**Appendix**

**Search Terms:**

**PubMed:** (Alpha-linolenic acid) and ((coronary heart disease) or (coronary artery disease) or (ischemic heart disease) or (myocardial infarction) or (cardiovascular disease))

**Web of Science:** TOPIC: ((Alpha-linolenic acid) and ((coronary heart disease) or (coronary artery disease) or (ischemic heart disease) or (myocardial infarction) or (cardiovascular disease)))

Refined by: LANGUAGES: ( ENGLISH ) AND DOCUMENT TYPES: ( ARTICLE )

Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.

**Embase:** 'alpha linolenic' AND ('acid'/exp OR acid) AND (coronary AND ('heart'/exp OR heart) AND ('disease'/exp OR disease) OR (coronary AND ('artery'/exp OR artery) AND ('disease'/exp OR disease)) OR (ischemic AND ('heart'/exp OR heart) AND ('disease'/exp OR disease)) OR (myocardial AND ('infarction'/exp OR infarction)) OR (('cardiovascular'/exp OR cardiovascular) AND ('disease'/exp OR disease))) AND [english]/lim AND ([article]/lim OR [article in press]/lim)

**Supplemental Table 1.** Characteristics of studies included in the meta-analysis\*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Sample size | Country | Women, % | Age, year | Follow-up time, year | Assessment of ALA intake | Amount of ALA, g/day | Outcome | Covariates |
| Dolecek, 1992 (MRFIT) (1) | 6,250 | US | 0 | 35 to 57 | 6 years | 24-hour recall | 1st quintile: 0.873  2nd quintile: 1.273  3rd quintile: 1.577  4th quintile: 1.926  5th quintile: 2.802 | CHD death RR=0.68 (95% CI: 0.16, 2.00) | Age, race, baseline smoking, DBP, HDL-C, LDL-C |
| Ascherio, 1996 (HPFS) (2) | 43,757 | US | 0 | Mean: 59  40 to 75 | 6 years | FFQ | 1st quintile: 0.8  2nd quintile: 0.9  3rd quintile: 1.1  4th quintile: 1.2  5th quintile: 1.5 | Total MI  RR=0.80 (95% CI: 0.63, 1.03)  Fatal CHD  RR=1.03 (95% CI: 0.66, 1.59) | Age, BMI, smoking, alcohol consumption, physical activity, history of hypertension or high cholesterol, family history of myocardial infarction before age 60, profession, fiber intake |
| Pietinen, 1997 (ATBC) (3) | 21,930 | Finland | 0 | Mean: 56.6  50 to 69 | 6.1 years | FFQ | 1st quintile: 0.9  2nd quintile: 1.2  3rd quintile: 1.5  4th quintile: 1.9  5th quintile: 2.5 | Total CHD  RR=0.96 (95% CI: 0.80, 1.14)  Fatal CHD  RR=0.99 (95% CI: 0.76, 1.28) | Age, supplementation, smoking, BMI, blood pressure, intakes of energy, alcohol, fiber, education, physical activity |
| Hu, 1999 (NHS) (4) † | 76,283 | US | 100 | Mean: 50.3 | 10 years | FFQ | 1st quintile: 0.71  2nd quintile: 0.86  3rd quintile: 0.98  4th quintile: 1.12  5th quintile: 1.36 | Fatal CHD RR=0.55 (95% CI: 0.32, 0.94)  Non-fatal MI  RR=0.85 (95% CI: 0.61, 1.19) | Age, time period, BMI, cigarette smoking, history of hypertension, diabetes, hypercholesterolemia, menopausal status, parental history of MI before 65 y of age, multiple vitamin use, vitamin E supplement use, alcohol consumption, aspirin use, vigorous exercise, dietary intakes of saturated fat, linoleic, acid, vitamins C and E, and total energy |
| Albert, 2005 (NHS) (5)‡ | 76,763 | US | 100 | Mean: 50.8 | 18 years | FFQ | 1st quintile: 0.66  2nd quintile: 0.80  3rd quintile: 0.93  4th quintile: 1.07  5th quintile: 1.39 | Fatal CHD RR=1.01 (95% CI: 0.77, 1.33)  Non-fatal MI  RR=1.09 (95% CI: 0.92, 1.29) | Age and for calories, BMI, smoking, 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 MI, prior CVD, intakes of trans-unsaturated fat, ratio of polyunsaturated fat to saturated fat, omega-3 fatty acids |
| Oomen, 2001 (ZES) (6)§ | 667 | Netherland | 0 | Mean: 71.1 | 10 years | Dietary history | 1st tertile: 1.00  2nd tertile: 1.27  3rd tertile: 0.93 | Total CAD  RR=1.68 (95% CI: 0.86, 3.29)  Fatal CAD  RR=1.59 (95% CI: 0.62, 4.08) | Age, BMI, smoking, alcohol intake, use of vitamin supplements, intake of saturated fatty acids, trans fatty acids, linoleic acid, EPA and DHA, other cis unsaturated fatty acids, protein, energy, dietary cholesterol, fiber, vitamin E, vitamin C, and β-carotene |
| de Goede, 2011 (MORGEN) (7) | 20,069 | Netherland | 55 | Mean: 41.5 | 10.5 years | FFQ | 1st quintile: 1.0  2nd quintile: 1.2  3rd quintile: 1.3  4th quintile: 1.5  5th quintile: 2.0 | Total CHD  RR=1.01 (95% CI: 0.66, 1.54) | Age, sex, BMI, total energy intake, smoking, education, parental history of MI, alcohol intake, intake of vitamin C, beta-carotene, fiber, saturated fatty acids, trans fatty acids, PUFA other than ALA |
| Vedtofte, 2011 (GPS) (8) | 3,277 | Denmark | 50.1 | Mean:  Men: 51.8  Women: 52.4 | 23.3 years | 7-day weighed food record | Men:  1st tertile: 1.09  2nd tertile: 1.61  3rd tertile: 2.27  Women:  1st tertile: 0.81  2nd tertile: 1.24  3rd tertile: 1.83 | Total IHD  Men:  HR=0.83 (95% CI: 0.56, 1.24)  Women:  HR=1.04 (95% CI: 0.58, 1.86) | Smoking, educational attainment, familial history of acute MI, SBP, alcohol intake, other PUFAs, total energy, leisure-time physical activity, and BMI |
| Otto, 2013 (MESA) (9) | 2,392 | US | 53.2 | Mean: 61.5 | 10 years | FFQ | 1st quartile: 0.45  2nd quartile: 0.76  3rd quartile: 1.08  4th quartile: 1.69 | Total CHD RR=0.60 (95% CI: 0.25, 1.41) | Field center, age, sex, race, education, smoking, physical activity, BMI, prevalent diabetes, dietary supplement use, hypertensive medication use, fruits and vegetables, fiber, processed and unprocessed meat, vitamin E, saturated fat, trans fat intake |
| Fretts, 2014 (CHS) (10)d | 2,709 | US | 63.9 | Median: 73 | 12 years | FFQ | 1st quintile: 0.77  2nd quintile: 0.84  3rd quintile: 0.92  4th quintile: 0.99  5th quintile: 1.14 | Total CHD  RR=0.93 (95% CI: 0.67, 1.30)  Fatal CHD RR=0.85 (95% CI: 0.58, 1.26) | Age, sex, race, enrolment site, education, smoking status, diabetes, BMI, alcohol consumption and treated hypertension. |
| Koh, 2015 (SCHS) (11) | 63,257 | Singapore | 52.9 | Mean: 56.4  (45 to 74) | 5 years | FFQ | 1st quartile: 0.36  2nd quartile: 0.49  3rd quartile: 0.57  4th quartile: 0.86 | Fatal IHD  RR=0.81 (95% CI: 0.72, 0.90) | Age, sex, dialect, year of interview, educational level, BMI, physical activity, smoking status, alcohol use, baseline history of self-reported diabetes, hypertension, CHD, stroke, total energy, intakes of protein, dietary fiber, MUFA, saturated fat, omega-6 fatty acids, and alternate omega-3 fatty acids |
| Sala-Vila, 2016 (PREDIMED) (12) | 7,202 | Spain | 57.5 | Mean: 67.0 | 5.9 years | FFQ | Low: 1.05  High: 2.63 | Fatal CHD  RR=0.75 (95% CI: 0.36, 1.58) | Age, sex, intervention group, BMI, smoking, physical activity, total energy intake, history of diabetes, hyperlipidemia, hypertension, alcohol intake, and dietary factors |
| Bork, 2016 (13) | 57,053 | Denmark | 52.2 | Mean:  Men: 55.9  Women: 56.2 | 4 years | FFQ | Men:  1st quintile: <1.67  2nd quintile: 1.67-1.94  3rd quintile: 1.94-2.19  4th quintile: 2.19-2.54  5th quintile: ≥2.54  Women:  1st quintile: <1.24  2nd quintile: 1.24-1.43  3rd quintile: 1.43-1.62  4th quintile: 1.62-1.88  5th quintile: ≥1.88 | Total MI  Men:  HR=0.90 (95% CI: 0.76, 1.07)  Women:  HR=1.10 (95% CI: 0.83, 1.45)  Fatal MI  Men:  HR=0.71 (95% CI: 0.47. 1.08) | BMI, waist circumference, smoking, physical activity, education, menopausal status, hormone replacement therapy, self-reported history of  hypercholesterolemia or use of lipid-lowering medication, hypertension or use of antihypertensive medication, self-reported diabetes mellitus |
| Rhee, 2017  (Women’s Health Study) (14) | 39,876 | US | 100 | ≥45 years | 22 years | FFQ | 1st quintile: 0.15  2nd quintile: 0.27  3rd quintile: 0.40  4th quintile: 0.62  5th quintile: 1.00 | Total MI:  HR=0.98 (0.76, 1.27) | Randomized treatment, age, BMI, smoking, alcohol intake, physical activity, oral contraceptive use, use of hormones as defined under HRT, multivitamin use, family history of MI, and baseline history of hypertension, high cholesterol, diabetes, intakes of dietary fiber, fruits and vegetables, trans fat, ratio of polyunsaturated to saturated fat, and sodium. |

\* ALA, α-linolenic acid; CHD, coronary heart disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; FFQ, food frequency questionnaire; MI, myocardial infarction; CVD, cardiovascular disease; CAD, coronary artery disease; EPA, eicosapentaenoic; DHA, docosahexaenoic; PUFA, polyunsaturated fatty acids; IHD: ischemic heart disease; SBP: systolic blood pressure; MUFA, monounsaturated fatty acids.

†. used for analysis for association between ALA intake with composite CHD and fatal CHD only.

‡. used for dose-response analysis only.

§. Intake of ALA (g/day) was calculated from percentage of total energy.

**Supplemental Table 2.** Quality assessment of the 14 cohort studies included in the meta-analysis according to the Newcastle-Ottawa Scale

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Selection | | | | Comparability | Outcome | | | Total |
|  | Exposed  Cohort  Representative | Selection of  Non-Exposed Cohort | Ascertainment  of Exposure | Outcome  not Present at Baseline | Analysis Adjusted  for Confounding Factors | Assessment of Outcome | Length  of Follow-up | Adequacy of  Follow-up |
| Dolecek, 1992 (1) | 0 | 1 | 0 | 1 | 2 | 1 | 1 | 1 | 7 |
| Ascherio, 1996 (2) | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 7 |
| Pietinen, 1997 (3) | 0 | 1 | 0 | 1 | 2 | 1 | 1 | 0 | 7 |
| Hu, 1999 (4) | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 7 |
| Albert, 2005 (5) | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Oomen, 2001 (6) | 0 | 1 | 0 | 1 | 2 | 1 | 1 | 1 | 7 |
| de Goede, 2011 (7) | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 7 |
| Vedtofte, 2011 (8) | 1 | 1 | 0 | 1 | 2 | 1 | 1 | 1 | 8 |
| Otto, 2013 (9) | 1 | 1 | 0 | 1 | 2 | 1 | 1 | 1 | 8 |
| Fretts, 2014 (10) | 1 | 1 | 0 | 1 | 2 | 1 | 1 | 0 | 7 |
| Koh, 2015 (11) | 1 | 1 | 0 | 1 | 2 | 1 | 1 | 1 | 8 |
| Sala-Vila, 2016 (12) | 0 | 1 | 0 | 1 | 2 | 1 | 1 | 0 | 6 |
| Bork, 2016 (13) | 1 | 1 | 0 | 1 | 2 | 1 | 1 | 1 | 8 |
| Rhee, 2017 (14) | 1 | 1 | 0 | 1 | 2 | 1 | 1 | 0 | 7 |

![A close up of a map

Description generated with high confidence]()

**Supplemental Figure 1.** Funnel plot of studies included in the meta-analysis of ALA intake and risk of composite CHD

![A close up of a map

Description generated with very high confidence]()

**Supplemental Figure 2.** Funnel plot of studies included in the meta-analysis of ALA intake and risk of fatal CHD

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