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Metabolic Syndrome Components Correlation with Colorectal Neoplasms: A Systematic Review and a Meta-analysis

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ABSTRACT

Background: Patients with metabolic syndrome (MetS) have a higher risk of developing colorectal neoplasms (CRN) including colorectal adenoma (CRA) and colorectal cancer (CRC). Nonetheless, the role and implication of each component of the syndrome, i.e. (hyperglycemia, hypertension, dyslipidemia, and visceral obesity) are not well ascertained. **Aims:** We conducted a systematic review and a meta-analysis in order to assess the association between MetS components and CRN. **Methods and Material:** A systematic literature search using the PubMed database was performed with the objective of identifying relevant English studies. Effect estimates were measured. Heterogeneity, subgroup, sensitivity analyses, and publication bias analyses were performed. **Results:** Thirty-one studies met our inclusion criteria. Generally, subjects with hyperglycemia (RR = 1.33; 95% CI 1.14-1.54), high waist circumference (RR = 1.30; 95% CI 1.19-1.42), high triglycerides (RR = 1.30; 95% CI 1.13-1.49), and hypertension (RR = 1.26; 95% CI 1.17-1.36) showed a stronger positive significant association with CRA formation risk. A similar pattern was found between high fasting blood glucose (RR = 1.35; 95% CI 1.23-1.47) and high blood pressure (RR = 1.28; 95% CI 1.20-1.37) with CRC incidence. A moderate association was found between hypertriglyceridemia and visceral obesity with CRC risk. Conversely, no significant association was found between low high-density lipoprotein-cholesterol (HDL-C) with both outcomes. **Conclusions:** Our results indicate that hyperglycemia, hypertension, visceral obesity, and hypertriglyceridemia increases CRA and CRC risk. Low HDL-C has no significant effect on those outcomes.

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1 INTRODUCTION

Metabolic syndrome (MetS) has become a global health issue [1]. According to the International Diabetes Federation (IDF), approximately a quarter of the world's adult population may have the MetS [2]. MetS is identified as an aggregation of prevalent metabolic, biochemical, physiological, and clinical disorders related to the risk of progression to cardiovascular diseases and type 2 diabetes mellitus [3–5]. Current MetS definitions include hyperglycemia, dyslipidemia, hypertension, and visceral (abdominal or central) obesity as diagnosis criteria [1–6]. Colorectal cancer (CRC) is a multistep process (stepwise model) of carcinogenesis. This process results from the progressive accumulation of genetic mutations and epigenetic alterations that activate oncogenes and inactivate tumor suppressor genes to substitute normal epithelial cells for adenocarcinomas [7–10]. Colorectal adenomas are recognized as the precursor lesions for CRC [11]. CRC is a malignancy characterized by high incidence

and mortality rates [12]. Moreover, CRC is the third prevailing cancer in men and the second in women worldwide. Therefore, 746,000 incident cases among men (10% of all new cancer cases in men) were estimated in 2012 and 614,000 new cases within women (9.2% of all incident cancer cases in women) [13]. In the same year, 373,640 deaths were recorded, making it the fourth cause of mortality by cancer worldwide within men (8% of all cancer deaths in men) and 320,300 deaths among women making it the third cause of death by cancer (9% of all cancer deaths in women) [13].

This high incidence and mortality could be attributed to various risk factors [14]. The increasingly aging population, male gender, and ethnicity are linked with a higher risk of developing this malignancy [15], along with a family history of CRC [16, 17], inherited genetic predispositions (Lynch syndrome, familial adenomatous polyposis, etc.) [18–20] and inflammatory bowel diseases (Crohn's disease, Ulcerative Colitis, etc.) [7, 14, 18, 21]. Other environmental and lifestyle-related risk factors are as well linked with CRC, including dietary habits [22–24], physical activity [25], smoking [9, 26], type 2 diabetes mellitus [27], and metabolic syndrome [28]. This latter has been suggested to be associated with risk of developing colorectal neoplasia (CRN) including colorectal adenoma (CRA) and CRC in several epidemiological studies that endeavored to address this issue, though the results were inconsistent [28–30]. In addition, the implication of each metabolic condition comprising the MetS in the carcinogenesis process remains ambiguous. We aimed to tackle those issues in our meta-analysis focusing especially on the study of the effect of each component of the MetS on developing both CRA and CRC.

2 MATERIAL AND METHODS

2.1 Search strategy

A systematic literature search was carried out on the PubMed database for relevant studies examining the impact of any single component of MetS, i.e. (hypertension, hyperglycemia, dyslipidemia, and visceral obesity) on CRA and/or CRC incidence. Solely full English studies published up to June 2018 were considered and no population limitation was applied. The following Medical subject headings key terms were used: "triglycerides", "HDL cholesterol", "high-density lipoprotein cholesterol", "hyperglycaemia", "hyperglycemia", "waist circumference", and "hypertension", in combination with "colorectal neoplasms", and "metabolic syndrome".

2.2 Study selection

The inclusion criteria used to determine the eligibility of any individual retrieved study were as follows: a full English published article, the study design was a cohort, case-control, or cross-sectional; CRA and/or CRC incidence as the outcome; the study must provide adequate data to estimate risk ratios (RR) and their 95% confidence intervals (CI) of CRA and/or CRC incidence among individuals with MetS and at least one of these parameters (high-density lipoprotein-cholesterol (HDL-C) concentrations, triglycerides (TG) values, fasting blood glucose levels (FBG), blood pressure (BP), and waist circumference measurements (WC)); the study must provide the MetS definition(s) used for diagnosis. Articles not published as full text such as case reports, letters, comments, editorials, news were excluded. In addition, review articles, meta-analyses, articles not published in English, and studies dealing with organisms other than humans or in vitro studies were also rejected. We examined titles, abstracts, and full texts to assess the studies relevance and to exclude studies unrelated to the topic. Relevant articles were subsequently examined based on the full text. Articles with inappropriate exposures or outcomes, with missing or inappropriate data, and studies dealing with cancer biology or genetics were left out as well. Two authors (S.E and Y.T) independently performed the literature search and study selection, any disagreement found was resolved by returning to the author (M.B.K) who made the final decision.

2.3 Data extraction and study quality assessment

Data extraction was independently undertaken by (S.E and Y.T). Relevant data extracted from each included study involved the first author's name, the year of publication, the study location, the number of subjects, the type of the lesion, the number of events, characteristics of the studied population, and the definition of MetS used.

The meta-analysis was performed in conformity with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations [31]. The methodological quality of the included studies was evaluated according to The Newcastle-Ottawa Scale (NOS) [32]. The NOS is a tool for assessing the quality of non-randomized studies which allocates a maximum of nine stars for each study on certain criteria including quality assessment of selection, comparability, exposure, and outcome.

2.4 Summary measures

Mantel-Haenszel statistical method was used for dichotomous data. Risk ratios (RR) with their 95% confidence intervals were estimated. The fixed-effects meta-analysis model was used when no evidence of statistical heterogeneity was observed and random-effects meta-analysis model was applied when statistical heterogeneity was detected. The fixed-effects model

assumes that only the chance is responsible for the differences between study results whilst the random-effects meta-analysis model allows for the variations across studies of the effects being estimated and presumes that there is a distribution of these effects [33].

2.5 Synthesis of results

Tau-squared (Tau^2) was obtained to estimate the between-study variance in the random effect model. Z-test of the null hypothesis, with no effect, was also obtained. Chi-squared test (Chi^2), which assesses whether observed differences in results are compatible with chance alone, was measured to assess heterogeneity. A ($P \leq 0.05$) was considered to indicate statistical significance. Besides, heterogeneity was assessed with the I^2 statistic, which unlike the Chi^2 test describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error [34, 35]. I^2 values were interpreted as follows: 0-40% inconsistency may not be important, 40-70% may represent moderate heterogeneity, and ≥ 70% may represent considerable heterogeneity.

2.6 Publication bias

Publication bias was assessed by a visual investigation of a potential asymmetry of funnel plots. Egger's regression test [36] and Begg's rank correlation test [37] for funnel plot asymmetry were performed afterward to investigate the small study effect and publication bias. The results were adjusted to publication bias using the trim and fill method [38].

2.7 Additional analyses

2.7.1 Sensitivity and subgroup analyses

With the aim of evaluating the influence of each study on the risk estimates and the heterogeneity, we carried out sensitivity analyses by excluding one dataset at a time. A pre-specified subgroup analyses according to study design (cohort, case-control, and cross-sectional), gender (men and women), MetS definition (NCEP-ATP III, IDF, the harmonized definition, and other definitions), study location (Asia, Europe, North America), and cancer site (colon or rectal cancer) were performed in order to explore heterogeneity and differences between subgroups. The NCEP-ATP III (National Cholesterol Education Program-Adult Treatment Panel III) definition was considered as the conventional definition for MetS diagnosis. Review Manager 5.3 program [39] was used for the meta-analysis, subgroup and sensitivity analyses. Publication bias analyses, test for identifying potential outliers and influential studies [40] and Baujat plots (which illustrates studies that may contribute to overall heterogeneity) [41] were conducted with R program (version 3.5.0) [42, 43].

3 RESULTS

3.1 Study selection

The process of study selection is demonstrated in the flow diagram (Figure 1). In order to determine their eligibility for inclusion, 292 articles were initially identified through the database search, and their titles and abstracts were reviewed afterward. Consequently, 198 studies were excluded consisting of non-full text articles (reviews, case reports, editorials, news, letters to editors, comments, etc.) as well as studies irrelevant to the topic in question. Subsequently, 94 publications were considered relevant to the topic and were carefully examined through an intensive reading to determine ultimately the pertinent studies to include in our meta-analysis. Eventually, 31 articles discussing the correlation between the MetS and its components and CRN (CRA and CRC) were included.

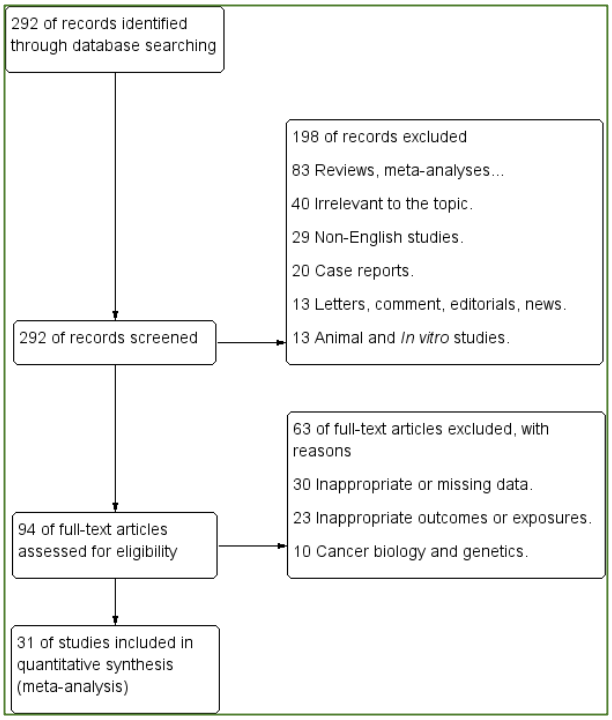

Figure 1: Flowchart of study selection

3.2 Study characteristics

Table 1 summarizes the characteristics of the included studies. The meta-analysis consisted of eight cohort studies [44–51], 13 case-control studies [52–64], and ten cross-sectional studies as well [65–74]. With the exception of ten studies, where five were carried out in European populations [47, 52, 55, 56, 58] and five in northern American populations [48, 49, 51, 62, 64], the remaining

were conducted in Asian populations. CRA was the outcome in 14 studies [44, 46–50, 52–58, 66], whereas 19 studies [44–46, 51, 59–65, 67–74] reported data on CRC incidence. The NCEP-ATPIII definition was utilized in 14 studies [44–46, 48, 49, 55, 56, 59, 67, 69–71, 73, 74], four applied the IDF definition for the diagnosis of individuals with MetS [56, 58, 63, 72], while two studies used the harmonized definition [56, 68], and 13 studies employed other definitions [47, 50–54, 57, 60–62, 64–66]. According to the NOS scales, the included cohort studies scored an average of eight stars, the case-control studies were awarded an average of 7.85 stars, while the cross-sectional studies were allocated an average of 7.6 stars.

3.3 Synthesis of results

3.3.1 Hyperglycemia and colorectal neoplasms

To examine the association between FBG and CRA, data from nine studies comprising 11 datasets were pooled.

Compared to individuals with normal FBG levels, patients with high FBG values (hyperglycemia) were more susceptible to developing CRA (RR = 1.33; 95% CI 1.14-1.54; I^2 = 92%) (Table 2, Figure 2). There was no evidence of significant publication bias with Begg's test (P = 0.5423), contrarily to Egger's test (P = 0.0232). None of the subgroups modified the risk estimate. The adjusted summary RR on publication bias was decreased by the trim and fill method to 1.28 (95% CI 1.11-1.46). The Baujat plot indicated that the dataset (Kim 2012 AA / NCEP-ATP III) [46] contributed to the overall heterogeneity and the dataset (Hu 2011 CRA / NCEP-ATP III) contributed to the overall result (Figure 3).

The risk estimates for the relationship between FBG levels and CRC were consistent with those expressed by the previous analysis concerning CRA. A summary RR of 1.35 (95% CI 1.23-1.47; I^2 = 59%) was found (Supplementary Figure 1.1), suggesting, therefore, a strong effect of hyperglycemia on both outcomes. There was no evidence of funnel plot asymmetry (P = 0.2792 with the Begg's test and P = 0.2360 with the Egger's test). The pooled analysis result was influenced by study type, study location, and gender. Cohort studies showed a higher association with a summary RR of 1.41 (95% CI 1.08-1.84; I^2 = 81%) than case-control studies (RR = 1.33; 95% CI 1.25-1.41; I^2 = 0%). Similarly, the association between hyperglycemia and CRC observed within Asian populations was stronger (RR = 1.42; 95% CI 1.21-1.67; I^2 = 78%) compared to Europeans (RR = 1.30; 95% CI 1.20-1.41; I^2 = 0%). When stratified by gender, a stronger association between high FBG and CRC risk was noticed for women (RR = 1.63; 95% CI 1.18-2.26; I^2 = 86%) than men (RR = 1.34; 95% CI 1.24-1.45; I^2 = 30%) (Supplementary Table 3). The trim and fill method reduced the summary RR to 1.29 (95% CI 1.17-1.43). Sensitivity analysis and the Baujat plot showed that the dataset (Lin 2014 CRC / NCEP-ATP III (W)) [44] contributed to the overall heterogeneity (RR = 1.30; 95% CI 1.22-1.38; I^2 = 18%), and it was considered as an influential study (Supplementary Figure 1.2, Supplementary Table 1.3).

3.3.2 Hypertension and colorectal neoplasms

Using a random-effects meta-analysis model, due to evidence of heterogeneity, in 17 studies with 23 datasets involving 38,510 participants, high BP was associated with an increase in CRA incidence (RR = 1.26; 95% CI 1.17-1.36; I^2 = 82%) (Supplementary Figure 2.1). There was no evidence of significant publication bias with Begg's test (P = 0.1715), contrarily to Egger's test (P = 0.0213). Subgroup analyses revealed that study type and MetS definitions slightly modified the risk estimates (Supplementary Table 2.1). The conventional definition showed a stronger significant positive association (RR = 1.31; 95% CI 1.18-1.46; I^2 = 88%) compared with studies using unconventional definitions (RR = 1.20; 95% CI 1.06-1.35; I^2 = 68%). The adjusted effect size to publication bias decreased with the trim and fill method (RR = 1.17; 95% CI 1.08-1.26). One study [45] contributed to overall heterogeneity and was considered potentially influential (Supplementary Figure 2.2).

Comparing individuals with and without hypertension, the summary of RR of 13 studies with 24 datasets including 615,867 participants of which 12,570 cases of a confirmed diagnosis of CRC showed an increased risk of developing this malignancy by 28% (RR = 1.28; 95% CI 1.20-1.37; I^2 = 66%) (Supplementary Figure 2.3). There was no evidence of funnel plot asymmetry in Begg's test (P = 0.6062) or in Egger's test (P = 0.5381). This analysis was subdivided according to study type, study location, MetS definition, gender, and cancer site. All the strata considerably changed the risk estimate (Supplementary Table 2.1). A stronger relationship between CRC risk and high BP was found in cohort studies (RR = 1.37; 95% CI 1.31-1.43; I^2 = 41%) than non-cohort studies (RR=1.23; 95% CI 1.12-1.35; I^2 = 68%). A similar pattern was noticed for studies conducted in Asian populations (RR = 1.43; 95% CI 1.32-1.56; I^2 = 60%) compared with (RR = 1.18; 95% CI 1.11-1.24; I^2 = 36%) for studies carried out in European countries. This association was more significant for colon cancer (RR = 1.29; 95% CI 1.14-1.45; I^2 = 76%) than rectal cancer (RR = 1.23; 95% CI 1.04-1.45; I^2 = 71%) and among men (RR = 1.22; 95% CI 1.08-1.38; I^2 = 59%) while a modest relationship was observed among women (RR = 1.12; 95% CI 1.02-1.22; I^2 = 12%). No study met the criteria as an influential study, however, the Baujat plot revealed that the dataset (Jeon 2014 RC / Other) [54] contributed to overall heterogeneity and result (Supplementary Figure 2.4).

Table 1: Characteristics of included studies

Cohort studies							
Author, year [ref]	Country	Follow up	Lesion type	№ events / № total	MetS definition	Quality score	Cohort/study center
Bowers *et al.* 2006 [47]	Finland	1985 - 1988	CC, RC	227 CC / 28573 183 RC/ 28573	Other	7	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
Huang *et al.* 2013 [45]	Taiwan	01/01/2003- 31/12/2010	CRA	216 / 1522	NCEP-ATP III	9	Taipei Veterans General Hospital
Kabat *et al.* 2012 [48]	The USA	1993 - 1998	CRC	81 CRC / 4821 65 CC / 4821	NCEP-ATP III	7	The Women's Health Initiative (WHI)
Kim *et al.* 2012 [46]	Korea	04/2007- 04/2009	CRA, AA	1771 CRA / 6438 1292 CC / 6438 146 RC / 6438	NCEP-ATP III	7	The National Cancer Center
Liang *et al.* 2017 [49]	The USA	1993 - 1998	CRA, CRC	114 CRC / 5068 88 CC / 5068	NCEP-ATP III	8	The Women's Health Initiative (WHI)
Lin *et al.* 2014 [44]	China	10/2007 -12/2011	CRC, CC	1500 CRA / 2315 446 CRC / 2315	NCEP-ATP III	8	The First Affiliated Hospital of Wenzhou Medical University
Shapero *et al.* 2017 [51]	Canada	2009 - 2014	CRA, CC, RC	383 CRA / 1534 99 AA / 1534	Other	9	The Scarborough Hospital, General and Birchmount Sites, The North Toronto Endoscopy Clinic, and The Intestinal Health Institute, Markham, Ontario
Shin *et al.* 2017 [50]	Korea	2003 - 2008	CRC, CC	5108 / 408931	Other	9	The National Health Insurance Service–National Sample Cohort
Case-control studies							
Author, year [ref]	Country	Follow up	Lesion type	Cases / controls	MetS definition	Quality score	Cohort/study center
Aleksandrova *et al.* 2011 [56]	European countries	1999 - 2003	CC, RC	689 CC / 689 404 RC / 404	IDF Harmonized	7	The European Prospective Investigation into Cancer and Nutrition Study (23 centers from 10 European countries)
Fliss-Isakov *et al.* 2017 [60]	Israel	2010 - 2015	CRA	347 / 407	Other	7	The Department of Gastroenterology and Hepatology at the Tel Aviv Medical Center
Harima *et al.* 2013 [61]	Japan	04/2009 - 03/2012	CRA	460 / 377	Other	7	Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine
Jeon *et al.* 2014 [54]	Korea	06/2004 -01/2009	CC, RC	264 CC / 400 186 RC / 400	Other	8	CHA Bundang Medical Center Seongnam
Kang *et al.* 2009 [59]	South Korea	01/2006 -12/2007	CRA	1122 / 1122	NCEP-ATP III	8	Seoul National University Hospital Healthcare System Gangnam Center
Kontou *et al.* 2012 [55]	Greece	12/2009 -12/2010	CRC	250 / 250	NCEP-ATP III	9	Saint Savvas Cancer hospital and Alexandra General hospital in Athens

Lipka *et al.* 2013 [62]	The USA	2007 - 2009	CRA	167 / 612	Other	8	Outpatient gastroenterology clinic
Morita *et al.* 2005 [63]	Japan	01/1995 -03/2002	CRA	756 / 1751	IDF	8	Two Self Defense Forces (SDF) hospitals
Pelluchi *et al.* 2010 [58]	Italy and Switzerland	1992 - 2001	CC, RC	1378 CC / 4661 878 RC / 4661	IDF	8	Six Italian areas and in Canton Vaud, Switzerland
Pyo *et al.* 2016 [53]	Korea	01/2002 -12/2012	RNETs	102 / 52583	Other	8	Center for Health Promotion of the Samsung Medical Center in Seoul
Shen *et al.* 2010 [57]	China	01/2002 -03/2007	CRC	507 / 507	Other	9	The Department of Gastroenterological Surgery, Peking University People's Hospital
Stocks *et al.* 2008 [52]	Sweden	1985 - 1996	CRC	306 / 595	Other	7	The Northern Sweden Health and Disease Cohort
Tsilidis *et al.* 2010 [64]	The USA	1989 - 2000	CRA	132 / 392	Other	8	CLUE II cohort
Cross-sectional studies							
Author, year [ref]	Country	Follow up	Lesion type	№ events / № total	MetS definition	Quality score	Cohort/study center
Hong *et al.* 2010 [70]	Korea	09/2005 -03/2009	CRA	339 / 1761	NCEP-ATP III	8	Healthcare Center of Konkuk University Medical Center in Seoul
Hong *et al.* 2015 [65]	Korea	01/2011 -12/2011	CRA	1258 / 3368	Other	7	Healthcare Center of Konkuk University Medical Center in Seoul
Hu *et al.* 2011 [69]	Taiwan	10/2004 -04/2006	CRA	397 / 3106	NCEP-ATP III	8	Shin Kong Wu Ho-Su Memorial Hospital
Hwang *et al.* 2010 [71]	Korea	2007	CRA	556 / 2917	NCEP-ATP III	8	The Kangbuk Samsung Hospital, College of Medicine at Sungkyunkwan University
Jung *et al.* 2014 [66]	Korea	2010 - 2011	RNETs	101 / 57819	Other	8	Total Healthcare Center of Kangbuk Samsung Hospital
Kim *et al.* 2007 [73]	Korea	03/2004 -12/2005	CRA	731 / 2531	NCEP-ATP III	8	The Center for Health Promotion, Samsung Medical Center in Seoul
Lee *et al.* 2014 [67]	Korea	07/2005 -12/2012	CRA	154 / 714	NCEP-ATP III	8	The Dongguk University Ilsan Hospital Medical Screening Center, Seoul
Oh *et al.* 2008 [72]	Korea	10/2005 -12/2005	CRA	53 / 200	IDF	7	The Health Promotion Center of Asan Medical Center Seoul
Sato *et al.* 2011 [68]	Japan	06/2008 -01/2010	CRA	261 / 963	Harmonized	7	Tohuku Central Hospital for Public School Teachers, Yamagata
Yang *et al.* 2016 [74]	Korea	5/2011 - 12/2011	CRA	406 M / 1056 151 W / 658	NCEP-ATP III	7	Seoul National University Hospital Healthcare System Gangnam Center

AA advanced adenoma, CC colon cancer, *CRA* colorectal adenoma, *CRC* colorectal cancer, *IDF* International Diabetes Foundation, *MetS* metabolic syndrome, *NCEP-ATP III* National Cholesterol Education Program-Adult Treatment Panel III, *RC* rectal cancer, *RNETs* rectal neuroendocrine tumors.

Table 2: Summary of results

Outcome	№ of studies (datasets) ref	Model	RR [95% CI]	Z-test (*P* value)	Heterogeneity			Publication bias (*P* value)	
					Tau^2	Chi^2 (*P* value)	I^2 (%)	Begg's test	Egger's test
Hyperglycemia and CRN risk									
CRA	9 (11) [44, 46, 63–65, 68, 69, 72, 73]	RE	1.33 [1.14-1.54]	3.75 (*P* = 0.0002)	0.05	123.99, df = 10 (*P* < 0.00001)	92	0.5423	0.0232
CRC	7 (14) [44, 46, 48, 52, 54, 56, 57]	RE	1.35 [1.23-1.47]	6.61 (*P* < 0.00001)	0.01	31.66, df = 13 (*P* = 0.003)	59	0.2792	0.2360
Hypertension and CRN risk									
CRA	17 (23) [44–46, 51, 59–64, 67–69, 71–74]	RE	1.26 [1.17-1.36]	5.79 (*P* < 0.00001)	0.02	120.97, df = 22 (*P* < 0.00001)	82	0.1715	0.0213
CRC	13 (24) [44, 46, 47, 49, 50, 52–58, 66]	RE	1.28 [1.20-1.37]	7.51 (*P* < 0.00001)	0.01	67.35, df = 23 (*P* < 0.00001)	66	0.6062	0.5381
AA	3 (3) [46, 51, 67]	FE	1.43 [1.14-1.79]	3.13 (*P* = 0.002)	NA	0.48, df = 2 (*P* = 0.79)	0		
Hypertriglyceridemia and CRN risk									
CRA	9 (12) [44, 46, 63–65, 67–69, 73]	RE	1.30 [1.13-1.49]	3.76 (*P* = 0.0002)	0.05	137.65, df = 11 (*P* < 0.00001)	92	0.5452	0.0518
CRC	6 (12) [44, 46, 54, 56, 57, 66]	RE	1.14 [1.01-1.28]	2.10 (*P* = 0.04)	0.03	49.46, df = 11 (*P* < 0.00001)	78	0.3108	0.7347
AA	2 (2) [46, 67]	FE	2.12 [1.62-2.77]	5.46 (*P* < 0.00001)	NA	0.56, df = 1 (*P* = 0.45)	0		
Visceral Obesity and CRN risk									
CRA	10 (13) [46, 60, 63, 65, 67–70, 72, 73]	RE	1.30 [1.19-1.42]	5.72 (*P* < 0.00001)	0.01	37.58, df = 12 (*P* = 0.0002)	68	0.7650	0.6954
CRC	4 (12) [46, 53, 55, 56]	RE	1.18 [1.07-1.31]	3.30 (*P* = 0.0010)	0.02	39.40, df = 11 (*P* < 0.0001)	72	0.8406	0.9420
AA	3 (3) [46, 67, 70]	RE	1.21 [0.74-1.96]	0.77 (*P* = 0.44)	0.12	5.83, df = 2 (*P* = 0.05)	66		
Low HDL-Cholesterol and CRN risk									
CRA	7 (10) [44, 46, 63, 67–69, 73]	RE	1.02 [0.92-1.12]	0.31 (*P* = 0.75)	0.01	34.52, df = 9 (*P* < 0.0001)	74	0.7275	0.0548
CRC	5 (12) [44, 46, 47, 54, 56]	RE	1.13 [0.93-1.37]	1.26 (*P* = 0.21)	0.10	102.94, df = 11 (*P* < 0.00001)	89	0.7373	0.8443
AA	2 (2) [46, 67]	FE	1.18 [0.84-1.66]	0.95 (*P* = 0.34)	NA	0.84, df = 1 (*P* = 0.36)	0		

AA advanced adenoma, *CRA* colorectal adenoma, *CRC* colorectal cancer, *df* degree of freedom, *FE* fixed-effects, *HDL* high-density lipoprotein, *NA* not applicable, *RE* random-effects, *RR* risk ratio.

3.3.3 Hypertriglyceridemia and colorectal neoplasms

In a pooled analysis of nine studies comprising 12 datasets, a summary RR of 1.30 (95% CI 1.13-1.49) was found (Supplementary Figure 3.1), with evidence of considerable heterogeneity (I^2 = 92%), suggesting that individuals with elevated levels of triglycerides are more prone to developing CRA than individuals with normal levels. The results of Begg's and Egger's tests revealed no sign of funnel plot asymmetry (*P* = 0.5452 and *P* = 0.0518 respectively). A stratified analysis by MetS definitions found a higher significant positive association with CRA risk in studies using the conventional definition (RR = 1.44; 95% CI 1.18-1.75; I^2 = 95%) compared to a non-significant modest increase of CRA incidence when using unconventional definitions (RR = 1.07; 95% CI 0.96-1.19; I^2 = 11%) (Supplementary Table 3.1). The Baujat plot illustrated that the dataset (Kim 2012 AA / NCEP-ATP III) [46] contributed to overall heterogeneity (Supplementary Figure 3.2).

A modest relationship between hypertriglyceridemia and risk of CRC was noticed in a meta-analysis of six studies with 12 datasets involving 73,856 participants (RR = 1.14; 95% CI 1.01-1.28; I^2 = 78%) (Supplementary Figure 3.3). Begg's test (*P* = 0.5452) and Egger's test (*P* = 0.0518) suggested no evidence of a small study effect. All the strata considerably influenced the risk estimate. Significant positive associations were noticed in cohort studies (RR = 1.33; 95% CI 1.15-1.54; I^2 = 60%), studies considering the conventional MetS definition (RR = 1.21; 95% CI 1.08-1.35; I^2 = 64%), and among men (RR = 1.16; 95% CI 1.05-1.28; I^2 = 0%), while a non-significant increase of CRC incidence was noticed in non-cohort studies (RR = 1.04; 95% CI 0.91-1.20; I^2 = 71%), in studies utilizing unconventional MetS definitions (RR = 1.01; 95% CI 0.73-1.38; I^2 = 86%), and among women (RR = 1.10; 95% CI 0.97-1.25; I^2 = 0%).

Sensitivity analysis revealed that two datasets (Kim 2012 CC / NCEP-ATP III) [46] and (Jeon 2014 CC / Other) [54] modified the heterogeneity estimation (Supplementary Table 3.3). However, one study contributed to overall heterogeneity and result according to the Baujat plot (Supplementary Figure 3.4).

There was a remarkable difference in the magnitude of the risk estimates about the involvement of high values of triglycerides with CRA and CRC.

3.3.4 Visceral obesity and colorectal neoplasms

Ten studies with 13 datasets on visceral obesity and CRA incidence were available for the analysis. The combined RRs for patients with versus without central obesity was 1.30 (95% CI 1.19-1.42, I^2 = 68%) (Supplementary Figure 4.1), suggesting a positive significant association. There was no evidence of small study effect or publication bias (P = 0.7650 with Begg's test and P = 0.6954 with Egger's test). MetS definition influenced the effect estimate. A significant association was found in studies considering the conventional MetS definition (RR = 1.23; 95% CI 1.07-1.42; I^2 = 71%), however, the result for the unconventional definitions was stronger (RR = 1.35; 95% CI 1.20-1.52; I^2 = 63%) (Supplementary Table 4.1). The Baujat plot illustrated that two studies [60, 68] contributed on the overall result, and one study [67] comprised of two datasets one contributed to the overall heterogeneity and the other on overall result (Supplementary Figure 4.2). This positive statistically significant association was similarly observed in four studies with 12 datasets on the relationship between WC and CRC (RR = 1.18; 95% CI 1.07-1.31; I^2 = 72%) (Supplementary Figure 4.3). Neither Begg's test (P = 0.8406) nor Egger's test (P = 0.9420) have shown statistical significance for publication bias. MetS definition and cancer site modified the pooled risk ratio. A higher risk estimate, but not statistically significant was observed in studies using unconventional MetS definitions (RR=1.26; 95% CI 0.99-1.60; I^2 = 85%) than studies applying the conventional definition (RR = 1.14; 95% CI 1.05-1.25; I^2 = 43%).

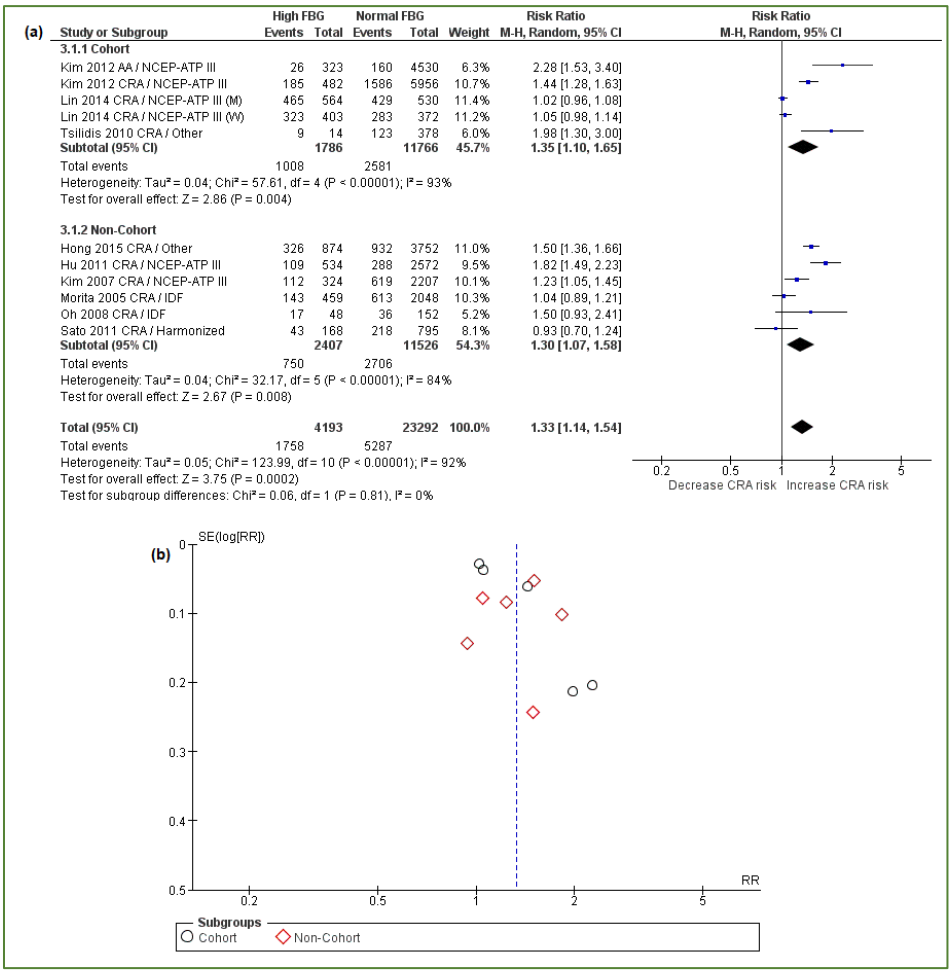

Figure 2: Association between FBG and CRA formation: (a) Forest plot; (b) Funnel plot.
AA advanced adenomas, *CI* confidence interval, *CRA* colorectal adenoma, *FBG* fasting blood glucose, *IDF* International Diabetes Foundation, *M* men, *M-H* Mantel-Haenszel, *NCEP-ATP III* National Cholesterol Education Program-Adult Treatment Panel III, *W* women.

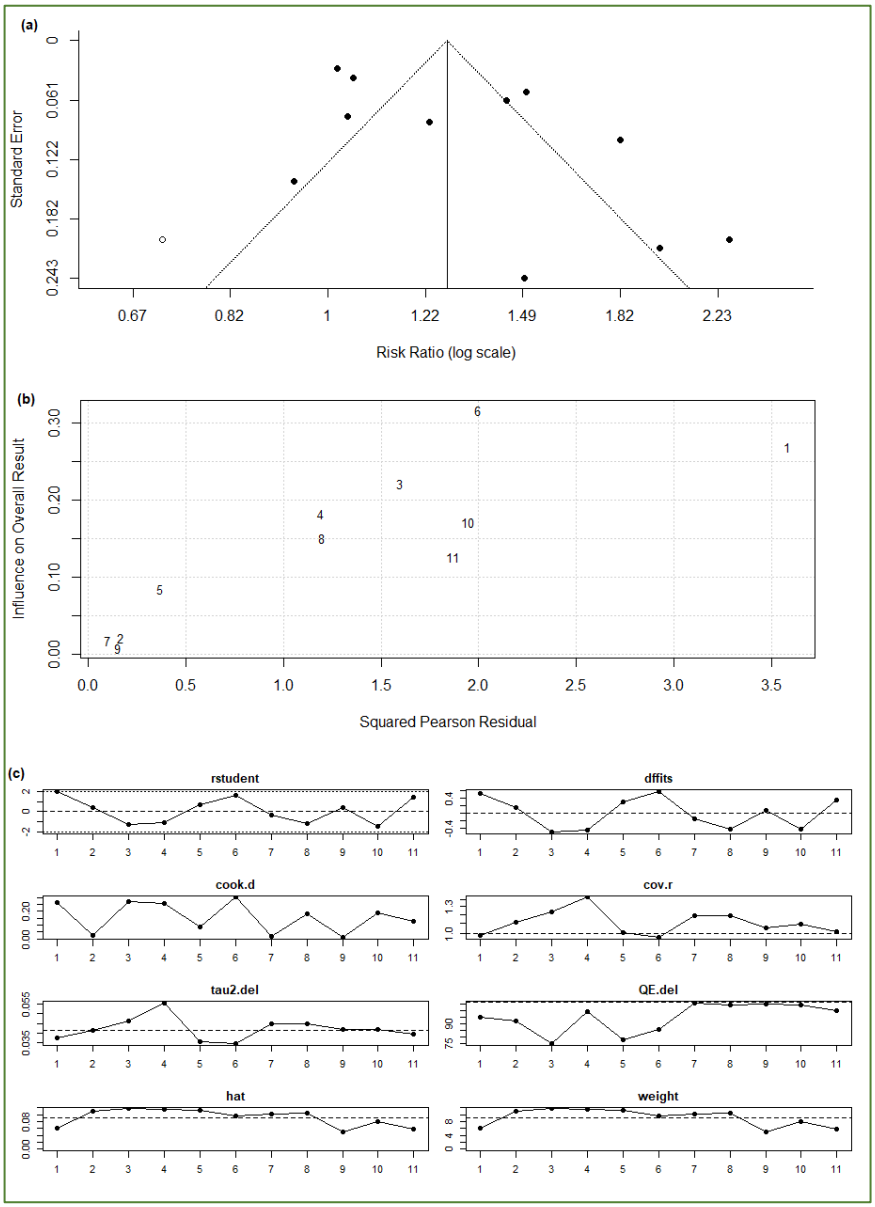

Figure 3: Additional analyses for the association between FBG and CRA development: (a) Funnel plot after adjustment to publication bias with the trim and fill method. One simulated negative study was added (hollow circle) to the pooled estimates from the meta-analysis (solid circles). The adjusted RR slightly decreased from (1.33; 95% CI 1.14-1.54) in the initial analysis to (1.28; 95% CI 1.11-1.46) after adjustment. (b) Baujat plot: indicates that the 1st dataset (that falls to the top right quadrant of the Baujat plot which corresponds to (Kim 2012 AA / NCEP-ATP III)) has contributed to the overall heterogeneity and the 6th dataset (which corresponds to (Hu 2011 CRA / NCEP-ATP III)) contributed on the overall result. (c) Influence plot: as there is no marked study, no study has met the criteria as an influential study.

A stratified analysis by cancer site yielded a stronger association between high waist circumference and colon cancer (RR = 1.31; 95% CI 1.12-1.52; I^2 = 83%) than rectal cancer (RR = 1.11; 95% CI 1.00-1.22; I^2 = 0%). The adjusted RR on publication bias was increased to 1.25 (95% CI 1.13-1.38). Following the sensitivity analysis, one dataset (Aleksandrova 2011 CC / IDF (M)) [56] significantly modified the heterogeneity evaluation, (RR = 1.15; 95% CI 1.09-1.22; I^2 = 28%) after its exclusion (Supplementary Table 4.3). The same dataset contributed to overall heterogeneity and was considered potentially influential (Supplementary Figure 4.4).

3.3.5 Low HDL-C and colorectal neoplasms

Seven studies, including ten datasets, have reported data about the relationship between CRA risk and low values of HDL-C. A non-significant positive association was found in a weighted analysis of individuals with normal levels of HDL-C against individuals with low HDL-C (RR = 1.02; 95% CI 0.92-1.12; I^2 = 74%) (Supplementary Figure 5.1).

Table 3: Subgroup analyses results of the association between hyperglycemia and colorectal neoplasms

Subgroup	№ of studies (datasets) ref	Model	RR [95% CI]	Z-test (*P* value)	Heterogeneity		
					Tau^2	Chi^2 (*P* value)	I^2 (%)
Hyperglycemia and colorectal adenomas							
All studies	9 (11) [44, 46, 63–65, 68, 69, 72, 73]	RE	1.33 [1.14-1.54]	3.75 (*P* = 0.0002)	0.05	123.99, df = 10 (*P* < 0.00001)	92
Study type							
Cohort	2 (4) [44, 46]	RE	1.27 [1.03-1.56]	2.25 (*P* = 0.02)	0.04	49.54, df = 3 (*P* < 0.00001)	94
Non-cohort	7 (7) [63–65, 68, 69, 72, 73]	RE	1.35 [1.12-1.63]	3.20 (*P* = 0.001)	0.05	35.49, df = 6 (*P* < 0.00001)	83
Cross-sectional	5 (5) [65, 68, 69, 72, 73]	RE	1.37 [1.13-1.67]	3.21 (*P* = 0.001)	0.03	18.57, df = 4 (*P* = 0.0010)	78
Case-control	2 (2) [63, 64]	FE	1.39 [0.74-2.64]	1.02 (*P* = 0.31)	0.19	8.36, df = 1 (*P* = 0.004)	88
Study location							
Asia	8 (10) [44, 46, 63, 65, 68, 69, 72, 73]	RE	1.29 [1.11-1.50]	3.35 (*P* = 0.0008)	0.05	117.99, df = 9 (*P* < 0.00001)	92
North America	1 (1) [64]	RE	1.98 [1.30-3.00]	3.20 (*P* = 0.001)	NA	NA	NA
MetS definition							
Conventional	4 (6) [44, 46, 69, 73]	RE	1.35 [1.11-1.64]	3.01 (*P* = 0.003)	0.05	86.30, df = 5 (*P* < 0.00001)	94
Unconventional	5 (5) [63–65, 68, 72]	RE	1.30 [1.01-1.67]	2.04 (*P* = 0.04)	0.06	25.61, df = 4 (*P* < 0.0001)	84
Hyperglycemia and colorectal cancer							
All studies	7 (14) [44, 46, 48, 52, 54, 56, 57]	RE	1.35 [1.23-1.47]	6.61 (*P* < 0.00001)	0.01	31.66, df = 13 (*P* = 0.003)	59
Study type							
Cohort	3 (6) [44, 46, 48]	RE	1.41 [1.08-1.84]	2.49 (*P* = 0.01)	0.08	26.39, df = 5 (*P* < 0.0001)	81
Case-control	4 (8) [52, 54, 56, 57]	FE	1.33 [1.25-1.41]	8.92 (*P* < 0.00001)	NA	5.72, df = 7 (*P* = 0.57)	0
Study location							
Asia	4 (7) [44, 46, 54, 57]	RE	1.42 [1.21-1.67]	4.18 (*P* < 0.0001)	0.03	27.26, df = 6 (*P* = 0.0001)	78
Europe	2 (4) [52, 56]	FE	1.30 [1.20-1.41]	6.52 (*P* < 0.00001)	NA	3.45, df = 4 (*P* = 0.49)	0
North America	1 (2) [48]	RE	1.21 [0.83-1.77]	1.00 (*P* = 0.32)	0.02	1.30, df = 1 (*P* = 0.25)	23
MetS definition							
Conventional	4 (10) [44, 46, 48, 56]	RE	1.33 [1.18-1.51]	4.50 (*P* < 0.00001)	0.02	28.42, df = 9 (*P* = 0.0008)	68
Unconventional	3 (4) [52, 54, 57]	FE	1.37 [1.25-1.51]	6.72 (*P* < 0.00001)	NA	2.63, df = 3 (*P* = 0.45)	0
Gender							
Men	2 (3) [44, 56]	FE	1.34 [1.24-1.45]	3.14 (*P* = 0.002)	NA	2.85, df = 2 (*P* = 0.24)	30
Women	2 (3) [44, 56]	RE	1.63 [1.18-2.26]	2.95 (*P* = 0.003)	0.07	14.26, df = 2 (*P* = 0.0008)	86
Cancer site							
Colon	4 (5) [46, 48, 54, 56]	FE	1.36 [1.25-1.47]	7.17 (*P* < 0.00001)	NA	2.45, df = 4 (*P* = 0.65)	0
Rectal	3 (4) [46, 54, 56]	FE	1.32 [1.18-1.49]	4.64 (*P* < 0.00001)	NA	3.70, df = 3 (*P* = 0.30)	19
Colorectal adenomas versus colorectal cancer							
CRA	2 (4) [44, 46]	RE	1.27 [1.03-1.56]	2.25 (*P* = 0.02)	0.04	49.54, df = 3 (*P* < 0.00001)	94
CRC	2 (4) [44, 46]	RE	1.50 [1.06-2.12]	2.30 (*P* = 0.02)	0.10	25.40, df = 3 (*P* < 0.0001)	88

CRA colorectal adenoma, *CRC* colorectal cancer, *df* degree of freedom, *FE* fixed-effects, *MetS* metabolic syndrome, *NA* not applicable, *RE* random-effects, *RR* risk ratio.

There was no evidence of significant publication bias with Begg's test (P = 0.7275) and with Egger's test (P = 0.0548). The result slightly decreased after adjusting to publication bias via the trim and fill method to 1.00 (95% CI 0.92-1.09). Two studies [44, 69] contributed to overall heterogeneity and result and one study [67] contributed to the overall heterogeneity according to the Baujat plot. One study was considered potentially influential [44] (Supplementary Figure 5.2).

Consistently, our results suggest a statistically non-significant increase for HDL-C on CRC incidence. The summary of RR was 1.13; 95% CI 0.93-1.37; I^2 = 89%) in five studies with 12 datasets comparing patients with low HDL-C levels and individuals with normal values (Supplementary Figure 5.3).

No evidence of the small study effect or publication bias was found (Begg's test P = 0.7373) and (Egger's test P = 0.8443). The study type, study location, and cancer site influenced the risk estimate (Supplementary Table 5.1). The adjusted RR for publication bias increased to 1.18 (95% CI 0.79-1.43) by the trim and fill method. The Baujat plot illustrated that the dataset (Jeon 2014 RC / Other) [54] contributed to overall heterogeneity and result (Supplementary Figure 5.4).

3.3.6 Advanced adenomas and components of the MetS

Four studies [46, 51, 67, 70] provided data on the correlation between advanced colorectal adenoma (AA) and components of the MetS. Our results showed that only hypertriglyceridemia and hypertension seem to significantly increase the AA incidence (Table 2).

3.3.7 Colorectal adenomas versus colorectal cancer

We performed an analysis with the purpose of comparing the effect estimates for the different metabolic factors between CRA and CRC using only studies that reported both outcomes. Two studies [44, 46] were available for all factors except for waist circumference. Our findings displayed a stronger association between hyperglycemia, hypertriglyceridemia, and hypertension with CRC than CRA (Supplementary Tables 1.1, 2.1, and 3.1). No difference in the magnitude of the effect was observed for the association between HDL-C and both outcomes (Supplementary Table 5.1).

4 DISCUSSION

We focused in this meta-analysis on answering the question of which condition(s) of the MetS are related to the developing of CRA and CRC since we have demonstrated the MetS association with both conditions in a previous study [75]. We also aimed to determine whether these elements influence the carcinogenesis process in its earlier or later stages. Our results suggest that individuals with hyperglycemia, hypertension, and visceral obesity, but not low values of HDL-C are associated with an increased risk of developing both CRA and CRC.

According to a recent worldwide estimate by the World Health Organization, the global prevalence of obesity has become three times as higher since 1975 [76]. Accordingly, in 2016, more than 13% of the world adults (above 18 years) were obese, that is more than 650 million cases. Additionally, 124 million children and adolescents (5-18 years) were considered obese in the same year [76]. Subsequently, the key element in the pathogenesis of MetS is the alteration of normal visceral adipose tissue function [6]. Visceral obesity regularly measured by WC has long been linked to certain types of cancer in several epidemiological studies, known also as obesity-related cancers [77, 78]. The relationship between WC and CRC was examined in a meta-analysis of 12 studies. The RR of CRC for the highest versus the lowest categories of WC was 1.455 (95% CI 1.327-1.569; I^2 = 10.8%) [79]. Our results suggested an implication of WC in CRC risk with an 18% increase, lower than previous findings (43%) [28].

Various factors could relate obesity to CRC. A chronic low-grade inflammation is associated with obesity attributable to the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6, leading to cell apoptosis inhibition and cell survival promotion [80, 81]. Besides, insulin resistance, which is a characteristic of the MetS, associated with hyperinsulinemia, increased secretion of insulin-like growth factor 1 (IGF1), and hyperglycemia are supposed to promote CRC carcinogenesis. High levels of insulin may lead to an overproduction of IGF1, causing an overstimulation of the receptors, and activation of insulin receptor substrate-1. This can activate various signal pathways, including mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3 kinase that decreases cell apoptosis and enhances cell proliferation [80–84]. Hyperglycemia is suggested to promote cancer development by way of a variety of mechanisms. A high glucose level leads to a state of an oxidative stress by increasing the production of reactive oxygen species [85] and enhances inflammatory pathways which lead also to a state of a chronic low-grade inflammation [86]. Hyperglycemia provides to cancer cells the necessary energy source which allows for cell survival and resistance to chemotherapy [87] and indirectly increases cancer progression by dysregulating signaling pathways in many types of cancer (breast, lung, and prostate cancer) [88]. However, hyperglycemia may be dependent on other factors like hyperinsulinemia and diet [89].

Our results indicated that hyperglycemia increases the risk by 35% for CRC. In a dose-response analysis performed by Shi *et al.* [90], an RR of 1.015 (95% CI 1.012-1.019; $P = 0.000$) was found for each 20 mg/dl increase in blood glucose concentration which agrees with our findings.

Furthermore, Esposito *et al.* [28] noticed a 9% increase in CRC risk in patients with high blood pressure. However, 25% was the increase that we found in our meta-analysis. The mechanisms by which hypertension affects the development of cancer remain unclear. The renin-angiotensin system which is implicated in the etiology of hypertension is linked to the development of many cancers. The angiotensin II activates downstream MAPK and STAT signal pathways throughout its effect on angiotensin type 1 receptor which induces the expression of proto-oncogenes and subsequently the promotion of cell proliferation [84]. Epidemiological studies have reported the association between hypertension and cancer development. Women with hypertension were at a high risk of endometrial cancer, while a history of hypertension has been related to kidney cancer [91]. The prevalence of hypertension was higher among subjects with prostate cancer [92]. Moreover, a long-term use of anti-hypertensive medication which is an indication of a long duration of hypertension increased the risk of invasive breast cancer [93].

The results of the association between dyslipidemia, a condition that includes high serum TG levels and low values of HDL-C, were inconsistent. We noticed that low HDL-C levels do not have a significant effect on the CRC incidence which matched previous findings. In a meta-analysis attempting to evaluate the association between serum lipids and CRN, the pooled RR of serum HDL-C for CRC was 0.97 (95% CI 0.80-1.18; $P = 0.77$), suggesting no significant relevance [94]. Another meta-analysis presented results for high versus low concentrations of serum HDL-C and CRC risk. A random-effects model yielded a summary RR of 0.84 (95% CI 0.69, 1.02), with evidence of moderate heterogeneity ($P = 0.059$, $I^2 = 42.5$ %) [95].

Tian *et al.* [94] stated that TG was associated with an increased incidence of CRA, but not CRC. Though, our results disagree with those findings. A stronger association was found among subjects with high TG values for developing CRA than for CRC in our analysis. Additionally, our results are not in line with those found by Tian *et al.* [94] (RR = 1.07; 95% CI 0.99-1.15; $P = 0.10$) and Esposito *et al.* [28] (RR = 1.12; 95% CI 0.98-1.27) where a non-significant association of serum TG with CRC risk was observed, our findings suggest a positive significant relationship. By contrast, our findings support those reported by Yao and Tian. [95] when assessing the implication of high levels of TG with CRC risk. Results for high versus low concentrations of serum TG and CRC occurrence yielded a summary RR of 1.18; 95 % CI 1.04-1.34), with evidence of moderate heterogeneity (P=0.011, $I^2 = 47.8$ %). A case-cohort study found that plasma triglycerides and HDL-C were unrelated to CRC risk [96].

The biological mechanisms linking dyslipidemia to CRC pathogenesis remain unknown. Nevertheless, some hypotheses were postulated. Fat intake increases bile acids production, which are transformed in the colon to secondary bile acids. The increase in the amounts of secondary bile salts may be carcinogenic for colon cells. Additionally, the constant damage to the colonic mucosa caused by secondary bile acids promotes the proliferation of colonocytes which may leads afterward to CRC development [81, 82, 97]. The results of epidemiological studies on the relationship involving dyslipidemia and cancer development were also conflicting [98, 99]. A weak inverse-association, which was dependent on smoking status, was noticed in a prospective cohort study between HDL-C and lung cancer [100]. Moreover, no correlation was observed between low HDL-C and breast cancer incidence for both the total sample and among postmenopausal women, while a modest association was noticed for premenopausal women [101]. Similarly, a retrospective cohort study found no significant association between both HDL-C and TG with liver and breast cancer [102]. Inversely, a strong association was remarked between low HDL-C and high TG values and prostate cancer incidence [92]. In vitro assays showed that HDL-C does not have a role in promoting breast cancer cell proliferation, angiogenesis or metastasis [103].

Research concerning the effect of the MetS and its individual conditions on CRA risk is limited. Tian *et al.* [94] indicated that serum TG was significantly associated with the CRA formation (RR = 1.06; 95% CI 1.03-1.10; $P = 0.0009$; $I^2 = 69\%$). Yet, this is lower than the 30% increase in the CRA risk observed in our analysis. The meta-analysis undertaken by Tian *et al.* [94] showed that the RR for CRA with serum HDL-C was 1.03 (95 % CI 0.99-1.06; $P=0.12$) with a moderate heterogeneity ($I^2 = 43$ %). Correspondingly, our analysis revealed a non-significant effect of low levels of HDL-C on CRA risk (RR = 1.02; 95% CI 0.92-1.12; $I^2 = 74\%$).

To the best of our knowledge, our study could be the first comprehensive meta-analysis that shed the light on the effect of each metabolic factor constituting the MetS and CRA formation in addition to their association with the risk of developing CRC. This could be of high importance, particularly to determine the implication of MetS components on CRC carcinogenesis. Future research should focus on determining whether the increased risk of CRN is attributable to the entire cluster or to every particular condition. Moreover, understanding the role of

each component and the biological mechanisms relating to those factors and CRN incidence may provide indications for colorectal cancer therapy. In general, no evidence of the small study effect or publication bias was found. Besides, the additional analyses including subgroup, influence, and sensitivity analyses were performed and the Baujat plots were constructed for all the analyses. The results showed that no dataset has contributed in a way that significantly alters the findings, apart from the exceptions mentioned, emphasizing therefore on the strength of our findings. Although, this study has certain limitations. Including case-control and cross-sectional studies may result in selection bias. Several analyses presented results with moderate or considerable heterogeneity, hence these findings should be interpreted with caution. Nevertheless, subgroup and sensitivity analyses were carried out with the aim of exploring the sources of heterogeneity.

5 CONCLUSIONS

In summary, our findings demonstrate that hyperglycemia, hypertension, hypertriglyceridemia, and central obesity are associated with a moderately increased risk of both CRA and CRC. In fact, the proportions for the augmentation of the risk oscillated between 26-33% for CRA, and between 14-35% for CRC. In general, regarding the relationship between the increased CRC risk and these conditions, the association was more noticeable in the colon than in rectal cancer and in men than women. Nonetheless, low HDL-C shows a statistically non-significant positive effect on both outcomes. Our results display stronger associations between MetS components and CRA risk compared with those of CRC. Thus, screening programs aiming to prevent CRC should take into consideration MetS patients. The management of MetS and its individual components is highly recommended. Further research should be focused on understanding the biological mechanisms underlying the relationship between MetS and CRC.

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