Selenium, antioxidants, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials
David JA Jenkins
ONLINE SUPPORTING MATERIAL

Selenium, antioxidants, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials.

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Supplementary Tables

Supplementary Figures

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Supplementary Table 1. **Search Strategy**. Search was done from databse inception to June 5th 2020.

Databases	Search Terms
MEDLINE	1. exp Dietary Supplements/ 2. supplement*.mp. 3. exp ANTIOXIDANTS/ 4. antioxidant*.mp. 5. exp Vitamin A/ 6. vitamin A.mp. 7. retinol.mp. 8. vitamin C.mp. 9. exp Ascorbic Acid/ 10. ascorbic acid.mp. 11. exp Vitamin E/ 12. vitamin E.mp. 13. alpha tocopherol.mp. 14. beta carotene.mp. 15. alpha carotene.mp. 16. selenium.mp. 17. zinc.mp. 18. copper.mp 19. exp Cardiovascular Diseases/ 20. cardiovascular disease*.mp. 21. coronary heart disease*.mp. 22. coronary artery disease*.mp. 23. acute coronary syndrome*.mp. 24. myocardial ischemia*.mp. 25. ischemic heart disease*.mp. 26. heart infarction*.mp. 27. myocardial infarction*.mp. 28. stroke*.mp. 29. cerebrovascular*.mp. 30. cardiovascular mortality.mp. 31. cardiovascular death.mp. 32. exp MORTALITY/ 33. mortality.mp. 34. exp DEATH/ 35. death.mp. 36. all cause mortality.mp.

	37. exp Neoplasms/ 38. neoplasm*.mp. 39. cancer*.mp. 40. 1 or 2 41. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 42. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 43. 40 and 41 and 42 44. "randomized controlled trial".pt. 45. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. 46. (retraction of publication or retracted publication).pt. 47. or/44-46 48. (animals not humans).sh. 49. ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt. 50. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt. 51. 47 not (48 or 49 or 50) 52. (review or review,tutorial or review, academic).pt. 53. (medline or medlars or embase or pubmed or cochrane).tw,sh. 54. (scisearch or psychinfo or psycinfo).tw,sh. 55. (psychlit or psyclit).tw,sh. 56. cinahl.tw,sh. 57. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh. 58. (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh. 59. (pooling or pooled or mantel haenszel).tw,sh. 60. (peto or dersimonian or der simonian or fixed effect).tw,sh. 61. (retraction of publication or retracted publication).pt. 62. or/53-61 63. 52 and 62 64. meta-analysis.pt. 65. meta-analysis.sh. 66. (meta-analys$ or meta analys$ or metaanalys$).tw,sh. 67. (systematic$ adj5 review$).tw,sh. 68. (systematic$ adj5 overview$).tw,sh. 69. (quantitativ$ adj5 review$).tw,sh. 70. (quantitativ$ adj5 overview$).tw,sh. 71. (quantitativ$ adj5 synthesis$).tw,sh. 72. (methodologic$ adj5 review$).tw,sh. 73. (methodologic$ adj5 overview$).tw,sh.

	74. (integrative research review$ or research integration).tw. 75. or/64-74 76. 63 or 75 77. 43 and 51 78. 43 and 76 79. 77 or 78 80. limit 79 to "all child (0 to 18 years)" 81. 79 not 80
EMBASE	1. exp nutrition supplement/ 2. supplement*.mp. 3. exp antioxidant/ 4. antioxidant*.mp. 5. vitamin A.mp. 6. retinol.mp. 7. exp ascorbic acid/ 8. vitamin C.mp. 9. ascorbic acid.mp. 10. vitamin E.mp. 11. alpha tocopherol.mp. 12. beta carotene.mp. 13. alpha carotene.mp. 14. selenium.mp. 15. zinc.mp. 16.copper.mp 17. exp cardiovascular disease/ 18. cardiovascular disease*.mp. 19. coronary heart disease*.mp. 20. coronary artery disease*.mp. 21. coronary disease*.mp. 22. acute coronary syndrome*.mp. 23. ischemic heart disease*.mp. 24. myocardial ischemia*.mp. 25. heart infarction*.mp. 26. acute heart infarction*.mp. 27. myocardial infarction*.mp. 28. stroke*.mp. 29. cerebrovascular*.mp. 30. cardiovascular mortality.mp. 31. cardiovascular death.mp. 32. exp mortality/

	33. mortality.mp. 34. exp death/ 35. death.mp. 36. all cause mortality.mp. 37. exp neoplasm/ 38. neoplasm*.mp. 39. cancer*.mp. 40. 1 or 2 41. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 42. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 43. 40 and 41 and 42 44. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. 45. RETRACTED ARTICLE/ 46. or/44-45 47. (animal$ not human$).sh,hw. 48. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/ 49. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/ 50. 46 not (47 or 48 or 49) 51. exp review/ 52. (literature adj3 review$).ti,ab. 53. exp meta analysis/ 54. exp "Systematic Review"/ 55. or/51-54 56. (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab. 57. RETRACTED ARTICLE/ 58. 56 or 57 59. 55 and 58 60. (systematic$ adj2 (review$ or overview)).ti,ab. 61. (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti,ab. 62. 59 or 60 or 61 63. 43 and 50 64. 43 and 62 65. 63 or 64 66. limit 65 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) 67. 65 not 66
COCHRANE	1. supplement*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]

	2. antioxidant*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 3. vitamin A.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 4. retinol.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 5. vitamin C.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 6. ascorbic acid.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 7. vitamin E.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 8. alpha tocopherol.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 9. beta carotene.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 10. alpha carotene.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 11. selenium.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 12. zinc.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 13. copper.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 14. cardiovascular disease*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 15. coronary heart disease*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 16. coronary artery disease*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 17. coronary disease*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 18. acute coronary syndrome*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 19. ischemic heart disease*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 20. myocardial ischemia*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 21. heart infarction*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 22. acute heart infarction*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 23. myocardial infarction*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 24. stroke*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 25. cerebrovascular*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 26. cardiovascular mortality.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 27. cardiovascular death.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 28. mortality.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 29. death.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 30. all cause mortality.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 31. cancer*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 32. neoplasm*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] 33. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 34. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 35. 1 and 33 and 34 36. limit 35 to (cochrane childhood cancer group or cochrane neonatal group or "cochrane pregnancy and childbirth group") [Limit not valid in CDSR; records were retained] 37. 35 not 36

Supplementary Table 2. NNT/NNH calculations
(Method A); NNT = 1/ARR, where ARR = CER*RRR; RRR = 1- RR
(Method B); NNT = 1/ARR, where ARR = CER - EER

METHOD A (NNT = 1/ARR, where ARR = CER*RRR; RRR = 1- RR)						
Antioxidants and CVD mortality (Studies with Selenium)						
Control						
Events	**Total**	**CER**	**RR**	**RRR**	**ARR**	**NNT**
176	10691	0.0164624	0.77	0.23	0.0037863	264
Antioxidants and all-cause mortality (Studies with Selenium)						
Control						
Events	**Total**	**CER**	**RR**	**RRR**	**ARR**	**NNT**
930	21016	0.0442519	0.9	0.1	0.0044251	226
Antioxidants and all-cause mortality (Studies without Selenium)						
Control						
Events	**Total**	**CER**	**RR**	**RRR**	**ARR**	**NNH**
3498	36067	0.0969861	1.09	-0.09	-0.0087287	115
Antioxidants and Stroke mortality (Studies with Retinol)						
Control						
Events	**Total**	**CER**	**RR**	**RRR**	**ARR**	**NNT**
77	3548	0.0217023	0.71	0.29	0.0062936	159
Antioxidants and Cancer mortality (Studies with Retinol)						
Control						
Events	**Total**	**CER**	**RR**	**RRR**	**ARR**	**NNT**
107	3548	0.0301578	0.75	0.25	0.0075394	133
Antioxidants and all-cause mortality (Studies without Retinol)						
Control						
Events	**Total**	**CER**	**RR**	**RRR**	**ARR**	**NNH**
3724	**44641**	**0.083421**	**1.04**	**-0.04**	**-0.0033368**	**300**
Antioxidants and stroke mortality (Studies with Zinc)						
Control						
Events	**Total**	**CER**	**RR**	**RRR**	**ARR**	**NNT**
77	**3548**	**0.0217023**	**0.71**	**0.29**	**0.0062936**	**159**
Antioxidants and all-cause mortality (Studies without Zinc)						

Control						
Events	Total	CER	RR	RRR	ARR	NNH
3742	44371	0.0843343	1.07	-0.07	-0.0059034	169

Method B (NNT = 1/ARR, where ARR = CER – EER)

Antioxidants and CVD mortality (Studies with Selenium)							
Antioxidants		Control					
Events	Total	Events	Total	EER	CER	ARR	NNT
136	10694	176	10691	0.0127174	0.0164624	0.003745	267
Antioxidants and all-cause mortality (Studies with Selenium)							
Antioxidants		Control					
Events	Total	Events	Total	EER	CER	ARR	NNT
948	21445	930	21016	0.0442061	0.0442519	0.0000458	21834
Antioxidants and all-cause mortality (Studies without Selenium)							
Antioxidants		Control					
Events	Total	Events	Total	EER	CER	ARR	NNH
4218	39678	3498	36067	0.1063057	0.0969861	-0.0093196	107
Antioxidants and stroke mortality (Studies with Retinol)							
Antioxidants		Control					
Events	Total	Events	Total	EER	CER	ARR	NNT
55	3570	77	3548	0.0154061	0.0217023	0.0062962	159
Antioxidants and cancer mortality (Studies with Retinol)							
Antioxidants		Control					
Events	Total	Events	Total	EER	CER	ARR	NNT
81	3570	107	3548	0.022689	0.0301578	0.0074688	134
Antioxidants and all-cause mortality (Studies without Retinol)							
Antioxidants		Control					
Events	Total	Events	Total	EER	CER	ARR	NNH
4372	48133	3724	44641	0.0908316	0.083421	-0.0074106	135
Antioxidants and stroke mortality (Studies with Zinc)							
Antioxidants		Control					
Events	Total	Events	Total	EER	CER	ARR	NNT
55	3570	77	3548	0.0154061	0.0215686	0.0061625	162

Antioxidants and all-cause mortality (Studies without Zinc)							
Antioxidants		**Control**					
Events	**Total**	**Events**	**Total**	**EER**	**CER**	**ARR**	**NNH**
4409	**48002**	**3742**	**44371**	**0.0918503**	**0.0843343**	**-0.007516**	**133**

ARR, absolute risk reduction; CER, control event rate; EER, experimental event rate; CVD, cardiovascular disease; NNH, number needed to harm; NNT, number needed to treat; RR, relative risk; RRR, relative risk reduction.

Supplementary Table 3. Characteristics of included RCT studies for CVD, CVD outcomes, cancer, cancer mortality, and all-cause mortality

Study (reference)	Country	Health status	Age (years)	Duration (mean, median or range)	Supplement intake assessment	Supplement exposure (median or range, units)	Participants (intervention /control)	Incident cases (intervention /control)	Outcome	Funding source
ANTIOXIDANTS ONLY										
McKeown-Eyssen et al., 1988(1)	Canada	History of polyp	58	2 years	Urine sample	Vitamin C – 400 mg Vitamin E – 400 mg	96/89	4/3	All-cause mortality	Industry
DeCosse et al., 1989(2)	USA	Familial Adenomatous Polyposis	35	4 years	Interview, urine sample	Vitamin C – 4 g Vitamin E – 400 mg	36/22 36/22	0/1 0/1	Total CVD Stroke	Agency-industry
Blot et al., 1993 – Linxian Trial (3)	China	Healthy	40 – 69	5 years	Pill count	Retinol – 5000 IU Vitamin E – 30 mg Beta-Carotene – 15 mg Selenium – 50 mcg Zinc – 22.5 mg	3570/3548 3570/3548 3570/3548	55/77 81/107 250/280	Stroke mortality Cancer mortality All-cause mortality	Agency-Industry
Omenn et al., 1996 – CARET(4)	USA	Smoked cigarettes or who have had occupational exposure to asbestos	45 – 74	4 years	Pill count	Retinol – 25 000 IU Beta-Carotene – 30 mg	9420/8894	544/424	All-cause mortality	Agency-industry
Girodon et	France	Institution	65 –	2 years	Pill count,	Vitamin C –	61/20	18/7	All-cause	Industry

Study (reference)	Country	Health status	Age (years)	Duration (mean, median or range)	Supplement intake assessment	Supplement exposure (median or range, units)	Participants (intervention /control)	Incident cases (intervention /control)	Outcome	Funding source
al., 1997(5)		alized	102		plasma conc.	120 mg Vitamin E – 15 mg Beta-carotene – 6 mg Selenium – 100 mcg Zinc – 20 mg			mortality	
Tardif et al., 1997 - MVP(6)	Canada	Scheduled angioplasty	58.5	7 months	Pill count, plasma conc.	Vitamin C – 500 mg Vitamin E – 700 IU Beta-Carotene – 30 000 IU	158/159	4/3	Total CVD	Agency-industry
							158/159	4/3	Total CHD	
							158/159	3/2	MI	
							158/159	1/1	CVD mortality	
							158/159	1/1	CHD mortality	
							158/159	1/1	All-cause mortality	
Girodon et al., 1999 – MINVITOAX (7)	France	Long-term institutionalized elderly patients	65 – 103	2 years	Pill count, plasma conc.	Vitamin C– 120 mg Vitamin E– 15 mg Beta-Carotene – 6 mg (1000 RE) Selenium Sulfide – 100 ug Zinc Sulfate – 20 mg	543/182	155/51	All-cause mortality	Agency-industry
Correa et al., 2000	Colombia	History of precancer	29 – 69	6 years	Pill count, plasma	Vitamin C – 2 g	255/237	6/2	All-cause mortality	Agency-Industry

Study (reference)	Country	Health status	Age (years)	Duration (mean, median or range)	Supplement intake assessment	Supplement exposure (median or range, units)	Participants (intervention /control)	Incident cases (intervention /control)	Outcome	Funding source
(8)		ous lesion			conc., interview	Beta-carotene – 30 mg				
Jacobson et al., 2000(9)	USA	Smokers	> 18	6 months	n/a	Vitamin C – 250 mg Vitamin E– 200 IU Beta-Carotene – 6mg	57/55	0/1	All-cause mortality	Agency-Industry
Leppala et al., 2000 - ATBC(10)	Finland	Smokers	50 – 69	6.1 years	Pill count, plasma conc.	Vitamin E – 50 mg Beta-Carotene – 20 mg	7118/7153	258/252	Stroke	Agency
							7118/7153	46/34	Stroke mortality	
Salonen et al., 2000 – ASAP(11)	Denmark	Hypercholesterolemia	45 – 69	3 years	Pill count	Vitamin C – 250 mg (136 IU) Vitamin E – 91 mg (136 IU)	130/130	1/1	Total CVD	Agency-industry
							130/130	1/1	CVD mortality	
							130/130	1/1	All-cause mortality	
AREDS 2001(12)	USA	Advanced Acute Degeneration (AMD)	55 – 80	6.3 years	Pill count, plasma conc.	Vitamin C – 500 mg Vitamin E – 400 IU Beta-Carotene – 15 mg Zinc – 80 mg	2370/2387	251/240	All-cause mortality	Agency-industry
Brown et al., 2001 – HATS (13)	USA	Previous CHD (with clinical coronary disease	53	3 years	Pill count	Vitamin C – 1000 mg Vitamin E – 800 IU Beta-	84/76	6/8	Total CVD	Agency-industry
							84/76	4/5	MI	
							84/76	2/2	Stroke	
							84/76	1/1	CVD mortality	

Study (reference)	Country	Health status	Age (years)	Duration (mean, median or range)	Supplement intake assessment	Supplement exposure (median or range, units)	Participants (intervention /control)	Incident cases (intervention /control)	Outcome	Funding source
		defined as previous MI, coronary interventions or confirmed angina)				Carotene – 25 mg Selenium – 100 mcg Simvastatin – Niacin	84/76	1/1	All-cause mortality	
Chylack et al., 2002 – REACT(14)	UK and USA	Cataract	67.8	3 years	Plasma conc.	Vitamin C – 750 mg Vitamin E – 600 mg Beta-Carotene – 18 mg	149/148	2/1	CVD mortality	Agency-industry
							149/148	2/1	CHD mortality	
							149/148	2/1	MI mortality	
							149/148	3/2	Cancer mortality	
							149/148	3/9	All-cause mortality	
HPS Collaborative Group 2002(15)	UK	Previous CHD	40 – 80	5 years	Capsule count	Vitamin C – 250 mg Vitamin E – 600 mg Beta-Carotene – 20 mg	10269/10267	2306/2312	Total CVD	Agency-industry
							10269/10267	1063/1047	Total CHD	
							10269/10267	464/467	MI	
							10269/10267	511/518	Stroke	
							10269/10267	878/840	CVD mortality	
							10269/10267	664/630	CHD mortality	
							10269/10267	108/107	Stroke mortality	
							10269/10267	1446/1389	All-cause mortality	
Waters et al., 2002 – WAVE(16)	USA and Canada	Coronary Stenosis	65 ± 9	3 years	Capsule count	Vitamin C – 500 mg Vitamin E – 400 IU	212/211	26/18	Total CVD	Agency
							212/211	14/8	Total CHD	
							212/211	4/4	MI	
							212/211	6/7	Stroke	

Study (reference)	Country	Health status	Age (years)	Duration (mean, median or range)	Supplement intake assessment	Supplement exposure (median or range, units)	Participants (intervention /control)	Incident cases (intervention /control)	Outcome	Funding source
							212/211	10/4	CVD mortality	
							212/211	6/5	Total cancer	
							212/211	16/6	All-cause mortality	
Virtamo et al., 2003 – ATBC(17)	Finland	Smokers	50 – 69	6.1 years	Pill count, plasma conc.	Vitamin E – 50 mg Beta-Carotene – 20 mg	7278/7287	579/551	Total cancer	Agency
							7278/7287	932/851	All-cause mortality	
Tornwall et al., 2004 – ATBC(18)	Finland	Smokers	50 – 69	6.1 years	Pill count, plasma conc.	Vitamin E – 50 mg Beta-Carotene – 20 mg	6781/6849	511/534	Total CHD	Agency
							497/438	123/93		
							6781/6849	289/296	MI	
							497/438	58/54		
							6781/6849	222/238	CHD mortality	
							497/438	65/39		
Mooney et al., 2005(19)	USA	Smokers	31.2 – 41.1	2 years (Data is presented on 15-month follow-up?)	Pill count, plasma conc.	Vitamin C – 500 mg Vitamin E – 400 IU	142/142	1/0	Total CVD	Agency-industry
							142/142	1/0	Total CHD	
							142/142	1/0	MI	
							142/142	1/0	CVD mortality	
							142/142	1/0	CHD mortality	
							142/142	1/0	MI mortality	
							142/142	1/1	Total cancer	
							142/142	1/0	All-cause mortality	
Stone et	USA	Previous	< 85	1 year	Pill count	Vitamin C –	101/96	7/8	Total CVD	Agency-

Study (reference)	Country	Health status	Age (years)	Duration (mean, median or range)	Supplement intake assessment	Supplement exposure (median or range, units)	Participants (intervention /control)	Incident cases (intervention /control)	Outcome	Funding source
al., 2005(20)		CHD				1000 mg/day Vitamin E – 800 mg/day	101/96	3/1	MI	industry
							101/96	0/1	Stroke	
							101/96	0/1	CVD mortality	
							101/96	0/1	All-cause mortality	
Bairati et al., 2006(21)	Canada	Stage I and II head and neck cancer	Not specifies for this specific group	3 years, however, beta-carotene supplementation stopped after first 156 enrolled. Duration period of beta-carotene supplementation not specified	Pill count	Vitamin E – 400 IU Beta-Carotene – 30 mg	79/77	37/30	All-cause mortality	Agency-industry
CLIPS 2007(22)	Europe	Pulmonary Artery Disease	66	2 years	Capsule count, interview	Vitamin C – 250 mg Vitamin E – 600 mg Beta-Carotene – 20 mg	185/181	16/11	Total CVD	Agency-Industry
							185/181	9/4	MI	
							185/181	6/5	Stroke	
							185/181	6/3	CVD mortality	
							185/181	2/2	MI mortality	
							185/181	3/0	Stroke mortality	
							185/181	1/1	Cancer	

Study (reference)	Country	Health status	Age (years)	Duration (mean, median or range)	Supplement intake assessment	Supplement exposure (median or range, units)	Participants (intervention /control)	Incident cases (intervention /control)	Outcome	Funding source
									mortality	
							185/181	7/4	All-cause mortality	
Cook et al., 2007-WACS (23)	USA	History of vascular disease or at least three cardiovascular risk factors	60.6	9.4 years	Pill count	Vitamin C – 500 mg Vitamin E – 600 IU (every other day) Beta-Carotene – 50 mg (every other day)	4085/1022	507/124	All-cause mortality	Agency-industry
Plummer et al., 2007(24)	Venezuela	Pre-cancerous lesions of the stomach	35 – 69	3 years	Pill count	Vitamin C – 750 mg Vitamin E – 600 mg Beta-Carotene – 18 mg/day	990/990	1/0	Total CVD	Agency-industry
							990/990	3/2	Total cancer	
							990/990	16/11	All-cause mortality	
Sesso et al., 2008 – PHS II (25)	USA	Physicians	64.3 ± 9.2	7.6 years	Questionnaire	Vitamin C – 500 mg Vitamin E – 400 IU (every other day)	3656/3653	310/316	Total CVD	Agency-industry
							3656/3653	133/144	MI	
							3656/3653	104/113	Stroke	
							3656/3653	127/122	CVD mortality	
Lippman et al., 2009 – SELECT(26)	USA, Canada, and Puerto Rico	Healthy	62.5	7 years	Pill count, plasma conc.	Vitamin E – 400 IU/day Selenium 200 mcg/day	8904/8910	1041/1050	Total CVD	Agency-industry
							8904/8910	111/100	Stroke	
							8904/8910	117/142	CVD mortality	
							8904/8910	12/8	Stroke mortality	
							8904/8910	846/824	Total cancer	

Study (reference)	Country	Health status	Age (years)	Duration (mean, median or range)	Supplement intake assessment	Supplement exposure (median or range, units)	Participants (intervention /control)	Incident cases (intervention /control)	Outcome	Funding source
							8904/8910	117/125	Cancer mortality	
							8904/8910	359/382	All-cause mortality	
Hercberg et al., 2010 – SUVIMAX (27)	France	Healthy	35 – 60	7.5 years	Questionnaire	Vitamin C – 120 mg Vitamin E – 30 mg Beta-Carotene – 6 mg Selenium – 100 mcg Zinc – 20 mg	6377/6364	137/143	Total CHD	Agency-industry
							6377/6364	278/300	Total cancer	
							6377/6364	77/99	All-cause mortality	
Ma et al., 2012 – SIT(28)	China	Healthy	35 – 64	7.3 years	Pill count	Vitamin C – 500 mg Vitamin E – 200 IU Beta-Carotene – 15 mg (stopped early) Selenium – 75 mcg	1706/1705	18/33	CVD mortality	Agency-industry
							1706/1705	10/14	Stroke mortality	
							1706/1705	41/42	Cancer mortality	
							1706/1705	82/101	All-cause mortality	
Arruda et al., 2013(29)	Brazil	Sickle cell anaemia patients	18 – 68	180 days	Pill count	Vitamin C – 1400 mg Vitamin E – 800 mg	46/42	2/0	Total CVD	Agency-Industry
							46/42	2/0	Stroke	
							46/42	0/1	All-cause mortality	
Bonelli et al.,	Italy	Removal of adenoid	29 – 83	5 years (or until	interview	Vitamin A – 2 mg	200/211	1/2	Total cancer	Agency-industry

Study (reference)	Country	Health status	Age (years)	Duration (mean, median or range)	Supplement intake assessment	Supplement exposure (median or range, units)	Participants (intervention /control)	Incident cases (intervention /control)	Outcome	Funding source
2013(30)		from large colon		recurrent adenoma occurrence)		Vitamin C – 180 mg Vitamin E – 30 mg Selenium – 200 mcg Zinc – 30 mg	200/211	6/9	All-cause mortality	
Wang et al., 2014 – PHS II (31)	USA	Physicians	64.3 ± 9.2	7.6 years	Questionnaire	Vitamin C – 500 mg Vitamin E – 400 IU (every other day)	3656/3653	504/486	Total cancer	Agency-industry
							3656/3653	440/406	All-cause mortality	
SELENIUM ONLY										
Korpela et al., 1989(32)	Finland	Previous MI	48-68	6 months	Serum selenium status	Selenium – 100 mcg	40/41	1/6	Total CVD	Unknown
							40/41	1/6	Total CHD	
							40/41	1/6	MI	
							40/41	0/4	CVD mortality	
							40/41	0/4	CHD mortality	
							40/41	0/4	MI mortality	
							40/41	0/4	All-cause mortality	
Duffield-Lillico et al.,2002 – NPC (33)	USA	Previous skin cancer	18-80	7.4 years	Patient-reported and blood samples	Selenium – 200 mcg	653/659	107/139	Total cancer	Agency-Industry
							653/659	40/66	Total cancer mortality	
Limburg et	China	Esophage	34-	10	Pill count and	Selenium –	180/180	1/1	Total CVD	Agency-

Study (reference)	Country	Health status	Age (years)	Duration (mean, median or range)	Supplement intake assessment	Supplement exposure (median or range, units)	Participants (intervention /control)	Incident cases (intervention /control)	Outcome	Funding source
al., 2005 (34)		al squamous dysplasia	68	months	direct observation	200 mcg	180/180	1/0	Total CHD	Industry
							180/180	1/0	MI	
							180/180	0/1	Stroke	
							180/180	1/0	CVD mortality	
							180/180	1/0	CHD mortality	
							180/180	1/0	MI mortality	
							180/180	0/1	Total cancer	
							180/180	1/0	All-cause mortality	
Stranges et al., 2006 – NPC (35)	USA	Previous skin cancer	52-73	7.6 years	Patient-reported and blood samples	Selenium – 200 mcg	504/500	103/96	Total CVD	Agency-Industry
							504/500	63/59	Total CHD	
							504/500	41/43	MI	
							504/500	35/32	Stroke	
							504/500	40/31	CVD mortality	
							504/500	9/8	MI mortality	
							504/500	110/111	All-cause mortality	
Lippman et al., 2009 – SELECT (26)	USA, Canada, Puerto Rico	Healthy	62.5	7 years	Pill count, plasma conc.	Selenium - 200 mcg/day	17760/17773	2121/2084	Total CVD	Agency-Industry
							17760/17773	172/162	Stroke	
							17760/17773	246/261	CVD mortality	
							17760/17773	21/17	Stroke mortality	
							17760/17773	1683/1680	Total cancer	
							17760/17773	245/231	Total cancer mortality	

Study (reference)	Country	Health status	Age (years)	Duration (mean, median or range)	Supplement intake assessment	Supplement exposure (median or range, units)	Participants (intervention /control)	Incident cases (intervention /control)	Outcome	Funding source
							17760/17773	737/740	All-cause mortality	
Stratton et al., 2010 (36)	USA	Prostate cancer	72.8 ± 6.65	5 years	Pill count	Selenium – 200 mcg	94/46	5/4	Total cancer	Agency-Industry
							94/46	4/1	All-cause mortality	
Rayman et al., 2011 – UK PRECISE (37)	UK	Healthy	60-74	6 months	Pill count	Selenium – 100 mcg	380/121	1/0	All-cause mortality	Agency-Industry
Marshall et al., 2011 – SWOG (38)	USA	High risk for prostate cancer	>40 yrs	3 years	Pill count, plasma selenium conc.	Selenium – 200mcg	227/225	4/6	All-cause mortality	Agency
Algotar et al., 2013 (39)	USA and New Zealand	Elevated PSA	65.4 ± 7.7	USA (5 years) New Zealand (3 years)	Pill count	Selenium – 200mcg or 400 mcg	467/232	52/29	Total cancer	Agency-Industry
							467/232	5/5	All-cause mortality	
Karp et al., 2013(40)	USA	Previous cancer	24-93	4 years	Pill count, compliance form	Selenium – 200 mcg	1040/521	18/12	All-cause mortality	Agency-Industry
Goossens et al., 2016 – SELEBLAT (41)	Belgium	Previous cancer	46-91	3 years	Pill count	Selenium – 200 mcg	151/141	1/0	All-cause mortality	Agency-Industry
Thompson et al., 2016 – SELCEL(42)	USA	Colorectal adenomas	40-80	2.75 years	Pill count, plasma selenium conc.	Selenium – 200 mcg	910/914	17/16	All-cause mortality	Agency-Industry
Rayman et	Denmar	Healthy	60-	5 years	Pill count	Selenium –	365/126	7/2	CVD	Agency-

Study (reference)	Country	Health status	Age (years)	Duration (mean, median or range)	Supplement intake assessment	Supplement exposure (median or range, units)	Participants (intervention /control)	Incident cases (intervention /control)	Outcome	Funding source
al., 2018 – DEN-MARK PRECISE (43)	k		74			100mcg, 200 mcg, 300 mcg			mortality	Industry-
							365/126	14/4	Total cancer mortality	
							365/126	23/8	All-cause mortality	

ATBC, The Alpha- Tocopherol, Beta-Carotene Cancer Prevention Study; AMD, advanced acute degeneration; AREDS, Age-Related Eye Disease Study; ASAP, Antioxidant Supplementation in Atherosclerosis Prevention; CVD, cardiovascular disease; CARET, Carotene and Retinol Efficacy Trial; CHD, coronary heart disease; CLIPS, Critical Leg Ischaemia Prevention Study; HATS, HDL-Atherosclerosis Treatment Study; HPS, Heart Protection Study Collaborative Group; IU, international units; MI, myocardial infarction; MINVITOAX, Mineral Vitamin Antioxidant; MVP, Multivitamins and Probucol Study Group; NPC, The Nutritional Prevention of Cancer; PHS, The Physicians Health Study; PRECISE, Prevention of Cancer by Intervention with Selenium; REACT, The Roche European American Cataract Trial; SELCEL, The Selenium and Celecoxib (Sel/Cel) Trial; SELEBLAT, Selenium and Bladder Cancer Trial; SELECT, The Selenium and Vitamin E Cancer Prevention; SIT, Shadong Intervention Trial; SU.VI.MAX, The Supplémentation en Vitamines et Minéraux AntioXydants study; WAVE, Women's Angiographic Vitamin and Estrogen; WACS, The Women's Antioxidant Cardiovascular Study; SWOG, Southwest Oncology Group.

Supplementary Table 4. GRADE assessment for antioxidants and CVD, cancer, cancer mortality, and all-cause mortality

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with Antioxidants			
Antioxiants and Total CVD	150 per 1,000	**150 per 1,000** (144 to 156)	**RR 1.00** (0.96 to 1.04)	49792 (13 RCTs)	⊕⊕⊕⊕ HIGH
Antioxidants and Total CHD	75 per 1,000	**76 per 1,000** (71 to 80)	**RR 1.01** (0.95 to 1.07)	48866 (7 RCTs)	⊕◯◯◯ VERY LOW [a,b,c,d]
Antioxidants and MI	44 per 1,000	**43 per 1,000** (40 to 47)	**RR 0.98** (0.90 to 1.07)	44157 (10 RCTs)	⊕⊕◯◯ LOW [e,f]
Antioxidants and Stroke	32 per 1,000	**32 per 1,000** (29 to 35)	**RR 1.00** (0.92 to 1.09)	61222 (10 RCTs)	⊕⊕⊕◯ MODERATE [g]
Antioxidants and Total CVD mortality	45 per 1,000	**44 per 1,000** (39 to 50)	**RR 0.98** (0.87 to 1.11)	51374 (12 RCTs)	⊕⊕⊕◯ MODERATE [h]
Antioxidants and Total CHD mortality	50 per 1,000	**53 per 1,000** (48 to 58)	**RR 1.05** (0.95 to 1.15)	35999 (6 RCTs)	⊕◯◯◯ VERY LOW [d,i,j,k]
Antioxidants and MI mortality	6 per 1,000	**10 per 1,000** (2 to 38)	**RR 1.51** (0.39 to 5.93)	947 (3 RCTs)	⊕◯◯◯ VERY LOW [d,l,m]
Antioxidants and Stroke mortality	8 per 1,000	**7 per 1,000** (6 to 10)	**RR 0.99** (0.75 to 1.32)	63516 (6 RCTs)	⊕⊕⊕◯ MODERATE [d,n]
Antioxidants and Total Cancer	78 per 1,000	**80 per 1,000** (76 to 84)	**RR 1.02** (0.97 to 1.08)	55527 (8 RCTs)	⊕⊕◯◯ LOW [d,o,p]
Antioxidants and Cancer Mortality	19 per 1,000	**17 per 1,000** (14 to 20)	**RR 0.88** (0.74 to 1.04)	29006 (5 RCTs)	⊕⊕⊕◯ MODERATE [d,q]
Antioxidants and all-cause mortality	78 per 1,000	**81 per 1,000** (76 to 85)	**RR 1.04** (0.98 to 1.10)	118206 (27 RCTs)	⊕⊕⊕◯ MODERATE [r]

CI, conficence interval; CVD, cardiovascular disease; CHD, coronary heart disease; GRADE, Grading of Recommendations Assessment Development and Evaluation; MI, Myocardial infaction; RR, risk ratio.

Explanations

a. Serious risk of bias for antioxidant supplementation and Total CHD risk as both allocation concealment and incomplete outcome data was either high or unclear in >70% of studies.

b. Serious indirectness for antioxidants supplementation and total CHD risk as the study population were mostly European (>95%) and all but one of the studies were conducted in specific populations: previous CHD (HPS Group, 2002); coronary stenosis (Waters et al., 2002); smokers (Tornwall et al., 2004 and Mooney et al., 2005; and in those undergoing angioplasty (Tardif et al., 1997).

c. Serious imprecision for antioxidant supplementation and total CHD risk as the 95% CI (RR, 0.95-1.07) overlaps with the minimally important difference for clinical harm (RR>1.05).

d. Publication bias was not assessed since there were <10 studies.

e. Serious risk of bias for antioxidant supplementation and MI risk as both allocation concealment and incomplete outcome data was either high or unclear in 70% and 60% of studies respectively.

f. Serious imprecision for antioxidant supplementation and MI risk as the 95% CI (RR, 0.90-1.07) includes both clinically important benefit (RR<0.95) and harm (RR>1.05).

g. Serious imprecision for antioxidant supplementation and stroke risk as the 95% CI (RR, 0.91-1.09) includes both clinically important benefit (RR<0.95) and harm (RR>1.05).

h. Serious imprecision for antioxidant supplementation and CVD mortality risk as the 95% CI (RR, 0.87-1.11) include both clinically important benefit (RR<0.95) and harm (RR>1.05).

i. Serious risk of bias for antioxidant supplementation and CHD mortality risk as incomplete outcome data was either high or unclear in >65% of studies.

j. Serious indirectness for antioxidants supplementation and CHD mortality risk as the study population were mostly European (>98%) and all of the studies were conducted in specific populations: previous CHD (HPS Group, 2002); smokers (Tornwall et al., 2004 and Mooney et al., 2005; in those undergoing angioplasty (Tardif et al., 1997) and in an older population with cataracts (Chylack et al., 2002).

k. Serious imprecision for antioxidant supplementation and CHD mortality risk as the 95% CI (RR, 0.95-1.15) overlaps with the minimally important difference for clinical harm (RR>1.05).

l. Serious indirectness for antioxidant supplementation and MI mortality risk, as the included studies were conducted in specific populations: smokers (Mooney et al., 2005), peripheral artery disease (CLIPS group 2007) and in an older population with cataracts (Chylack et al., 2002).

m. Very serious imprecision for antioxidant supplementation and MI mortality risk as the 95% CI (RR, 0.39-5.93) include both clinically important benefit (RR<0.95) and harm (RR>1.05).

n. Serious imprecision for antioxidant supplementation and stroke mortality risk as the 95% CI (RR, 0.75-1.32) include both clinically important benefit (RR<0.95) and harm (RR>1.05).

o. Serious indirectness for antioxidant supplementation and total cancer risk as three studies accounting for more than 70% of the population were conducted in males only.

p. Serious imprecision for antioxidant supplementation and total cancer risk as the 95% CI (RR, 0.97-1.08) overlaps with the minimally important difference for clinical harm (RR>1.05).

q. Serious imprecision for antioxidant supplementation and cancer mortality risk as the 95% CI (RR, 0.74-1.04) overlaps with the minimally important difference for clinical benefit (RR<0.95).

r. Serious imprecision for antioxidant supplementation and all-cause mortality risk as the 95% CI (RR, 0.98-1.10) overlaps with the minimally important difference for clinical harm (RR>1.05).

Supplementary Table 5. GRADE assessment for selenium and CVD, cancer, cancer mortality, and all-cause mortality.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with Selenium			
Selenium and total CVD	118 per 1,000	**121 per 1,000** (114 to 128)	**RR 1.02** (0.96 to 1.08)	36978 (4 RCTs)	⨁⨁◯◯ LOW [a,b,c]
Selenium and total CHD	90 per 1,000	**71 per 1,000** (22 to 240)	**RR 0.79** (0.24 to 2.66)	1445 (3 RCTs)	⨁◯◯◯ VERY LOW [c,d,e]
Selenium and MI	68 per 1,000	**50 per 1,000** (16 to 157)	**RR 0.74** (0.24 to 2.31)	1445 (3 RCTs)	⨁◯◯◯ VERY LOW [c,f,g]
Selenium and Stroke	11 per 1,000	**11 per 1,000** (9 to 14)	**RR 1.06** (0.87 to 1.29)	36897 (3 RCTs)	⨁⨁◯◯ LOW [c,h,i]
Selenium and CVD mortality	16 per 1,000	**16 per 1,000** (13 to 20)	**RR 1.00** (0.81 to 1.22)	37469 (5 RCTs)	⨁⨁◯◯ LOW [c,j,k]
Selenium and CHD mortality	18 per 1,000	**10 per 1,000** (0 to 248)	**RR 0.54** (0.02 to 13.71)	441 (2 RCTs)	⨁◯◯◯ VERY LOW [c,l,m]
Selenium and MI mortality	17 per 1,000	**14 per 1,000** (3 to 57)	**RR 0.85** (0.21 to 3.43)	1445 (3 RCTs)	⨁◯◯◯ VERY LOW [c,n,o]
Selenium and Stroke mortality	1 per 1,000	**1 per 1,000** (1 to 2)	**RR 1.24** (0.65 to 2.34)	35533 (1 RCT)	⨁⨁◯◯ LOW [c,p,q,r]
Selenium and Total cancer	98 per 1,000	**89 per 1,000** (77 to 105)	**RR 0.91** (0.78 to 1.07)	38044 (5 RCTs)	⨁⨁◯◯ LOW [c,s,t]
Selenium and cancer mortality	16 per 1,000	**14 per 1,000** (9 to 22)	**RR 0.87** (0.56 to 1.37)	37336 (3 RCTs)	⨁◯◯◯ VERY LOW [c,u,v,w]
Selenium and all-cause mortality	43 per 1,000	**43 per 1,000** (39 to 47)	**RR 0.99** (0.90 to 1.08)	42938 (12 RCTs)	⨁⨁◯◯ LOW [x,y]

CI, conficence interval; CVD, cardiovascular disease; CHD, coronary heart disease; GRADE, Grading of Recommendations Assessment Development and Evaluation; MI, Myocardial infaction; RR, risk ratio.

Explanations

a. Serious indirectness for selenium supplementation and total CVD risk as >98% of the population were men.

b. Serious imprecision for selenium supplementation and total CVD risk as the 95% CI (RR, 0.96-1.08) overlaps with the minimally important difference for clinical harm (RR>1.05).

c. Publication bias was not assessed since there were <10 studies.

d. Serious indirectness for selenium supplementation and total CHD risk as all of the studies were conducted in specific populations: previous MI (Korpela et al., 1989); esophageal squamous dysplasia (Limburg et al., 2005) and previous skin cancer (Stranges et al., 2006).

e. Very serious imprecision for selenium supplementation and total CHD risk as the 95% CI (RR, 0.24-2.66) includes both clinically important benefit (RR<0.95) and harm (RR>1.05).

f. Serious indirectness for selenium supplementation and MI risk as all of the studies were conducted in specific populations: previous MI (Korpela et al., 1989); esophageal squamous dysplasia (Limburg et al., 2005) and previous skin cancer (Stranges et al., 2006).

g. Very serious imprecision for selenium supplementation and MI risk as the 95% CI (RR, 0.24-2.31) includes both clinically important benefit (RR<0.95) and harm (RR>1.05).

h. Serious indirectness for selenium supplementation and stroke risk as >98% of the population were men.

i. Serious imprecision for selenium supplementation and stroke risk as the 95% CI (RR, 0.87-1.29) includes both clinically important benefit (RR<0.95) and harm (RR>1.05).

j. Serious indirectness for selenium supplementation and CVD mortality risk as >95% of the population were men.

k. Serious imprecision for selenium supplementation and CVD mortality risk as the 95% CI (RR, 0.81-1.22) includes both clinically important benefit (RR<0.95) and harm (RR>1.05).

l. Serious indirectness for selenium supplementation and CHD mortality risk as both studies were conducted in specific populations: previous MI (Korpela et al., 1989) and esophageal squamous dysplasia (Limburg et al., 2005).

m. Very serious imprecision for selenium supplementation and CHD mortality risk as the 95% CI (RR, 0.02-13.71) includes both clinically important benefit (RR<0.95) and harm (RR>1.05).

n. Serious indirectness for selenium supplementation and MI mortality risk as all of the studies were conducted in specific populations: previous MI (Korpela et al., 1989); esophageal squamous dysplasia (Limburg et al., 2005) and previous skin cancer (Stranges et al., 2006).

o. Very serious imprecision for selenium supplementation and MI mortality risk as the 95% CI (RR, 0.21-3.43) includes both clinically important benefit (RR<0.95) and harm (RR>1.05).

p. Unable to assess inconsistency as only one study was included.

q. Serious indirectness for selenium supplementation and stroke mortality risk as the sole study included was conducted in men only.

r. Serious imprecision for selenium supplementation and stroke mortality risk as the 95% CI (RR, 0.65-2.34) includes both clinically important benefit (RR<0.95) and harm (RR>1.05).

s. Serious indirectness for selenium supplementation and total cancer risk as >98% of the population were men.

t. Serious imprecision for selenium supplementation and total cancer risk as the 95% CI (RR, 0.78-1.07) includes both clinically important benefit (RR<0.95) and harm (RR>1.05).

u. Serious inconsistency for selenium supplementation and cancer mortality risk, as I^2 = 71% and P=0.03.

v. Serious indirectness for selenium supplementation and cancer mortality risk as >98% of the population were men.

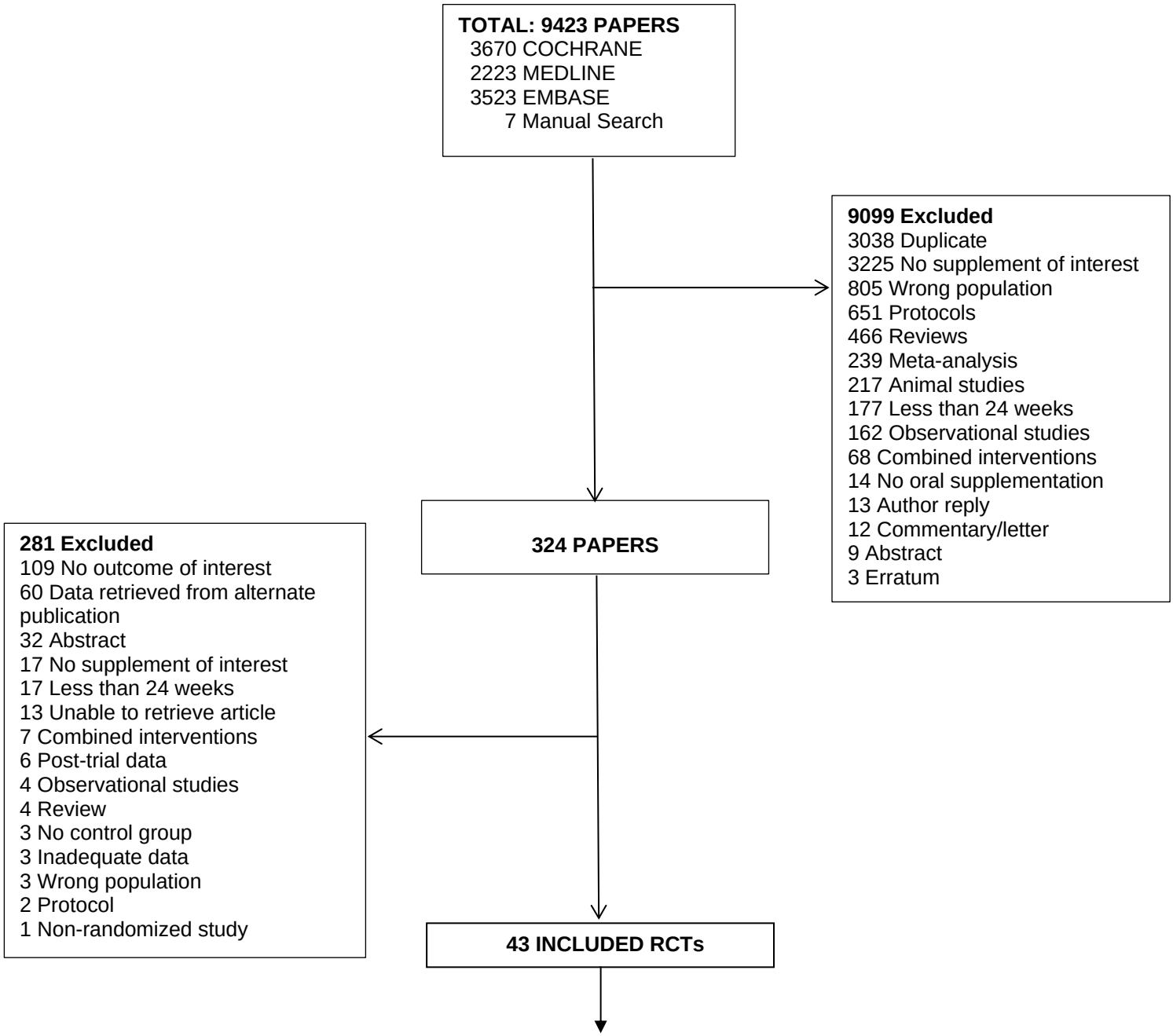
w. Serious imprecision for selenium supplementation and cancer mortality risk as the 95% CI (RR, 0.56-1.37) includes both clinically important benefit (RR<0.95) and harm (RR>1.05).

x. Serious indirectness for selenium supplementation and total cancer risk as >90% of the population were men.

y. Serious imprecision for selenium supplementation and all-cause mortality risk as the 95% CI (RR, 0.90-1.08) includes both clinically important benefit (RR<0.95) and harm (RR>1.05).

ONLINE SUPPORTING MATERIAL

Antioxidant supplements and risk of CVD, cancer & all-cause mortality

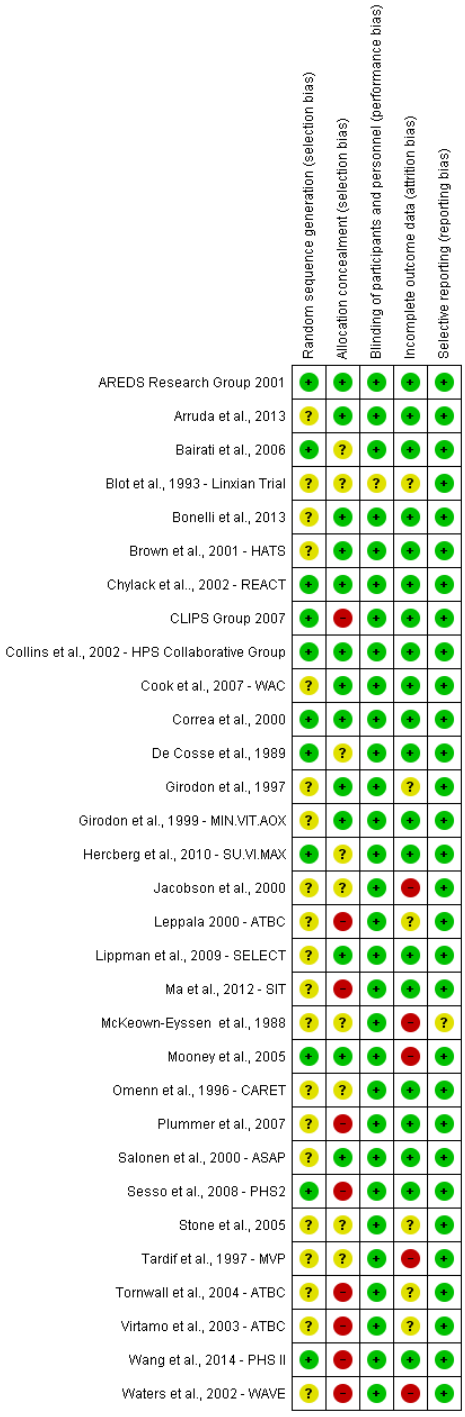


Number of RCTs for each outcome

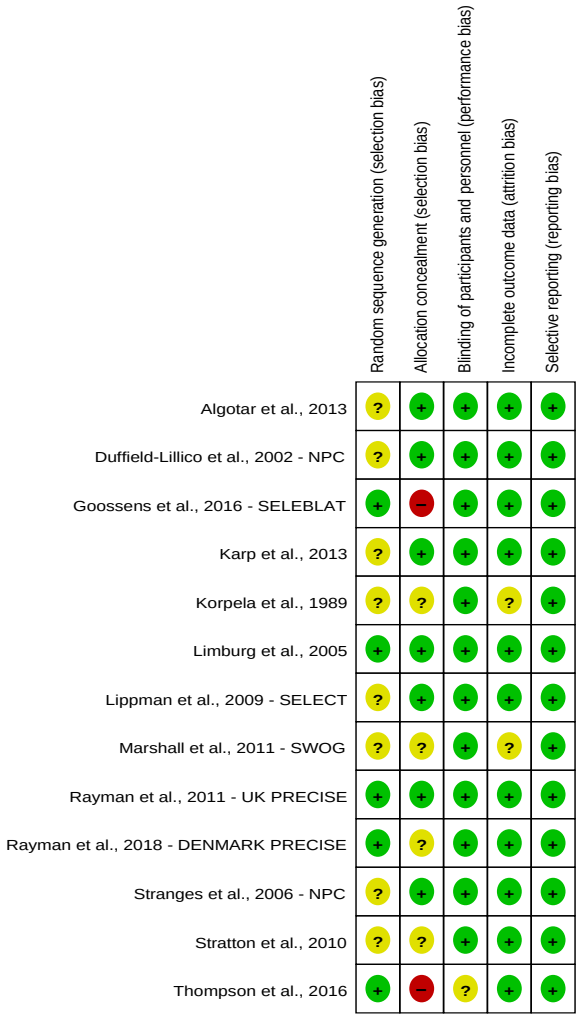
	Antioxidants	Selenium
Total CVD	13	4
Total CHD	7	3
MI	10	3
Stroke	10	3
CVD mortality	12	5
CHD mortality	6	2
MI mortality	3	3
Stroke mortality	6	1
Cancer	8	5
Cancer mortality	5	3
All-cause mortality	27	12

ONLINE SUPPORTING MATERIAL

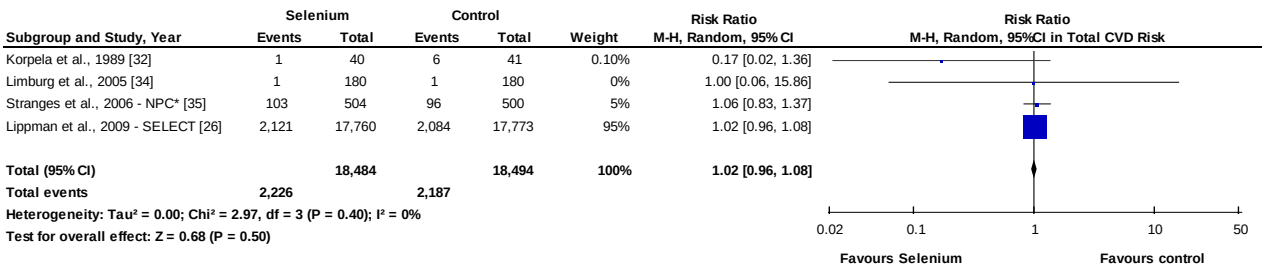
Supplementary Figure 1. Search Summary. Flow diagram outlining the search strategy used to identify publications that report RCT data on antioxidant supplementation and risk of CVD, CVD outcomes, cancer and all-cause mortality. The publications are from database inceptions to June 5, 2020 of single RCTs identified by searching Cochrane, Medline, Embase and by manual searches. Titles and abstracts were reviewed in the first stage of screening while full manuscript review was done in the second stage. RCT, randomized controlled trial; CVD, cardiovascular disease; CHD, coronary heart disease; MI, myocardial infarction.



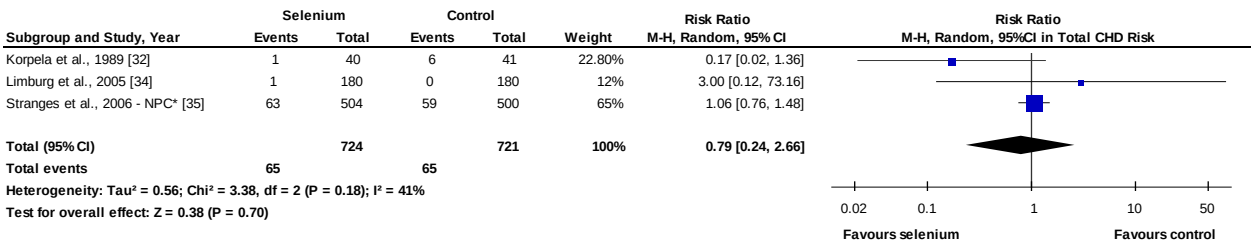
Supplementary Figure 2. Risk of bias summary for antioxidant supplementation and CVD, CVD outcomes, cancer, cancer mortality, and all-cause mortality. Review authors' judgments about each risk of bias item for each included study.



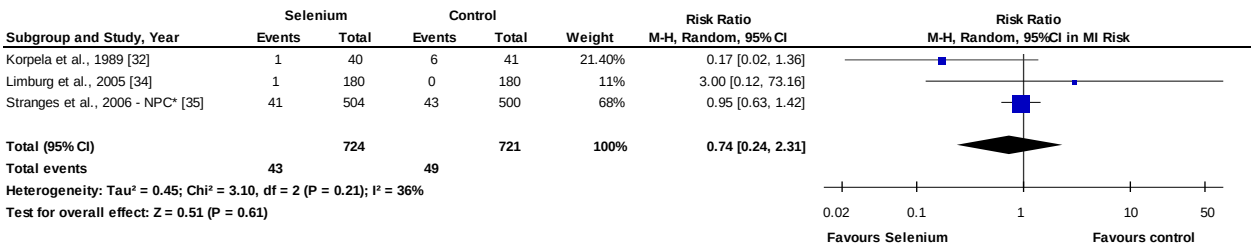
Supplementary Figure 3. Risk of bias summary for selenium supplementation and CVD, CVD outcomes, cancer, cancer mortality, and all-cause mortality. Review authors' judgments about each risk of bias item for each included study.



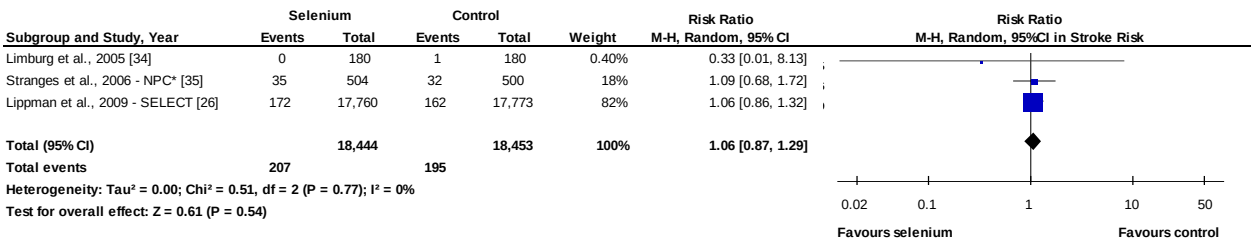
Supplementary Figure 4. Forest plot of selenium supplementation only and total CVD risk. M-H, Manthel-Haenszel, CVD, cardiovascular disease. ***Stranges et al., 2006 was used as it contained data up until the end of treatment but only in those free of CVD at baseline (35).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



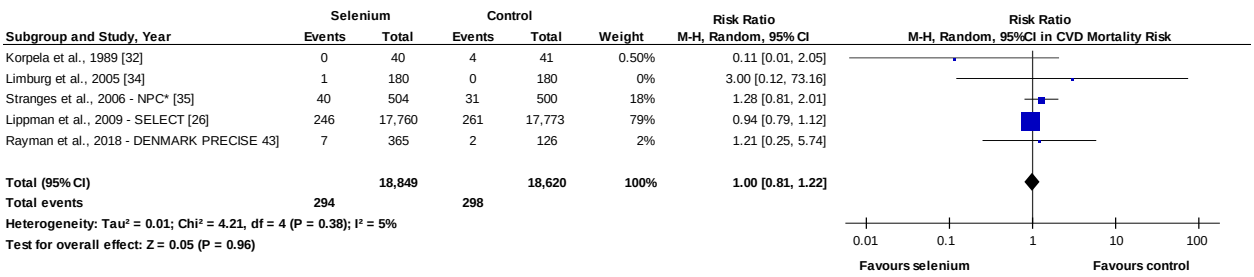
Supplementary Figure 5. Forest plot of selenium supplementation only and total CHD risk. M-H, Manthel-Haenszel, CHD, coronary heart disease. ***Stranges et al., 2006 was used as it contained data up until the end of treatment but only in those free of CVD at baseline (35).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



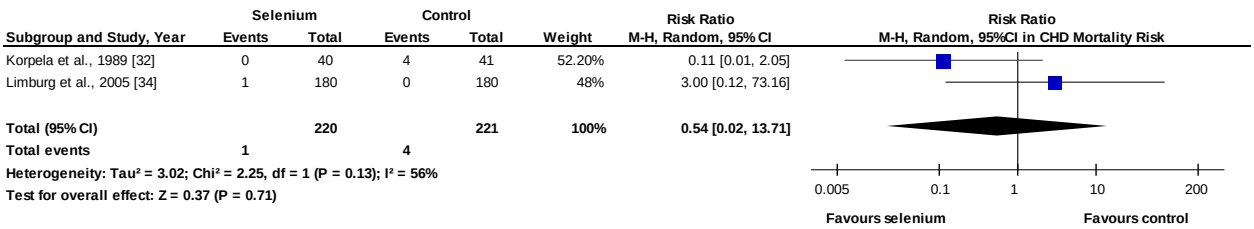
Supplementary Figure 6. Forest plot of selenium supplementation only and MI risk. M-H, Manthel-Haenszel, MI, myocardial infarction. ***Stranges et al., 2006 was used as it contained data up until the end of treatment but only in those free of CVD at baseline (35).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



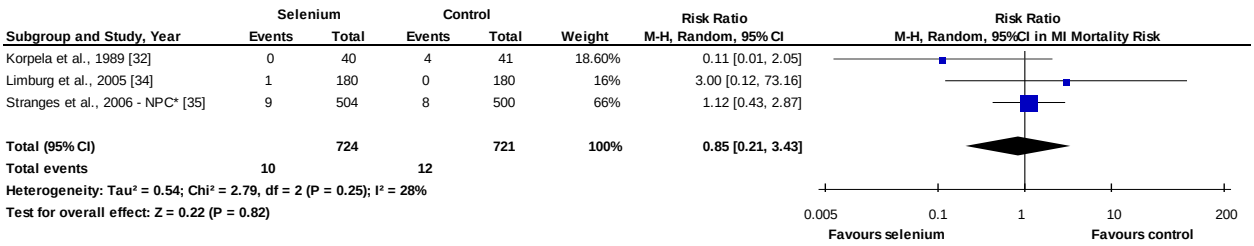
Supplementary Figure 7. Forest plot of selenium supplementation only and stroke risk. M-H, Manthel-Haenszel. ***Stranges et al., 2006 was used as it contained data up until the end of treatment but only in those free of CVD at baseline (35).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



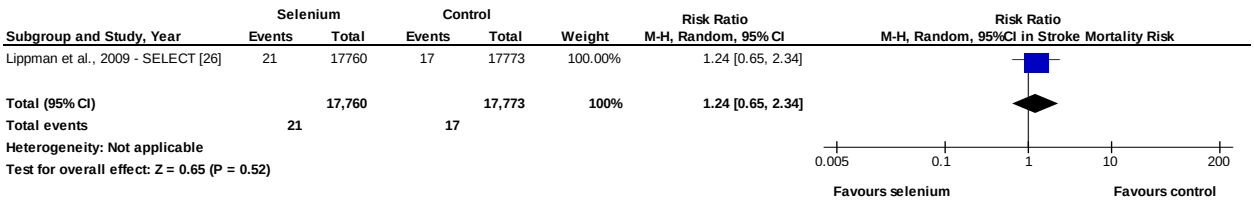
Supplementary Figure 8. Forest plot of selenium supplementation only and CVD mortality risk. M-H, Manthel-Haenszel, CVD, cardiovascular disease. ***Stranges et al., 2006 was used as it contained data up until the end of treatment but only in those free of CVD at baseline (35).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



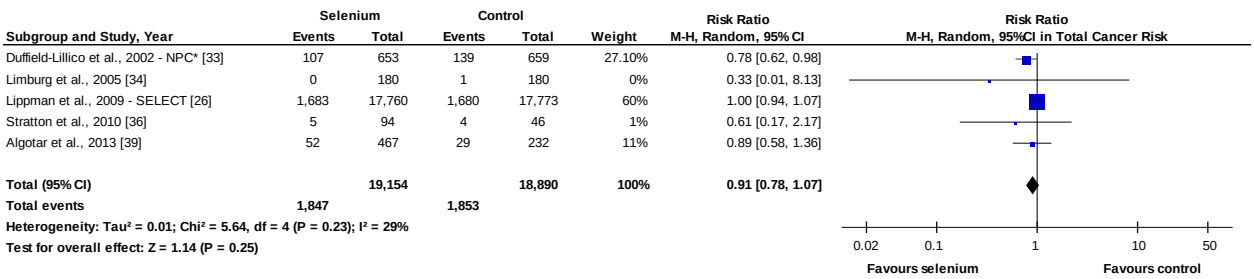
Supplementary Figure 9. Forest plot of selenium supplementation only and CHD mortality risk. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



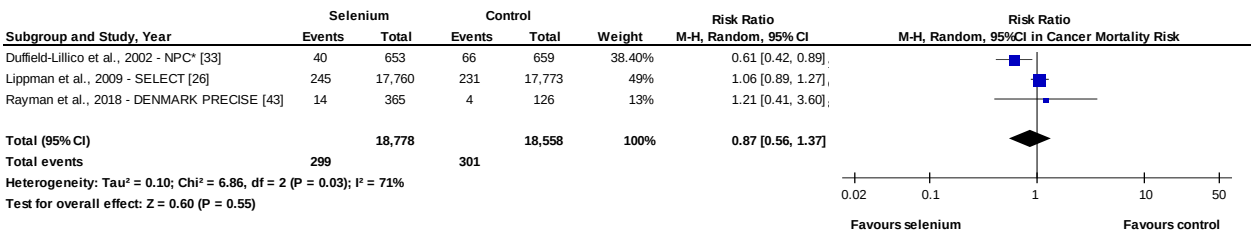
Supplementary Figure 10. Forest plot of selenium supplementation only and MI mortality risk. M-H, Manthel-Haenszel, MI, myocardial infarction. ***Stranges et al., 2006 was used as it contained data up until the end of treatment but only in those free of CVD at baseline (35).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



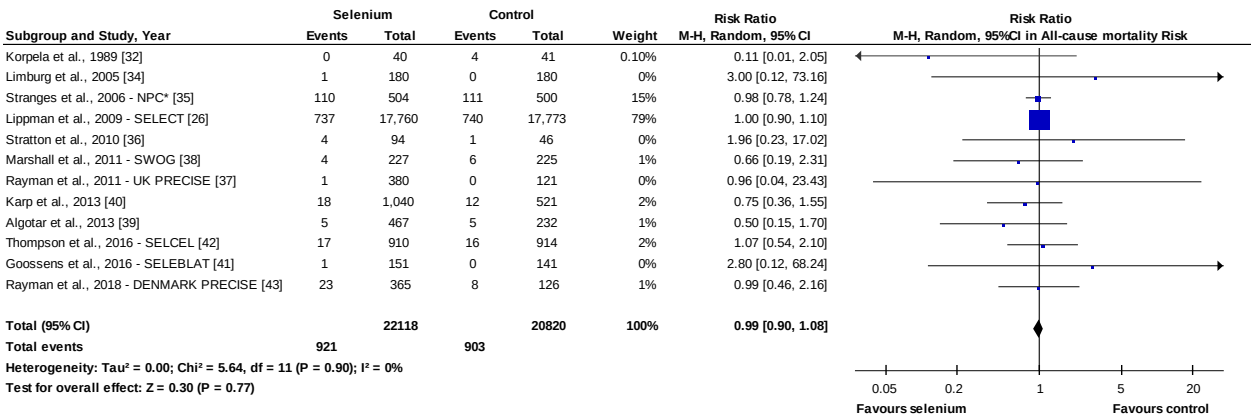
Supplementary Figure 11. Forest plot of selenium supplementation only and stroke mortality risk. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



Supplementary Figure 12. Forest plot of selenium supplementation only and total cancer risk. M-H, Manthel-Haenszel. ***Duffield-Lillico et al., 2002 excluded 62 participants from their analysis, including 4 cancer cases; these were re-added to the events and totals(33).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



Supplementary Figure 13. Forest plot of selenium supplementation only and cancer mortality risk. M-H, Manthel-Haenszel. *** Duffield-Lillico et al., 2002 excluded 62 participants from their analysis; these were re-added to the totals(33).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



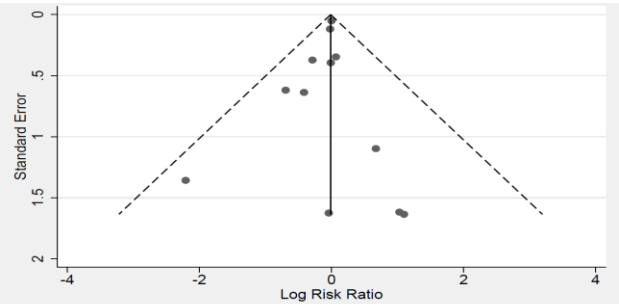
Subgroup and Study, Year	Selenium Events	Selenium Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Korpela et al., 1989 [32]	0	40	4	41	0.10%	0.11 [0.01, 2.05]
Limburg et al., 2005 [34]	1	180	0	180	0%	3.00 [0.12, 73.16]
Stranges et al., 2006 - NPC* [35]	110	504	111	500	15%	0.98 [0.78, 1.24]
Lippman et al., 2009 - SELECT [26]	737	17,760	740	17,773	79%	1.00 [0.90, 1.10]
Stratton et al., 2010 [36]	4	94	1	46	0%	1.96 [0.23, 17.02]
Marshall et al., 2011 - SWOG [38]	4	227	6	225	1%	0.66 [0.19, 2.31]
Rayman et al., 2011 - UK PRECISE [37]	1	380	0	121	0%	0.96 [0.04, 23.43]
Karp et al., 2013 [40]	18	1,040	12	521	2%	0.75 [0.36, 1.55]
Algotar et al., 2013 [39]	5	467	5	232	1%	0.50 [0.15, 1.70]
Thompson et al., 2016 - SELCEL [42]	17	910	16	914	2%	1.07 [0.54, 2.10]
Goossens et al., 2016 - SELEBLAT [41]	1	151	0	141	0%	2.80 [0.12, 68.24]
Rayman et al., 2018 - DENMARK PRECISE [43]	23	365	8	126	1%	0.99 [0.46, 2.16]
Total (95% CI)		**22118**		**20820**	**100%**	**0.99 [0.90, 1.08]**
Total events	**921**		**903**			

Heterogeneity: Tau² = 0.00; Chi² = 5.64, df = 11 (P = 0.90); I² = 0%

Test for overall effect: Z = 0.30 (P = 0.77)

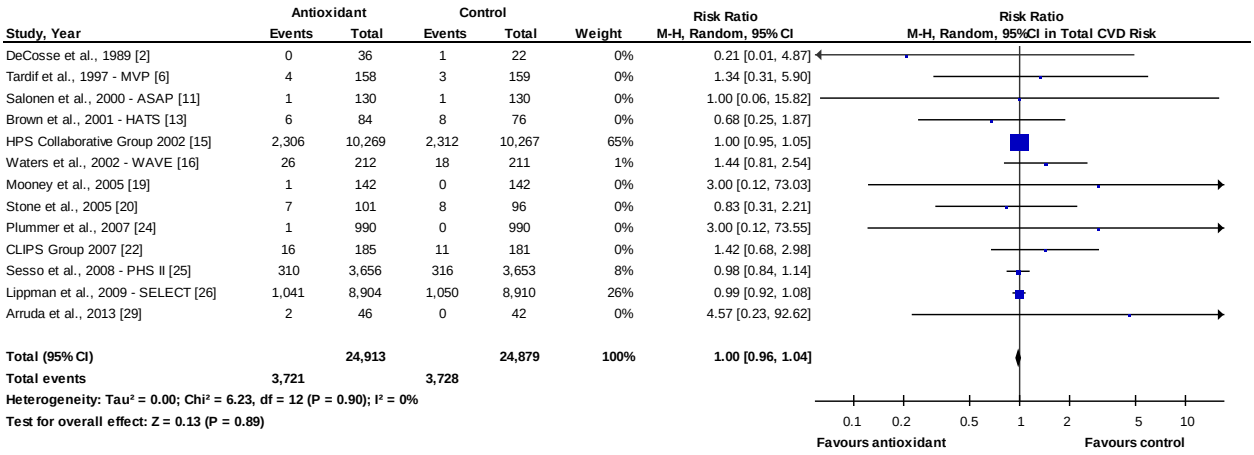
Supplementary Figure 14. Forest plot of selenium supplementation only and all-cause mortality risk. M-H, Manthel-Haenszel. ***Stranges et al., 2006 was used as it contained data up until the end of treatment but only in those free of CVD at baseline (35).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

A. Selenium supplementation and all-cause mortality risk

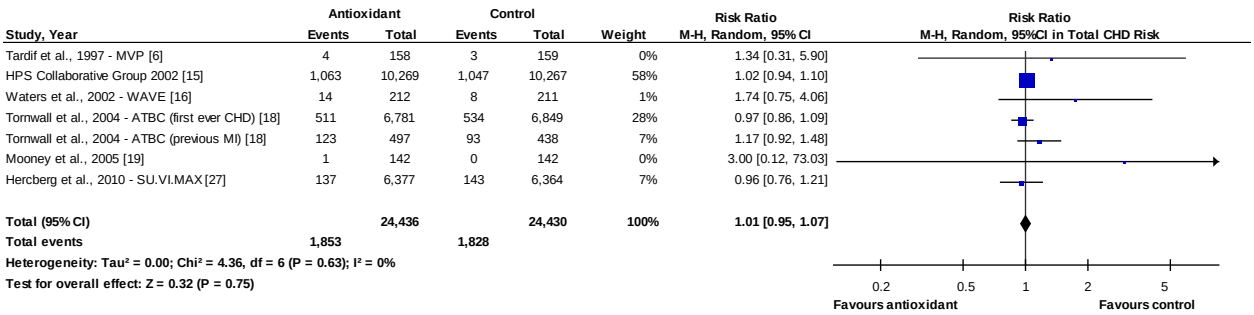


Begg's test = 0.63 **Egger's test = 0.44**

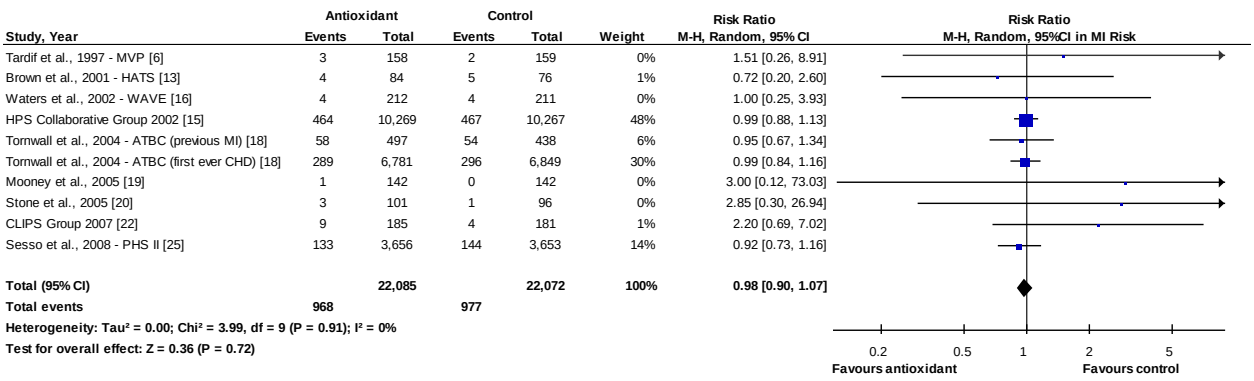
Supplementary Figure 15. Funnel plot of selenium supplementation and all-cause mortality risk. Dashed lines represent pseudo – 95% confidence intervals (CI). The circles represent risk estimates for each study, and the horizontal lines represent standard errors of the RR. We were unable to test for funnel plot asymmetry for other CVD and cancer outcomes (<10 RCTs).



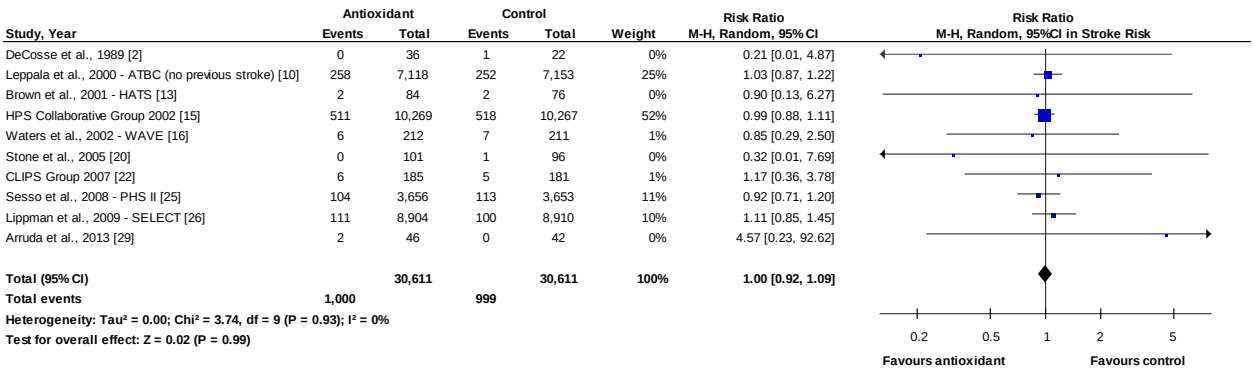
Supplementary Figure 16. Forest plot of antioxidant supplementation and total CVD risk. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



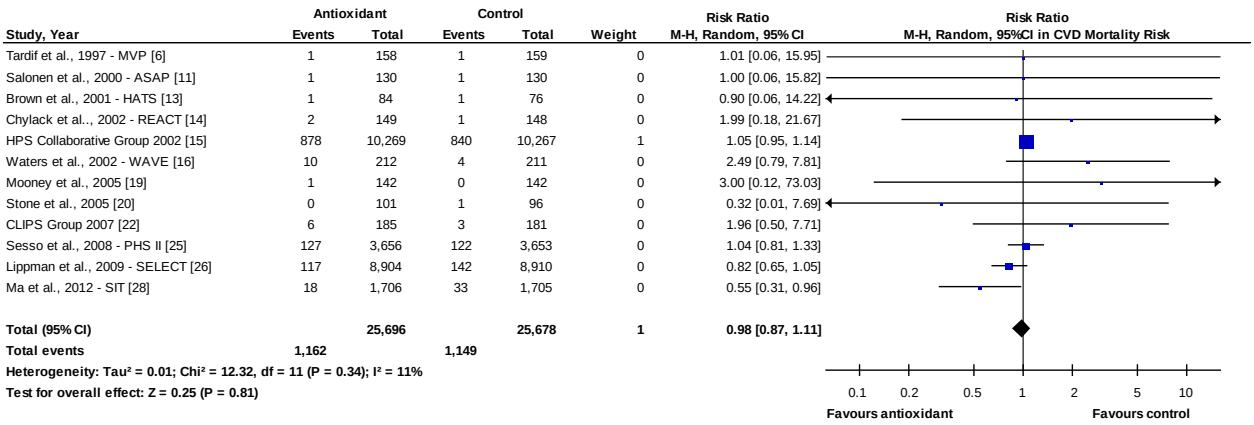
Supplementary Figure 17. Forest plot of antioxidant supplementation and total CHD risk. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



Supplementary Figure 18. Forest plot of antioxidant supplementation and MI risk. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



Supplementary Figure 19. Forest plot of antioxidant supplementation and stroke risk. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

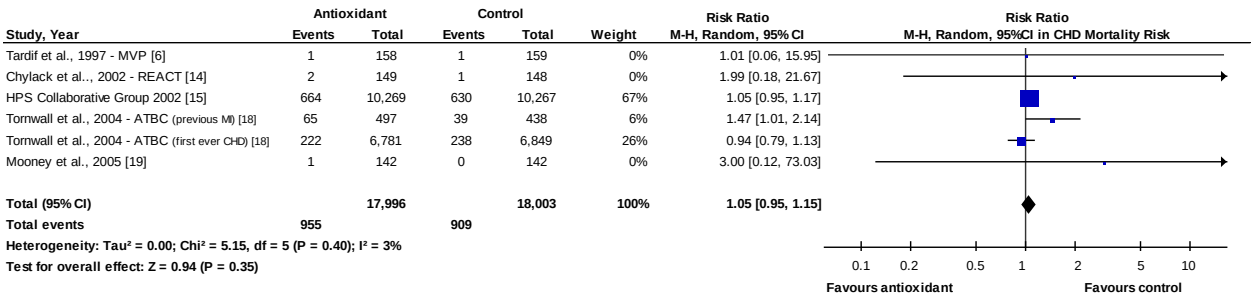


Study, Year	Antioxidant Events	Antioxidant Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Tardif et al., 1997 - MVP [6]	1	158	1	159	0	1.01 [0.06, 15.95]
Salonen et al., 2000 - ASAP [11]	1	130	1	130	0	1.00 [0.06, 15.82]
Brown et al., 2001 - HATS [13]	1	84	1	76	0	0.90 [0.06, 14.22]
Chylack et al.., 2002 - REACT [14]	2	149	1	148	0	1.99 [0.18, 21.67]
HPS Collaborative Group 2002 [15]	878	10,269	840	10,267	1	1.05 [0.95, 1.14]
Waters et al., 2002 - WAVE [16]	10	212	4	211	0	2.49 [0.79, 7.81]
Mooney et al., 2005 [19]	1	142	0	142	0	3.00 [0.12, 73.03]
Stone et al., 2005 [20]	0	101	1	96	0	0.32 [0.01, 7.69]
CLIPS Group 2007 [22]	6	185	3	181	0	1.96 [0.50, 7.71]
Sesso et al., 2008 - PHS II [25]	127	3,656	122	3,653	0	1.04 [0.81, 1.33]
Lippman et al., 2009 - SELECT [26]	117	8,904	142	8,910	0	0.82 [0.65, 1.05]
Ma et al., 2012 - SIT [28]	18	1,706	33	1,705	0	0.55 [0.31, 0.96]
Total (95% CI)		**25,696**		**25,678**	**1**	**0.98 [0.87, 1.11]**
Total events	**1,162**		**1,149**			

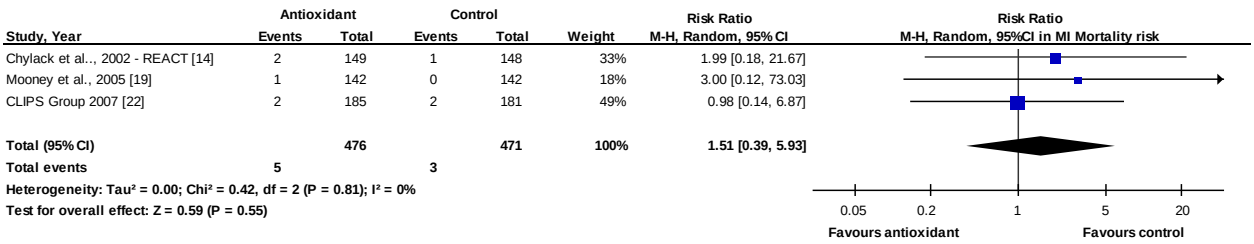
Heterogeneity: Tau² = 0.01; Chi² = 12.32, df = 11 (P = 0.34); I² = 11%

Test for overall effect: Z = 0.25 (P = 0.81)

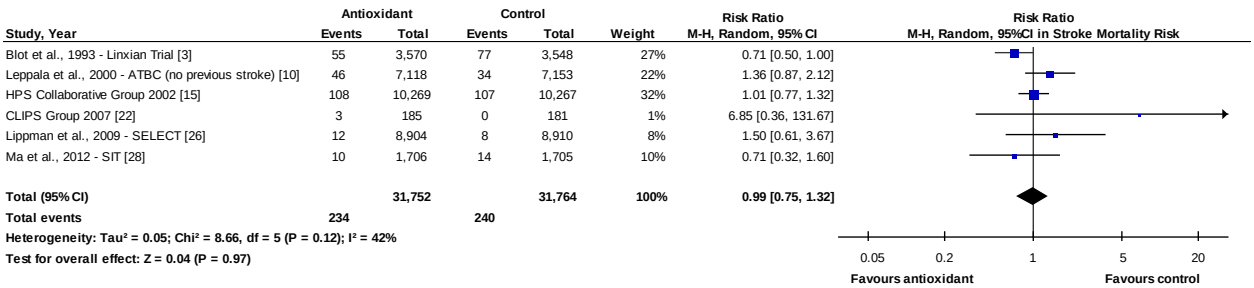
Supplementary Figure 20. Forest plot of antioxidant supplementation and CVD mortality risk. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



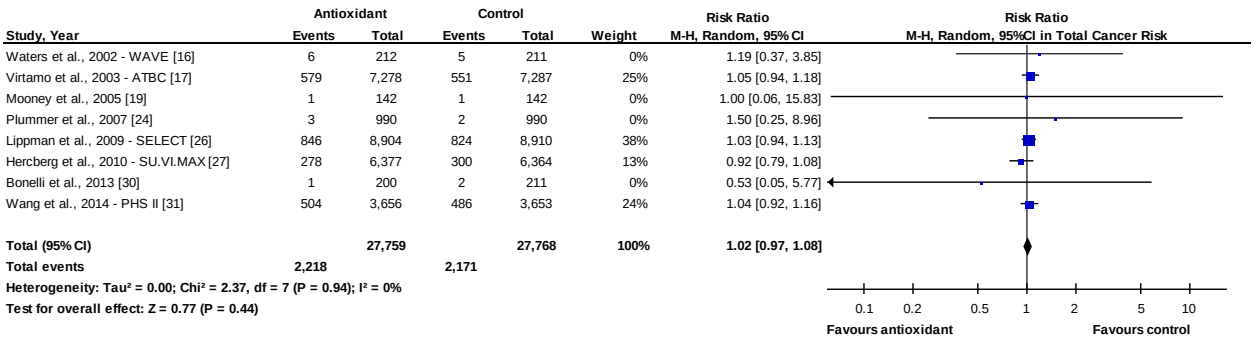
Supplementary Figure 21. Forest plot of antioxidant supplementation and CHD mortality risk. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



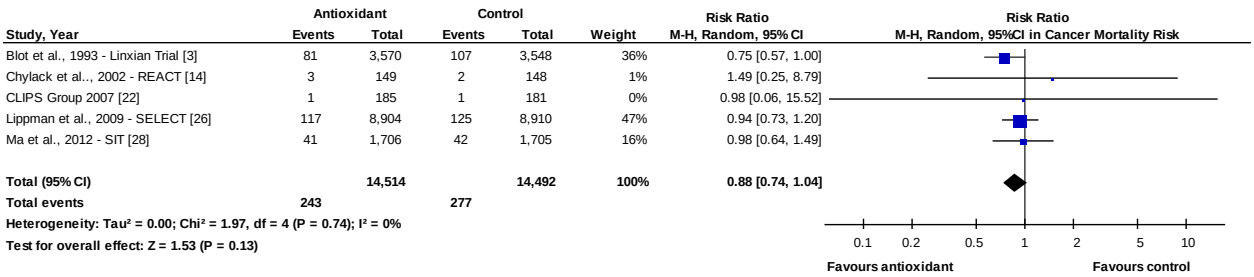
Supplementary Figure 22. Forest plot of antioxidant supplementation and MI mortality risk. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



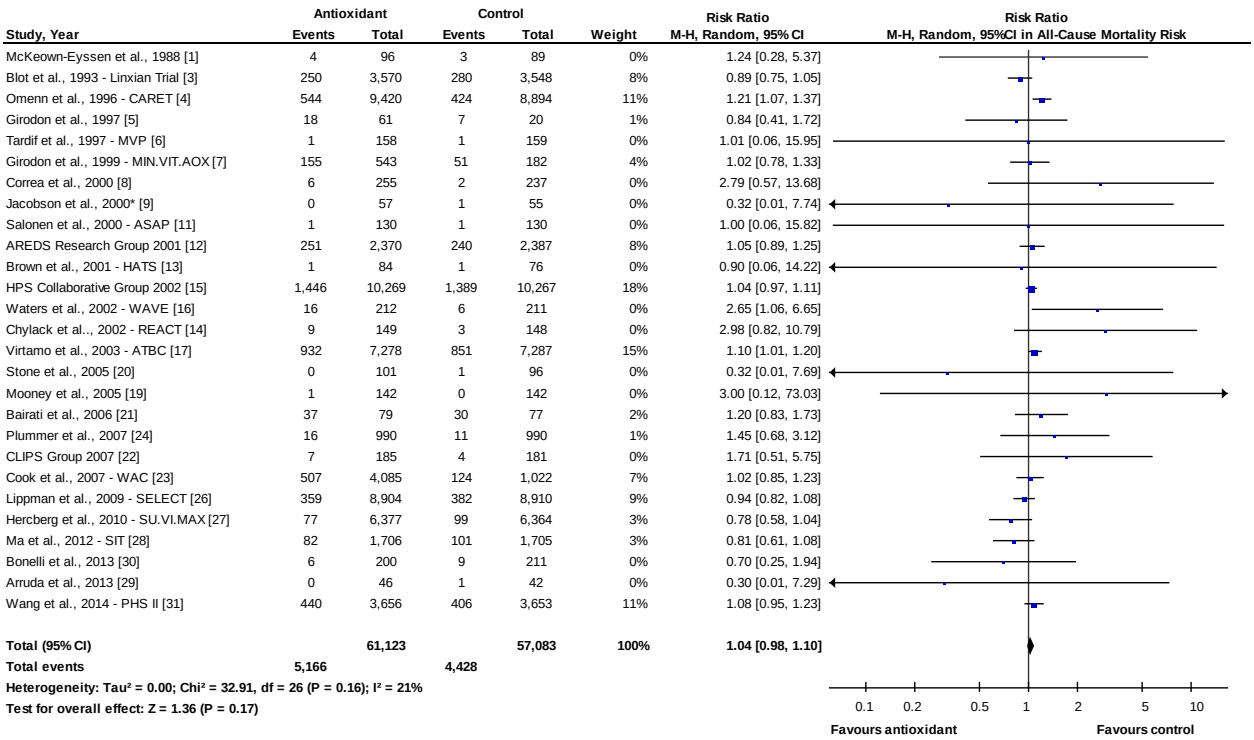
Supplementary Figure 23. Forest plot of antioxidant supplementation and stroke mortality risk. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



Supplementary Figure 24. Forest plot of antioxidant supplementation and total cancer risk. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

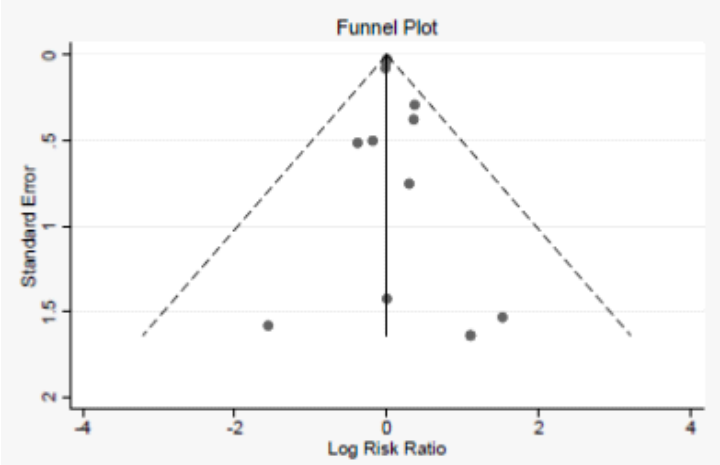


Supplementary Figure 25. Forest plot of antioxidant supplementation and cancer mortality risk. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



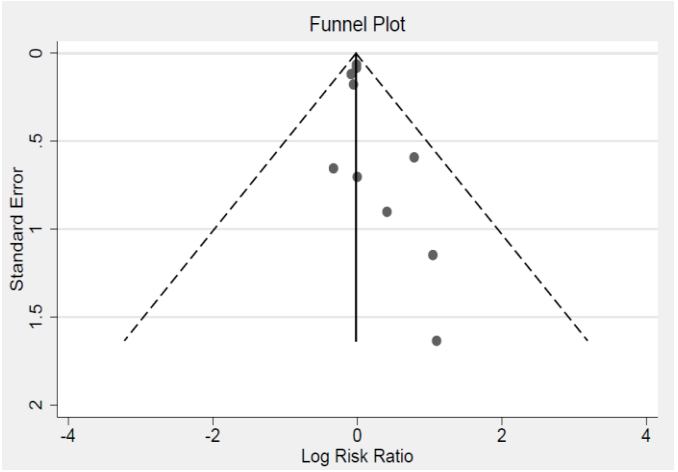
Supplementary Figure 26. Forest plot of antioxidant supplementation and all-cause mortality risk. M-H, Manthel-Haenszel. ***Jacobson et al., 2000 – data retrieved from meta-analysis Bjelakovic 2012 (44).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

A. Antioxidant supplementation and total CVD risk



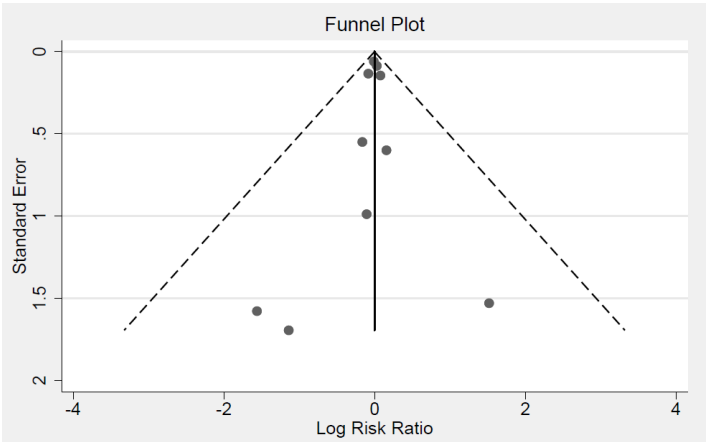
Begg's test = 1.00 **Egger's test = 0.29**

B. Antioxidant supplementation and MI risk



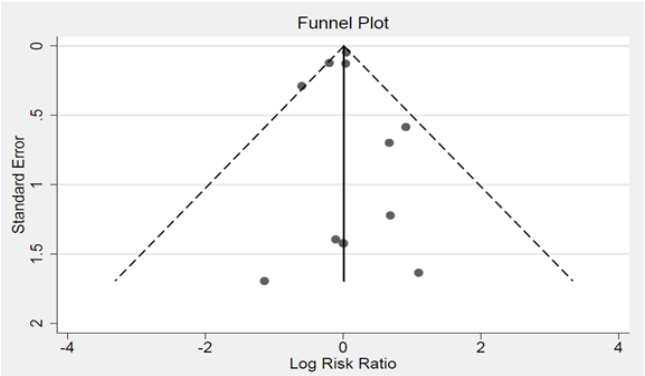
Begg's test = 0.24 **Egger's test = 0.12**

C. Antioxidant supplementation and stroke risk



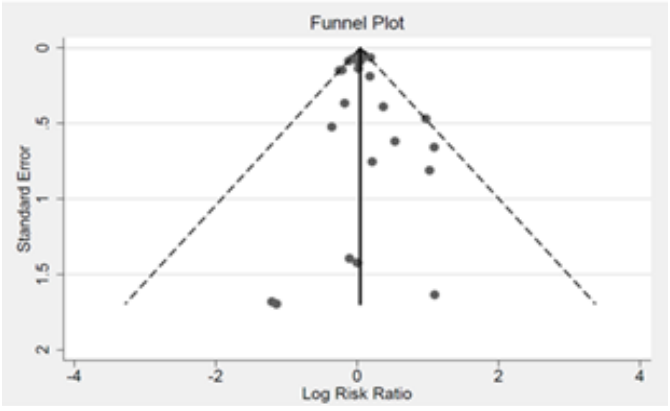
Begg's test = 0.53 **Egger's test = 0.66**

D. Antioxidant supplementation and CVD mortality



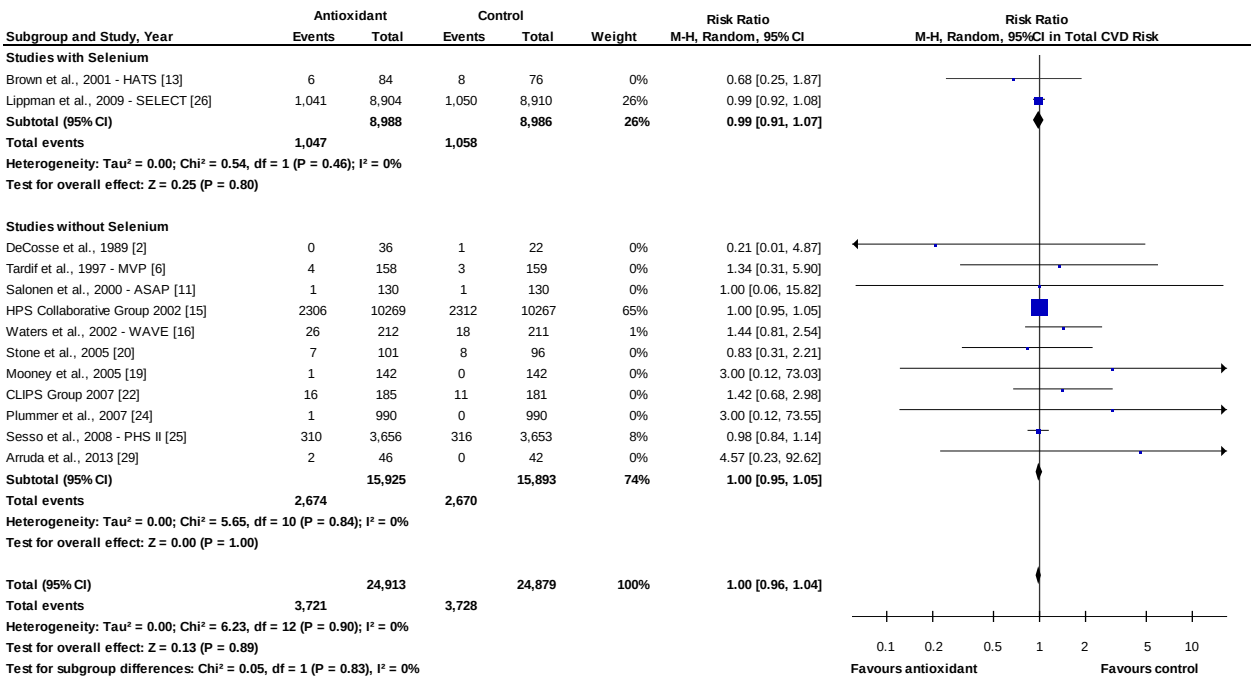
Begg's test = 0.58 **Egger's test = 0.99**

E. Antioxidant supplementation and all-cause mortality

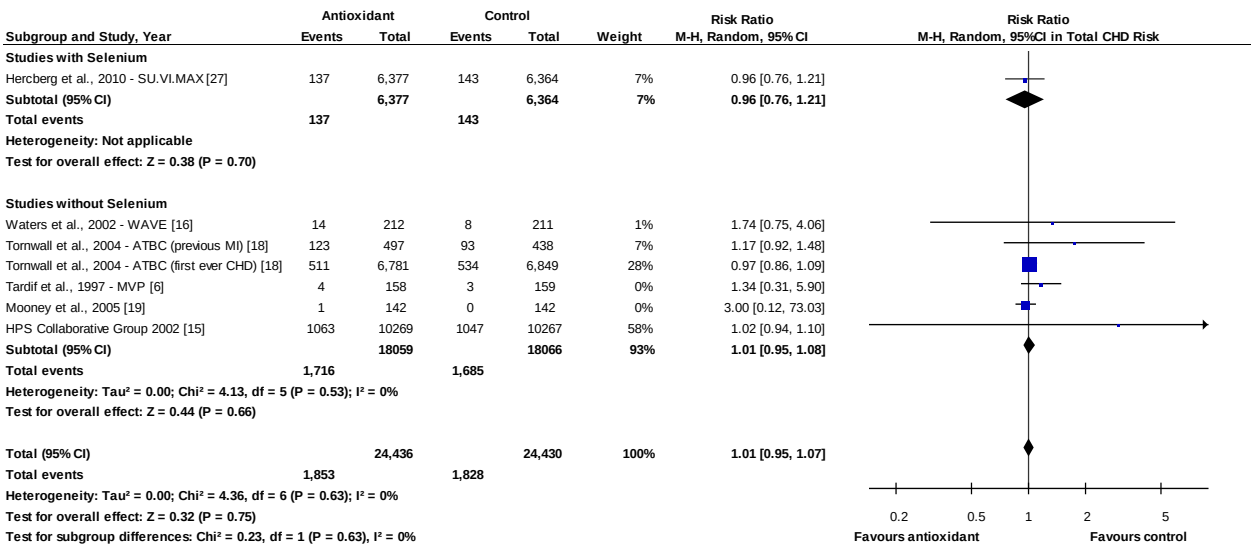


Begg's test = 0.82 **Egger's test = 0.95**

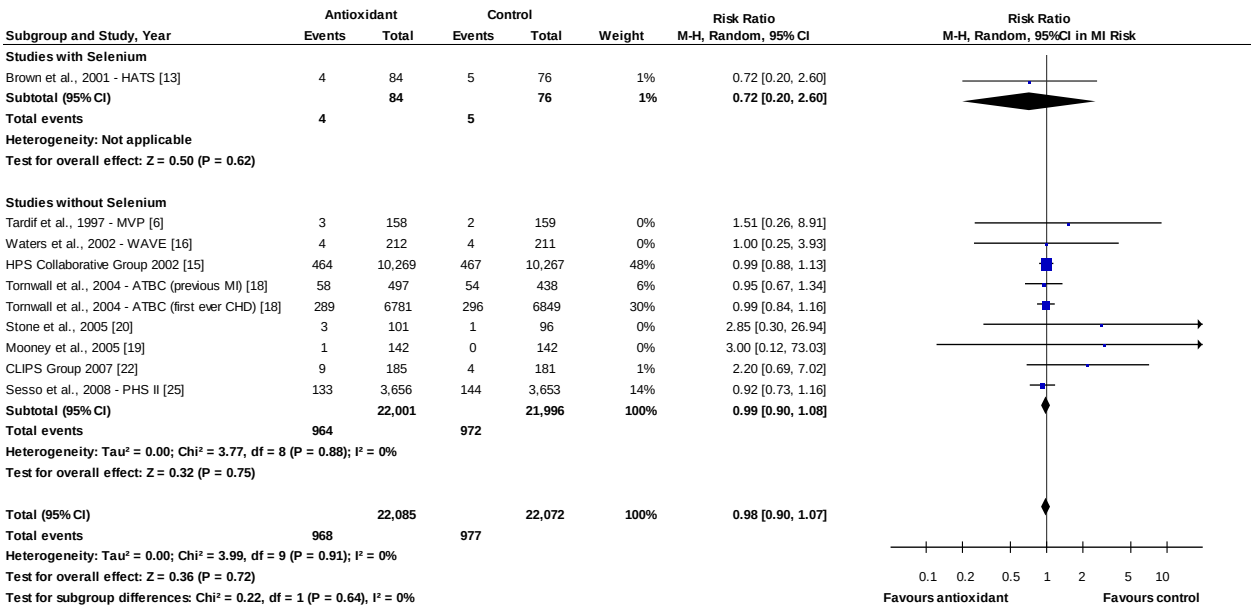
Supplementary Figure 27. Funnel plots of antioxidant supplementation and total CVD, MI, stroke, CVD mortality, and all-cause mortality risk. Dashed lines represent pseudo – 95% confidence intervals (CI). The circles represent risk estimates for each study, and the horizontal lines represent standard errors of the RR. We were unable to test for funnel plot asymmetry for other CVD and cancer outcomes (<10 RCTs).



Supplementary Figure 28. Sensitivity analysis of antioxidant supplementation and total CVD risk for studies with and without selenium. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

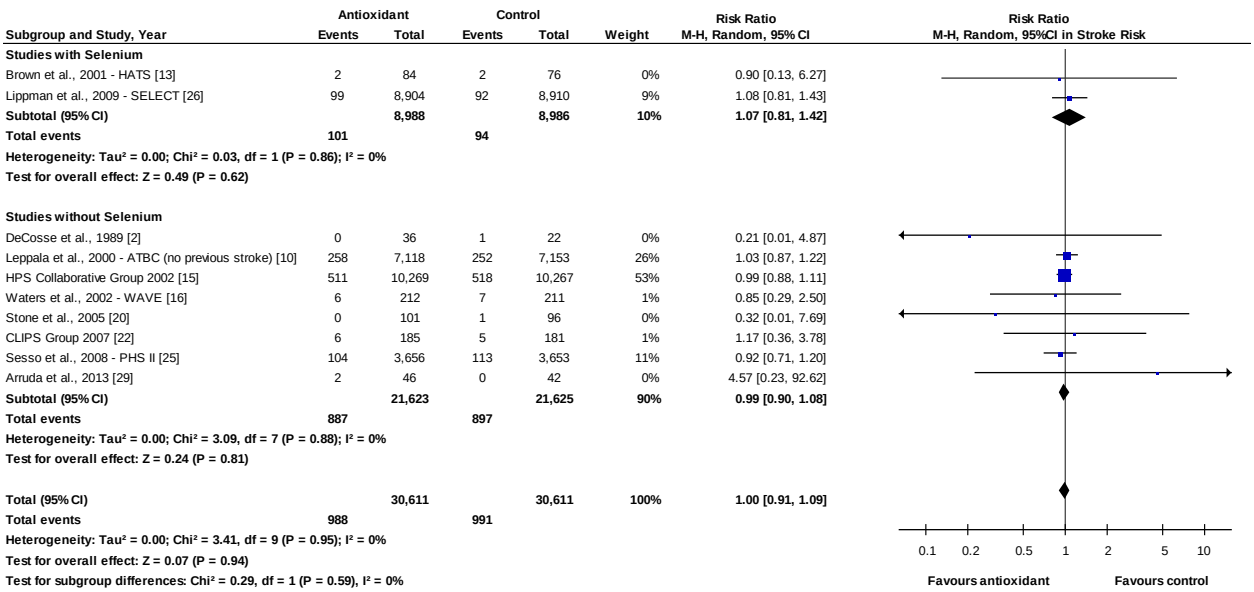


Supplementary Figure 29. Sensitivity analysis of antioxidant supplementation and total CHD risk for studies with and without selenium. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

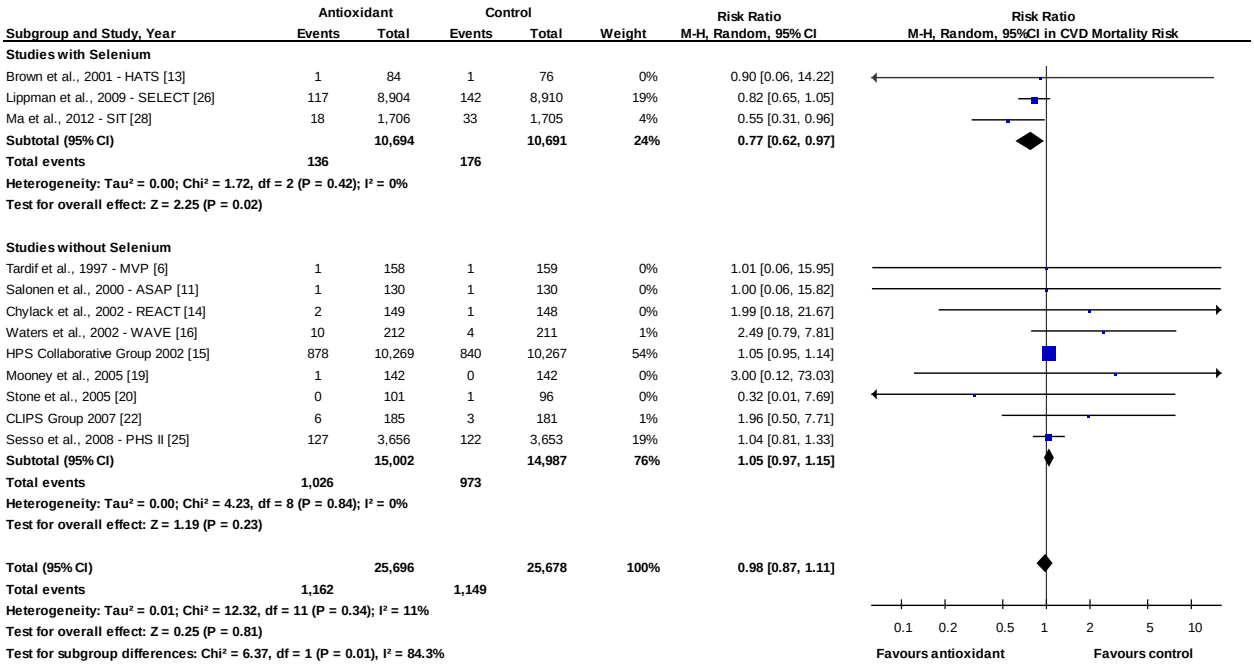


Subgroup and Study, Year	Antioxidant Events	Antioxidant Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Studies with Selenium						
Brown et al., 2001 - HATS [13]	4	84	5	76	1%	0.72 [0.20, 2.60]
Subtotal (95% CI)		**84**		**76**	**1%**	**0.72 [0.20, 2.60]**
Total events	**4**		**5**			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
Studies without Selenium						
Tardif et al., 1997 - MVP [6]	3	158	2	159	0%	1.51 [0.26, 8.91]
Waters et al., 2002 - WAVE [16]	4	212	4	211	0%	1.00 [0.25, 3.93]
HPS Collaborative Group 2002 [15]	464	10,269	467	10,267	48%	0.99 [0.88, 1.13]
Tornwall et al., 2004 - ATBC (previous MI) [18]	58	497	54	438	6%	0.95 [0.67, 1.34]
Tornwall et al., 2004 - ATBC (first ever CHD) [18]	289	6781	296	6849	30%	0.99 [0.84, 1.16]
Stone et al., 2005 [20]	3	101	1	96	0%	2.85 [0.30, 26.94]
Mooney et al., 2005 [19]	1	142	0	142	0%	3.00 [0.12, 73.03]
CLIPS Group 2007 [22]	9	185	4	181	1%	2.20 [0.69, 7.02]
Sesso et al., 2008 - PHS II [25]	133	3,656	144	3,653	14%	0.92 [0.73, 1.16]
Subtotal (95% CI)		**22,001**		**21,996**	**100%**	**0.99 [0.90, 1.08]**
Total events	**964**		**972**			
Heterogeneity: Tau² = 0.00; Chi² = 3.77, df = 8 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.32 (P = 0.75)						
Total (95% CI)		**22,085**		**22,072**	**100%**	**0.98 [0.90, 1.07]**
Total events	**968**		**977**			
Heterogeneity: Tau² = 0.00; Chi² = 3.99, df = 9 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%						

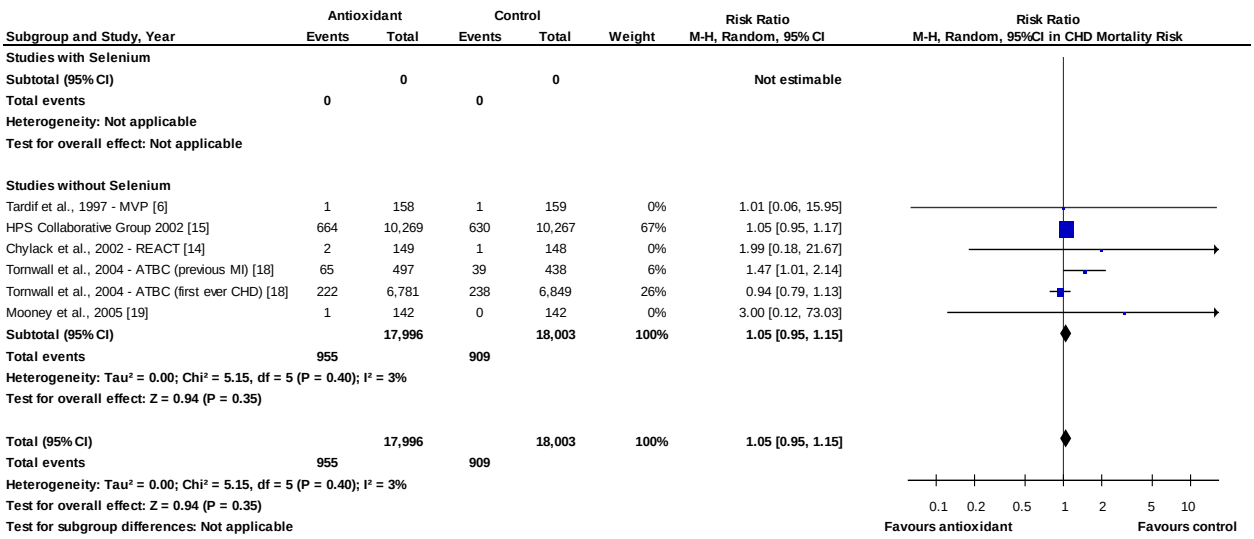
Supplementary Figure 30. Sensitivity analysis of antioxidant supplementation and MI risk for studies with and without selenium. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



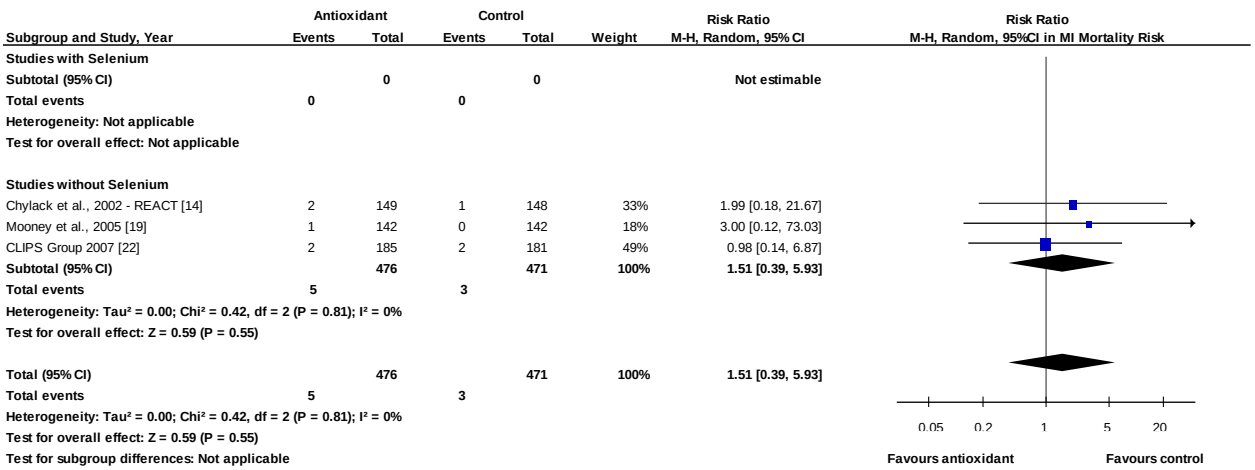
Supplementary Figure 31. Sensitivity analysis of antioxidant supplementation and stroke risk for studies with and without selenium. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



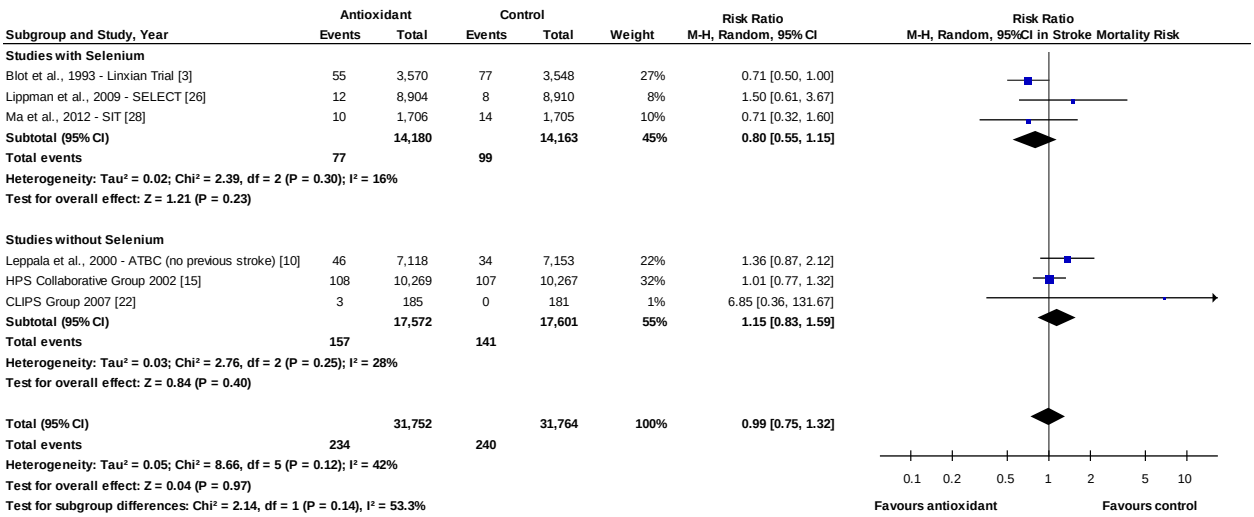
Supplementary Figure 32. Sensitivity analysis of antioxidant supplementation and CVD mortality risk for studies with and without selenium. NNT for antioxidant supplementation and CVD mortality risk for studies with selenium is 264. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



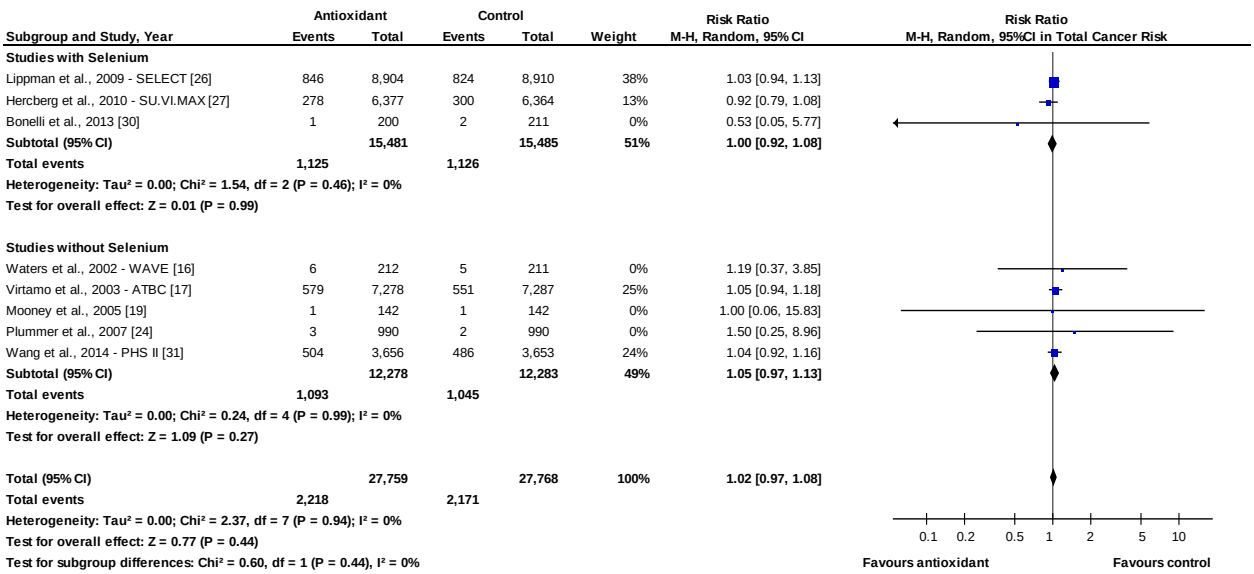
Supplementary Figure 33. Sensitivity analysis of antioxidant supplementation and CHD mortality risk for studies with and without selenium. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



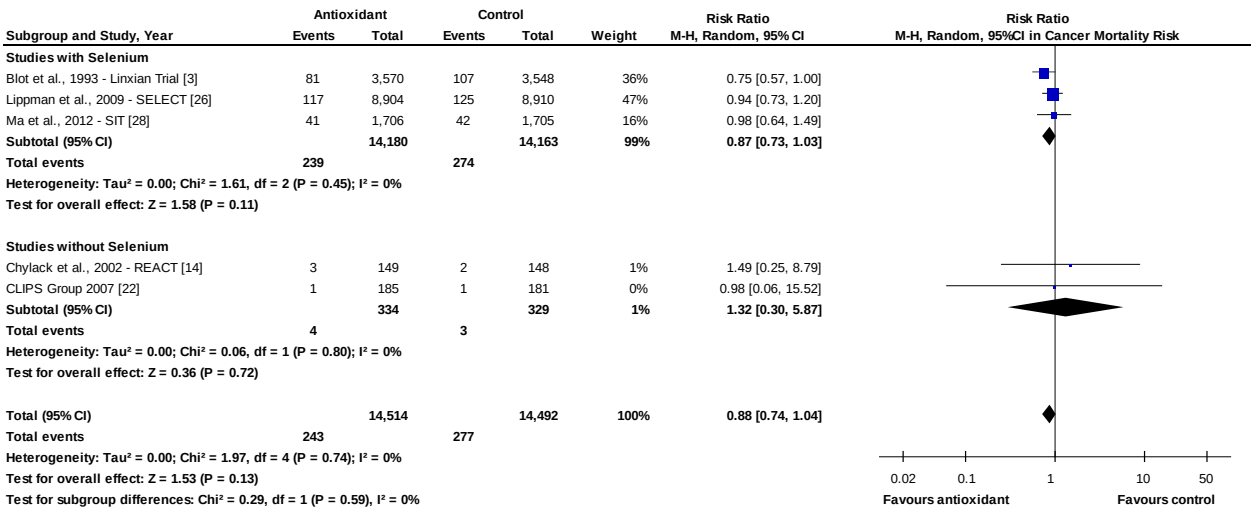
Supplementary Figure 34. Sensitivity analysis of antioxidant supplementation and MI mortality risk for studies with and without selenium. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



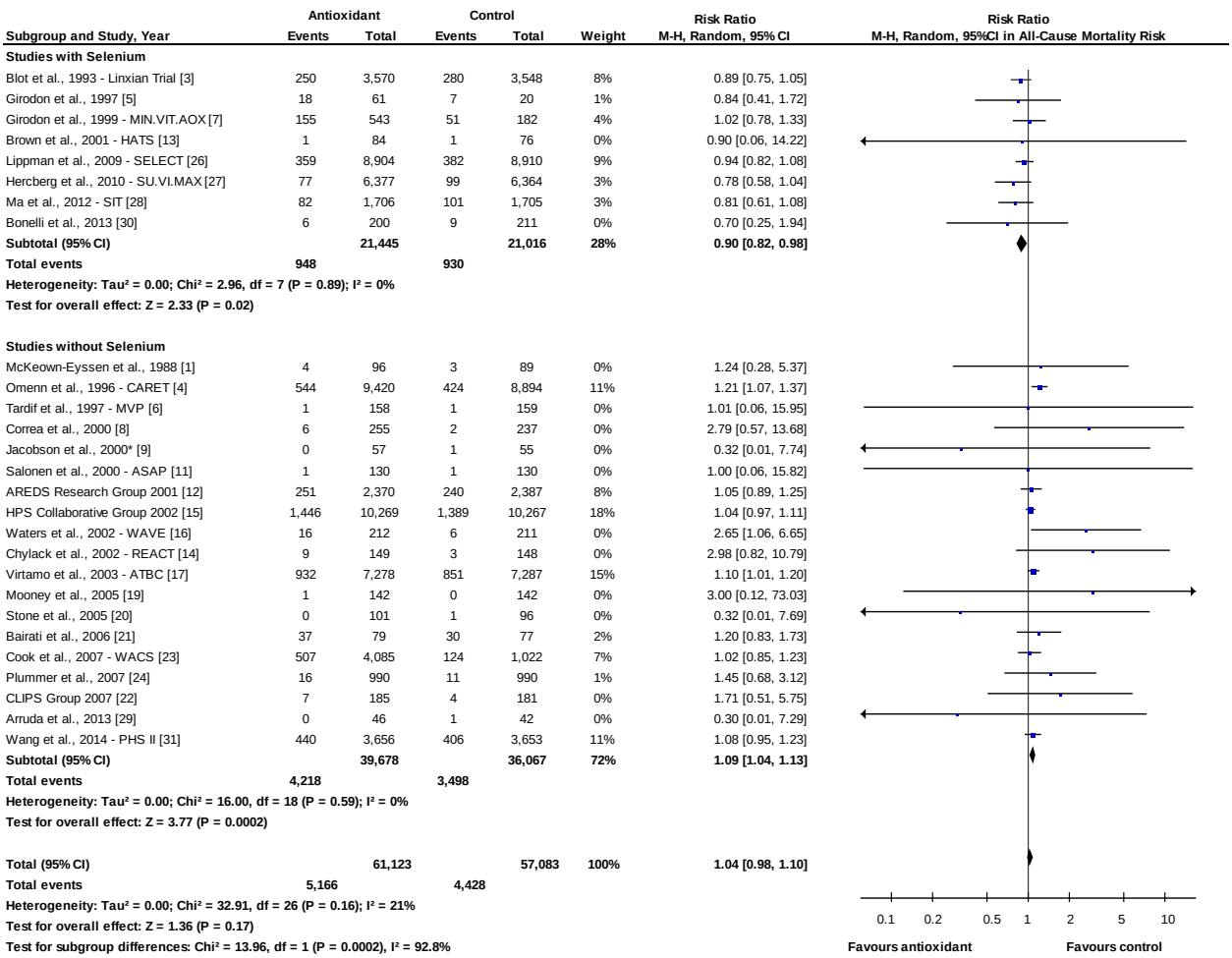
Supplementary Figure 35. Sensitivity analysis of antioxidant supplementation and stroke mortality risk for studies with and without selenium. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



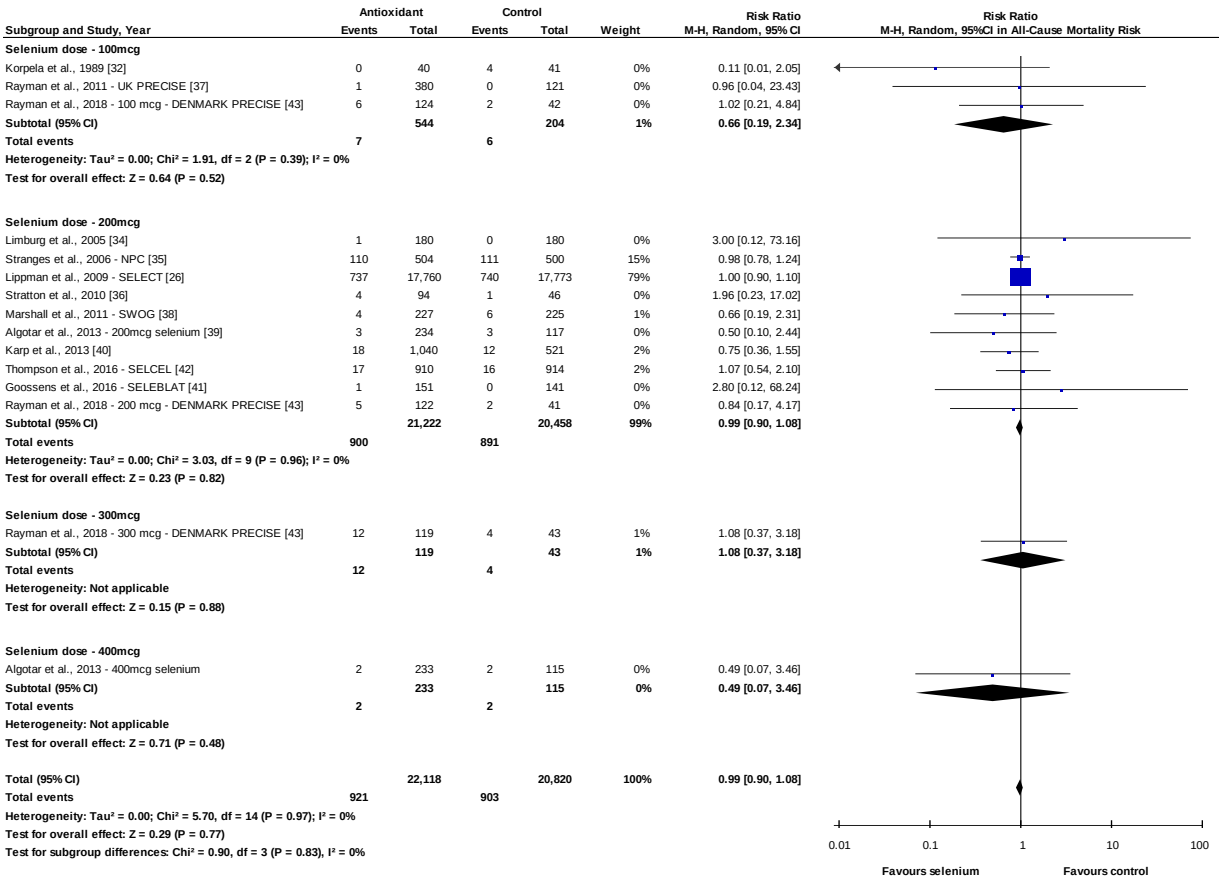
Supplementary Figure 36. Sensitivity analysis of antioxidant supplementation and total cancer risk for studies with and without selenium. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



Supplementary Figure 37. Sensitivity analysis of antioxidant supplementation and cancer mortality risk for studies with and without selenium. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

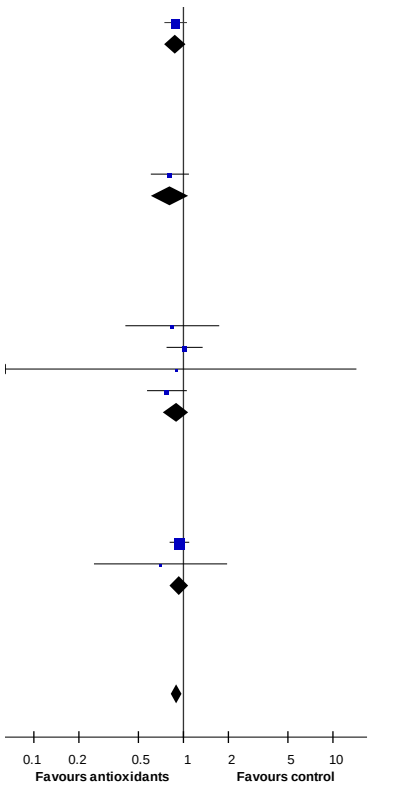


Supplementary Figure 38. Sensitivity analysis of antioxidant supplementation and all-cause mortality risk for studies with and without selenium. NNT for antioxidant supplementation and all-cause mortality risk for studies with selenium is **226**. **NNH** for antioxidant supplementation and all-cause mortality risk for studies without selenium is **115**. M-H, Manthel-Haenszel. ***Jacobson et al., 2000 – Data retrieved from meta-analysis Bjelakovic 2012 (44).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

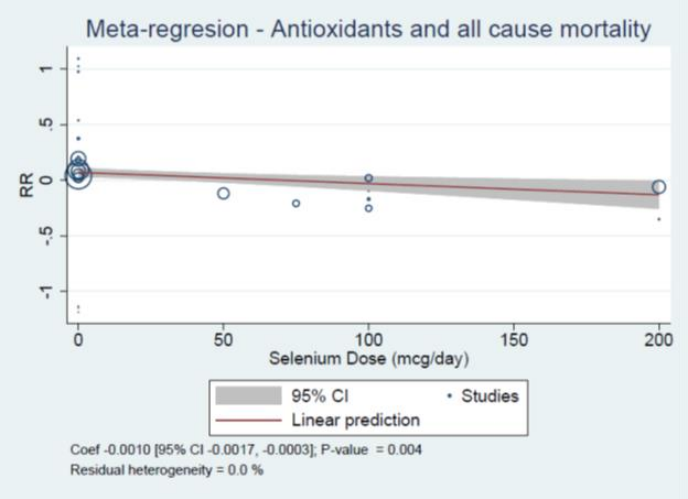


Supplementary Figure 39. Forest plot showing the dose response analysis of selenium supplementation only and all-cause mortality. M-H, Manthel-Haenszel. ***Stranges et al., 2006 was used as it contained data up until the end of treatment but only in those free of CVD at baseline(35)**. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

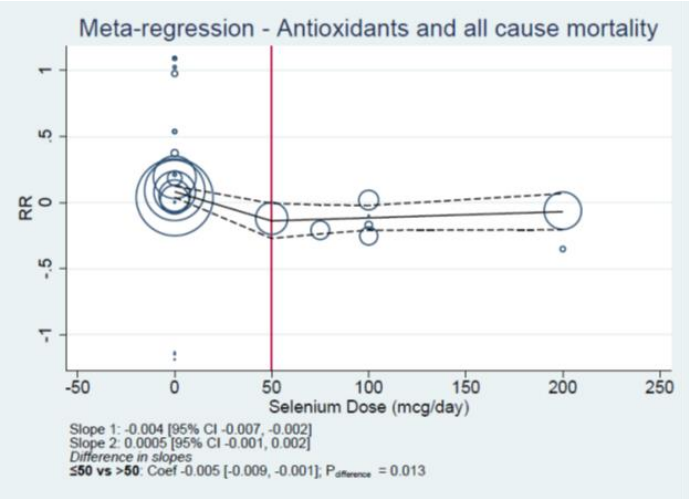
Subgroup and Study, Year	Antioxidant Events	Antioxidant Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Selenium dose - 50mcg						
Blot et al., 1993 - Linxian Trial [3]	250	3,570	280	3,548	29%	0.89 [0.75, 1.05]
Subtotal (95% CI)		**3,570**		**3,548**	**29%**	**0.89 [0.75, 1.05]**
Total events	**250**		**280**			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						
Selenium dose - 75mcg						
Ma et al., 2012 - SIT [28]	82	1,706	101	1,705	10%	0.81 [0.61, 1.08]
Subtotal (95% CI)		**1,706**		**1,705**	**10%**	**0.81 [0.61, 1.08]**
Total events	**82**		**101**			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.44 (P = 0.15)						
Selenium dose - 100mcg						
Girodon et al., 1997 [5]	18	61	7	20	2%	0.84 [0.41, 1.72]
Girodon et al., 1999 - MIN.VIT.AOX [7]	155	543	51	182	11%	1.02 [0.78, 1.33]
Brown et al., 2001 - HATS [13]	1	84	1	76	0%	0.90 [0.06, 14.22]
Hercberg et al., 2010 - SU.VI.MAX [27]	77	6,377	99	6,364	9%	0.78 [0.58, 1.04]
Subtotal (95% CI)		**7,065**		**6,642**	**21%**	**0.90 [0.74, 1.09]**
Total events	**251**		**158**			
Heterogeneity: Tau² = 0.00; Chi² = 1.85, df = 3 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.12 (P = 0.26)						
Selenium dose - 200mcg						
Lippman et al., 2009 - SELECT [26]	359	8,904	382	8,910	39%	0.94 [0.82, 1.08]
Bonelli et al., 2013 [30]	6	200	9	211	1%	0.70 [0.25, 1.94]
Subtotal (95% CI)		**9,104**		**9,121**	**40%**	**0.94 [0.81, 1.08]**
Total events	**365**		**391**			
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Total (95% CI)		**21,445**		**21,016**	**100%**	**0.90 [0.82, 0.98]**
Total events	**948**		**930**			
Heterogeneity: Tau² = 0.00; Chi² = 2.96, df = 7 (P = 0.89); I² = 0%						
Test for overall effect: Z = 2.33 (P = 0.02)						
Test for subgroup differences: Chi² = 0.83, df = 3 (P = 0.84), I² = 0%						



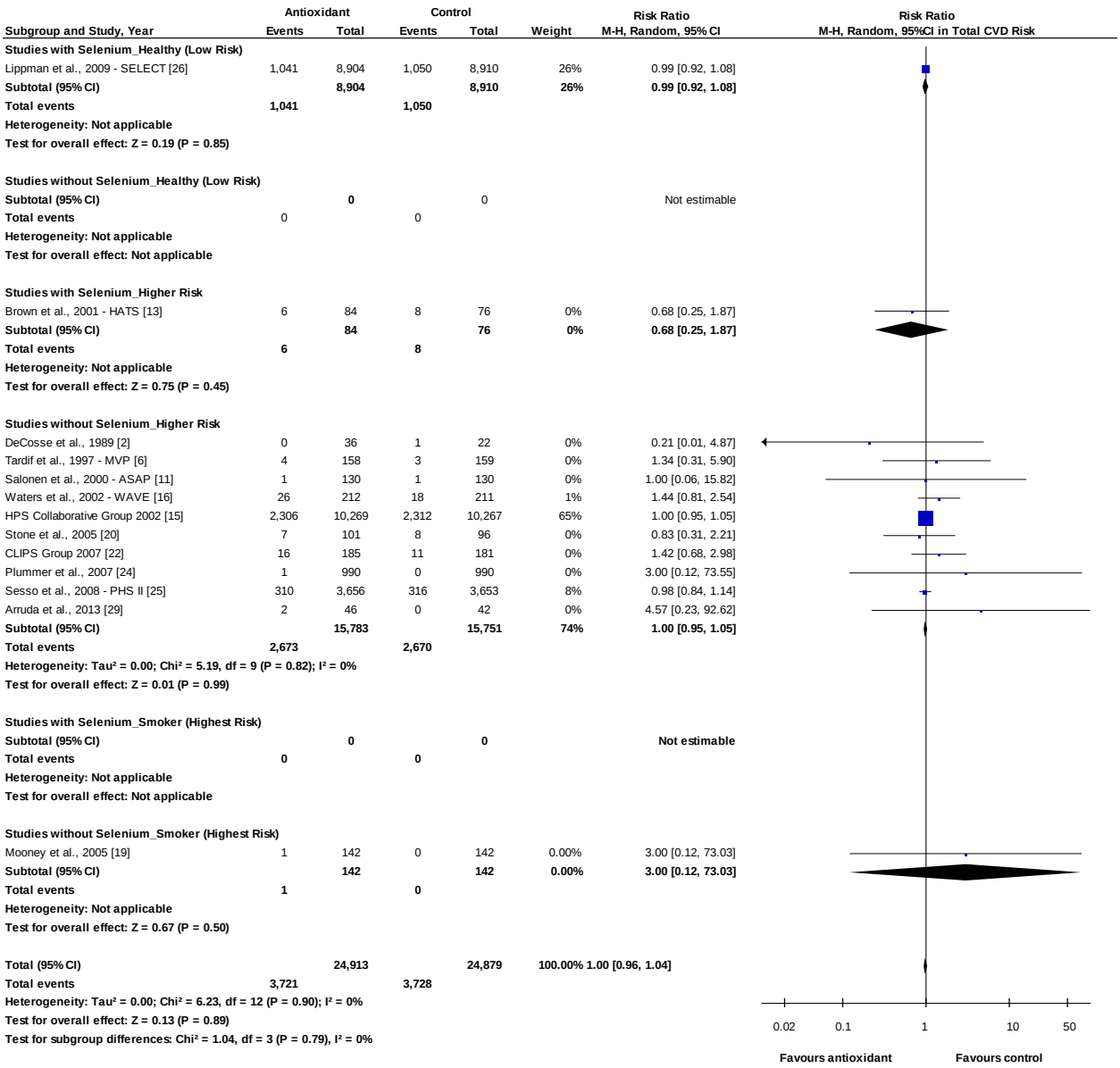
Supplementary Figure 40. Forest plot showing the dose response analysis of antioxidant supplementation for studies with selenium and all-cause mortality. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



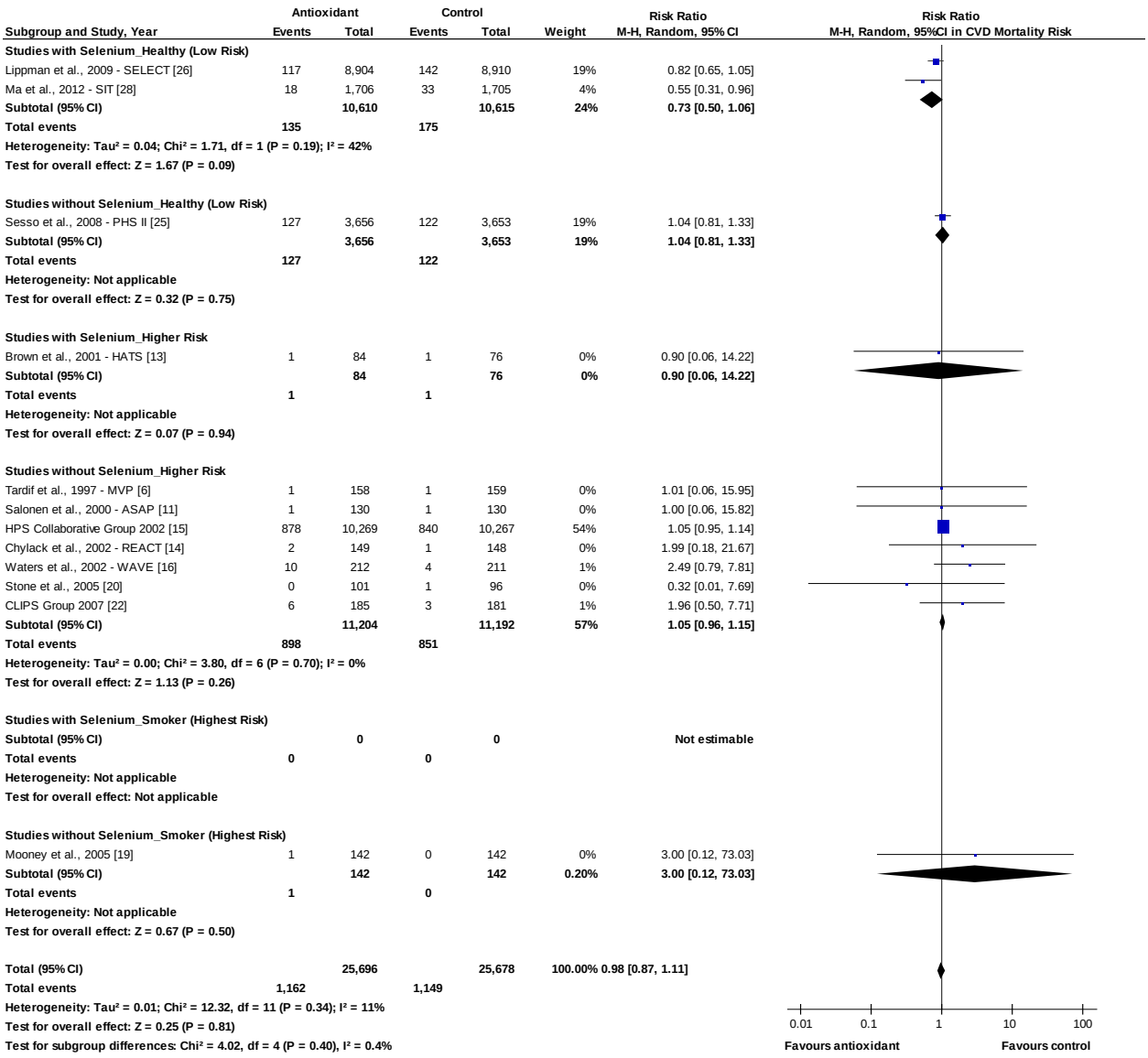
Supplementary Figure 41. Linear dose-response relationship between selenium intake and all-cause mortality risk in studies with antioxidant intake. Individual studies are represented by the circles, with their weight in the overall analysis represented by the size of the circles. The straight red line represents the estimate linear dose response and the grey area represent the upper and lower 95% Confidence Intervals.



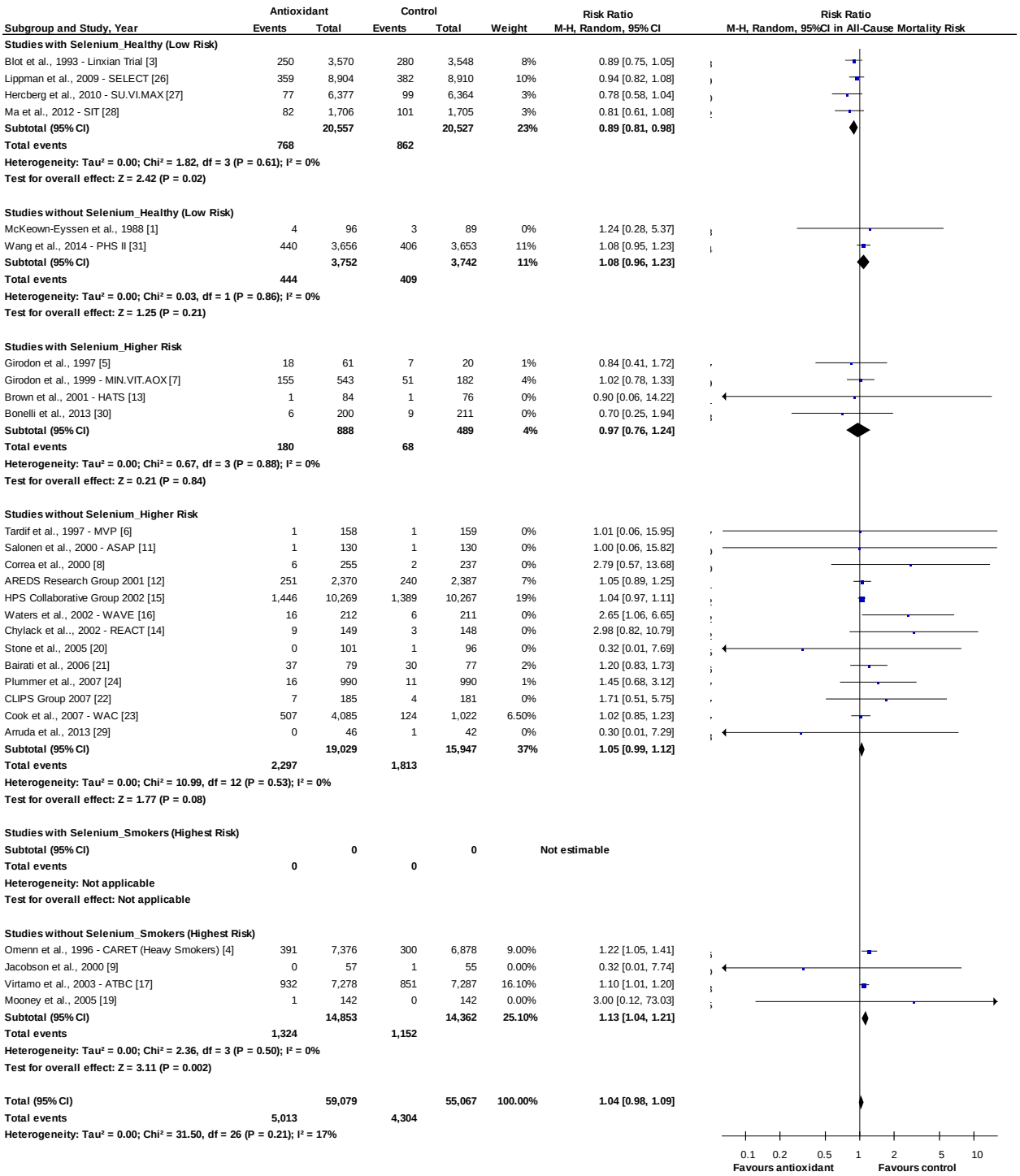
Supplementary Figure 42. Non-linear dose-response relationship between selenium intake and all-cause mortality risk in studies with antioxidant intake. Individual studies are represented by the circles, with their weight in the overall analysis represented by the size of the circles. The straight lines represent the estimate dose response and the dashed lines represent the upper and lower 95% Confidence Intervals. The red line represents the knot at 50 mcg/day of selenium.



Supplementary Figure 43. Forest plot showing antioxidants (with and without selenium) and total CVD by risk group. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



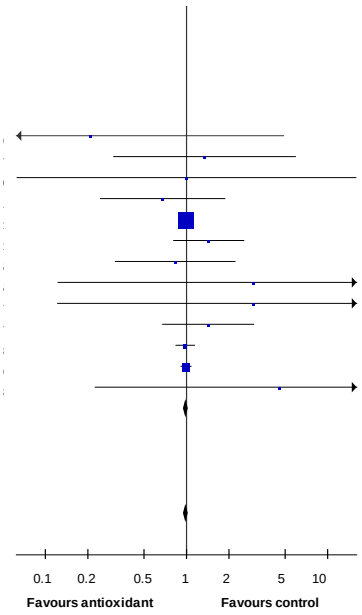
Supplementary Figure 44. Forest plot showing antioxidants (with and without selenium) and total CVD mortality by risk group. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



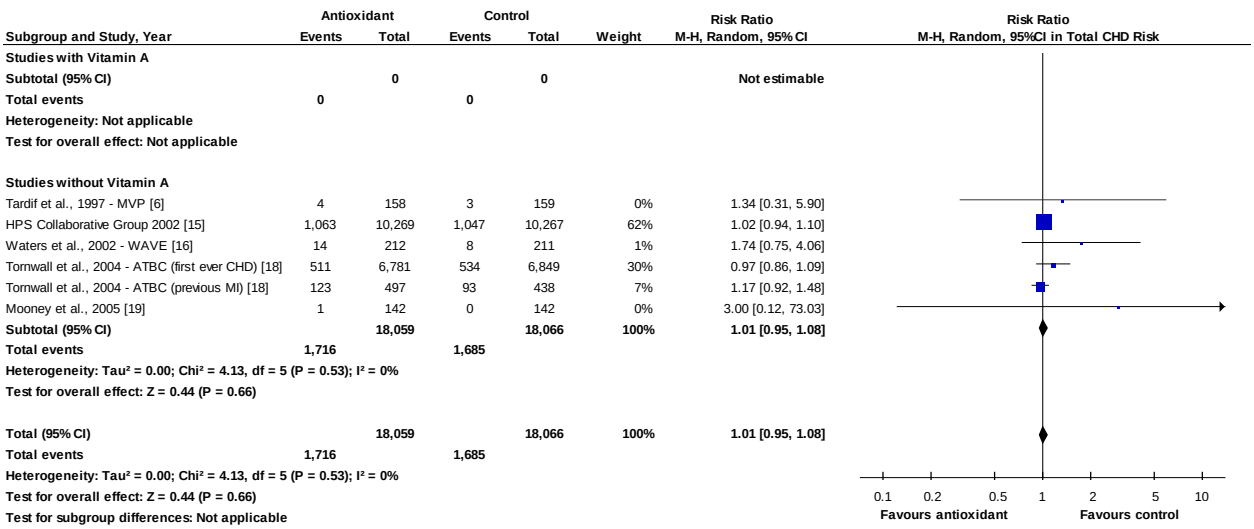
Supplementary Figure 45. Forest plot showing antioxidants (with and without selenium) and all-cause mortality by risk group. M-H, Manthel-Haenszel. ***Jacobson et al., 2000 – data retrieved from meta-analysis Bjelakovic 2012(44).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model. The sub

group difference between studies with and without selenium among the healthy (low risk) group was significant ($p = 0.01$, $I^2 = 83.4\%$) while the subgroup difference within the higher risk group was not significant ($p = 0.54$, $I^2 = 0\%$).

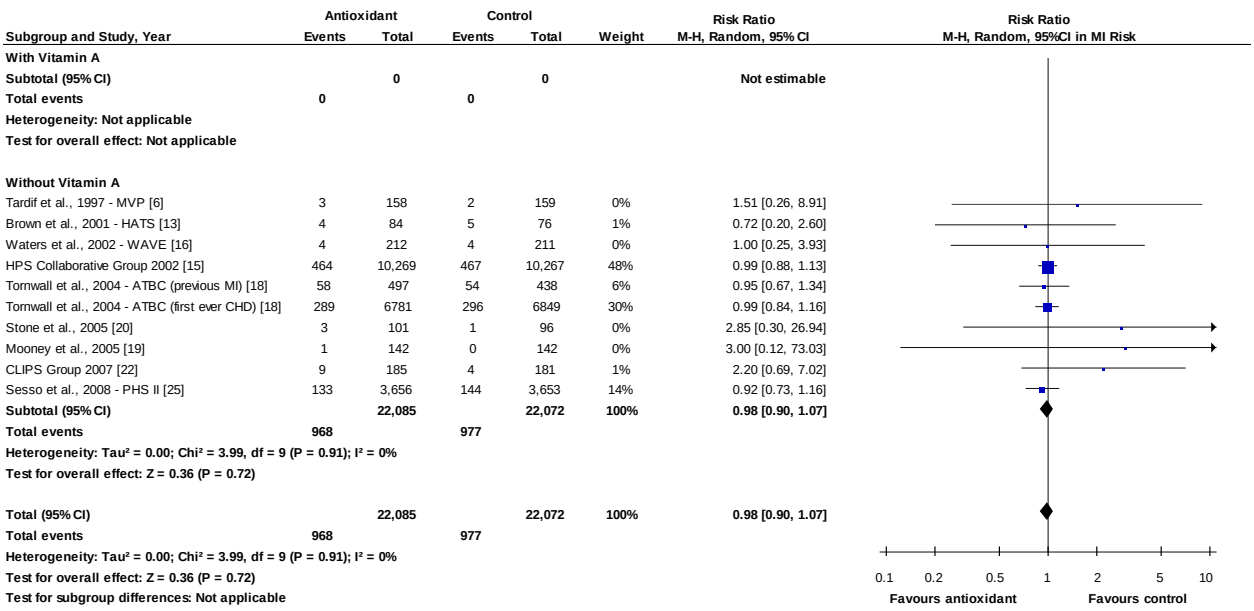
Subgroup and Study, Year	Antioxidant Events	Antioxidant Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Studies with Vitamin A						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	**0**		**0**			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Studies without Vitamin A						
DeCosse et al., 1989 [2]	0	36	1	22	0%	0.21 [0.01, 4.87]
Tardif et al., 1997 - MVP [6]	4	158	3	159	0%	1.34 [0.31, 5.90]
Salonen et al., 2000 - ASAP [11]	1	130	1	130	0%	1.00 [0.06, 15.82]
Brown et al., 2001 - HATS [13]	6	84	8	76	0%	0.68 [0.25, 1.87]
HPS Collaborative Group 2002 [15]	2,306	10,269	2,312	10,267	65%	1.00 [0.95, 1.05]
Waters et al., 2002 - WAVE [16]	26	212	18	211	1%	1.44 [0.81, 2.54]
Stone et al., 2005 [20]	7	101	8	96	0%	0.83 [0.31, 2.21]
Mooney et al., 2005 [19]	1	142	0	142	0%	3.00 [0.12, 73.03]
CLIPS Group 2007 [22]	16	185	11	181	0%	1.42 [0.68, 2.98]
Plummer et al., 2007 [24]	1	990	0	990	0%	3.00 [0.12, 73.55]
Sesso et al., 2008 - PHS II [25]	310	3,656	316	3,653	8%	0.98 [0.84, 1.14]
Lippman et al., 2009 - SELECT [26]	1,041	8,904	1,050	8,910	26%	0.99 [0.92, 1.08]
Arruda et al., 2013 [29]	2	46	0	42	0%	4.57 [0.23, 92.62]
Subtotal (95% CI)		**24,913**		**24,879**	**100%**	**1.00 [0.96, 1.04]**
Total events	**3,721**		**3,728**			
Heterogeneity: Tau² = 0.00; Chi² = 6.23, df = 12 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.89)						
Total (95% CI)		**24,913**		**24,879**	**100%**	**1.00 [0.96, 1.04]**
Total events	**3,721**		**3,728**			
Heterogeneity: Tau² = 0.00; Chi² = 6.23, df = 12 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.89)						
Test for subgroup differences: Not applicable						



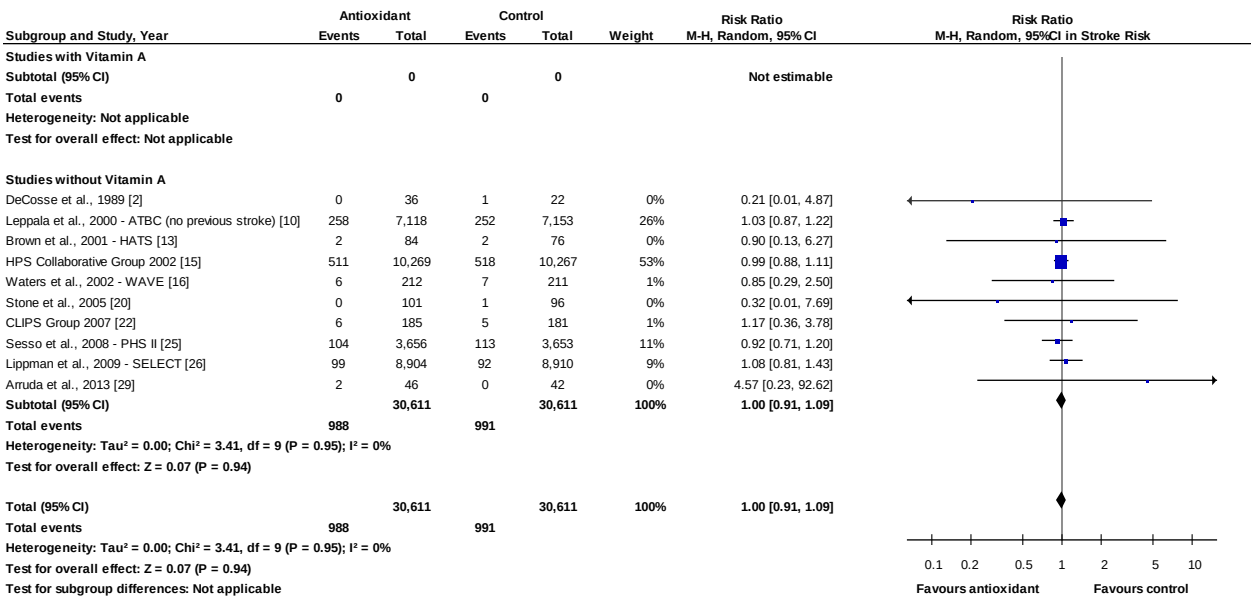
Supplementary Figure 46. Sensitivity analysis of antioxidant supplementation and total CVD risk for studies with and without vitamin A. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



Supplementary Figure 47. Sensitivity analysis of antioxidant supplementation and total CHD risk for studies with and without vitamin A. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

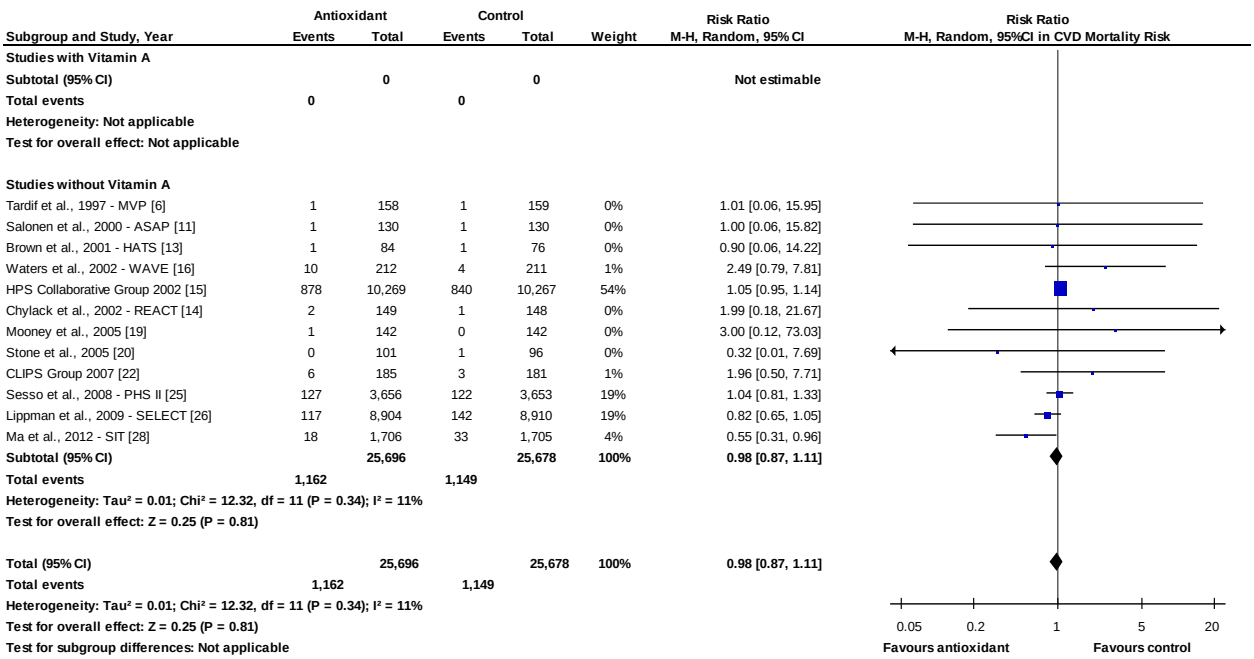


Supplementary Figure 48. Sensitivity analysis of antioxidant supplementation and MI risk for studies with and without vitamin A. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

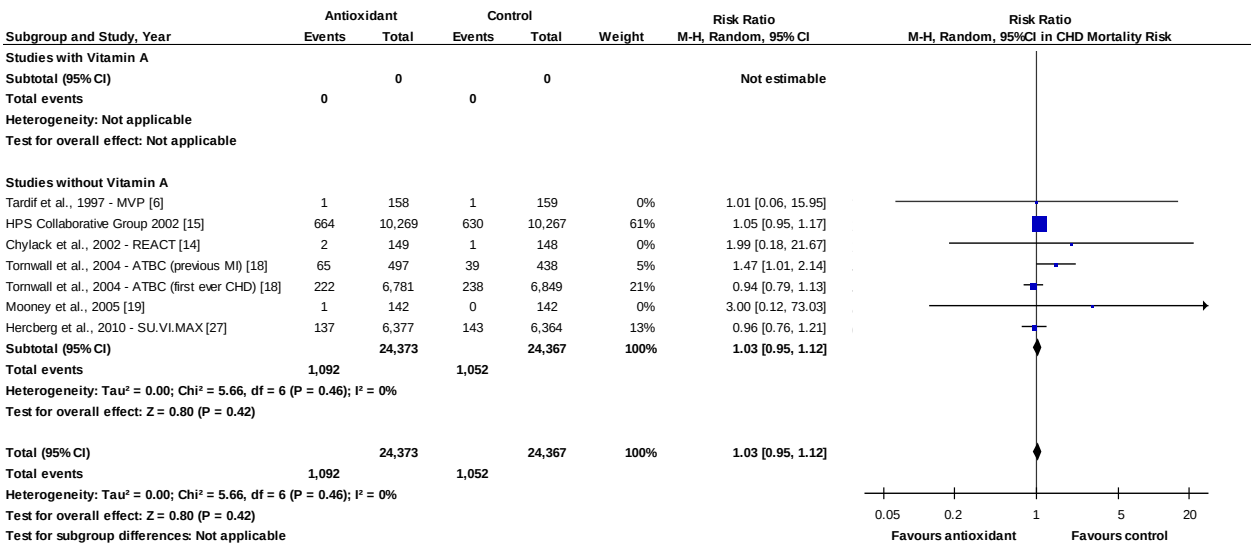


Subgroup and Study, Year	Antioxidant Events	Antioxidant Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Studies with Vitamin A						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	**0**		**0**			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Studies without Vitamin A						
DeCosse et al., 1989 [2]	0	36	1	22	0%	0.21 [0.01, 4.87]
Leppala et al., 2000 - ATBC (no previous stroke) [10]	258	7,118	252	7,153	26%	1.03 [0.87, 1.22]
Brown et al., 2001 - HATS [13]	2	84	2	76	0%	0.90 [0.13, 6.27]
HPS Collaborative Group 2002 [15]	511	10,269	518	10,267	53%	0.99 [0.88, 1.11]
Waters et al., 2002 - WAVE [16]	6	212	7	211	1%	0.85 [0.29, 2.50]
Stone et al., 2005 [20]	0	101	1	96	0%	0.32 [0.01, 7.69]
CLIPS Group 2007 [22]	6	185	5	181	1%	1.17 [0.36, 3.78]
Sesso et al., 2008 - PHS II [25]	104	3,656	113	3,653	11%	0.92 [0.71, 1.20]
Lippman et al., 2009 - SELECT [26]	99	8,904	92	8,910	9%	1.08 [0.81, 1.43]
Arruda et al., 2013 [29]	2	46	0	42	0%	4.57 [0.23, 92.62]
Subtotal (95% CI)		**30,611**		**30,611**	**100%**	**1.00 [0.91, 1.09]**
Total events	**988**		**991**			
Heterogeneity: Tau² = 0.00; Chi² = 3.41, df = 9 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.94)						
Total (95% CI)		**30,611**		**30,611**	**100%**	**1.00 [0.91, 1.09]**
Total events	**988**		**991**			
Heterogeneity: Tau² = 0.00; Chi² = 3.41, df = 9 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.94)						
Test for subgroup differences: Not applicable						

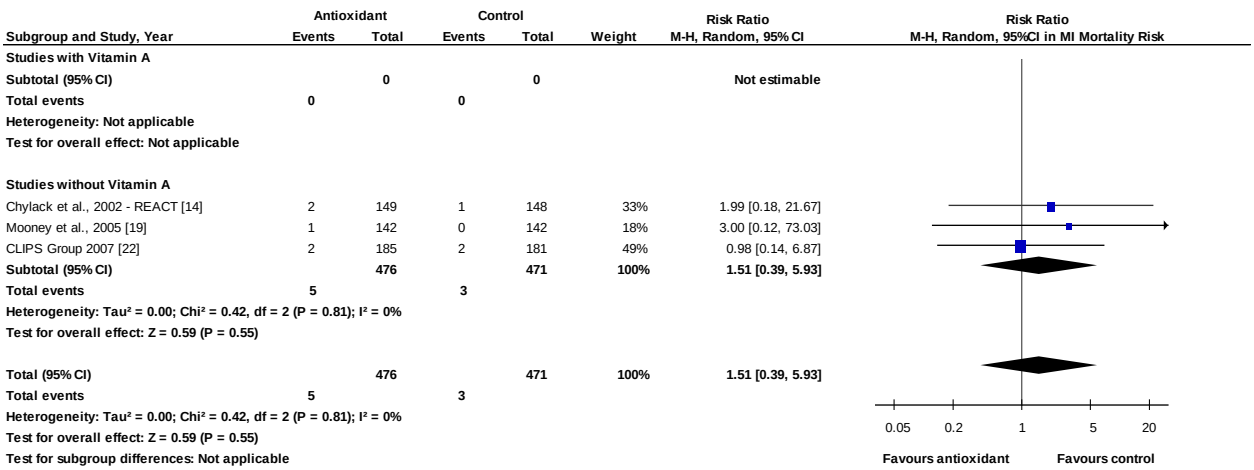
Supplementary Figure 49. Sensitivity analysis of antioxidant supplementation and stroke risk for studies with and without vitamin A. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



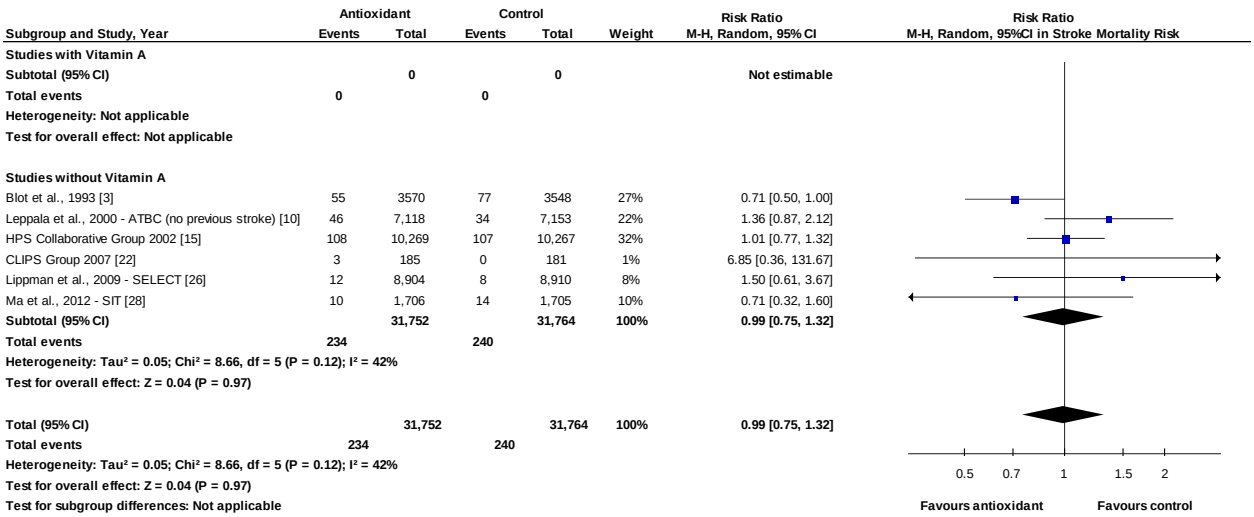
Supplementary Figure 50. Sensitivity analysis of antioxidant supplementation total CVD mortality risk for studies with and without vitamin A. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



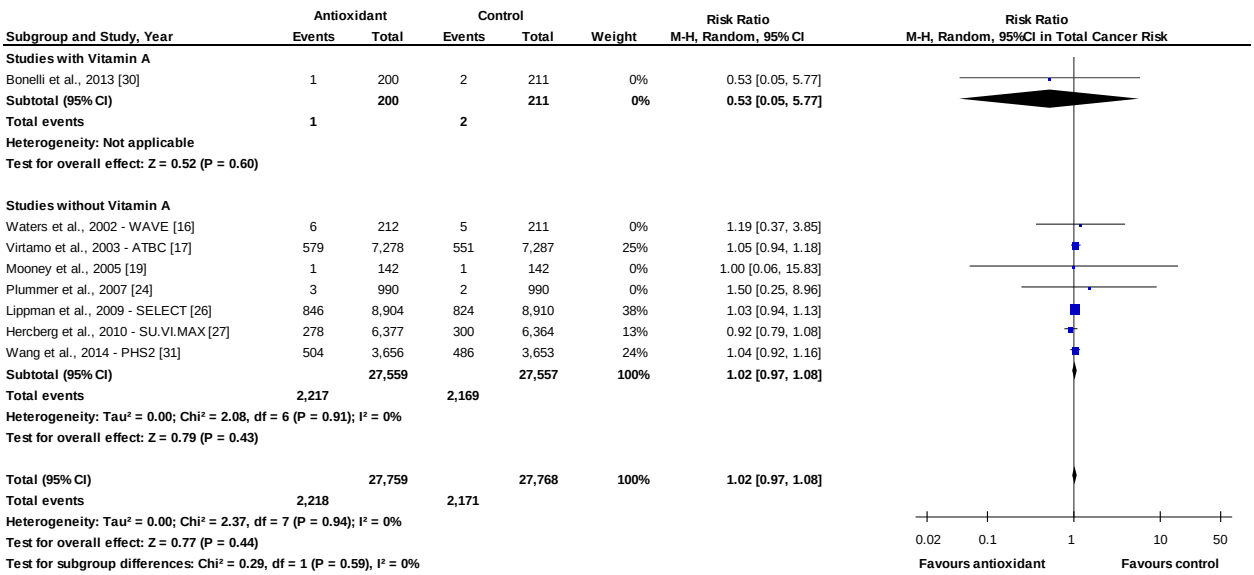
Supplementary Figure 51. Sensitivity analysis of antioxidant supplementation and CHD mortality risk for studies with and without vitamin A. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



Supplementary Figure 52. Sensitivity analysis of antioxidant supplementation and MI mortality risk for studies with and without vitamin A. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

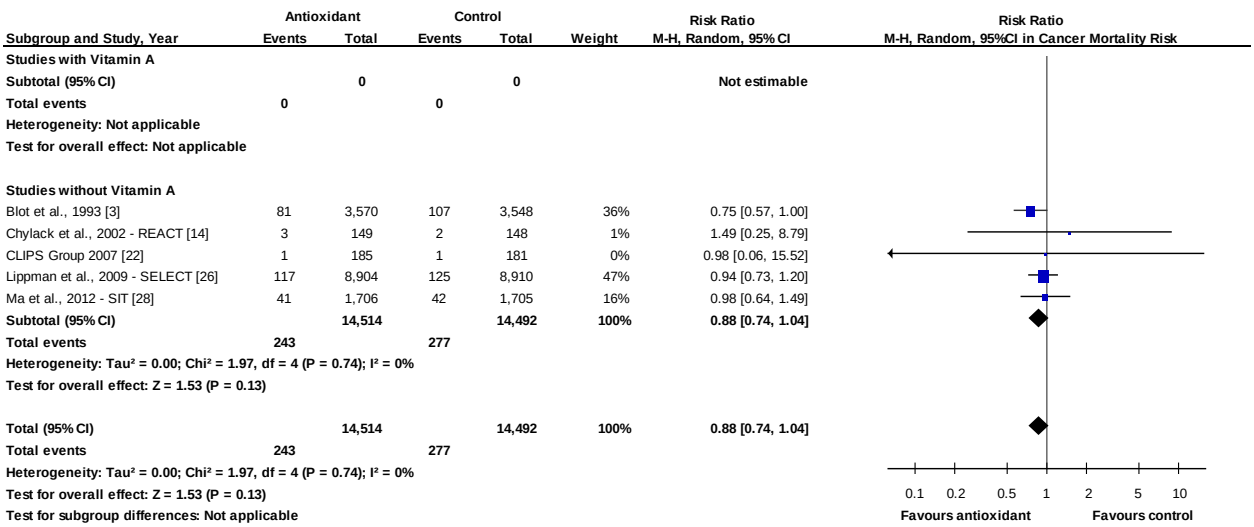


Supplementary Figure 53. Sensitivity analysis of antioxidant supplementation and stroke mortality risk for studies with and without vitamin A. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

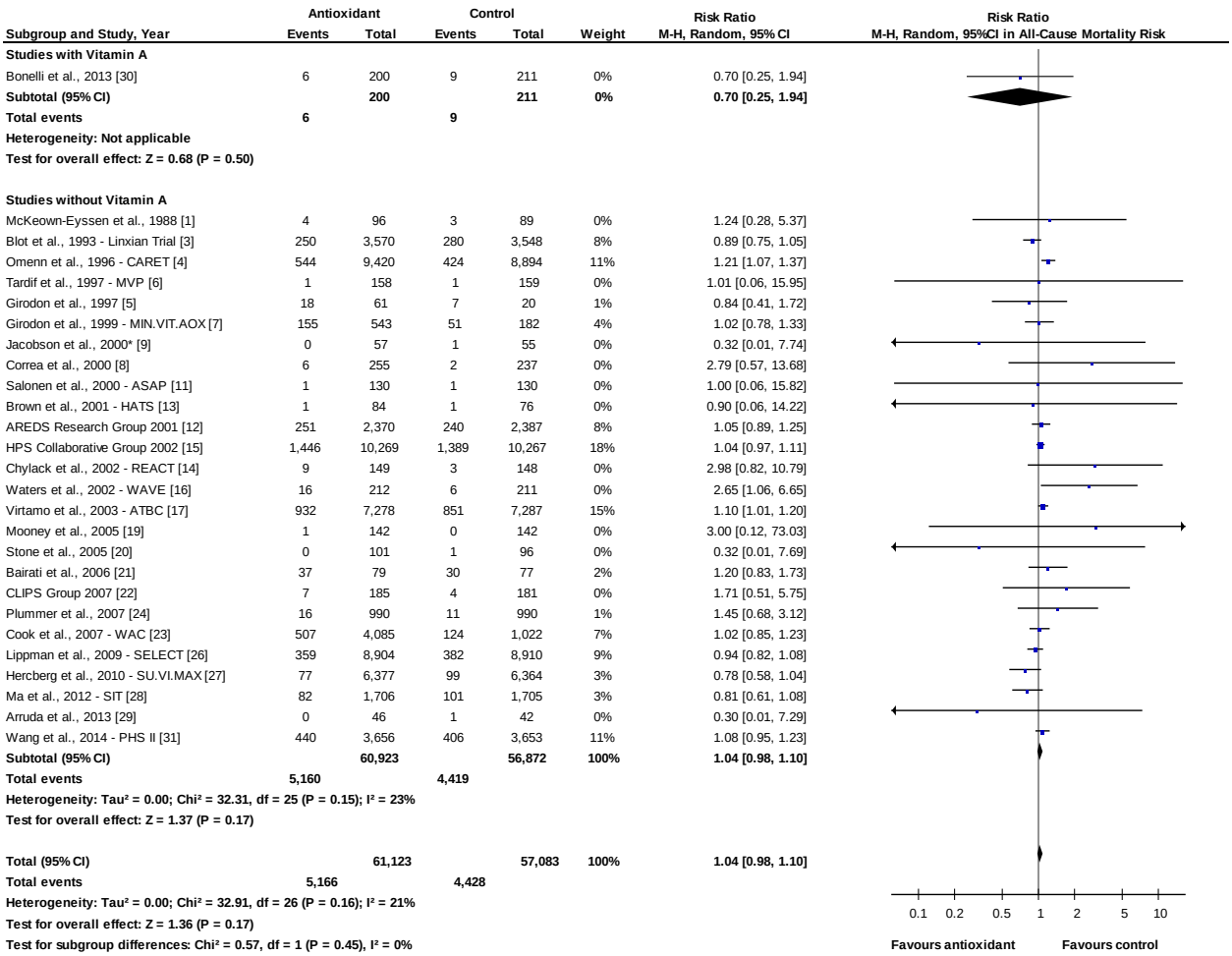


Subgroup and Study, Year	Antioxidant Events	Antioxidant Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Studies with Vitamin A						
Bonelli et al., 2013 [30]	1	200	2	211	0%	0.53 [0.05, 5.77]
Subtotal (95% CI)		**200**		**211**	**0%**	**0.53 [0.05, 5.77]**
Total events	**1**		**2**			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.60)						
Studies without Vitamin A						
Waters et al., 2002 - WAVE [16]	6	212	5	211	0%	1.19 [0.37, 3.85]
Virtamo et al., 2003 - ATBC [17]	579	7,278	551	7,287	25%	1.05 [0.94, 1.18]
Mooney et al., 2005 [19]	1	142	1	142	0%	1.00 [0.06, 15.83]
Plummer et al., 2007 [24]	3	990	2	990	0%	1.50 [0.25, 8.96]
Lippman et al., 2009 - SELECT [26]	846	8,904	824	8,910	38%	1.03 [0.94, 1.13]
Hercberg et al., 2010 - SU.VI.MAX [27]	278	6,377	300	6,364	13%	0.92 [0.79, 1.08]
Wang et al., 2014 - PHS2 [31]	504	3,656	486	3,653	24%	1.04 [0.92, 1.16]
Subtotal (95% CI)		**27,559**		**27,557**	**100%**	**1.02 [0.97, 1.08]**
Total events	**2,217**		**2,169**			
Heterogeneity: Tau² = 0.00; Chi² = 2.08, df = 6 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Total (95% CI)		**27,759**		**27,768**	**100%**	**1.02 [0.97, 1.08]**
Total events	**2,218**		**2,171**			
Heterogeneity: Tau² = 0.00; Chi² = 2.37, df = 7 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.77 (P = 0.44)						
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%						

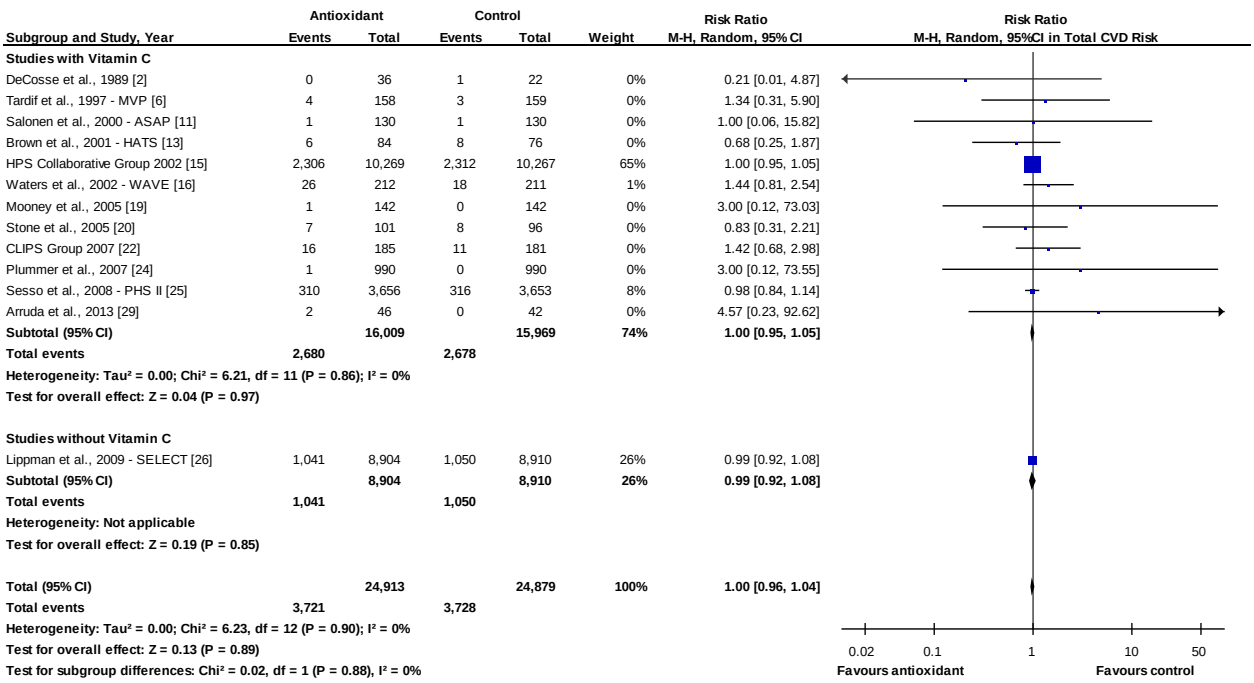
Supplementary Figure 54. Sensitivity analysis of antioxidant supplementation and total cancer risk for studies with and without vitamin A. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



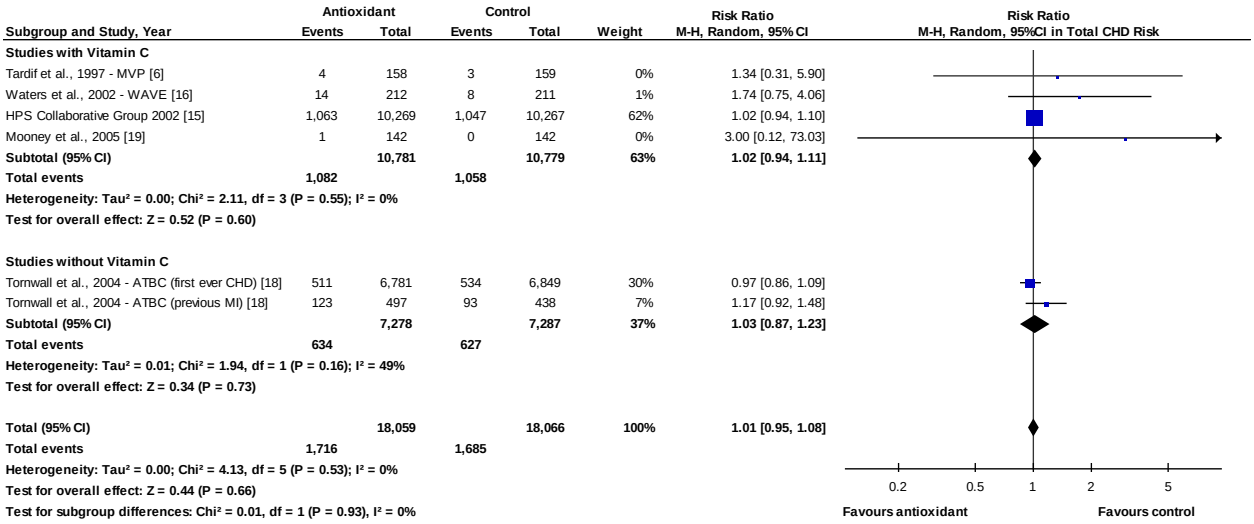
Supplementary Figure 55. Sensitivity analysis of antioxidant supplementation and cancer mortality risk for studies with and without vitamin A. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



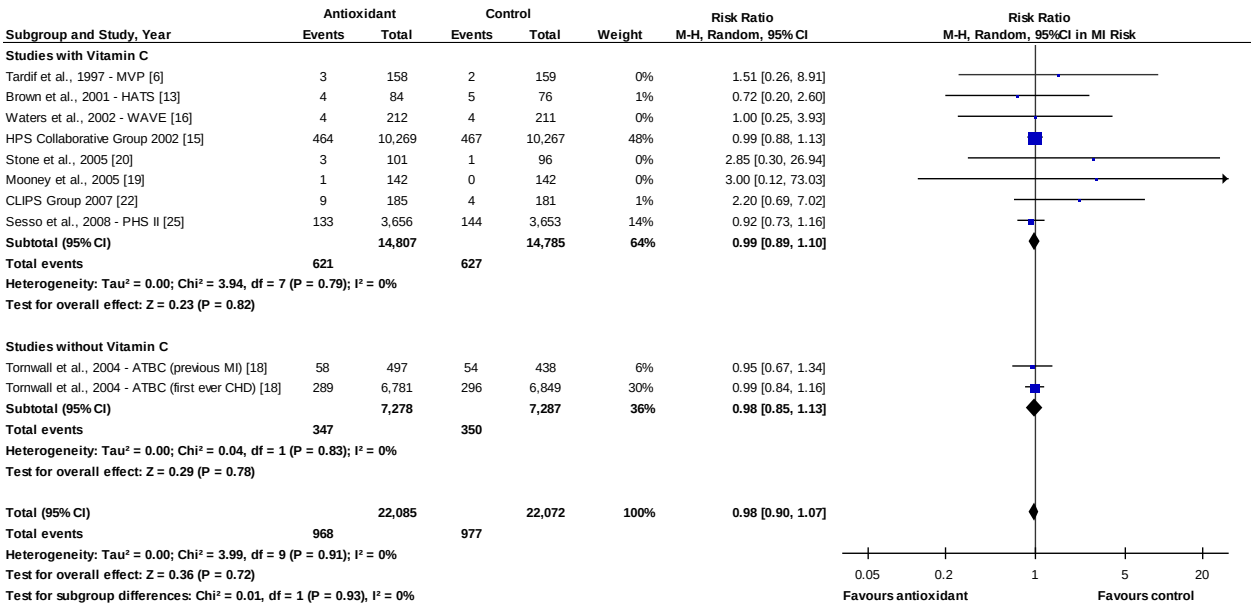
Supplementary Figure 56. Sensitivity analysis of antioxidant supplementation and all-cause mortality risk for studies with and without vitamin A. M-H, Manthel-Haenszel. ***Jacobson et al., 2000 – data retrieved from meta-analysis Bjelakovic 2012 (44).**The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random.



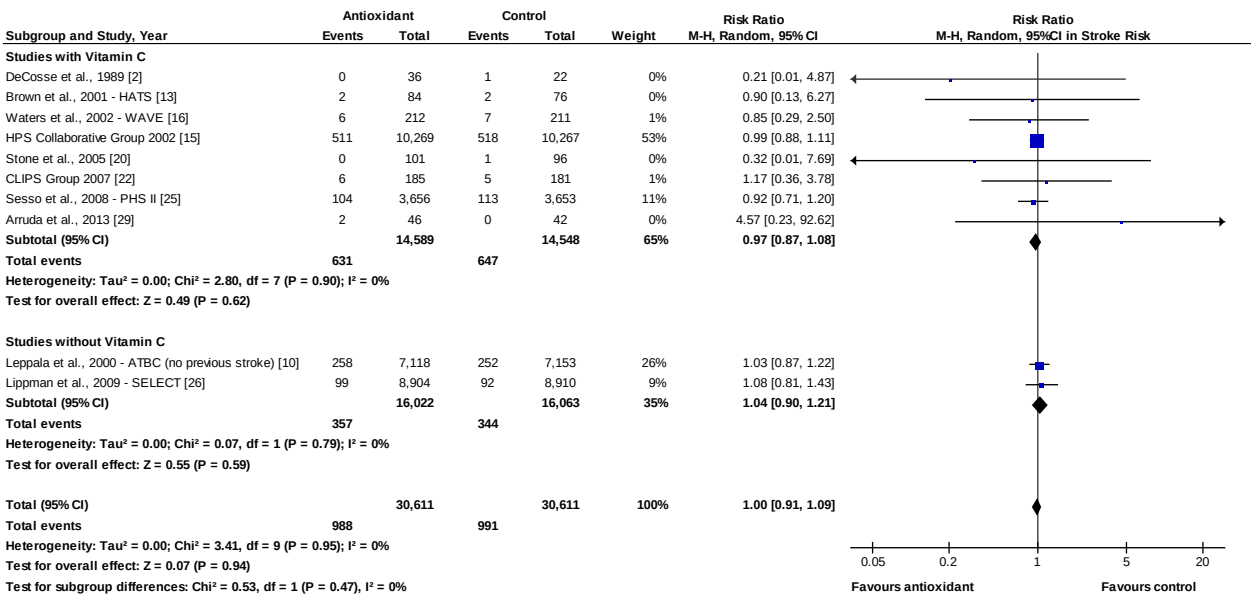
Supplementary Figure 57. Sensitivity analysis of antioxidant supplementation and total CVD risk for studies with and without vitamin C. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



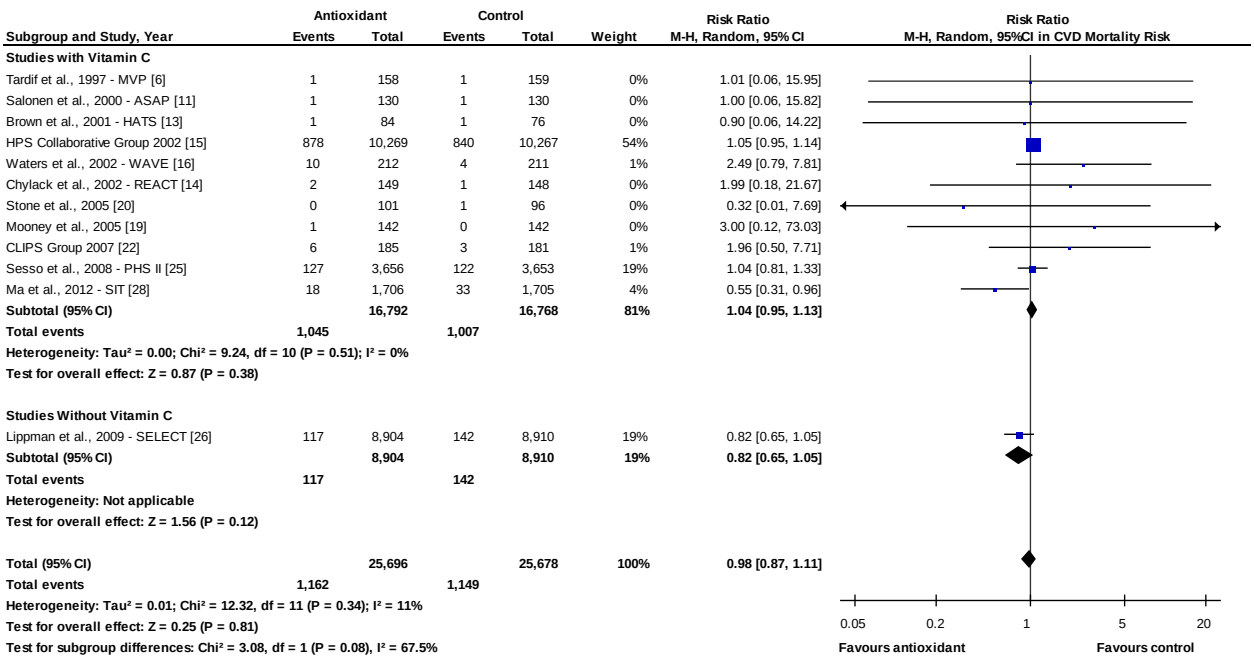
Supplementary Figure 58. Sensitivity analysis of antioxidant supplementation and total CHD risk for studies with and without vitamin C. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



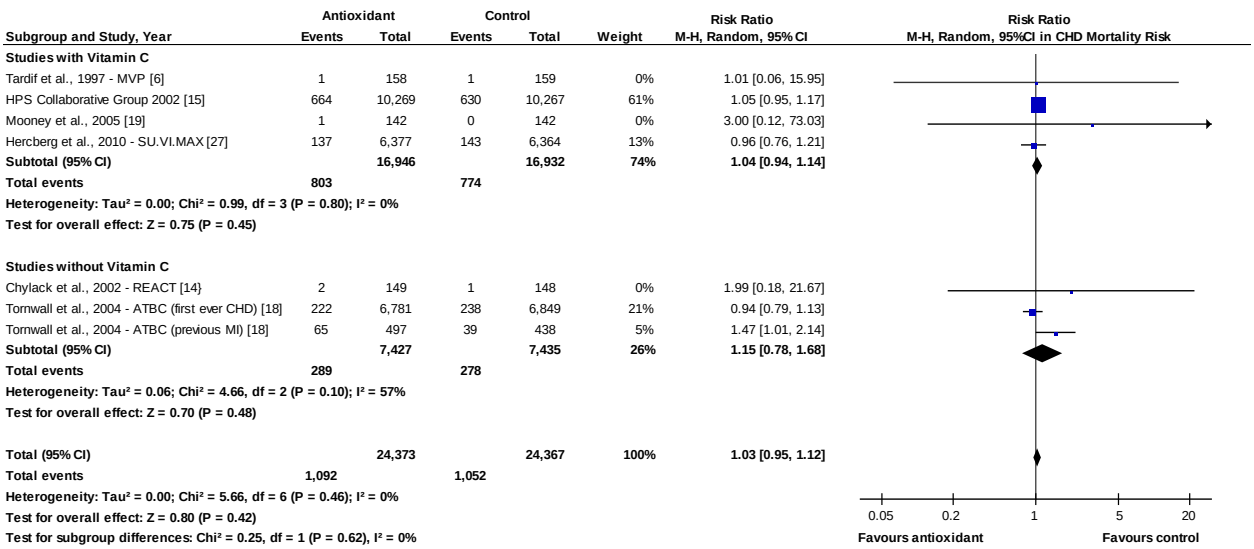
Supplementary Figure 59. Sensitivity analysis of antioxidant supplementation and MI risk for studies with and without vitamin C. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



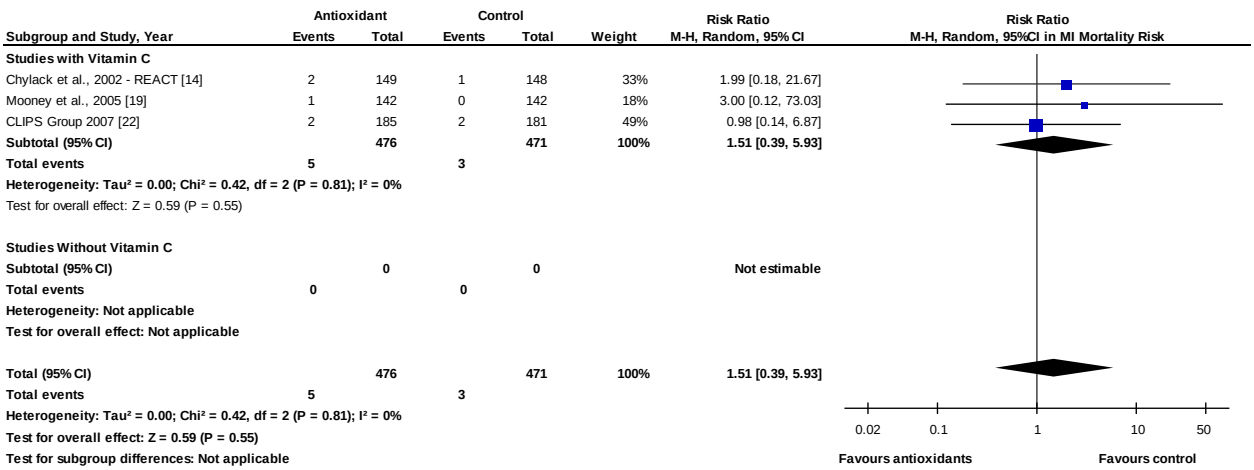
Supplementary Figure 60. Sensitivity analysis of antioxidant supplementation and stroke risk for studies with and without vitamin C. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



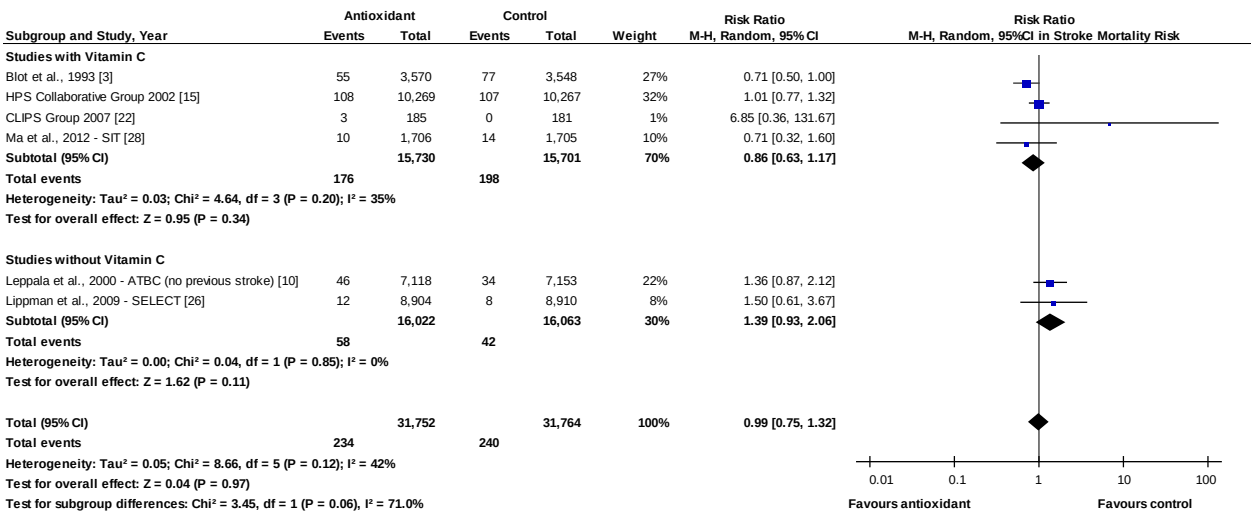
Supplementary Figure 61. Sensitivity analysis of antioxidant supplementation and CVD mortality risk for studies with and without vitamin C. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



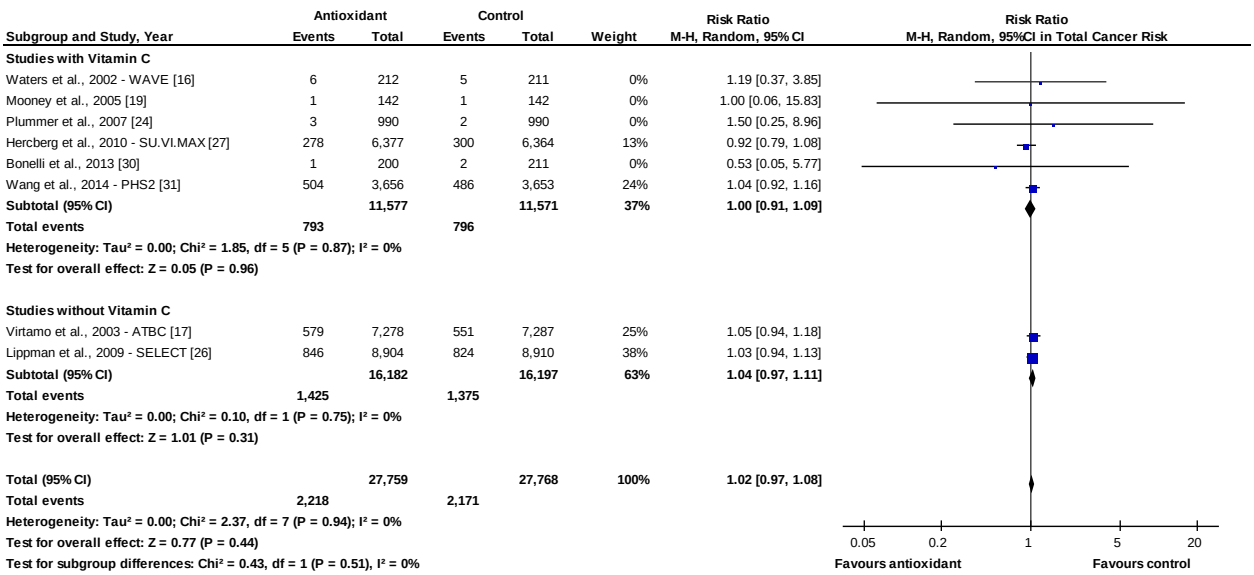
Supplementary Figure 62. Sensitivity analysis of antioxidant supplementation and CHD mortality risk for studies with and without vitamin C. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



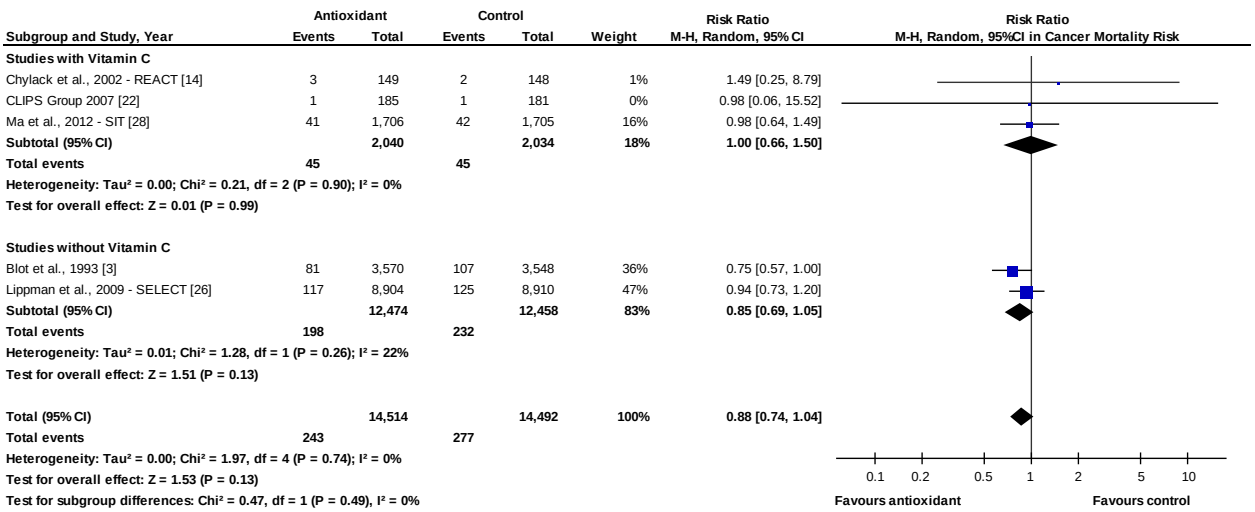
Supplementary Figure 63. Sensitivity analysis of antioxidant supplementation and MI mortality risk for studies with and without vitamin C. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



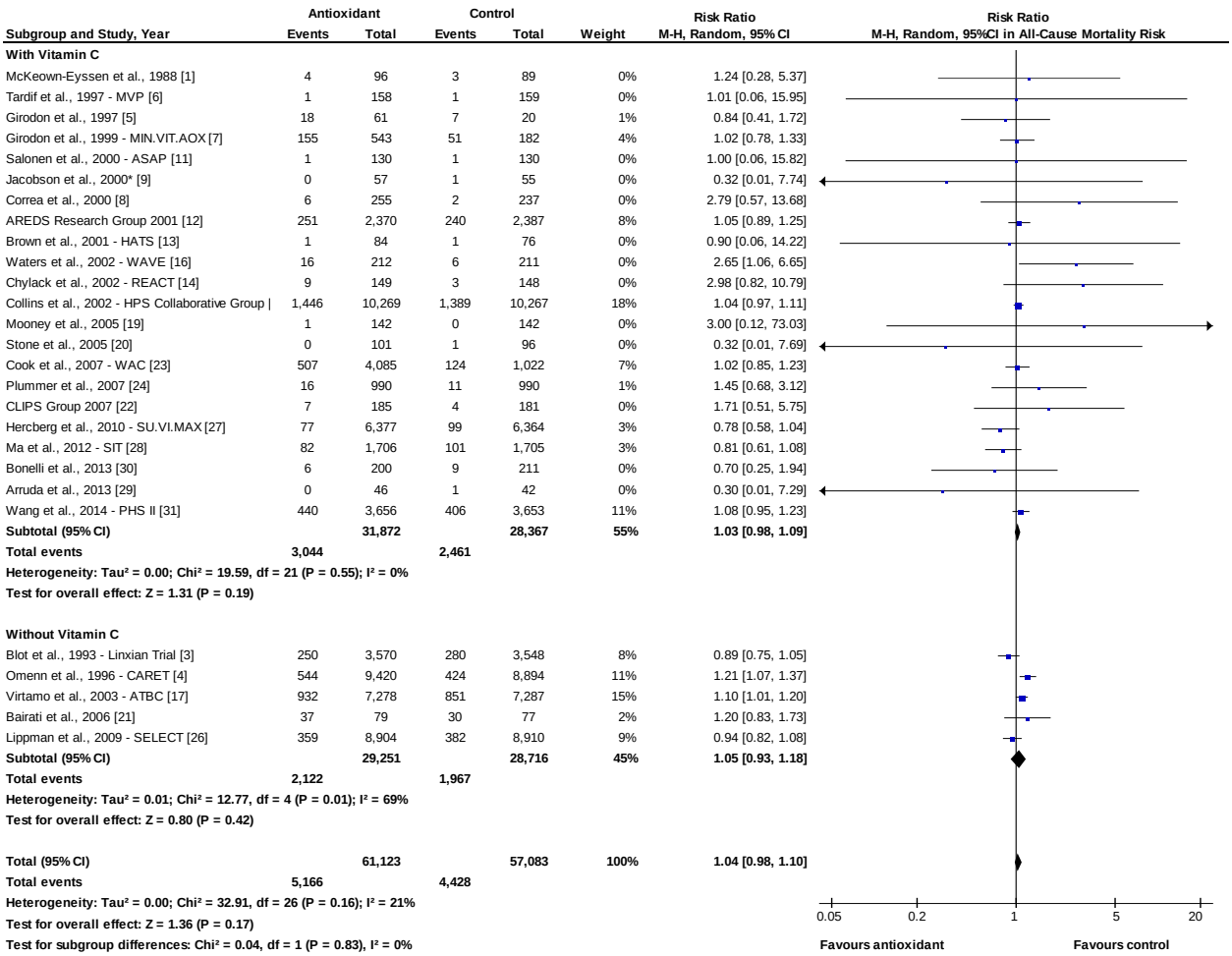
Supplementary Figure 64. Sensitivity analysis of antioxidant supplementation and stroke mortality risk for studies with and without vitamin C. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



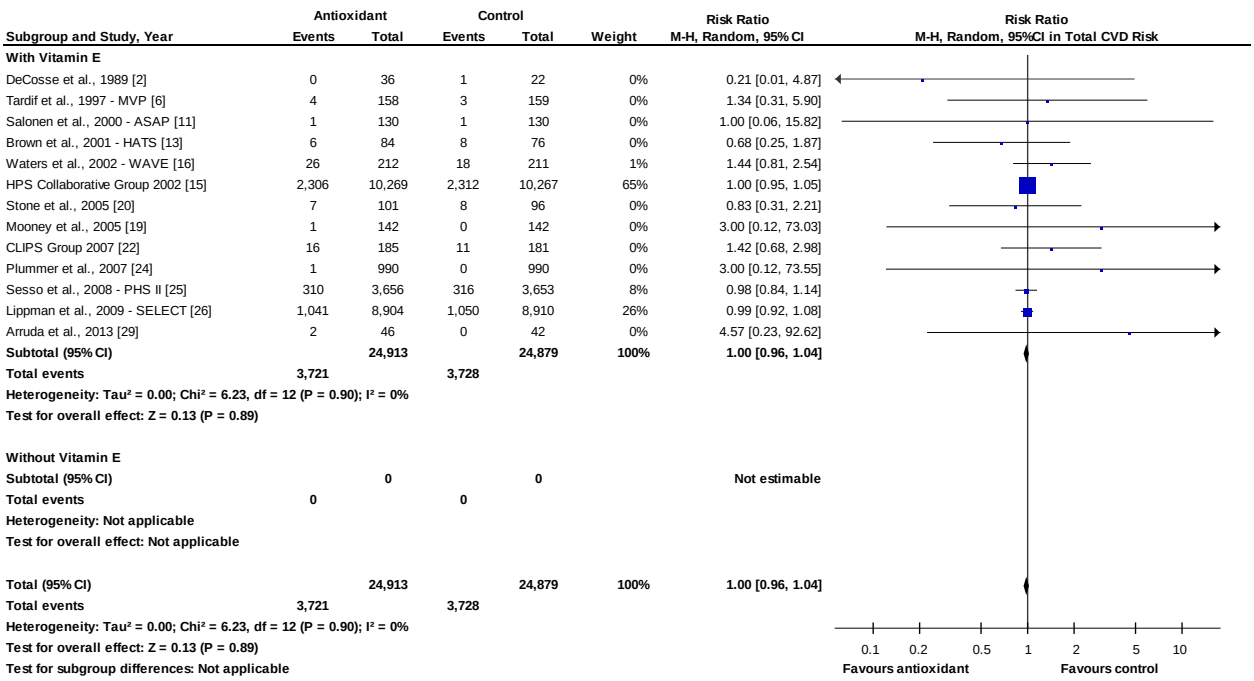
Supplementary Figure 65. Sensitivity analysis of antioxidant supplementation and total cancer risk for studies with and without vitamin C. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



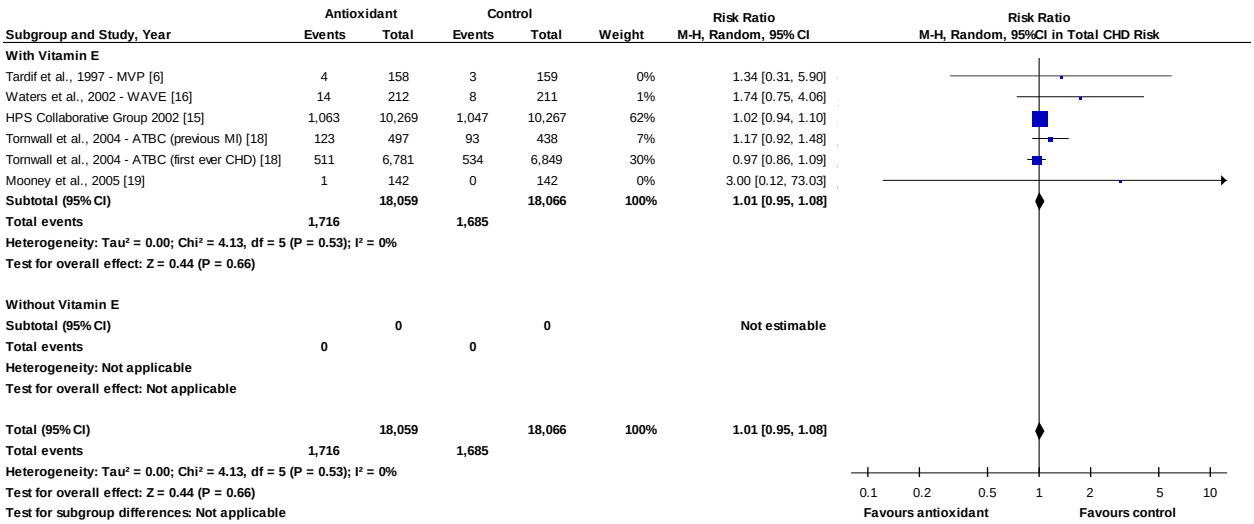
Supplementary Figure 66. Sensitivity analysis of antioxidant supplementation and cancer mortality risk for studies with and without vitamin C. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



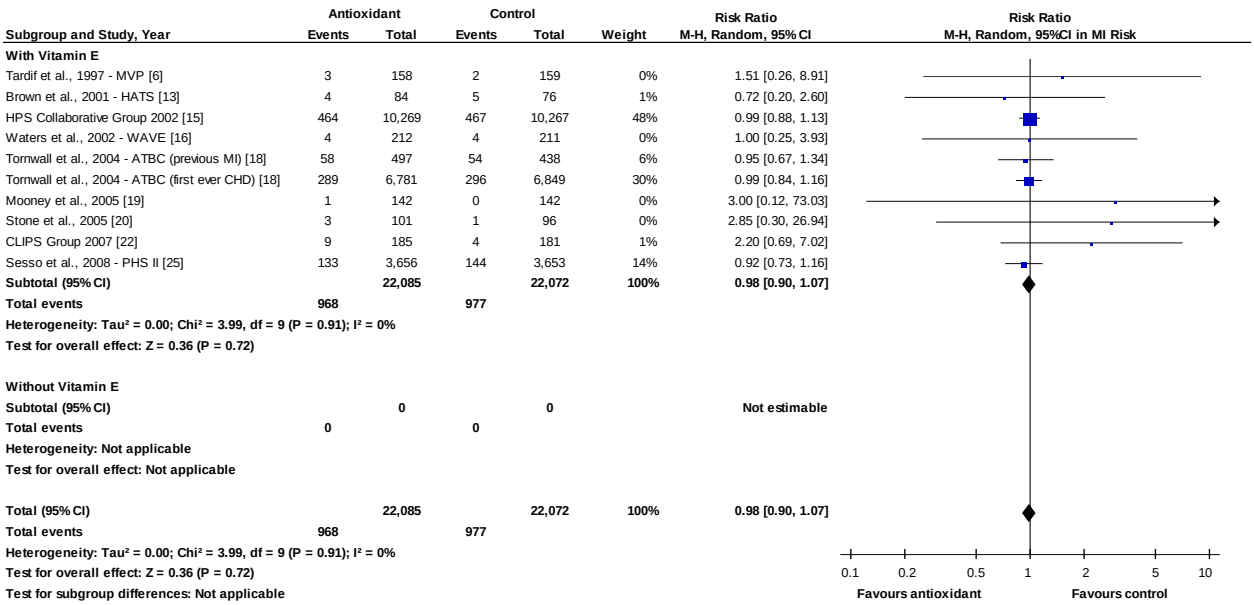
Supplementary Figure 67. Sensitivity analysis of antioxidant supplementation and all-cause mortality risk for studies with and without vitamin C. M-H, Manthel-Haenszel. ***Jacobson et al., 2000 – data retrieved from meta-analysis Bjelakovic 2012 (44).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random.



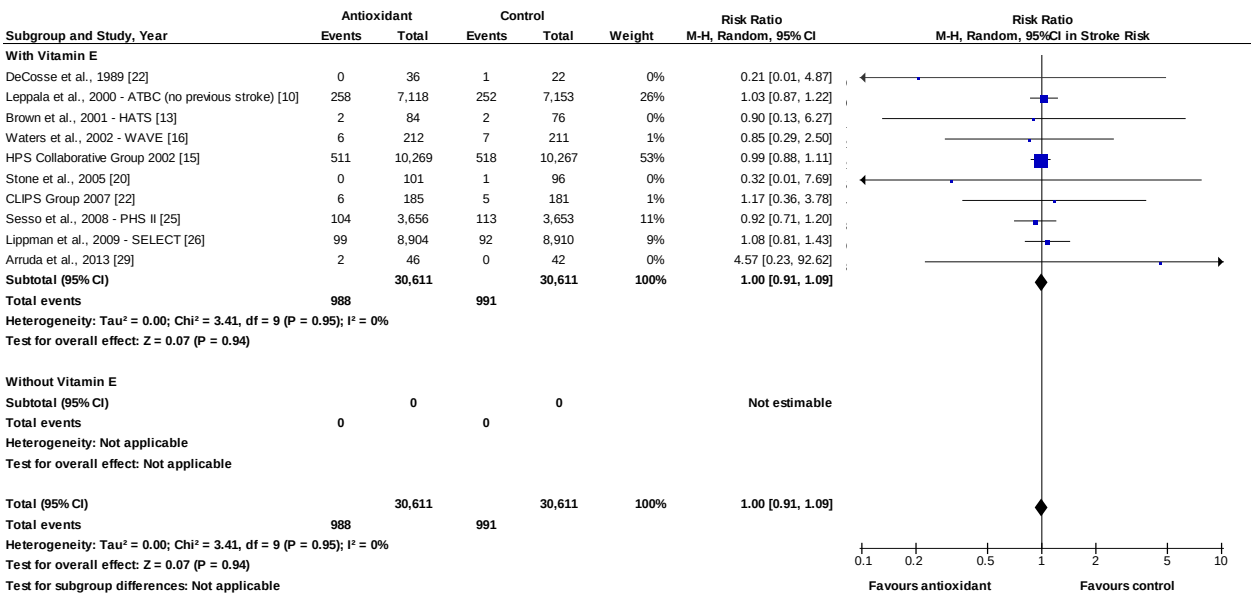
Supplementary Figure 68. Sensitivity analysis of antioxidant supplementation and total CVD risk for studies with and without vitamin E. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



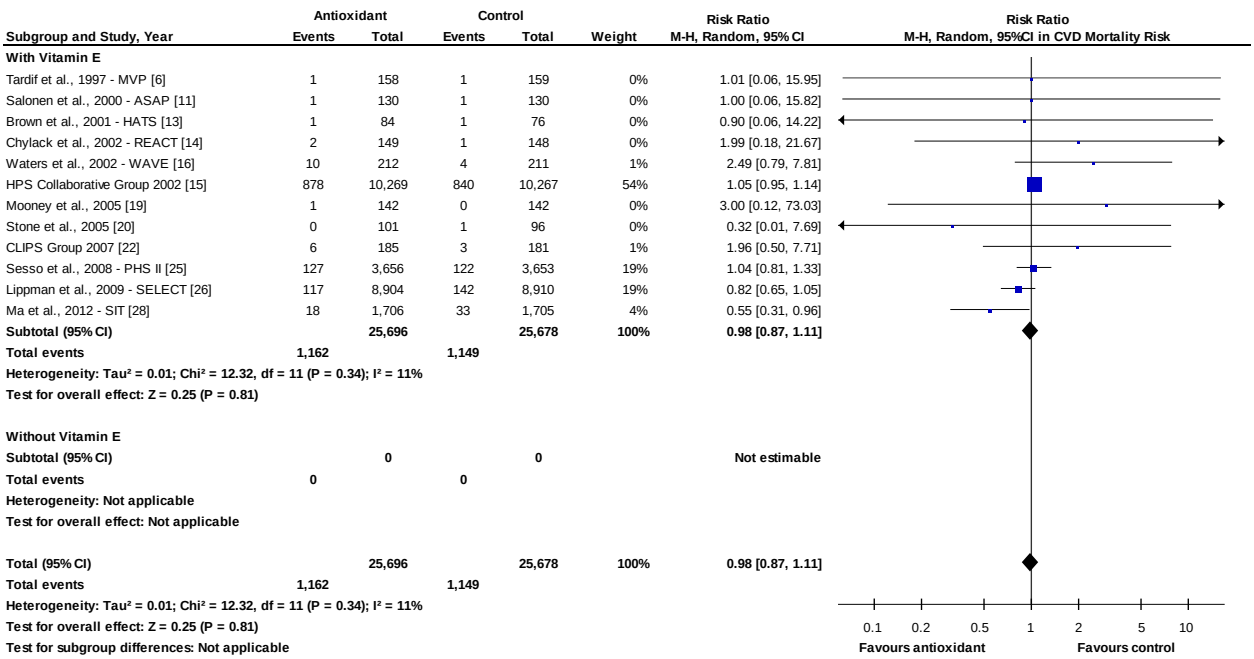
Supplementary Figure 69. Sensitivity analysis of antioxidant supplementation and total CHD risk for studies with and without vitamin E. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



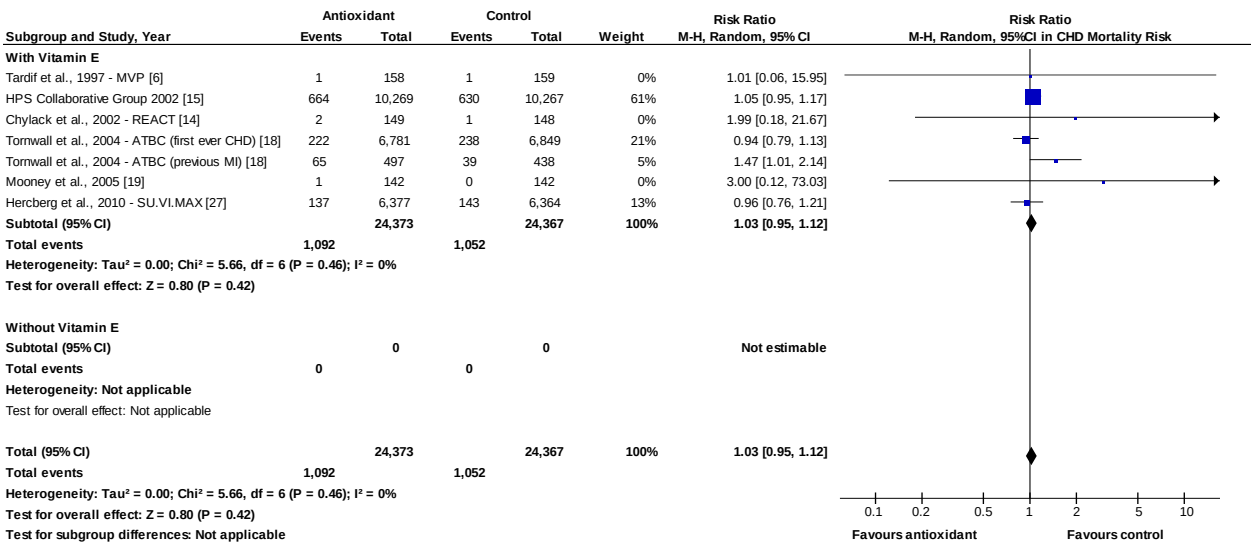
Supplementary Figure 70. Sensitivity analysis of antioxidant supplementation and MI risk for studies with and without vitamin E. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



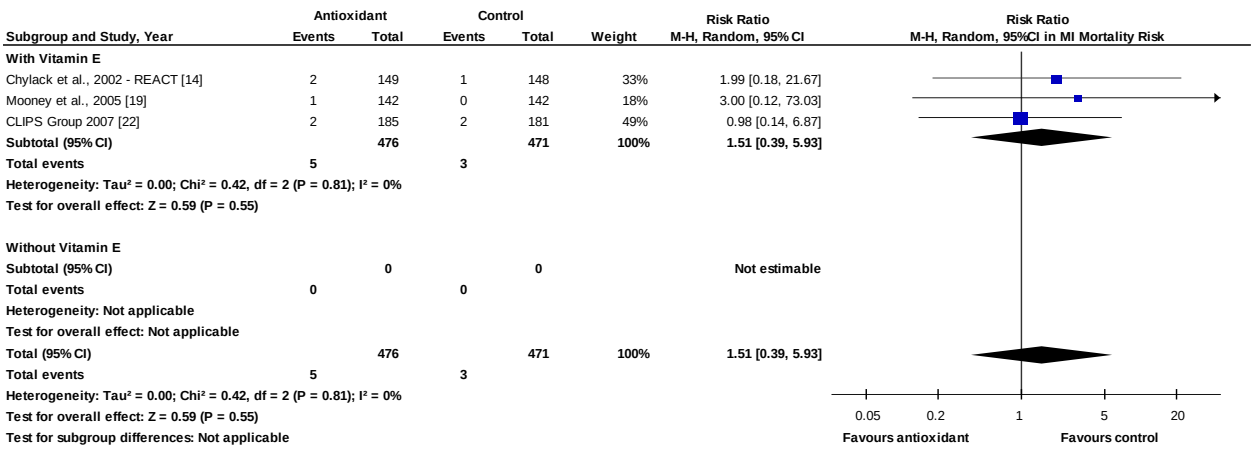
Supplementary Figure 71. Sensitivity analysis of antioxidant supplementation and stroke risk for studies with and without vitamin E. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



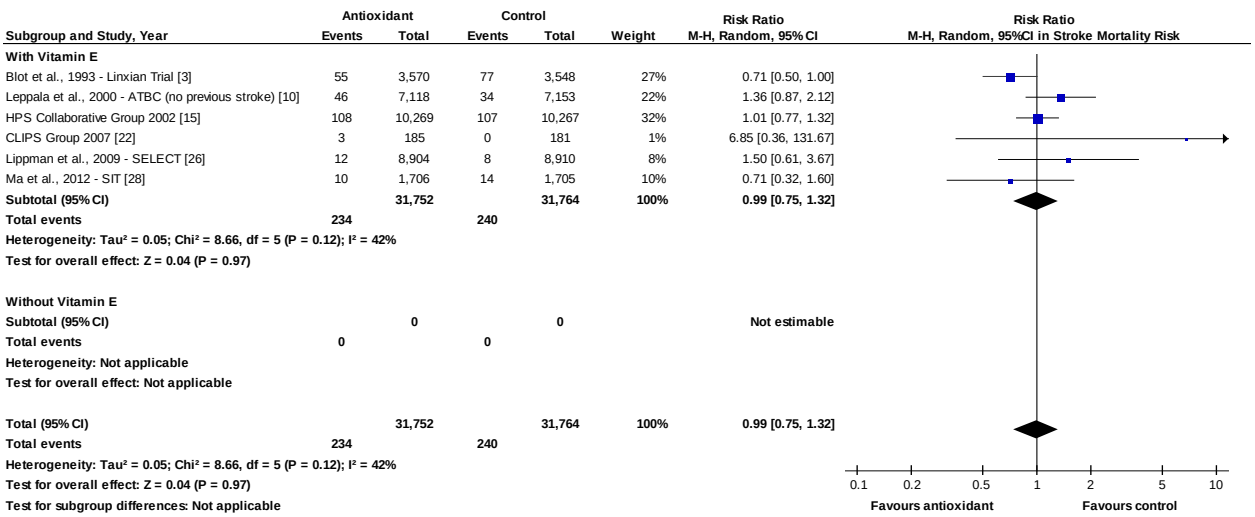
Supplementary Figure 72. Sensitivity analysis of antioxidant supplementation and CVD mortality risk for studies with and without vitamin E. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



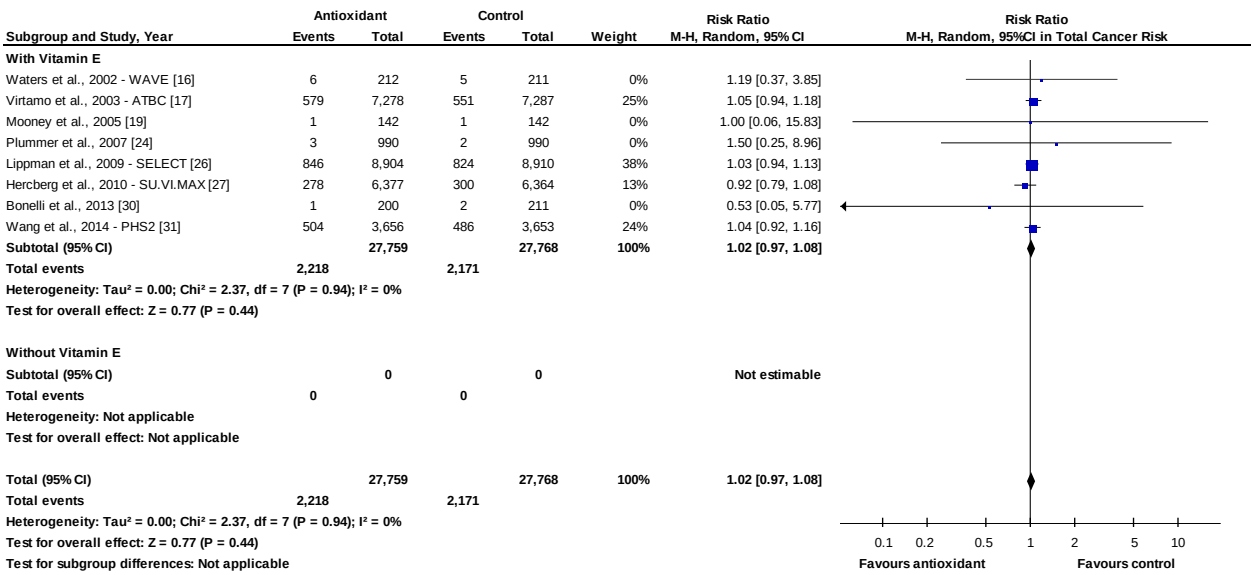
Supplementary Figure 73. Sensitivity analysis of antioxidant supplementation and CHD mortality risk for studies with and without vitamin E. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



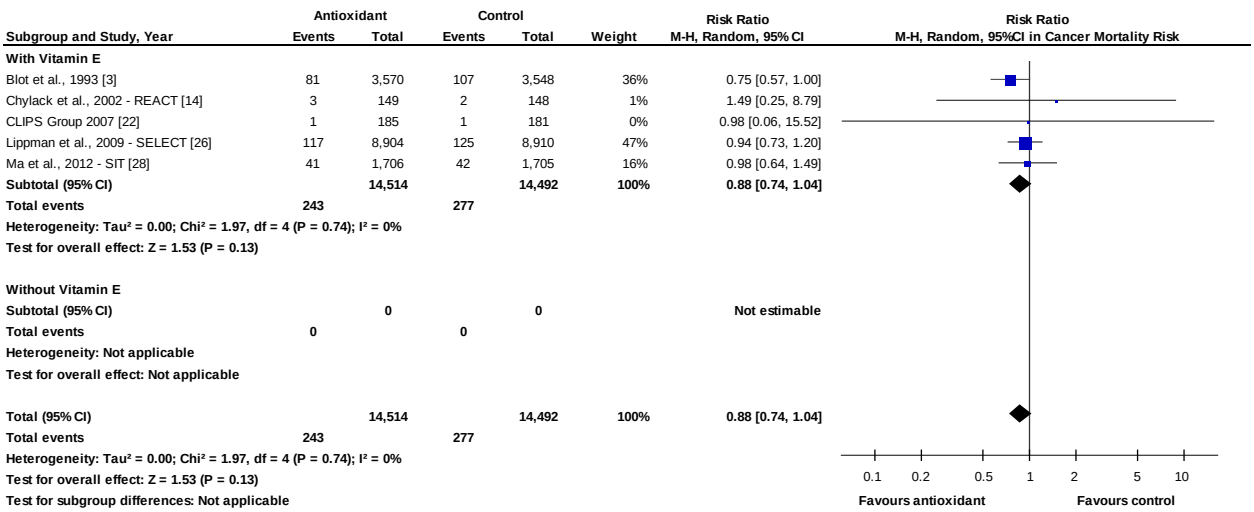
Supplementary Figure 74. Sensitivity analysis of antioxidant supplementation and MI mortality risk for studies with and without vitamin E. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



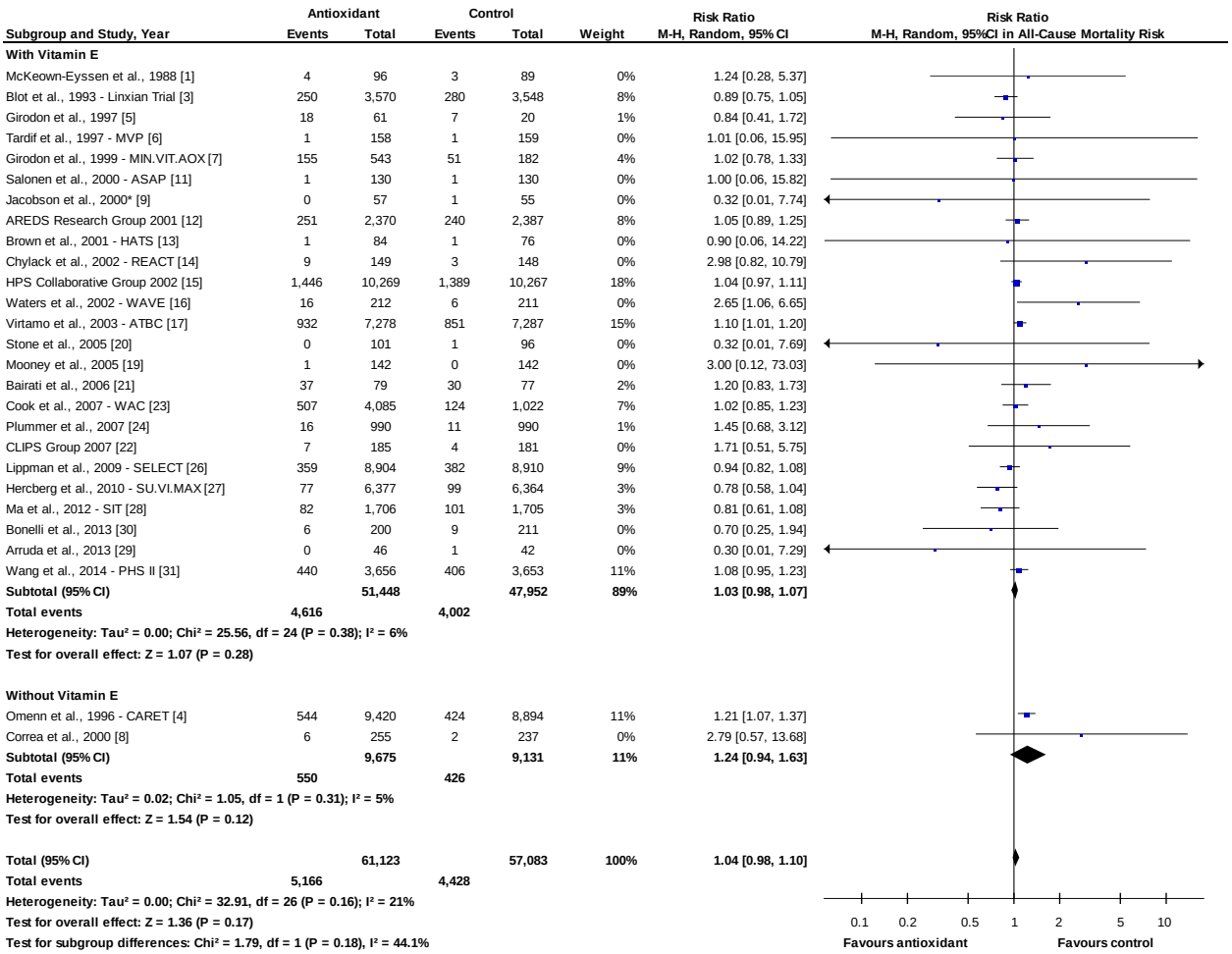
Supplementary Figure 75. Sensitivity analysis of antioxidant supplementation and stroke mortality risk for studies with and without vitamin E. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



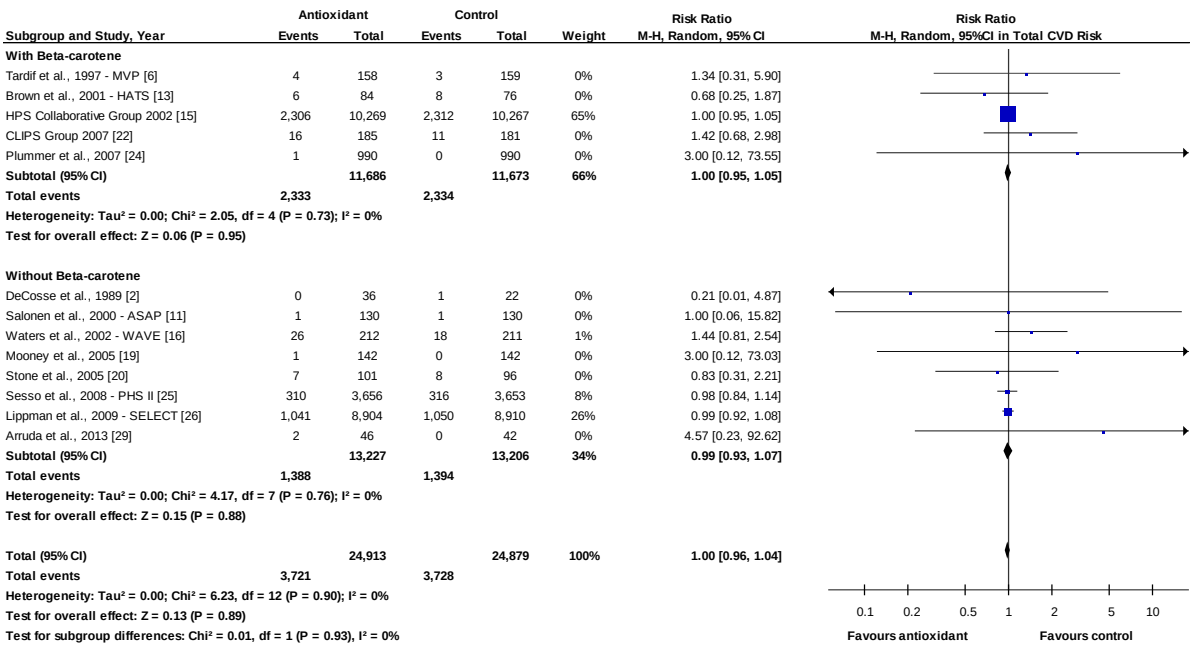
Supplementary Figure 76. Sensitivity analysis of antioxidant supplementation and total cancer risk for studies with and without vitamin E. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



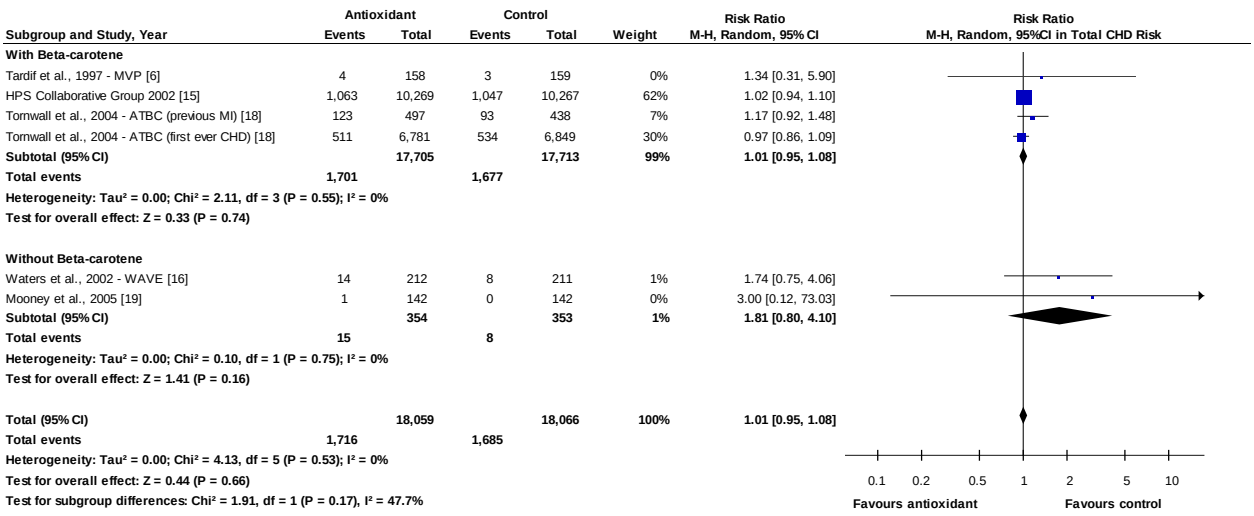
Supplementary Figure 77. Sensitivity analysis of antioxidant supplementation and cancer mortality risk for studies with and without vitamin E. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of P < 0.10, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



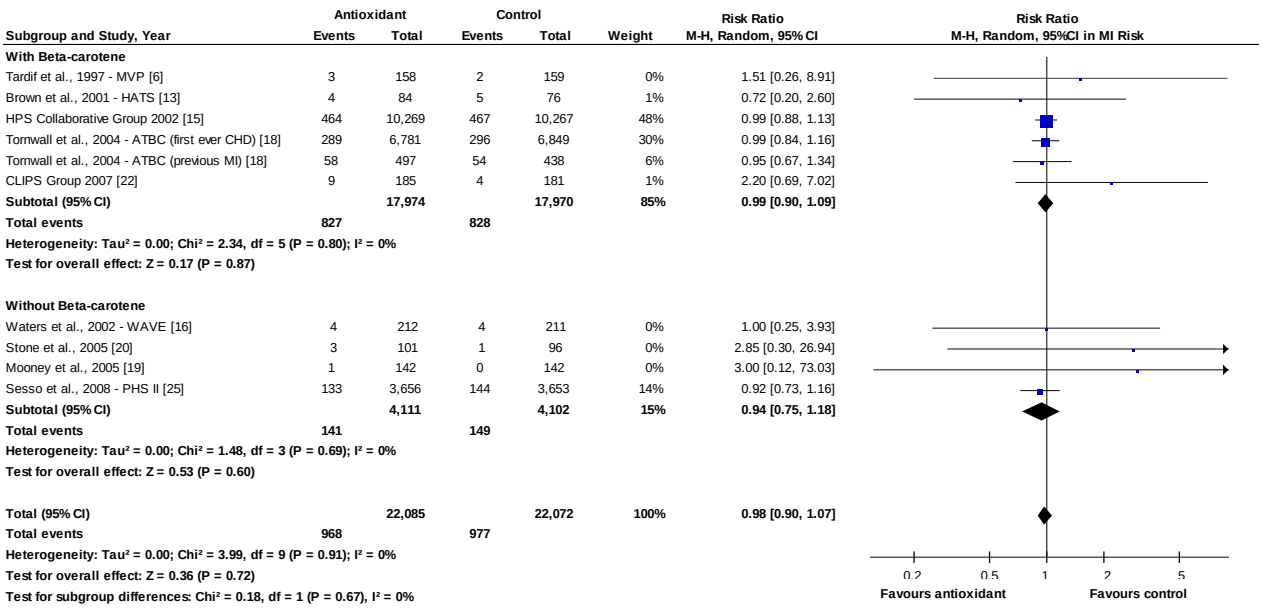
Supplementary Figure 78. Sensitivity analysis of antioxidant supplementation and all-cause mortality risk for studies with and without vitamin E. M-H, Manthel-Haenszel. ***Jacobson et al., 2000 – Data retrieved from meta-analysis Bjelakovic 2012 (44).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects.



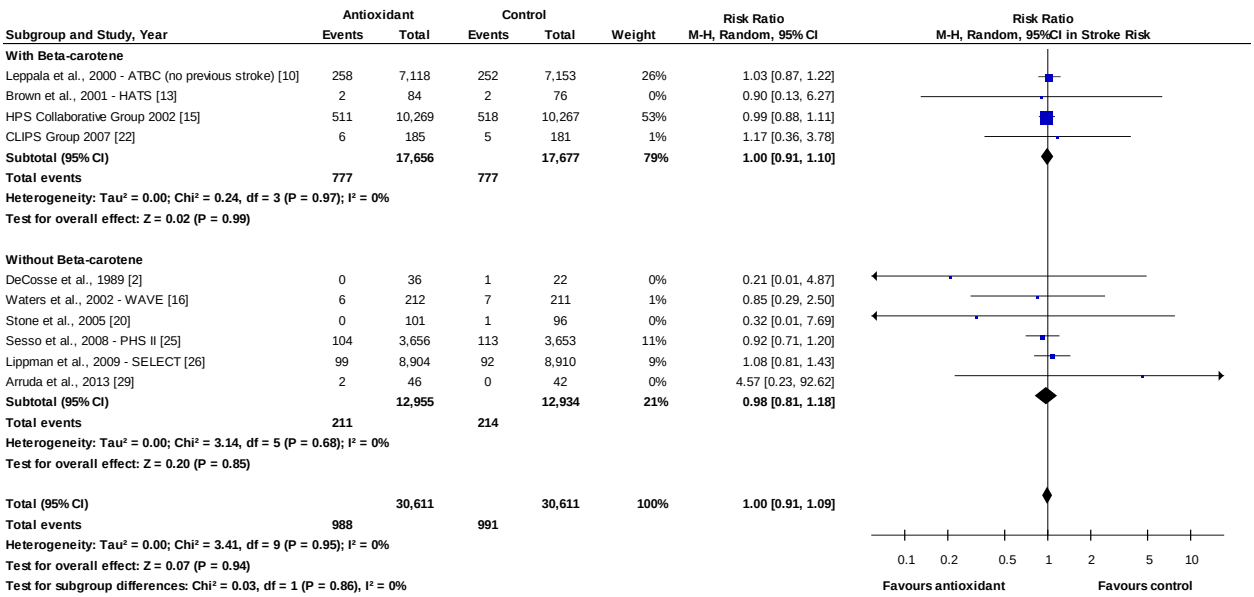
Supplementary Figure 79. Sensitivity analysis of antioxidant supplementation and total CVD risk for studies with and without beta-carotene. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



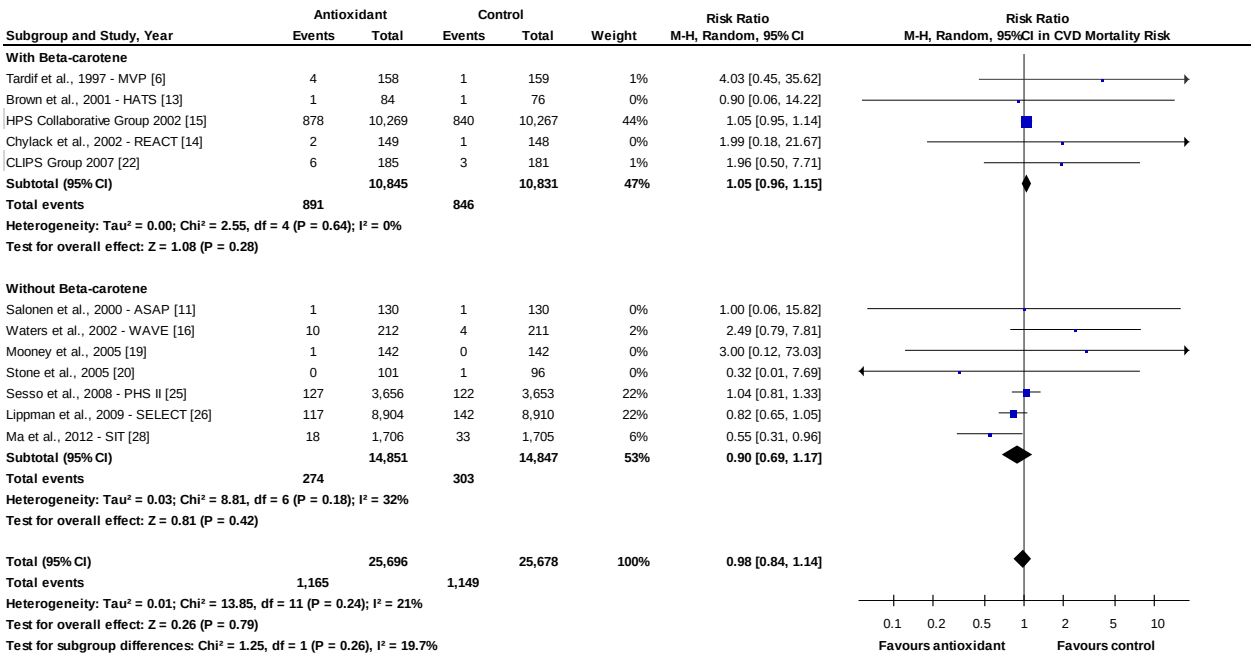
Supplementary Figure 80. Sensitivity analysis of antioxidant supplementation and total CHD risk for studies with and without beta-carotene. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



Supplementary Figure 81. Sensitivity analysis of antioxidant supplementation and MI risk for studies with and without beta-carotene. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

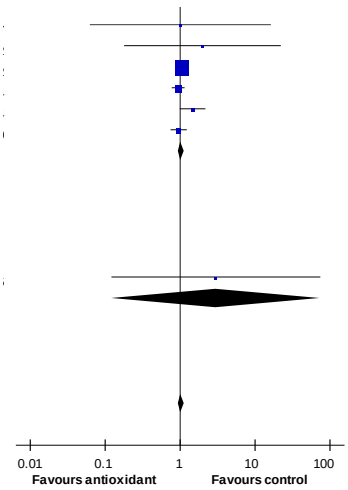


Supplementary Figure 82. Sensitivity analysis of antioxidant supplementation and stroke risk for studies with and without beta-carotene. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

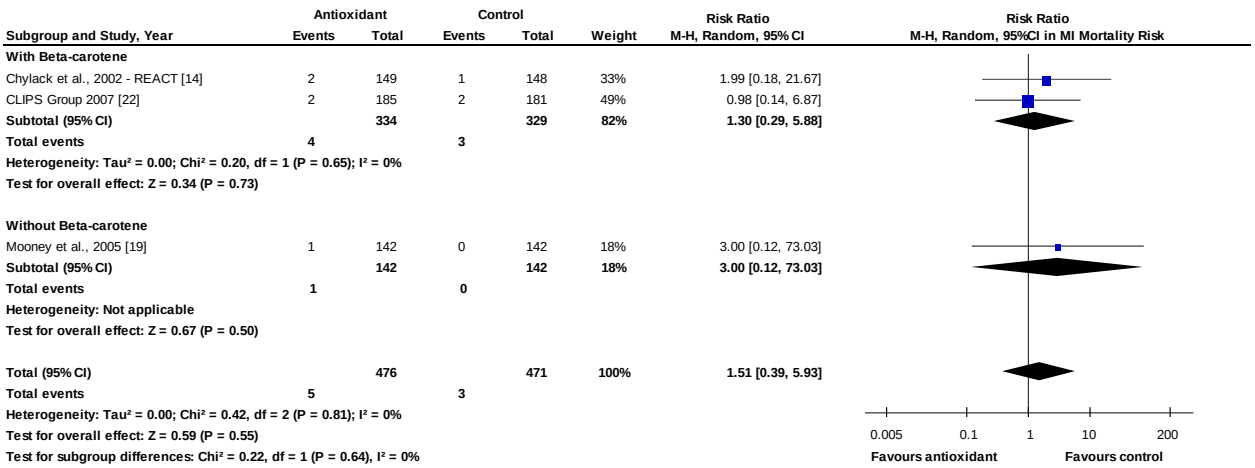


Supplementary Figure 83. Sensitivity analysis of antioxidant supplementation and CVD mortality risk for studies with and without beta-carotene. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

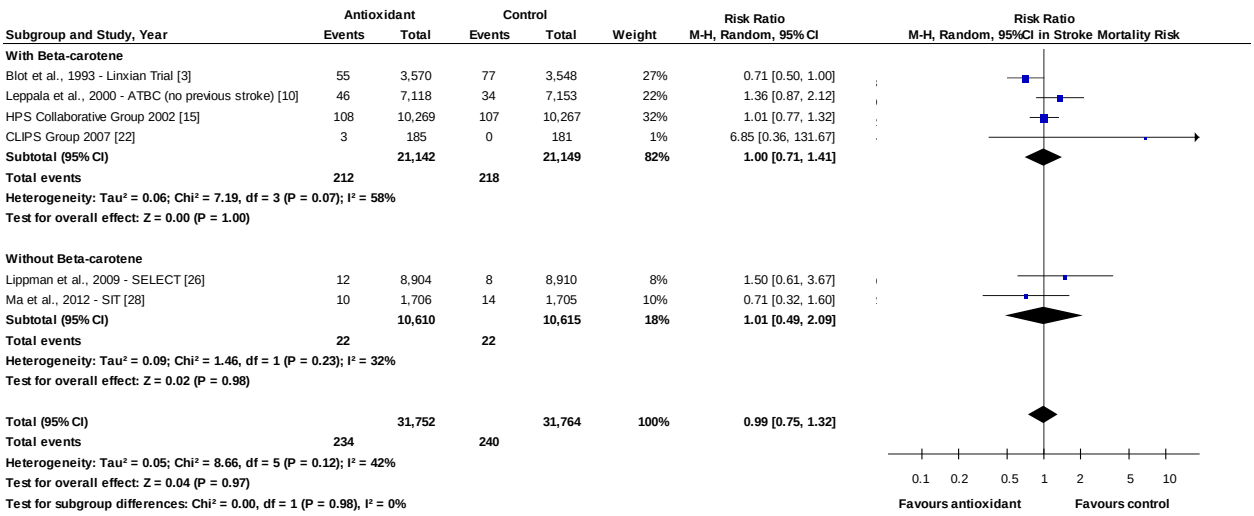
Subgroup and Study, Year	Antioxidant Events	Antioxidant Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
With Beta-carotene						
Tardif et al., 1997 - MVP [6]	1	158	1	159	0%	1.01 [0.06, 15.95]
Chylack et al.., 2002 - REACT [14]	2	149	1	148	0%	1.99 [0.18, 21.67]
HPS Collaborative Group 2002 [15]	664	10,269	630	10,267	61%	1.05 [0.95, 1.17]
Tornwall et al., 2004 - ATBC (first ever CHD) [18]	222	6,781	238	6,849	21%	0.94 [0.79, 1.13]
Tornwall et al., 2004 - ATBC (previous MI) [18]	65	497	39	438	5%	1.47 [1.01, 2.14]
Hercberg et al., 2010 - SU.VI.MAX [27]	137	6,377	143	6,364	13%	0.96 [0.76, 1.21]
Subtotal (95% CI)		**24,231**		**24,225**	**100%**	**1.03 [0.94, 1.13]**
Total events	**1,091**		**1,052**			
Heterogeneity: Tau² = 0.00; Chi² = 5.23, df = 5 (P = 0.39); I² = 4%						
Test for overall effect: Z = 0.71 (P = 0.48)						
Without Beta-carotene						
Mooney et al., 2005 [19]	1	142	0	142	0%	3.00 [0.12, 73.03]
Subtotal (95% CI)		**142**		**142**	**0%**	**3.00 [0.12, 73.03]**
Total events	**1**		**0**			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**24,373**		**24,367**	**100%**	**1.03 [0.95, 1.12]**
Total events	**1,092**		**1,052**			
Heterogeneity: Tau² = 0.00; Chi² = 5.66, df = 6 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.42)						
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%						



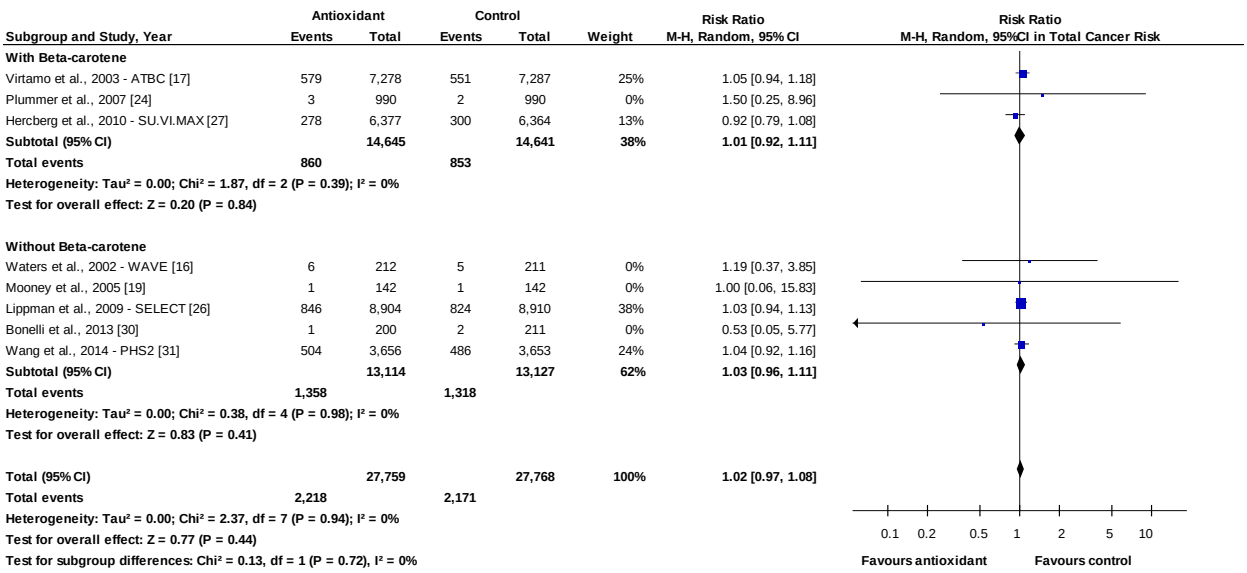
Supplementary Figure 84. Sensitivity analysis of antioxidant supplementation and CHD mortality risk for studies with and without beta-carotene. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



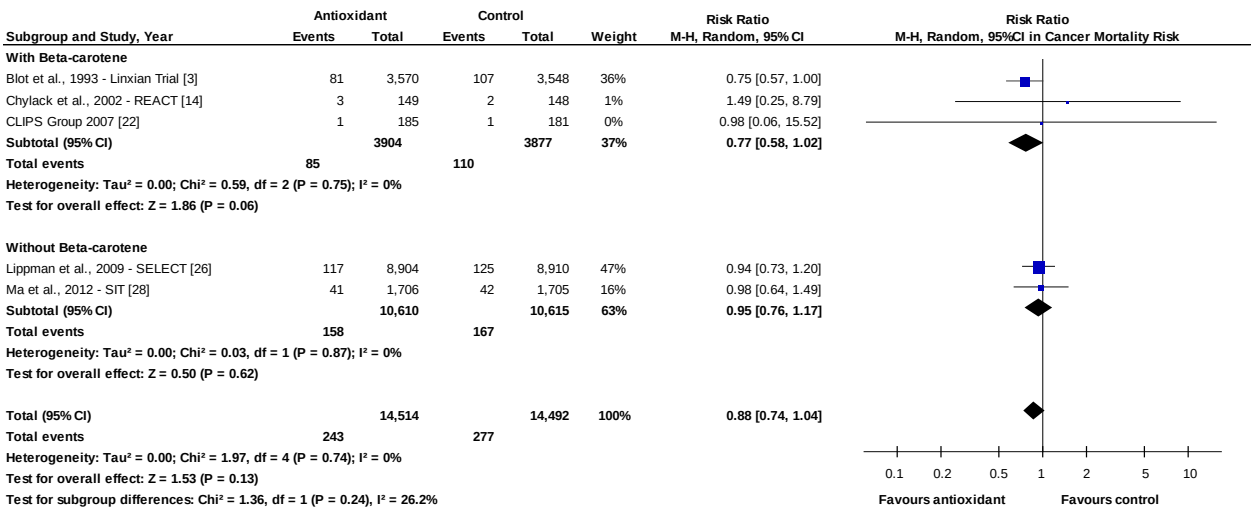
Supplementary Figure 85. Sensitivity analysis of antioxidant supplementation and MI mortality risk for studies with and without beta-carotene. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



Supplementary Figure 86. Sensitivity analysis of antioxidant supplementation and stroke mortality risk for studies with and without beta-carotene. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

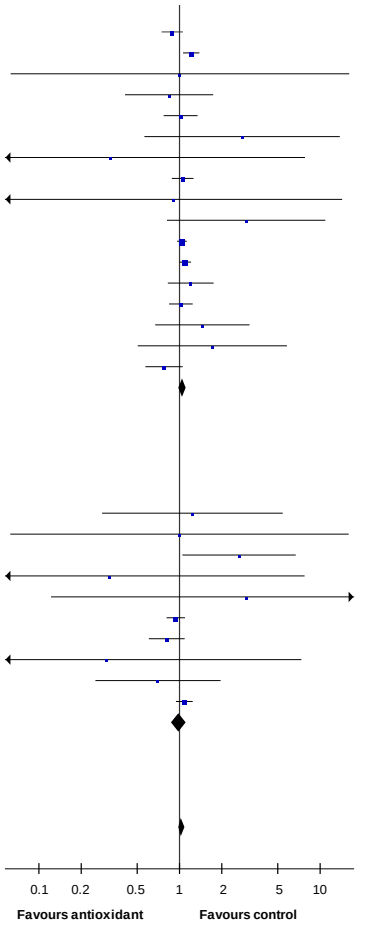


Supplementary Figure 87. Sensitivity analysis of antioxidant supplementation and total cancer risk for studies with and without beta-carotene. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

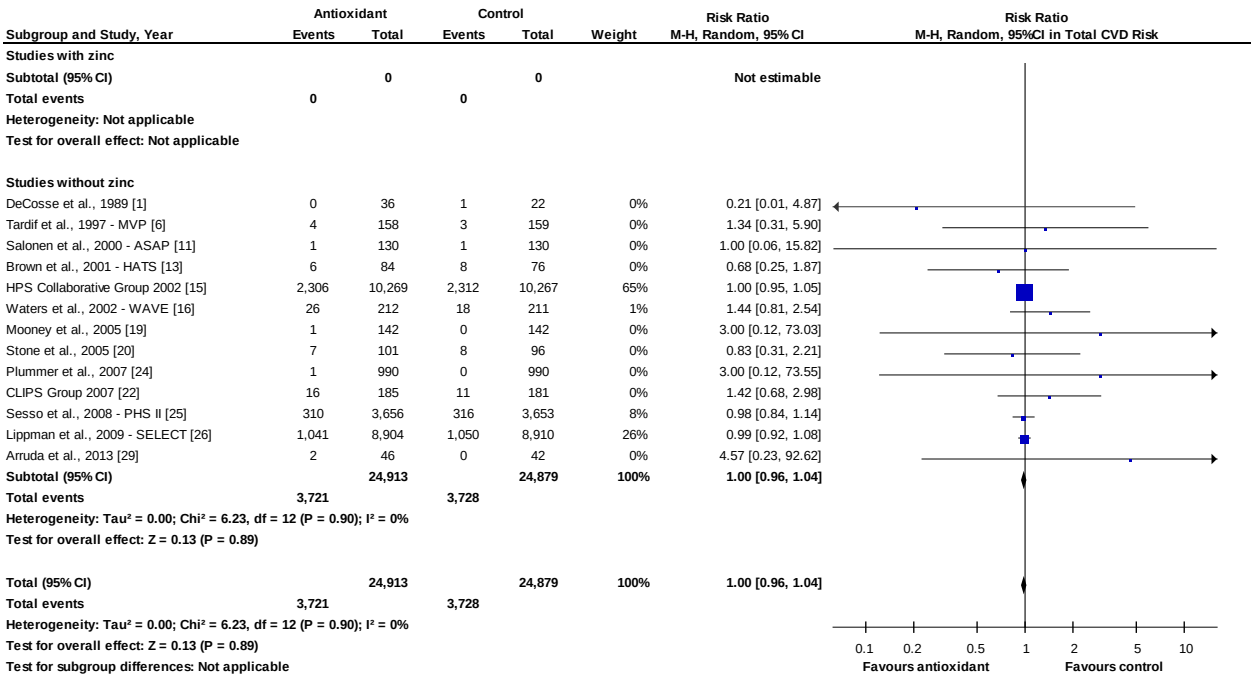


Supplementary Figure 88. Sensitivity analysis of antioxidant supplementation and cancer mortality risk for studies with and without beta-carotene. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

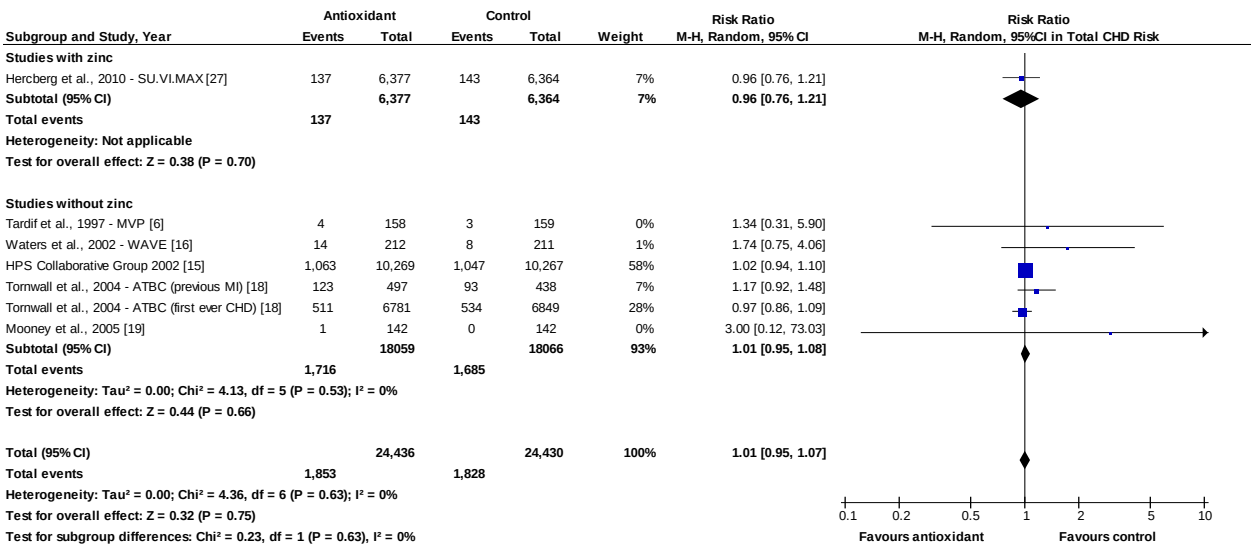
Subgroup and Study, Year	Antioxidant Events	Antioxidant Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
With Beta-carotene						
Blot et al., 1993 - Linxian Trial [3]	250	3,570	280	3,548	8%	0.89 [0.75, 1.05]
Omenn et al., 1996 - CARET [4]	544	9,420	424	8,894	11%	1.21 [1.07, 1.37]
Tardif et al., 1997 - MVP [6]	1	158	1	159	0%	1.01 [0.06, 15.95]
Girodon et al., 1997 [5]	18	61	7	20	1%	0.84 [0.41, 1.72]
Girodon et al., 1999 - MIN.VIT.AOX [7]	155	543	51	182	4%	1.02 [0.78, 1.33]
Correa et al., 2000 [8]	6	255	2	237	0%	2.79 [0.57, 13.68]
Jacobson et al., 2000 [9]	0	57	1	55	0%	0.32 [0.01, 7.74]
AREDS Research Group 2001 [12]	251	2,370	240	2,387	8%	1.05 [0.89, 1.25]
Brown et al., 2001 - HATS [13]	1	84	1	76	0%	0.90 [0.06, 14.22]
Chylack et al., 2002 - REACT [14]	9	149	3	148	0%	2.98 [0.82, 10.79]
HPS Collaborative Group 2002 [15]	1446	10269	1389	10267	18%	1.04 [0.97, 1.11]
Virtamo et al., 2003 - ATBC [17]	932	7278	851	7287	15%	1.10 [1.01, 1.20]
Bairati et al., 2006 [21]	37	79	30	77	2%	1.20 [0.83, 1.73]
Cook et al., 2007 - WAC [23]	507	4085	124	1022	7%	1.02 [0.85, 1.23]
Plummer et al., 2007 [24]	16	990	11	990	1%	1.45 [0.68, 3.12]
CLIPS Group 2007 [22]	7	185	4	181	0%	1.71 [0.51, 5.75]
Hercberg et al., 2010 - SU.VI.MAX [27]	77	6,377	99	6,364	3%	0.78 [0.58, 1.04]
Subtotal (95% CI)		**45,930**		**41,894**	**76%**	**1.05 [0.99, 1.12]**
Total events	**4,257**		**3,518**			
Heterogeneity: Tau² = 0.00; Chi² = 20.91, df = 16 (P = 0.18); I² = 23%						
Test for overall effect: Z = 1.66 (P = 0.10)						
Without Beta-carotene						
McKeown-Eyssen et al., 1988 [1]	4	96	3	89	0%	1.24 [0.28, 5.37]
Salonen et al., 2000 - ASAP [11]	1	130	1	130	0%	1.00 [0.06, 15.82]
Waters et al., 2002 - WAVE [16]	16	212	6	211	0%	2.65 [1.06, 6.65]
Stone et al., 2005 [20]	0	101	1	96	0%	0.32 [0.01, 7.69]
Mooney et al., 2005 [19]	1	142	0	142	0%	3.00 [0.12, 73.03]
Lippman et al., 2009 - SELECT [26]	359	8,904	382	8,910	9%	0.94 [0.82, 1.08]
Ma et al., 2012 - SIT [28]	82	1,706	101	1,705	3%	0.81 [0.61, 1.08]
Arruda et al., 2013 [29]	0	46	1	42	0%	0.30 [0.01, 7.29]
Bonelli et al., 2013 [30]	6	200	9	211	0%	0.70 [0.25, 1.94]
Wang et al., 2014 - PHS II [31]	440	3,656	406	3,653	11%	1.08 [0.95, 1.23]
Subtotal (95% CI)		**15,193**		**15,189**	**24%**	**0.99 [0.87, 1.12]**
Total events	**909**		**910**			
Heterogeneity: Tau² = 0.01; Chi² = 10.70, df = 9 (P = 0.30); I² = 16%						
Test for overall effect: Z = 0.16 (P = 0.87)						
Total (95% CI)		**61,123**		**57,083**	**100%**	**1.04 [0.98, 1.10]**
Total events	**5,166**		**4,428**			
Heterogeneity: Tau² = 0.00; Chi² = 32.91, df = 26 (P = 0.16); I² = 21%						



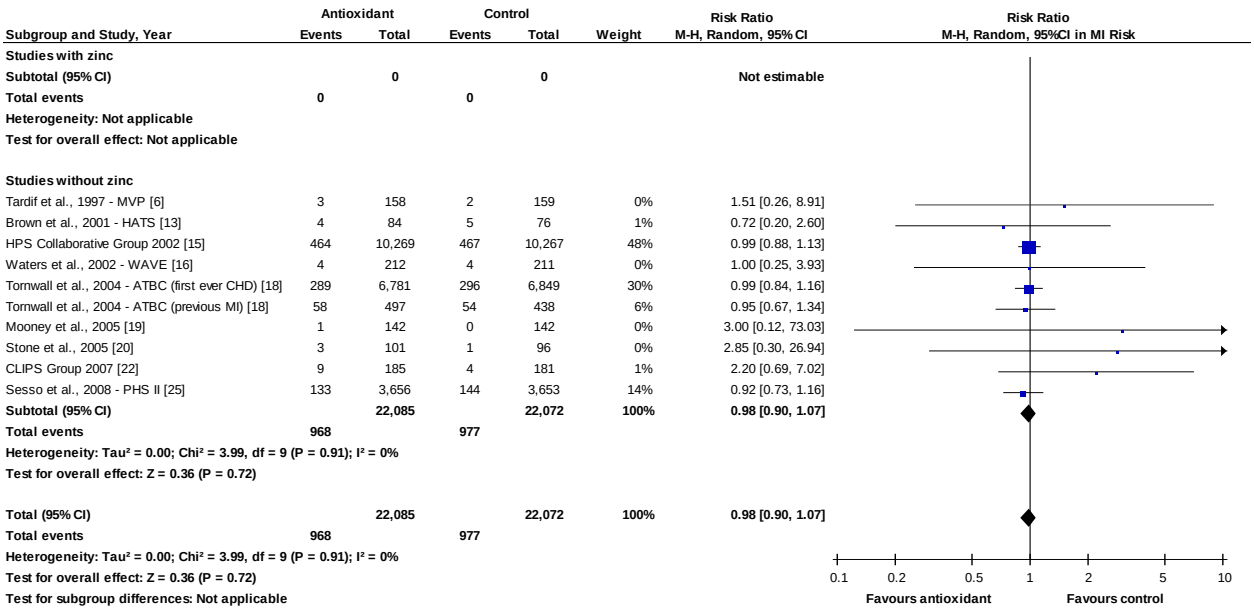
Supplementary Figure 89. Sensitivity analysis of antioxidant supplementation and all-cause mortality risk for studies with and without beta-carotene. M-H, Manthel-Haenszel. ***Jacobson et al., 2000 – Data retrieved from meta-analysis Bjelakovic 2012 (44).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random.



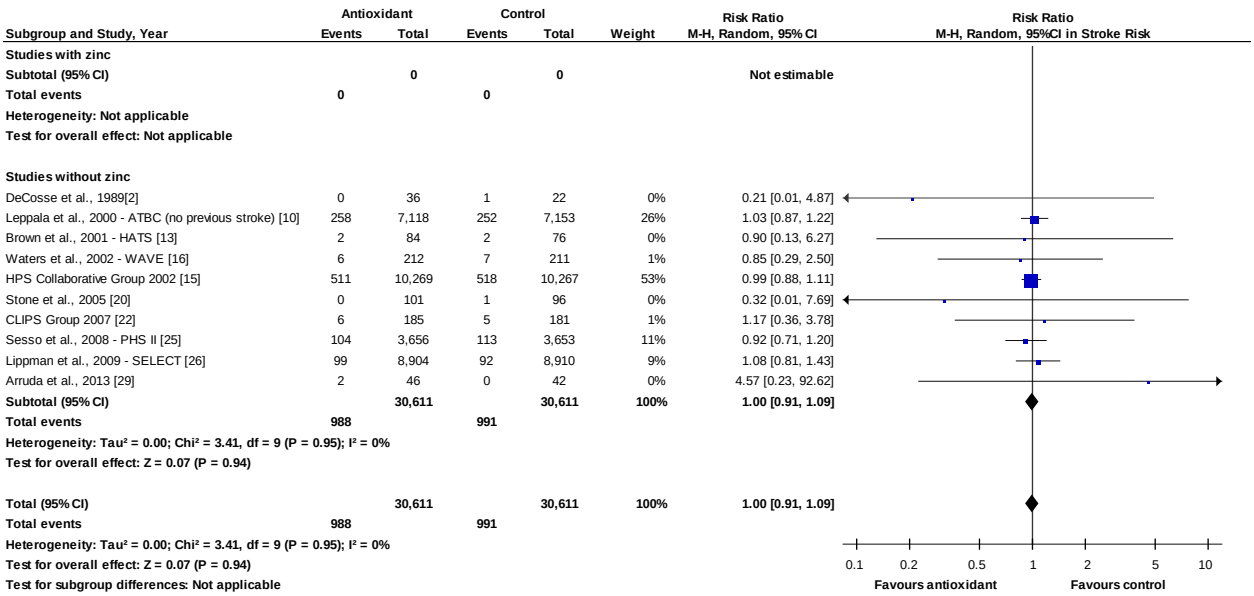
Supplementary Figure 90. Sensitivity analysis of antioxidant supplementation and total CVD risk for studies with and without zinc. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



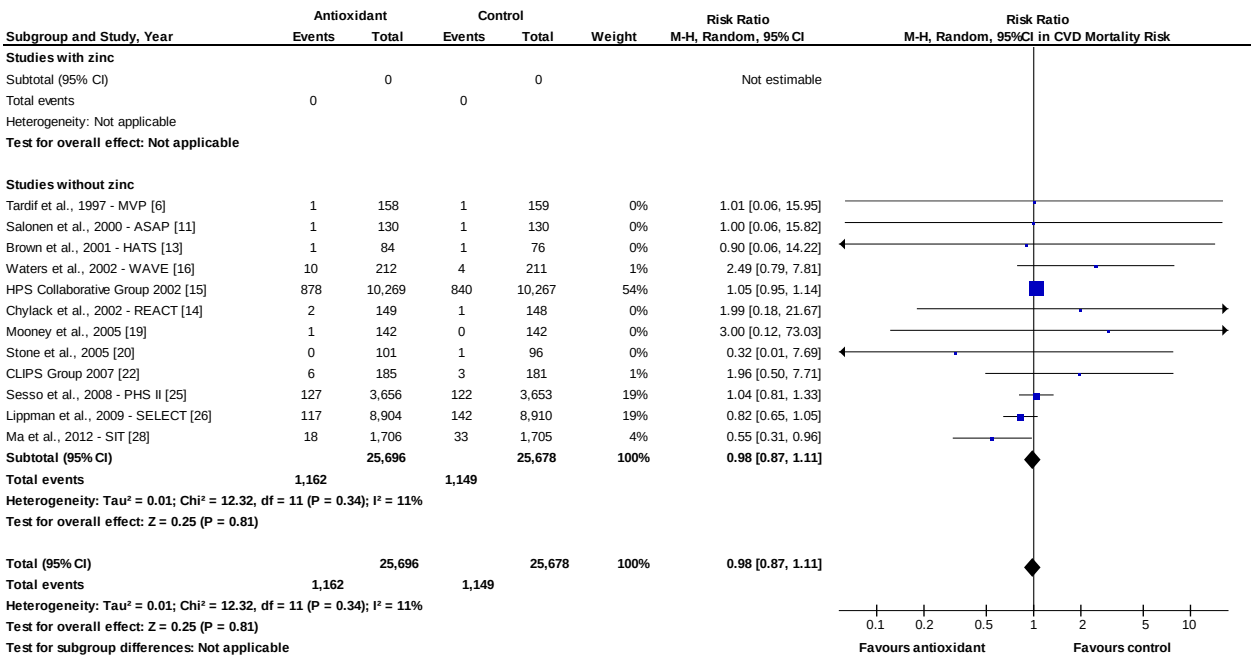
Supplementary Figure 91. Sensitivity analysis of antioxidant supplementation and total CHD risk for studies with and without zinc. Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



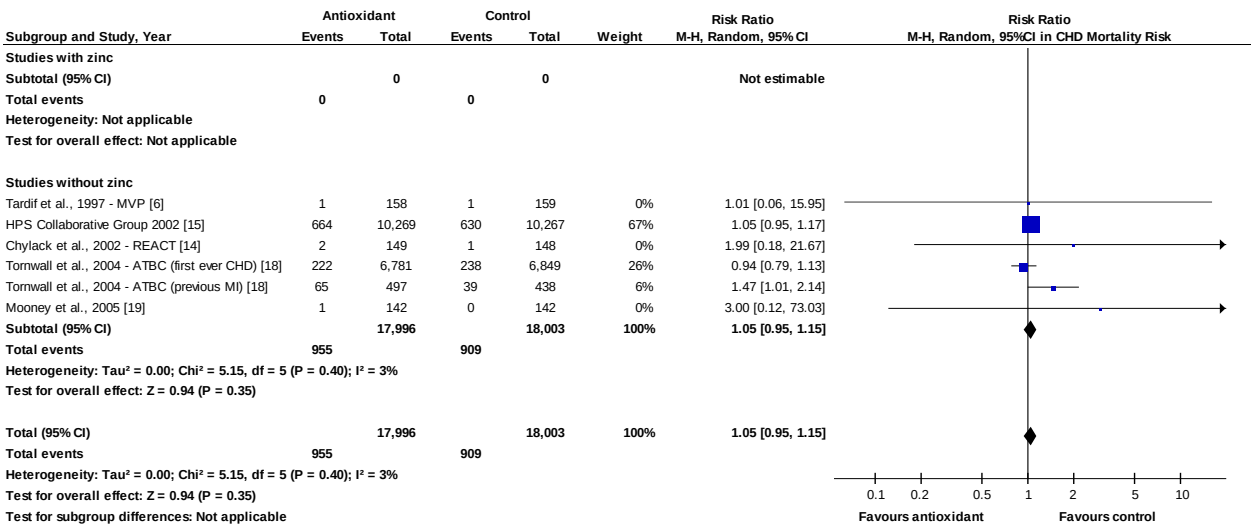
Supplementary Figure 92. Sensitivity analysis of antioxidant supplementation and MI risk for studies with and without zinc. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



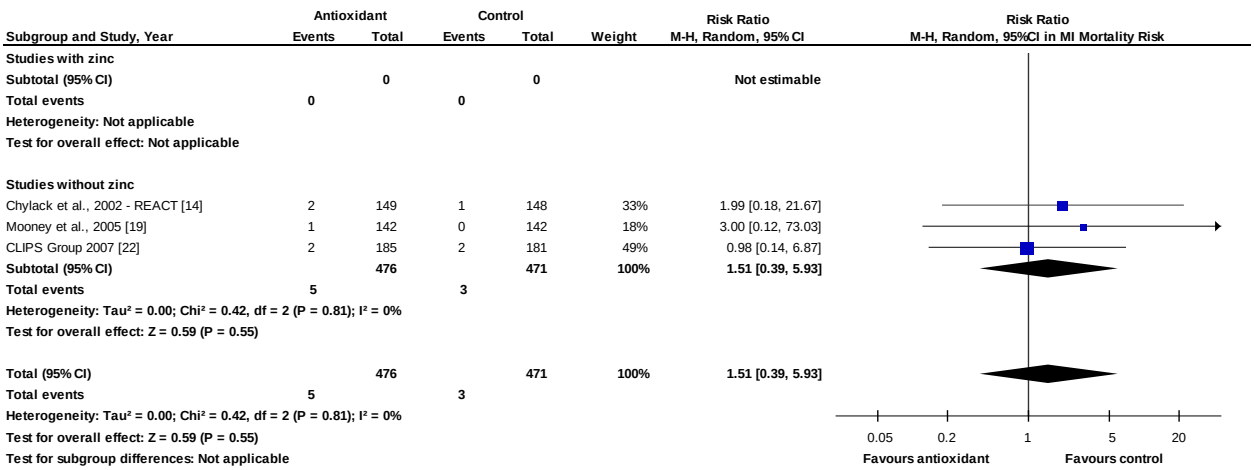
Supplementary Figure 93. Sensitivity analysis of antioxidant supplementation and stroke risk for studies with and without zinc. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



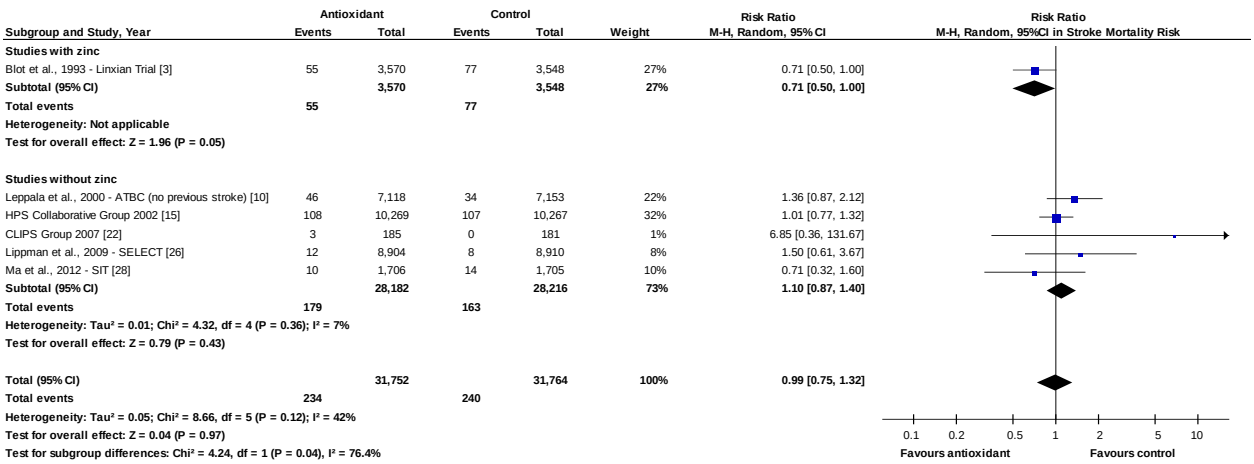
Supplementary Figure 94. Sensitivity analysis of antioxidant supplementation and CVD mortality risk for studies with and without zinc. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



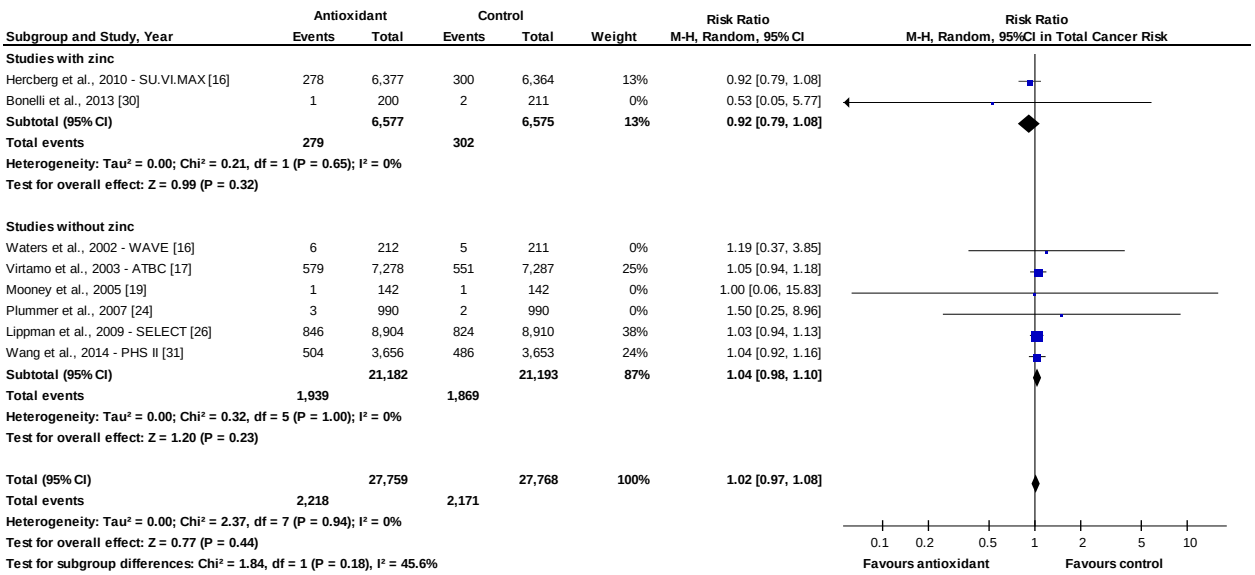
Supplementary Figure 95. Sensitivity analysis of antioxidant supplementation and CHD mortality risk for studies with and without zinc. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



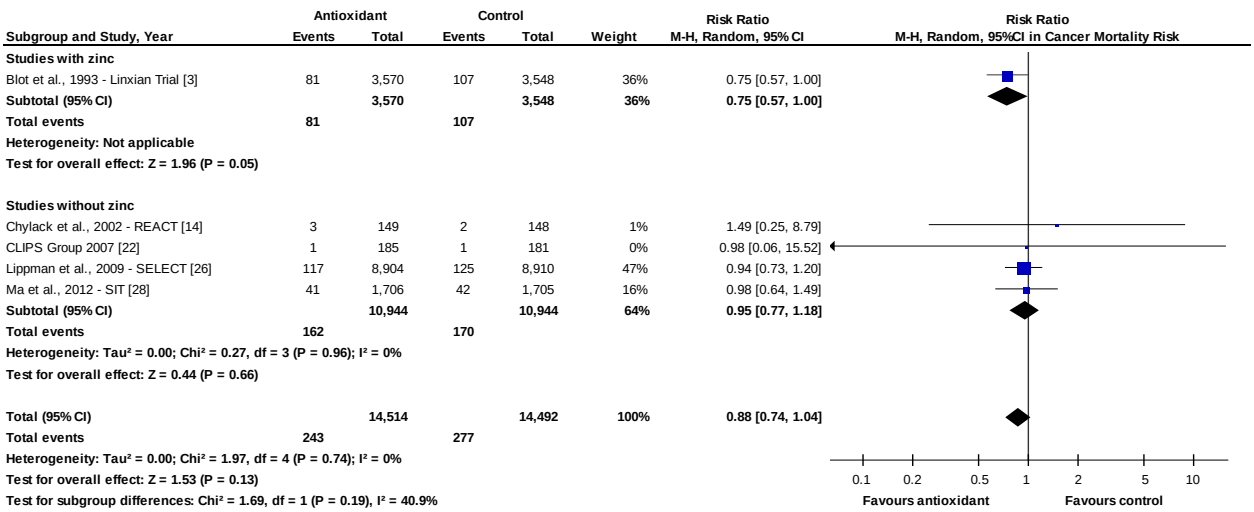
Supplementary Figure 96. Sensitivity analysis of antioxidant supplementation and MI mortality risk for studies with and without zinc. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



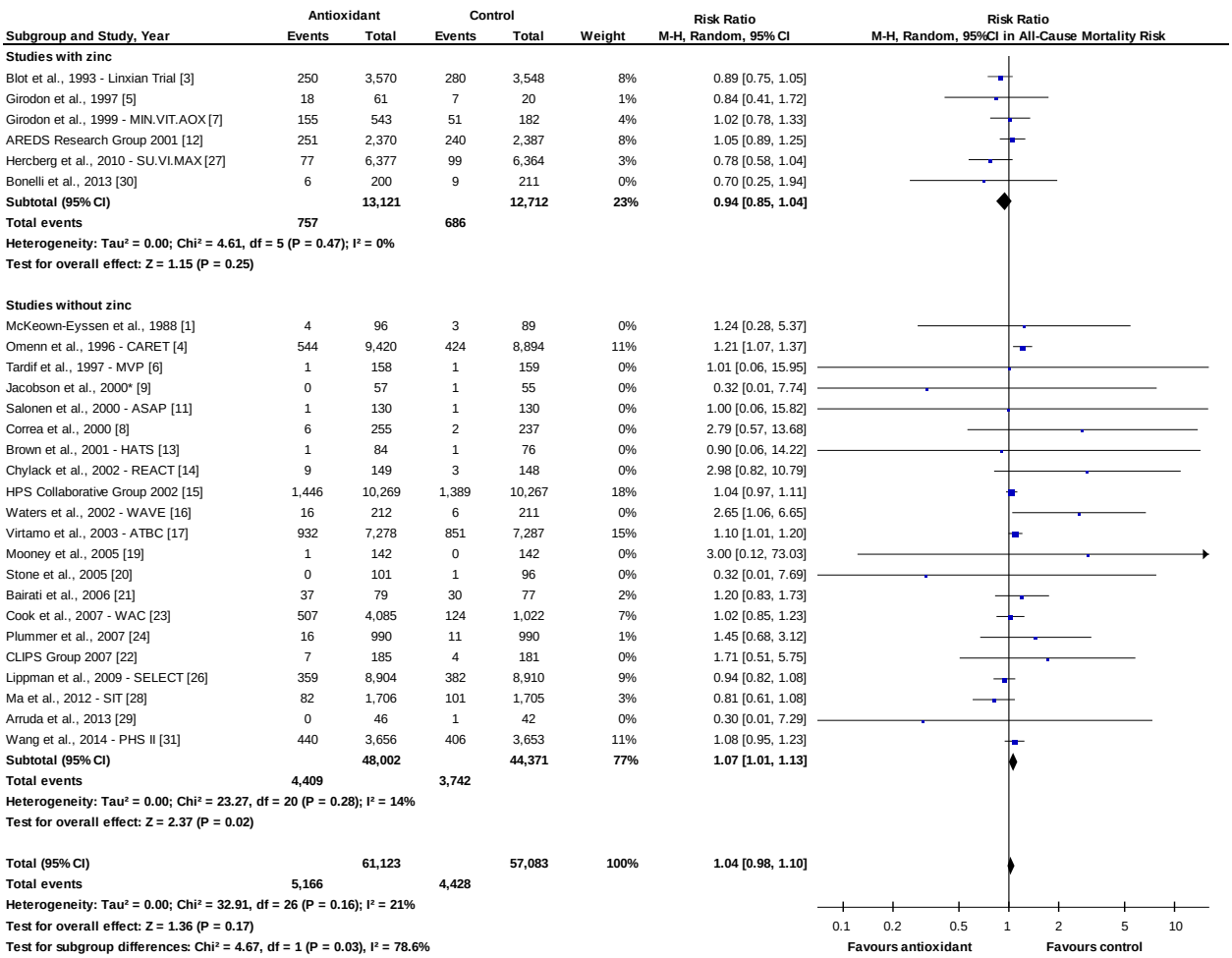
Supplementary Figure 97. Sensitivity analysis of antioxidant supplementation and stroke mortality risk for studies with and without zinc. NNT for antioxidant supplementation and stroke mortality risk for studies with zinc is 159. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



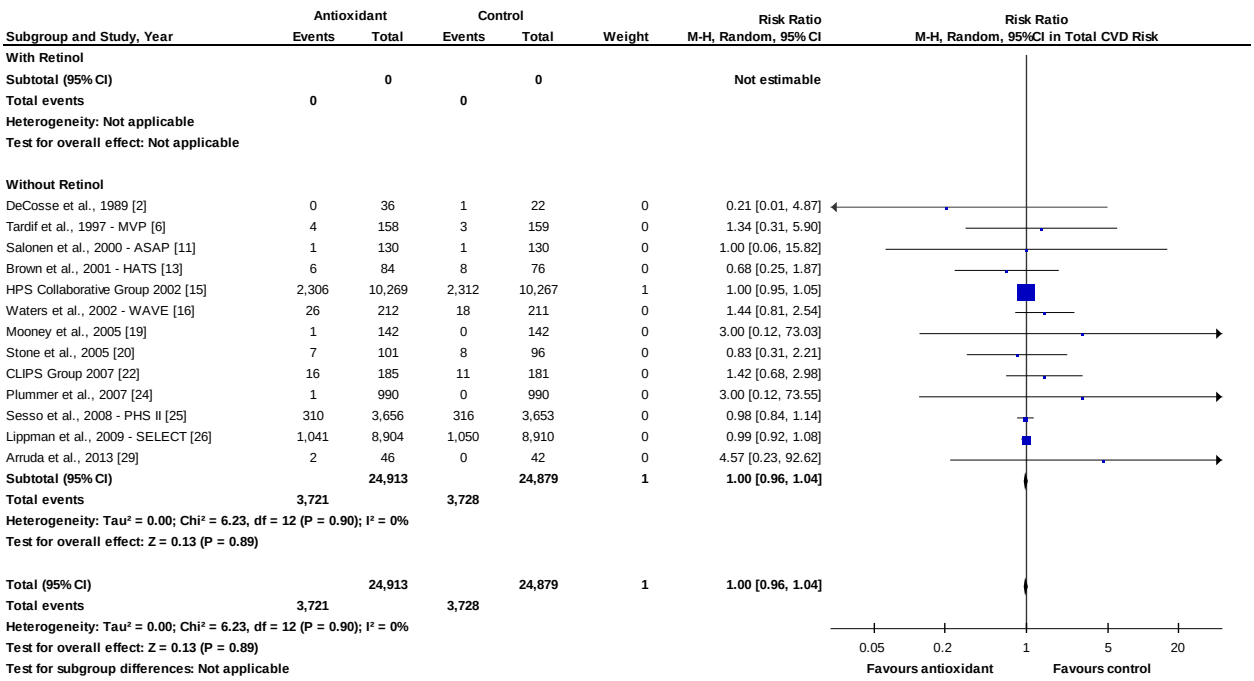
Supplementary Figure 98. Sensitivity analysis of antioxidant supplementation and total cancer risk for studies with and without zinc. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



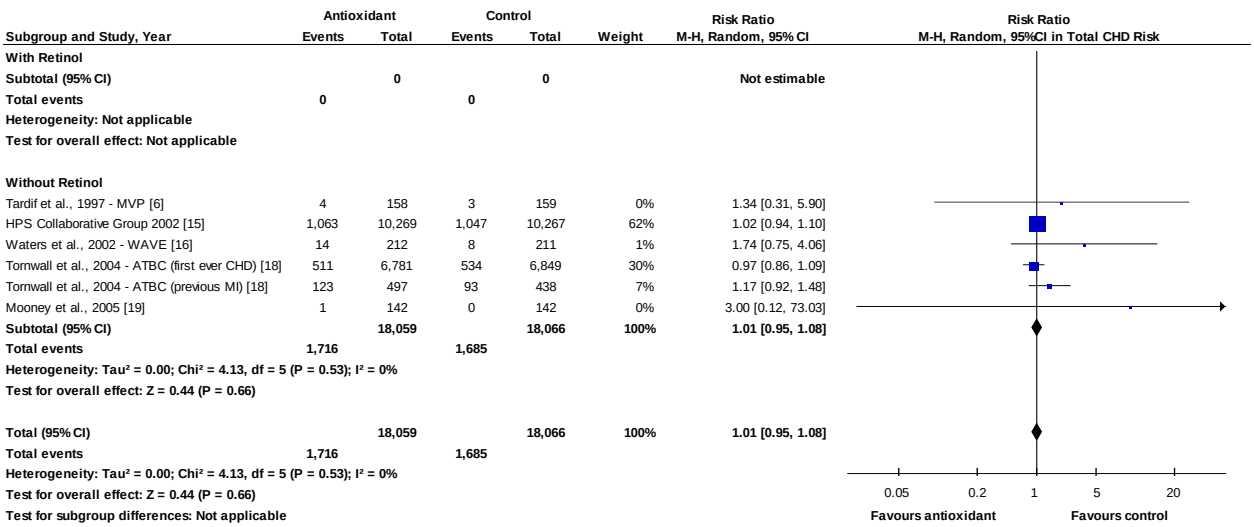
Supplementary Figure 99. Sensitivity analysis of antioxidant supplementation and cancer mortality risk for studies with and without zinc. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



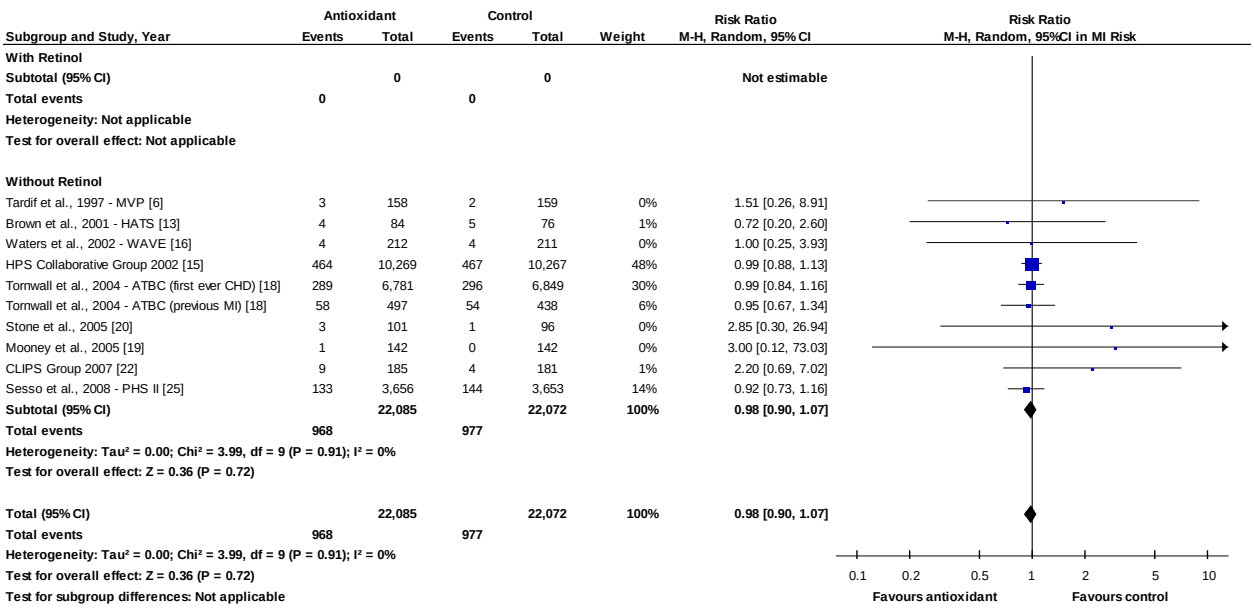
Supplementary Figure 100. Sensitivity analysis of antioxidant supplementation and all-cause mortality risk for studies with and without zinc. NNH for antioxidant supplementation and all-cause mortality risk for studies without zinc is 169. M-H, Manthel-Haenszel. ***Jacobson et al., 2000 – Data retrieved from meta-analysis Bjelakovic 2012 (44).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



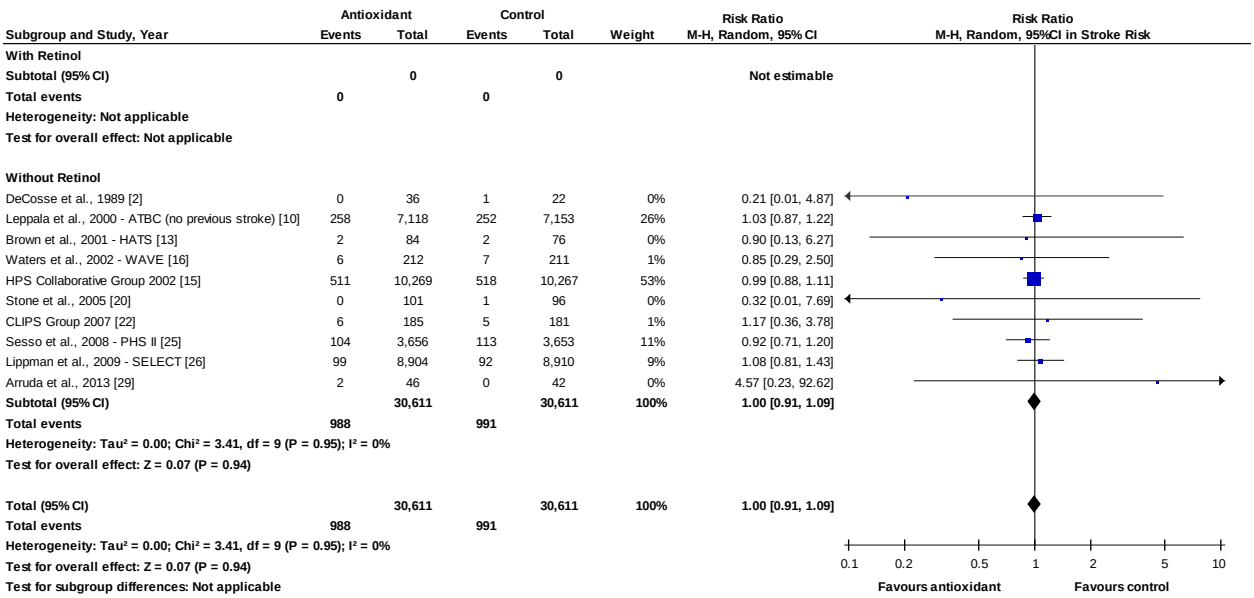
Supplementary Figure 101. Sensitivity analysis of antioxidant supplementation and total CVD risk for studies with and without retinol. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



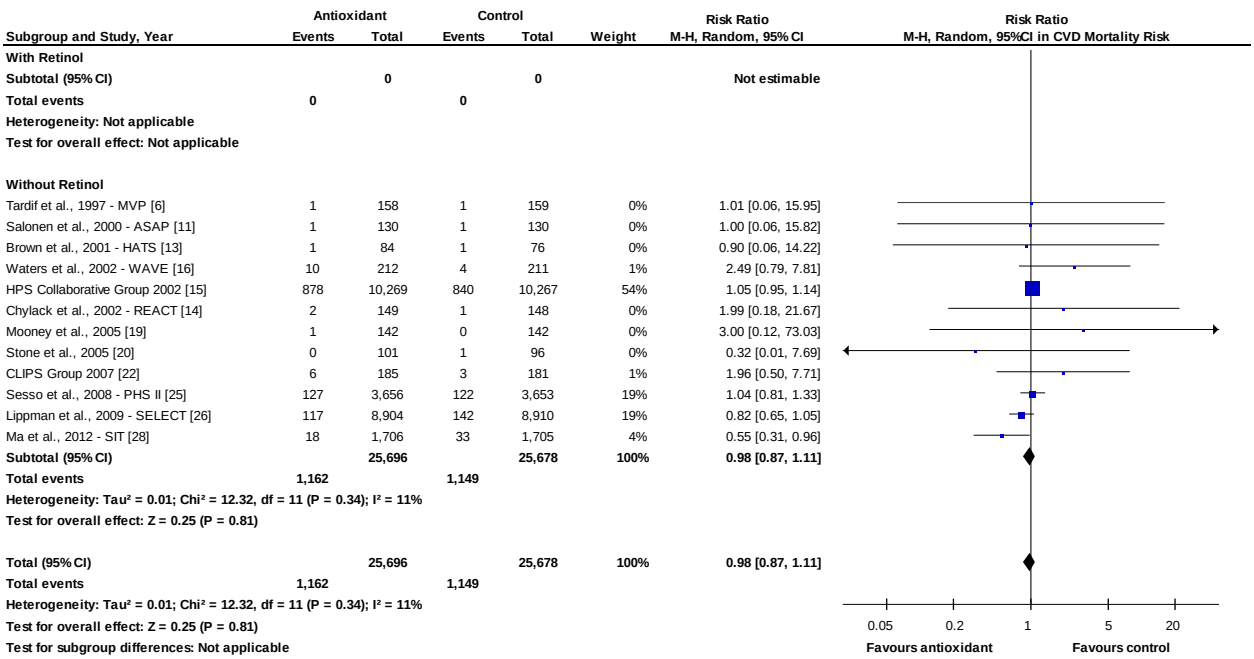
Supplementary Figure 102. Sensitivity analysis of antioxidant supplementation and total CHD risk for studies with and without retinol. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



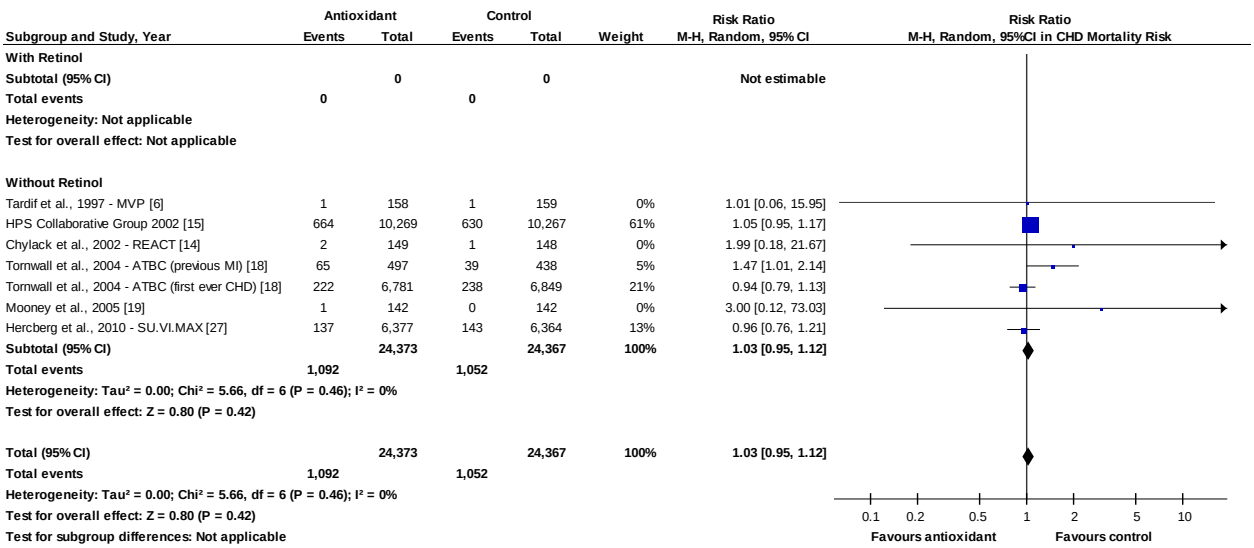
Supplementary Figure 103. Sensitivity analysis of antioxidant supplementation and MI risk for studies with and without retinol. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



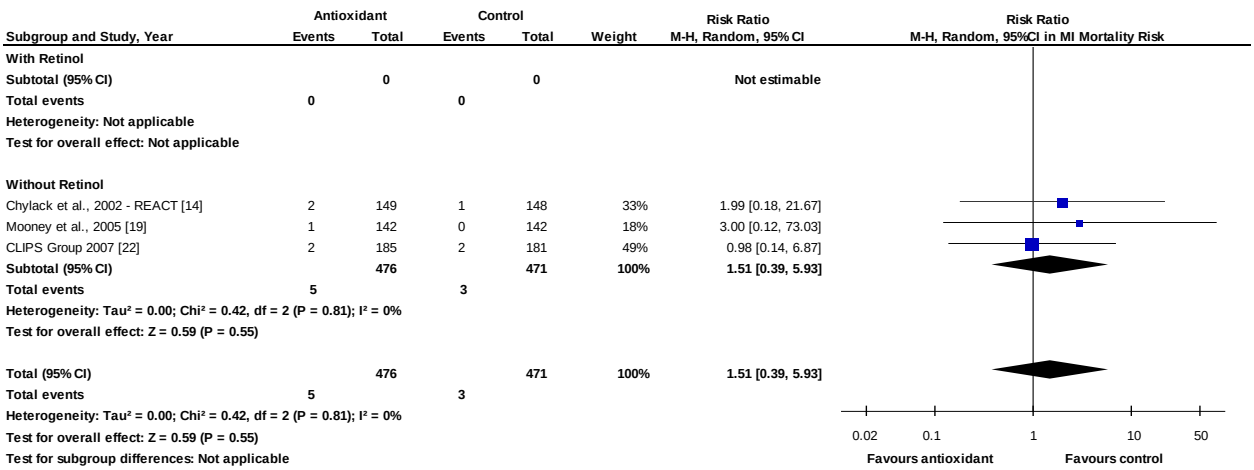
Supplementary Figure 104. Sensitivity analysis of antioxidant supplementation and stroke risk for studies with and without retinol. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



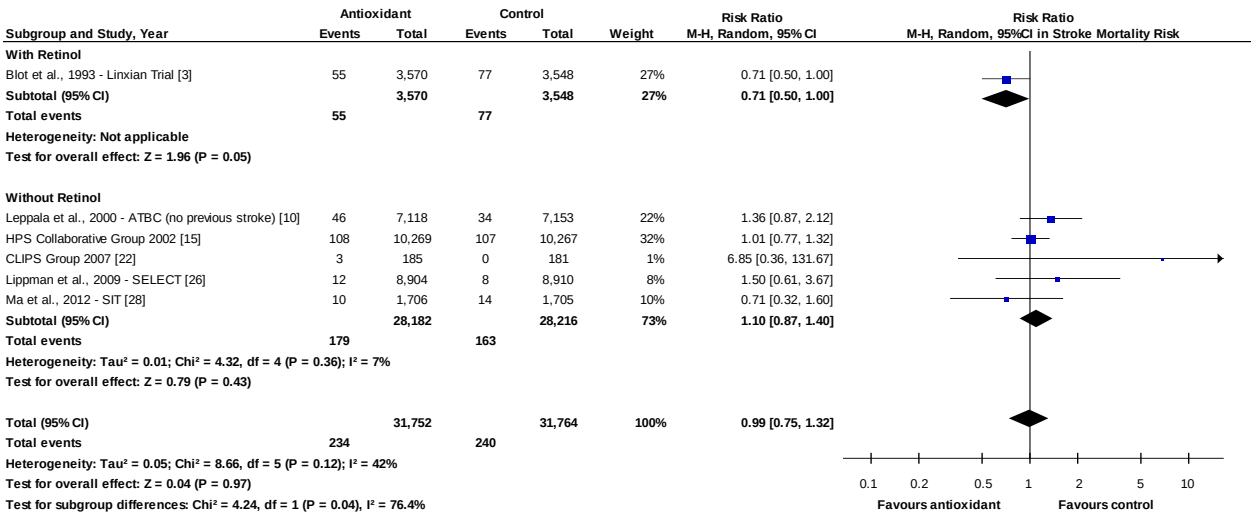
Supplementary Figure 105. Sensitivity analysis of antioxidant supplementation and CVD mortality risk for studies with and without retinol. M-H, Manthel-Haenszel, CVD, cardiovascular disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



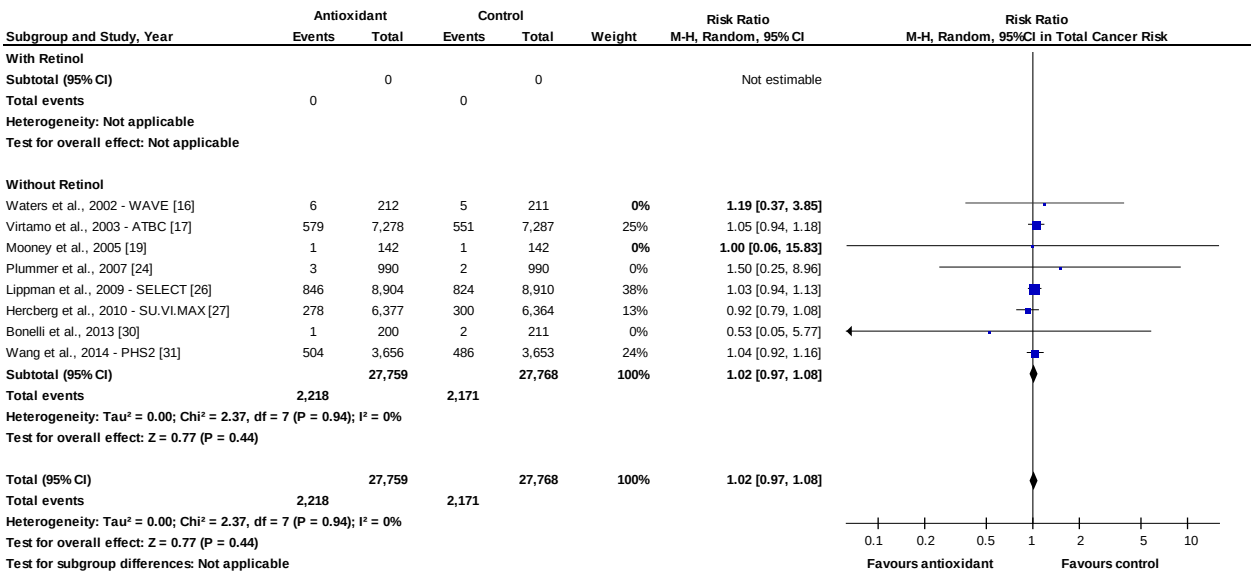
Supplementary Figure 106. Sensitivity analysis of antioxidant supplementation and CHD mortality risk for studies with and without retinol. M-H, Manthel-Haenszel, CHD, coronary heart disease. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



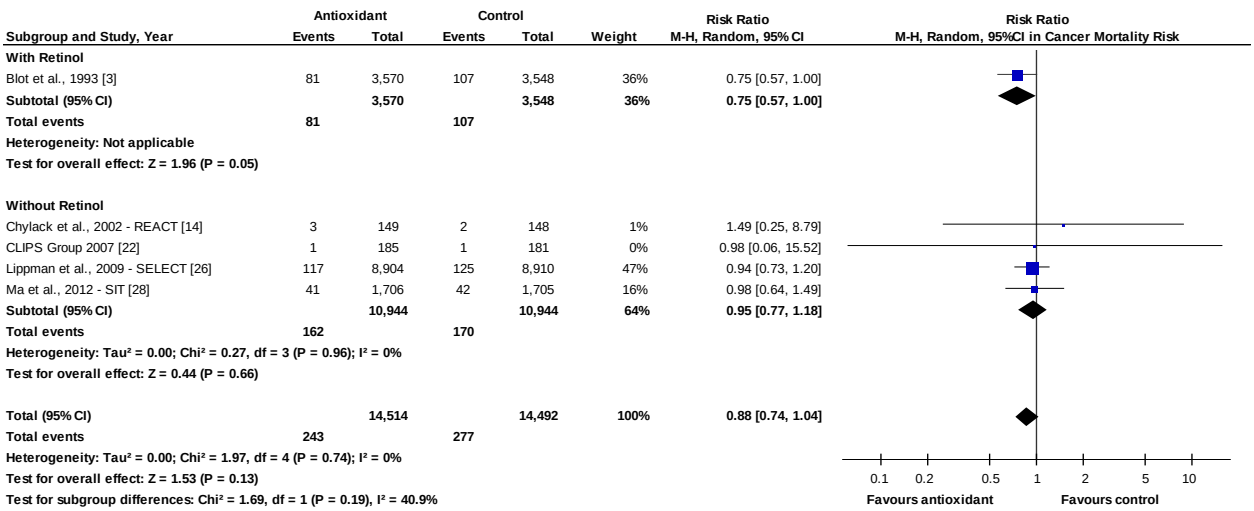
Supplementary Figure 107. Sensitivity analysis of antioxidant supplementation and MI mortality risk for studies with and without retinol. M-H, Manthel-Haenszel, MI, myocardial infarction. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



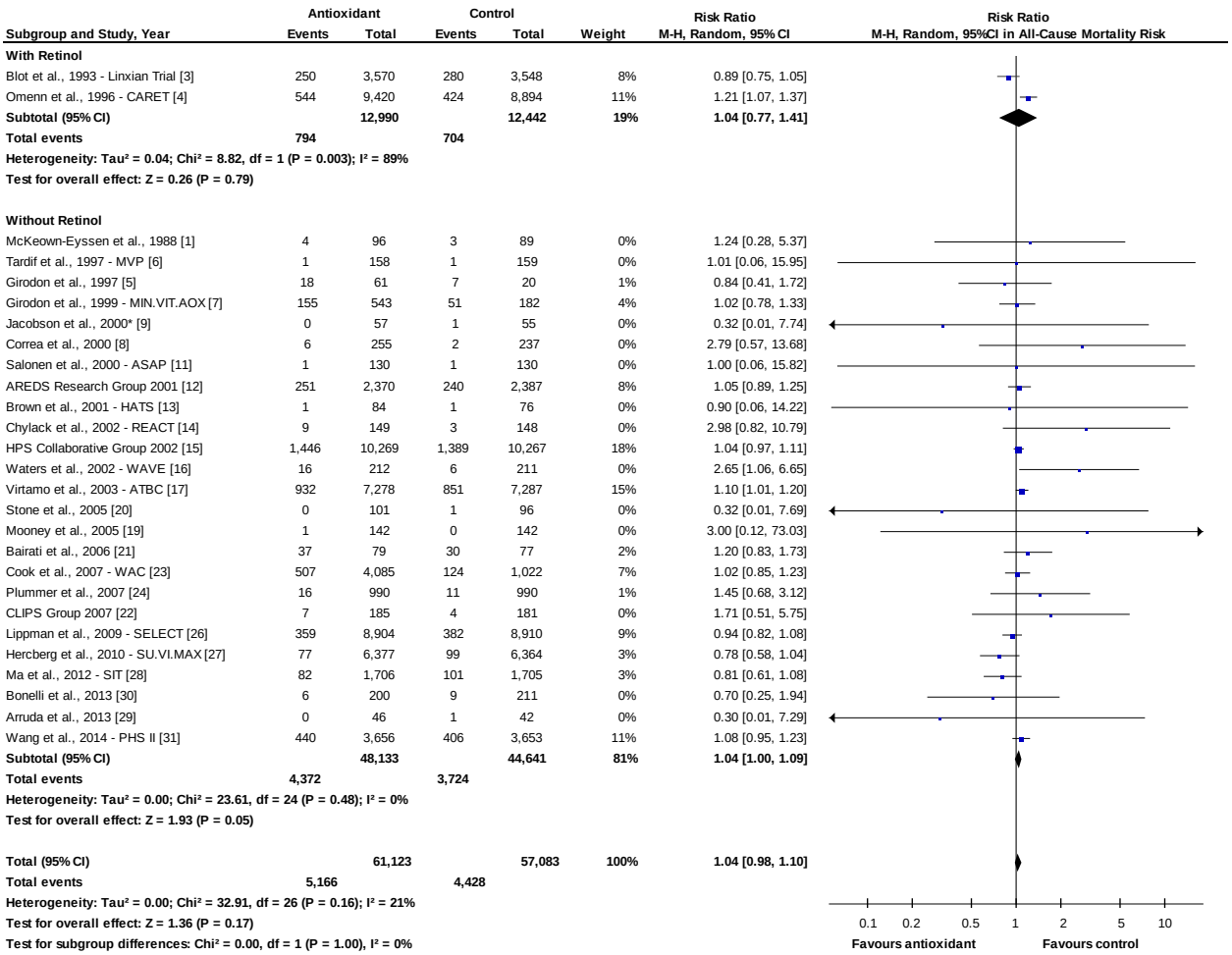
Supplementary Figure 108. Sensitivity analysis of antioxidant supplementation and stroke mortality risk for studies with and without retinol. NNT for antioxidant supplementation and stroke mortality risk for studies with retinol is 159. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



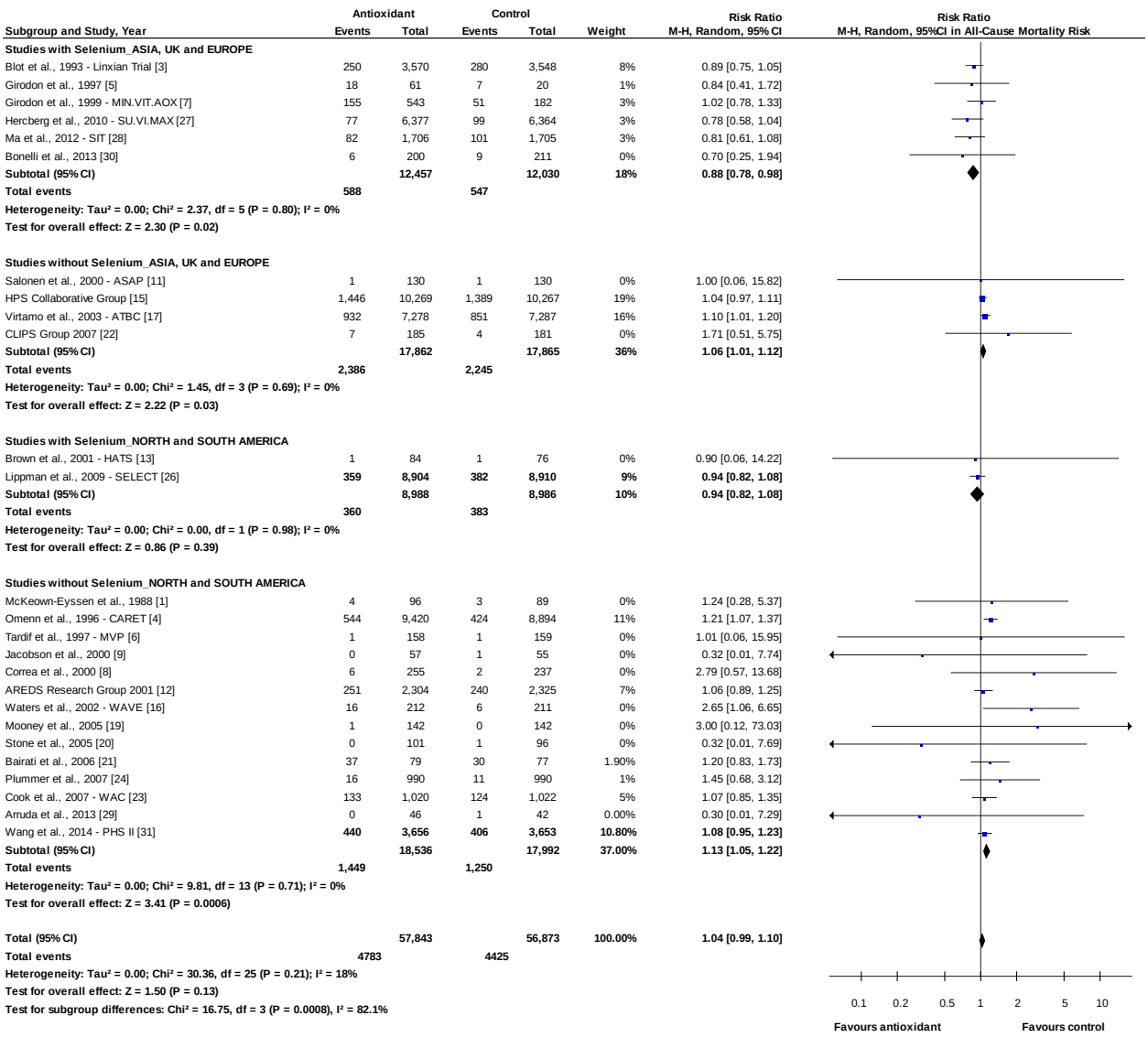
Supplementary Figure 109. Sensitivity analysis of antioxidant supplementation and total cancer risk for studies with and without retinol. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



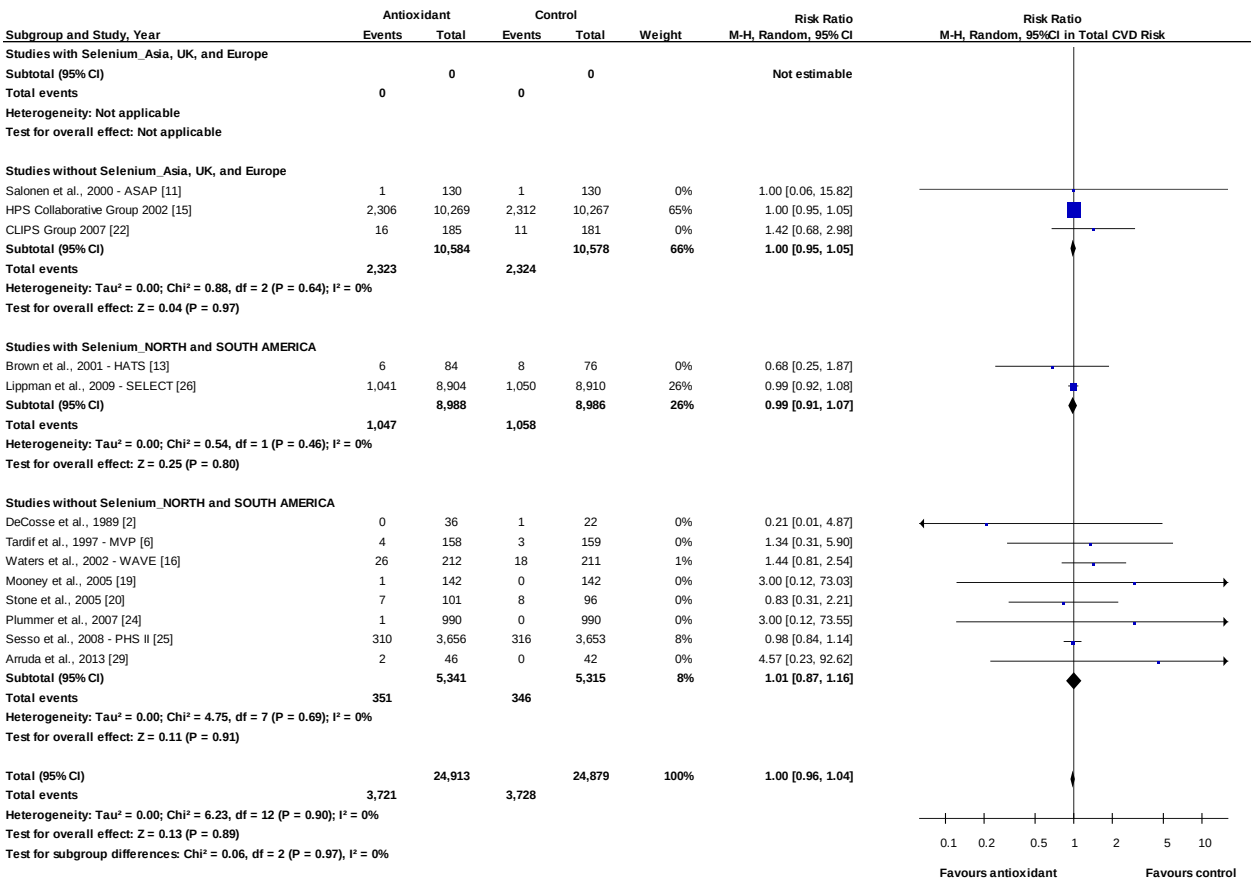
Supplementary Figure 110. Sensitivity analysis of antioxidant supplementation and cancer mortality risk for studies with and without retinol. NNT for antioxidant supplementation and cancer mortality risk for studies with retinol is 133. M-H, Manthel-Haenszel. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



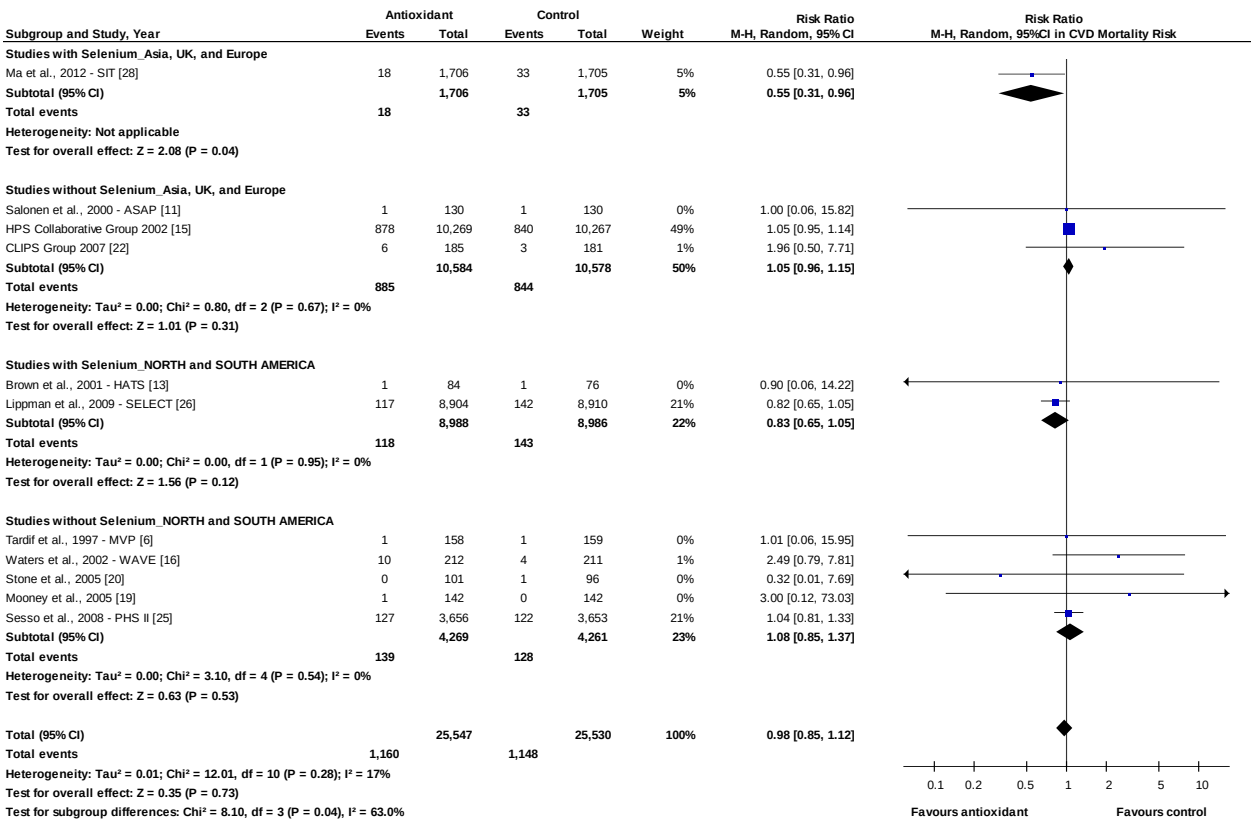
Supplementary Figure 111. Sensitivity analysis of antioxidant supplementation and all-cause mortality risk for studies with and without Retinol. NNH for antioxidant supplementation and all-cause mortality risk for studies without retinol is 300. M-H, Manthel-Haenszel. ***Jacobson et al., 2000 – Data retrieved from meta-analysis Bjelakovic 2012 (44).** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



Supplementary Figure 112. Forest plot showing antioxidants (with and without selenium) by region and all-cause mortality. M-H, Manthel-Haenszel. **Chylack et al., 2002 – REACT was excluded from the plot as the study was conducted in both the USA and UK.** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



Supplementary Figure 113. Forest plot showing antioxidants (with and without selenium) by region and total CVD. M-H, Manthel-Haenszel. **Chylack et al., 2002 – REACT was excluded from the plot as the study was conducted in both the USA and UK.** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.



Supplementary Figure 114. Forest plot showing antioxidants (with and without selenium) by region and CVD mortality. M-H, Manthel-Haenszel. **Chylack et al., 2002 – REACT was excluded from the plot as the study was conducted in both the USA and UK.** The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $P < 0.10$, and quantified by the I^2 statistic. An I^2 value ≥ 50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% Confidence Intervals, using the Manthel-Haenszel method with random effects model.

References

1. McKeown-Eyssen G, Holloway C, Jazmaji V, Bright-See E, Dion P, Bruce WR. A randomized trial of vitamins C and E in the prevention of recurrence of colorectal polyps. Cancer research 1988;48(16):4701-5.
2. DeCosse JJ, Miller HH, Lesser ML. Effect of wheat fiber and vitamins C and E on rectal polyps in patients with familial adenomatous polyposis. Journal of the National Cancer Institute 1989;81(17):1290-7. doi: 10.1093/jnci/81.17.1290.
3. Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, Yang CS, Zheng SF, Gail M, Li GY, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. Journal of the National Cancer Institute 1993;85(18):1483-92. doi: 10.1093/jnci/85.18.1483.
4. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL, Valanis B, Williams JH, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. The New England journal of medicine 1996;334(18):1150-5. doi: 10.1056/nejm199605023341802.
5. Girodon F, Lombard M, Galan P, Brunet-Lecomte P, Monget AL, Arnaud J, Preziosi P, Hercberg S. Effect of micronutrient supplementation on infection in institutionalized elderly subjects: a controlled trial. Annals of nutrition & metabolism 1997;41(2):98-107.
6. Tardif JC, Cote G, Lesperance J, Bourassa M, Lambert J, Doucet S, Bilodeau L, Nattel S, de Guise P. Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. Multivitamins and Probucol Study Group. The New England journal of medicine 1997;337(6):365-72. doi: 10.1056/nejm199708073370601.
7. Girodon F, Galan P, Monget AL, Boutron-Ruault MC, Brunet-Lecomte P, Preziosi P, Arnaud J, Manuguerra JC, Herchberg S. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial. MIN. VIT. AOX. geriatric network. Archives of internal medicine 1999;159(7):748-54.
8. Correa P, Fontham ET, Bravo JC, Bravo LE, Ruiz B, Zarama G, Realpe JL, Malcom GT, Li D, Johnson WD, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. Journal of the National Cancer Institute 2000;92(23):1881-8.
9. Jacobson JS, Begg MD, Wang LW, Wang Q, Agarwal M, Norkus E, Singh VN, Young TL, Yang D, Santella RM. Effects of a 6-month vitamin intervention on DNA damage in heavy smokers. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2000;9(12):1303-11.
10. Leppala JM, Virtamo J, Fogelholm R, Albanes D, Taylor PR, Heinonen OP. Vitamin E and beta carotene supplementation in high risk for stroke: a subgroup analysis of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Archives of neurology 2000;57(10):1503-9. doi: 10.1001/archneur.57.10.1503.
11. Salonen JT, Nyyssonen K, Salonen R, Lakka HM, Kaikkonen J, Porkkala-Sarataho E, Voutilainen S, Lakka TA, Rissanen T, Leskinen L, et al. Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study: a randomized trial of the effect of vitamins E and C on 3-year progression of carotid atherosclerosis. Journal of internal medicine 2000;248(5):377-86.
12. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Archives of ophthalmology (Chicago, Ill : 1960) 2001;119(10):1439-52.

13. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, Alaupovic P, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. The New England journal of medicine 2001;345(22):1583-92. doi: 10.1056/NEJMoa011090.
14. Chylack LT, Jr., Brown NP, Bron A, Hurst M, Kopcke W, Thien U, Schalch W. The Roche European American Cataract Trial (REACT): a randomized clinical trial to investigate the efficacy of an oral antioxidant micronutrient mixture to slow progression of age-related cataract. Ophthalmic epidemiology 2002;9(1):49-80.
15. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet (London, England) 2002;360(9326):23-33. doi: 10.1016/s0140-6736(02)09328-5.
16. Waters DD, Alderman EL, Hsia J, Howard BV, Cobb FR, Rogers WJ, Ouyang P, Thompson P, Tardif JC, Higginson L, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. Jama 2002;288(19):2432-40.
17. Virtamo J, Pietinen P, Huttunen JK, Korhonen P, Malila N, Virtanen MJ, Albanes D, Taylor PR, Albert P. Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: a postintervention follow-up. Jama 2003;290(4):476-85. doi: 10.1001/jama.290.4.476.
18. Tornwall ME, Virtamo J, Korhonen PA, Virtanen MJ, Taylor PR, Albanes D, Huttunen JK. Effect of alpha-tocopherol and beta-carotene supplementation on coronary heart disease during the 6-year post-trial follow-up in the ATBC study. European heart journal 2004;25(13):1171-8. doi: 10.1016/j.ehj.2004.05.007.
19. Mooney LA, Madsen AM, Tang D, Orjuela MA, Tsai WY, Garduno ER, Perera FP. Antioxidant vitamin supplementation reduces benzo(a)pyrene-DNA adducts and potential cancer risk in female smokers. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2005;14(1):237-42.
20. Stone PH, Lloyd-Jones DM, Kinlay S, Frei B, Carlson W, Rubenstein J, Andrews TC, Johnstone M, Sopko G, Cole H, et al. Effect of intensive lipid lowering, with or without antioxidant vitamins, compared with moderate lipid lowering on myocardial ischemia in patients with stable coronary artery disease: the Vascular Basis for the Treatment of Myocardial Ischemia Study. Circulation 2005;111(14):1747-55. doi: 10.1161/01.cir.0000160866.90148.76.
21. Bairati I, Meyer F, Jobin E, Gelinas M, Fortin A, Nabid A, Brochet F, Tetu B. Antioxidant vitamins supplementation and mortality: a randomized trial in head and neck cancer patients. International journal of cancer 2006;119(9):2221-4. doi: 10.1002/ijc.22042.
22. Catalano M, Born G, Peto R. Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial. Journal of internal medicine 2007;261(3):276-84. doi: 10.1111/j.1365-2796.2006.01763.x.
23. Cook NR, Albert CM, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, Buring JE, Manson JE. A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women's Antioxidant Cardiovascular Study. Archives of internal medicine 2007;167(15):1610-8. doi: 10.1001/archinte.167.15.1610.
24. Plummer M, Vivas J, Lopez G, Bravo JC, Peraza S, Carillo E, Cano E, Castro D, Andrade O, Sanchez V, et al. Chemoprevention of precancerous gastric lesions with antioxidant vitamin supplementation: a randomized trial in a high-risk population. Journal of the National Cancer Institute 2007;99(2):137-46. doi: 10.1093/jnci/djk017.

25. Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, Bubes V, Manson JE, Glynn RJ, Gaziano JM. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. Jama 2008;300(18):2123-33. doi: 10.1001/jama.2008.600.
26. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, Parnes HL, Minasian LM, Gaziano JM, Hartline JA, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). Jama 2009;301(1):39-51. doi: 10.1001/jama.2008.864.
27. Hercberg S, Kesse-Guyot E, Druesne-Pecollo N, Touvier M, Favier A, Latino-Martel P, Briancon S, Galan P. Incidence of cancers, ischemic cardiovascular diseases and mortality during 5-year follow-up after stopping antioxidant vitamins and minerals supplements: a postintervention follow-up in the SU.VI.MAX Study. International journal of cancer 2010;127(8):1875-81. doi: 10.1002/ijc.25201.
28. Ma JL, Zhang L, Brown LM, Li JY, Shen L, Pan KF, Liu WD, Hu Y, Han ZX, Crystal-Mansour S, et al. Fifteen-year effects of Helicobacter pylori, garlic, and vitamin treatments on gastric cancer incidence and mortality. Journal of the National Cancer Institute 2012;104(6):488-92. doi: 10.1093/jnci/djs003.
29. Arruda MM, Mecabo G, Rodrigues CA, Matsuda SS, Rabelo IB, Figueiredo MS. Antioxidant vitamins C and E supplementation increases markers of haemolysis in sickle cell anaemia patients: a randomized, double-blind, placebo-controlled trial. Br J Haematol 2013;160(5):688-700. doi: 10.1111/bjh.12185.
30. Bonelli L, Puntoni M, Gatteschi B, Massa P, Missale G, Munizzi F, Turbino L, Villanacci V, De Censi A, Bruzzi P. Antioxidant supplement and long-term reduction of recurrent adenomas of the large bowel. A double-blind randomized trial. J Gastroenterol 2013;48(6):698-705. doi: 10.1007/s00535-012-0691-z.
31. Wang L, Sesso HD, Glynn RJ, Christen WG, Bubes V, Manson JE, Buring JE, Gaziano JM. Vitamin E and C supplementation and risk of cancer in men: posttrial follow-up in the Physicians' Health Study II randomized trial. The American journal of clinical nutrition 2014;100(3):915-23. doi: 10.3945/ajcn.114.085480.
32. Korpela HK, J. Jussila, E. Kemila, S. Kaariainen, M. Kaariainen, T. Sotaniemi, E. A. Effect of selenium supplementation after acute myocardial infarction. Research communications in chemical pathology and pharmacology 1989;65(2):249-52.
33. Duffield-Lillico AJR, M. E. Turnbull, B. W. Combs, G. F. Slate, E. H. Fischbach, L. A. Marshall, J. R. Clark, L. C. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. Cancer epidemiology, biomarkers & prevention 2002;11(7):630-9.
34. Limburg PJ, Wei W, Ahnen DJ, Qiao Y, Hawk ET, Wang G, Giffen CA, Wang G, Roth MJ, Lu N, et al. Randomized, placebo-controlled, esophageal squamous cell cancer chemoprevention trial of selenomethionine and celecoxib. Gastroenterology 2005;129(3):863-73. doi: 10.1053/j.gastro.2005.06.024.
35. Stranges S, Marshall JR, Trevisan M, Natarajan R, Donahue RP, Combs GF, Farinaro E, Clark LC, Reid ME. Effects of selenium supplementation on cardiovascular disease incidence and mortality: secondary analyses in a randomized clinical trial. American journal of epidemiology 2006;163(8):694-9. doi: 10.1093/aje/kwj097.
36. Stratton MS, Algotar AM, Ranger-Moore J, Stratton SP, Slate EH, Hsu CH, Thompson PA, Clark LC, Ahmann FR. Oral selenium supplementation has no effect on prostate-specific antigen velocity

in men undergoing active surveillance for localized prostate cancer. Cancer prevention research (Philadelphia, Pa) 2010;3(8):1035-43. doi: 10.1158/1940-6207.Capr-09-0143.

37. Rayman MP, Winther KH, Pastor-Barriuso R, Cold F, Thvilum M, Stranges S, Guallar E, Cold S. Effect of long-term selenium supplementation on mortality: Results from a multiple-dose, randomised controlled trial. Free radical biology & medicine 2018;127:46-54. doi: 10.1016/j.freeradbiomed.2018.02.015.
38. Marshall JR, Tangen CM, Sakr WA, Wood DP, Jr., Berry DL, Klein EA, Lippman SM, Parnes HL, Alberts DS, Jarrard DF, et al. Phase III trial of selenium to prevent prostate cancer in men with high-grade prostatic intraepithelial neoplasia: SWOG S9917. Cancer prevention research (Philadelphia, Pa) 2011;4(11):1761-9. doi: 10.1158/1940-6207.capr-10-0343.
39. Algotar AM, Stratton MS, Ahmann FR, Ranger-Moore J, Nagle RB, Thompson PA, Slate E, Hsu CH, Dalkin BL, Sindhwani P, et al. Phase 3 clinical trial investigating the effect of selenium supplementation in men at high-risk for prostate cancer. The Prostate 2013;73(3):328-35. doi: 10.1002/pros.22573.
40. Karp DD, Lee SJ, Keller SM, Wright GS, Aisner S, Belinsky SA, Johnson DH, Johnston MR, Goodman G, Clamon G, et al. Randomized, double-blind, placebo-controlled, phase III chemoprevention trial of selenium supplementation in patients with resected stage I non-small-cell lung cancer: ECOG 5597. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013;31(33):4179-87. doi: 10.1200/jco.2013.49.2173.
41. Goossens MEZ, M. P. van Poppel, H. Joniau, S. Ackaert, K. Ameye, F. Billiet, I. Braeckman, J. Breugelmans, A. Darras, J. Dilen, K. Goeman, L. Tombal, B. Van Bruwaene, S. Van Cleyenbreugel, B. Van der Aa, F. Vekemans, K. Buntinx, F. Phase III randomised chemoprevention study with selenium on the recurrence of non-invasive urothelial carcinoma. The SELEnium and BLAdder cancer Trial. European journal of cancer 2016;69:9-18.
42. Thompson PA, Ashbeck EL, Roe DJ, Fales L, Buckmeier J, Wang F, Bhattacharyya A, Hsu CH, Chow HH, Ahnen DJ, et al. Selenium Supplementation for Prevention of Colorectal Adenomas and Risk of Associated Type 2 Diabetes. Journal of the National Cancer Institute 2016;108(12). doi: 10.1093/jnci/djw152.
43. Rayman MP, Stranges S, Griffin BA, Pastor-Barriuso R, Guallar E. Effect of supplementation with high-selenium yeast on plasma lipids: a randomized trial. Annals of internal medicine 2011;154(10):656-65. doi: 10.7326/0003-4819-154-10-201105170-00005.
44. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. The Cochrane database of systematic reviews 2012(3):Cd007176. doi: 10.1002/14651858.CD007176.pub2.