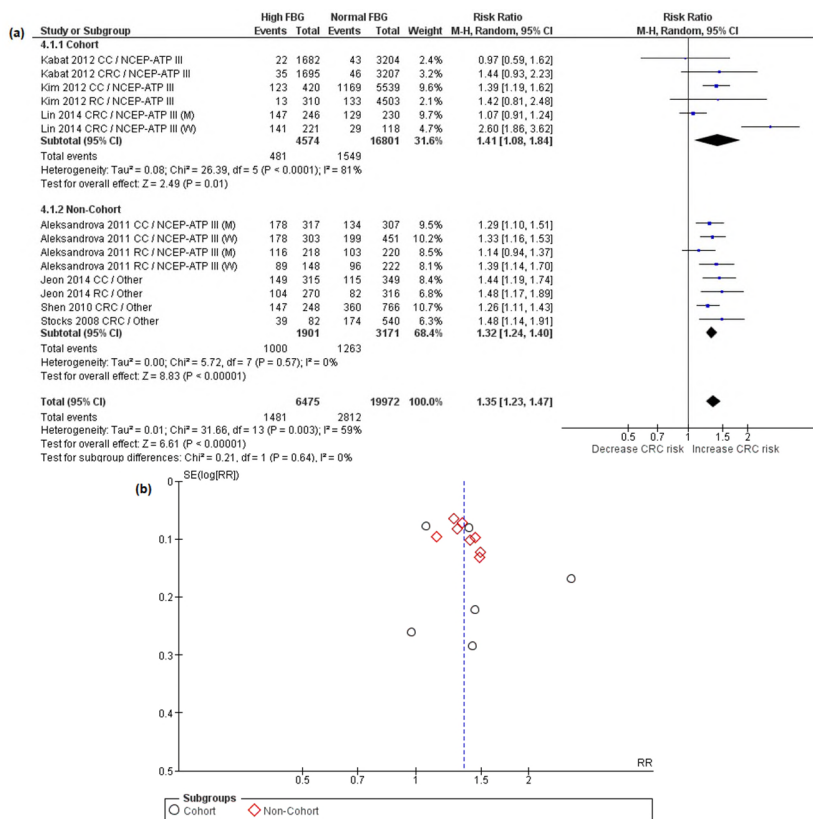# Metabolic syndrome components correlation with colorectal neoplasms: a systematic review and a meta-analysis

Salah Eddine ELHERRAG [a], Youssouf TRAORÉ [a], Méghit Boumediène KHALED [a, b] *

[a] Department of Biology, Faculty of Natural and Life Sciences, Djillali Liabes University, PO Box 89, Sidi-Bel-Abbes (22000), Algeria
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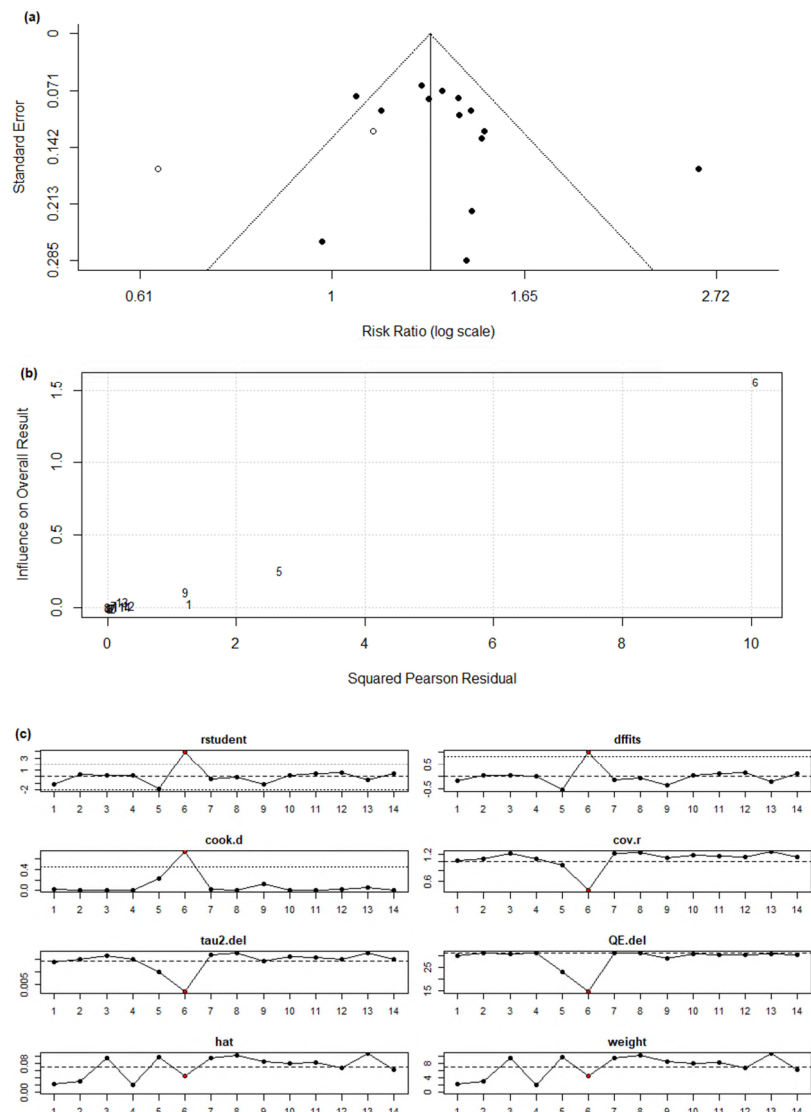
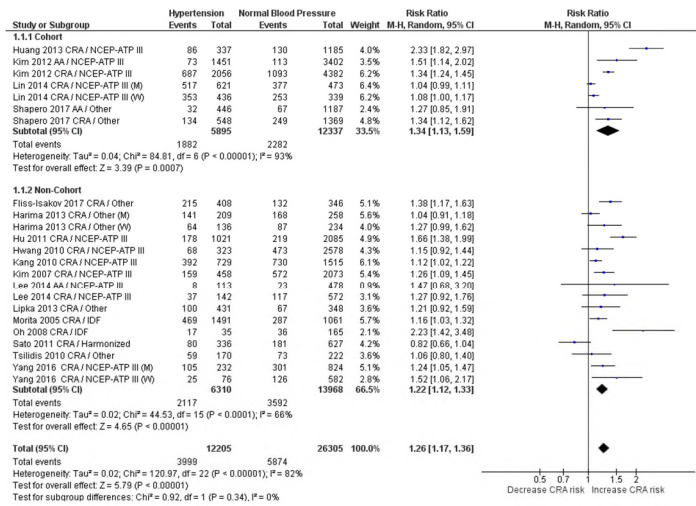* Corresponding author's e-mail: khaled@khaledmb.co.uk

(a)

Study or Subgroup	High FBG Events	Total	Normal FBG Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Cohort						
Kabat 2012 CC / NCEP-ATP III	22	1682	43	3204	2.4%	0.97 [0.59, 1.62]
Kabat 2012 CRC / NCEP-ATP III	35	1695	46	3207	3.2%	1.44 [0.93, 2.23]
Kim 2012 CC / NCEP-ATP III	123	420	1169	5539	9.6%	1.39 [1.19, 1.62]
Kim 2012 RC / NCEP-ATP III	13	310	133	4503	2.1%	1.42 [0.81, 2.48]
Lin 2014 CRC / NCEP-ATP III (M)	147	246	129	230	9.7%	1.07 [0.91, 1.24]
Lin 2014 CRC / NCEP-ATP III (W)	141	221	29	118	4.7%	2.60 [1.86, 3.62]
Subtotal (95% CI)		4574		16801	31.6%	1.41 [1.08, 1.84]
Total events	481		1549			

Heterogeneity: Tau² = 0.08; Chi² = 26.39, df = 5 (P < 0.0001); I² = 81%
Test for overall effect: Z = 2.49 (P = 0.01)

	High FBG Events	Total	Normal FBG Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.2 Non-Cohort						
Aleksandrova 2011 CC / NCEP-ATP III (M)	178	317	134	307	9.5%	1.29 [1.10, 1.51]
Aleksandrova 2011 CC / NCEP-ATP III (W)	178	303	199	451	10.2%	1.33 [1.16, 1.53]
Aleksandrova 2011 RC / NCEP-ATP III (M)	116	218	103	220	8.5%	1.14 [0.94, 1.37]
Aleksandrova 2011 RC / NCEP-ATP III (W)	89	148	96	222	8.1%	1.39 [1.14, 1.70]
Jeon 2014 CC / Other	149	315	115	349	8.4%	1.44 [1.19, 1.74]
Jeon 2014 RC / Other	104	270	82	316	6.8%	1.48 [1.17, 1.89]
Shen 2010 CRC / Other	147	248	360	766	10.7%	1.26 [1.11, 1.43]
Stocks 2008 CRC / Other	39	82	174	540	6.3%	1.48 [1.14, 1.91]
Subtotal (95% CI)		1901		3171	68.4%	1.32 [1.24, 1.40]
Total events	1000		1263			

Heterogeneity: Tau² = 0.00; Chi² = 5.72, df = 7 (P = 0.57); I² = 0%
Test for overall effect: Z = 8.83 (P < 0.00001)

	High FBG		Normal FBG			Risk Ratio M-H, Random, 95% CI
Total (95% CI)		6475		19972	100.0%	1.35 [1.23, 1.47]
Total events	1481		2812			

Heterogeneity: Tau² = 0.01; Chi² = 31.66, df = 13 (P = 0.003); I² = 59%
Test for overall effect: Z = 6.61 (P < 0.00001)
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.64), I² = 0%

(b)

Supplementary Figure 1.1 Association between FBG and CRC incidence: (a) Forest plot; (b) Funnel plot.
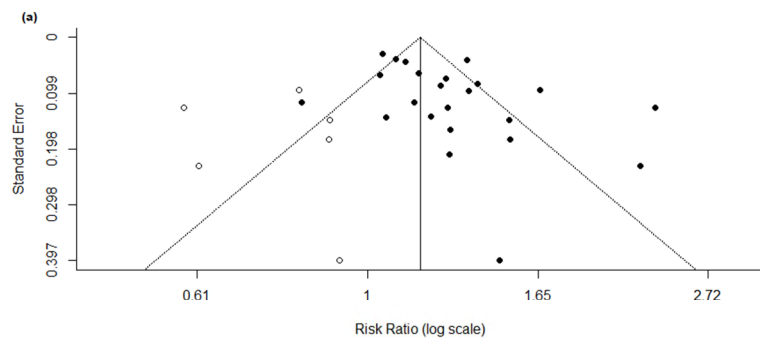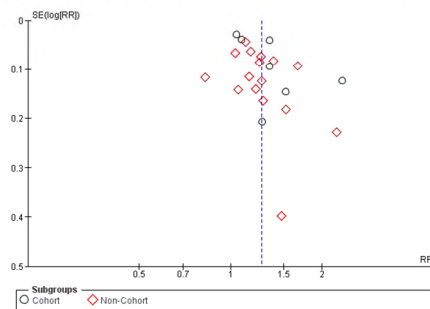
CC colon cancer, CI confidence interval, CRC colorectal cancer, FBG fasting blood glucose, M men, M-H Mantel-Haenszel, NCEP-ATP III National Cholesterol Education Program-Adult Treatment Panel III, RC rectal cancer, RR risk ratio, W women.

Supplementary Figure 1.2 Additional analyses for the association between FBG and CRC incidence: (a) Funnel plot after adjustment to publication bias with the trim and fill method. Two simulated negative studies were added (hollow circles) to the pooled estimates from the meta-analysis (solid circles). The adjusted RR decreased from (1.35; 95% CI 1.23-1.47) in the initial analysis to (1.29; 95% CI 1.17-1.43) after adjustment. (b) Baujat plot: indicates that the 6th dataset (that falls to the top right quadrant of the Baujat plot which corresponds to (Lin 2014 CRC / NCEP-ATP III (W))) has contributed to the overall heterogeneity and result. (c) Influence plot: as there are one marked datasets (which corresponds to (Lin 2014 CRC / NCEP-ATP III (W))), this dataset has met the criteria as an influential study.

Study or Subgroup	Hypertension Events	Hypertension Total	Normal Blood Pressure Events	Normal Blood Pressure Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Cohort						
Huang 2013 CRA / NCEP-ATP III	86	337	130	1185	4.0%	2.33 [1.82, 2.97]
Kim 2012 CRA / NCEP-ATP III	73	1451	113	3402	3.5%	1.51 [1.14, 2.02]
Kim 2012 CRA / NCEP-ATP III	687	2056	1093	4382	6.2%	1.34 [1.24, 1.45]
Lin 2014 CRA / NCEP-ATP III (M)	517	621	377	473	6.4%	1.04 [0.99, 1.11]
Lin 2014 CRA / NCEP-ATP III (W)	353	436	253	339	6.2%	1.08 [1.00, 1.17]
Shapero 2017 AA / Other	32	446	67	1187	2.4%	1.27 [0.85, 1.91]
Shapero 2017 CRA / Other	134	548	249	1369	4.8%	1.34 [1.12, 1.62]
Subtotal (95% CI)		5895		12337	33.5%	1.34 [1.13, 1.59]
Total events	1882		2282			

Heterogeneity: Tau² = 0.04; Chi² = 84.81, df = 6 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.39 (P = 0.0007)

Study or Subgroup	Hypertension Events	Hypertension Total	Normal Blood Pressure Events	Normal Blood Pressure Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.2 Non-Cohort						
Fliss-Isakov 2017 CRA / Other	215	408	132	346	5.1%	1.38 [1.17, 1.63]
Harima 2013 CRA / Other (M)	141	209	168	258	5.6%	1.04 [0.91, 1.18]
Harima 2013 CRA / Other (W)	64	136	87	234	4.0%	1.27 [0.99, 1.62]
Hu 2011 CRA / NCEP-ATP III	178	1021	219	2085	4.9%	1.66 [1.38, 1.99]
Hwang 2010 CRA / NCEP-ATP III	68	323	473	2578	4.3%	1.15 [0.92, 1.44]
Kang 2010 CRA / NCEP-ATP III	392	729	730	1515	6.1%	1.12 [1.02, 1.22]
Kim 2007 CRA / NCEP-ATP III	159	458	572	2073	5.4%	1.26 [1.09, 1.45]
Lee 2014 AA / NCEP-ATP III	8	113	23	478	0.9%	1.47 [0.68, 3.20]
Lee 2014 CRA / NCEP-ATP III	37	142	117	572	3.1%	1.27 [0.92, 1.76]
Lipka 2013 CRA / Other	100	431	67	348	3.6%	1.21 [0.92, 1.59]
Morita 2005 CRA / IDF	469	1491	287	1061	5.7%	1.16 [1.03, 1.32]
Oh 2008 CRA / IDF	17	35	36	165	2.1%	2.23 [1.42, 3.48]
Sato 2011 CRA / Harmonized	80	336	181	627	4.2%	0.82 [0.66, 1.04]
Tsilidis 2010 CRA / Other	59	170	73	222	3.6%	1.06 [0.80, 1.40]
Yang 2016 CRA / NCEP-ATP III (M)	105	232	301	824	5.1%	1.24 [1.05, 1.47]
Yang 2016 CRA / NCEP-ATP III (W)	25	76	126	582	2.8%	1.52 [1.06, 2.17]
Subtotal (95% CI)		6310		13968	66.5%	1.22 [1.12, 1.33]
Total events	2117		3592			

Heterogeneity: Tau² = 0.02; Chi² = 44.53, df = 15 (P < 0.0001); I² = 66%
Test for overall effect: Z = 4.65 (P < 0.00001)

Total (95% CI)		12205		26305	100.0%	1.26 [1.17, 1.36]
Total events	3999		5874			

Heterogeneity: Tau² = 0.02; Chi² = 120.97, df = 22 (P < 0.00001); I² = 82%
Test for overall effect: Z = 5.79 (P < 0.00001)
Test for subgroup differences: Chi² = 0.92, df = 1 (P = 0.34), I² = 0%

Risk Ratio — M-H, Random, 95% CI
0.5 0.7 1 1.5 2
Decrease CRA risk   Increase CRA risk

Supplementary Figure 2.1 Association between BP and CRA formation: (a) Forest plot; (b) Funnel plot.
AA advanced adenomas, *CI* confidence interval, *CRA* colorectal adenoma, *df* degree of freedom, *IDF* International Diabetes Foundation, *M* men, *M-H* Mantel-Haenszel, *NCEP-ATP III* National Cholesterol Education Program-Adult Treatment Panel III, *W* women.

SE(log[RR])

Subgroups
○ Cohort ◇ Non-Cohort

(a)

Standard Error

Risk Ratio (log scale)

(b)

Influence on Overall Result

Squared Pearson Residual

Supplementary Figure 2.2 Additional analyses for the association between BP and CRA development: (a) Funnel plot after adjustment to publication bias with the trim and fill method. Six simulated negative studies were added (hollow circles) to the pooled estimates from the meta-analysis (solid circles). The adjusted RR decreased from (1.26; 95% CI 1.17-1.36) in the initial analysis to (1.17; 95% CI 1.08-1.26) after adjustment. (b) Baujat plot: indicates that the 1st dataset (that falls to the top right quadrant of the Baujat plot which corresponds to (Huang 2013 CRA / NCEP-ATP III)) has contributed to the overall heterogeneity and result. (c) Influence plot: as there are one marked datasets (which corresponds to (Huang 2013 CRA / NCEP-ATP III)), this dataset has met the criteria as an influential study.

(c)

rstudent   dffits
cook.d   cov.r
tau2.del   QE.del
hat   weight
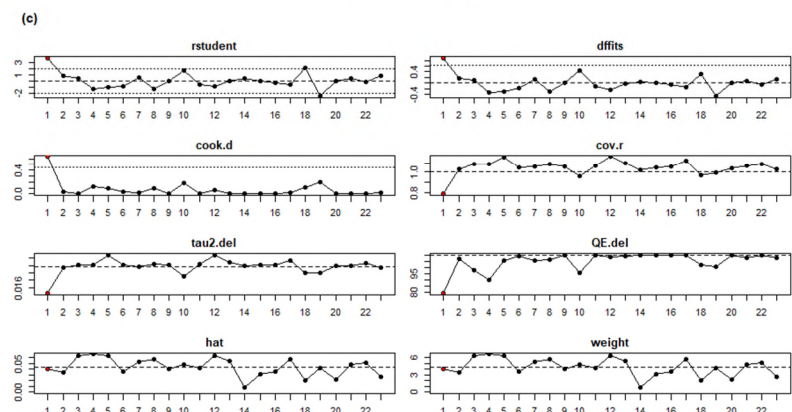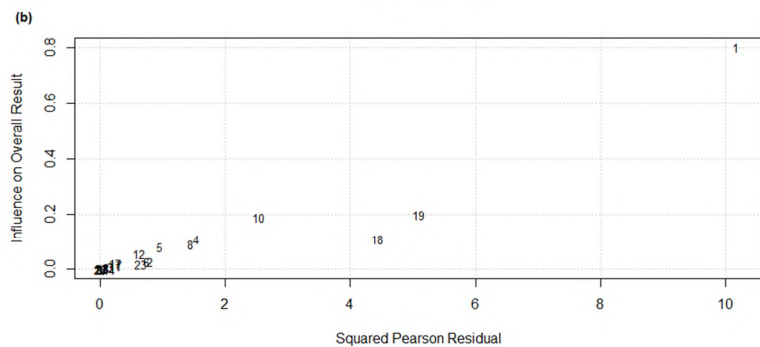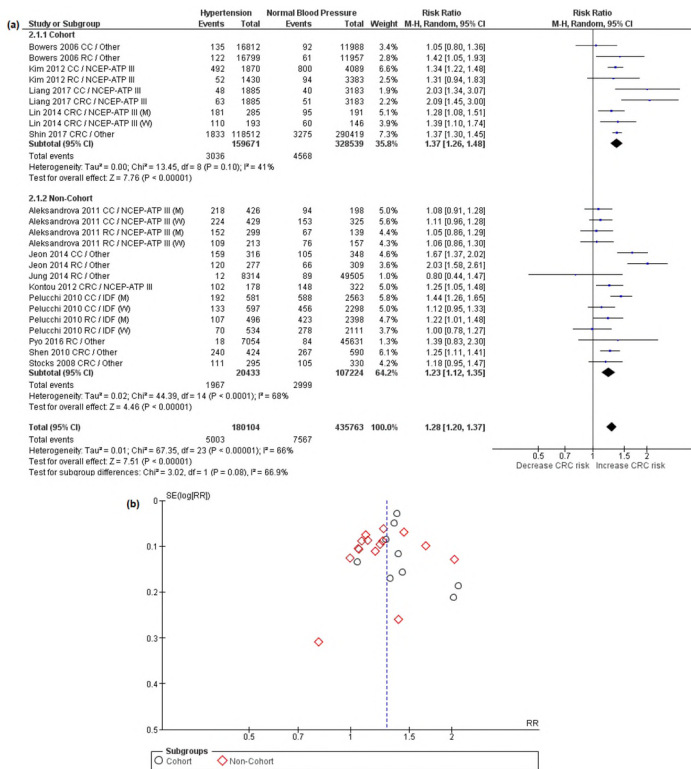
Supplementary Figure 2.3 Association between BP and CRC incidence: (a) Forest plot; (b) Funnel plot.
CC colon cancer, CI confidence interval, CRC colorectal cancer, df degree of freedom, IDF International Diabetes Foundation, M men, M-H Mantel-Haenszel, NCEP-ATP III National Cholesterol Education Program-Adult Treatment Panel III, RC rectal cancer, W women.

Supplementary Figure 2.4 Additional analyses for the association between BP and CRC incidence: (a) Funnel plot after adjustment to publication bias with the trim and fill method. No studies were estimated missing. (b) Baujat plot: indicates that the 15th dataset (that falls to the top right quadrant of the Baujat plot which corresponds to (Jeon 2014 RC / Other)) has contributed to the overall heterogeneity and result. (c) Influence plot: as there is no marked study, no study has met the criteria as an influential study.
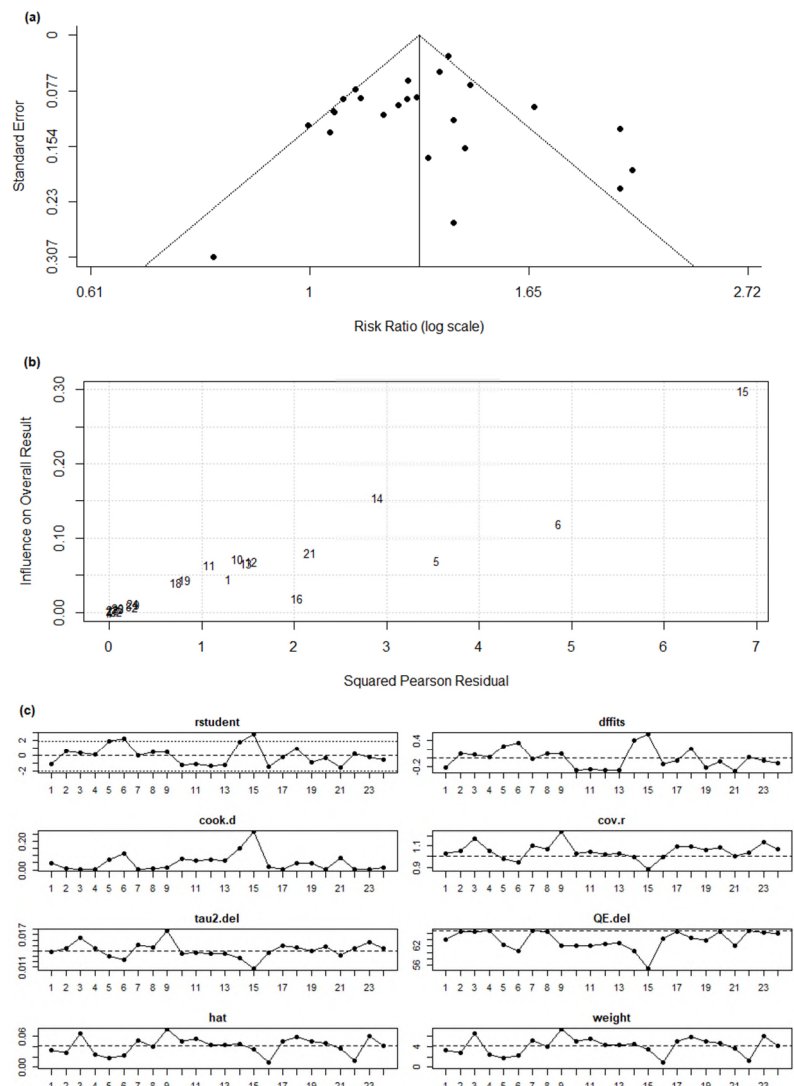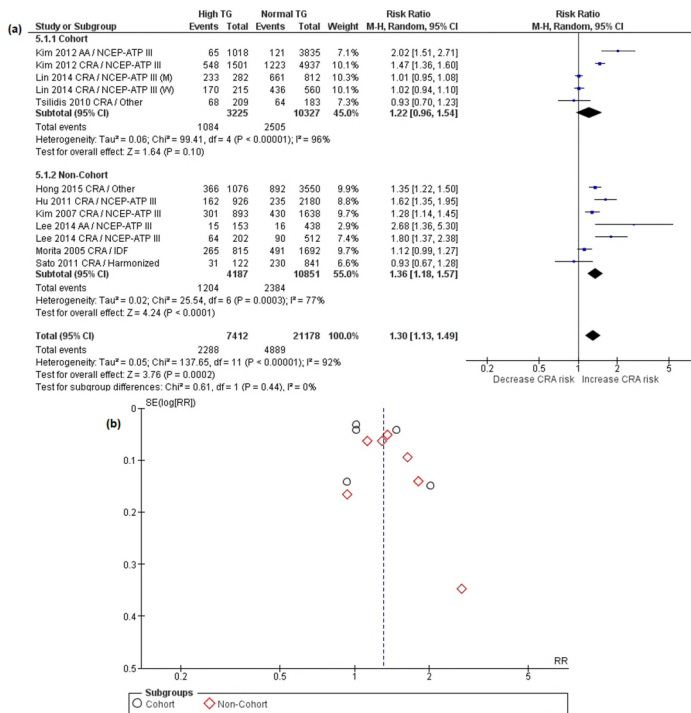
Supplementary Figure 3.1 Association between TG and CRA formation: (a) Forest plot; (b) Funnel plot.
AA advanced adenomas, *CI* confidence interval, *CRA* colorectal cancer, *IDF* International Diabetes Foundation, *M* men, *M-H* Mantel-Haenszel, *NCEP-ATP III* National Cholesterol Education Program-Adult Treatment Panel III, *TG* triglycerides, *W* women.

Supplementary Figure 3.2 Additional analyses for the association between TG and CRA development: (a) Funnel plot after adjustment to publication bias with the trim and fill method. No studies were estimated missing. (b) Baujat plot: indicates that the 1st and 8th dataset (which corresponds to (Kim 2012 AA / NCEP-ATP III) and (Lee 2014 AA / NCEP-ATP III)) has contributed to the overall heterogeneity, while only the first contributed to the overall result. (c) Influence plot: as there is no marked study, no study has met the criteria as an influential study.

(a)

Study or Subgroup	High TG Events	Total	Normal TG Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Cohort						
Kim 2012 CC / NCEP-ATP III	382	1335	910	4624	10.8%	1.45 [1.31, 1.61]
Kim 2012 RC / NCEP-ATP III	44	997	102	3816	6.0%	1.65 [1.17, 2.33]
Lin 2014 CRC / NCEP-ATP III (M)	98	147	178	329	9.9%	1.23 [1.06, 1.43]
Lin 2014 CRC / NCEP-ATP III (W)	54	99	116	240	8.4%	1.13 [0.90, 1.41]
Subtotal (95% CI)		2578		9009	35.1%	1.33 [1.15, 1.54]
Total events	578		1306			
Heterogeneity: Tau² = 0.01; Chi² = 7.56, df = 3 (P = 0.06); I² = 60%						
Test for overall effect: Z = 3.91 (P < 0.0001)						
6.1.2 Non-Cohort						
Aleksandrova 2011 CC / NCEP-ATP III (M)	81	150	231	474	9.4%	1.11 [0.93, 1.32]
Aleksandrova 2011 CC / NCEP-ATP III (W)	70	123	307	631	9.5%	1.17 [0.98, 1.39]
Aleksandrova 2011 RC / NCEP-ATP III (M)	72	133	147	305	9.0%	1.12 [0.92, 1.36]
Aleksandrova 2011 RC / NCEP-ATP III (W)	22	48	163	322	6.3%	0.91 [0.65, 1.25]
Jeon 2014 CC / Other	67	202	197	462	8.4%	0.78 [0.62, 0.97]
Jeon 2014 RC / Other	46	181	140	405	7.1%	0.74 [0.55, 0.98]
Jung 2014 RC / Other	32	12815	69	45004	4.9%	1.63 [1.07, 2.48]
Shen 2010 CRC / Other	125	218	382	796	10.2%	1.19 [1.04, 1.37]
Subtotal (95% CI)		13870		48399	64.9%	1.04 [0.91, 1.20]
Total events	515		1636			
Heterogeneity: Tau² = 0.03; Chi² = 23.87, df = 7 (P = 0.001); I² = 71%						
Test for overall effect: Z = 0.60 (P = 0.55)						
Total (95% CI)		16448		57408	100.0%	1.14 [1.01, 1.28]
Total events	1093		2942			
Heterogeneity: Tau² = 0.03; Chi² = 49.46, df = 11 (P < 0.00001); I² = 78%						
Test for overall effect: Z = 2.10 (P = 0.04)						
Test for subgroup differences: Chi² = 5.60, df = 1 (P = 0.02), I² = 82.2%						

Decrease CRC risk — Increase CRC risk

(b)

Supplementary Figure 3.3 Association between TG and CRC incidence: (a) Forest plot; (b) Funnel plot.
CC colon cancer, CI confidence interval, CRC colorectal cancer, M men, M-H Mantel-Haenszel, NCEP-ATP III National Cholesterol Education Program-Adult Treatment Panel III, RC rectal cancer, RR risk ratio, TG triglycerides, W women.

(a)

Supplementary Figure 3.4 Additional analyses for the association between TG and CRC incidence: (a) Funnel plot after adjustment to publication bias with the trim and fill method. No studies were estimated missing. (b) Baujat plot: indicates that the 9th and 10th datasets (that falls to the top right quadrant of the Baujat plot which corresponds to (Jeon et al., 2014) has contributed to the overall heterogeneity and result. (c) Influence plot: as there is no marked study, no study has met the criteria as an influential study.
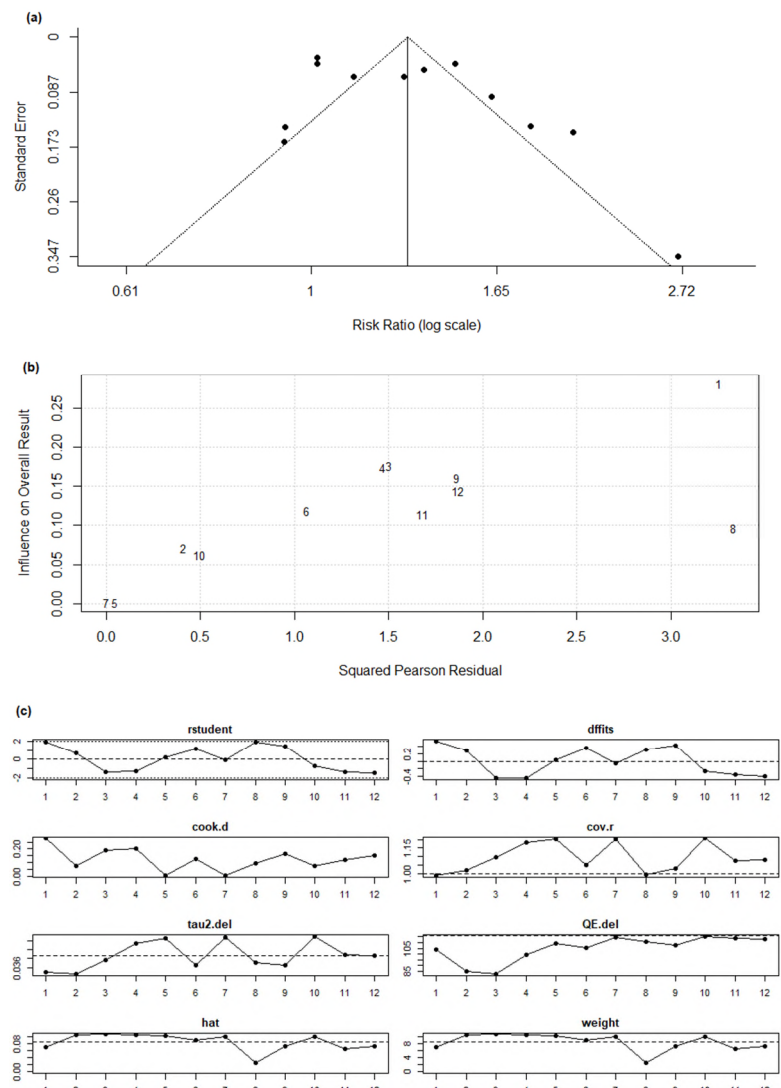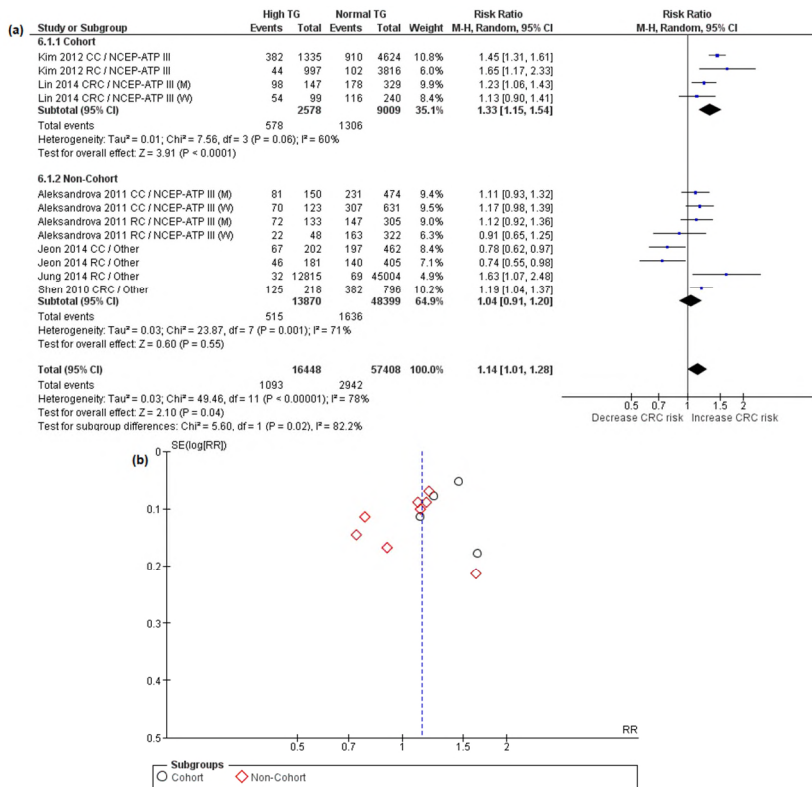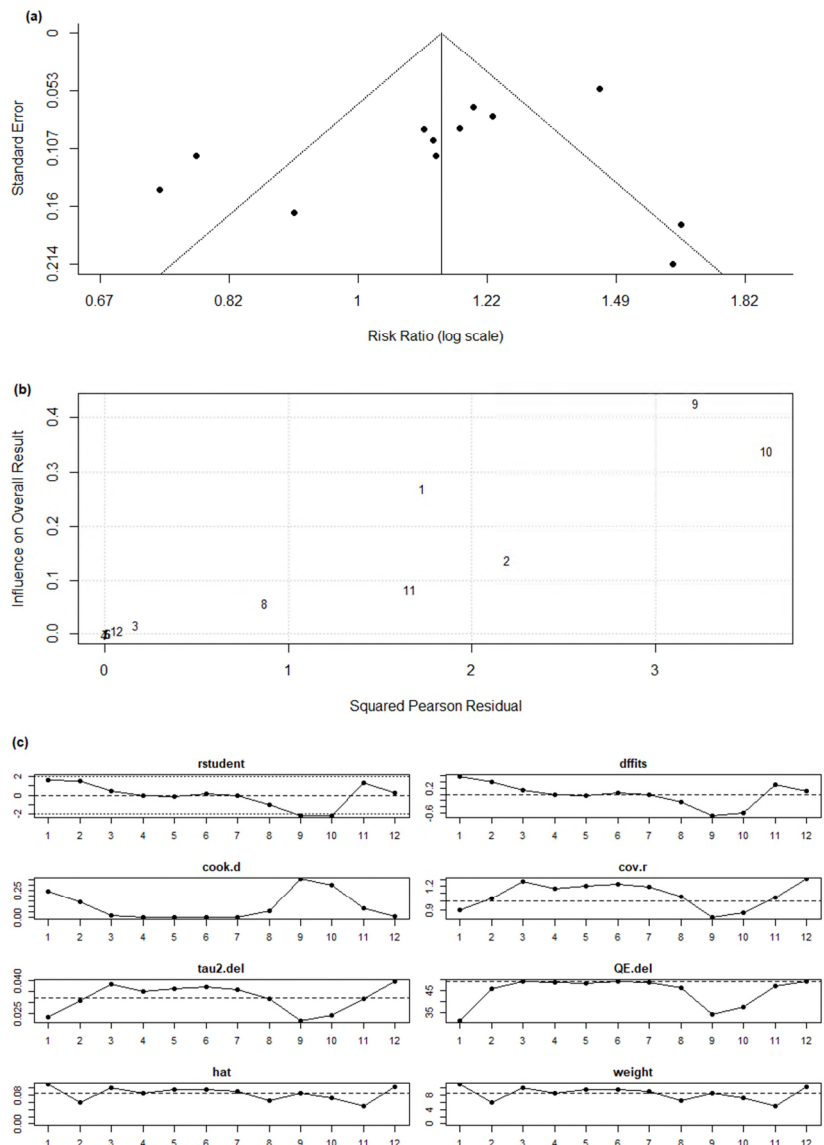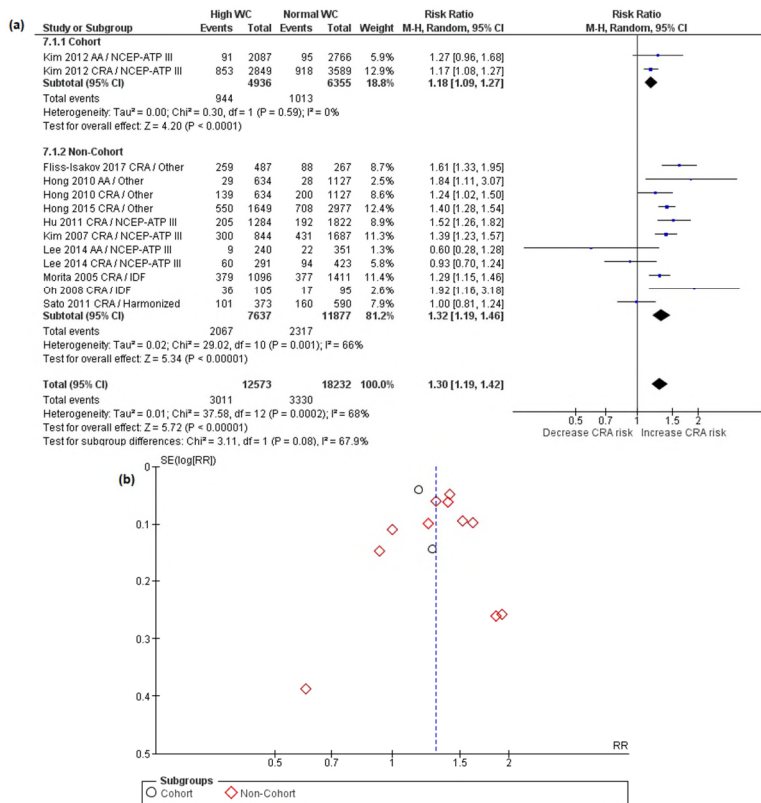
(b)

(c)

(a)

Study or Subgroup	High WC Events	High WC Total	Normal WC Events	Normal WC Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Cohort						
Kim 2012 AA / NCEP-ATP III	91	2087	95	2766	5.9%	1.27 [0.96, 1.68]
Kim 2012 CRA / NCEP-ATP III	853	2849	918	3589	12.9%	1.17 [1.08, 1.27]
Subtotal (95% CI)		4936		6355	18.8%	1.18 [1.09, 1.27]
Total events	944		1013			
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 4.20 (P < 0.0001)						
7.1.2 Non-Cohort						
Fliss-Isakov 2017 CRA / Other	259	487	88	267	8.7%	1.61 [1.33, 1.95]
Hong 2010 AA / Other	29	634	28	1127	2.5%	1.84 [1.11, 3.07]
Hong 2010 CRA / Other	139	634	200	1127	8.6%	1.24 [1.02, 1.50]
Hong 2015 CRA / Other	550	1649	708	2977	12.4%	1.40 [1.28, 1.54]
Hu 2011 CRA / NCEP-ATP III	205	1284	192	1822	8.9%	1.52 [1.26, 1.82]
Kim 2007 CRA / NCEP-ATP III	300	844	431	1687	11.3%	1.39 [1.23, 1.57]
Lee 2014 AA / NCEP-ATP III	9	240	22	351	1.3%	0.60 [0.28, 1.28]
Lee 2014 CRA / NCEP-ATP III	60	291	94	423	5.8%	0.93 [0.70, 1.24]
Morita 2005 CRA / IDF	379	1096	377	1411	11.4%	1.29 [1.15, 1.46]
Oh 2008 CRA / IDF	36	105	17	95	2.6%	1.92 [1.16, 3.18]
Sato 2011 CRA / Harmonized	101	373	160	590	7.9%	1.00 [0.81, 1.24]
Subtotal (95% CI)		7637		11877	81.2%	1.32 [1.19, 1.46]
Total events	2067		2317			
Heterogeneity: Tau² = 0.02; Chi² = 29.02, df = 10 (P = 0.001); I² = 66%						
Test for overall effect: Z = 5.34 (P < 0.00001)						
Total (95% CI)		12573		18232	100.0%	1.30 [1.19, 1.42]
Total events	3011		3330			
Heterogeneity: Tau² = 0.01; Chi² = 37.58, df = 12 (P = 0.0002); I² = 68%						
Test for overall effect: Z = 5.72 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.11, df = 1 (P = 0.08), I² = 67.9%						

Supplementary Figure 4.1 Association between WC and CRA formation: (a) Forest plot; (b) Funnel plot. *AA* advanced adenomas, *CI* confidence interval, *CRA* colorectal cancer, *M-H* Mantel-Haenszel, *NCEP-ATP III* National Cholesterol Education Program-Adult Treatment Panel III, *WC* waist circumference.
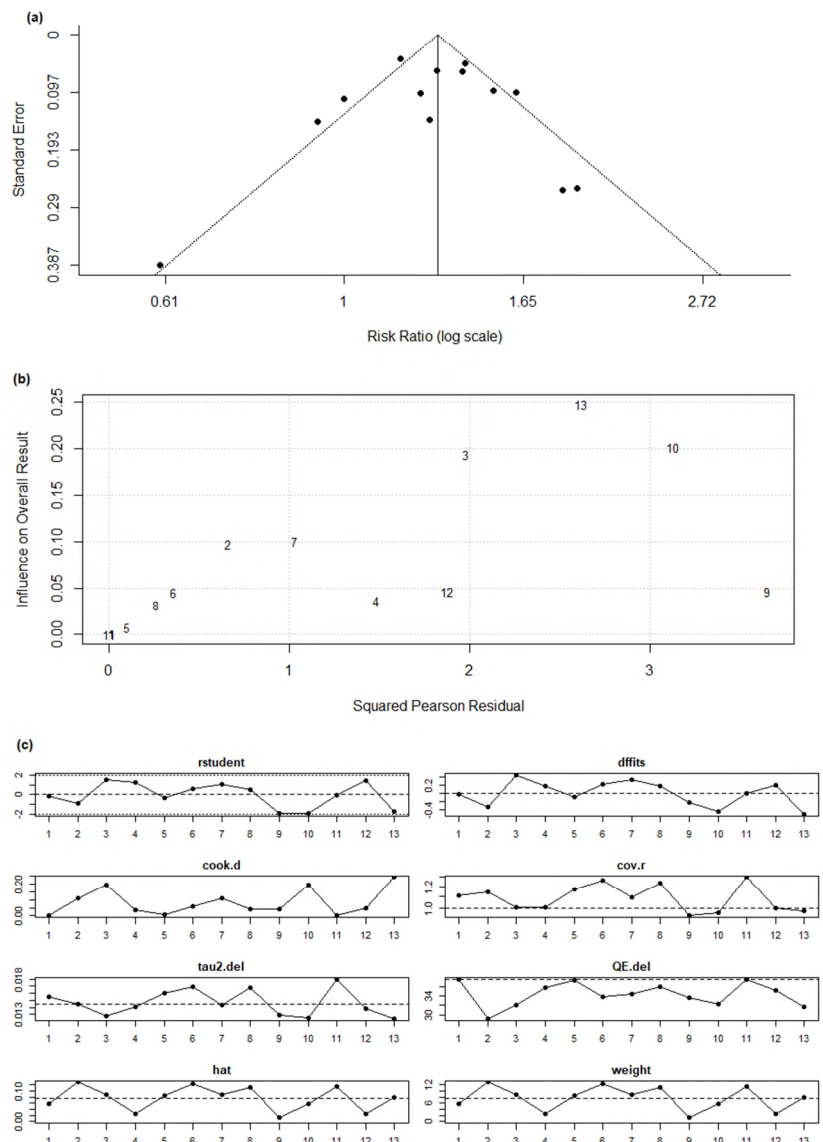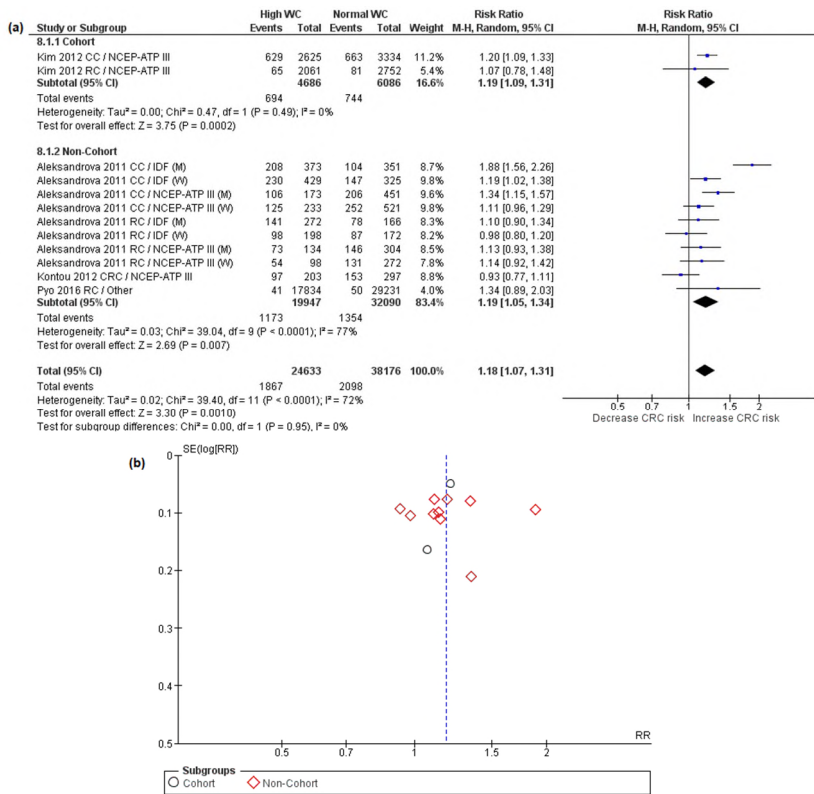
Supplementary Figure 4.2 Additional analyses for the association between WC and CRA development: (a) Funnel plot after adjustment to publication bias with the trim and fill method. No studies were estimated missing. (b) Baujat plot: indicates that the 9th dataset contributed to the overall heterogeneity, the 3rd and the 13th datasets contributed to the overall result, and the 10th dataset contributed to both overall heterogeneity and result (which corresponds to (Lee et al., 2014), (Fliss-Isakov 2017 CRA / AHA), (Sato 2011 CRA / Harmonized)). (c) Influence plot: as there is no marked study, no study has met the criteria as an influential study.
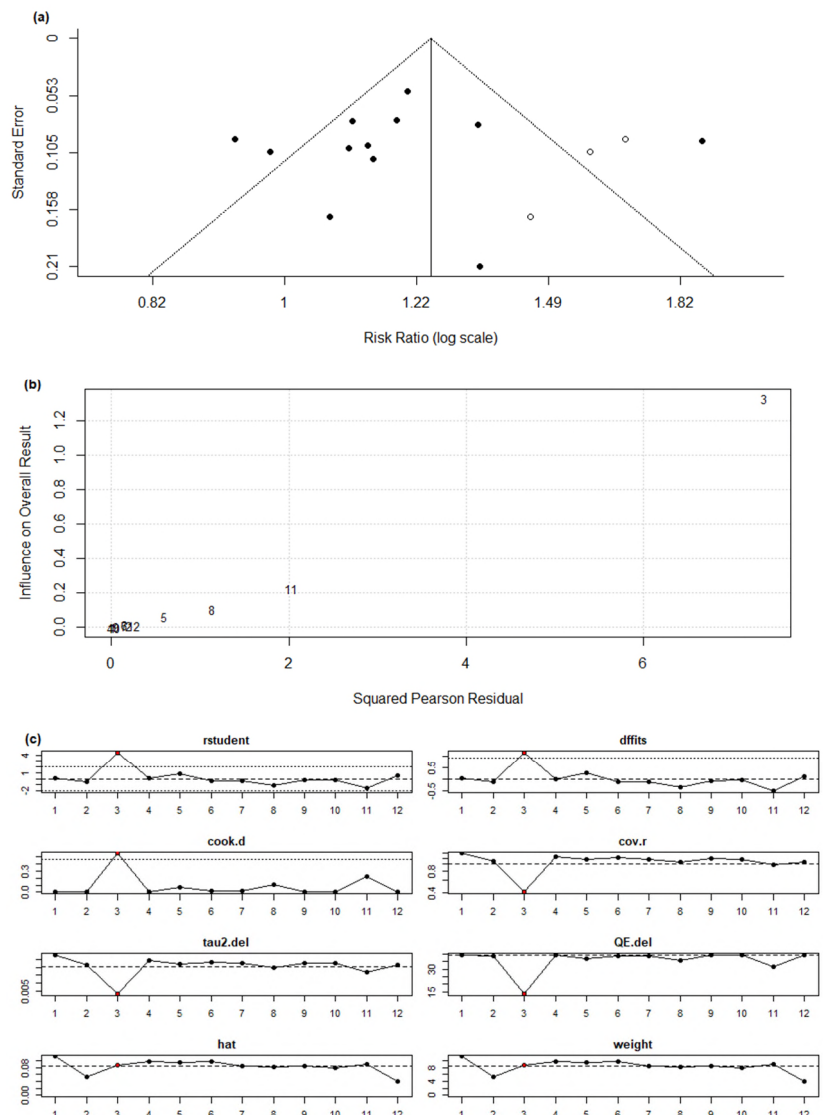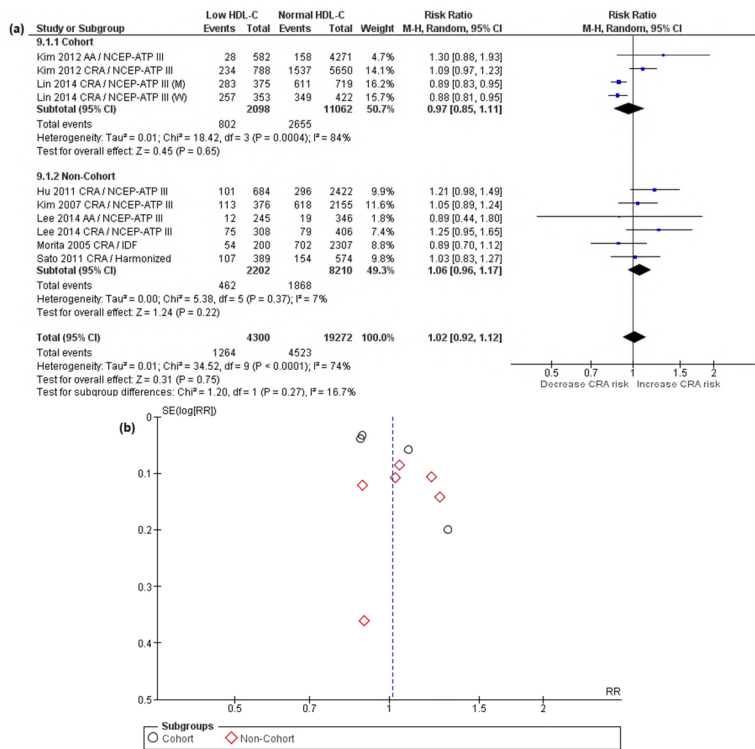
Study or Subgroup	High WC Events	Total	Normal WC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Cohort						
Kim 2012 CC / NCEP-ATP III	629	2625	663	3334	11.2%	1.20 [1.09, 1.33]
Kim 2012 RC / NCEP-ATP III	65	2061	81	2752	5.4%	1.07 [0.78, 1.48]
Subtotal (95% CI)		4686		6086	16.6%	1.19 [1.09, 1.31]
Total events	694		744			
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 3.75 (P = 0.0002)						
8.1.2 Non-Cohort						
Aleksandrova 2011 CC / IDF (M)	208	373	104	351	8.7%	1.88 [1.56, 2.26]
Aleksandrova 2011 CC / IDF (W)	230	429	147	325	9.8%	1.19 [1.02, 1.38]
Aleksandrova 2011 CC / NCEP-ATP III (M)	106	173	206	451	9.6%	1.34 [1.15, 1.57]
Aleksandrova 2011 CC / NCEP-ATP III (W)	125	233	252	521	9.8%	1.11 [0.96, 1.29]
Aleksandrova 2011 RC / IDF (M)	141	272	78	166	8.3%	1.10 [0.90, 1.34]
Aleksandrova 2011 RC / IDF (W)	98	198	87	172	8.2%	0.98 [0.80, 1.20]
Aleksandrova 2011 RC / NCEP-ATP III (M)	73	134	146	304	8.5%	1.13 [0.93, 1.38]
Aleksandrova 2011 RC / NCEP-ATP III (W)	54	98	131	272	7.8%	1.14 [0.92, 1.42]
Kontou 2012 CRC / NCEP-ATP III	97	203	153	297	8.8%	0.93 [0.77, 1.11]
Pyo 2016 RC / Other	41	17834	50	29231	4.0%	1.34 [0.89, 2.03]
Subtotal (95% CI)		19947		32090	83.4%	1.19 [1.05, 1.34]
Total events	1173		1354			
Heterogeneity: Tau² = 0.03; Chi² = 39.04, df = 9 (P < 0.0001); I² = 77%						
Test for overall effect: Z = 2.69 (P = 0.007)						
Total (95% CI)		24633		38176	100.0%	1.18 [1.07, 1.31]
Total events	1867		2098			
Heterogeneity: Tau² = 0.02; Chi² = 39.40, df = 11 (P < 0.0001); I² = 72%						
Test for overall effect: Z = 3.30 (P = 0.0010)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						

Decrease CRC risk — Increase CRC risk

Supplementary Figure 4.3 Association between WC and CRC incidence: (a) Forest plot; (b) Funnel plot.

CC colon cancer, CI confidence interval, CRC colorectal cancer, IDF International Diabetes Foundation, M men, M-H Mantel-Haenszel, NCEP-ATP III National Cholesterol Education Program-Adult Treatment Panel III, RC rectal cancer, RR risk ratio, W women, WC waist circumference.
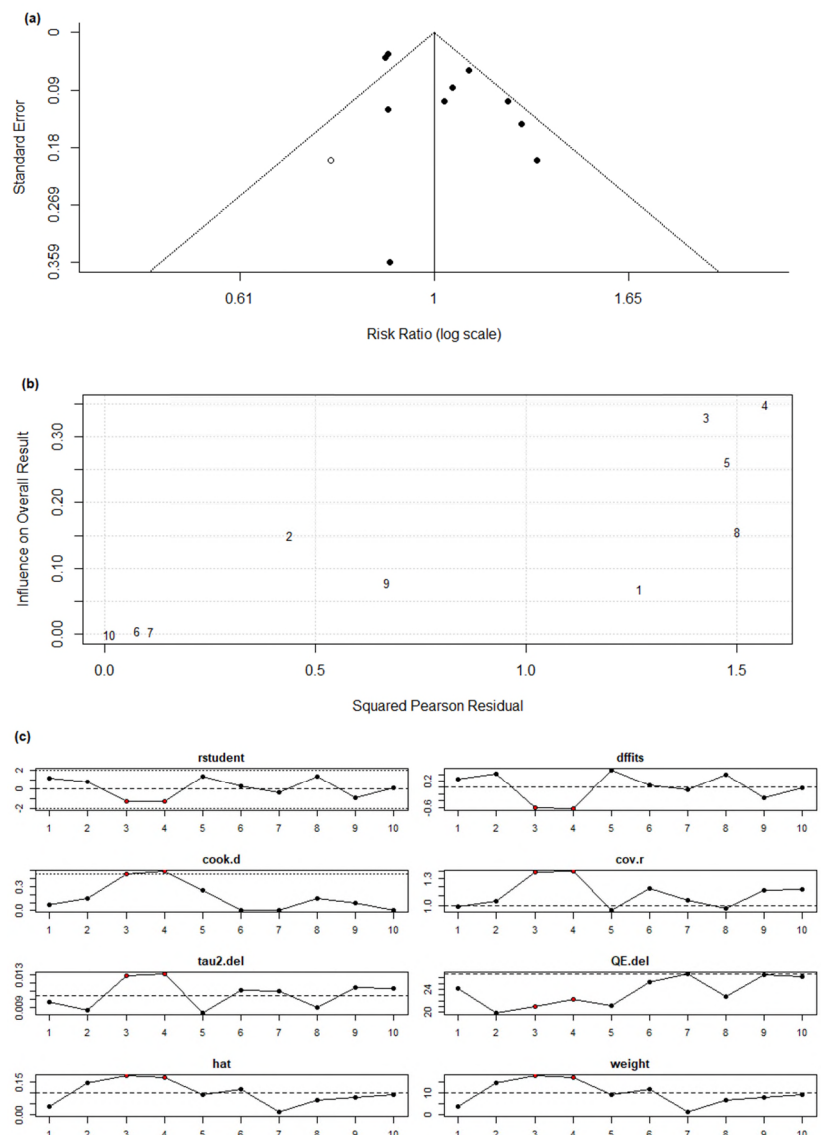

Supplementary Figure 4.4 Additional analyses for the association between WC and CRC incidence: (a) Funnel plot after adjustment to publication bias with the trim and fill method. Three simulated positive studies were added (hollow circles) to the pooled estimates from the meta-analysis (solid circles). The adjusted RR increased from (1.18; 95% CI 1.07-1.31) in the initial analysis to (1.25; 95% CI 1.13-1.38) after adjustment. (b) Baujat plot: indicates that the 3rd dataset (that falls to the top right quadrant of the Baujat plot which corresponds to (Aleksandrova 2011 CC / IDF (M))) has contributed to the overall heterogeneity and result. (c) Influence plot: as there are one marked datasets (which corresponds to (Aleksandrova 2011 CC / IDF (M)), this dataset has met the criteria as an influential study.
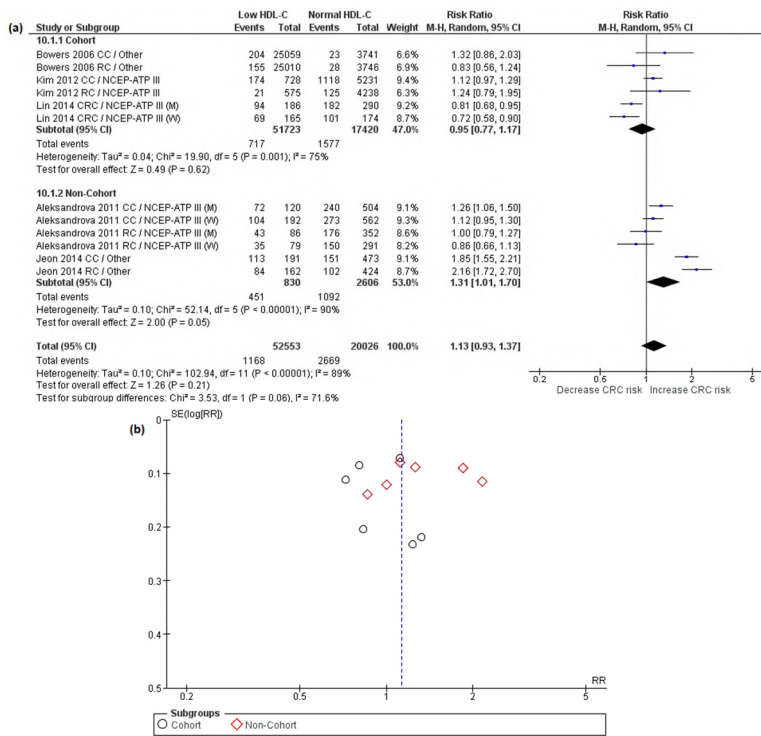
Study or Subgroup	Low HDL-C Events	Low HDL-C Total	Normal HDL-C Events	Normal HDL-C Total	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 Cohort						
Kim 2012 AA / NCEP-ATP III	28	582	158	4271	4.7%	1.30 [0.88, 1.93]
Kim 2012 CRA / NCEP-ATP III	234	788	1537	5650	14.1%	1.09 [0.97, 1.23]
Lin 2014 CRA / NCEP-ATP III (M)	283	375	611	719	16.2%	0.89 [0.83, 0.95]
Lin 2014 CRA / NCEP-ATP III (W)	257	353	349	422	15.7%	0.88 [0.81, 0.95]
Subtotal (95% CI)		2098		11062	50.7%	0.97 [0.85, 1.11]
Total events	802		2655			
Heterogeneity: Tau² = 0.01; Chi² = 18.42, df = 3 (P = 0.0004); I² = 84%						
Test for overall effect: Z = 0.45 (P = 0.65)						
9.1.2 Non-Cohort						
Hu 2011 CRA / NCEP-ATP III	101	684	296	2422	9.9%	1.21 [0.98, 1.49]
Kim 2007 CRA / NCEP-ATP III	113	376	618	2155	11.6%	1.05 [0.89, 1.24]
Lee 2014 AA / NCEP-ATP III	12	245	19	346	1.8%	0.89 [0.44, 1.80]
Lee 2014 CRA / NCEP-ATP III	75	308	79	406	7.4%	1.25 [0.95, 1.65]
Morita 2005 CRA / IDF	54	200	702	2307	8.8%	0.89 [0.70, 1.12]
Sato 2011 CRA / Harmonized	107	389	154	574	9.8%	1.03 [0.83, 1.27]
Subtotal (95% CI)		2202		8210	49.3%	1.06 [0.96, 1.17]
Total events	462		1868			
Heterogeneity: Tau² = 0.00; Chi² = 5.38, df = 5 (P = 0.37); I² = 7%						
Test for overall effect: Z = 1.24 (P = 0.22)						
Total (95% CI)		4300		19272	100.0%	1.02 [0.92, 1.12]
Total events	1264		4523			
Heterogeneity: Tau² = 0.01; Chi² = 34.52, df = 9 (P < 0.0001); I² = 74%						
Test for overall effect: Z = 0.31 (P = 0.75)						
Test for subgroup differences: Chi² = 1.20, df = 1 (P = 0.27), I² = 16.7%						

Decrease CRA risk   Increase CRA risk

Supplementary Figure 5.1 Association between HDL-C and CRA formation: (a) Forest plot; (b) Funnel plot. *AA* advanced adenomas, *CI* confidence interval, *CRA* colorectal cancer, *HDL-C* high-density lipoprotein-cholesterol, *M* men, *M-H* Mantel-Haenszel, *NCEP-ATP III* National Cholesterol Education Program-Adult Treatment Panel III, *W* women.

Supplementary Figure 5.2 Additional analyses for the association between HDL-C and CRA development: (a) Funnel plot after adjustment to publication bias with the trim and fill method. One simulated negative study was added (hollow circle) to the pooled estimates from the meta-analysis (solid circles). The adjusted RR slightly decreased from (1.02; 95% CI 0.92-1.12) in the initial analysis to (1.00; 95% CI 0.92-1.09) after adjustment. (b) Baujat plot: indicates that the 3rd, 4th, and 5th datasets contributed to the overall heterogeneity and result, and the 8th contributed to the overall heterogeneity (which corresponds to (Lin et al., 2014), (Hu 2011 CRA / NCEP-ATP III), and (Lee 2014 CRA / NCEP-ATP III)). (c) Influence plot: as there are two marked datasets (which corresponds to Lin et al., 2014), this study has met the criteria as an influential study.

(a)

Study or Subgroup	Low HDL-C Events	Total	Normal HDL-C Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
10.1.1 Cohort						
Bowers 2006 CC / Other	204	25059	23	3741	6.6%	1.32 [0.86, 2.03]
Bowers 2006 RC / Other	155	25010	28	3746	6.9%	0.83 [0.56, 1.24]
Kim 2012 CC / NCEP-ATP III	174	728	1118	5231	9.4%	1.12 [0.97, 1.29]
Kim 2012 RC / NCEP-ATP III	21	575	125	4238	6.3%	1.24 [0.79, 1.95]
Lin 2014 CRC / NCEP-ATP III (M)	94	186	182	290	9.2%	0.81 [0.68, 0.95]
Lin 2014 CRC / NCEP-ATP III (W)	69	165	101	174	8.7%	0.72 [0.58, 0.90]
Subtotal (95% CI)		51723		17420	47.0%	0.95 [0.77, 1.17]
Total events	717		1577			

Heterogeneity: Tau² = 0.04; Chi² = 19.90, df = 5 (P = 0.001); I² = 75%
Test for overall effect: Z = 0.49 (P = 0.62)

Study or Subgroup	Low HDL-C Events	Total	Normal HDL-C Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
10.1.2 Non-Cohort						
Aleksandrova 2011 CC / NCEP-ATP III (M)	72	120	240	504	9.1%	1.26 [1.06, 1.50]
Aleksandrova 2011 CC / NCEP-ATP III (W)	104	192	273	562	9.3%	1.12 [0.95, 1.30]
Aleksandrova 2011 RC / NCEP-ATP III (M)	43	86	176	352	8.6%	1.00 [0.79, 1.27]
Aleksandrova 2011 RC / NCEP-ATP III (W)	35	79	150	291	8.2%	0.86 [0.66, 1.13]
Jeon 2014 CC / Other	113	191	151	473	9.1%	1.85 [1.55, 2.21]
Jeon 2014 RC / Other	84	162	102	424	8.7%	2.16 [1.72, 2.70]
Subtotal (95% CI)		830		2606	53.0%	1.31 [1.01, 1.70]
Total events	451		1092			

Heterogeneity: Tau² = 0.10; Chi² = 52.14, df = 5 (P < 0.00001); I² = 90%
Test for overall effect: Z = 2.00 (P = 0.05)

Total (95% CI)		52553		20026	100.0%	1.13 [0.93, 1.37]
Total events	1168		2669			

Heterogeneity: Tau² = 0.10; Chi² = 102.94, df = 11 (P < 0.00001); I² = 89%
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Chi² = 3.53, df = 1 (P = 0.06), I² = 71.6%

Decrease CRC risk   Increase CRC risk

(b)

Supplementary Figure 5.3 Association between HDL-C and CRC incidence: (a) Forest plot; (b) Funnel plot. *CC* colon cancer, *CI* confidence interval, *CRC* colorectal cancer, *HDL-C* high-density lipoprotein-cholesterol, *M* men, *M-H* Mantel-Haenszel, *NCEP-ATP III* National Cholesterol Education Program-Adult Treatment Panel III, *RC* rectal cancer, *RR* risk ratio, *W* women.

Supplementary Figure 5.4 Additional analyses for the association between HDL-C and CRC incidence: (a) Funnel plot after adjustment to publication bias with the trim and fill method. One simulated positive study was added (hollow circle) to the pooled estimates from the meta-analysis (solid circles). The adjusted RR increased from (1.13; 95% CI 0.93-1.37) in the initial analysis to (1.18; 95% CI = 0.79-1.43) after adjustment. (b) Baujat plot: indicates that the 12th dataset (that falls to the top right quadrant of the Baujat plot which corresponds to (Jeon 2014 RC / Other)) has contributed to the overall heterogeneity and result. (c) Influence plot: as there is no marked study, no study has met the criteria as an influential study.