Effects of folic acid on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50000 individuals

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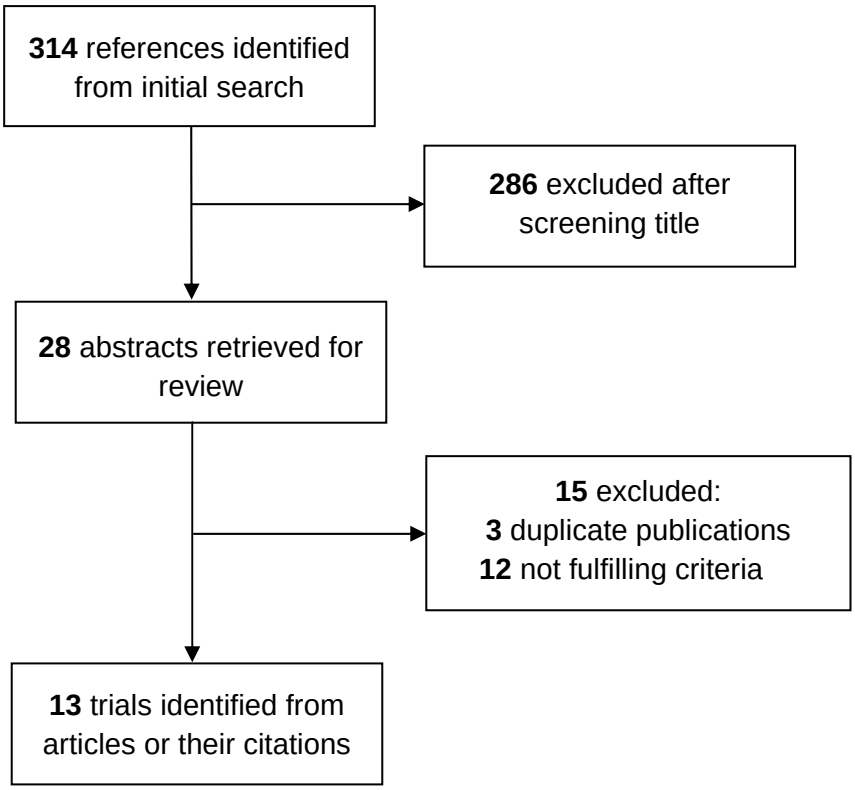
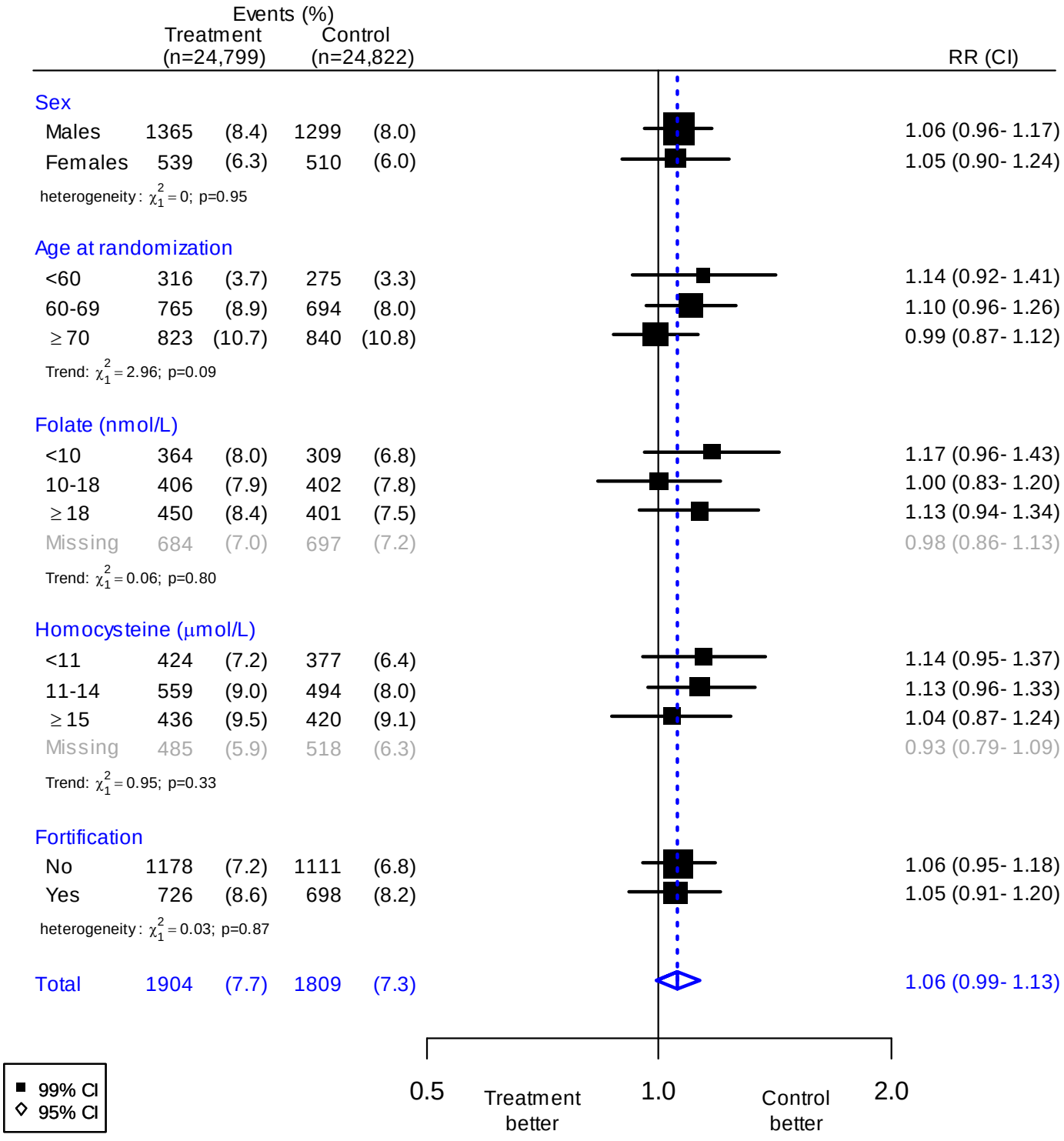
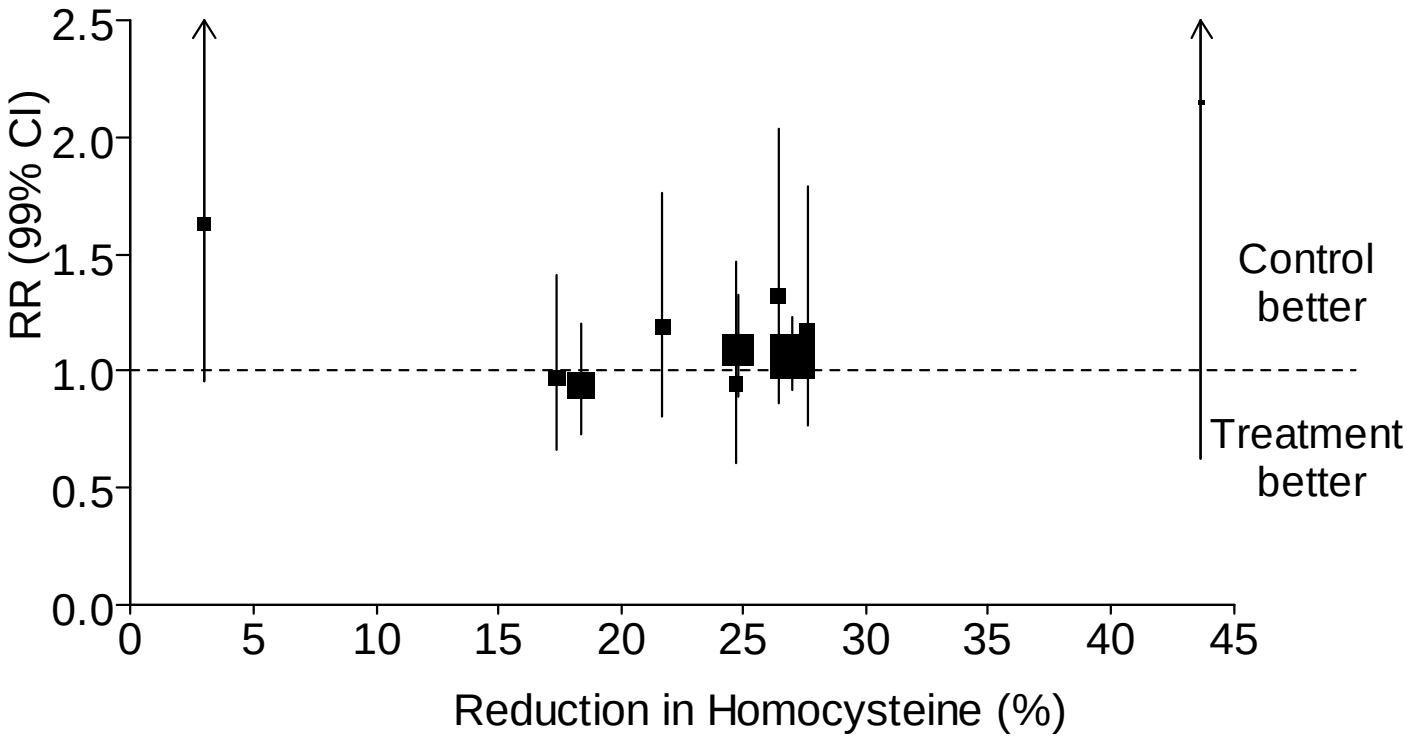
webfigure 1: Screening and selection of included trials

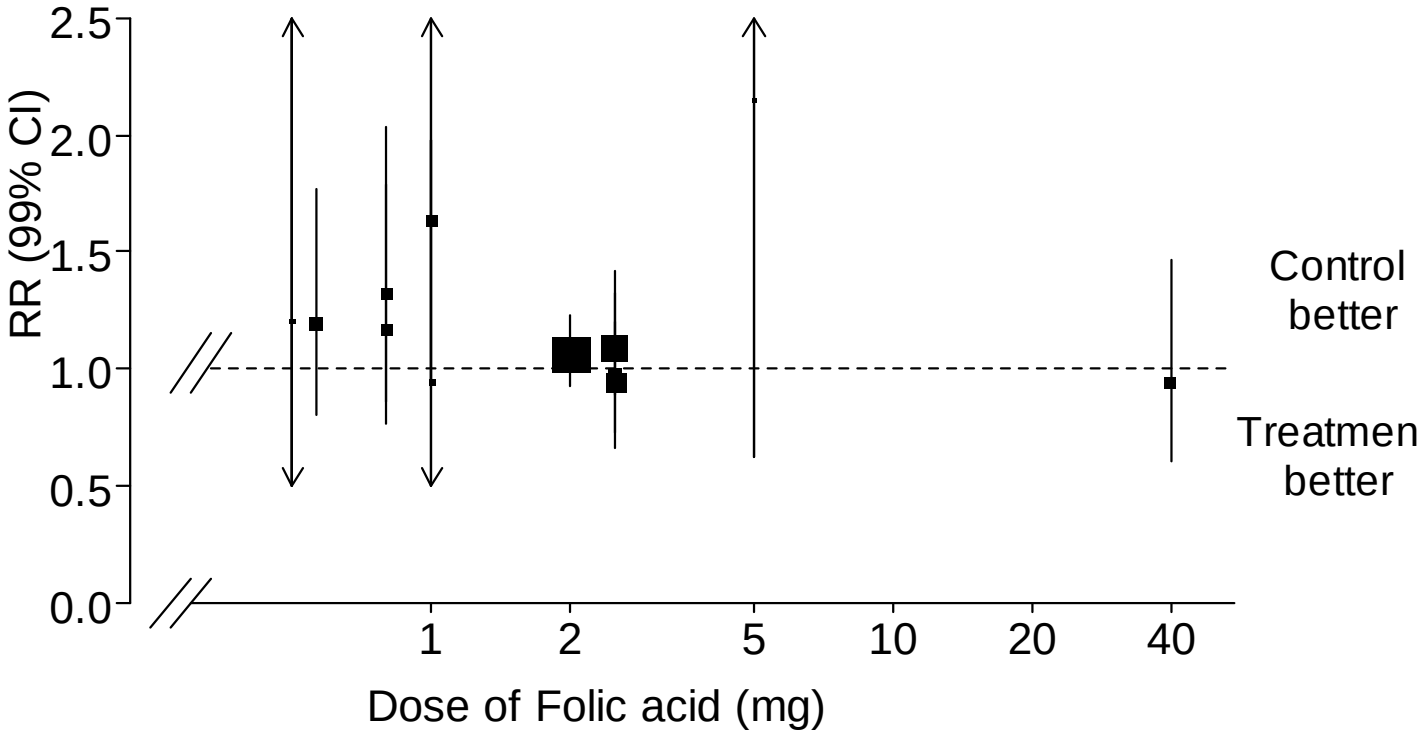


webfigure 2: Effects of folic acid on cancer incidence, in pre-specified subgroups



webfigure 3: Effects of folic acid on overall first cancer incidence, by percentage reduction in homocysteine or dose of folic acid





webtable 1: Selected characteristics at baseline of included trials

Trial	Number randomised	Existing Cancer (%)	Male (%)	Age in years Mean (SD)	Current smoker (%)	Current drinker (%)	Obesity* (%)
Colorectal adenoma trials							
ukCAP	939	24 (2.6)	56	58 (9)	16	66	10
HARVARD	692	16 (2.3)	40	65 (7)	6	67	13
AFPPS	1021	50 (4.9)	63	57 (10)	14	64	23
Sub-total	**2652**		**55**	**60 (9)**	**13**	**66**	**15**
Vascular trials							
VITRO	701	0 (0.0)	51	52 (15)	28	55	20
HOST	2056	172 (8.4)	98	66 (12)	19	18	28
SU-FOL-OM3	2501		79	61 (9)	11	81	23
WENBIT	3090	124 (4.0)	79	62 (10)	24		18
VISP	3680	27 (0.7)	62	66 (11)	16	57	31
NORVIT	3749	202 (5.4)	73	63 (12)	46	44	14
WAFACS	5442	432 (7.9)	0	63 (9)	11	45	50
HOPE-2	5522		71	69 (7)	11	41	34
VITATOPS	8164		63	63 (12)	22	28	0
SEARCH	12064	0 (0.0)	82	64 (9)	12	61	28
Sub-total	**46969**		**66**	**64 (10)**	**18**	**44**	**24**
Total	**49621**	**1047 (3.1)**	**65**	**64 (10)**	**18**	**46**	**24**

* defined as BMI ≥ 30

webtable 2: Median plasma levels of folate and homocysteine before and after study treatment in the vascular disease trials

Trial	Number with both baseline & follow-up folate data	Folate (nmol/L)				Percent increase in folate	Number with both baseline & follow-up homocysteine	Homocysteine (μmol/L)				Percent homocysteine reduction
		Before		After[1]				Before		After[1]		
		Treated	Control	Treated	Control			Treated	Control	Treated	Control	
Fortified												
VISP	2599	22.9	23.2	62.9	22.6	293	3114	12.3	12.3	9.8	11.7	17
HOST	1179	15.7	15.5	2019.0	16.5	4788	1844	22.5	22.2	16.5	21.6	25
HOPE-2	884	28.8	28.9	45.3	23.2	179	897	11.0	11.0	9.0	12.0	24
WAFACS	300	19.9	20.1	88.1	35.0	206	300	12.5	12.5	9.8	11.8	18
VITATOPS	-	-	-	-	-	-	-	-	-	-	-	-
Subtotal	2399	22.4	22.3	69.2	22.3	†1687	6156	13.2	13.2	11.0	13.5	†20
Non-fortified												
VISP	36	17.6	13.2	65.9	12.6	502	41	13.5	14.0	8.7	14.4	35
VITRO	-	8.1	7.7				587	11.1	11.5	7.6	11.6	44
HOPE-2	250	14.5	13.3	45.4	14.0	238	256	13.0	12.7	9.0	13.1	29
WENBIT	2760	9.7	10.1	61.6	8.5	588	2760	10.0	10.1	7.7	10.2	26
NORVIT	3316	8.1	8.0	62.4	7.3	656	3374	12.1	12.1	8.9	12.4	28
SEARCH	1152	14.0	13.8	52.4	12.5	378	393	12.6	12.5	8.8	12.5	27
VITATOPS	-	20.7	18.9	-	-	-	923	12.5	12.8	9.6	13.0	26
SU-FOL-OM3	2043	15.2	15.4	37.8	15.4	232	2114	13.0	12.8	9.7	12.2	22
Subtotal	12120	12.2	12.1	53.5	9.8	†394	10448	12.2	12.2	8.7	11.8	†27
Total	14519	13.9	13.7	57.3	13.5	†827	16604	12.4	12.4	9.3	12.3	†25

[1] First available post-randomization

† The values shown are the weighted mean values (with weights equal to the variance of the logrank statistic for cancer events). For calculation of percent homocysteine reduction, the analysis used the average of the first four follow-up values (where present).

webtable 3: Cancer sub-types by study

Characteristic	ukCAP	HARVARD	AFPPS	VITRO	HOST	WENBIT	NORVIT	SU-FOL-OM3	VISP	VITATOPS	WAFACS	HOPE-2	SEARCH	Total
Number randomized	939	692	1021	701	2056	3090	3749	2501	3680	8164	5442	5522	12064	49621
- Cancer deaths	0	0	14	.	39	29	50	58	45	181	129	189	510	
Cancer subtypes														
Lip, mouth, pharynx	0	2	0	1	4	2	3	2	4	0	4	7	21	50
Esophagus	2	0	1	0	2	1	1	2	5	0	1	7	33	55
Stomach	2	0	4	0	1	7	8	5	1	0	1	15	44	88
Liver	0	0	1	0	3	1	1	6	2	0	4	7	21	46
Pancreas	2	0	4	1	0	5	5	5	2	0	15	16	22	77
Colorectal	10	4	7	4	7	21	17	16	7	38	45	85	168	429
Larynx	0	0	0	0	1	1	1	0	0	0	0	5	9	17
Lung	5	7	7	2	22	13	24	26	10	59	45	96	209	525
Melanoma	0	5	4	2	0	9	6	7	3	14	7	14	55	126
Breast	4	11	5	2	1	5	4	9	8	25	154	21	48	297
Uterus	0	2	6	1	0	2	2	1	1	0	28	10	6	59
Ovary	0	0	1	1	1	0	1	1	0	0	14	7	8	34
Prostate	2	11	33	1	14	37	33	50	28	39	0	127	281	656
Kidney	0	0	5	1	15	5	4	1	1	0	14	19	41	106
Bladder	0	3	1	0	6	10	6	18	5	0	9	35	114	207
Brain	0	0	0	1	1	2	2	3	1	9	3	9	17	48
Haematological	0	3	10	0	10	15	13	14	4	17	1	33	113	233
Other site	0	0	0	1	47	5	4	4	6	116	39	137	34	393
Unspecified/no ICD	0	1	3	1	2	3	14	1	99	28	30	12	73	267
Any cancer	27	49	92	19	137	144	149	171	187	345	414	662	1317	3713

webtable 4: Effects of folic acid allocation on colorectal cancer incidence, by trial

	Folic acid events	Control events	O-E	Var	Z-value	p-value	RR	(95% CI)
Colorectal Adenoma trials								
HARVARD	5 / 470	5 / 469	-0.1	2.5	-0.07	0.94	1.05	
ukCAP	1 / 346	3 / 346	1.0	1.0	0.96	0.34	0.38	
AFPPS	3 / 516	4 / 505	0.6	1.7	0.44	0.66	0.72	
Subtotal	**9 / 1332**	**12 / 1320**	**1.4**	**5.2**	**0.62**	**0.53**	**0.76**	**(0.32-1.80)**
Vascular disease trials								
VITRO	3 / 353	1 / 348	-1.0	1.0	-0.97	0.33	2.64	
HOST	5 / 1032	2 / 1024	-1.6	1.7	-1.20	0.23	2.46	
WENBIT	13 / 1540	8 / 1550	-2.9	5.2	-1.30	0.21	1.73	
NORVIT	9 / 1872	8 / 1877	-0.2	4.2	-0.11	0.92	1.05	
SU-FOL-OM3	6 / 1242	10 / 1259	1.9	4.0	0.96	0.34	0.62	
VISP	4 / 1827	3 / 1853	-0.5	1.7	-0.37	0.71	1.32	
VITATOPS	19 / 4088	19 / 4074	0.1	9.5	0.02	0.98	0.99	
WAFACS	20 / 2721	25 / 2721	2.6	11.2	0.79	0.43	0.79	
HOPE-2	49 / 2758	36 / 2764	-6.7	21.2	-1.50	0.14	1.37	
SEARCH	84 / 6033	84 / 6031	-0.3	41.9	-0.05	0.96	1.01	
Subtotal	**212 / 23466**	**196 / 23501**	**-8.5**	**101.8**	**-0.85**	**0.40**	**1.09**	**(0.90-1.32)**
Total	**221 / 24798**	**208 / 24821**	**-7.1**	**107.1**	**-0.69**	**0.49**	**1.07**	**(0.88-1.29)**
Total (except AFPPS)	**218 / 24282**	**204 / 24316**	**-7.7**	**105.3**	**-0.75**	**0.45**	**1.08**	**(0.89-1.30)**

Heterogeneity (AFPPS vs rest): $\chi^2_1 = 0.28$ p=0.6

webtable 5: Effects of folic acid allocation on prostate cancer incidence, by trial

	Folic acid events	Control events	O-E	Var	Z-value	p-value	RR	(95% CI)
Colorectal Adenoma trials								
HARVARD	1 / 470	1 / 469	-0.1	0.5	-0.14	0.89	1.23	
ukCAP	5 / 346	6 / 346	0.5	2.7	0.30	0.76	0.83	
AFPPS	24 / 516	9 / 505	-7.2	8.2	-2.50	0.01	2.39	
Subtotal	**30 / 1332**	**16 / 1320**	**-6.8**	**11.5**	**-2.00**	**0.05**	**1.80**	**(1.01-3.22)**
Vascular disease trials								
VITRO	1 / 353	0 / 348	-0.5	0.3	-1.00	0.32	7.39	
HOST	7 / 1032	7 / 1024	-0.2	3.5	-0.09	0.93	1.05	
WENBIT	21 / 1540	16 / 1550	-2.8	9.2	-0.91	0.36	1.35	
NORVIT	15 / 1872	18 / 1877	1.8	8.2	0.63	0.53	0.80	
SU-FOL-OM3	27 / 1242	23 / 1259	-1.6	12.5	-0.45	0.65	1.14	
VISP	17 / 1827	11 / 1853	-3.0	7.0	-1.10	0.26	1.54	
VITATOPS	14 / 4088	25 / 4074	5.8	9.7	1.84	0.07	0.55	
HOPE-2	69 / 2758	58 / 2764	-6.2	31.7	-1.10	0.27	1.22	
SEARCH	150 / 6033	131 / 6031	-9.6	70.2	-1.10	0.25	1.15	
Subtotal	**321 / 20745**	**289 / 20780**	**-16.3**	**152.4**	**-1.30**	**0.19**	**1.11**	**(0.95-1.30)**
Total	**351 / 22077**	**305 / 22100**	**-23.1**	**163.9**	**-1.80**	**0.07**	**1.15**	**(0.99-1.34)**
Total (except AFPPS)	**327 / 21561**	**296 / 21595**	**-15.9**	**155.6**	**-1.30**	**0.20**	**1.11**	**(0.95-1.30)**

Heterogeneity (AFPPS vs rest): $\chi^2_1 = 4.46$ **p=0.03**

webtable 6: Effects of folic acid allocation on cancer incidence, by trial

	Folic acid events	Control events	O-E	Var	Z-value	p-value	RR	(95% CI)
Colorectal Adenoma trials								
HARVARD	14 / 470	13 / 469	-1.2	6.4	-0.46	0.65	1.20	
ukCAP	24 / 346	25 / 346	0.7	12.2	0.20	0.84	0.94	
AFPPS	58 / 516	34 / 505	-11.3	22.9	-2.30	0.02	1.63	
Subtotal	**96 / 1332**	**72 / 1320**	**-11.7**	**41.6**	**-1.80**	**0.07**	**1.33**	**(0.98-1.80)**
Vascular disease trials								
VITRO	12 / 353	7 / 348	-3.3	4.3	-1.60	0.11	2.15	
HOST	65 / 1032	72 / 1024	2.0	34.1	0.34	0.74	0.94	
WENBIT	81 / 1540	63 / 1550	-10.1	35.9	-1.70	0.09	1.32	
NORVIT	82 / 1872	67 / 1877	-5.7	37.2	-0.94	0.35	1.17	
SU-FOL-OM3	93 / 1242	78 / 1259	-7.3	42.7	-1.10	0.26	1.19	
VISP	92 / 1827	95 / 1853	1.4	46.7	0.20	0.84	0.97	
VITATOPS	162 / 4088	183 / 4074	12.0	86.1	1.29	0.20	0.87	
WAFACS	201 / 2721	213 / 2721	6.9	103.5	0.68	0.50	0.94	
HOPE-2	342 / 2758	320 / 2764	-13.6	165.3	-1.10	0.29	1.09	
SEARCH	678 / 6033	639 / 6031	-20.6	329.1	-1.10	0.26	1.06	
Subtotal	**1808 / 23466**	**1737 / 23501**	**-38.3**	**884.9**	**-1.30**	**0.20**	**1.04**	**(0.98-1.12)**
Total	**1904 / 24798**	**1809 / 24821**	**-50.0**	**926.5**	**-1.60**	**0.10**	**1.06**	**(0.99-1.13)**
Total (except AFPPS)	**1846 / 24282**	**1775 / 24316**	**-39.2**	**903.5**	**-1.30**	**0.19**	**1.04**	**(0.98-1.11)**

Heterogeneity (AFPPS vs rest): $\chi^2_1 = 2.24$ p=0.1