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Metabolic Syndrome and Risk of Colorectal Adenoma and Colorectal Cancer: A Meta-Analysis

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ABSTRACT

BACKGROUND: Growing evidence suggests that metabolic syndrome (MetS) could be linked with the incidence of colorectal adenoma and cancer (CRA and CRC). **AIMS:** Conducting a meta-analysis to assess the association of MetS with both CRA and CRC. **METHODS AND MATERIAL:** Relevant studies were identified by systematically searching PubMed database for articles published in the last ten years. A random effect analysis model and Mantel-Haenszel statistical method were used to obtain pooled risk ratios (RRs) and their 95% confidence intervals (CIs) for dichotomous data. The analyses were assessed for heterogeneity and publication bias. **RESULTS:** 35 studies were included in the meta-analysis involving approximately 1300000 participants. A significant high risk for CRA was observed among patients with MetS compared to those without (RR = 1.43; 95% CI = 1.31, 1.57). The pooled RRs of CRC were 1.46 (95% CI = 1.36, 1.56). The risk estimates varied according to the type of the study (cohorts and non-cohorts), gender (men and women), MetS definition (NCEP-ATPIII, IDF, harmonized and others), populations (Asia, Europe, and the USA), and cancer location (colon and rectum). **CONCLUSIONS:** MetS is associated with an increased risk of CRA and CRC. The risk was higher for advanced adenomas. Taking into consideration MetS patients in the secondary prevention programs and the management of this condition in the aim of the primary prevention is highly recommended.

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1. INTRODUCTION

Colorectal cancer (CRC) is a true public health burden recording more than 1.3 million cases (9.7% of all cancers), and approximately 0.7 million deaths (8.5% of all cancers) worldwide [1].

Age, sex, ethnicity [2], family history of CRC [3], inherited genetic predispositions [4–6], and inflammatory diseases [7, 8] play an essential role in CRC pathophysiology along with other risk factors including diet [9–11], smoking [12], physical inactivity [13], diabetes [14], and MetS [15].

MetS has become a growing public health and a clinical challenge too. 20-25% of world's adult population has MetS according to the International Diabetes Federation (IDF) [16]. MetS is defined by a cluster of correlated physiological, biochemical, clinical, and metabolic factors reflecting a cohesive pathophysiology. Those factors include visceral obesity, dyslipidemia, hyperglycemia, and hypertension that increase the risk of developing type 2 diabetes mellitus and cardiovascular diseases [17–19].

The association between MetS and CRC has been previously addressed in several studies, although the unavailability of evidence linking MetS with the precancerous lesions (adenomas, adenomatous polyps). Additionally, CRC is supposed to develop following the adenoma-carcinoma sequence [4], and those adenomas precede the cancer stage by several years which could allow for its prevention by targeting those precancerous lesions in the screening programs. Hence, understanding the correlation between CRA and MetS is crucial in clinical practice.

Results from studies that addressed the association linking MetS and colorectal neoplasms (CRN) (CRA (colorectal adenoma) and CRC) were inconsistent [20, 21]. In the present meta-analysis, we aimed to tackle this issue, focusing especially on the effect of the full syndrome on CRC and CRA incidence.

2. METHODS

Search strategy

The meta-analysis was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22].

The literature search was independently undertaken by two authors (S.E and Y.T). The author (MB.K) made the final decision in case of any discrepancy.

Key terms according to the Medical subject headings (MeSh) were used to identify relevant studies on the relationship between colorectal neoplasm and MetS in PubMed database. Full English studies, published during the past 10 years until 2017/08/01, were systematically searched and the terms used were: "colorectal neoplasms", "colorectal cancer", and "metabolic syndrome".

Study selection

Study eligibility was independently assessed by two reviewers (S.E and Y.T), and resolutions, in case of disagreements, were achieved by the author (MB.K).

Cohort, case-control, and cross-sectional studies with MetS as well as CRA and/or CRC incidence were eligible for the analysis. Studies were included if they met the following criteria: (a) CRA and/or CRC as the outcomes considered in the study, (b) MetS as the exposure, (c) the study must provide sufficient data to calculate the RRs and their 95% CIs, (d) the study must state the definition of MetS used.

Furthermore, reviews, meta-analyses, articles not published in English, articles not published as full text (case reports, letters to editors, editorials, comments, news etc.), and in vitro or studies where the subjects were organisms other than humans were excluded. The selection of any article was primarily based on title and abstract in order to exclude irrelevant studies. Subsequently, the full texts were strictly analyzed to determine the relevancy of any retrieved study.

Data extraction

Data extracted from each included study were: the first author's name, the year of publication, the country where the study was undertaken, duration of the study, type of lesions, number of subjects, number of events, and the definition of MetS used. Two authors (S.E and Y.T) independently gathered the relevant data.

Statistical analysis

Summary measures

A random effect meta-analysis model, which represents the assumption that there is a distribution of true effect sizes and aims to estimate the mean of this distribution [23], was used in our main meta-analysis to assess the relative risks (RRs) and their 95% confidence intervals (CIs) for dichotomous data. Mantel-Haenszel method was used to estimate the amount of the between-study variation. The between-study variance was assessed using the Tau-squared (T^2) statistic. Z-test of the null hypothesis was calculated and $P < 0.05$ was considered statistically significant.

Synthesis of results

Cochran's test or Q-test (X^2) was used to indicate the extent of heterogeneity and $P < 0.05$ was considered statistically significant. The I^2 statistic, which measures the degree of inconsistency across studies in a meta-analysis and which describes the percentage of total variation across studies that is due to heterogeneity rather than chance [24], was as well obtained. A value of 40% suggests low heterogeneity, 40-70% indicates moderate heterogeneity, and a value of > 70% may suggest high heterogeneity. Funnel plots were obtained and visually assessed for risk of publication bias.

Subgroup analysis

Subgroup analysis was undertaken to explore source of heterogeneity according to study design (cohort, case-control, and cross-sectional), gender (men and women), MetS definition (NCEP-ATPIII, IDF, the harmonized definition, and other definitions), geography (the USA, Asia, and Europe), cancer site (colon or rectal cancer).

3. RESULTS

Study selection

The process of selecting studies is displayed in the flowchart on Figure 1. 263 studies were identified through a database search. 179 studies unrelated to the topic and studies unpublished as full text or in the English language were excluded. 84 eligible studies reported MetS and CRA/CRC were retrieved and scanned carefully. 49 studies providing inadequate exposures, outcomes, or data and studies unfitting inclusion criteria were excluded out of the eligible studies. Eventually, 35 studies fulfilled the inclusion criteria comprised the meta-analysis.

Study characteristics

Table 1 summarizes properties of the included studies. Our meta-analysis comprised nine cohort studies [20, 21, 25–31], 13 case-control studies [32–44], and 13 cross-sectional studies [45–57]. 26 studies were undertaken in Asia [25, 26, 28–31, 33–35, 37, 38, 42, 44–57] while eight were carried out in European countries [20, 27, 32, 36, 39–41, 43], and only one study was performed in the USA [21]. Regarding the outcomes considered, 22 studies provided data on CRA risk [21, 25, 26, 28–31, 34–36, 44, 46, 47, 49–57], 18 concerning CRC [20, 26, 27, 29, 30, 32, 33, 36–43, 45, 46, 48], whereas 5 studies on both outcomes [26, 29, 30, 36, 46]. Furthermore, 20 studies utilized the definition formulated by the NCEP/ATPIII as diagnosis criteria in clinical practice [20, 25–29, 34, 36, 40, 41, 44, 46, 47, 49, 50, 52–55, 57], six studies provided the exposure data in basis of the IDF definition of MetS [20, 32, 38, 41, 43, 56], three used the harmonized definition [39, 41, 51], and nine presented MetS data patients using other definitions [21, 30, 31, 33, 35, 37, 42, 45, 48].

Association of MetS with CRA

A random effect meta-analysis model of 22 studies comprising 30 datasets of CRA incidence in individuals with MetS versus without MetS supported the association between MetS and CRA (RR = 1.43; 95% CI = 1.31, 1.57) (Figure 2; Table 2). No evidence of publication bias was observed (Figure 3). The risk estimation showed significant differences between cohort, case-control, and cross-sectional studies, this latter revealed a moderate heterogeneity (I^2 = 32%).

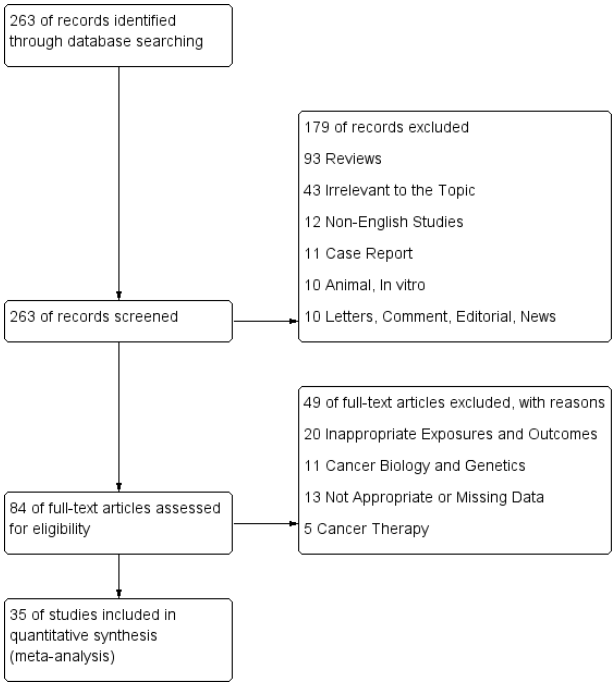

Figure 1: Flowchart of study selection

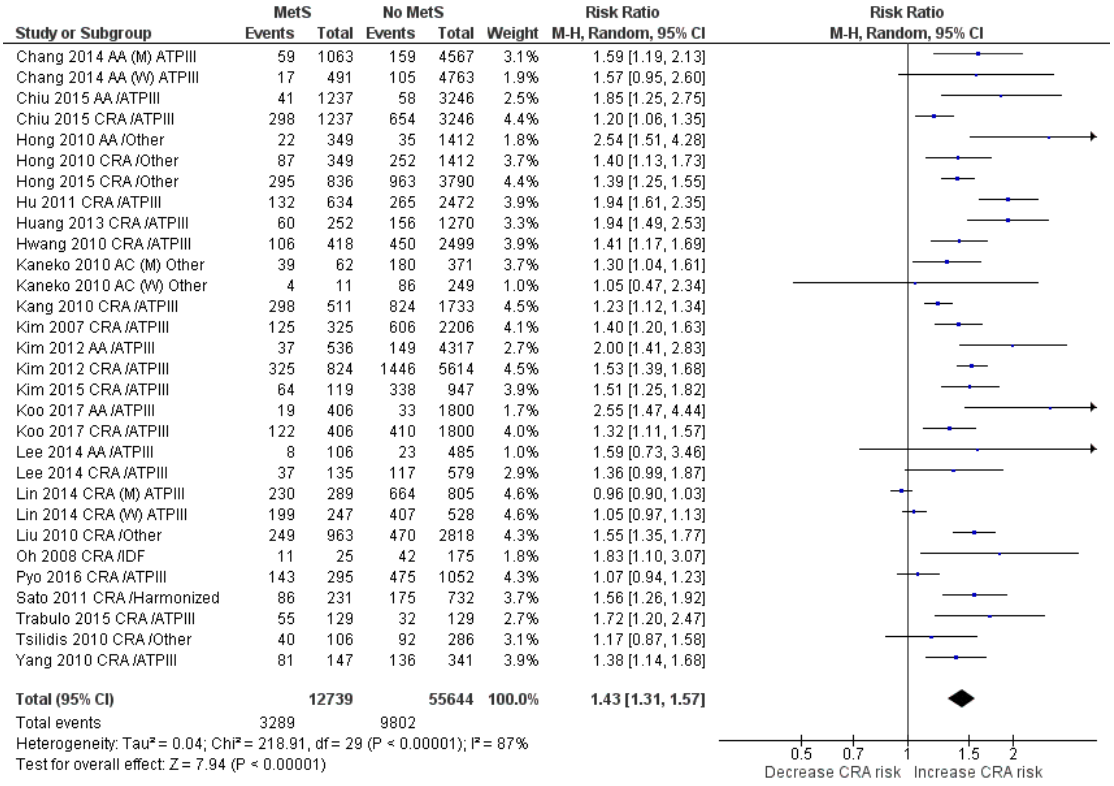

Figure 2: Forest plot of association between MetS and CRA risk

AA Advanced Adenoma, ATPIII (NCEP-ATPIII) National Cholesterol Education Program-Adult Treatment Panel III, CRA Colorectal Adenoma, IDF International Diabetes Foundation, M Men, W Women.

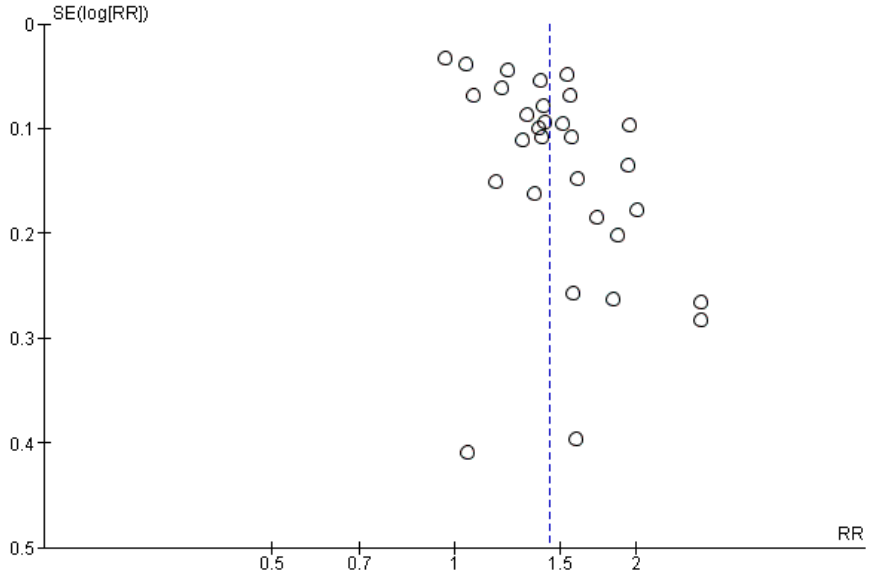

Figure 3: Funnel plot of the association between MetS and CRA

The summary of RRs for Asians was significant, but not for the other populations, similarly to studies reporting results for both sexes. The pooled analysis for risk estimates of studies using the NCEP/ATPIII definition of MetS were similar to studies using other definitions (RR = 1.43; 95% CI = 1.28, 1.59) and (RR = 1.45; 95% CI = 1.36, 1.55) respectively.

Table 1: Characteristics of included studies

Cohorts						
Authors , year of publication [Ref]	Country	Years	Type of lesion	№ events / № total	№ of MetS patients	MetS definition
Lu *et al*, 2015 [20]	Norway	1995-2010	Colorectal cancer	2044 / 143 477	43775[a] 40234[b]	IDF NCEP-ATPIII
Chiu *et al*, 2015 [25]	Taiwan	12/2003-07/2011	Colorectal adenomas	952 / 4 483	1237	NCEP-ATPIII
Lin *et al*, 2014 [26]	China	10/2007-12/2011	Colorectal adenomas and cancer	1500 CRA + 446 CRC / 2 315	705	NCEP-ATPIII
Van Kruijsdijk *et al*, 2013 [27]	Netherlands	09/1996-03/2011	Colorectal cancer	71 / 5937	3179	NCEP-ATPIII
Huang *et al*, 2013 [28]	Taiwan	01/2003-12/2010	Colorectal adenomas	216 / 1522	252	NCEP-ATPIII
Kim *et al*, 2012 [29]	South Korea	04/2007-04/2009	Colorectal adenomas Colon and rectal cancer	1771 CRA + 1292 CC + 146 RC / 6438	5614	NCEP-ATPIII
Kaneko *et al*, 2010 [30]	Japan	2007 and 2008	Colorectal adenomas and cancer	309 CRA + 34 AC / 727	80	Other
Liu *et al*, 2010 [31]	China	01/2006-05/2008	Colorectal adenomas	719 / 4122	963	Other
Tsilidis *et al*, 2010 [21]	The USA	1989-2000	Colorectal adenomas	132 / 392	106	Other
Case-control						
Authors , year of publication [Ref]	Country	Years	Type of lesion	Cases/controls	№ of MetS patients	MetS definition
Harlid *et al*, 2017 [32]	Sweden	1985-2014	Colorectal cancer	69 / 69	24	IDF
Pyo *et al*, 2016 [33]	South Korea	01/2002-12/2012	Rectal neuroendocrine tumors	102 / 52583	7137	Other
Pyo *et al*, 2016 [34]	South Korea	10/2009-12/2011	Colorectal adenomas	618 / 729	295	NCEP-ATPIII
Hong *et al*, 2015 [35]	South Korea	01/2011-21/2011	Colorectal adenomas	1258 / 3368	863	Other
Trabulo *et al*, 2015 [36]	Portugal	03/2013-03/2014	Colorectal adenomas and cancer	87 CRA / 171 23 AC / 235	129	NCEP-ATPIII
Jeon *et al*, 2014 [37]	South Korea	06/2004-01/2009	Colon and rectal cancer	264 CC / 400 186 RC / 400	193	Other
Ulaganathan *et al*, 2012 [38]	Malaysia	12/2009-01/2011	Colorectal cancer	140 / 140	196	IDF
Danese *et al*, 2012 [39]	Italy	01/2011-08/2011	Colorectal cancer	40 / 40	36	Harmonized

Kontou *et al*, 2012 [40]	Greece	12/2009-12/2010	Colorectal cancer	250 / 250	127	NCEP-ATPIII
Aleksandrova *et al*, 2011 [41]	Europe[c]	1999-2003	Colon and rectal cancer	689 CC / 689 404 RC / 404	424[d] 461[e] 350[f]	IDF Harmonized NCEP-ATPIII
Shen *et al*, 2010 [42]	China	01/2002-03/2007	Colorectal cancer	507 / 507	248	Other
Pelluchi *et al*, 2010 [43]	Italy and Switzerland	1992-2001	Colon and rectal cancer	1378 CC + 878 RC / 4 661	159	IDF
Kang *et al*, 2009 [44]	South Korea	01/2006-12/2007	Colorectal adenomas	1 122 / 1 122	511	NCEP-ATPIII
Cross-sectional						
Authors , year of publication [Ref]	Country	Years	Type of lesion	**№** events / **№** total	**№** of MetS patients	MetS definition
Pan *et al*, 2017 [45]	China	01/2011-11/2015	Colorectal cancer	27 / 1793	262	Other
Koo *et al*, 2017 [46]	South Korea	01/2010-12/2010	Colorectal adenomas and cancer	588 CRA + 4 CRC / 2206	142	NCEP-ATPIII
Kim *et al*, 2015 [47]	South Korea	01/2011-12/2011	Colorectal adenomas	402 / 1066	119	NCEP-ATPIII
Jung *et al*, 2014 [48]	South Korea	2010-2011	Rectal neuroendocrine tumors	101 / 57819	9297	Other
Chang *et al*, 2014 [49]	Taiwan	01/2006-12/2009	Colorectal adenomas	340 / 10884	1554	NCEP-ATPIII
Lee *et al*, 2014 [50]	South Korea	07/2005-12/2012	Colorectal adenomas	154 / 714	135	NCEP-ATPIII
Sato *et al*, 2011 [51]	Japan	06/2008-01/2010	Colorectal adenomas	261 / 963	231	Harmonized
Hu *et al*, 2011 [52]	Taiwan	10/2004-04/2006	Colorectal adenomas	397 / 3106	634	NCEP-ATPIII
Yang *et al*, 2010 [53]	South Korea	10/2003-06/2008	Colorectal adenomas	217 / 488	147	NCEP-ATPIII
Hong *et al*, 2010 [54]	South Korea	09/2005-03/2009	Colorectal adenomas	339 / 1761	349	NCEP-ATPIII
Hwang *et al*, 2010 [55]	South Korea	2007	Colorectal adenomas	556 / 2917	418	NCEP-ATPIII
Oh *et al*, 2008 [56]	South Korea	10/2005-12/2005	Colorectal adenomas	53 / 200	25	IDF
Kim *et al*, 2007 [57]	South Korea	03/2004-12/2005	Colorectal adenomas	731 / 2531	325	NCEP-ATPIII

AC adenocarcinomas, AHA/NHLBI America Heart Association and National Heart Lung Blood Institute, CC colon cancer, CRA colorectal adenoma, CRC colorectal cancer, IDF International Diabetes Foundation, MetS metabolic syndrome, NCEP-ATPIII National Cholesterol Education Program-Adult Treatment Panel III, RC rectal cancer.

[a], [d] According to IDF definition.

[b], f According to the NCEP-ATPIII definition.

[c] Participants are from Denmark, France, Germany, Greece, Italy, Spain, the Netherlands, and the United Kingdom.

[e] According to the harmonized definition.

Table 2: Results of subgroup analysis

Subgroups	№ of studies (№ of datasets)	[References]	Meta-analysis model	RR (95% CI)	Z-test	Heterogeneity		
						I^2 (%)	T^2	X^2
Colorectal adenomas								
All studies	22 (30)	[21, 25, 26, 28–31, 34–36, 44, 46, 47, 49–57]	RE	1.43 [1.31, 1.57]	7.94 *(P < 0.00001)*	87	0.04	218.91, df = 29 *(P < 0.00001)*
Type of study								
Cohort	7 (11)	[21, 25, 26, 28–31]	RE	1.36 [1.15, 1.61]	3.62 *(P = 0.0003)*	93	0.06	143.81, df = 10 *(P < 0.00001)*
Case-control	4 (4)	[34–36, 44]	RE	1.27 [1.11, 1.46]	3.47 *(P = 0.0005)*	75	0.01	11.89, df = 3 *(P = 0.008)*
Cross-sectional	11 (15)	[46, 47, 49–57]	RE	1.52 [1.40, 1.64]	10.38 *(P < 0.00001)*	32	0.01	20.49, df = 14 *(P = 0.12)*
Study location								
Asia	20 (28)	[25, 26, 28–31, 34, 35, 44, 46, 47, 49–57]	RE	1.44 [1.31, 1.58]	7.71 *(P < 0.00001)*	87	0.04	215.89, df = 27 *(P < 0.00001)*
Other	2 (2)	[21, 36]	RE	1.40 [0.96, 2.03]	1.76 *(P = 0.08)*	61	0.04	2.58, df = 1 *(P = 0.11)*
MetS definition								
NCEP-ATPIII	15 (21)	[25, 26, 28, 29, 34, 36, 44, 46, 47, 49, 50, 52, 53, 55, 57]	RE	1.43 [1.28, 1.59]	6.38 *(P < 0.00001)*	89	0.05	187.17, df = 20 *(P < 0.00001)*
Other	7 (9)	[21, 30, 31, 35, 51, 54, 56]	FE	1.45 [1.36, 1.55]	10.91 *(P < 0.00001)*	27	NA	11.00, df = 8 *(P = 0.20)*
Gender								
Men	3 (3)	[26, 30, 49]	RE	1.24 [0.87, 1.75]	1.19 *(P = 0.23)*	90	0.08	21.05, df = 2 *(P < 0.0001)*
Women	3 (3)	[26, 30, 49]	RE	1.13 [0.88, 1.45]	0.95 *(P = 0.34)*	30	0.02	2.86, df = 2 *(P = 0.24)*
Advanced adenomas	6 (7)	[25, 29, 46, 49, 50, 54]	FE	1.85 [1.58, 2.17]	7.55 *(P < 0.00001)*	0	NA	4.48, df = 6 *(P = 0.61)*
Colorectal cancer								
All studies	18 (45)	[20, 26, 27, 29, 30, 32, 34, 36–43, 45, 46, 48]	RE	1.46 [1.36, 1.56]	10.89 *(P < 0.00001)*	74	0.03	166.67, df = 44 *(P < 0.00001)*
Type of study								
Cohort	5 (15)	[20, 26, 27, 29, 30]	RE	1.63 [1.46, 1.82]	8.49 *(P < 0.00001)*	76	0.03	57.26, df = 14 *(P < 0.00001)*
Case-control	10 (27)	[32, 33, 36–43]	RE	1.35 [1.26, 1.45]	8.41 *(P < 0.00001)*	62	0.02	67.57, df = 26 *(P < 0.0001)*

Cross-sectional	3 (3)	[45, 46, 48]	FE	1.77 [1.20, 2.62]	2.85 *(P = 0.004)*	0	NA	0.78, df = 2 *(P = 0.68)*
Study location								
Asia	10 (16)	[26, 29, 30, 33, 37, 38, 42, 45, 46, 48]	RE	1.60 [1.42, 1.79]	7.93 *(P < 0.00001)*	60	0.02	37.20, df = 15 *(P = 0.001)*
Europe	8 (29)	[20, 27, 32, 36, 39–41, 43]	RE	1.40 [1.29, 1.52]	7.88 *(P < 0.00001)*	78	0.04	127.03, df = 28 *(P < 0.00001)*
MetS definition								
NCEP-ATPIII	8 (16)	[20, 26, 27, 29, 36, 40, 41, 46]	RE	1.41 [1.28, 1.56]	6.86 *(P < 0.00001)*	71	0.02	52.59, df = 15 *(P < 0.00001)*
IDF	5 (15)	[20, 32, 38, 41, 43]	RE	1.48 [1.29, 1.69]	5.69 *(P < 0.00001)*	79	0.05	66.43, df = 14 *(P < 0.00001)*
Harmonized	2 (5)	[39, 41]	RE	1.22 [1.07, 1.38]	3.05 *(P = 0.002)*	52	0.01	8.27, df = 4 *(P = 0.08)*
Other	6 (9)	[30, 33, 37, 42, 45, 48]	FE	1.74 [1.58, 1.91]	11.58 *(P < 0.00001)*	14	NA	9.30, df = 8 *(P = 0.32)*
Gender								
Men	6 (15)	[20, 26, 30, 38, 41, 43]	RE	1.41 [1.25, 1.60]	5.52 *(P < 0.00001)*	82	0.04	78.45, df = 14 *(P < 0.00001)*
Women	6 (15)	[20, 26, 30, 38, 41, 43]	RE	1.47 [1.32, 1.63]	7.11 *(P < 0.00001)*	70	0.03	47.43, df = 14 *(P < 0.0001)*
Cancer site								
Colon	6 (15)	[20, 29, 37, 41–43]	RE	1.53 [1.41, 1.67]	9.80 *(P < 0.00001)*	77	0.02	59.86, df = 14 *(P < 0.00001)*
Rectum	8 (17)	[20, 29, 33, 37, 41–43, 48]	RE	1.45 [1.29, 1.63]	6.19 *(P < 0.00001)*	72	0.04	56.50, df = 16 *(P < 0.00001)*
Colorectal adenomas versus colorectal cancer								
CRA	5 (9)	[26, 29, 30, 36, 46]	RE	1.38 [1.13, 1.68]	3.19 *(P = 0.001)*	93	0.07	118.45, df = 8 *(P < 0.00001)*
CRC	5 (8)	[26, 29, 30, 36, 46]	RE	1.48 [1.20, 1.82]	3.69 *(P = 0.0002)*	65	0.04	20.23, df = 7 *(P = 0.005)*

df degree of freedom, FE fixed effect, MetS metabolic syndrome, NA not applicable, NCEP-ATPIII National Cholesterol Education Program-Adult Treatment Panel III, RE random effect, RR risk ratio

Association of MetS with advanced adenomas

A fixed-effect meta-analysis model, since there was no evidence of heterogeneity, consisting of six studies and seven datasets reporting the incidence of advanced adenomas among individuals with MetS as compared with individuals without MetS gave evidence of a strong association (Table 2). A RR of 1.85 (95% CI = 1.58, 2.17) was observed, with no heterogeneity (P = 0.61, I2 = 0%).

Association of MetS with CRC

Eighteen studies including 45 datasets were available for the meta-analysis (Figure 4; Table 2). MetS patients showed an RR of 1.46 (95% CI = 1.36, 1.56) to develop CRC compared with individuals without MetS.

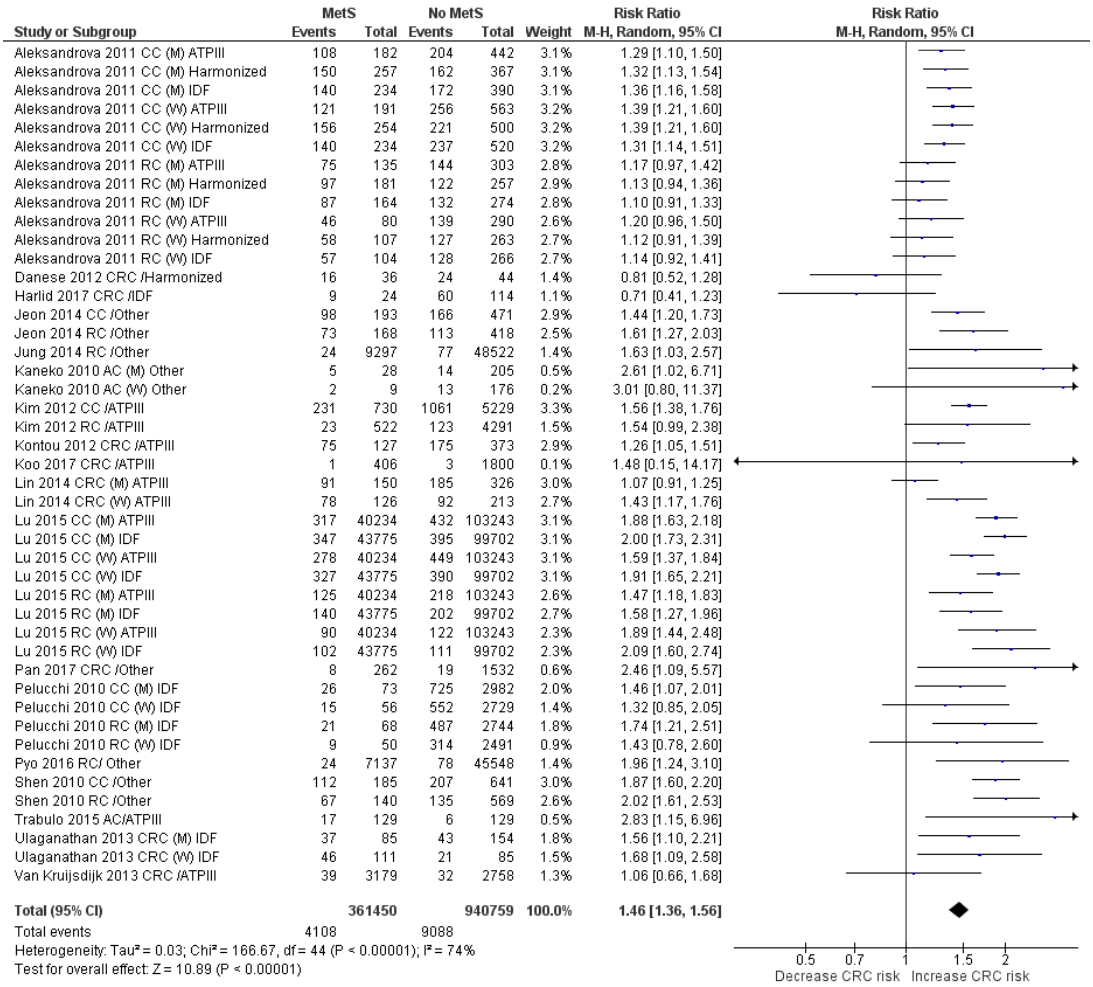

Figure 5: Forest plot of association between MetS and CRC risk

AC Adenocarcinoma, ATPIII (NCEP-ATPIII) National Cholesterol Education Program-Adult Treatment Panel III, CC Colon Cancer, CI confidence interval, CRC Colorectal Cancer, IDF International Diabetes Foundation, M Men, RC Rectal Cancer, W Women.

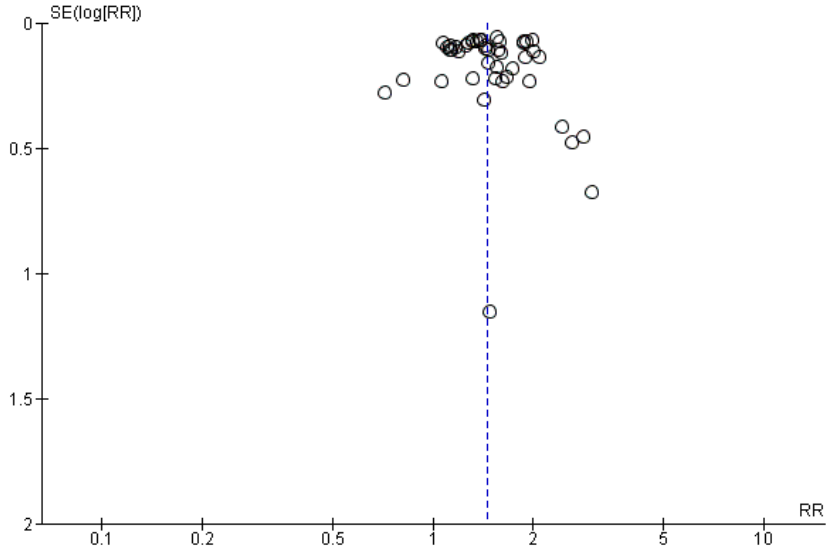

Figure 4: Funnel plot of the association between MetS and CRC

Differences between cohort, case-control, and cross-sectional studies were noticed. No significant heterogeneity was observed for cross-sectional studies (P = 0.68) and no evidence of publication bias was noticed (Figure 5). Positive and significant risk estimates were obtained for both Asian and European populations and for studies provided data for both sexes separately. Comparing studies using different definitions of MetS, studies using the harmonized definition and the other definitions had the lowest and the highest risk with no significant heterogeneity (RR = 1.22; 95% CI = 1.07, 1.38; P value for heterogeneity = 0.08) and (RR = 1.74; 95% CI = 1.58, 1.91; P value for heterogeneity = 0.32) respectively. Our results showed that the risk of developing rectal cancer is slightly lower than that of colon cancer with an RR of 1.45 (95% CI = 1.29, 1.63) and 1.53 (95% CI = 1.41, 1.67) correspondingly.

Colorectal adenomas versus colorectal cancer

We weighted the association of MetS with CRA and CRC using the same datasets. Five studies reported data for both CRA and CRC. The comparison showed that the risk of developing CRC is 10% higher than the risk of developing CRA (RR = 1.48; 95% CI = 1.20, 1.82) and (RR = 1.38; 95% CI = 1.13, 1.68) respectively.

4. DISCUSSION

Our meta-analysis of 35 studies provided evidence that metabolic syndrome increases the risk of colorectal neoplasm, especially for advanced adenoma and colorectal cancer. To sum up, the results showed 46% and 43% increased CRC and CRA risk among subjects with MetS compared to those without MetS.

Including different types of studies (cohort, case-control, and cross-sectional), MetS definition (NCEP/ATPIII, IDF, the harmonized, and other), gender (men and women), populations (Asia, Europe, and the USA), and the type and location of the lesion slightly influenced the risk estimates.

Several factors and signaling pathways are reported to be implicated. The insulin receptor and the IGF-1 receptor are over-stimulated which reduces apoptosis and promotes cancer cells proliferation. Insulin favors type II T helper cell production by modulating the polarization of effector T cells which indirectly favors cancer cells progression and metastasis [58]. In a case-control study including 615 CRC patients and 650 control healthy individuals, high levels of IGF-1 were possibly linked with the initiation of CRC [59].

Moreover, the adipose tissue is the largest endocrine organ of the human body producing free fatty acids, different cytokines (interleukin 6, monocyte chemoattractant protein1, tumor necrosis factor-α) and hormones (leptin, aromatase, adiponectin, plasminogen activator inhibitor 1), which may be involved in cancer genesis and progression [60, 61].

TNF-α, IL-6, and IL-1β can promote pro-inflammatory gene expression and induce CRC cell lines to express a variety of cytokines and chemokines that recruit and activate APCs and granulocytes through numerous signaling pathways such as MAPK-, JAK/STAT, and NF-κ B-mediated signaling. Similarly, inflammation-induced DNA damage has been linked to altered expression of genes involved in CRC such as p53, APC, KRAS, and BCL-2 [62]. For instance, the expression of leptin in tissues of 80 CRC patients was assessed in a research study and the results revealed that leptin affects CRC stem cells growth and survival and induces the activation of JAK and ERK signaling pathways that regulate the invasion and adhesion of these cells [63].

MetS is as well strongly associated with other types of cancer [58]. A study was undertaken in the USA has concluded that subjects with prostate cancer have a high prevalence of MetS [64]. In accordance, a Japanese retrospective cohort study endeavored to elucidate the relationship between MetS and the incidence of cancer found that MetS increased the risk of breast cancer and prostate cancer [65].

Although, epidemiological studies provide a strong evidence of an association between MetS and colorectal neoplasm, our understanding of the biological mechanism underlying this association is incomplete. This may be due to the complex pathophysiology and the numerous common factors such as those shared between both diseases [66].

Concerning incidence risk of CRC and MetS, our results agree with several studies. Although the incidence was low compared to our findings, Jinjuvadia et al. reported an increased risk of developing CRA, and CRC among MetS patients (RR = 1.37; 95% CI = 1.26, 1.49) and (RR = 1.30; 95% CI = 1.18, 1.43) respectively [67].

Esposito et al. observed, in a meta-analysis of 17 studies, that MetS was linked with a higher incidence of CRC for women compared to men (RR = 1.41; 95% CI = 1.18, 1.70) for women and (RR = 1.33; 95% CI = 1.18, 1.50) for men [68] which is consistent with our results (RR = 1.47; 95% CI=1.32, 1.63) for women and (RR = 1.41; 95% CI = 1.25, 1.60) for men, though the difference in the magnitude of the risk estimate.

To the best of our knowledge, our meta-analysis could be the first investigating the association between MetS and CRA incidence.

There were some potential limitations in the current study such as the loss of some studies due to inclusion criteria,

where non-English articles were excluded. Nevertheless, we found only one Chinese case-control study (included 135 CRC cases and 120 controls) that met the inclusion criteria [69]. There were 46 and 27 MetS patients in the case and control groups respectively. Some analyses showed evidence of heterogeneity. However, subgroup analysis demonstrated sources of heterogeneity. Furthermore, heterogeneity could be attributable to using different definitions of MetS and including cohorts and non-cohorts in the analyses.

5. CONCLUSION

In conclusion, our meta-analysis showed that MetS is associated not only with colorectal cancer but with earlier precancerous conditions such as colorectal adenomas and advanced adenomas too. Those conditions are the primary targets for screening programs aiming for an early detection and prevention of this malignancy. Patients with MetS should be included in such programs. Besides, subjects with MetS should consider lifestyle modifications like weight loss, physical activity, and diet [17, 70], along with management of its individual components. The implication of some pharmacological treatments with CRC development should be taking into consideration [71, 72].

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