

Online Supporting Material Appendix 4: GRADE Evidence Profile for prospective cohort studies of nut consumption on all-cause mortality and cardiovascular disease

Quality Assessment									Summary of Findings			
Exposure	Outcome	Participants (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision ¹	Publication bias	Overall quality of evidence	Study event rate (%)	Dose-Response	Most-adjusted MV RR	Least-adjusted MV RR
Nut Consumption	All-cause mortality	277,432(10) ²	Not serious ³	Not serious (I ² = 43%)	Not serious	Not serious ⁴	Not serious ⁵	⊕⊕⊕○ MODERATE ⁶	49232/277432 (17.7%)	Yes ⁷	0.81 (0.77, 0.85) ⁸	0.78 (0.73, 0.82)
	Total cardiovascular disease	6,309 (1) ⁹	Not serious ¹⁰	Not applicable	Not serious	Not serious ¹¹	Not assessed, but unlikely ¹²	⊕⊕⊕○ MODERATE ¹³	634/6309 (10.0%)	Yes ¹⁴	0.56 (0.36, 0.88)	0.43 (0.30, 0.61)

¹ Studies were considered at risk for imprecision if the optimal information size criteria was not met (<400 cases) or if the optimal information size criteria is met, if the 95% confidence interval includes 1.00.

² Included data from 10 prospective cohort studies, with duration of follow-up ranging from 4.6 to 30 years enrolling participants from 4 different countries.

³ Possibility of residual confounding must always be considered in observational studies. Newcastle-Ottawa Scale scores ranged from 5 to 9.

⁴ Optimal information size was met. Not downgraded despite seven subgroups having a 95% CI that crossed one. The overall 95% CI of the pooled effect did not cross 1.00

⁵ A visual inspection of the funnel plot and Egger's test (p=0.006) revealed the potential for publication bias to be present while the Begg's test (p=0.067) and trim and fill method did not indicate the presence of publication bias. Because the trim and fill method did not suggest that the presence of unpublished studies would alter our estimate we determined that there was not a high risk of publication bias.

⁶ Data from cohort studies begin with a grade of "LOW". Upgraded because of evidence of dose response.

⁷ Dose response noted in Bao et al., (p<0.001), Levitan et al., (p=0.049), Guasch-Ferré et al. (p=0.012), Luu et al. (p<0.001) and van den Brandt et al., (p=0.003) Evidence of association found in Fraser et al. 1997a and a borderline association (p=0.058) in Fernandez-Montero et al. No dose response reported by Blomhoff et al., and Mann et al. Dose response analysis revealed a significant linear association across all studies (5% reduction per serving of nuts consumed per week, p<0.001)

⁸ RR is 0.84 (0.81-0.88) in females, 0.78 (0.69-0.88) in males, and 0.81 (0.77-0.85) in data from studies pooling data from males and females.

⁹ Included data from 1 prospective cohort study including 1 comparison with 8.6 years of follow up with female participants from the United States.

¹⁰ Possibility of residual confounding must always be considered in observational studies. Newcastle-Ottawa Scale score is 9.

¹¹ Optimal information size was met

¹² Due to small number of studies (n<10) risk of publication bias not formally assessed.

¹³ Data from cohort studies begin with a grade of "LOW. Evidence was neither upgraded because of evidence of a dose response.

¹⁴ Does response analysis across all studies reported a 8% lower risk of all CVD per serving of nuts consumed per week (p=0.018).

Cardiovascular disease mortality	243,795 (5) ¹⁵	Not serious ¹⁶	Not serious ($I^2=16\%$)	Not serious	Not serious ¹⁷	Not assessed, but unlikely ¹⁸	⊕⊕○○ LOW ¹⁹	13726/243795 (5.6%)	No ²⁰	0.73 (0.68, 0.78) ²¹	0.73 (0.67, 0.80)
Total coronary heart disease	123,971 (3) ²²	Not serious ²³	Serious ($I^2=88\%$) ²⁴	Not serious	Not serious ²⁵	Not assessed, but unlikely ²⁶	⊕○○○ VERY LOW ²⁷	4757/123971 (3.8%)	No ²⁸	0.66 (0.48-0.91) ²⁹	0.57 (0.45-0.72)
Coronary heart disease mortality	278,584 (7) ³⁰	Not serious ³¹	Not serious ($I^2=0\%$)	Not serious	Not serious ³²	Not serious ³³	⊕⊕⊕○ MODERATE ³⁴	8454/278584 (3.0%)	Yes ³⁵	0.70 (0.64-0.76) ³⁶	0.62 (0.55-0.70)

¹⁵ Included data from 5 prospective cohort studies, with 7 comparisons, duration of follow-up ranging from 4.8 to 30 years enrolling participants from 3 countries.

¹⁶ Possibility of residual confounding must always be considered in observational studies. Newcastle-Ottawa Scale scores ranged from 6-9.

¹⁷ Optimal information size was met

¹⁸ Due to small number of studies ($n<10$) risk of publication bias not formally assessed.

¹⁹ Data from cohort studies begin with a grade of "LOW". Neither upgraded nor downgraded.

²⁰ Despite a significant dose response noted in Bao et al. ($p<0.001$ for men, $p=0.04$ for women), Blomhoff et al. ($p=0.0008$), Luu et al., ($p<0.03$), and van den Brandt et al., (0.013) and trend towards a dose response in Guasch-Ferré et al. ($p=0.091$), the results of the dose response analysis was non-significant ($p=0.054$).

²¹ RR in females is 0.76 (0.66-0.88), 0.74 (0.64-0.83) in males, and 0.72 (0.64-0.81) in studies pooling data from males and females

²² Includes data from 3 prospective cohort studies

²³ Possibility of residual confounding must always be considered in observational studies. Newcastle-Ottawa Scale scores ranged from 6 to 9.

²⁴ Serious inconsistency: There does not appear to be important subgroup differences with males and females having overlapping 95% CI for estimated relative risk. The inconsistency appears to come from between study differences.

²⁵ Optimal information size was met. Not downgraded despite one study having a 95% CI that crossed one. The overall 95% CI of the pooled effect did not cross 1.00.

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 evidence because of inconsistency.

²⁸ Bernstein et al. found evidence of a dose response ($p<0.001$) however Haring et al. did not ($p=0.67$) and dose response was not evaluated in Fraser et al.

²⁹ RR in females is 0.68 (0.60-0.77) and in studies pooling data from males and females the RR is 0.64 (0.32-1.28)

³⁰ Included data from 7 prospective cohort studies with 10 comparisons, duration of follow-up ranges from 6 to 30 years enrolling participants from 2 countries.

³¹ Possibility of residual confounding must always be considered in observational studies. Newcastle-Ottawa Scale scores ranged from 5 to 9.

³² Optimal information size was met. Not downgraded despite three studies having a 95% CI that crossed 1.00. The overall 95% CI of the pooled effect did not cross 1.00.

³³ Due to small number of studies ($n<10$) risk of publication bias not formally assessed.

³⁴ Data from cohort studies begin with a grade of "LOW". Upgraded because of evidence of dose response.

³⁵ Significant dose response noted in Bao et al. ($p<0.001$), Blomhoff et al. ($p=0.008$) Fraser et al. 1992 ($p<0.01$), Luu et al., ($p=0.01$) and van den Brandt et al., ($p=0.026$) and evidence of a dose response in Fraser et al. 1997. Dose response was not evaluated by Mann et al. A non-linear but significant dose response was found in the dose response analysis. For up to 1 serving per week, there was a 7% lower risk of CHD mortality per serving of nuts consumed per week ($p<0.001$)

³⁶ RR in females is 0.69 (0.59-0.82), 0.71 (0.61-0.82) in males, and 0.68 (0.55-0.83) in s pooling male and female data

Non-fatal coronary heart disease	138,678 (3) ³⁷	Not serious ³⁸	Serious ($I^2 = 68\%$) ³⁹	Not serious	Serious ⁴⁰	Not assessed, but unlikely ⁴¹	⊕○○○ VERY LOW ⁴²	1565/138678 (1.1%)	Yes ⁴³	0.71 (0.49, 1.03) ⁴⁴	0.65 (0.43, 0.98)
Sudden cardiac death	21,454 (1) ⁴⁵	Not serious ⁴⁶	Not applicable	Not serious	Serious ⁴⁷	Not assessed, but unlikely ⁴⁸	⊕○○○ VERY LOW ⁴⁹	201/21454 (0.9%)	Yes ⁵⁰	0.53 (0.30, 0.93)	0.64 (0.40, 1.02)
Total stroke	157,826 (2) ⁵¹	Not serious ⁵²	Serious ($I^2 = 77\%$)	Not serious	Serious ⁵³	Not assessed, but unlikely ⁵⁴	⊕○○○ VERY LOW ⁵⁵	4318/157826 (2.7%)	No ⁵⁶	1.05 (0.69-1.61) ⁵⁷	1.01 (0.71-1.44)

³⁷ Included data from 3 prospective cohort studies, with duration of follow-up ranging from 6 to 17 years, with participants from 1 country.

³⁸ Possibility of residual confounding must always be considered in observational studies. Newcastle-Ottawa Scale scores ranged from 7 to 9.

³⁹ Serious inconsistency: There does not appear to be important subgroup differences with males and females having overlapping 95% CI for estimated relative risk. The inconsistency appears to come from between study differences.

⁴⁰ Optimal information size was met but outcome is at risk for imprecision because the 95% CI for the most adjusted model crosses a relative risk of 1.00.

⁴¹ Due to small number of studies (n<10) risk of publication bias not formally assessed.

⁴² Data from cohort studies begin with a grade of "LOW". Despite evidence of a dose response, the quality of evidence was downgraded because of inconsistency and imprecision.

⁴³ The dose response analysis revealed a significant linear trend (0.95, 95%CI: 0.91-0.99, p=0.008) for each additional serving of nuts consumed per week.

⁴⁴ RR is 0.71 (0.47-1.07) in females, 1.04 (0.82-1.32) in males, and 0.49 (0.29-0.85) in studies pooling data from males and females.

⁴⁵ Prospective cohort study with follow-up of 17 years.

⁴⁶ Newcastle-Ottawa score of 8.

⁴⁷ Outcome is at risk for imprecision because optimal information size is not met.

⁴⁸ Due to small number of studies (n<10) risk of publication bias not formally assessed.

⁴⁹ Data from cohort studies begin with a grade of "LOW". Evidence was downgraded for imprecision.

⁵⁰ The dose response analysis revealed a significant linear dose response for each additional serving of nuts consumed per week (0.71, 95% CI: 0.55 to 0.93, p=0.014).

⁵¹ Includes data from 2 prospective cohort studies (2 comparisons) with a follow-up of 8 to 26 years.

⁵² Possibility of residual confounding must always be considered in observational studies. Newcastle-Ottawa Scale scores are 8 and 9.

⁵³ Optimal information size is met but outcome is at risk for imprecision because the 95% CI for the most adjusted model crosses a relative risk of 1.00.

⁵⁴ Due to small number of studies (n<10) risk of publication bias not formally assessed.

⁵⁵ Data from cohort studies begin with a grade of "LOW". Downgraded for inconsistency.

⁵⁶ P-value for trend in Bernstein et al., is 0.06 and 0.94 for the di Giuseppe et al.

⁵⁷ RR for men is 0.92 [0.77-1.09] and for women it is 0.86 [0.75, 0.98]

	Stroke mortality	161,488 (3) ⁵⁸	Not serious ⁵⁹	Not serious (<i>I</i> ² = 0%)	Not serious	Serious ⁶⁰	Not assessed, but unlikely ⁶¹	⊕○○○ VERY LOW ⁶²	2166/161488 (1.3%)	No ⁶³	0.83 (0.69, 1.00) ⁶⁴	0.70 (0.58-0.84)
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⁵⁸ Includes data from 3 prospective cohort studies (4 comparisons) with a follow up of between 8.3 and 26 years.

⁵⁹ Possibility of residual confounding must always be considered in observational studies. Newcastle-Ottawa Scale scores are 8 and 9.

⁶⁰ Optimal information size is met, however the outcome is at risk for imprecision because the summary and subgroup RR crosses 1.

⁶¹ Due to small number of studies (n<10) risk of publication bias not formally assessed.

⁶² Data from cohort studies begin with a grade of "LOW". Downgraded because of imprecision.

⁶³ The dose response analysis did not indicate there was a significant dose response.

⁶⁴ RR for men is 0.78 (0.58, 1.05) and 1.05 (0.73, 1.52) in women