19)	KIHD	2,480	317	0.90 (0.78, 1.03)	***P* =0.14**
All Tissue types combined					
Zureik 1995 (37)	PPSII	3,277	59	0.45 (0.24, 0.84)	1.45
Kilander 2001 (26)	ULSAM 50	1,990	216	0.83 (0.72, 0.95)	20.06
Virtanen 2018 (19)	KIHD	2,480	317	0.90 (0.78, 1.03)	19.98
Wu 2014 (22)	CHS	2,792	411	0.93 (0.81, 1.07)	20.39
Harris 2018 (35)	Framingham	2,500	146	0.93 (0.73, 1.20)	8.07
Harris 2017 (29)	WHIMS	6,501	462	0.94 (0.83, 1.07)	22.38
Simon 1998 (38)	MRFIT	323	108	1.05 (0.81, 1.36)	7.68
Total: Cohorts=7		**19,863**	**1,719**		
Overall (*I*^{2} =26.3%, *P* <0.23)		**Random effect**		**0.91 (0.84, 0.98)**	***P* =0.01**



Supplement Figure 3 Baseline mean age (A) and dietary assessment frequency (B) are potential sources of heterogeneity for the association between dietary linoleic acid (LA) intake and total mortality; baseline mean age (C and F), sex (D and G), and study location (E) are potential sources of heterogeneity for associations between LA biomarkers with total and CVD mortality. Each circle denotes one study, with the size proportional to the weight of the study in meta-analyses. The x-axis is the scale for populational characteristics, and the y-axis shows the relative risks (comparing extreme quantiles for studies of dietary intakes; per standard deviation increment in LA biomarkers for studies of biomarkers).



Supplement Figure 4 Funnel plots for meta-analysis of dietary linoleic acid intake with mortality from all-causes (A), CVD (B), and cancers (C), and for meta-analysis of biomarkers of linoleic acid with mortality from all-causes (D), CVD (E), and cancers (F). We used funnel plots and the Egger's tests to evaluate publication bias and small-study effects.



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