Supplementary data

Dietary intake of linoleic acid, its concentrations and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of prospective cohort studies

***Corresponding author:** Ahmad Esmaillzadeh, Professor, Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, P. O. Box 14155/6117, Tehran, Iran Telefax: +98(21)88955979, Email: a-esmaillzadeh@tums.ac.ir

Supplementary data including 9 supplemental Tables, and 7 supplemental Figures

Supplementary data

Supplemental Table 1. Search strategy to find the relevant articles for inclusion in this meta-analysis of dietary intake and biomarkers of Linoleic acid and the risk of type 2 diabetes

PubMed

"Fatty Acids"[Mesh] OR "Fatty Acids, Unsaturated"[Mesh] OR "Fatty Acids, Essential"[Mesh] OR "Linoleic Acid"[Mesh] OR "Linoleic Acids"[Mesh] OR "Fatty Acids, Omega-6"[Mesh] OR "n-6 fatty acid*"[Title/Abstract] OR "omega-6 fatty acid*"[Title/Abstract] OR "Omega 6 Fatty Acids"[Title/Abstract] OR "N-6 Fatty Acids"[Title/Abstract] OR "Linoleic Acids"[Title/Abstract] OR "Linoleic Acid"[Title/Abstract] OR "α-linoleic acid*"[Title/Abstract] OR "Linoleic Acids"[Title/Abstract] OR "Linoleic Acid"[Title/Abstract] OR "Linoelaidic Acid"[Title/Abstract] OR "Linolelaidic Acid"[Title/Abstract] OR "essential fatty acid*"[Title/Abstract] OR "polyunsaturated fatty acid*"[Title/Abstract] OR "fatty acid"[Title/Abstract] OR "sunflower oil"[Title/Abstract] OR "corn oil"[Title/Abstract

AND

"Diabetes Mellitus, Type 2"[Mesh] OR "Diabetes Mellitus"[Mesh] OR Diabetes[Title/Abstract] OR Diabetic[Title/Abstract]) OR "Diabetes type 2"[Title/Abstract] OR "Type II diabetes"[Title/Abstract] OR "Type 2 diabetes"[Title/Abstract]) OR "Type 2 diabetes mellitus"[Title/Abstract] OR "Diabetes mellitus non-insulin dependent"[Title/Abstract] OR "Noninsulin dependent diabetes mellitus"[Title/Abstract]

AND

"Cohort Studies"[Mesh]) OR "Observation"[Mesh]) OR "Prospective Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR Cohort*[Title/Abstract]) OR "Cohort Studies"[Title/Abstract] OR "Concurrent Study"[Title/Abstract] OR "Incidence Studies"[Title/Abstract]) OR incident*[Title/Abstract] OR incidence*[Title/Abstract]) OR Observation[Title/Abstract] OR "Prospective Studies"[Title/Abstract] OR Prospectively[Title/Abstract] OR Prospective[Title/Abstract] OR Longitudinal[Title/Abstract] OR Observational[Title/Abstract] OR Follow-Up[Title/Abstract] OR Nested[Title/Abstract] OR "Relative risk"[Title/Abstract] OR "Hazard ratio"[Title/Abstract] OR RR[Title/Abstract] OR HR[Title/Abstract]

Supplementary data

Scopus

TITLE-ABS-KEY ("n-6 fatty acid") OR TITLE-ABS-KEY ("omega-6 fatty acid") OR TITLE-ABS-KEY ("Omega 6 Fatty Acids") OR TITLE-ABS-KEY ("N-6 Fatty Acids") OR TITLE-ABS-KEY ("Linoleic Acids") OR TITLE-ABS-KEY ("Linoleic Acid") OR TITLE-ABS-KEY ("α-linolenic acid") OR TITLE-ABS-KEY ("Linoleic Acids") OR TITLE-ABS-KEY ("Linoleic Acid") OR TITLE-ABS-KEY ("Linoelaidic Acid") OR TITLE-ABS-KEY ("Linolelaidic Acid") OR TITLE-ABS-KEY ("essential fatty acid") OR TITLE-ABS-KEY ("polyunsaturated fatty acid") OR TITLE-ABS-KEY ("fatty acid") OR TITLE-ABS-KEY ("sunflower oil") OR TITLE-ABS-KEY ("corn oil")
AND
TITLE-ABS-KEY ("Diabetes") OR TITLE-ABS-KEY ("Diabetic") OR TITLE-ABS-KEY ("Diabetes type 2") OR TITLE-ABS-KEY ("Type II diabetes") OR TITLE-ABS-KEY ("Type 2 diabetes") OR TITLE-ABS-KEY ("Type 2 diabetes mellitus") OR TITLE-ABS-KEY ("Non-insulin dependent diabetes") OR TITLE-ABS-KEY ("Noninsulin dependent diabetes mellitus") OR TITLE-ABS-KEY ("Diabetes mellitus non-insulin dependent")
AND
TITLE-ABS-KEY ("Cohort Studies") OR TITLE-ABS-KEY (observation) OR TITLE-ABS-KEY ("Prospective Studies") OR TITLE-ABS-KEY ("Longitudinal Studies") OR TITLE-ABS-KEY ("Observational Study") OR TITLE-ABS-KEY ("Follow-Up Studies") OR TITLE-ABS-KEY ("Case-Control Studies") OR TITLE-ABS-KEY (cohorts) OR TITLE-ABS-KEY (cohort) OR TITLE-ABS-KEY ("Cohort Studies") OR TITLE-ABS-KEY ("Concurrent Study") OR TITLE-ABS-KEY ("Incidence Studies") OR TITLE-ABS-KEY (incident) OR TITLE-ABS-KEY (incidence) OR TITLE-ABS-KEY (observation) OR TITLE-ABS-KEY ("Prospective Studies") OR TITLE-ABS-KEY (prospectively) OR TITLE-ABS-KEY (prospective) OR TITLE-ABS-KEY (longitudinal) OR TITLE-ABS-KEY (observational) OR TITLE-ABS-KEY (follow-up) OR TITLE-ABS-KEY (nested) OR TITLE-ABS-KEY ("Relative risk") OR TITLE-ABS-KEY ("Hazard ratio")

Supplementary data

Web of Science

TS= ("n-6 fatty acid" OR "omega-6 fatty acid" OR "Omega 6 Fatty Acids" OR "N-6 Fatty Acids" OR "Linoleic Acids" OR "Linoleic Acid" OR "Linoleic Acids" OR "Linoelaidic Acid" OR "Linolelaidic Acid" OR "essential fatty acid" OR "polyunsaturated fatty acid" OR "fatty acid" OR "sunflower oil" OR "corn oil")
AND
TS= ("Diabetes" OR "Diabetic" OR "Diabetes type 2" OR "Type II diabetes" OR "Type 2 diabetes" OR "Type 2 diabetes mellitus" OR "Diabetes Mellitus" OR "Noninsulin dependent diabetes mellitus" OR "Diabetes mellitus non-insulin-dependent")
AND
TS= ("Cohorts" OR "Cohort" OR "Cohort Studies" OR "Concurrent Study" OR "Incidence Studies" OR "incident" OR "incidence" OR "Observation" OR "Prospective Studies" OR "Prospectively" OR "Prospective" OR "Longitudinal" OR "Observational" OR "Follow-Up " OR "Nested" OR "Relative risk" OR "Hazard ratio" OR "Case-Control Studies")

Supplementary data

Supplemental Table 2: Reason for exclusion of retrieved articles

References	Reason for exclusion
1. Feskens EJM, Virtanen SM, Räsänen L, Tuomilehto J, Stengård J, Pekkanen J, et al. Dietary factors determining diabetes and impaired glucose tolerance: A 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. Diabetes Care. 1995;18(8):1104-12.	Not assessed LA as exposure
2. Harding AH, Day NE, Khaw KT, Bingham S, Luben R, Welsh A, et al. Dietary Fat and the Risk of Clinical Type 2 Diabetes: The European Prospective Investigation of Cancer-Norfolk Study. American Journal of Epidemiology. 2004;159(1):73-82.	Not assessed LA as exposure
3. Pankow JS, Duncan BB, Schmidt MI, Ballantyne CM, Couper DJ, Hoogeveen RC, et al. Fasting plasma free fatty acids and risk of type 2 diabetes: The Atherosclerosis Risk in Communities study. Diabetes Care. 2004;27(1):77-82.	Not assessed LA as exposure
4. Kaushik M, Mozaffarian D, Spiegelman D, Manson JE, Willett WC, Hu FB. Long-chain omega-3 fatty acids, fish intake, and the risk of type 2 diabetes mellitus. American Journal of Clinical Nutrition. 2009;90(3):613-20.	Not assessed LA as exposure
5. Brostow DP, Odegaard AO, Koh WP, Duval S, Gross MD, Yuan JM, et al. Omega-3 fatty acids and incident type 2 diabetes: The Singapore Chinese Health Study. American Journal of Clinical Nutrition. 2011;94(2):520-6.	Not assessed LA as exposure
6. Djousse L, Biggs ML, Lemaitre RN, King IB, Song X, Ix JH, et al. Plasma omega-3 fatty acids and incident diabetes in older adults. The American journal of clinical nutrition. 2011;94(2):527-33.	Not assessed LA as exposure
7. Djoussé L, Gaziano JM, Buring JE, Lee IM. Dietary omega-3 fatty acids and fish consumption and risk of type 2 diabetes. American Journal of Clinical Nutrition. 2011;93(1):143-50.	Not assessed LA as exposure
8. Villegas R, Xiang YB, Elasy T, Li HL, Yang G, Cai H, et al. Fish, shellfish, and long-chain n-3 fatty acid consumption and risk of incident type 2 diabetes in middle-aged Chinese men and women. American Journal of Clinical Nutrition. 2011;94(2):543-51.	Not assessed LA as exposure

Supplementary data

9. Djousse L, Khawaja O, Bartz TM, Biggs ML, Ix JH, Zieman SJ, et al. Plasma fatty acid-binding protein 4, nonesterified fatty acids, and incident diabetes in older adults. Diabetes Care. 2012;35(8):1701-7.	Not assessed LA as exposure
10. Patel PS, Forouhi NG, Kuijsten A, Schulze MB, Van Woudenbergh GJ, Ardanaz E, et al. The prospective association between total and type of fish intake and type 2 diabetes in 8 European countries: EPIC-InterAct study. American Journal of Clinical Nutrition. 2012;95(6):1445-53.	Not assessed LA as exposure
11. Imamura F, Lemaitre RN, King IB, Song XL, Siscovick DS, Mozaffarian D. Circulating Fatty Acid Patterns and Incidence of Type 2 Diabetes Mellitus: The Cardiovascular Health Study. Circulation. 2013;127(12).	Not assessed LA as exposure
12. Mozaffarian D, De Oliveira Otto MC, Lemaitre RN, Fretts AM, Hotamisligil G, Tsai MY, et al. Trans-Palmitoleic acid, other dairy fat biomarkers, and incident diabetes: The multi-ethnic study of atherosclerosis (MESA). American Journal of Clinical Nutrition. 2013;97(4):854-61.	Not assessed LA as exposure
13. Alhazmi A, Stojanovski E, McEvoy M, Garg ML. Macronutrient intake and type 2 diabetes risk in middle-aged Australian women. Results from the australian longitudinal study on women's health. Public Health Nutrition. 2014;17(7):1587-94.	Not assessed LA as exposure
14. Forouhi NG, Koulman A, Sharp SJ, Imamura F, Kröger J, Schulze MB, et al. Differences in the prospective association between individual plasma phospholipid saturated fatty acids and incident type 2 diabetes: The EPIC-InterAct case-cohort study. The Lancet Diabetes and Endocrinology. 2014;2(10):810-8.	Not assessed LA as exposure
15. Koloverou E, Panagiotakos DB, Pitsavos C, Chrysohoou C, Georgousopoulou EN, Pitaraki E, et al. 10-year incidence of diabetes and associated risk factors in Greece: the ATTICA study (2002-2012). The review of diabetic studies : RDS. 2014;11(2):181-9.	Not assessed LA as exposure
16. Virtanen JK, Mursu J, Voutilainen S, Uusitupa M, Tuomainen TP. Serum omega-3 polyunsaturated fatty acids and risk of incident type 2 diabetes in men: The kuopio ischemic heart disease risk factor study. Diabetes Care. 2014;37(1):189-96.	Not assessed LA as exposure
17. Ericson U, Hellstrand S, Brunkwall L, Schulz CA, Sonestedt E, Wallström P, et al. Food sources of fat may clarify the inconsistent role of dietary fat intake for incidence of type 2 diabetes. American Journal of Clinical Nutrition. 2015;101(5):1065-80.	Not assessed LA as exposure

Supplementary data

18. Jacobs S, Schiller K, Jansen E, Boeing H, Schulze MB, Kroger J. Evaluation of various biomarkers as potential mediators of the association between Delta 5 desaturase, Delta 6 desaturase, and stearoyl-CoA desaturase activity and incident type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition-Potsdam Study. American Journal of Clinical Nutrition. 2015;102(1):155-64.	Not assessed LA as exposure
19. Lemaitre RN, Fretts AM, Sitlani CM, Biggs ML, Mukamal K, King IB, et al. Plasma phospholipid very-long-chain saturated fatty acids and incident diabetes in older adults: the Cardiovascular Health Study. The American journal of clinical nutrition. 2015;101(5):1047-54.	Not assessed LA as exposure
20. Ma W, Wu JH, Wang Q, Lemaitre RN, Mukamal KJ, Djousse L, et al. Prospective association of fatty acids in the de novo lipogenesis pathway with risk of type 2 diabetes: the Cardiovascular Health Study. The American journal of clinical nutrition. 2015;101(1):153-63.	Not assessed LA as exposure
21. Wang Q, Imamura F, Ma W, Wang M, Lemaitre RN, King IB, et al. Circulating and dietary trans fatty acids and incident type 2 diabetes in older adults: The cardiovascular health study. Diabetes Care. 2015;38(6):1099-107.	Not assessed LA as exposure
22. Wenjie M, Wu JHY, Wang Q, Lemaitre RN, Mukamal KJ, Djoussé L, et al. Prospective association of fatty acids in the de novo lipogenesis pathway with risk of type 2 diabetes: The Cardiovascular Health Study. American Journal of Clinical Nutrition. 2015;101(1):153-63.	Not assessed LA as exposure
23. Yakoob MY, Shi PL, Willett WC, Rexrode KM, Campos H, Orav EJ, et al. Circulating Biomarkers of Dairy Fat and Risk of Incident Diabetes Mellitus Among Men and Women in the United States in Two Large Prospective Cohorts. Circulation. 2016;133(17):1645-54.	Not assessed LA as exposure
24. Imamura F, Sharp SJ, Koulman A, Schulze MB, Kröger J, Griffin JL, et al. A combination of plasma phospholipid fatty acids and its association with incidence of type 2 diabetes: The EPIC-InterAct case-cohort study. PLoS Medicine. 2017;14(10).	Not assessed LA as exposure
25. Itcho K, Yoshii Y, Ohno H, Oki K, Shinohara M, Irino Y, et al. Association between serum elaidic acid concentration and insulin resistance in two Japanese cohorts with different lifestyles. Journal of Atherosclerosis and Thrombosis. 2017;24(12):1206-14.	Not assessed LA as exposure

26. Krishnan S, Steffen LM, Paton CM, Cooper JA. Impact of dietary fat composition on prediabetes: a 12-year follow-up study. Public Health Nutr. 2017;20(9):1617-26.	Not assessed LA as exposure
27. Lin JS, Dong HL, Chen GD, Chen ZY, Dong XW, Zheng JS, et al. Erythrocyte saturated fatty acids and incident type 2 diabetes in chinese men and women: A prospective cohort study. Nutrients. 2018;10(10).	Not assessed LA as exposure
28. Shi L, Brunius C, Lehtonen M, Auriola S, Bergdahl IA, Rolandsson O, et al. Plasma metabolites associated with type 2 diabetes in a Swedish population: a case–control study nested in a prospective cohort. Diabetologia. 2018;61(4):849-61.	Not assessed LA as exposure
29. Wang Y, Meng X, Deng X, Okekunle AP, Wang P, Zhang Q, et al. Postprandial Saturated Fatty Acids Increase the Risk of Type 2 Diabetes: A Cohort Study in a Chinese Population. Journal of Clinical Endocrinology and Metabolism. 2018;103(4):1438-46.	Not assessed LA as exposure
30. Gaeini Z, Bahadoran Z, Mirmiran P, Djazayery A. The association between dietary fat pattern and the risk of type 2 diabetes. Preventive Nutrition and Food Science. 2019;24(1):1-7.	Not assessed LA as exposure
31. Liu S, van der Schouw YT, Soedamah-Muthu SS, Spijkerman AMW, Sluijs I. Intake of dietary saturated fatty acids and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition-Netherlands cohort: associations by types, sources of fatty acids and substitution by macronutrients. European Journal of Nutrition. 2019;58(3):1125-36..	Not assessed LA as exposure
32. Qian F, Korat AVA, Imamura F, Marklund M, Tintle N, Virtanen JK, et al. Omega-3 Fatty Acid Biomarkers and Incident Type 2 Diabetes: An Individual Participant-level Pooling Project of 20 Prospective Cohort Studies. Circulation. 2019;139.	Not assessed LA as exposure
33. Seah JYH, Ong CN, Koh WP, Yuan JM, Van Dam RM. A Dietary Pattern Derived from Reduced Rank Regression and Fatty Acid Biomarkers Is Associated with Lower Risk of Type 2 Diabetes and Coronary Artery Disease in Chinese Adults. Journal of Nutrition. 2019;149(11):2001-10.	Not assessed LA as exposure
34. Zhang Y, Zhuang P, Mao L, Chen XQ, Wang J, Cheng LF, et al. Current level of fish and omega-3 fatty acid intakes and risk of Type 2 diabetes in China. Journal of Nutritional Biochemistry. 2019;74.	Not assessed LA as exposure

35. Zheng JS, Lin JS, Dong HL, Zeng FF, Li D, Song YQ, et al. Association of erythrocyte n-3 polyunsaturated fatty acids with incident type 2 diabetes in a Chinese population. Clinical Nutrition. 2019;38(5):2195-201.	Not assessed LA as exposure
36. Korat AVA, Malik VS, Furtado JD, Sacks F, Rosner B, Rexrode KM, et al. Circulating Very-Long-Chain SFA Concentrations Are Inversely Associated with Incident Type 2 Diabetes in US Men and Women. Journal of Nutrition. 2020;150(2):340-9.	Not assessed LA as exposure
37. Li N, Qiu Y, Wu Y, Zhang M, Lai Z, Wang Q, et al. Association of serum total fatty acids with type 2 diabetes. Clinica Chimica Acta. 2020;500:59-68.	Not assessed LA as exposure
38. Weir NL, Steffen BT, Guan W, Johnson LM, Djousse L, Mukamal KJ, et al. Circulating omega-7 fatty acids are differentially related to metabolic dysfunction and incident type II diabetes: The Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes and Metabolism. 2020;46(4):319-25.	Not assessed LA as exposure
39. Lindström J, Peltonen M, Eriksson JG, Louheranta A, Fogelholm M, Uusitupa M, et al. High-fibre, low-fat diet predicts long-term weight loss and decreased type 2 diabetes risk: The Finnish Diabetes Prevention Study. Diabetologia. 2006;49(5):912-20.	Not assessed LA as exposure
40. Tso AW, Xu A, Sham PC, Wat NM, Wang Y, Fong CH, et al. Serum adipocyte fatty acid binding protein as a new biomarker predicting the development of type 2 diabetes: a 10-year prospective study in a Chinese cohort. Diabetes Care. 2007;30(10):2667-72.	Not assessed LA as exposure
41. Meyer KA, Kushi LH, Jacobs Jr DR, Folsom AR. Dietary fat and incidence of type 2 diabetes in older Iowa women. Diabetes Care. 2001;24(9):1528-35.	Not assessed LA as exposure
42. Laaksonen DE, Lakka TA, Lakka HM, Nyyssönen K, Rissanen T, Niskanen LK, et al. Serum fatty acid composition predicts development of impaired fasting glycaemia and diabetes in middle-aged men. Diabetic Medicine. 2002;19(6):456-64.	Not relevant outcome
43. Wurtz P, Tiainen M, Makinen VP, Kangas AJ, Soininen P, Saltevo J, et al. Circulating metabolite predictors of glycemia in middle-aged men and women. Diabetes Care. 2012;35(8):1749-56.	Not relevant outcome

44. Clandinin MT, Wilke MS. Do trans fatty acids increase the incidence of type 2 diabetes? American Journal of Clinical Nutrition. 2001;73(6):1001-2.	Other study designs
45. Liu W. Concerns regarding the interpretation of fatty fish intake and type 2 diabetes in the EPIC-InterAct Study. American Journal of Clinical Nutrition. 2012;96(4):941.	Other study designs
46. Jeppesen C, Schiller K, Schulze MB. Omega-3 and omega-6 fatty acids and type 2 diabetes. Current Diabetes Reports. 2013;13(2):279-88.	Other study designs
47. Henderson G, Crofts C, Schofield G. Linoleic acid and diabetes prevention. The Lancet Diabetes and Endocrinology. 2018;6(1):12-3.	Other study designs
48. Fretts AM, Imamura F, Marklund M, Micha R, Wu JHY, Murphy RA, et al. Associations of circulating very-long-chain saturated fatty acids and incident type 2 diabetes: A pooled analysis of prospective cohort studies. American Journal of Clinical Nutrition. 2019;109(4):1216-23.	Other study designs
49. Imamura F, Fretts AM, Marklund M, Ardisson Korat AV, Yang WS, Lankinen M, et al. Fatty acids in the de novo lipogenesis pathway and incidence of type 2 diabetes: A pooled analysis of prospective cohort studies. PLoS Medicine. 2020;17(6).	Other study designs
50. Shetty SS, Kumari NS, Shetty PK. omega-6/omega-3 fatty acid ratio as an essential predictive biomarker in the management of type 2 diabetes mellitus. Nutrition. 2020;79-80:110968.	Other study designs
51. Zulyniak MA, Fuller H, Iles MM. Investigation of the Causal Association between Long-Chain n-6 Polyunsaturated Fatty Acid Synthesis and the Risk of Type 2 Diabetes: A Mendelian Randomization Analysis. Lifestyle Genomics. 2020;13(5):146-53.	Other study designs
52. Hernández-Alonso P, Salas-Salvadó J, Ruiz-Canela M, Corella D, Estruch R, Fitó M, et al. High dietary protein intake is associated with an increased body weight and total death risk. Clinical Nutrition. 2016;35(2):496-506.	Duplicate report
53. Salmeron J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB, et al. Dietary fat intake and risk of type 2 diabetes in women. The American journal of clinical nutrition. 2001;73(6):1019-26.	Duplicate report

54. van Dam RM, Stampfer M, Willett WC, Hu FB, Rimm EB. Dietary fat and meat intake in relation to risk of type 2 diabetes in men. Diabetes Care. 2002;25(3):417-24.	Duplicate report
55. Wang L, Folsom AR, Zheng ZJ, Pankow JS, Eckfeldt JH. Plasma fatty acid composition and incidence of diabetes in middle aged adults: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2002;106(19):731-.	Duplicate report
56. Dow C, Mangin M, Balkau B, Affret A, Boutron-Ruault MC, Clavel-Chapelon F, et al. Fatty acid consumption and incident type 2 diabetes: evidence from the E3N cohort study. Diabetologia. 2016;59:S145-S.	Duplicate report
57. Wu JH, Marklund M, Imamura F, Tintle N, Korat AVA, de Goede J, et al. Omega-6 Fatty Acid Biomarkers and Incident Type 2 Diabetes: A Pooled Analysis of 20 Cohort Studies. Circulation. 2017;135.	Duplicate report
58. Lu Y, Wang Y, Zou L, Liang X, Ong CN, Tavintharan S, et al. Serum lipids in association with type 2 diabetes risk and prevalence in a Chinese population. Journal of Clinical Endocrinology and Metabolism. 2018;103(2):671-80.	Duplicate report
59. Zong G, Liu G, Wanders AJ, Alssema M, Zock PL, Willett W, et al. Dietary Linoleic Acid Intake Is Inversely Associated With Type 2 Diabetes Risk In Three Large Prospective Cohort Studies Of U.s. Men And Women. Circulation. 2018;137.	Duplicate report
60. Ahola-Olli AV, Mustelin L, Kalimeri M, Kettunen J, Jokelainen J, Auvinen J, et al. Circulating metabolites and the risk of type 2 diabetes: a prospective study of 11,896 young adults from four Finnish cohorts. Diabetologia. 2019;62(12):2298-309.	Duplicate report
61. Ahola-Olli AV, Mustelin L, Kalimeri M, Kettunen J, Jokelainen J, Auvinen J, et al. Circulating metabolites and the risk of type 2 diabetes: a prospective study of 11,896 young adults from four Finnish cohorts. Diabetologia. 2019;62(12):2298-309.	Duplicate report
62. Harbers MC, Pertiwi K, Soedamah-Muthu SS, de Goede J, Molenberg FJ, Wanders AJ, et al. Plasma and Dietary Linoleic Acid and Diabetes Incidence After Myocardial Infarction. Circulation. 2018;137.	Conducted on patients

Supplementary data

63. Pertiwi K, Wanders AJ, Harbers MC, Kupers LK, Soedamah-Muthu SS, de Goede J, et al. Plasma and Dietary Linoleic Acid and 3-Year Risk of Type 2 Diabetes After Myocardial Infarction: A Prospective Analysis in the Alpha Omega Cohort. Diabetes Care. 2020;43(2):358-65.	Conducted on patients
64. Vessby B, Aro A, Skarfors E, Berglund L, Salminen I, Lithell H. The risk to develop NIDDM is related to the fatty acid composition of the serum cholesterol esters. Diabetes. 1994;43(11):1353-7.	No risk estimates
65. Alhazmi A, Stojanovski E, McEvoy M, Garg ML. Macronutrient intake and type 2 diabetes risk in middle-aged Australian women. Results from the australian longitudinal study on women's health. Public Health Nutrition. 2014;17(7):1587-94.	without sufficient data

Supplementary data

Supplemental Table 3. General characteristics of prospective cohort studies that investigated the association between LA intake and risk of type 2 diabetes.

First Author ,year	Study name, location	Age at entry (range, mean)	Total sample size	Mean follow-up (years)	Gender	Total cases	Dietary assessment	Outcome assessment	LA intake	RR (95% CI) (High vs. low intake category)	Adjustments*
Hodge et al, 2007	MCCS, Australia	36-72	3,737	4	M/F	346	Baseline FFQ	Self-reported confirmed by a doctor	Q5 vs. Q1	1.41 (0.92 - 2.17)	age, sex, country of birth, family history of diabetes, physical activity, alcohol intake, BMI, and waist-hip ratio
Patel et al, 2010	EPIC-Norfolk, England	40-79	383	10	M/F	199	Baseline FFQ	self-report of a physician's diagnosis/ diabetes medication	T3 vs. T1	0.72 (0.40 - 1.29)	age, sex, family history of diabetes, BMI, smoking status, physical activity, and alcohol intake
Kroger et al. 2011	EPIC-Potsdam, Germany	35-65	2,724	7	M/F	673	Baseline FFQ	Self-reported/ diabetes medication/dietary treatment	3.55 (% energy) 4.78 5.84 6.87 8.61	1.00 0.9 (0.63, 1.28) 1.14 (0.80, 1.63) 1.08 (0.76, 1.54) 1.11 (0.79 - 1.56)	age, sex, BMI, waist circumference, cycling, sports activity, education, smoking status, alcohol intake, occupational activity, coffee intake, fiber intake, total fat intake, and total energy intake
Dow et al. 2016	E3N, France	50-75	71,334	18	F	2,610	Baseline FFQ	Self-reported/ diabetes medication/dietary treatment/ hospitalization due to diabetes	<10·3 (g/d) 10·3–13·5 ≥13·5	1.00 0.98 (0.89, 1.08) 0.97 (0.87 - 1.07)	energy intake, alcohol consumption, education, family history of diabetes, physical activity, hypertension, hypercholesterolemia, smoking status, fatty acid groups, BMI
Guasch-Ferre et al. 2017	PREDIMED, Spain	55-80	3,339	4.3	M/F	226	Repeated FFQ	ADA criteria	3.5 (% energy) 4.6 5.6 7.3	1.00 0.92 (0.61, 1.39) 1.45 (0.95, 2.24) 1.01 (0.60 - 1.69)	age, sex, BMI, smoking status, educational status, leisure-time physical activity, yearly updated total energy intake, alcohol intake, yearly updated quartiles of fiber, protein intake, dietary cholesterol, baseline hypertension or the use of antihypertensive medication, baseline hypercholesterolemia or the use of lipid-lowering drugs, and fasting plasma glucose at baseline, specific subtypes of fat
Mirmiran et al. 2018	TLGS, Iran	20-70	2,139	5.8	M/F	143	Baseline FFQ	Participants who had FPG ≥126 mg/dl, or 2h plasma glucose ≥ 200 mg/dl during OGTT / using anti-diabetic medications	T3 vs. T1	0.72 (0.36 - 1.42)	age, energy intake, total fiber, magnesium, family history of diabetes, baseline SBP
Zong et al. 2019	NHS, USA	30-55	83,648	32	F	9375	Repeated FFQ	Self-reported/extra questionnaire	2.54 (% energy) 3.39	1.00 0.96 (0.89, 1.02)	Age, ethnicity, smoking status, alcohol intake, family history of diabetes, menopausal status,

Supplementary data

								e/National Diabetes Data Group criteria	4.07 4.86 6.23	0.99 (0.93, 1.07) 0.96 (0.89, 1.03) 0.98 (0.91 – 1.06)	postmenopausal hormone use, physical activity, multivitamin use, baseline hypertension, baseline hypercholesterolemia, BMI, total energy intake, intake of fruits and vegetables, fats, trans fats, MUFAs, and other PUFAs
Zong et al. 2019	NHSII, USA	25-44	88,610	22	F	5460	Repeated FFQ	Self-reported/extra questionnaire e/National Diabetes Data Group criteria	3.33 (% energy) 4.08 4.68 5.35 6.51	1.00 0.95 (0.87, 1.04) 0.91 (0.82, 1.00) 0.94 (0.85, 1.04) 0.93 (0.82, 1.05)	Age, ethnicity, smoking status, alcohol intake, family history of diabetes, menopausal status, postmenopausal hormone use, physical activity, multivitamin use, baseline hypertension, baseline hypercholesterolemia, BMI, total energy intake, intake of fruits and vegetables, fats, trans fats, MUFAs, and other PUFAs.
Zong et al. 2019	HPFS, USA	40-75	41,771	26	M	3607	Repeated FFQ	Self-reported/extra questionnaire e/National Diabetes Data Group criteria	3.45 (% energy) 4.35 5.05 5.83 7.16	1.00 0.87 (0.78, 0.97) 0.88 (0.79, 0.99) 0.83 (0.74, 0.94) 0.77 (0.67, 0.88)	Age, ethnicity, smoking status, alcohol intake, family history of diabetes, menopausal status, postmenopausal hormone use, physical activity, multivitamin use, baseline hypertension, baseline hypercholesterolemia, BMI, total energy intake, intake of fruits and vegetables, fats, trans fats, MUFAs, and other PUFAs
Abbreviations: CHD; coronary heart disease, HTN; hypertension, IHD; ischemic heart disease, MI; myocardial infarction, FFQ; food frequency questionnaire, HR; Risk ratio, CI; confidence interval, M; male, F; female, Q; quintile or quartile, T; tertile, BMI; body mass index, PUFA; polyunsaturated fatty acid, SFA; saturated fatty acid, US; United States America											

Supplementary data

Supplemental Table 4. General characteristics of prospective cohort studies (including nested case-control and case-cohort studies) that investigated the associations between LA biomarkers and risk of type 2 diabetes.

First Author ,year	Study name, location	Study design	Age at entry (range, mean)	Total sample size	Mean follow-up (years)	Gender	Total cases	Tissue type	Measuring method	Outcome assessment	Mean/median of LA, %FA	RR (95% CI) (High vs. low intake category)	Adjustments*
Wang et al, 2003	ARIC , USA	Cohort	53.6	2909	9	M/F	252	Cholesteryl esters (CE) plasma phospholipids (PL)	gas-liquid chromatography (GLC)	self-reported/ diabetes medications/ 8-h fasting serum glucose concentration ~ 126 mg/dL/ non-fasting serum glucose concentration ~ 200 mg/dL	22.03	CE: 0.47 (0.29 – 0.73) PL: 0.73 (0.50 – 0.99)	age , sex, BMI, waist-to-hip ratio, cigarette-years of smoking , alcohol intake , sports index , education, and parental history of diabetes
Hodge et al. 2007	MCCS, Australia	Case-cohort	54.8	3737	4	M/F	346	plasma phospholipids	gas-liquid chromatography with flame ionization detection (GLC-FID)	Self-reported	20.13	0.33 (0.20 – 0.56)	age, sex, country of birth, family history of diabetes, physical activity, alcohol intake, BMI, and waist-hip ratio
Krachler et al. 2008	VIP, Sweden	nested case-referent	51.6	450	5.4	M/F	159	Erythrocyte membrane	Gas-liquid chromatography (GLC)	WHO criteria	14.91	0.51 (0.39 – 0.68)	Alcohol intake, dietary fat-intake, BMI, HbA1c
Patel et al, 2010	EPIC-Norfolk, England	Cohort	64	383	10	M/F	199	Plasma phospholipids Erythrocyte membrane	Gas chromatography with flame ionization detection (GLC-FID)	Self-reported/ diabetes medication	23.76	PL: 0.50 (0.28 – 0.91) ER: 0.77 (0.43 – 1.37)	age, sex, family history of diabetes, BMI, smoking status, physical activity, and alcohol intake
Kroger et al. 2011	EPIC-Potsdam, Germany	nested case-cohort	51.2	2,724	7	M/F	673	Erythrocyte membrane	Gas chromatography with flame ionization detection (GLC-FID)	Self-reported/ diabetes medication/dietary treatment	10.7	0.76 (0.54 – 1.08)	age, sex, BMI, waist circumference, cycling, sports activity, education, smoking status, alcohol intake, occupational activity, coffee intake, fiber intake, total fat intake, and total energy intake
Mahendran et al. 2013	METSIM, Finland	Cohort	57	4335	4.5	M	276	Total serum	Nuclear magnetic resonance spectroscopy (NMRS)	Oral-glucose tolerance test	27.9	0.92 (0.89 – 0.95)	age, BMI, smoking, and physical activity

Supplementary data

Mahendran et al. 2014	METSIM, Finland	Cohort	54.9	735	5	M	30	Erythrocyte membrane	gas chromatography (GC)	Oral-glucose tolerance test	8.3	0.54 (0.35 – 0.82)	age, BMI, smoking, and physical activity
Lankinen et al. 2015	METSIM, Finland	Cohort	55	1301	5.9	M	71	plasma Phospholipids cholesteryl esters	gas chromatography (GC)	Oral-glucose tolerance test	18.6	PL: 0.78 (0.61 – 1.00) CE: 0.79 (0.46 – 1.00)	age, BMI, smoking, physical activity and fasting glucose at baseline
Forouhi et al. 2016	EPIC-InterAct, eight European countries	Case-cohort	53.5	28051	9.8	M/F	12,132	Plasma phospholipids	Gas chromatography with flame ionization detection (GC-FID)	Self-reported/ medication use/ hospital admissions	22.61	0.80 (0.77 - 0.83)	age, sex, physical activity, smoking status, education level, BMI, total energy intake, alcohol, intake of meat, fruits, vegetables, dairy products, soft drinks, fish and shellfish, nuts and seeds, vegetable oil, olive oil, and margarine
Harris et al. 2016	WHIMS, USA	Cohort	70.1	6379	11	F	703	Erythrocyte membrane	Gas chromatography with flame ionization detection (GC-FID)	Treatment for diabetes with pills or insulin shots	11.94	0.98 (0.90 – 1.06)	age, race, waist circumference, highest education, current smoking status, physical activity, weekly alcohol intake, glycemic load, and family history of diabetes
Lu et al. 2016	SCHS, Singapore	Cohort	55.1	394	6	M/F	197	Total serum	Gas chromatography-mass spectrometry (GC-MS)	ADA criteria	-	1.44 (1.01 – 2.08)	BMI, smoking status and history of hypertension
Takkunen et al. 2016	DPS, Finland	Cohort	58.6	383	11	M/F	155	Total serum	Gas chromatography with flame ionization detection (GC-FID)	Oral-glucose tolerance test	25.2	1.26 (1.03 – 1.55)	age, sex, study group, smoking, alcohol intake, waist circumference and physical activity at leisure time, fiber intake, carbohydrate intake, energy intake and serum triglyceride, plasma fasting and 2-h glucose
Yary et al. 2016	KIHD, Finland	Cohort	53.5	2189	19.3	M	417	Total serum	Gas chromatography with flame ionization detection (GC-FID)	Self-reported/ physician-diagnosed/ fasting plasma glucose ≥7.0 mmol/L/ 2-h oral-glucose-tolerance test plasma glucose ≥11.1 mmol/L	26.64	0.52 (0.32 – 0.70)	Age, family history of T2D, smoking, education years, leisure-time physical activity, BMI, serum long-chain n–3 PUFAs, and intakes of alcohol and energy

Supplementary data

Akter et al. 2017	HHS, Japan	nested case-control	51.3	1014	5	M/F	336	Total serum	gas chromatography (GC)	ADA criteria	16.5	0.80 (0.57 – 1.11)	Age, sex, and month of examination, leisure-time physical activity, occupational physical activity , smoking , alcohol consumption , shift work, sleep duration, family history of diabetes, hypertension, BMI
Savolainen et al. 2017	Gothenburg, Sweden	Cohort	64	399	5.5	F	69	Total serum	Gas chromatography-mass spectrometry (GC-MS)	Fasting capillary whole blood glucose measurements	-	0.79 (0.58 – 1.08)	No
Wu et al. 2017	AGES−Reykjavik, Iceland	prospective cohort (PC)	75.5	753	5.2	M/F	28	Plasma phospholipids	Gas chromatography with flame ionization detection (GC-FID)	Self-reported diabetes/ diabetes medication use/ fasting plasma glucose ≥7.0mmol/L	17.9	0.27 (0.08 – 0.91)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and biomarker omega-3 PUFA concentrations
Wu et al. 2017	FHS, USA	prospective cohort (PC)	64.4	1913	5.8	M/F	98	Erythrocyte phospholipids	Gas chromatography (GC)	Glucose concentration ≥ 7.0mmol/L, HBA1C ≥ 6.5 / new use of insulin or oral hypoglycemic medication	11.2	0.48 (0.26 – 0.90)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and biomarker omega-3 PUFA concentrations
Wu et al. 2017	3C, France	prospective cohort (PC)	76.6	574	8	M/F	36	Erythrocyte phospholipids	Gas chromatography with flame ionization detection (GC-FID)	Self -reported / use of insulin or oral hypoglycemic medication	9.6	0.51 (0.19 – 1.37)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and biomarker omega-3 PUFA concentrations
Wu et al. 2017	3C, France	prospective cohort (PC)	74.4	1220	8	M/F	83	Total plasma	Gas chromatography with flame ionization detection (GC-FID)	Self -reported / use of insulin or oral hypoglycemic medication	25.0	0.57 (0.34 – 0.94)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and biomarker omega-3 PUFA concentrations

Supplementary data

Wu et al. 2017	CHS, USA	prospective cohort (PC)	72.4	3179	10.6	M/F	284	Plasma phospholipids	Gas chromatography (GC)	Fasting glucose concentration ≥7.0mmol/L, non-fasting or 2-h postchallenge glucose concentration ≥11.1mmol/L/ new use of an insulin or oral hypoglycemic medication	19.8	0.66 (0.46 – 0.95)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and biomarker omega-3 PUFA concentrations
Wu et al. 2017	PIVUS, Sweden	prospective cohort (PC	70.2	861	10	M/F	69	Plasma phospholipids	Gas chromatography (GC)	Fasting plasma glucose ≥ 7.0mmol/L/ self-reported/ medical records/ use of insulin or oral hypoglycemic agents	19.6	0.70 (0.26 – 1.86)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and biomarker omega-3 PUFA concentrations
Wu et al. 2017	PIVUS, Sweden	prospective cohort (PC	70.2	822	10	M/F	67	Cholesterol esters	Gas chromatography (GC)	Fasting plasma glucose ≥ 7.0mmol/L/ self-reported/ medical records/ use of insulin or oral hypoglycemic agents	48.2	0.80 (0.34 – 1.87)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and biomarker omega-3 PUFA concentrations
Wu et al. 2017	HPFS, USA	prospective cohort (PC	64.7	1545	14.8	M	113	Erythrocyte phospholipids	Gas-liquid chromatography (GLC)	Self-reports and confirmed by National Diabetes Data Group criteria	12.9	0.81 (0.58 – 1.15)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and biomarker omega-3 PUFA concentrations
Wu et al. 2017	HPFS, USA	prospective cohort (PC	64.6	1497	14.8	M	109	Total plasma	Gas-liquid chromatography (GLC)	Self-reports and confirmed by National Diabetes Data Group criteria	30.3	0.42 (0.26 – 0.69)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and biomarker omega-3 PUFA concentrations
Wu et al. 2017	NHS, USA	prospective cohort (PC	60.4	1500	20.2	F	154	Erythrocyte phospholipids	Gas-liquid chromatography (GLC)	Self-reports and confirmed by National Diabetes Data Group criteria	12.1	1.15 (0.77 – 1.70)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and

Supplementary data

													biomarker omega-3 PUFA concentrations
Wu et al. 2017	NHS, USA	prospecti ve cohort (PC	60.4	1595	20.2	F	159	Total plasma	Gas-liquid chromatography (GLC)	Self-reports and confirmed by National Diabetes Data Group criteria	29.0	0.44 (0.30 – 0.64)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and biomarker omega-3 PUFA concentrations
Wu et al. 2017	IRAS, USA	prospecti ve cohort (PC	55.1	719	5	M/F	146	Total plasma	Gas chromatography with flame ionization detection (GC-FID)	Fasting glucose concentration ≥ 7.0mmol/L/ 2-hour post-oral glucose concentration ≥ 11.1mmol/L/ new use of insulin or oral hypoglycemic medication,/ Fasting or non-fasting HbA1C concentration ≥ 6·5%	30.2	0.56 (0.33 – 0.95)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and biomarker omega-3 PUFA concentrations
Wu et al. 2017	CCCC, Taiwan	prospecti ve cohort (PC	59.2	616	6	M/F	128	Total plasma	Gas chromatography with flame ionization detection (GC-FID)	Fasting glucose levels ≥ 7.0mmol/L / use of hypoglycemic medication	16.1	1.03 (0.62 – 1.69)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and biomarker omega-3 PUFA concentrations
Wu et al. 2017	ULSAM-50, Sweden	prospecti ve cohort (PC	49.7	1891	21.4	M	332	Cholesterol esters	gas-liquid chromatography with flame ionization detection (GLC-FID)	Fasting plasma glucose ≥ 7.0mmol/L/ use of glucose-lowering medication	54.0	0.57 (0.41 – 0.79)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and biomarker omega-3 PUFA concentrations
Wu et al. 2017	ULSAM-70, Sweden	prospecti ve cohort (PC	71	738	14.1	M	99	Adipose tissue	gas-liquid chromatography (GLC)	Fasting plasma glucose ≥ 7.0mmol/L/ use of glucose-lowering medication	12.6	0.82 (0.49 – 1.35)	age, sex, race, site of patient recruitment, BMI, education, smoking, physical activity, alcohol intake, prevalent coronary heart disease, treatment for hypertension, treatment for hypercholesterolemia, and

Supplementary data

													biomarker omega-3 PUFA concentrations
Ahola-Olli et al. 2019	Pooled analysis of four finish cohorts	Cohort	33.5	11896	8-15	M/F	392	Total serum	gas chromatography (GC)	Nationwide register data	3.18 mmol/l	0.75 (0.68 – 0.83)	sex, baseline age, BMI and fasting glucose
Miao et al. 2020	GNHS, China	Cohort	58.1	2731	6.2	M/F	276	Erythrocyte membrane	gas chromatography (GC)	ADA criteria	9.81	0.98 (0.72 – 1.33)	age, sex, BMI, WHR, education, household income, smoking and alcohol drinking status, physical activity, total energy intake, and family history of diabetes, baseline erythrocyte total n-3 PUFAs and fasting glucose
Weir et al. 2020	MESA, USA	Cohort	45-84	5508	8.6	M/F	635	Plasma Phospholipids	Gas chromatography with flame ionization detection (GC-FID)	Physician diagnosis/ use of anti-diabetes medications/ fasting glucose>126 mg/dL	20.7	0.67 (0.43 – 0.86)	age, race/ethnicity, gender, waist circumference, education level, hypertension medication use, cigarette smoking, alcohol intake, and HOMA-IR

Abbreviations: CHD; coronary heart disease, HTN; hypertension, IHD; ischemic heart disease, MI; myocardial infarction, FFQ; food frequency questionnaire, RR; Risk ratio, CI; confidence interval, M; male, F; female, Q; quintile or quartile, T; tertile, BMI; body mass index, PUFA; polyunsaturated fatty acid, USA; United States of America

ARIC: Atherosclerosis Risk in Communities Study, MCCS: Melbourne Collaborative Cohort Study, VIP: Vasterbotten Intervention Program, EPIC-Norfolk: European Prospective Investigation into Cancer (Norfolk), EPIC-Potsdam: European Prospective Investigation into Cancer (Potsdam), METSIM: Metabolic Syndrome in Men Study, HCS: Hunter Community Study, EPIC-InterAct: European Prospective Investigation into Cancer and Nutrition (InterAct), WHIMS: Women's health initiative memory study, SCHS: Singapore Chinese Health Study, DPS: Diabetes Prevention Study, KIHD: Kuopio Ischemic Heart Disease Risk Factor Study, HHS: Hitachi Health Study, AGES-Reykjavik: Age, Gene/Environment Susceptibility Study (Reykjavik), FHS: Framingham Heart Study, 3C Study: Three-City Study, CHS: Cardiovascular Health Study, PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors, HPFS: Health Professionals Follow-up Study, NHS: Nurses' Health Study, IRAS: Insulin Resistance Atherosclerosis Study, CCCC: ChinShan Community Cardiovascular study, ULSAM 50 & 70: Uppsala Longitudinal Study of Adult Men, GNHS: Guangzhou Nutrition and Health Study, MESA: Multi-Ethnic Study of Atherosclerosis

Supplementary data

Supplemental Table 5. Quality assessment for studies included the meta-analysis of LA and the risk of type 2 diabetes (Newcastle-Ottawa Scale).

Cohort	**Study**	**Selection**				**Comparability**		**Outcome**			**Score**	**Quality**
		(1)	(2)	(3)	(4)	(1)	(2)	(1)	(2)	(3)		
Studies reported dietary LA intake and type 2 diabetes												
E3N	Dow 2016	*	*	*	*	*		*	*	*	8	High
PREDIMED	Guasch-Ferre 2017		*	*	*	*	*	*	*	*	8	High
TLGS	Mirmiran 2018	*	*	*	*	*		*	*	*	8	High
NHS	Zong 2019		*	*	*	*	*	*	*	*	8	High
NHSII	Zong 2019		*	*	*	*	*	*	*	*	8	High
HPFS	Zong 2019		*	*	*	*	*	*	*	*	8	High
Studies reported dietary intake and biomarkers of LA and type 2 diabetes												
MCCS	Hodge 2007	*	*	*	*	*		*		*	7	High
EPIC-Norfolk	Patel 2010	*	*	*	*	*		*	*	*	8	High
EPIC-Potsdam	Kroger 2011	*	*	*	*	*	*	*	*	*	9	High
Studies reported biomarkers of LA and type 2 diabetes												
ARIC	Wang 2003	*	*	*	*	*	*	*	*		8	High
VIP	Krachler 2008	*	*	*	*	*		*	*		7	High
METSIM	Mahendran 2013	*	*	*	*	*		*	*	*	8	High
METSIM	Mahendran 2014	*	*	*	*	*		*	*		7	High
METSIM	Lankinen 2015	*	*	*	*	*		*	*		7	High

Supplementary data

EPIC-InterAct	Forouhi 2016	*	*	*	*	*	*	*	*	*	9	High
WHIMS	Harris 2016		*	*	*	*	*	*	*	*	8	High
SCHS	Lu 2016	*	*	*	*	*		*	*		7	High
DPS	Takkunen 2016	*	*	*	*	*	*	*	*		8	High
KIHD	Yary 2016	*	*	*	*	*	*	*	*	*	9	High
HHS	Akter 2017		*	*	*	*	*	*	*		7	High
Gothenburg	Savolainen 2017	*	*	*	*			*	*		6	Moderate
AGES	Wu 2017		*	*	*	*	*	*	*		7	High
FHS	Wu 2017	*	*	*	*	*	*	*	*		8	High
3C	Wu 2017	*	*	*	*	*	*	*	*		8	High
CHS	Wu 2017	*	*	*	*	*	*	*	*	*	9	High
PIVUS	Wu 2017	*	*	*		*	*	*	*		7	High
HPFS	Wu 2017		*	*	*	*	*	*	*	*	8	High
NHS	Wu 2017		*	*	*	*	*	*	*	*	8	High
IRAS	Wu 2017	*	*	*	*	*	*	*	*	*	9	High
CCCC	Wu 2017		*	*	*	*	*	*	*	*	8	High
ULSAM-50	Wu 2017	*	*	*		*	*	*	*	*	8	High
ULSAM-70	Wu 2017	*	*	*		*	*	*	*		7	High
4Finish cohorts	Ahola-Olli 2019	*	*	*	*	*	*	*	*	*	9	High
GNHS	Miao 2020	*	*	*	*	*	*	*	*		8	High

Supplementary data

MESA	Weir 2020	*	*	*	*	*	*	*	*	*	9	High

Supplementary data

Supplementary Table 6. Relative risks from non-linear dose-response analysis of LA intake and type 2 diabetes (% of energy)	
LA intake (% of energy)	RR (95% CI)
2.5	1.00 (1.00-1.00)
3	0.99 (0.98-1.00)
3.5	0.98 (0.95-1.00)
4	0.97 (0.93-1.00)
4.5	0.95 (0.91-1.00)
5	0.95 (0.90-1.00)
5.5	0.94 (0.89-0.99)
6	0.93 (0.88-0.98)
6.5	0.92 (0.87-0.98)
7	0.92 (0.85-0.99)
7.5	0.91 (0.84-0.99)
8	0.90 (0.82-1.00)
8.5	0.90 (0.80-1.00)

Supplementary data

Supplementary Table 7. Scoring for the different components of the NutriGrade.

Exposure	Outcome	Comparison	Risk of bias	Precision	Heterogeneity	Directness	Publication bias	Funding bias	Effect size	Dose-response	Sum	NutriGrade
Dietary linoleic acid	Type 2 diabetes	Per 10% energy	2	1	0.3	1	0.5	1	0	1	6.8	Moderate
Biomarkers of linoleic acid	Type 2 diabetes	Per SD increment	2	1	0.4	1	1	1	0	0	6.4	Moderate

Supplementary data

Supplementary Table 8. Subgroup analyses of dietary linoleic acid intake in relation to risk of type 2 diabetes.						
		n	**RR (95%CI)**	I^2 **(%),**	P_h[1]	P_h[2]
All studies		9	0.94 (0.90, 0.99)	48.5	0.05	
Gender						
Men		1	0.77 (0.67, 0.88)	-		0.02
Women		3	0.96 (0.91, 1.02)	0.0	0.77	
Both		5	1.05 (0.85, 1.29)	14.8	0.32	
Geographic region						
US		3	0.92 (0.87, 0.98)	78.2	0.01	0.23
Europe		4	0.97 (0.88, 1.07)	0.0	0.65	
Asia & Australia		2	1.16 (0.81, 1.68)	62.3	0.10	
Follow-up duration						
<10 years		4	1.11 (0.88, 1.39)	0.0	0.41	0.19
≥10 years		5	0.93 (0.89, 0.98)	61.9	0.03	
Number of cases						
<1000			1.05 (0.85, 1.29)	14.8	0.32	0.36
>1000			0.93 (0.89, 0.98)	69.2	0.02	
Dietary assessment						
Baseline FFQ		5	0.98 (0.89, 1.08)	22.3	0.27	0.35
Repeated FFQ		4	0.92 (0.87, 0.98)	67.6	0.02	
Adjustment for confounders						
Energy intake	Yes	7	0.94 (0.89,0.99)	47.0	0.08	0.42
	No	2	1.11 (0.79, 1.57)	69.6	0.07	
Physical activity	Yes	7	0.94 (0.89, 0.99)	57.3	0.03	0.70
	No	2	1.01 (0.75, 1.38)	18.5	0.27	
Smoking status	Yes	7	0.94 (0.89, 0.99)	48.0	0.07	0.33
	No	2	1.16 (0.81, 1.70)	62.3	0.10	
Fiber intake	Yes	3	1.01 (0.78, 1.32)	0.0	0.54	0.64
	No	6	0.94 (0.89, 0.99)	64.2	0.01	
Trans fat intake	Yes	5	0.94 (0.89, 0.99)	59.3	0.04	0.38
	No	4	1.06 (0.84, 1.33)	35.7	0.20	
Family history of diabetes	Yes	7	0.94 (0.89, 0.99)	58.8	0.02	0.41
	No	2	1.08 (0.81, 1.43)	0.0	0.76	

[1]P for heterogeneity within each subgroup
[2]P for heterogeneity between subgroups with meta-regression analysis

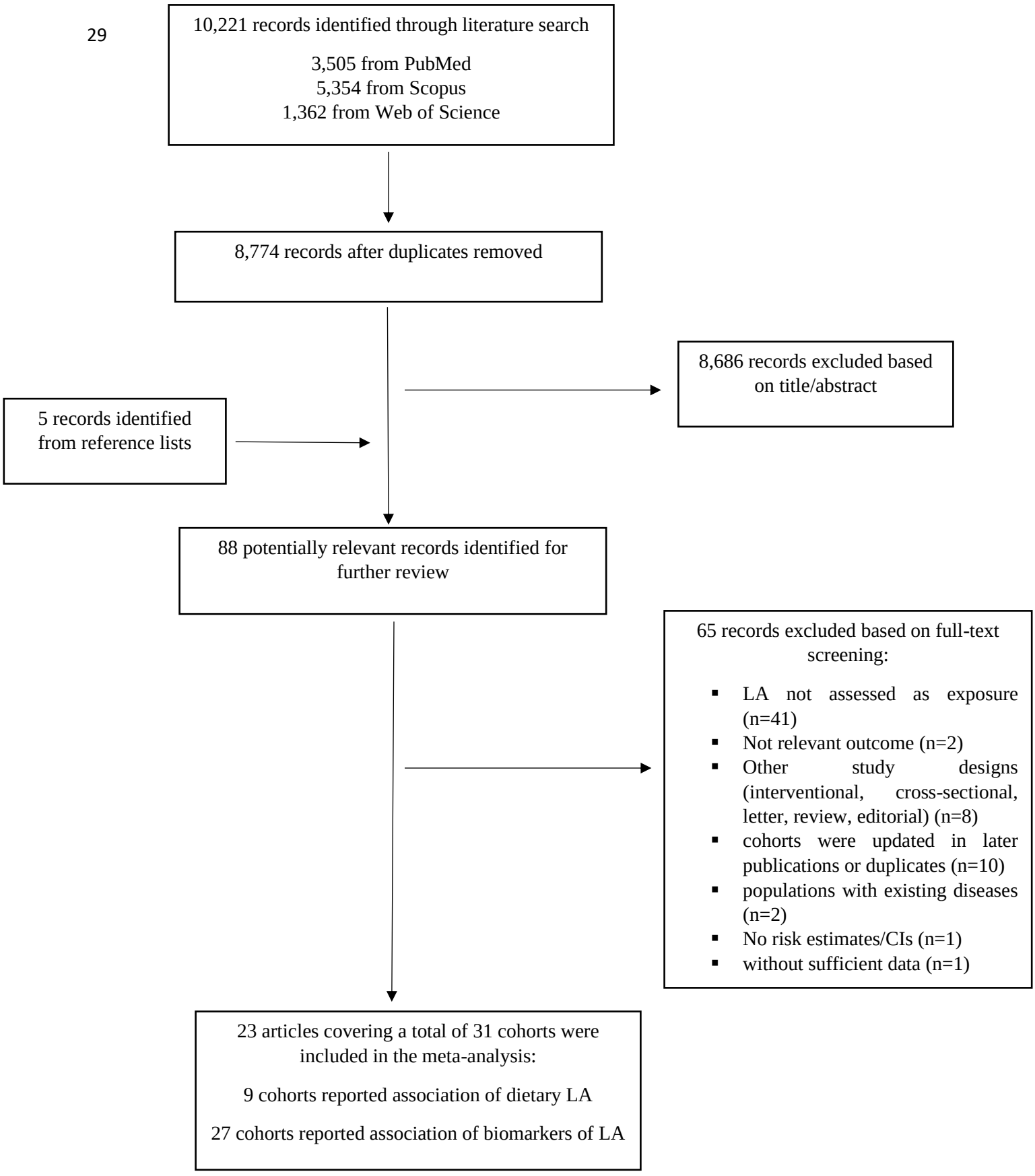
Supplementary data

Supplementary Table 9. Subgroup analyses of linoleic acid biomarkers in relation to risk of type 2 diabetes.						
		n	**RR (95%CI)**	I^2 **(%)**	P_h^1	P_h^2
All studies		27	0.83 (0.81, 0.85)	70.6	0.001	
Tissue types						
Adipose tissue		1	0.89 (0.66, 1.20)	-		0.29
Erythrocytes		10	0.91 (0.86, 0.96)	72.3	0.001	
Phospholipids		9	0.80 (0.77, 0.83)	48.7	0.05	
Total serum or plasma		12	0.80 (0.75, 0.84)	77.1	0.001	
Cholesteryl esters		4	0.74 (0.65, 0.82)	0.0	0.78	
Gender						
Men		5	0.77 (0.70, 0.85)	36.6	0.17	0.68
Women		3	0.98 (0.91, 1.05)	19.3	0.29	
Both		19	0.81 (0.79, 0.84)	69.1	0.001	
Geographic region						
US		8	0.91 (0.86, 0.96)	49.9	0.05	0.89
Europe		14	0.80 (0.77, 0.83)	70.0	0.001	
Asia & Australia		5	0.88 (0.80, 0.96)	69.8	0.03	
Follow-up duration						
<10 years		16	0.81 (0.79, 0.84)	64.1	0.001	0.24
≥10 years		11	0.83 (0.81, 0.85)	75	0.001	
Number of cases						
<250		16	0.88 (0.81, 0.95)	68.9	0.01	0.89
250-500		7	0.80 (0.75, 0.84)	58.1	0.02	
>500		4	0.83 (0.81, 0.86)	85.9	0.01	
Adjustment for confounders						
Energy intake	Yes	5	0.82 (0.79, 0.84)	82.3	0.001	0.25
	No	22	0.85 (0.81, 0.88)	67.2	0.001	
Physical activity	Yes	21	0.84 (0.81, 0.86)	70.7	0.001	0.50
	No	6	0.80 (0.75, 0.85)	73.3	0.002	
Smoking status	Yes	23	0.85 (0.82, 0.87)	66.5	0.001	0.01
	No	4	0.71 (0.66, 0.77)	59.6	0.06	
BMI	Yes	23	0.81 (0.78, 0.83)	58.3	0.001	0.08
	No	4	0.96 (0.90, 1.03)	74.5	0.008	
Alcohol drinking	Yes	23	0.84 (0.81, 0.86)	71.5	0.001	0.50
	No	4	0.76 (0.69, 0.83)	58.7	0.06	
Family history of diabetes	Yes	6	0.90 (0.85, 0.95)	72.7	0.003	0.69

Supplementary data

	No	21	0.81 (0.79, 0.84)	67.5	0.001	

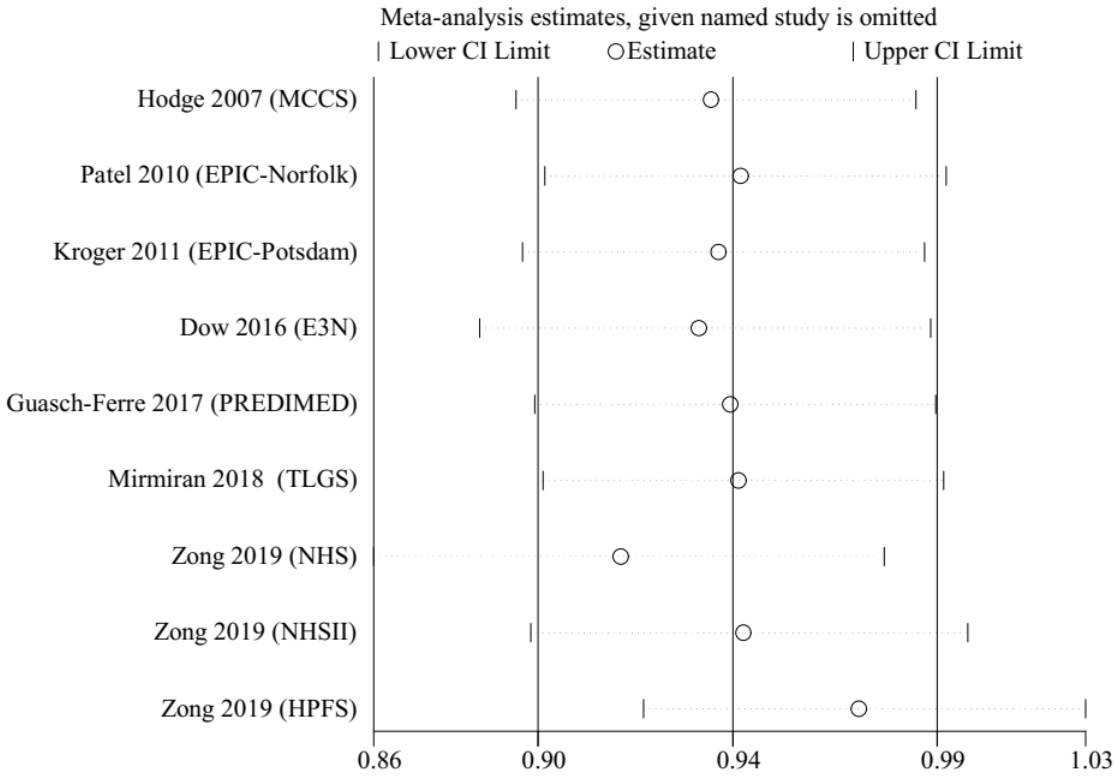
[1]P for heterogeneity within each subgroup
[2]P for heterogeneity between subgroups with meta-regression analysis



Supplemental Figure 1. Flow diagram of study selection process. LA; linoleic acid

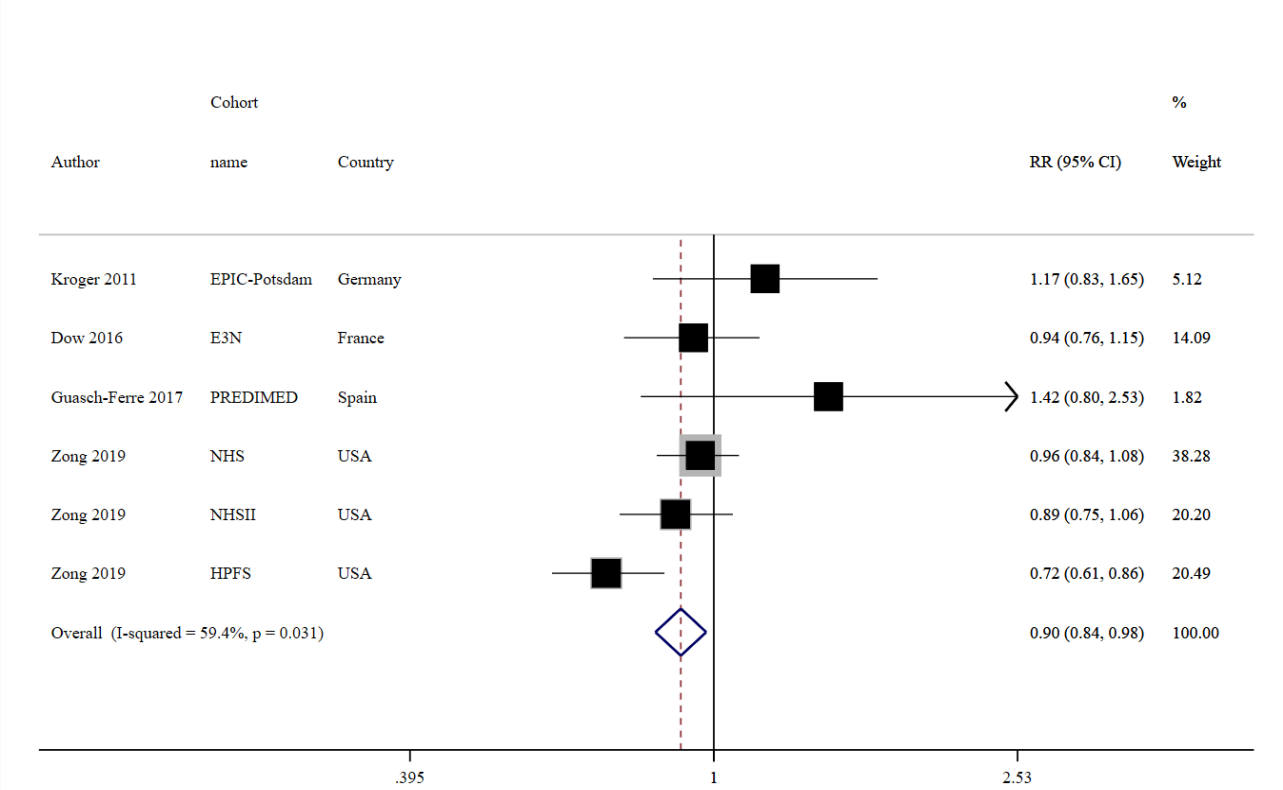
Supplementary data

Supplemental Figure 2. Leave-one-out sensitivity analysis of the association between LA intake and risk of type 2 diabetes.



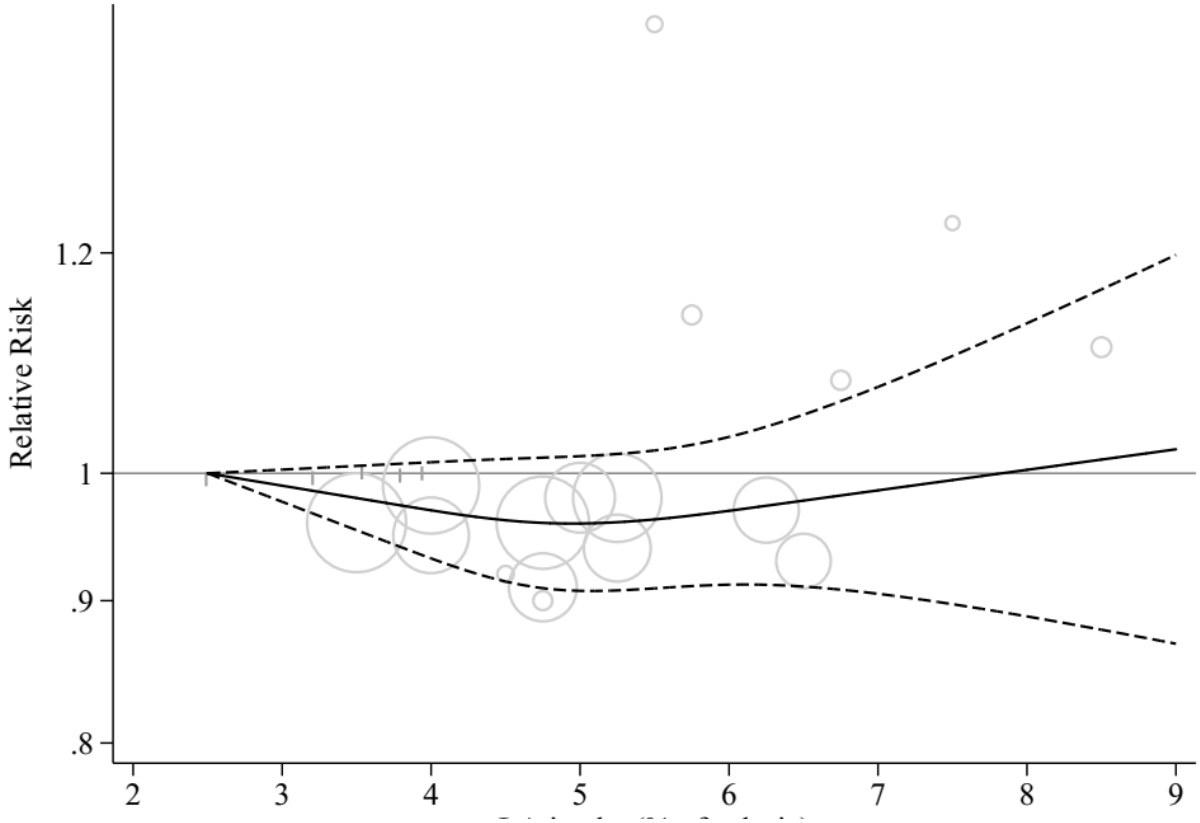
Study omitted	Estimate	[95% Conf.	Interval]
Hodge 2007 (MCCS)	0.93771207	0.89208478	0.98567307
Patel 2010 (EPIC-Norfolk)	0.94466263	0.89883679	0.99282491
Kroger 2011 (EPIC-Potsdam)	0.93949765	0.89360452	0.98774779
Dow 2016 (E3N)	0.93488795	0.88358289	0.98917198
Guasch-Ferre 2017 (PREDIMED)	0.94222748.	0.89647484	0.99031514
Mirmiran 2018 (TLGS)	0 .94416046	0.89840269	0.99224877
Zong 2019 (NHS)	0.91660023	0.8587774	0 .97831643
Zong 2019 (NHSII)	0.94530207	0.89553595	0.99783373
Zong 2019 (HPFS)	**0.97233933**	**0.92197621**	**1.0254536**
Combined	0.94282697	0.89725019	0.99071888

Supplementary data



Supplemental Figure 3. Relative risk of T2DM for a 5% increase in energy intake form linoleic acid

Supplementary data



Supplemental Figure 4. Nonlinear dose-response association between linoleic acid intake and the risk of type 2 diabetes (with the exclusion of HPFS study). P for nonlinearity was 0.22, and P for linearity was 0.37. Solid line represents non-linear dose response and dotted lines represent 95% confidence interval. Circles represent relative risk point estimates for LA intake categories from each study with circle size proportional to inverse of standard error. Small vertical grey lines are baseline LA intake categories in each study

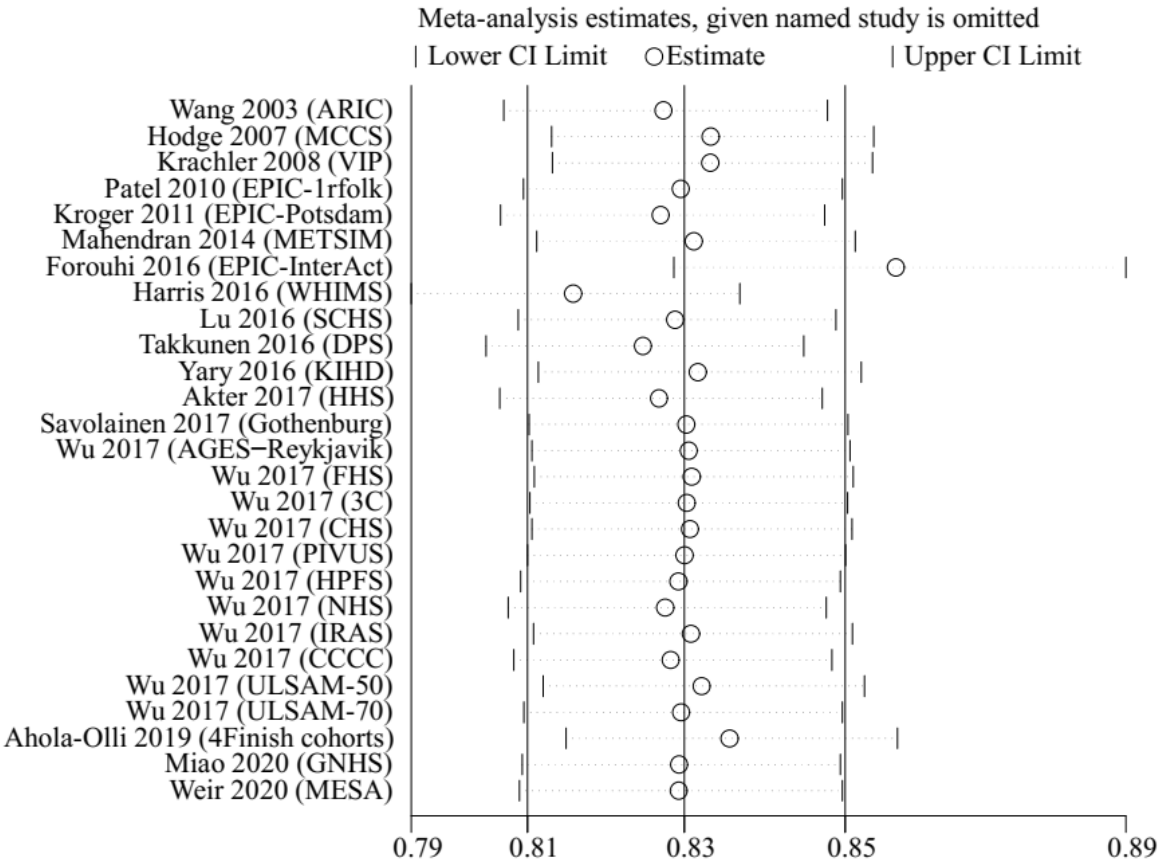
Relative risks from non-linear dose-response analysis of LA intake and type 2 diabetes (with the exclusion of HPFS study)	
LA intake (% of energy)	RR (95% CI)
2.5	1.00 (1.00 to1.00)
3	0.99 (0.98 to 1.00)
3.5	0.98 (0.95 to 1.01)

Supplementary data

4	0.97 (0.93 to 1.01)
4.5	0.96 (0.91 to 1.01)
5	0.96 (0.91 to 1.01)
5.5	0.96 (0.91 to 1.02)
6	0.97 (0.91 to 1.03)
6.5	0.98 (0.91 to 1.05)
7	0.99 (0.91 to 1.07)
7.5	0.99 (0.90 to 1.10)
8	1.00 (0.89 to 1.13)
8.5	1.01 (0.88 to 1.16)

Supplementary data

Supplemental Figure 5. Leave-one-out sensitivity analysis of the association between LA biomarkers and risk of type 2 diabetes.



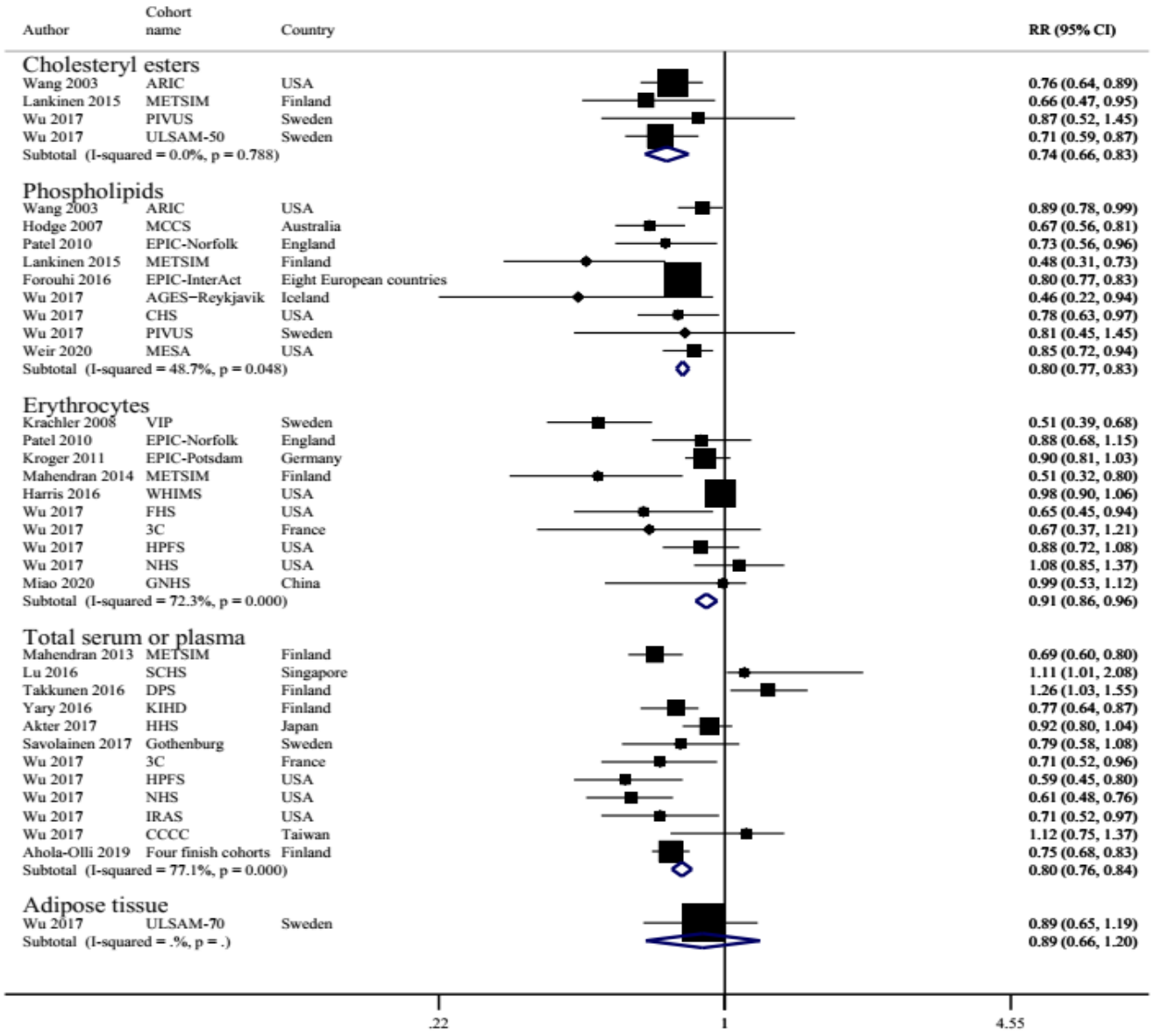
Study omitted	Estimate	[95% Conf.	Interval]
Wang 2003 (ARIC)	0.82800281	0.80642682	0.85015607
Hodge 2007 (MCCS)	0.83436763	0.81292611	0.85637462
Krachler 2008 (VIP)	0.83432788	0.8130042	0.85621083
Patel 2010 (EPIC-1rfolk)	0.83033895	0.8091063	0.85212874
Kroger 2011 (EPIC-Potsdam)	0.82760185	0.8060444	0.84973586
Mahendran 2014 (METSIM)	0.83209211	0.8108828	0.85385609
Forouhi 2016 (EPIC-InterAct)	0.85935616	0.8294003	0.89039397
Harris 2016 (WHIMS)	0.81581628	0.79395521	0.83827931
Lu 2016 (SCHS)	0.82957214	0.8084069	0.85129148

Supplementary data

Takkunen 2016 (DPS)	0.8252269	0.80405861	0.84695244
Yary 2016 (KIHD)	0.83263773	0.8111465	0.85469836
Akter 2017 (HHS)	0.82740724	0.80593711	0 .84944928
Savolainen 2017 (Gothenburg)	0.83109325	0.80987048	0.85287225
Wu 2017 (AGES−Reykjavik)	0.83142352	0.8102513	0.85314894
Wu 2017 (FHS)	0.83180779	0.8105876	0.85358351
Wu 2017 (3C)	0.83114254	0.8099708	.85286766
Wu 2017 (CHS)	0.83156282	0.81024951	0.85343671
Wu 2017 (PIVUS)	0.83084446	0.80967987	0.85256231
Wu 2017 (HPFS)	0.83001834	0.80872446	0.85187298
Wu 2017 (NHS)	0.82823485	0.8070344	0.8499921
Wu 2017 (IRAS)	0.83170283	0.81046486	0.85349733
Wu 2017 (CCCC)	0.8289749	0.80780149	0.8507033
Wu 2017 (ULSAM-50)	0.83314866	0.81175882	0.85510212
Wu 2017 (ULSAM-70)	0.83038491	0.80917603	0.85214967
Ahola-Olli 2019 (4Finish)	0.83692056	0.81488127	0.85955596
Miao 2020 (GNHS)	0.83010888	0.80893362	0.85183847
Weir 2020 (MESA)	0.83006662	0.80854106	0 .85216528
Combined	**0.83080347**	**0.8096602**	**0.85249887**

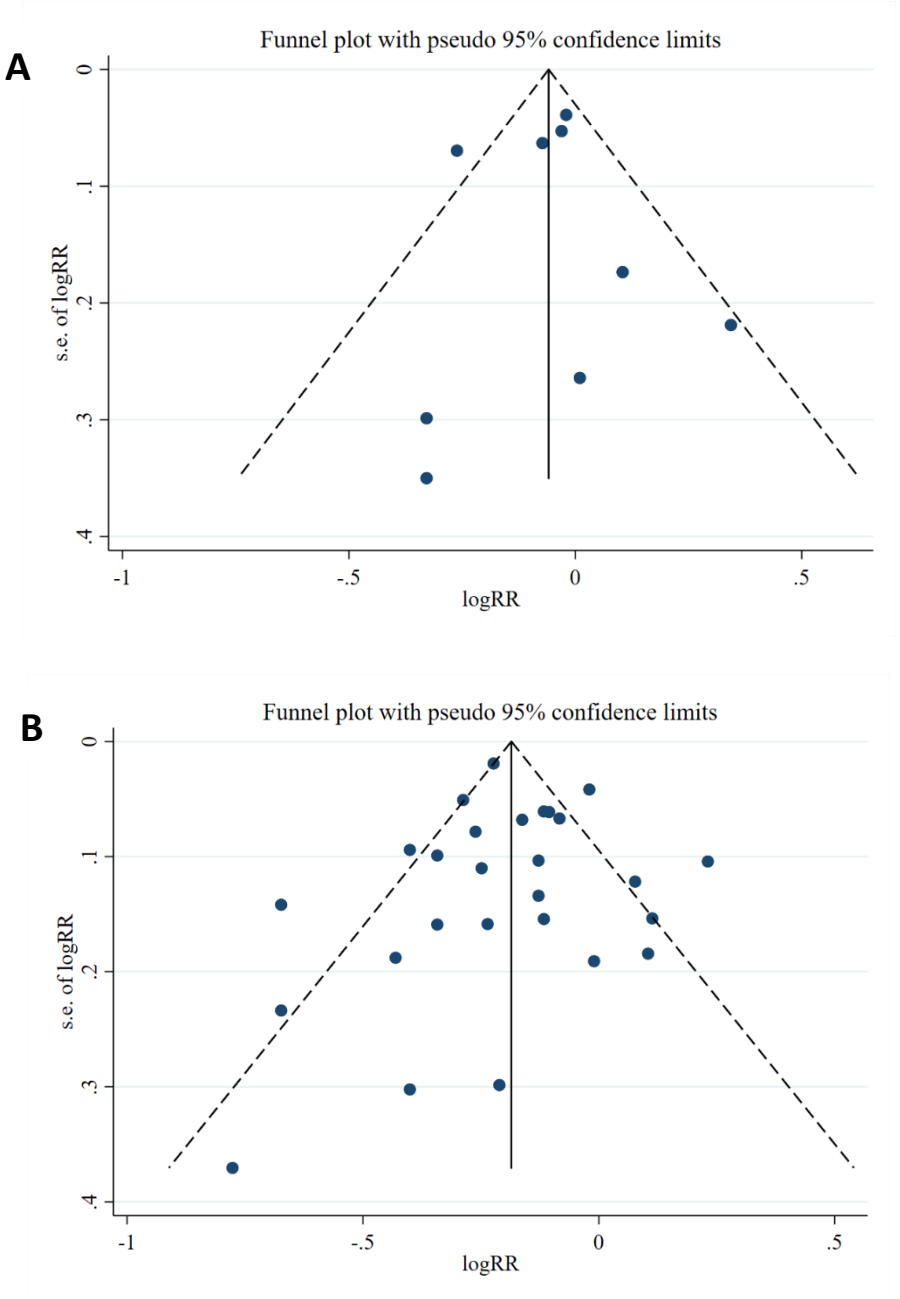
.

Supplementary data



Supplemental Figure 6. Pooled relative risks of type 2 diabetes for each standard deviation increment in linoleic acid biomarker, per lipid compartment.

Supplementary data



Supplemental Figure 7. Funnel plot demonstrating publication bias in the studies reporting the association of A) dietary intake, and B) biomarkers of LA and type 2 diabetes

Supplementary data

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, paragraph 1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction, paragraph 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods, paragraph 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods, Eligibility criteria, paragraphs 3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, Literature search, paragraph 1 and 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods, Literature search, paragraph 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Results, paragraph 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, data extraction, paragraph 1
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, data extraction, paragraph 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods, data extraction, paragraph 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods, Data synthesis and statistical analysis, paragraph 1
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods, Data synthesis and statistical analysis, paragraphs 1 and 2

Supplementary data

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods, data extraction, paragraph 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods, Data synthesis and statistical analysis, paragraph 2
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results, paragraph 1 & Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary Table 3 and 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results, LA intake and risk of T2DM, paragraph1 Supplementary Table 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary Table 3 and 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results, paragraph 1 for each outcome; Fig. 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results, end of the paragraph 1 for each outcome
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results, LA intake and risk of T2DM; paragraph 2 Biomarkers of LA and risk of T2DM; paragraph 2 Tables 1-2; Supplementary Fig. 1-5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, paragraph 1
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, paragraph 6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, paragraph 7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Footnotes, funding

Supplementary data

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary data

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	5-6
2	Hypothesis statement	6
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	6
5	Type of study designs used	6
6	Study population	6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Title page, 6
8	Search strategy, including time period included in the synthesis and key words	6
9	Effort to include all available studies, including contact with authors	6-7
10	Databases and registries searched	6
11	Search software used, name and version, including special features used (e.g., explosion)	None
12	Use of hand searching (eg, reference lists of obtained articles)	7
13	List of citations located and those excluded, including justification	Supplementary Table 1-2
14	Method of addressing articles published in languages other than English	7
15	Method of handling abstracts and unpublished studies	7
16	Description of any contact with authors	None
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	8
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	8
22	Assessment of heterogeneity	9-10
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of	5-6

	study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	
24	Provision of appropriate tables and graphics	Tables 1-2 Figures 1-4
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 1
26	Table giving descriptive information for each study included	Table S 3-4
27	Results of sensitivity testing (eg, subgroup analysis)	12-13
28	Indication of statistical uncertainty of findings	12-14 Table S7

Item No	**Recommendation**	**Reported on Page No**
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	14
30	Justification for exclusion (eg, exclusion of non-English language citations)	7
31	Assessment of quality of included studies	Table S5
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	15-1
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	15-1
34	Guidelines for future research	19
35	Disclosure of funding source	21