**Appendix 6** GRADE Evidence Profile for prospective cohort studies of trans-fatty acids and health outcomes [posted as supplied by author]

| Exposure | Outcome | Participants (# studies) | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall quality of evidence | Study event rate (%) | Absolute – adjusted (per 10,000)[1] | Dose-Response | Most-adjusted MV RR | Least-adjusted MV RR | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total TFA | Total mortality | 20,346 (2 studies; 2 comparisons)[2] | No serious risk of bias[3] | No serious inconsistency[4] | No serious indirectness | No serious imprecision[5] | Not assessed[6] | ⊕⊕◯◯ **LOW**[7] | 2,141/20,346(8.5%) | 388 more (from 182 more to 639 more) | Yes[8] | 1.34(1.16 to 1.56)[9i] | 1.80(1.57 to 2.07) | CRITICAL |
| | CHD mortality | 70,864 (5 studies; 6 comparisons)[10] | No serious risk of bias[11] | No serious inconsistency[12] | No serious indirectness | No serious imprecision[13] | Not assessed[14] | ⊕⊕⊕◯ **MODERATE**[15] | 1,234/70,864 (1.7%) | 56 more (from 18 more to 101 more) | Yes[16] | 1.28 (1.09 to 1.50) | 1.34 (1.00 to 1.79) | CRITICAL |
| | CHD total | 145,922 (6 studies; 7 comparisons)[17] | No serious risk of bias[18] | No serious inconsistency[19] | No serious indirectness | No serious imprecision[20] | Not assessed[21] | ⊕⊕⊕◯ **MODERATE**[22] | 4,579/145,922 (3.1%) | 88 more (from 42 more to 139 more) | Yes[23] | 1.21(1.10 to 1.33) | 1.31(1.15 to 1.48) | CRITICAL |
| Total TFA | Ischemic Stroke | 190,284 (3 studies; 4 comparisons)[24] | No serious risk of bias[25] | Serious inconsistency[26] | No serious indirectness | Serious imprecision[27] | Not assessed[28] | ⊕◯◯◯ **VERY LOW**[29] | 1,905/190,284 (1.0%) | 5 more (from 8 fewer to 20 more) | No[30] | 1.07(0.88 to 1.28) | 1.13(0.94 to 1.37) | CRITICAL |
| | Type 2 diabetes | 230,135(6 studies; 6 comparisons)[31] | Serious risk of bias[32] | Serious inconsistency[33] | No serious indirectness | Serious imprecision[34] | Not assessed[35] | ⊕◯◯◯ **VERY LOW**[36] | 8,690/230,135 (3.8%) | 56 more (from 28 fewer to 151 more) | Unclear[37] | 1.10 (0.95 to 1.27) | 1.28 (1.05 to 1.55) | CRITICAL |
| Industrial TFA | Total mortality | 71,464 (1 study; 2 comparisons)[38] | Serious risk of bias[39] | No serious inconsistency[40] | No serious indirectness | Serious imprecision[41] | Not assessed[42] | ⊕◯◯◯**VERY LOW**[43] | 11,890/71,464 (16.7%) | 23 fewer (from 91 fewer to 46 more) | No[44] | 0.98(0.92 to 1.04) | 1.09(1.05 to 1.14) | CRITICAL |
| | CHD mortality | 93,394(2 studies; 2 comparisons)[45] | Serious risk of bias[46] | No serious inconsistency[47] | No serious indirectness | No serious imprecision[48] | Not assessed[49] | ⊕◯◯◯ **VERY LOW**[50] | 3,018/93,394 (3.2%) | 36 more (from 8 more to 67 more) | Unclear[51] | 1.18(1.04 to 1.33) | 1.16(1.02 to 1.31) | CRITICAL |
| | CHD total | 69,848 (2 studies; 2 comparisons)[52] | Serious risk of bias[53] | No serious inconsistency[54] | No serious indirectness | No serious imprecision[55] | Not assessed[56] | ⊕◯◯◯ **VERY LOW**[57] | 454/69,848 (0.7%) | 176 more (from 21 more to 387 more) | Yes[58] | 1.42 (1.05 to 1.92) | 1.42 (1.05 to 1.92) | CRITICAL |
| | Ischemic stroke | No studies | - | - | - | - | - | - | - | | - | - | - | |
| | Type 2 | No studies | - | - | - | - | - | - | - | | - | - | - | |

| Exposure | Outcome | Participants (# studies) | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall quality of evidence | Study event rate (%) | Absolute – adjusted (per 10,000)[1] | Dose-Response | Most-adjusted MV RR | Least-adjusted MV RR | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | diabetes | | | | | | | | | | | | | |
| Ruminant TFA | Total mortality | 71,464 (1 studies; 2 comparisons)[59] | Serious risk of bias[60] | No serious inconsistency[61] | No serious indirectness | Serious imprecision[62] | Not assessed[63] | ⊕OOO **VERY LOW**[64] | 11,890/71,464 (16.7%) | 46 more (from 91 fewer to 205 more) | Unclear[65] | 1.04 (0.92 to 1.18) | 1.16 (1.05 to 1.30) | CRITICAL |
| | CHD mortality | 93,394 (2 studies; 3 comparisons)[66] | Serious risk of bias[67] | Serious inconsistency[68] | No serious indirectness | Serious imprecision[69] | Not assessed[70] | ⊕OOO **VERY LOW**[71] | 3,018/93,394 (3.2%) | 2 more (from 58 fewer to 86 more) | Unclear[72ii] | 1.01 (0.71 to 1.43) | 1.12 (0.90 to 1.40) | CRITICAL |
| | CHD total | 73,546 (3 studies; 4 comparisons)[73] | Serious risk of bias[74] | No serious inconsistency[75] | No serious indirectness | Serious imprecision[76] | Not assessed[77] | ⊕OOO **VERY LOW**[78] | 828/73,546 (1.1%) | 29 fewer (from 114 fewer to 76 more) | No[79] | 0.93 (0.73 to 1.18) | 0.99 (0.94 to 1.04) | CRITICAL |
| | Ischemic stroke | No studies | - | - | - | - | - | - | - | | - | - | - | |
| | Type 2 diabetes | 12,942 (5 studies; 5 comparisons)[80] | Serious risk of bias[81] | No serious inconsistency[82] | No serious indirectness | No serious imprecision[83] | Not assessed[84] | ⊕OOO **VERY LOW**[85] | 1,153/12,492 (8.4%) | 235 fewer (from 292 fewer to 146 fewer) | Likely[86] | 0.58 (0.48 to 0.74) | 0.59 (0.48 to 0.72) | 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. Included data from 2 prospective cohort studies (2 comparisons), with 7-10 (median=8.5) years of follow-up, enrolling participants from the United States and China.

3. Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa scores were 7-8 (median=7.5). Fully-adjusted model yielded weaker estimate than minimally-adjusted model, suggesting that these variables captured some important confounders. Since the direction of the bias is likely towards the null, and the pooled estimate exceeded the threshold of harm (>1.2), not downgraded.

4. $I^2$=70%; $P_{het}$=0.07 [random effects]; $I^2$=0%; $P_{het}$=0.71 [fixed effect]. Not downgraded; small # of studies makes estimation of between-studies heterogeneity for random-effects analysis unreliable. Both studies' MVRR point estimates were >1.2 and lower bounds >1.0

5. Optimal information size met (n= 2,141 events); summary RR does not cross 1.0, however upper 95% CI exceeds threshold of harm (>1.2) and lower 95% CI excludes meaningful benefit. Not downgraded because of consistency of strength and direction of point estimates of each study.
6. Unable to formally assess with only 2 studies.
7. Data from cohort studies begin with a grade of "LOW". Not downgraded.
8. P-value for trend of increased risk across quintiles of intake=0.004 (U.S.) and 0.0003 (China), however the individual studies did not present data for the continuous association. Because only 2 cohorts provided data for these tests for trend, we did not feel confident upgrading for possible dose-response.
9. Judgement was made to use fixed effect model in spite of high heterogeneity, owing to low power for estimating $tau^2$ (between-studies variance) with only 2 studies. With this model, the 95% CI: 1.16 to 1.56, a range consistent with harm.
10. Included data from 5 prospective cohort studies (6 comparisons), with a duration of follow-up from 6 to 21.4 years (median=6.6), enrolling participants from 3 different countries (USA, Finland, and the Netherlands).
11. Possibility of residual confounding always must be considered in observational studies. Fully-adjusted model yielded weaker estimates than minimally-adjusted models, suggesting that these variables captured some important confounders. Newcastle-Ottawa scores of these studies range from 7 to 9 (median=7.5). Diet assessment in 3 studies (Ascherio et al., Pietinen et al., Oomen et al.) was by validated instrument. In Xu et al., a single 24-h recall was used. Using a single dietary assessment may induce misclassification of true diet over the longer term, as during the follow-up period, it is likely that the composition of the food supply changed substantially. Since the direction of the bias is likely towards the null, and the pooled estimate exceeded the threshold of harm (>1.2), not downgraded.
12. $I^2$=0%; $P_{het}$=0.66. 5 studies had point estimates >1.0 and 95% CI and in the 1 study that did not, the 95% CI of this estimate was 0.42 to 1.65.
13. Optimal information size met (n=1,234 events); summary RR does not cross 1.0, however upper 95% CI exceeds threshold of harm (>1.2) and lower 95% CI bound excludes meaningful benefit.
14. Due to small number of studies (n<10) risk of publication bias not formally assessed. However, inclusion of additional "underpublished" data from the Iowa Womens' Health study + Finnish Mobile Health Clinics Study (see eFigure 17) results in pooled estimate of 1.22 (95% CI: 1.07 to 1.36; P=0.002; $I^2$=0%; $P_{het}$=0.46)
15. Data from cohort studies begin with a grade of "LOW". Upgraded (+1) due to evidence for dose-response.
16. Continuous dose-response relationship was assessed in 4 studies (n=1,002 events; RR per 2% increase in TFA at the expense of carbohydrate: 1.31 (1.13 to 1.56).
17. Included data from 6 prospective cohort studies (7 comparisons), with a duration of follow-up from 1 to 20 years (median=6), enrolling participants from 3 different countries (USA, Finland, Netherlands).
18. Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa scores of these studies range from 7 to 9 (median=8). Fully-adjusted model yielded weaker estimates than minimally-adjusted models, suggesting that these variables captured some important confounders. Both studies assessed diet with validated instruments, at multiple time points. Not downgraded.
19. $I^2$=0%; $P_{het}$=0.43. All 7 comparisons reported point estimates >1.0.
20. Optimal information size met (n=4,579 events); summary RR does not cross 1.0, however upper 95% CI exceeds threshold of harm (>1.2) and lower 95% CI bound excludes meaningful benefit.
21. Due to small number of studies (n<10) risk of publication bias not formally assessed.
22. Data from cohort studies begin with a grade of "LOW". Upgraded (+1) due to evidence for dose-response.

23. Continuous dose-response relationship was assessed in 4 studies (n=1,852 events; pooled mvRR per 2% increase in TFA at the expense of carbohydrate: 1.25 (1.15 to 1.36); meta-analyses of non-referent quantiles found statistically significant increased risk within all quantiles.
24. Included data from 3 prospective cohort studies (4 comparisons), with a duration of follow-up from 7 to 14 years (median=7.3), enrolling participants from the United States.
25. Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa scores for 3 studies ranged from 7 to 8 (median=7.5). Common limitations were failure to control for family history, and unclear attrition rates.
26. $I^2$=67%; 2/4 >1.0. Notably, an important inconsistency is that one study (He et al.) suggests important benefit (RR at the lower bound of clinically relevant benefit, RR=0.8) while and another study (Yaemsiri et al.) suggests clinically important harm (RR=1.39, greater than 1.2). The 95% CI of each individual study would exclude the point-estimate of the other.
27. Optimal information size met (n=1,905 events); summary RR crosses 1.0: lower bound of 95% CI approaches 0.8 and the upper bound is >1.2, which is consistent with is approaching clinically significant benefit and exceeding the upper threshold for harm.
28. Due to small number of studies (n<10) risk of publication bias not formally assessed
29. Data from cohort studies begin with a grade of "LOW". Downgraded due to serious inconsistency, and serious imprecision.
30. Two studies directly assessed dose-response (He et al. and Yaemsiri et al.); no continuous association seen in either study.
31. Included data from 6 prospective cohort studies (6 comparisons), with a duration of follow-up from 8.8 to 20 years (median=12), enrolling participants from the United States (n=5) and Finland (n=1).
32. Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa scores of these studies range from 6 to 9 (median=8). Fully-adjusted model yielded weaker estimates than minimally-adjusted models, suggesting that these variables captured some important confounders. A sensitivity analysis suggested the positive association seen in Salmeron et al. may be attributable to other dietary variables. Pooling the models which did not adjust for fiber and magnesium (Salmeron et al., van Dam et al., Simila et al.), resulted in a MVRR = 1.28 (95% CI: 1.16 to 1.41) though this may reflect failure to adjust for other important confounders. Pooling 5 studies that did not adjust for Mg or Fiber (and other confounders) yields an mVRR = 1.25 (95% CI: 1.15 to 1.36; P<0.001; $I^2$=0%; $P_{het}$=0.72)
33. $I^2$=66%; $P_{het}$=0.01. Point estimates for 4 studies >1.0; point estimates for 2 studies <1.0. Upper bound of 95% CI >1.2 but lower bound >0.8.
34. Optimal information size met (n=8,690 events); summary 95% CI of the RR includes 1.0, but upper bound >1.25, consistent with possible harm. Lower CI excludes meaningful benefit.
35. Due to small number of studies (n<10) risk of publication bias not formally assessed
36. Cohort studies start with a GRADE of "LOW". Downgraded for serious risk of bias, inconstancy, and imprecision.
37. Two studies (n=3,605 cases) directly assessed the dose-response association. In these 2 studies, a 2% increase in energy from trans fatty acids (at the expense of carbohydrate) was associated with a 41% increased risk of type 2 diabetes (MVRR: 1.41; 95% CI: 1.20 to 1.67). However, studies which did not directly assess this association failed to find associations between extreme quintiles.
38. Included data from 1 prospective cohort study (2 comparisons), with 26 years of follow-up, enrolling participants from Norway.
39. Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa score was 6, as the authors did not formally adjudicate outcomes, and did not adjust for family history. There may also be methodological limitations in the ability to accurately ascertain the source of certain *trans* isomers (industrial vs. ruminant), owing to the fact that some isomers are shared by both sources. Fully-adjusted model yielded weaker and non-signficant estimates than minimally-adjusted model, suggesting that multivariable adjustment captured some important confounders; minimally-adjusted model suggests harm.

40. Both sources of industrial trans fatty acids (partially hydrogenated vegetable oil and partially hydrogenated fish oil) were pooled; $I^2$=0% $P_{het}$=0.52
41. Optimal information size met (n=11,890 deaths); summary RR crosses 1.0: lower bound of 95% CI >0.8 and upper bound <1.2, suggesting no clinically relevant benefit or harm.
42. Due to small number of studies (n<10) risk of publication bias not formally assessed.
43. Cohort studies start with GRADE of "LOW". Downgraded due to serious risk of bias, and serious imprecision.
44. Wald-test P-value for trend across quintiles was reported for both PHVO and PHFO; neither was significant (both P=0.11).
45. Included data from 2 prospective cohort studies (2 comparisons), with 6 and 26 years of follow-up (median=16), enrolling participants from Finland and Norway.
46. Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa score was 6 for Laake et al., as the authors did not formally adjudicate outcomes, and did not adjust for family history and 8 for Pietinen et al. There may also be methodological limitations in the ability to accurately ascertain the source of certain *trans* isomers (industrial vs. ruminant), owing to the fact that some isomers are shared by both sources.
47. $I^2$=0%; $P_{het}$=.68; both point estimates >1.0. Lower bound of pooled 95% CI excludes possible benefit.
48. Optimal information size met (n=3,018 events); summary RR does not include RR=1.0; 95% CI of pooled effect consistent with possible harm (UCL=1.33) and excludes possible benefit (LCL=1.04).
49. Due to small number of studies (n<10) risk of publication bias not formally assessed.
50. Cohort studies start with GRADE of "LOW". Downgraded due to serious risk of bias.
51. Not directly assessed. In the 2 studies, 2 of 3 comparisons reported P<0.05 for trend tests across quantiles, suggestive of harm (Laake et al., for both PHVO and PHFO). Overall, 3 of 4 non-referent quantiles showed statistically signficant harm only for PHVO, but this was not seen for PHFO, or in Pietinen et al.
52. Included data from 2 prospective cohort studies (2 comparisons), with 6 and 8 years of folllow-up (median=7), enrolling participants in the United States and Netherlands.
53. Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa score was 9 for Willett et al. and 7 for Ooomen et al. (median=8). There may also be methodological limitations in the ability to accurately ascertain the source of certain *trans* isomers (industrial vs. ruminant), owing to the fact that some isomers are shared by both sources.
54. $I^2$=34%; $P_{het}$=0.22; after rescaling Oomen et al. to provide the ≈2% contrast provided in Willett et al., both individual point estimates were >1.00, and lower bounds of 95% CI both ≥1.00.
55. Optimal information size met (n=454 events); summary RR does not include RR=1.0; 95% CI of pooled effect consistent with possible harm (UCL=1.92) and excludes possible benefit (LCL=1.05).
56. Due to small number of studies (n<10) risk of publication bias not formally assessed.
57. Cohort studies start with GRADE of "LOW". Downgraded due to serious risk of bias.
58. Directly assessed in Oomen et al., who report a 6% increased in risk per 0.5% energy from industrial TFA (RR=1.06; 95% CI: 1.00 to 1.13). Willett et al. (1993) report a P-for trend across quintiles of intake of 0.009, and in 2 of the 4 non-referent quantiles, increased risk was found.
59. Included data from 1 prospective cohort study (2 comparisons), with 26 years of follow-up, enrolling participants from Norway. Results presented stratified by sex.

60. Possibility of residual confounding always must be considered in observational studies. Fully-adjusted model yielded weaker estimates than minimally-adjusted model, suggesting that these variables captured some important confounders; minimally-adjusted model suggests harm. Newcastle-Ottawa score was 6, as the authors did not adjust for family history or formally adjudicate outcomes. There may also be methodological limitations in the ability to accurately ascertain the source of certain *trans* isomers (industrial vs. ruminant), owing to the fact that some isomers are shared by both sources.
61. The authors report significant effect modification of the association between ruminant TFA and total mortality, measuring rTFA on the continuous scale ($P_{interaction}$=0.03). In men, the MVRR for highest vs. lowest TFA = 0.98 (95% CI: 0.83 to 1.16) and in women it was 1.11 (95% CI: 0.93 to 1.31). Despite associations in opposing directions, not downgraded because within-gender effects were not significantly different from 1.0
62. Optimal information size met (n=11,890 deaths). The 95% CI of the pooled effect included 1.0, and the upper bound approached the threshold for harm (1.2). Within men (n=7,582 deaths), the 95% CI included 1.0; the lower bound (0.83) approached threshold for benefit (0.8), and the upper bound (1.16) approached threshold of harm (1.2). In women (n=4,308 deaths), the 95% CI included 1.0, and the upper bound =1.31, which met the threshold for harm (1.2).
63. Due to small number of studies (n<10) risk of publication bias not formally assessed.
64. Cohort studies begin with a GRADE of "LOW". Downgraded due to serious risk of bias, serious imprecision.
65. The test for trend across quintiles of increasing intake suggested a dose-response, but the directions of association differed by gender: P-trend for men = 0.02 (suggesting higher intakes of rTFA were protective); P-trend for women=0.15 (suggesting higher intakes of rTFA were harmful)
66. Included data from 2 prospective cohort studies (3 comparisons), with 6 to 26 years of follow-up (median=16), enrolling participants from Norway and Finland. Results presented stratified by sex by Laake et al., and Pietinen et al. enrolled only men.
67. Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa scores were 6 for Laake et al., as the authors did not formally adjudicate outcomes and 8 for Pietinen et al. (median=7). Neither study controlled for CHD history. Fully-adjusted model yielded weaker estimates than minimally-adjusted model, suggesting that these multivariable adjustment accounted for some important confounders, but both models failed to find a statistically-significant association. There may also be methodological limitations in the ability to accurately ascertain the source of certain *trans* isomers (industrial vs. ruminant), owing to the fact that some isomers are shared by both sources. Downgraded.
68. $I^2$=79%; $P_{het}$=.01; both point estimates in cohorts of men (Pietinen et al., and Laake et al; n=2,521 cases) suggest clinically relevant benefit (mvRR of 0.83 and 0.87, respectively), while the single cohort of women (Laake et al.; n=497 cases) report clinically significant harm (mvRR=1.35; 95% CI: 1.11 to 1.64).
69. Optimal information size met (n=3,018 events). The 95% CI of the pooled effect included 1.0; the lower bound (0.73) exceeded the threshold for clinically relevant benefit (<0.8) and the upper bound of 1.43 exceeded the threshold for harm (1.2). The individual estimates from both cohorts of men (n=7,582 cases) had 95% CI which 1.0, and the lower bounds approached 0.6, which met the threshold for benefit (<0.8), and the upper bound of Laake et al., 1.26, exceeded threshold for harm (1.2). In women (n=497 cases), the point estimate of 1.35 suggested clinically relevant harm (>1.2) the 95% CI of 1.11 to 1.64 excluded relevant benefit.
70. Due to small number of studies (n<10) risk of publication bias not formally assessed.
71. Cohort studies start with a GRADE of "LOW". Downgraded due to serious risk of bias, serious inconsistency, and serious imprecision.
72. In men, Pietinen et al. found a significant trend for protection across increasing quintile of ruminant TFA (P-trend = 0.035), however Laake et al. found no trend (P-trend = 0.92). In women, no trend across quintiles was seen (P=0.30). None of the individual non-referent quantiles reported significant effects (0/12 referents).

73. Included data from 3 prospective cohort studies (4 comparisons), with 6 to 18 years of follow-up (median=13) enrolling participants from the United States, the Netherlands, and Denmark.
74. Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa scores ranged from 7 to 9 (median=8). There may also be methodological limitations in the ability to accurately ascertain the source of certain *trans* isomers (industrial vs. ruminant), owing to the fact that some isomers are shared by both sources.
75. $I^2$=46%; $P_{het}$=.13; 95% CI of all studies overlap.
76. Optimal information size met (n=828 events); the pooled 95% CI of effect includes 1.0; range of effects consistent with both protection (RR=0.73) and at threshold of harm (RR=1.18); all individual study estimates cross 1.0; 3 of 4 lower bounds from individual studies consistent with clinically meaningful reduction in risk (RR<0.80); 1 of 4 upper bounds consistent with harm (RR>1.2)
77. Due to small number of studies (n<10) risk of publication bias not formally assessed.
78. Cohort studies begin with a GRADE of "LOW". Downgraded due to serious risk of bias and serious imprecision.
79. Two studies (Oomen et al. and Jakobsen et al.) provided direct dose-response estimates. Oomen at al report 17% increased risk per 0.5%E (RR: 1.17; 95% CI: 0.69 to 1.98); Jakobsen et al report different effects in men (RR per 0.5 g: 1.05; 95% CI: 0.94 to 1.17) compared with women (RR per 0.5 g: 0.77; 95% CI: 0.55 to 1.09). All RR non-significant for linear dose-response.
80. Included data from 5 prospective cohort studies (5 comparisons), with 5-20 years of follow-up (median=14) enrolling participants from the United States. Two datasets derived mainly from the *Cardiovascular Health Study* are included (Mozaffarian, 2010; and Wang, 2015) because though some participants are the same in these two reports, the two studies do include slightly different groups of participants. Removing Mozaffarian, 2010 (new HR from 4 studies is 0.64; 95% CI: 0.57 to 0.80) or Wang, 2015 (new HR from 4 studies is 0.54; 95% CI: 0.41 to 0.71) would not appreciably change the pooled effect estimate or our confidence in the estimates.
81. Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa score for studies ranged from 8 to 9 (median=9). There may also be methodological limitations in the ability to accurately ascertain the source of certain *trans* isomers (industrial vs. ruminant), owing to the fact that some isomers are shared by both sources. *trans*-palmitoleic acid is predominantly found dairy foods (a ruminant source), but small amounts are also present in meat, and may be formed from industrial trans fats. Downgrade.
82. $I^2$=30%; $P_{het}$=0.22.
83. Optimal information size met (n=1,153 cases). Pooled effect does not include 1.0, and width of 95% CI does not cross 1.0; both lower and upper CI consistent with important benefit.
84. Due to small number of studies (n<10) risk of publication bias not formally assessed.
85. Cohort studies begin with GRADE of "LOW". Downgraded for serious risk of bias.
86. In 3 studies, the P-value for trend across increasing quintiles of intake was ≤0.02 (n=663 cases from Mozaffarian 2010; Mozaffarian 2013; Yakoob 2014). In 2 studies, the trend was not significant (n=490 cases from Santaren et al., 2014: P=0.20; Wang et al., 2014: P=0.10).

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[i] Judgement was made to use fixed effect model in spite of high heterogeneity, owing to low power for estimating $tau^2$ (between-studies variance) with only 2 studies. With this model, the 95% CI: 1.16 to 1.56, a range consistent with harm.

[ii] In men, Pietinen et al. found a significant trend for protection across increasing quintile of ruminant TFA (P-trend = 0.035), however Laake et al. found no trend (P-trend = 0.92). In women, no trend across quintiles was seen (P=0.30). None of the individual non-referent quantiles reported significant effects (0/12 referents).