Appendix 5 GRADE Evidence Profile for prospective cohort studies of saturated-fatty acids and health outcomes [posted as supplied by author]

Outcome	Participants (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rate (%)	Dose-Response	Most-adjusted MV RR	Absolute – adjusted (per 10,000)[1]	Least-adjusted MV RR	Importance
All-cause mortality	99,906 (5 studies; 7 comparisons)[2]	Serious risk of bias[3]	No serious inconsistency[4]	No serious indirectness	No serious imprecision[5]	Not assessed[6]	⊕OOO **VERY LOW**[7]	14,090/99,906 (14.1%)	No[8]	RR: 0.99 (0.91, 1.09)	11 fewer (from 103 fewer to 103 more)	RR: 0.99 (0.91 to 1.08)	CRITICAL
CHD mortality	101,712 (11 studies, 15 comparisons)[9]	Serious risk of bias[10]	Serious inconsistency[11]	No serious indirectness	Serious imprecision[12]	Possible publication bias[13]	⊕OOO **VERY LOW**[14]	2,970/101,712 (2.9%)	No[15]	1.15 (0.97 to 1.36)	3 more (from 6 fewer to 73 more)	1.20 (1.02 to 1.41)	CRITICAL
CHD total	267,416 (12 studies, 17 comparisons)[16]	No serious risk of bias[17]	Serious inconsistency[18]	No serious indirectness	Serious imprecision[19]	No serious publication bias[20]	⊕OOO **VERY LOW**[21]	6,383/267,416 (2.4%)	No	1.06 (0.95 to 1.17)	25 more (from 21 fewer to 72 more)	1.12 (1.00 to 1.26)	CRITICAL
CVD Mortality	90,501 (3 studies; 5 comparisons)[22]	Serious risk of bias[23]	No serious inconsistency[24]	No serious indirectness	Serious imprecision[25]	Not assessed[26]	⊕OOO **VERY LOW**[27]	3,792/90,501 (4.2%)	No	0.97 (0.84 to 1.12)	13 fewer (from 67 fewer to 50 more)	0.97 (0.84 to 1.12)	CRITICAL
Ischemic Stroke	339,090 (12 studies; 15 comparisons)[28]	Serious risk of bias[29]	Serious inconsistency[30]	No serious indirectness	Serious imprecision[31]	No serious publication bias[32]	⊕OOO **VERY LOW**[33]	6,226/339,090 (1.8%)	No	1.02 (0.90 to 1.15)	1 more (from 7 fewer to 11 more)	1.03 (0.91 to 1.16)	CRITICAL
Type 2 diabetes	237,454 (8 studies; 8 comparisons)[34]	No serious risk of bias[35]	No serious inconsistency[36]	No serious indirectness	Serious imprecision[37]	Not assessed[38]	⊕OOO **VERY LOW**[39]	8,739/237,454 (3.7%)	No	0.95 (0.88 to 1.03)[40]	28 fewer (from 67 fewer to 17 more)	1.23(0.98 to 1.52)	CRITICAL

Explanatory Notes: [1]Absolute risk was estimated using a procedure called Method of Variance Estimates Recovery (MOVER) proposed by Newcombe et al. (*Evid Based Med* 2014;19;6-8). Estimates of baseline risk and associated 95% confidence levels, were obtained from the Emerging Risk Factors Consortium (*Lancet* 2010 Jun 26;375(9733):2215-22) which included 691,872 people from 102

prospective studies. Overall, the mean age of participants at entry was 52 (SD 13) years, and 297,081 (43%) were women. (96%) were in Europe, North America, and Australasia, with the remainder in Japan or the Caribbean. These risks were 11.4% (11.2% to 11.6%) for total mortality; 2.0% (1.9% to 2.2%) for CHD mortality, 4.2% (4.1% to 4.4%) for total CHD: 0.7% (0.5% to 0.8%) for ischemic stroke; and 5.6% (5.5% to 5.8%) for type 2 diabetes.

[2]The meta-analysis pooled estimate Included data from 5 prospective cohort studies (7 comparisons), with average duration of follow-up ranging from 6.6 to 19.3 y (median=13.3), enrolling participants from 5 different countries (UK, USA, Sweden, Taiwan, and Japan). Also reviewed in the text but not included in the meta-analysis was the Seven Countries Study, which followed 12,763 men from 7 different countries (USA, Finland, Netherlands, Italy, Croatia, Serbia, Greece, and Japan) for 25 years, and observed 5,973 deaths (31.9%)

[3]Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa score for 6 studies range from 6 to 8 (median=7). Main study limitations included incomplete adjustment for confounders, and measurement error related to saturated fat intake.

[4]Though not included in the meta-analysis, our review identified the findings of the 7 Countries' study (Kromhout et al.) which supported a continuous dose-response association for reduced SFA: a 5% reduction in %E from saturated fat was associated with 4.7% reduction in total mortality risk; however meta-analysis of 5 prospective cohort studies (7 comparisons) consistent with no effect of increased SFA on mortality (I^2=33%; P_{het}=0.17). Not downgraded.

[5]Optimal information size met (n=14,090 events); summary RR crosses 1.0, but bounds of 95% CL >0.8 and <1.2. Not downgraded.

[6]Due to small number of studies (n<10) risk of publication bias not formally assessed.

[7]Data from cohort studies begin with a grade of "LOW". Downgraded for serious risk of bias.

[8]Though not included in the meta-analysis, the 7 Countries' study (Kromhout et al.) found a continuous dose-response association for reduced SFA: a 5% reduction in %E from saturated fat associated with 4.7% reduction in total mortality risk); no dose-response noted by Mann et al., Tucker et al., Chien et al., Wakai et al., or Leosdottir et al.

[9]Included data from 11 prospective cohort studies (15 comparisons), with a duration of follow-up from 6 to 23 y (median=16), enrolling participants from 6 different countries.

[10]Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa score for 11 studies ranged from 6 to 9 (median=7). Main study limitations included incomplete adjustment for confounders, high attrition, and uncertain outcome confirmation. Fully-adjusted models yield weaker effects than minimally-adjusted models, suggesting that these variables captured some important confounders.

[11]I^2=70%; P_{het}<.0001; 9 studies had point estimates >1.0 and 5 had point estimates <1.0; 1 study had point estimate=1.0.

[12]Optimal information size met (n=2,970 events); summary RR crosses 1.0: lower bound of 95% CI >0.8 but upper bound > = 1.36, which exceeds the threshold for important harm.

[13]funnel plot asymmetry suggestive of publication bias; Egger's test P=0.191 and Begg's test P=0.138. Trim-and-fill analysis identified 2 "missed" studies. "Filled" random-effects RR: 1.09 (95% CI: 0.91 to 1.30; P=0.361; P_{het}<0.001) [eFigure 66]

[14]Data from cohort studies begin with a grade of "LOW". Downgraded for serious risk of bias, serious inconsistency, serious imprecision, and possible publication bias

[15]No evidence of dose-response association in 2 studies which directly measured it (Xu et al., Ascherio et al.; n=367 observed events in 46,335 individuals, combined, followed for 6-7 years).

[16]Included data from 12 prospective cohort studies (17 comparisons), with a duration of follow-up from 1 to 20 y (median=11.1), enrolling participants from 7 different countries.

[17]Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa score for 9 assessable studies range from 6 to 9 (median=8). Main study limitations included incomplete adjustment for confounders (most commonly family history), uncertain outcome validation, and use of a single 24-h recall to represent long-term diet. Fully-adjusted models yield weaker effects than minimally-adjusted models, suggesting that these variables captured some important confounders. Not downgraded.

[18]I^2=47%; P_{het}=.02; 8 studies had point estimates >1.0 and 9 had point estimates <1.0.

[19]Optimal information size met (n=6,383 events); summary RR crosses 1.0, however both bounds of 95% >0.8 and <1.2.

[20]Funnel plot revealed no asymmetry; neither test of publication bias approached P<0.10; "filled" random-effects RR: 1.03 (95% CI: 0.92 to 1.15; P=0.586; P_{het}=0.003). [eFigure 67]

[21]Data from cohort studies begin with a grade of "LOW". Downgraded for serious inconsistency.

[22]Included data from 3 prospective cohort studies (5 comparisons), with a duration of follow-up of 6.6 to 19.3 y (median=14), enrolling participants from Sweden and Japan.

[23]Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa scores for 3 studies ranged from 5 to 8 (median=7). Main limitations related to potential for measurement error of saturated fat; and incomplete adjustment for confounders. Downgraded.

[24]I^2=19%; P_{het}=.29; 4 of 5 point estimates <1.0

[25]Optimal information size met (n=3,792 events); summary RR crosses 1.0, but lower bound of 95% CI = 0.84 and upper bound of 95% CI = 1.12. Not downgraded.

[26]Due to small number of studies (n<10) risk of publication bias not formally assessed.

[27]Data from cohort studies begin with a grade of "LOW". Downgraded for serious risk of bias.

[28]Included data from 12 prospective cohort studies (15 comparisons), with a duration of follow-up from 7.6 to 32 y (median=14), enrolling participants from 6 different countries.

[29]Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa score for 12 studies ranged from 5 to 8 (median=7). Main study limitations included incomplete adjustment for confounders (most commonly family history, and socioeconomic status), and failure to document losses to follow-up, and unclear outcome validation.

[30]I^2=59%; P_{het}=.002; 8 studies had point estimates >1.0 and 7 had point estimates <1.0.

[31]Optimal information size met (n=6,226 events); summary RR crosses 1.0, however both bounds of 95% >0.8 and <1.2.

[32]Funnel plot revealed no asymmetry; neither test of publication bias approached P<0.10. Trim-and-fill identified no "missed" studies. [eFigure 68]

[33]Data from cohort studies begin with a grade of "LOW". Downgraded for serious risks of bias, serious inconsistency.

[34]Included data from 8 prospective cohort studies (8 comparisons), with a duration of follow-up from 5 to 14 y (median=9.9), enrolling participants from 3 different countries (USA, Finland, Australia).

[35]Possibility of residual confounding always must be considered in observational studies. Fully-adjusted models yield weaker effects than minimally-adjusted models, suggesting that these variables captured some important confounders. Newcastle-Ottawa score for 8 studies range from 5 to 9 (median=6.5). Main study limitations included incomplete adjustment for confounders (most commonly family history and socioeconomic status), uncertain outcome validation.

[36]I^2=0%; P=.61; 1 study had RR >1.0, 7 had RR<1.0.

[37]Optimal information size met (n=8,739 events); summary RR crosses 1.0, however both bounds of 95% >0.8 and <1.2.

[38]Due to small number of studies (n<10) risk of publication bias not formally assessed.

[39]Data from cohort studies begin with a grade of "LOW". Downgraded for serious imprecision.

[40]When we pool prospective cohort studies and nested case-control studies (n=2; 1,019 cases; pooled mvRR=1.49; 95% CI: 0.99 to 2.23), the pooled effect is 1.00 (95% CI: 0.90 to 1.12; I^2=41% P_{het}=.08)