Table S1. Quality score items for meta-analysis of gene mutations between case and control groups.

Item	Score	Notes
External validity (0–11)		
Age	0/1	Ranges or statistics per groups
Gender	0/1	Gender data per groups
Race/ethnicity	0/1	Race or ethnic data per groups
Matched groups	0/1	Demographic data matched
Disease progression	0–2	Cancer site and stages
Diagnosis method	0/1	Cancer diagnosis method
Health status	0/1	Health status of control group
Case random sample	0/1	Random sample for cancer group
Control random sample	0/1	Random sample for control group
HWE	0/1	Hardy-Weinberg equilibrium for control group
Internal validity (0–12)		
Case recruitment	0/1	Case group recruitment and sampling indicated
Control recruitment	0/1	Control group recruitment and sampling
Same period	0/1	Groups recruited over the same period
Data source	0/1	Sample sources such as blood or tissue indicated
Setting	0/1	Data collection setting indicated
Procedure	0/1	Data collection procedures indicated

Blind	0/1	Data analysis blinding method indicated
Sample handling	0/1	Specimen handling procedures indicated
DNA analysis	0/1	DNA analysis procedure described
Accuracy	0/1	Accuracy of instrumentation analysis indicated
Precision	0/1	Precision of instrumentation indicated
Reliability	0/1	Reliability of instrumentation analysis indicated
Reporting quality (0–6)		
Sample Size Estimate	0/1	A-priori sample size estimate
Tables	0/1	At least two tables for data report
Table Footnote	0/1	Tables with footnotes
Details	0/1	Results with detailed quality
Clear	0/1	Results are clearly reported
Valid Sense	0/1	Results are valid, making sense without bias
Confounding	0/1	Subgroups or confounding variables included

Note. Total possible score = 29.

Table S2. Summary of participant characteristics and *MTHFR* 677 and 1298 loci distributions for studies on colorectal (CR) cancer included in this review, by geographic location.

				MTHFR 677							*MTHFR* 1298									
				Cases *n* (%)			Controls *n* (%)				Cases *n* (%)			Controls *n* (%)				Quality Score[2]		
First Author, Year (Ref. No.)[1]	Ethnicity (Country)	Source (Controls)	Cancer Site (Cases) & Sex	CC	CT	TT	CC	CT	TT	HWE	AA	AC	CC	AA	AC	CC	HWE	External Validity	Internal Validity	Reporting Quality
Australia																				
Liu, 2012 (37)	Caucasian (Australia)	Healthy adults	CR mixed	50 (45)	47 (42)	15 (13)	43 (38)	53 (47)	18 (16)	Yes								7	8	6
Iacopetta, 2009 (38)	Caucasian (Australia)	Adults w/o CR cancer	Colon	382 (44.9)	386 (45.4)	82 (9.7)	428 (44.7)	429 (44.8)	101 (10.5)	Yes								10	9	6
			Male	222 (43.1)	245 (47.6)	48 (9.3)	240 (42.7)	260 (46.3)	62 (11.0)											
			Female	160 (47.8)	141 (42.1)	34 (10.1)	188 (47.5)	169 (42.7)	39 (9.8)											
			Proximal	107 (38.9)	137 (49.8)	31 (11.3)														
			Male	56 (38.4)	75 (51.4)	15 (10.3)														
			Female	51 (39.8)	61 (47.7)	16 (12.5)														
			Distal	275 (47.8)	249 (43.3)	51 (8.9)														
			Male	166 (45.1)	169 (45.9)	33 (9.0)														
			Female	109 (52.7)	80 (38.6)	18 (8.7)														
Reeves, 2009 (39)	Caucasian (Australia)	Adults w/o CR cancer	CR mixed	105 (51.0)	83 (40.3)	18 (8.7)	101 (47.9)	91 (43.1)	19 (9.0)	Yes	92 (44.7)	89 (43.2)	25 (12.1)	86 (40.8)	98 (46.4)	27 (12.8)	Yes	7	6	6
Shannon, 2002 (40)	Caucasian (Australia)	Adults w/other health conditions	Colon	249 (49.7)	197 (39.3)	55 (11.0)	533 (44.2)	560 (46.4)	114 (9.4)	Yes								7	6	6
			Male	115 (49.8)	96 (41.6)	20 (8.6)														
			Female	134 (49.6)	101 (37.4)	35 (13.0)														
			Proximal	129 (46.4)	118 (42.4)	31 (11.2)														
			Distal	120 (53.8)	79 (35.4)	24 (10.8)														
Europe																				
Eussen, 2010 (41)	Caucasian (10 countries[3])	Adults w/o cancer	CR mixed	567 (42.7)	608 (45.7)	154 (11.6)	1019 (43.1)	1076 (45.5)	271 (11.4)	Yes	605 (45.5)	574 (43.2)	151 (11.3)	1099 (46.5)	1007 (42.6)	259 (10.9)	Yes	9	8	6
Osian, 2007 (42)	Caucasian (Romania)	Healthy adults	CR mixed	38 (55.1)	25 (36.2)	6 (8.7)	47 (70.1)	17 (25.4)	4 (4.5)	Yes	33 (47.8)	32 (46.4)	4 (5.8)	41 (61.2)	25 (37.3)	1 (1.5)	Yes	10	7	4
Jokić, 2011 (43)	Caucasian (Croatia)	Healthy adults	Colon	139 (46.3)	130 (43.3)	31 (10.4)	142 (47.3)	130 (43.3)	28 (9.4)	Yes	137 (45.7)	136 (45.3)	27 (9.0)	140 (46.7)	128 (42.7)	32 (10.6)	Yes	7	4	6
Battistelli, 2006	Caucasian	Healthy	CR mixed	32 (34.4)	40 (43.0)	21 (22.6)	30 (30.0)	51 (51.0)	19	Yes								8	6	4

(44)	(Italy)	adults							(19.0)											
	Caucasian	Adults w/o							56											
Toffoli, 2003 (45)	(Italy)	cancer	Colon	93 (33.7)	145 (52.5)	38 (13.8)	83 (29.7)	140 (50.2)	(20.1)	Yes	122 (44.2)	129 (46.7)	25 (6.9)	133 (47.6)	121 (43.4)	25 (9.0)	Yes	7	6	6
									34											
			Male	51 (34.0)	75 (50.0)	24 (16.0)	51 (29.5)	88 (50.9)	(19.6)		70 (46.7)	65 (43.3)	15 (10.0)	87 (50.3)	71 (41.0)	15 (8.7)				
									22											
			Female	42 (33.3)	70 (55.6)	14 (11.1)	32 (30.2)	52 (49.1)	(20.7)		52 (41.3)	64 (50.8)	10 (7.9)	46 (43.4)	50 (47.2)	10 (9.4)				
			Proximal	46 (34.3)	78 (58.2)	10 (7.5)					65 (45.8)	59 (41.5)	18 (12.7)							
			Distal	47 (33.1)	67 (47.2)	28 (19.7)					57 (42.5)	70 (52.2)	7 (5.2)							
		Adults																		
		w/other																		
	Caucasian	health				126			117											
Komlósi, 2010 (46)	(Hungary)	conditions	CR each	398 (41.9)	427 (44.9)	(13.2)	442 (47.0)	380 (40.5)	(12.5)	No[4]								7	10	6
									59											
			Colon	208 (44.1)	196 (41.5)	68 (14.4)	216 (46.9)	186 (40.3)	(12.8)											
									58											
			Rectum	190 (39.7)	231 (48.2)	58 (12.1)	226 (47.3)	194 (40.6)	(12.1)											
	Caucasian	Healthy							136							156				
Pardini, 2011 (47)	(Czech)	adults	CR mixed	317 (47.6)	307 (46.1)	42 (6.3)	613 (44.5)	627 (45.6)	(9.9)	Yes	281 (42.2)	309 (46.4)	76 (11.4)	583 (42.3)	638 (46.4)	(11.3)	Yes	7	11	5
Karpinski, 2010	Caucasian	Adults w/o							14											
(48)	(Poland)	cancer	CR mixed	74 (39.8)	97 (52.2)	15 (8.0)	71 (50.7)	55 (39.3)	(10.0)	Yes								8	5	5
	Caucasian	Adults w/o				202			209											
Vossen, 2011 (49)	(Germany)	CR cancer	CR mixed	737 (41.8)	823 (46.7)	(11.5)	795 (43.9)	807 (44.6)	(11.5)	Yes								10	7	6
Plaschke, 2002	Caucasian	Healthy							38							41				
(50)	(Germany)	adults	CR mixed	133 (46.3)	120 (41.8)	34 (11.9)	149 (43.1)	159 (46.0)	(10.9)	Yes	134 (46.7)	124 (43.2)	29 (10.1)	154 (44.5)	151 (43.6)	(11.9)	Yes	5	5	5
	Caucasian	Adults w/o				136			149				107							
Küry, 2008 (51)	(France)	CR cancer	CR mixed	435 (42.5)	452 (44.2)	(13.3)	457 (40.8)	515 (45.9)	(13.3)	Yes	484 (47.3)	432 (42.2)	(10.5)	577 (51.5)	443 (39.5)	101 (9.0)	Yes	8	7	5
DeVogel, 2009	Caucasian	Healthy							167				110			258				
(52)	(Netherlands)	adults	CR mixed	318 (46.2)	320 (46.4)	51 (7.4)	876 (48.9)	750 (41.8)	(9.3)	Yes	299 (43.7)	275 (40.2)	(16.1)	735 (41.6)	774 (43.8)	(14.6)	No	8	10	6
									87							110				
			Male	179 (46.8)	184 (48.2)	19 (5.0)	409 (45.4)	405 (44.9)	(9.6)		167 (43.8)	166 (43.6)	48 (12.6)	345 (39.3)	423 (48.2)	(12.5)				
									80							148				
			Female	139 (45.3)	136 (44.3)	32 (10.4)	467 (52.3)	345 (38.7)	(9.0)		132 (43.6)	109 (36.0)	62 (20.4)	390 (43.9)	351 (39.5)	(16.6)				
Heijmans, 2003	Caucasian	Adults w/o							65											
(53)	(Netherlands)	cancer	CR mixed	7 (38.9)	7 (38.9)	4 (22.2)	399 (50.3)	329 (41.5)	(8.2)	Yes								7	10	6
Wettergren, 2010	Caucasian	Healthy							25											
(54)	(Sweden)	adults	CR mixed	81 (46.3)	76 (43.4)	18 (10.3)	167 (55.9)	107 (35.8)	(8.3)	Yes								10	6	5
Derwinger, 2009	Caucasian	Healthy							25											
(55)	(Sweden)	adults	CR mixed	273 (50.2)	216 (39.7	55 (10.1)	167 (55.9)	107 (35.8)	(8.3)	Yes[4]								7	11	6

Van Guelpen, 2006	Caucasian	Adults w/o							42											
(56)	(Sweden)	cancer	CR mixed	123 (55.9)	85 (38.6)	12 (5.5)	212 (51.1)	161 (38.8)	(10.1)	Yes	85 (38.6)	103 (46.8)	32 (14.6)	189 (45.9)	173 (42.0	50 (12.1)	Yes	10	9	5
	Caucasian						1092		212											
Ulvik , 2004 (57)	(Norway)	-	CR each	1103 (51.3)	899 (40.6)	157 (8.0)	(52.8)	886 (39.0)	(8.2)	Yes								9	10	5
									133											
			Male	710 (51.8)	560 (40.8)	102 (7.4)	695 (50.0)	562 (40.4)	(9.6)											
									79											
			Female	393 (49.9)	339 (43.1)	55 (7.0)	397 (49.6)	324 (40.5)	(9.9)											
			Colon	656 (50.8)	530 (41.1)	105 (8.1)														
			Rectum	411 (51.1)	341 (42.4)	52 (6.5)														
	Caucasian	Healthy							83											
Ryan, 2001 (58)	(Ireland)	newborns	CR mixed	49 (36.0)	73 (53.7)	14 (10.3)	439 (51.8)	326 (38.4)	(9.8)	Yes								7	8	6
Lightfoot, 2008	Caucasian	Adults w/o							49											
(59)	(UK)	CR cancer	CR mixed	238 (48.6)	199 (40.6)	53 (10.8)	271 (45.8)	272 (46.0)	(8.2)	Yes	231 (47.3)	200 (41.0)	57 (11.7)	288 (48.6)	259 (43.7)	46 (7.8)	Yes	7	10	5
			Male	159(53.5)	116(39.1)	22(7.4)	147(45.6)	150(46.6)	25(7.8)		125(42.2)	133(44.9)	38(12.8)	158(48.9)	150(46.4)	15(4.6)				
			Female	79(40.9)	83(43.0)	31(16.1)	124(45.9)	122(45.2)	24(8.9)		106(55.2)	67(34.9)	19(9.9)	130(48.1)	109(40.4)	31(11.5)				
Theodoratou,	Caucasian	Healthy				111			116				106			102				
2008 (60)	(UK)	adults	CR mixed	447 (44.7)	441 (44.2)	(11.1)	439 (43.5)	455 (45.0)	(11.5)	Yes	465 (46.7)	425 (42.7)	(10.6)	462 (45.8)	445 (44.1)	(10.1)	Yes	8	4	5
	Caucasian	Healthy							47											
Sharp, 2007 (61)	(UK)	adults	CR mixed	117 (46.6)	111 (44.2)	23 (9.2)	170 (43.2)	177 (44.9)	(11.9)	Yes	105 (42.9)	111 (45.3)	29 (11.8)	177 (44.9)	157 (39.9)	60 (15.2)	No	8	6	5
		Family																		
	Caucasian	members					1173	1193	326											
Hubner, 2007 (62)	(UK)	of patients	CR mixed	743 (46.6)	759 (44.2)	183 (9.2)	(43.2)	(44.9)	(11.9)	Yes								8	6	6
Pufulete , 2003	Caucasian	Adults w/o											2			3				
(63)	(UK)	CR cancer	CR mixed	16 (57.2)	6 (21.4)	6 (21.4)	41 (53.9)	29 (38.2)	6 (7.9)	Yes	16 (57.2)	10 (35.7)	(7.1)	47 (61.8)	26 (34.2)	(4.0)	Yes	6	10	6
	Caucasian	Adults w/o							49											
Sachse, 2002 (64)	(UK)	cancer	CR mixed	238 (48.6)	199 (40.6)	53 (10.8)	271 (45.8)	272 (45.9)	(8.3)	Yes								8	7	4
Delgado-Plasencia,	Caucasian	Healthy		32	16	2	44	50	9											
2013 (65)	(Spain)	adults	CR mixed	(64)	(32)	(4)	(43)	(49)	(9)	Yes								8	5	5
	Caucasian	Adults w/o							69											
Abuli, 2011 (66)	(Spain)	cancer	CR mixed	169 (32.8)	274 (53.2)	72 (14.0)	189 (38.1)	238 (48.0)	(13.9)	Yes								5	6	5
Fernandez-Peralta,	Caucasian	Adults w/o				2							6			2				
2010 (67)	(Spain)	cancer	CR mixed	89 (62.2)	52 (36.4)	(1.4)	44 (42.7)	50 (48.6)	9 (8.7)	Yes	84 (58.7)	53 (37.1)	(4.2)	57 (55.3)	44 (42.7)	(2.0)	No[4]	10	7	4
	Caucasian	Adults w/o							61											
Landi, 2005 (68)	(Spain)	cancer	CR mixed	128 (36.6)	158 (45.1)	64 (18.3)	109 (35.3)	139 (45.0)	(19.7)	Yes	189 (52.5)	146 (40.6)	25 (6.9)	170 (53.3)	127 (39.8)	22 (6.9)	Yes	8	6	5
Guerreiro, 2008	Caucasian	Adults w/o																		
(69)	(Portugal)	cancer	CR mixed	94 (48.0)	76 (38.8)	26 (13.2)	84 (42.0)	107 (53.5)	9 (4.5)	No		NA						6	5	5
North America																				
Ashmore, 2013	Caucasian (US)	Adults w/o	CR mixed	241	309	75	263	259	81	Yes[4]								6	9	6

(70)		CR cancer		(39)	(49)	(12)	(44)	(43)	(13)											
	Caucasian	Healthy	CR mixed						149							114				
Lee, 2012 (71)	(US)	adults		250 (47.1)	229 (43.1)	52 (9.8)	464 (46.2)	391 (39.0)	(14.8)	No[4]	246 (45.5)	255 (47.1)	40 (7.4)	495 (48.0)	423 (41.0)	(11.0)	Yes	5	9	5
		Adults w/o							227											
Curtin, 2007 (72)	Caucasian (US)	CR cancer	Colon	432 (47.2)	402 (43.9)	82 (8.9)	887 (45.0)	858 (43.5)	(11.5)	Yes								7	7	5
		Adults w/o							84			18								
Chen, 1996 (73)	Caucasian (US)	CR cancer	CR mixed	67 (46.5)	64 (44.4)	13 (9.0)	280 (44.6)	263 (41.9)	(13.4)	Yes[4]		(5, 8, 5)								
LeMarchand, 2002																				
(74)		Healthy							24											6
	Caucasian (US)	adults	CR mixed	66 (44.3)	64 (43.0)	19 (12.7)	66 (38.6)	81 (47.4)	(14.0)	Yes	78 (52.7)	56 (37.8)	14 (9.5)	86 (50.3)	65 (38.0)	20 (11.7)	No	7	6	
	Asian	Healthy							77											
	American (US)	adults	CR mixed	126 (39.1)	153 (47.5)	43 (13.4)	138 (34.8)	182 (45.8)	(19.4)		205 (65.1)	100 (31.7)	10 (3.2)	244 (61.8)	136 (34.4)	15 (3.8)	No			
		Healthy				6							2							
	Hawaiian (US)	adults	CR mixed	44 (57.1)	27 (35.1)	(7.8)	53 (60.2)	32 (36.4)	3 (3.4)		41 (54.0)	33 (43.4)	(2.6)	50 (57.5)	34 (39.1)	3 (3.4)	No			
		Adults w/o							51											
Keku, 2002 (75)	Caucasian (US)	CR cancer	Colon	144 (46.8)	140 (45.4)	24 (7.8)	265 (49.2)	223 (41.4)	(9.4)	Yes	156 (50.5)	132 (42.7)	21 (6.8)	237 (43.8)	236 (43.6)	68 (12.6)	Yes	7	9	6
	African	Adults w/o				3							8							
	American (US)	CR cancer	Colon	198 (81.2)	43 (17.6)	(1.2)	264 (80.2)	59 (18.0)	6 (1.8)	Yes	157 (64.6)	78 (32.1)	(3.3)	217 (66.0)	99 (30.0)	13 (4.0)	Yes			
Murphy, 2008		Adults w/o					7		453	384				24						
(76)	Mixed (US)	CR cancer	CR mixed		48 (48.5)	44 (44.4)	(7.1)		(48.2)	(40.9)	102 (10.9)	Yes	NA	(11, 8, 5)						
Murtaugh, 2007		Adults w/o							112							111				
(77)	Mixed (US)	CR cancer	Rectum	362 (48.2)	305 (40.6)	84 (11.2)	469 (47.9)	398 (40.7)	(11.4)	Yes[4]	364 (48.5)	320 (42.6)	67 (8.9)	438 (44.8)	430 (43.9)	(11.3)	Yes	8	6	6
									65											
			Male	195 (43.7)	193 (43.3)	58 (13.0)	267 (48.2)	222 (40.1)	(11.7)		223 (50.0)	186 (41.7)	37 (8.3)	252 (45.5)	235 (42.4)	67 (12.1)				
									47											
			Female	167 (54.8)	112 (36.7)	26 (8.5)	202 (47.5)	176 (41.4)	(11.1)		141 (46.2)	134 (43.9)	30 (9.8)	186 (43.8)	195 (45.9)	44 (10.3)				
		Adults w/o							112				33							
Koushik, 2006 (78)	Mixed (US)	cancer	CR mixed	166 (47.6)	145 (41.5)	38 (10.9)	355 (44.7)	327 (41.2)	(14.1)	No[4]	154 (43.6)	166 (47.0)	(9.4)	389 (48.3)	332 (41.2)	85 (10.5)	Yes	6	10	5
LeMarchand, 2005		Adults w/o							255											
(79)	Mixed (US)	CR cancer	CR each	394 (48.2)	336 (41.1)	87 (10.7)	987 (48.8)	779 (38.6)	(12.6)	No[4]								8	10	6
			Colon	295 (49.4)	246 (41.2)	56 (9.4)		NA												
			Rectum	99 (45.0)	90 (40.9)	31 (14.1)		NA												
			In situ or regional	202 (44.4)	200 (44.0)	53 (11.6)		NA												
			Metastasis	183 (52.3)	133 (38.0)	34 (9.7)		NA												

		Adults w/o							227							216				
Curtin, 2004 (80)	Mixed (US)	CR cancer	Colon	734 (45.7)	724 (45.0)	150 (9.3)	887 (45.0)	858 (43.5)	(11.5)	Yes	757 (47.1)	698 (43.4)	153 (9.5)	929 (47.1)	827 (41.9)	(11.0)	Yes	8	7	6
									123											
			Male	402 (45.1)	412 (46.2)	78 (8.7)	465 (44.8)	451 (43.4)	(11.8)		420 (47.1)	379 (42.5)	93 (10.4)	504 (48.5)	432 (41.6)	103 (9.9)				
									103							113				
			Female	327 (46.5)	305 (43.4)	71 (10.1)	421 (45.5)	401 (43.4)	(11.1)		331 (47.1)	312 (44.4)	60 (8.5)	422 (45.6)	390 (42.2)	(12.2)				
		Adults w/o							49											
Ma, 1997 (81)	Mixed (US)	CR cancer	CR mixed	92 (45.5)	92 (45.5)	18 (9.0)	145 (44.5)	132 (40.5)	(15.0)	No[4]								7	9	6
Gallegos-Arreola,	Hispanic	Healthy				119			32											
2009 (82)	(Mexico)	adults	CR mixed	124 (33.6)	126 (34.1)	(32.3)	59 (34.7)	79 (46.5)	(18.8)	Yes								7	4	4
Delgado-Enciso,	Hispanic								24											
2001 (83)	(Mexico)	-	CR mixed	15 (20.3)	42 (56.7)	17 (23.0)	34 (30.9)	52 (47.3)	(21.8)	Yes								5	7	3
South America																				
Guimarães, 2011		Healthy							17				8							
(84)	Mixed (Brazil)	adults	CR mixed	48 (42.5)	50 (44.2)	15 (13.3)	92 (48.9)	79 (42.0)	(9.1)	Yes	67 (59.3)	38 (33.6)	(7.1)	127 (67.5)	49 (26.1)	12 (6.4)	No[4]	9	6	5
		Healthy							30				6							
Lima, 2007 (85)	Mixed (Brazil)	adults	CR each	41 (40.2)	46 (45.1)	15 (14.7)	143 (47.7)	127 (42.3)	(10.0)	Yes	68 (66.7)	28 (27.4)	(5.9)	191 (63.7)	93 (31.0)	16 (5.3)	Yes	8	5	6
			Colon	40 (40.4)	44 (44.4)	15 (15.2)	67 (67.7)	26 (26.3)	6 (6.1)											
			Rectum	1 (33.3)	2 (67.7)	0 (0)	1 (33.3)	2 (67.7)	0 (0)											
			Proximal	12 (38.7)	15 (48.4)	4 (12.9)	23 (74.2)	7 (22.6)	1 (3.2)											
			Distal	28 (41.2)	29 (42.6)	11 (16.2)	44 (64.7)	19 (27.9)	5 (7.4)											
			Male	26 (47.3)	22 (40.0)	7 (12.7)	37 (67.3)	14 (25.4)	4 (7.3)											
			Female	15 (31.9)	24 (51.1)	8 (17.0)	31 (66.0)	14 (29.8)	2 (4.2)											
	Caucasian								5											
	(Brazil)			36 (40)	40 (44.4)	14 (15.6)	61 (67.8)	24 (26.7)	(5.5)											
				4	5	1	5	4	1											
	African (Brazil)			(40)	(50)	(10)	(50)	(40)	(10)											
Asia																				
		Adults w/o							134				9							
Matsuo, 2005 (86)	Asian (Japan)	cancer	CR mixed	106 (41.4)	114 (44.5)	36 (14.1)	289 (37.5)	348 (45.1)	(17.4)	Yes	163 (63.4)	85 (33.1)	(3.5)	479 (62.5)	257 (33.5)	31 (4.0)	Yes	9	9	6
		Adults w/o							57				1							
Otani, 2005 (87)	Asian (Japan)	cancer	CR mixed	32 (30.2)	49 (46.2)	25 (23.6)	51 (23.0)	114 (51.3)	(25.7)	Yes	73 (68.9)	32 (30.2)	(0.9)	156 (69.7)	63 (28.1)	5 (2.2)	Yes	8	8	6
		Adults w/o							133											
Yin, 2004 (88)	Asian (Japan)	CR cancer	CR each	270 (39.4)	330 (48.2)	85 (12.4)	278 (35.7)	367 (47.2)	(17.1)	Yes	438 (64.0)	220 (32.1)	27 (3.9)	515 (66.2)	244 (31.4)	19 (2.4)	Yes	10	4	6
			Colon	154 (40.3)	180 (47.1)	48 (12.6)					236 (61.8)	128 (33.5)	18 (4.7)							
			Rectum	110 (37.9)	144 (49.7)	36 (12.4)					192 (66.2)	90 (31.0)	8 (2.8)							
			Proximal	59 (39.3)	75 (50.0)	16 (10.7)					96 (64.0)	47 (31.3)	7 (4.7)							
			Distal	95 (40.9)	105 (45.3)	32 (13.8)					140 (60.3)	81 (34.9)	11 (4.7)							
Matsuo, 2002 (89)	Asian (Japan)	Adults w/o	CR each	39 (27.5)	81 (57.0)	22 (15.5)	81 (33.6)	124 (51.5)	36	Yes	94 (66.7)	44 (31.2)	3	157 (65.2)	75 (31.1)	9 (3.7)	Yes	8	5	6

		cancer							(14.9)				(2.1)							
			Colon	23 (31.9)	39 (54.2)	10 (13.9)					50 (69.4)	19 (26.4)	3 (4.2)							
			Rectum	16 (22.9)	42 (60.0)	12 (17.1)					44 (63.8)	25 (36.2)	0 (0)							
		Adults w/o				129			162											
Kim, 2012 (90)	Asian (Korea)	cancer	CR each	265 (33.7)	393 (49.9)	(16.4)	205 (31.3)	289 (44.1)	(24.7)	No								7	9	6
			Colon	121 (33.3)	185 (51.0)	57 (15.7)														
			Rectum	109 (33.0)	164 (49.7)	57 (17.3)														
		Adults w/o							17				1	36						
Kim, 2011 (91)	Asian (Korea)	cancer	CR mixed	30 (44.8)	30 (44.8)	7 (10.4)	15 (28.3)	21 (39.6)	(32.1)	Yes	44 (65.7)	22 (32.8)	(1.5)	(67.9)	16 (30.2)	1 (1.9)	Yes	9	5	5
		Healthy							65											16
Kang, 2011 (92)	Asian (Korea)	adults	CR mixed	87 (34.1)	134 (52.6)	34 (13.3)	145 (32.4)	238 (53.1)	(14.5)	No[4]										(5, 5, 6)
			Male	46 (32.2)	81 (56.6)	16 (11.2)														
			Female	41 (36.6)	53 (47.3)	18 (16.1)														
		Adults w/other health				284			297											
Cui, 2010 (93)	Asian (Korea)	conditions	CR mixed	622 (34.0)	923 (50.5)	(15.5)	540 (31.8)	863 (50.7)	(17.5)	Yes								7	7	6
		Healthy							74											
Park, 1999 (94)	Asian (Korea)	adults	CR mixed	65 (32.5)	107 (53.5)	28 (14.0)	140 (30.4)	246 (53.5)	(16.1)	No[4]								7	4	6
			Male	39 (38.2)	52 (51.0)	11 (10.8)														
			Female	26 (26.5)	55 (56.1)	17 (17.4)														
Chang, 2007		Healthy							16											
(95)	Asian (Taiwan)	adults	CR mixed	85 (43.6)	86 (44.1)	24 (12.3)	92 (47.2)	87 (44.6)	(8.2)	Yes	120 (61.6)	65 (33.3)	10 (5.1)	127 (65.1)	55 (28.2)	13 (6.7)	No[4]	9	8	5
		Healthy							53											
Yin, 2012 (96)	Asian (Chi)	adults	CR mixed	124 (33.5)	167 (45.1)	79 (21.4)	139 (37.6)	178 (48.1)	(14.3)	Yes[4]								7	6	5
		Adults w/o							26				2							
Li, 2011 (97)	Asian (Chi)	cancer	CR mixed	68 (49.6)	54 (39.4)	15 (10.9)	55 (37.9)	64 (44.2)	(17.9)	Yes	88 (64.2)	47 (34.3)	(1.5)	76 (52.4)	60 (41.4)	9 (6.2)	Yes	7	5	6
		Healthy							10											
Zhu, 2011 (98)	Asian (Chi)	adults	CR mixed	29 (33.7)	42 (48.8)	15 (17.4)	49 (49.0)	41 (41.0)	(10.0)	Yes								8	6	6
			Male	16 (32.0)	24 (48.0)	10 (20.0)														
			Female	13 (36.1)	18 (50.0)	5 (13.9)														
		Healthy							66				6							
Cao, 2008 (99)	Asian (Chi)	adults	CR each	109 (34.6)	154 (48.9)	52 (16.5)	121 (32.7)	183 (49.5)	(17.8)	Yes	204 (64.8)	105 (33.3)	(1.9)	239 (64.4)	119 (32.1)	13 (3.5)	Yes	8	6	6
									33											
			Male	67 (35.3)	95 (50.0)	28 (14.7)	72 (32.3)	118 (52.9)	(14.8)		124 (65.3)	62 (32.6)	4 (2.1)	138 (61.9)	77 (34.5)	8 (3.6)				
									33											
			Female	42 (33.6)	59 (47.2)	24 (19.2)	49 (33.3)	65 (44.2)	(22.5)		80 (64.0)	43 (34.4)	2 (1.6)	101 (68.2)	42 (28.4)	5 (3.4)				
			Colon	30 (28.6)	53 (50.5)	22 (20.9)					66 (62.9)	38 (36.2)	1 (1.0)							
			Male	18 (27.7)	31 (47.7)	16 (24.6)					39 (60.0)	25 (38.5)	1 (1.5)							

			Female	12 (30.0)	22 (55.0)	6 (15.0)						27 (67.5)	13 (32.5)	0 (0)								
			Rectum	79 (37.6)	101 (48.1)	30 (14.3)						138 (65.7)	67 (31.9)	5 (2.4)								
			Male	49 (39.2)	64 (51.2)	12 (9.6)						85 (68.0)	37 (29.6)	3 (2.4)								
			Female	30 (35.3)	37 (43.5)	18 (21.2)						53 (62.4)	30 (35.3)	2 (2.4)								
Zhang, 2008		Adults w/o			136	67	91	139	69			189	93		196	89	15					
(100)	Asian (Chi)	cancer	CR mixed	97 (32.3)	(45.3)	(22.3)	(30.4)	(46.5)	(23.1)	Yes		(63.2)	(31.1)	17 (5.7)	(65.3)	(29.7)	(5.0)	Yes	7	7	6	
		Healthy		182	211	56	211	325	136													
Jin, 2007 (101)	Asian (Chi)	adults	CR mixed	(40.5)	(47.0)	(12.5)	(31.4)	(48.4)	(20.2)	Yes[4]									7	7	6	
Miao, 2005		Healthy			87	58	133	201	86			147	48		282	132						
(102)	Asian (Chi)	adults	CR mixed	53 (26.8)	(44.0)	(29.2)	(31.7)	(47.8)	(20.5)	Yes		(74.3)	(24.2)	3 (1.5)	(67.1)	(31.5)	6 (1.4)	No[4]	7	7	3	
		Healthy			53	22	121	183	66			66	38	1	239	119	13					
Gao, 2005 (103)	Asian (Chi)	adults	CR mixed	30 (28.5)	(50.5)	(21.0)	(32.7)	(49.5)	(17.8)	Yes[4]		(62.8)	(36.2)	(10)	(64.4)	(32.1)	(3.5)	Yes[4]	7	8	6	
		Adults w/o			59	15	133	144	63			93	30		227	103						
Jiang, 2004 (104)	Asian (Chi)	cancer	CR mixed	51 (40.8)	(47.2)	(12.0)	(39.1)	(42.4)	(18.5)	No[4]		(75.0)	(24.2)	1 (0.8)	(67.5)	(30.7)	6 (1.8)	Yes[4]	7	7	6	
		Adults w/other																				
Promthet, 2010	Asian	health		104	26	0	94	31	5			43	84		54	71						
(105)	(Thailand)	conditions	Colon	(80.0)	(20.0)	(0)	(72.3)	(23.8)	(3.9)	Yes		(33.1)	(64.6)	3 (2.3)	(41.5)	(54.6)	5 (3.9)	No	8	4	5	
		Adults w/o		118	37	0	261	31	2			33	108		158	129	7					
Rai, 2014 (106)	Asian (India)	cancer	Colon	(76.1)	(23.9)	(0)	(88.8)	(10.5)	(0.7)	Yes		(22.0)	(70.0)	14 (8.0)	(25.6)	(58.1)	(16.3)	No	6	5	5	
Prasad, 2011					12	1	228		1													
(107)	Asian (India)	-	CR mixed	97 (88.2)	(10.9)	(0.9)	(94.6)	12 (5.0)	(0.4)	Yes									4	5	6	
Sameer, 2011		Healthy			18	9	121	27	12													
(108)	Asian (India)	adults	CR mixed	59 (68.6)	(20.9)	(10.5)	(75.6)	(16.9)	(7.5)	No									7	8	6	
					10	5																
			Male	34 (69.4)	(20.4)	(10.2)																
						4																
			Female	25 (67.6)	8 (21.6)	(10.8)																
		Family																				
Chandy, 2010		members			25	1	66	19	1			22	70		22	50	14					
(109)	Asian (India)	of patients	CR mixed	74 (74.0)	(25.0)	(1.0)	(76.7)	(22.1)	(1.2)	Yes		(22.0)	(70.0)	8 (8.0)	(25.6)	(58.1)	(16.3)	Yes	9	10	4	
		Family																				
Wang, 2006		members		257	43	2	255	36	0			141	130	31	105	135	51					
(110)	Asian (India)	of patients	CR each	(85.1)	(14.2)	(0.7)	(87.6)	(12.4)	(0)	Yes		(46.7)	(43.0)	(10.3)	(36.1)	(46.4)	(17.5)	Yes	7	10	6	
												32	22									
			Colon	53 (89.8)	6 (10.2)	0 (0)						(54.2)	(37.3)	5 (8.5)								
				204	37							109	108	26								
			Rectum	(83.9)	(30.3)	2 (0.8)						(44.9)	(44.4)	(10.7)								

Middle-East Asia

Naghibalhossaini,	Mid-Eastern	Healthy				7			13						85	22					
2010 (111)	(Iran)	adults	Colon	64 (42.4)	80 (53.0)	(4.6)	150 (64.9)	68 (29.5)	(5.6)	Yes	38 (37.2)	52 (51.0)	12 (11.8)	79 (42.5)	(45.7)	(11.8)	Yes	7	5	6
			Male	33 (36.7)	51 (56.7)	6 (6.7)	87 (62.1)	46 (32.9)	7 (5.0)		26 (38.2)	41 (60.3)	1 (1.5)	48 (41.0)	60 (51.3)	9 (7.7)				
			Female	31 (50.8)	29 (47.5)	1 (1.6)	63 (69.2)	22 (24.2)	6 (6.6)		12 (35.3)	11 (32.4)	11 (32.4)	31 (44.9)	25 (36.2)	13 (18.8)				
			Proximal	22 (36.7)	37 (61.7)	1 (1.7)					6 (36.7)	16 (61.7)	7 (1.7)							
			Distal	42 (46.2)	43 (47.3)	6 (6.6)					32 (46.2)	36 (47.3)	5 (6.6)							
		Adults w/other																		
Haghighi, 2008	Mid-Eastern	health							63											
(112)	(Iran)	conditions	CR mixed	117 (50.0)	68 (29.1)	49 (20.9)	76 (29.6)	118 (45.9)	(24.5)	Yes								7	8	6
	Mid-Eastern	Healthy		79	45	4	59	45	12		51	59	21	43	58	14				
Yousef, 2013 (113)	(Jordan)	adults	CR mixed	(62)	(35)	(3)	(51)	(39)	(10)	Yes	(39)	(45)	(16)	(37)	(50)	(12)	Yes	9	8	6
Zeybek, 2006	Mid-Eastern	Adults w/o				7			15											
(114)	(Turkey)	cancer	CR mixed	18 (34.6)	27 (51.9)	(13.5)	64 (44.4)	65 (45.1)	(10.4)	Yes								7	6	5
Africa																				
El Awady, 2009		Adults w/o				6														
(115)	African (Egypt)	cancer	CR mixed	6 (17.1)	23 (65.8)	(17.1)	44 (64.7)	20 (29.4)	4 (5.9)	Yes	5 (14.3)	21 (60.0)	9 (25.7)	26 (38.2)	37 (54.4)	5 (7.4)	Yes	6	8	5

Note. C = colon; HWE = Hardy-Weinberg equilibrium; R = rectum.

[1]Reference numbers refer to the Reference List that follows this table.

[2]Quality score ranges: Total score 0–29; external validity 0– 11; internal validity 0–12; report quality 0–6.

[3]10 European Countries: Denmark, France, Greece, Germany, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom.

[4]HWE updated from the original report based on our calculations using the formula available at http://www.koonec.com/k-blog/2010/06/20/hardy-weinberg-equilibrium-calculator.

Table S3a. Differences between risk ratio and odds ratio for *MTHFR* 677 genotypes for colorectal cancer (CRC). (92 studies)

	CRC Cases	Controls		Test of Heterogeneity				Test of Association	
Genotype (no. of studies)	(*N* = 33626) *n* (%)	(*N* = 48688) *n* (%)	Ratio Type	Q	*p*	I^2	Statistical Model	Risk Ratio (95% Cl)	*p*
TT (92)	3886 (11.56)	6016 (12.36)	Risk	183.18	<0.0001	50.3%	Random	0.93 (0.87 - 0.99)	0.0172
			Odds	184.19	<0.0001	50.6%	Random	0.92 (0.85 - 0.98)	0.0151
CT (92)	14802 (44.02)	20922 (42.97)	Risk	179.61	<0.0001	49.3%	Random	1.02 (1.00 - 1.05)	0.0952
			Odds	180.25	<0.0001	48.7%	Random	1.04 (0.99 - 1.09)	0.0998
CC (92)	14938 (44.42)	21750 (44.67)	Risk	202.80	<0.0001	55.1%	Random	1.00 (0.98 - 1.03)	0.7775
			Odds	216.90	<0.0001	58.0%	Random	1.00 (0.95 - 1.05)	0.9871
CC+CT (92)	29740 (88.44)	42672 (87.64)	Risk	197.38	<0.0001	53.9%	Random	1.01 (1.00 - 1.02)	0.0017

				195.2	<0.000	50.6		1.09 (1.02 -	
			Odds	0	1	%	Random	1.17)	0.0151
	18688	26938		223.4	<0.000	59.3		1.00 (0.98 -	
TT +CT (92)	(55.58)	(55.33)	Risk	9	1	%	Random	1.02)	0.9745
				222.5	<0.000	58.0		1.00 (0.95 -	
			Odds	1	1	%	Random	1.05)	0.9871

Table S3b. Differences between risk ratio and odds ratio for *MTHFR* 1298 genotypes for colorectal cancer (CRC). (54 studies)

	CRC Case	Control		Test of Heterogeneity				Test of Association	
Genotype	(*N* =	(*N* =							
(number of	16384)	24874)	Ratio				Statistic	Risk Ratio	
studies)	*n* (%)	*n* (%)	Type	Q	*p*	I^2	al Model	(95% CI)	*p*
				183.1	<0.000	50.3		0.93 (0.87 -	
CC (54)	1439 (8.78)	2332 (9.38)	Risk	8	1	%	Random	0.99)	0.0172
				184.1	<0.000	50.6		0.92 (0.85 -	
			Odds	9	1	%	Random	0.98)	0.0151
	6792	10059		179.6	<0.000	49.3		1.02 (1.00 -	
AC (54)	(41.46)	(40.44)	Risk	1	1	%	Random	1.05)	0.0952
			Odds	180.2	<0.000	48.7	Random	1.04 (0.99 -	0.0998

				5	1	%		1.09)	
	8136	12483		202.8	<0.000	55.1		1.00 (0.98 -	
AA (54)	(49.66)	(50.18)	Risk	0	1	%	Random	1.03)	0.7775
				216.9	<0.000	58.0		1.00 (0.95 -	
			Odds	0	1	%	Random	1.05)	0.9871
	14928	22542		197.3	<0.000	53.9		1.01 (1.00 -	
AA+AC (54)	(91.11)	(90.62)	Risk	8	1	%	Random	1.02)	0.0017
				195.2	<0.000	50.6		1.09 (1.02 -	
			Odds	0	1	%	Random	1.17)	0.0151
	8231	12391		223.4	<0.000	59.3		1.00 (0.98 -	
CC +AC (54)	(55.58)	(49.82)	Risk	9	1	%	Random	1.02)	0.9745
				222.5	<0.000	58.0		1.00 (0.95 -	
			Odds	1	1	%	Random	1.05)	0.9871

Table S4. Meta-prediction: Death from air pollution (AP Death) on *MTHFR* 1209 genotypes for controls (ct) and colorectal cancer cases (CRC), and CRC risk.

	Partition Tree					Tukey Test					
		AP				Levels		SE	Lower	Upper	
Variable	AICc	Death	count	Mean	SD	Compared	Difference	Difference	CI	CI	*p*
CC%ct	363.077	2 & 3	33	30.453	5.56	2/4	3.438	1.732	-0.742	7.618	0.126
		4	21	24.156	5.769	3/4	2.932	1.360	-0.351	6.216	0.089
						2/3	0.505	1.707	-3.616	4.626	0.953
CC%ca	349.494	2 & 3	33	9.324	6.261	3/4	3.230	1.800	-1.114	7.575	0.182
		4	21	6.189	5.289	2/4	2.917	2.291	-2.613	8.447	0.417
						3/2	0.313	2.259	-5.139	5.765	0.990
AC%ct	364.824	2 & 3	33	42.281	7.122	2/4	7.203	2.636	0.840	13.566	0.023
		4	21	35.859	6.271	3/4	6.082	2.071	1.084	11.081	0.014
						2/3	1.120	2.599	-5.153	7.394	0.903
AC%ca	395.392	2 & 3	33	44.625	10.266	2/4	12.595	3.420	4.339	20.851	0.002
		4	21	35.788	6.601	3/4	7.205	2.687	0.719	13.690	0.026
						2/3	5.390	3.372	-2.749	13.530	0.256
AA%ct	402.407	2 & 3	33	48.407	9.494	4/2	10.641	3.733	1.630	19.652	0.017
		4	21	57.914	9.869	4/3	9.015	2.932	1.936	16.094	0.009
						3/2	1.626	3.680	-7.258	10.509	0.898
AA%ca	423.32	2 & 3	33	45.07	12.305	4/2	15.479	4.481	4.663	26.295	0.003

		4	21	57.99	10.661	4/3	10.372	3.520	1.875	18.869	0.013
						3/2	5.107	4.417	-5.557	15.770	0.485
RR8CC	132.705	2	10	1.203	0.947	2/3	0.152	0.303	-0.581	0.884	0.871
		3 & 4	44	1.065	0.757	2/4	0.123	0.308	-0.620	0.866	0.916
						4/3	0.029	0.242	-0.554	0.613	0.992
RR8AC	-58.959	2	10	1.121	0.211	2/4	0.116	0.052	-0.009	0.242	0.075
		3 & 4	44	1.015	0.112	2/3	0.096	0.051	-0.028	0.220	0.160
						3/4	0.021	0.041	-0.078	0.120	0.867
RR8AA	-45.118	2	10	0.911	0.233	4/2	0.093	0.059	-0.049	0.236	0.263
		3 & 4	44	0.985	0.129	3/2	0.057	0.058	-0.083	0.198	0.590
						4/3	0.036	0.046	-0.076	0.148	0.719

Note. AICc = Akaike's information criterion correction; AP death = death rates from air pollution, levels per million (2 = 50–100, 3 = 100–250, 4 = 250–400 and greater); RR = risk ratio.