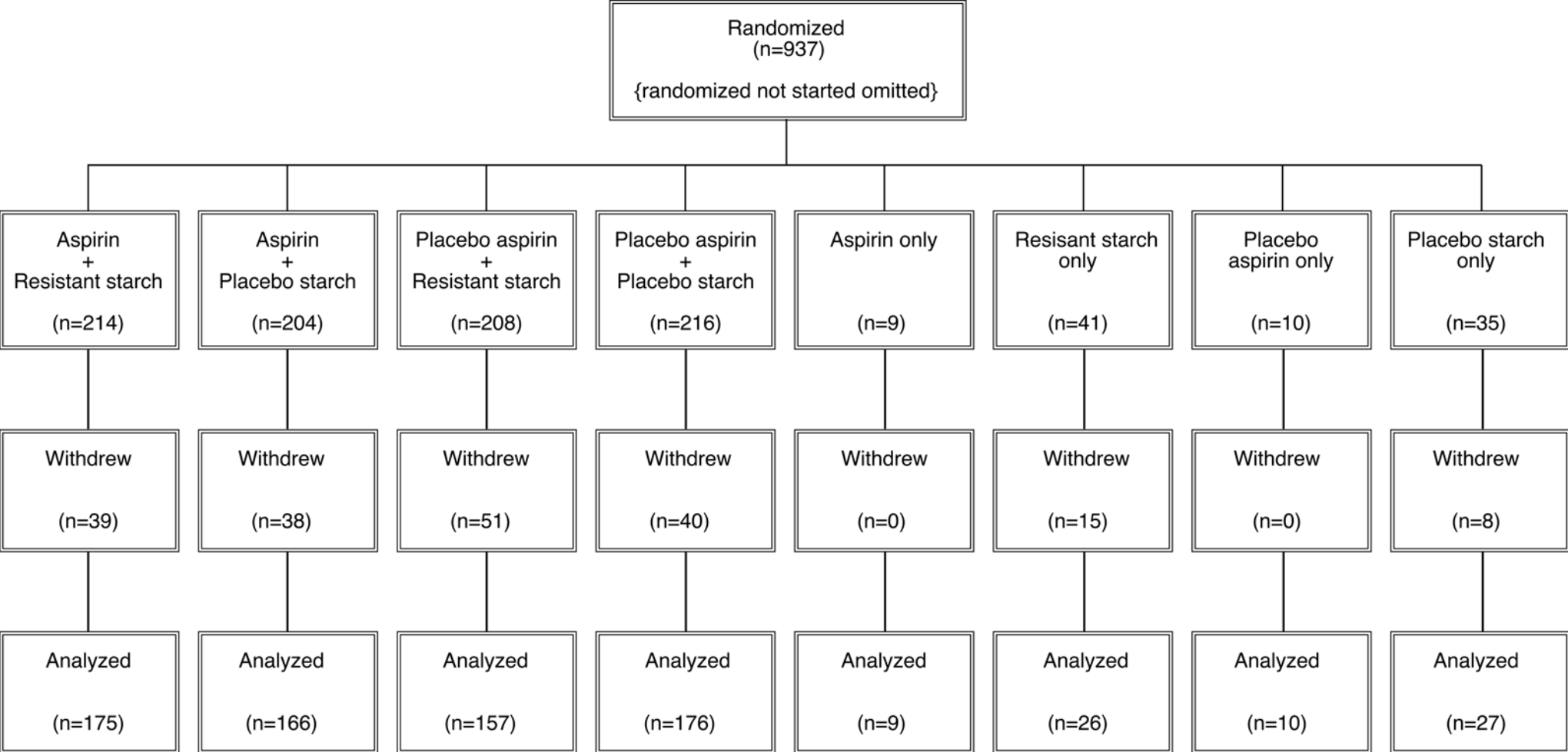


Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Burn J, Bishop DT, Mecklin J-P, et al. Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. N Engl J Med 2008;359:2567-78.



Supplementary Table 1 by randomisation group

Aspirin Starch	Statistic	Distribution at analysis (N=746)	Participants randomised to both interventions				Participants randomised to a single intervention			
			aspirin Resistant starch	aspirin Placebo	Placebo resistant starch	Placebo Placebo	aspirin None	Placebo None	None resistant starch	None Placebo
Age (years) at start of treatment	Mean	46	45	44	44	45	59	47	55	58
	Range	25-79	25-69	25-69	25-76	26-78	37-71	33-57	28-79	41-75
Gender	Female	410 (55.0)	94 (53.7)	103 (62.0)	80 (51.0)	96 (54.6)	4 (44.4)	4 (40.0)	14 (53.9)	15 (55.6)
	Male	336 (45.0)	81 (46.3)	63 (38.0)	77 (49.0)	80 (45.4)	5 (55.6)	6 (60.0)	12 (46.1)	12 (44.4)
Centre	Northern Europe	334 (44.8)	84 (48.0)	75 (45.2)	71 (45.2)	76 (43.2)	7 (77.8)	6 (60.0)	8 (30.8)	7 (25.9)
	UK	218 (29.2)	50 (28.6)	47 (28.3)	45 (28.7)	54 (30.7)	2 (22.2)	3 (30.0)	8 (30.8)	9 (33.3)
	Southern Europe	46 (6.2)	11 (6.3)	11 (6.6)	11 (7.0)	11 (6.3)	0 (0.0)	0 (0.0)	1 (3.9)	1 (3.7)
	South Africa	29 (3.9)	4 (2.3)	7 (4.2)	6 (3.8)	8 (4.6)	0 (0.0)	0 (0.0)	3 (11.5)	1 (3.7)
	Americas	3 (0.4)	1 (0.6)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Rest of World	116 (15.6)	25 (14.3)	25 (15.1)	23 (14.7)	27 (15.3)	0 (0.0)	1 (10.0)	6 (23.1)	9 (33.3)
Eligibility status	Clinical	132 (17.7)	21 (12.0)	29 (17.5)	33 (21.0)	31 (17.6)	2 (22.2)	1 (10.0)	9 (34.6)	6 (22.2)
	Genetic	614 (82.3)	154 (88.0)	137 (82.5)	124 (79.0)	145 (82.4)	7 (77.8)	9 (90.0)	17 (65.4)	21 (77.8)
Type of mutation	MLH1	358 (58.3)	96 (62.3)	75 (54.7)	73 (58.9)	81 (55.9)	5 (71.4)	6 (66.7)	9 (52.9)	13 (61.9)
	MSH2	235 (38.3)	52 (33.8)	59 (43.1)	46 (37.1)	58 (40.0)	1 (14.3)	3 (33.3)	8 (47.1)	8 (38.1)
	MSH6	21 (3.4)	6 (3.9)	3 (2.2)	5 (4.0)	6 (4.1)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Time on study (months)	Mean	29.0	28.4	28.4	29.8	29.6	23.3	32.4	29.3	28.7
	Range	7.4-74.4	10.2-55.9	8.7-54.3	10.8-74.4	10.5-58.9	18.8-25.8	22.4-54.8	7.4-51.1	12.0-57.9
Time taking treatment (months)	Mean	26.5	25.6	26.0	27.4	27.4	21.3	28.9	26.5	25.5
	Range	1.3-66.7	1.3-53.0	2.0-53.7	2.4-66.7	4.6-58.1	17.4-24.9	18.3-47.4	3.9-49.1	10.4-47.0
Number of colonoscopies	Mean	2.6	2.6	2.6	2.7	2.7	2.0	2.7	2.7	2.8
	Range	2-7	2-7	2-6	2-6	2-5	2-2	2-5	2-5	2-5

Supplementary Table 2: Other outcomes - The distributions of Lynch Syndrome cancer outcomes by treatment group

	Aspirin	Placebo	p-value (*)	resistant starch	Placebo	p-value (*)
Number of participants with cancer:						
colorectal cancer	10 (3.4)	10 (3.5)	0.96 (1.0)	10 (3.3)	12 (3.8)	0.73 (0.66)
colorectal cancer or other Lynch syndrome cancer	18 (6.1)	24 (8.3)	0.31 (0.31)	17 (5.6)	29 (9.2)	0.09 (0.13)
Other Lynch syndrome cancer						
Endometrial cancer	3	4	0.18 (0.17)	3	5	0.05 (0.10)
Ovarian cancer	1	3	†	0	4	†
Urinary tract	1	3		3	1	
Small bowel	0	1		0	2	
Pancreatic cancer	1	1		0	2	
Hepatobiliary	2	1		1	2	
Skin	0	1		0	1	

* P-value from model adjusted for age and gender comparing those on aspirin treatment (independent of starch treatment status) with aspirin placebo (independent of starch treatment status); similarly for the comparisons involving resistant starch.

† P-value for having at least one 'other' cancer

Supplementary Table 3: The distribution of withdrawal reasons by randomisation group

Aspirin Starch	Participants randomised to both interventions				Participants randomised to a single intervention			
	aspirin Resistant starch	aspirin Placebo	Placebo Resistant starch	Placebo Placebo	aspirin None	Placebo None	None resistant starch	None Placebo
GI bleed/duodenal ulcer	2	3	1	1	0	0	0	0
Cerebrovascular	0	0	0	0	0	0	0	1
Cardiovascular	0	0	1	0	0	0	0	0
Deep Venous Thrombosis	0	1	0	0	0	0	0	0
Non-LS cancers	0	0	0	1	0	0	1	0
Non-CRC LS cancers	1	0	1	2	0	0	0	0
Major other	0	0	1	1	0	0	0	0
Minor other	36	34	47	35	0	0	14	7

N=191

Supplementary Table 4: The distribution of Serious Adverse Events by randomisation group

Aspirin Starch	Participants randomised to both interventions				Participants randomised to a single intervention			
	aspirin Resistant starch	aspirin Placebo	Placebo Resistant starch	Placebo Placebo	aspirin None	Placebo None	None resistant starch	None Placebo
Probable or possible peptic ulcer	2	5	6	2	0	0	0	0
Cerebrovascular events	2	0	1	1	0	0	0	1
Cardiovascular events	1	0	4	1	0	0	0	0
Deep Venous thrombosis	0	2	0	0	0	0	0	0
Non-LS cancers	1	3	2	3	0	0	1	0
Non-CRC LS cancers	0	1	0	0	0	0	0	0
Major other	2	3	5	5	0	0	6	2
Minor Other including bleeding	2	2	0	0	0	0	0	1
TOTALS	10	16	18	12	0	0	7	4
Abdominal abscess	0	2	0	0	0	0	0	0
Acute cholecystitis	0	1	0	1	0	0	0	0
Anaemia	1	0	0	0	0	0	0	0
Anal epithelioma	0	0	0	1	0	0	0	0
Aspergillosis	1	0	0	0	0	0	0	0
Atrial fibrillation	0	0	0	0	0	0	2	0
Black stools	0	1	0	1	0	0	0	0
Bladder stone	0	0	1	0	0	0	0	0
Bleeding from femoral artery	1	0	0	0	0	0	0	0
Breast cancer	0	1	1	1	0	0	1	0
Caecal spirochaetosis	0	0	0	0	0	0	0	1
Cardiac pain	0	0	1	0	0	0	0	0
Cellulitis in leg	0	0	0	0	0	0	1	0
Cerebral haemorrhage	0	0	0	0	0	0	0	1
Cerebral vasculitis	0	0	0	1	0	0	0	0
Coronary arterial stenosis	0	0	1	0	0	0	0	0
Coronary thrombosis	1	0	0	0	0	0	0	0
Died (before receiving therapy)	0	0	0	0	0	0	0	1
Duodenal ulcers	0	3	2	1	0	0	0	0
Deep venous thrombosis	0	2	0	0	0	0	0	0
Endophlebitis	0	0	0	0	0	0	1	0
Failure of anal stoma repair to heal	0	0	0	1	0	0	0	0
Gastric ulcer	0	0	1	0	0	0	0	0
Gastritis	0	0	1	0	0	0	0	0
Gastrointestinal bleed	0	1	1	0	0	0	0	0
Gum bleeding	1	0	0	0	0	0	0	0

Hernia operation	1	0	0	0	0	0	0	0
Hernia with gastric reflux	0	0	0	0	0	0	0	1
Hip replacement	0	0	1	0	0	0	0	0
Liver cancer	0	1	0	0	0	0	0	0
Lung sarcoidosis	0	0	0	1	0	0	0	0
Malignant melanoma	0	1	0	0	0	0	0	0
Meningioma brain tumour	0	0	1	0	0	0	0	0
Myocardial infarction	0	0	1	1	0	0	0	0
Numbness on one side of body	0	0	1	0	0	0	0	0
Operation to close abdominal jejunostomy	0	0	0	1	0	0	0	0
Pancreatic cancer	0	1	0	0	0	0	0	0
Pancreatic cyst	0	0	0	1	0	0	0	0
Hysterectomy	0	0	1	0	0	0	1	0
Pre-tracheal lymphoma	0	0	0	1	0	0	0	0
Prostate cancer	1	0	0	0	0	0	0	0
Pyelonephritis	0	0	0	0	0	0	1	0
Rectal bleed	1	0	1	0	0	0	0	0
Severe nose bleed	0	1	0	0	0	0	0	0
Spinal canal stenosis	0	0	1	0	0	0	0	0
Stroke	2	0	0	0	0	0	0	0
Testicular mass (non neoplastic)	0	0	1	0	0	0	0	0
Vaginal bleeding	0	1	0	0	0	0	0	0
Ventricular fibrillation	0	0	1	0	0	0	0	0

N=67

Supplementary Table 5: Analysis of neoplasia incidence from all colonoscopies within four time groups. Neoplasms are treated as individual events

Time on study (months)	N(%)	No neoplasia	Neoplasia	Relative Risk (95% CI)
Aspirin versus placebo				
	Placebo	133 (86.4)	21 (13.6)	1.0
6-18	Aspirin	134 (91.8)	12 (8.2)	0.6 (0.3, 1.2)
	Placebo	231 (86.2)	37 (13.8)	1.0
19-30	Aspirin	234 (84.2)	44 (15.8)	1.1 (0.8, 1.7)
	Placebo	63 (90.0)	7 (10.0)	1.0
31-42	Aspirin	53 (88.3)	7 (11.7)	1.2 (0.4, 3.1)
	Placebo	63 (91.3)	6 (8.7)	1.0
43 or more	Aspirin	41 (83.7)	8 (16.3)	1.9 (0.7, 5.1)
Resistant starch versus placebo				
	Placebo	154 (91.7)	14 (8.3)	1.0
6-18	Resistant Starch	139 (88.5)	18 (11.5)	1.4 (0.7, 2.7)
	Placebo	242 (83.5)	48 (16.5)	1.0
19-30	Resistant Starch	243 (87.7)	34 (12.3)	0.7 (0.5, 1.1)
	Placebo	66 (91.7)	6 (8.3)	1.0
31-42	Resistant Starch	62 (84.9)	11 (15.1)	1.8 (0.7, 4.6)
	Placebo	54 (88.5)	7 (11.5)	1.0
43 or more	Resistant Starch	54 (87.1)	8 (12.9)	1.1 (0.4, 2.9)

Note participants may be included more than once in this analysis