EClinicalMedicine 34 (2021) 100794

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: www.elsevier.com/locate/eclinm

Research Paper

Association between cardiovascular risk factors and colorectal cancer: A systematic review and meta-analysis of prospective cohort studies

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ARTICLE INFO

Article history:
Received 26 December 2020
Revised 22 February 2021
Accepted 24 February 2021
Available online 18 March 2021

Keywords:
Cardiovascular risk factors
Colorectal cancer
Association
Meta-analysis and systematic review

ABSTRACT

Background: Emerging data have suggested colorectal cancer (CRC) often coexists with cardiovascular diseases, but whether cardiovascular risk factors play a role in CRC remains unclear. We performed a systematic review and meta-analysis to better illustrate the associations between cardiovascular risk factors and CRC.

Methods: We searched EMBASE, MEDLINE and Web of Science databases from inception up to June 14, 2020. Prospective cohort studies were included if they evaluated the association between at least one of cardiovascular risk factors and CRC incidence, containing sufficient data to obtain relative risk (RR) and 95% confidence interval (CI). We performed separate meta-analyses for each cardiovascular risk factor using random-effect model. PROSPERO registration number: CRD42020175537.

Findings: Data from 84 studies, reporting 52, 348, 827 individuals and 384, 973 incident cases were included in the analysis. Overall, the risk of CRC was 1.31(95% CI, 1.21–1.42) for obesity, 1.14 (95% CI, 1.09–1.20) for per 5 kg/m^2 increase in body mass index, 1.18 (95% CI, 1.14–1.23) for former smoker, 1.20 (95% CI, 1.11–1.30) for current smoker, 1.25 (95% CI, 1.16–1.35) for diabetes, 1.07 (95% CI, 1.02–1.12) for hypertension. The summary RRs of CRC for the highest versus lowest quartiles of total cholesterol, triglyceride, low-density lipoprotein were 1.12 (95% CI, 1.03–1.22), 1.18 (95% CI, 1.04–1.35), 0.85 (95% CI, 0.62–1.17) respectively and the pooled RR for the lowest versus highest quartile of high-density lipoprotein was 1.14 (95% CI, 1.02–1.28).

Interpretation: Unfavorable cardiovascular risk factors are associated with increased risk of CRC, which may provide novel insight into the screening strategies of CRC in patient with these risk factors.

Research in context

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https://doi.org/10.1016/j.eclinm.2021.100794

Evidence before this study

Cardiovascular disease and colorectal cancer are the two leading causes of death around the world. Previous studies have suggested the coexistence of these two conditions. It remains unclear whether cardiovascular risk factors play a role in colorectal cancer.

Added value of this study

With the large sample size and the generalized population, our study confirmed that obesity, increased body mass index and smoking were associated with increased risk of CRC. Our study also demonstrated that less well-described risk factors including hypertension, triglycerides, total cholesterol and high-density lipoprotein were also associated with higher risk of CRC. Low-density lipoprotein was not significantly associated with CRC risk.

Implications of all the available evidence

The findings may have great clinical significance on new screening strategies for CRC especially for individuals with unfavorable cardiovascular risk factors.

1. Introduction

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer death worldwide, accounting for over 1.8 million new cases and approximately 881, 000 deaths in 2018 [1]. Cardiovascular disease (CVD) is another leading cause of death and chronic disability for all regions of the world [2,3]. Although initially thought of as two separate disease entities, emerging evidence has suggested that there may be some common features linking both of them [4,5]. Several studies have demonstrated that patients with coronary heart disease are at a higher risk of developing CRC [6–8].

Nonmodifiable risk factors, including age, sex and race, are uncontrollable features that have been demonstrated to influence incidence rates of both CRC and CVD [9,10]. It is well known that obesity, smoking, diabetes mellitus, hypertension and dyslipidemia are common risk factors for CVD [11]. In previous studies, obesity, increased body mass index (BMI), smoking and diabetes have been demonstrated to be associated with increased risk of CRC [12–17]. However, these meta-analyses included studies only published before 2012. Furthermore, data on hypertension and dyslipidemia are limited and rather inconsistent. While several cohort studies reported a positive association between hypertension and CRC [18,19], Siddiqui et al. [20] and Suchanek et al. [21] showed that hypertension was not associated with risk of CRC. Some studies reported an increased risk of CRC in subjects with higher serum triglyceride and total cholesterol [19,22,23] whereas other studies found nonsignificant or inverse association [24–26].

In the present study, we conducted a systematic review and meta-analysis of prospective cohort studies to evaluate the associations between major cardiovascular risk factors and the incidence of CRC, paying particular attention to the strength of the association by individual risk factor.

2. Materials and methods

2.1. Search strategy

We systematically searched Medline databases, EMBASE and Web of Science from inception to June 14, 2020 for studies on the association between cardiovascular risk factors and CRC. The detailed search strategy is presented in supplement. All reference lists from the main reports, relevant reviews and previous meta-analyses were hand searched for additional eligible studies.

2.2. Study selection

Titles and abstracts of retrieved articles were independently screened by two authors (Zhang C and Cheng Y). Articles deemed potentially eligible by either reviewer were retrieved for full-text studies were included if they 1) were prospective cohort studies. 2) evaluated the association between at least one of the cardiovascular risk factors and the incidence of colonic, rectal or colorectal cancer. 3) reported results with relative risk (RR) or hazard ratio (HR) with 95% confidence intervals (CIs) or provided sufficient data to calculate these. In case of multiple publications from the same population, we included the data from the most informative one (with sufficient baseline characteristics and most comprehensively adjusted risk estimates). The detailed exclusion criterion is presented in supplement.

2.3. Date extraction and quality assessment

Data extraction was conducted independently by two authors (Zhang C and Cheng Y) with disagreements resolved by consensus. The following characteristics of each eligible study were extracted: the first author's name, year of publication, geographical location, population source, mean follow-up time, mean age at baseline, gender category, methods for assessment of exposure and outcome, number of events, number of participants, RR with corresponding 95% CIs and covariates adjusted for in the multivariable analysis.

We used the Newcastle-Ottawa quality assessment scale (NOS) [27] to evaluate the quality of included studies. In the current study, we considered a study awarded six or more points as a high-quality study. Discrepancies were resolved by discussion.

2.4. Data synthesis and analysis

We calculated summary RRs using random-effects models of RR or HR from each study. When RRs were available, we used the most comprehensively adjusted risk estimates reported in the publications. When the actual RR was not available, we calculated RRs with 95% CIs from raw data. To enable a consistent approach to analysis for triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), RRs for each study were transformed to involve comparisons between the 4th quartile and 1st quartile using methods previously described [28,29]. Heterogeneity across studies was assessed using I^2 (95% CI) statistic, applying the following interpretation for I^2: <50%, low heterogeneity; 50–75%, moderate heterogeneity; > 75%, high heterogeneity [30].

The publication bias was evaluated by the funnel plot and quantified by Begg's test [31] and Egger's test [32]. The Duval and Tweedie nonparametric trim and fill procedure [30] was further used to adjust for the publication bias. Briefly, this method firstly trimmed off the asymmetric outlying part of the funnel plot after estimating how many studies are in the asymmetric part. The symmetric remaining studies were applied to estimate the true center of the funnel. Then, using the true center as the axis of symmetry, studies trimmed in the first step were firstly added back to the trimmed funnel plot, and the same number of projected studies which are symmetric to those trimmed studies were also added to the funnel plot. Final pooled estimate was obtained based on the filled funnel plot [33]. Several sensitivity

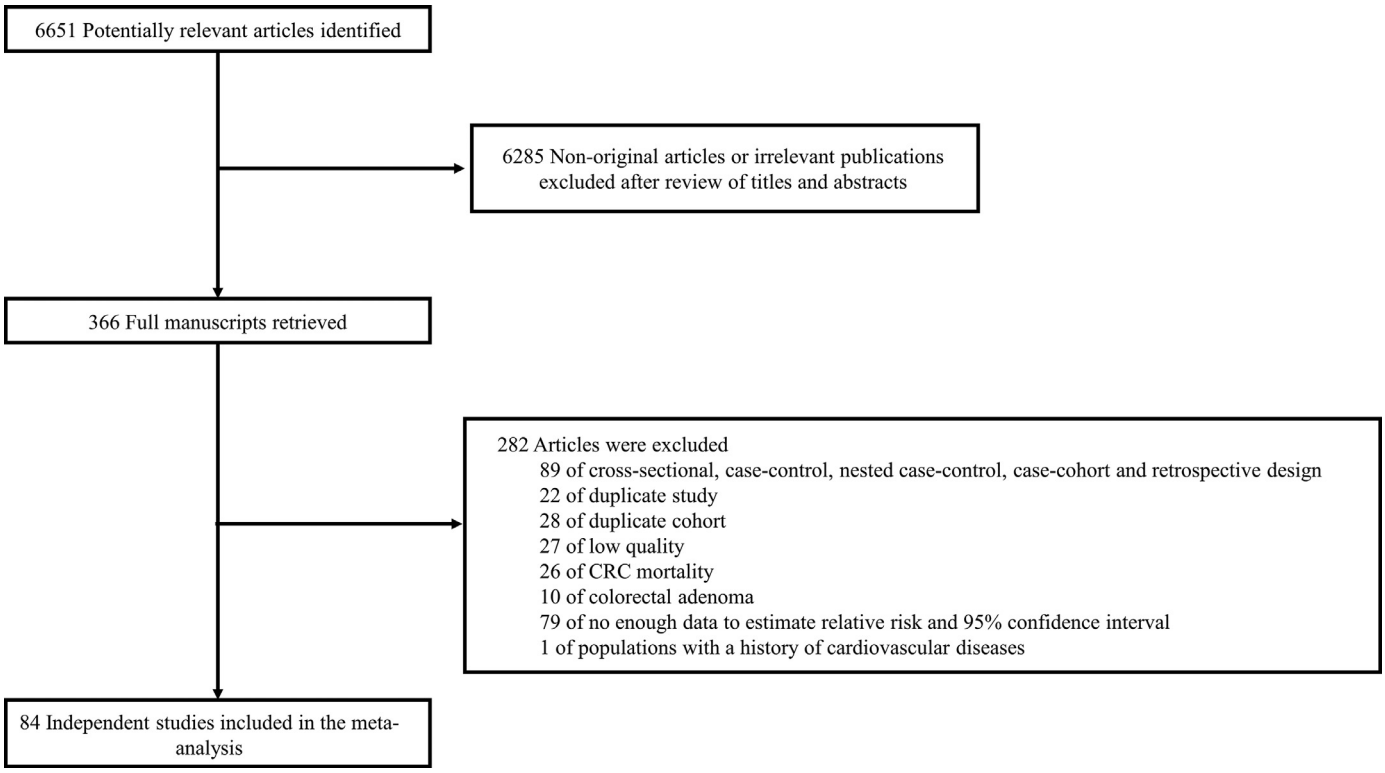

Fig. 1. Flowchart of study selection.

analyses were conducted to test the robustness of the main findings and assess the potential sources of heterogeneity. First, fixed-effect meta-analysis was used to evaluate the consistency of the main results from random-effect model. Second, to explore the impact of study quality, we conducted sensitivity analyses by important quality components including subjective representativeness (population/community-based or occupational-based), the method of case determination (measured or self-reported), mean follow-up ($\geq$10 years or $<$ 10 years), covariates adjusted for in the multivariable analysis ($\geq$3 factors or $<$ 3 factors) and NOS ($\geq$ 6 or $<$ 6). Finally, we excluded individual study estimates 1 at a time to examine the influence of each study on the overall RR. All statistical analyses were performed with Stata software, version 10 (Stata Corp, College Station, Texas). $p < 0.05$ was considered statistically significant.

2.5. Role of funding sources

The funders of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Study selection and baseline characteristics

From a total of 6651 potentially relevant studies identified by the search we assessed 366 full-text articles, leaving 84 articles finally included in the meta-analysis (Fig. 1). Study characteristics is presented in Table 1 with detail information in etable 1–9. The general findings of this study are summarized in Fig. 2. Overall, 52, 348, 827 participants were included in this study to exam the risk of CRC in individuals with cardiovascular risk factors compared to those without, with 384,973 incident cases of CRC. The mean age of participants at entry was 46.6 years (ranging from 17.4 to 72.9 years in each study). The selected studies were published between 1986 and 2019. Of them, 36 studies were conducted in Europe, 29 in North American, 17 in Asia and 2 in Oceania.

With respect to study quality, 67% of included studies were deemed high-quality (NOS $\geq$ 6). Of the 84 included studies, 52 were population-based studies, 12 were community-based studies and 20 studies were sampled from occupational populations. The exposure of risk factors was measured in 42 studies, was self-reported in 29 studies, and was determined by other methods (combination of measurement and self-reported data/medical history/current medication/physician-diagnosis) in 13 studies. Fifty-eight studies provided adjusted RRs, 45 of them adjusted for age and 34 adjusted for at least 3 of the most important confounding factors (BMI/obesity, smoking, alcohol, physical activity and diet). Twenty-three studies reported unadjusted RRs and 3 studies did not provide adjusted confounders.

3.2. Obesity/BMI

A total of 14,583,001 participants with 112,391 events were included to investigate the association between obesity/BMI and the risk of CRC. Overall, the pooled RRs of CRC were 1.31 (95% CI, 1.21–1.42) for obesity, 1.14 (95% CI, 1.09–1.20) for 5unit increment in BMI, with evidence of high heterogeneity across these studies (I^2 = 83.9%, $P < 0.01$ for obesity, I^2 = 85.1%, $P < 0.01$ for BMI increment) (Fig. 3A and B). Risk estimates of CRC associated with obesity or BMI did not materially change after analyses with fixed-effect models, inclusion of population/community-based studies, high-quality studies, studies with measured height and weight, studies with mean follow-up duration more than 10 years, yet high heterogeneity was still present (etable 10). The omission of any one study did not appreciably change the pooled RR, and the estimates in each case were well within the confidence limits of the overall

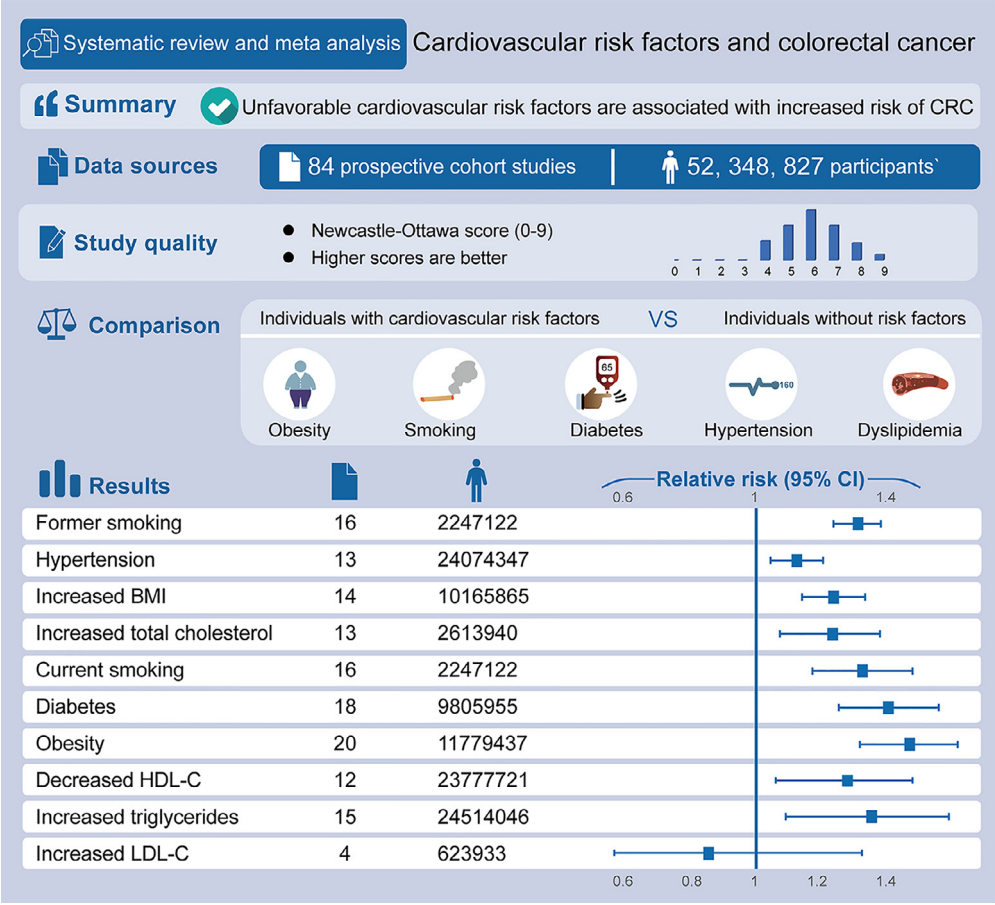

Fig. 2. Central Illustration of the Association Between Cardiovascular Risk Factors and Colorectal Cancer.

estimate (etable 10). However, when the analysis of increased BMI and CRC was confined to studies with follow-up of more than 10 years, the pooled RRs showed no substantial change, but no evidence of heterogeneity was observed (I^2 =0.0%, P = 0.44) (etable 10). There was no evidence of publication bias with funnel plots, Egger's test or Begg's test (eFig. 1A and 1B).

3.3. Smoking

Sixteen studies reporting the risk estimates of CRC for both current and former smokers versus never smokers were included for this analysis, involving 2247,122 participants and 25,378 events. Overall, the pooled RRs for former versus never smokers and current versus never smokers were 1.18 (95% CI, 1.14–1.23), 1.20 (95% CI, 1.11–1.30) respectively (Fig. 3C and D). We observed consistent increased risks of CRC both in former smokers and current smokers when analyses were repeated using fixed-effects model, including high-quality studies, population/community-based studies, studies with mean follow-up time more than 10 years, studies with adjustment for 3 or more confounding factors (etable 11). Between-study heterogeneity was statistically significant in the analyses for current smokers but not for former smokers (I^2 ranged from 47.7% to 67.9% for current smokers and 0.0% to 14.2% for former smokers, etable 11). The sensitivity analyses demonstrated no meaningful differences in the RRs upon omission of each study from the primary analyses (etable 11). There was no statistical evidence of publication bias for former smokers (Begg's, z = 1.13, P = 0.26; Egger's, t = 1.36, P = 0.20) and current smokers (Begg's, z = 0.86, P = 0.39; Egger's, t = 0.65, P = 0.52) (Data not shown).

3.4. Diabetes mellitus

For diabetes mellitus, eighteen studies were included for the analyses, reporting 71,672 events among 9805,955 participants. The overall pooled RR for CRC risk associated with diabetes was 1.25 (95% CI, 1.16–1.35), with moderate between-study heterogeneity (I^2 = 73.7%, P < 0.01) (Fig. 4A). The summary RRs did not vary substantially after analyses with fixed-effect model, inclusion of population/community-based studies, high-quality studies or studies with mean follow-up time more than 10 years, with moderate-to-high heterogeneity across studies (etable 12). There was no evidence of heterogeneity after excluding three largest studies (I^2 = 0.0%, P = 0.63) (data not shown). A sensitivity analysis of omitting 1 study in each turn showed no substantial change on the results with pooled RRs ranging from 1.20 to 1.27 (etable 12). No significant publication bias was observed according to the Begg's test (z = 0.98, P = 0.33) or Egger's test (t = 1.18, P = 0.26) (data not shown).

3.5. Hypertension

Thirteen studies reporting 24,074,347 individuals and 162,495 incident cases were included to evaluate the risk for CRC among participants with hypertension. Overall, participants with hypertension experienced an increased risk for developing CRC compared to those with normotension [RR=1.07 (95% CI, 1.02–1.12) for random-effects model; RR=1.05 (95% CI, 1.02–1.07) for fixed-effects model] (Fig. 4B). There was low heterogeneity across the studies (I^2=22.2%, P = 0.22) (Fig. 4B). The findings from the sensitivity analyses showed that risk estimates changed little based

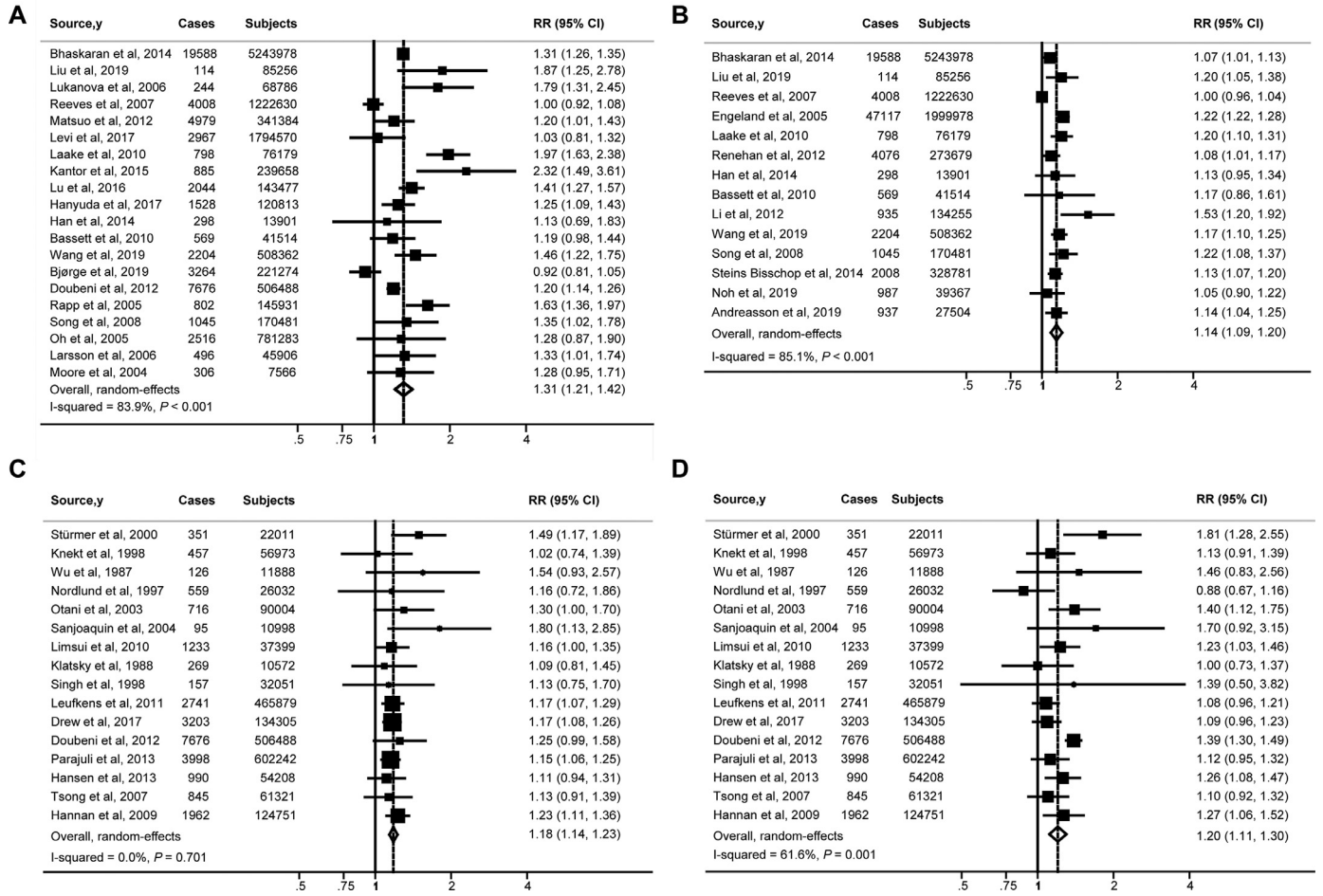

Fig. 3. Forest Plots for Colorectal Cancer Incidence (A) Summary Relative Risks for Obesity; (B) Summary Relative Risks for Per 5 kg/m^2 Increase in Body Mass Index; (C) Summary Relative Risks for former smokers versus Nonsmokers; (D) Summary Relative Risks for current smokers versus Nonsmokers.

on different inclusion and exclusion criteria, but heterogeneity was still present (etable 12). We observed potential publication bias according to asymmetric funnel plot and the Egger's test ($t = 2.26$, $P = 0.05$) but not according to Begg's test ($z = 0.55$, $P = 0.58$) (data not shown). To evaluate the influence of potential publication bias, we used the trim and fill method with six additional imputed studies to balance the funnel plot and calculated an adjusted pooled random-effects RR, which did not show a statistically significant association between hypertension and CRC [RR=1.04 (95% CI, 0.99–1.09)], suggesting the positive association may dissipate when we considered the effects of publication bias (efigure 3).

3.6. Dyslipidemia

The analyses involving 25,908,256 participants and 178,121 events were conducted to explore the association between CRC incidence and dyslipidemia. In a comparison of individuals in the highest quartile of baseline levels of serum lipid levels, the risk of CRC was 1.12 (95%CI, 1.03–1.22) for total cholesterol, 1.18 (95% CI, 1.04–1.35) for triglyceride, 0.85 (95% CI, 0.62–1.17) for LDL-C (Figs. 4C, D and 5B). And the risk of CRC for individuals in the lowest versus highest quartile of HDL was 1.14 (95% CI, 1.02–1.28) (Fig. 5A).

The positive association between total cholesterol and CRC incidence persisted in analyses with population/community-based studies, studies with an average follow-up of 10 years or more (I^2 statistic ranging from 28.6% to 45.2%), but dissipated in analysis with studies adjusted for at least 3 confounding factors (etable 13). When we repeated analyses of triglyceride and CRC in population/community-based studies, high-quality studies, and studies with longer follow-up duration ($\geq$ 10 years), the pooled RRs still reached statistical significance (etable 13). However, the RRs became nonsignificant when we used fixed-effect models or included studies adjusted for 3 or more confounding factors (etable 13). With respect to the relationship of HDL-C and CRC, the inverse association was still observed when we restricted the meta-analysis to population-based studies, high-quality studies or full adjusted studies (etable 14). However, exclusion of study by Choi *et al.* [18] yielded nonsignificant summary RRs [RR=1.11 (95% CI, 0.98-1.26)](etable 14).

Publication bias was not suggested in analyses of total cholesterol and HDL-C according to Begg's test and Egger's test (data not shown). However, for triglyceride, there was indication of publication bias with Egger's test ($t = 3.81$, $P = 0.00$) and the asymmetry of funnel plot but not Begg's test (efigure 4). A sensitivity analysis using the trim and fill method was performed with 7 additional studies, which produced a pooled RR of 1.00 (95% CI, 0.88–1.13), suggesting that the relationship of triglyceride and CRC may be interpreted with caution (efigure 4).

4. Discussion

In this meta-analysis with a large sample size (more than 52 million participants), we found that major risk factors for cardiovascular diseases were associated with increased risk of colorectal cancer. Our findings extend the results of previous reports, not only

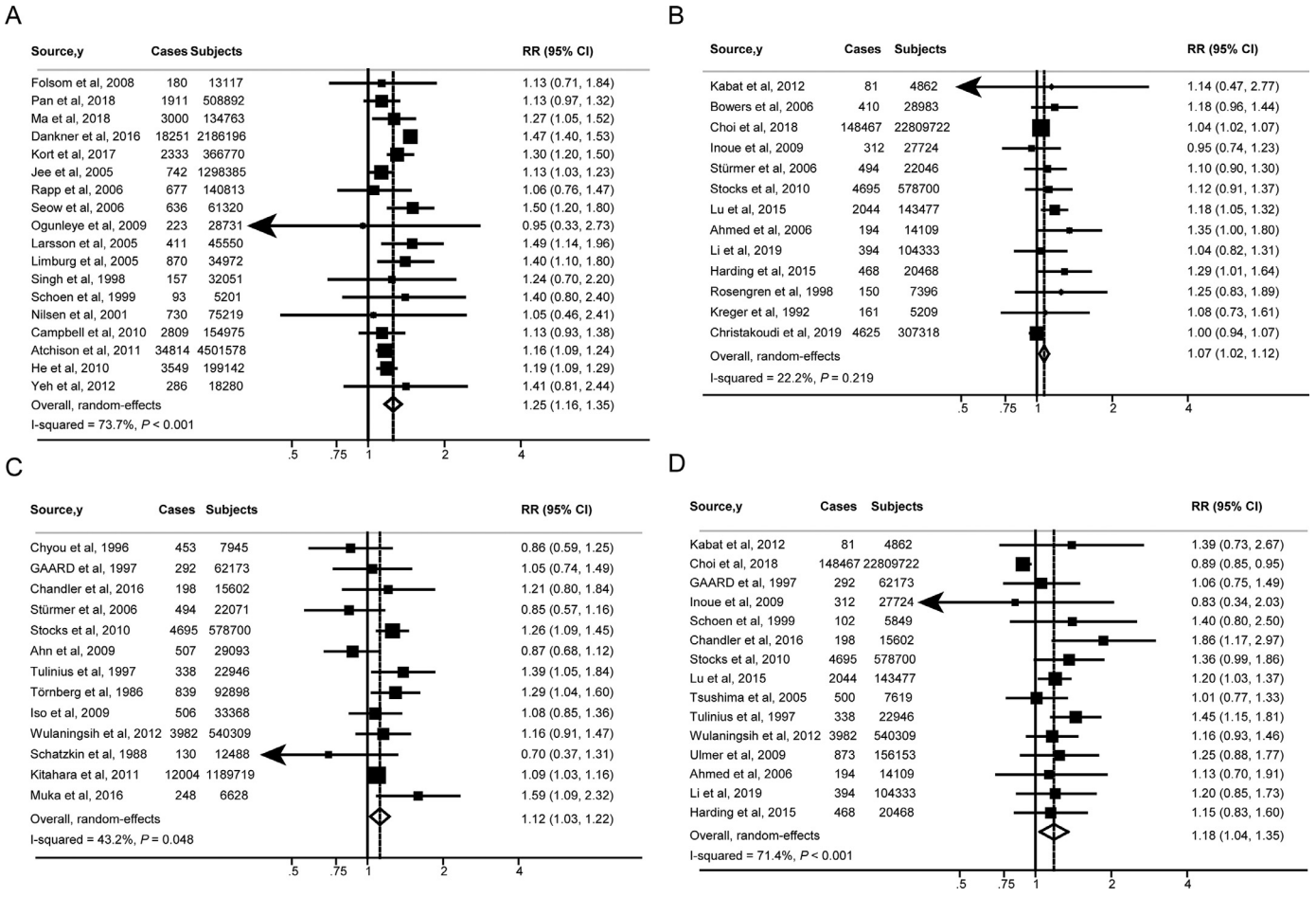

Fig. 4. Forest Plots for Colorectal Cancer Incidence (A) Summary Relative Risks for Diabetes; (B) Summary Relative Risks for hypertension; (C) Summary Relative Risks for Individuals in the highest quartile versus those in the lowest quartile of Total Cholesterol; (D) Summary Relative Risks for Individuals in the highest quartile versus those in the lowest quartile of Triglyceride.

to evidence that participants with established risk factors consistently experienced increased risks of CRC, but also to show positive associations between CRC and less well-described risk factors. Of note, LDL-C was not significantly associated with CRC risk.

In line with previous studies, our study also confirmed the positive associations between obesity, increased BMI, smoking, diabetes and CRC. Although obesity has been an established risk factor for CRC, it often coexists with other metabolic abnormalities such hyperglycemia, dyslipidemia and hypertension, which may mediate this association between obesity and CRC risk [34–36]. Recent studies found that obese individuals without metabolic abnormalities which were referred to “metabolically health obesity (MHO) ” had no increased risk of incident CRC whereas those with “metabolically unhealthy obesity (MUO)” showed a higher risk of CRC, raising special concern of MUO [35]. Consistent with these findings, our study included obese individuals with at least one of metabolic abnormalities and did observe a 31% greater risk of CRC. Additionally, the coexistence of risk factors may be associated with an additive effect. In a prospective cohort study, the HRs of CRC increased with the increasing number of metabolic syndrome components [18]. Therefore, when assessing the CRC risk, a comprehensive evaluation of the associated risk factors is warranted.

Regarding smoking, data were inconclusive. In studies reported by Limburg et al. and Gram et al., the positive association between smoking and CRC was significant for former smokers but not for currents smokers [37,38], while in our study, this association existed both in former and current smokers. This discrepancy may be ascribed to limited data obtained from female smokers only in studies by Limburg et al. and Gram et al., which could not be directly extrapolated to male smokers or general populations. With regard to hypertension, studies were sparse and inconclusive. In a report from the Physician’s Health Study, no increased risk of CRC was observed in participants with hypertension [39]. Likewise, in a population-based cohort study from Japan, it was also shown that hypertension was not significantly associated with higher risk of CRC [40]. However, these studies involved a restricted subgroup of the general population and were based on self-reported blood pressures, which could potentially bias the results. On the contrary, in a more generalized population, we did observe a 7% increased risk of CRC in those with preexisting hypertension.

Although dyslipidemia is an established risk factor for cardiovascular disease and several type of cancers, the relationship on dyslipidemia and CRC still remains unclear [11,41,42]. In the present analysis, we found increased risk of CRC in participants with elevated serum cholesterol, triglyceride and decreased HDL-C. In contrast, a study based on Japanese-American men followed for over 20 years demonstrated that increased serum cholesterol levels were associated with decreased risk of colon cancer. Of note, the inverse association was only present for colon cancer cases diagnosed within the first 10 years but not statistically significant for colon cancer diagnosed after 10 years [43]. This suggested that the relationship may be more complex and changed with the follow-up duration. Long follow-up of our study, with all but one study followed up for more than 10 years may lead to a more reliable

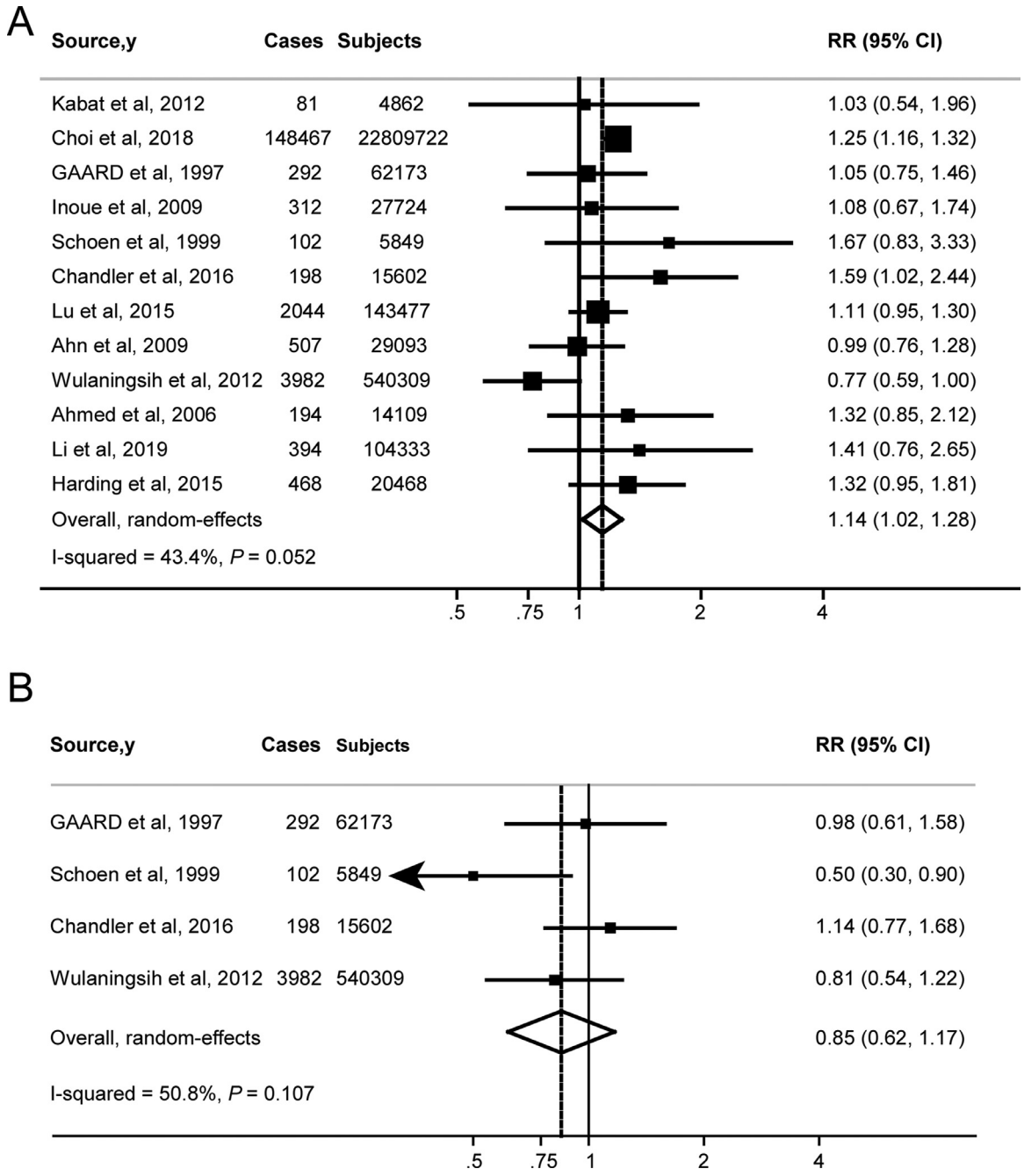

Fig. 5. Forest Plots for Colorectal Cancer Incidence (A) Summary Relative Risks for Individuals in the lowest quartile versus those in the highest quartile of High-density lipoprotein; (B) Summary Relative Risks for Individuals in the highest quartile versus those in the lowest quartile of Low-density lipoprotein.

conclusion. Inconsistent with our results, Li et al. observed no significant association between CRC and elevated triglyceride or decreased HDL-C in a population-based cohort study of Chinese men [44]. These could be interpreted with the small number of cases (394 CRC cases) and relatively short follow-up duration (median, 8.9 years). With respect to LDL-C, the evidence is limited and inconclusive. Consistent with our results, a meta-analysis involved only 3 studies on the relationship between LDL-C and CRC, found a nonsignificant risk of CRC associated with LDL-C.

Although we demonstrated an increased risk for CRC in patients with hypertension and dyslipidemia, whether modifications of risk factors could reduce the risk of CRC remains uncertain. Results from recent meta-analyses have suggested that treatment of hypertension could reduce the risk of CRC [45,46]. A meta-analysis in 2015 by Dai et al. included 11 observational studies indicated a 6% decreased risk of CRC in angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) users compared to non-users [45]. An updated meta-analysis in 2020 also suggested renin-angiotensin system (RAS) inhibitor use was associated with CRC risk decrement [46], which further indicated hypertension may be a causal factor for CRC. For treatment of dyslipidemia, a meta-analysis based on eight randomized controlled trials did not find a statistically significant association between statin use and CRC risk, which also indicated the nonsignificant association between LDL-C and the risk of CRC [47].

The exact biologic mechanisms underlying these associations are not fully understood, but could to some extend be ascribed to chronic inflammation, insulin resistance or oxidative stress. It

Table 1
Characteristics of All Studies Included in the Meta-analysis.

		Obesity	Increased BMI	Smoking	Diabetes	Hypertension	Triglyceride	Total cholesterol	HDL-C	LDL-C
Number of studies		20	14	16	18	13	15	13	12	4
Published year		2005–2009	2005–2009	1987–2017	1998–2018	1992–2019	1997–2019	1986–2016	1997–2019	1997–2016
Location	Europe	9	7	6	4	5	6	7	4	2
	North America	5	3	8	9	4	5	4	4	2
	Asia	5	3	2	4	3	3	2	3	0
	Oceania	1	1	0	1	1	1	0	1	0
Sex	Men &Women	14	10	13	15	8	11	9	8	3
	Men	3	0	1	2	4	2	3	2	0
	Women	3	4	2	1	1	2	1	2	1
Source	Population based	14	9	9	9	9	11	6	10	4
	Community-based	2	2	2	4	1	2	4	0	0
	other	4	3	5	5	3	2	3	2	0
Mean follow-up (y)		11.3	10.7	12.4	11.0	5.8	5.8	12.6	5.7	12.1
Mean follow-up≥10 year		12	7	9	10	10	11	13	8	3
Mean age (y)		39.3	44.8	52.0	50.7	47.6	47.3	46.1	47.4	43.8
Exposure confirmation	Measured	14	9	0	1	11	15	12	12	4
	Self-reported	6	3	16	6	2	0	1	0	0
	Measured/Self-reported	0	2	0	0	0	0	0	0	0
	Other	0	0	0	11*	0	0	0	0	0
Number of cases		56,331	84,684	25,378	71,672	162,495	162,940	24,686	157,041	4574
Number of subjects		11,779,437	10,165,865	2,247,122	9,805,955	24,074,347	24,514,046	2,613,940	23,777,721	623,933
Newcastle-Ottawa score≥6		10	11	11	11	10	13	13	11	4
Adjustment for age		0	10	11	13	8	12	12	10	4
Adjustment for 3 or more most important confounding factors[a]		0	10	8	8	5	6	7	6	1

Abbreviations: HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol.
[a] Most important confounding factors: BMI/obesity, smoking, alcohol, physical activity and diet.
* The confirmations of diabetes cases in the other 8 studies were combination of physician-diagnosed, measured and current treatment (1), combination of physician-diagnosed and measured (1), medical records/measured (2), current medication (2), medical records (3), combination of current treatment and measured (1), physician-diagnosed (1).

has been demonstrated that obesity, smoking and dyslipidemia are associated with chronic inflammation and elevated inflammation cytokines, which may also mediate the risk of CRC [48–51]. It is of note that the effect of smoking on inflammatory cytokines appeared to persist for several years after smoking cessation [52]. This may be a possible explanation for former smokers experiencing similar increased risks of CRC compared to current smokers in some of the previous studies [53,54]. Diabetes and hypertriglyceridemia are characterized by hyperinsulinemia and increased levels of bioavailable IGF-1, which has been reported to be involved in the developmental process of CRC [55–58]. Additionally, it has been reported that dysregulated lipid metabolism was associated with increased bile acid excretion and provided energy supply to neoplastic cells [58]. Although the mechanistic studies for hypertension and CRC are limited, the corresponding oxidative stress or chronic inflammation could play a role [59,60].

Our results have important clinical and public health implications. In our study, we pooled the RRs of each included study to evaluate the strength of association, performed sensitivity analyses to test the consistency of the association and discussed the possible biological mechanism. Additionally, all studies included in our analysis were prospective cohort design which support the temporality of exposure preceding outcome. Furthermore, we also added the evidence that treatment of some risk factors could reduce the risk of CRC. This suggested that cardiovascular risk factors may also be causal factors for CRC and more intensive CRC screening program in patients with these risk factors is needed.

Several limitations of this meta-analysis should be acknowledged. First, our analysis was restricted to separate risk factors, and the distinct possibility exists that the strength of association may be weaker when using a multifactorial analysis. Second, despite our attempt to manage cross-study heterogeneity with appropriate meta-analytic techniques, substantial heterogeneity was still observed in the analysis of obesity. However, risk estimates did not change materially in multiple sensitivity analyses, suggesting heterogeneity might not affect the primary results. Third, although we included studies attempted to control for various known risk factors, the possibility of residual or unmeasured confounding cannot be ruled out. Fourth, there was some evidence of publication bias, only in the analyses of hypertension and triglyceride. The funnel plot indicated the presence of missing studies with neutral or negative results, suggesting a possible overestimation of the association. Fifth, although our findings were robust and consistent in multiple sensitivity analyses, causality could not be established according to our current data based on observational studies. Sixth, some studies included in our meta-analysis had relatively younger patient cohorts and shorter of follow-up duration which may lead to a lower incident rate of CRC. However, when we repeated analyses of studies with more than 10 years follow-up, the pooled RRs did not change substantially. Seventh, our meta-analysis was mostly based on non-African studies and generalizing these findings to African population should be taken with caution and warrants further investigation.

In conclusion, unfavorable cardiovascular risk factors were associated with an increased risk colorectal cancer. However, caution is needed in interpreting the association between hypertension/triglyceride and CRC since the publication bias is needed to be taken into account. Additionally, our data derived from observational studies could not directly demonstrated the causal relationships. Further investigations are warrant to explore whether modification of cardiovascular risk factors could benefit CRC prevention.

Data sharing statement

The datasets used and analyses during the current study are available from the corresponding author upon reasonable request.

Author contributions

ZC contributed to conception of the study, study search, study selection, data extraction, quality assessment, statistical analysis, interpretation of data and manuscript draft. CYJ contributed to conception of the study, supervision, study search, study selection, data extraction, statistical analysis, interpretation of data and manuscript draft. LDL contributed to quality assessment, statistical analysis, interpretation of data manuscript draft. WJH contributed to statistical analysis, interpretation of data and manuscript draft. LJH contributed to statistical analysis, interpretation of data and manuscript draft. LYJ, ZWJ, ZZW, GKH, ZRJ contributed to statistical analysis, interpretation of data. YJ contributed to statistical analysis, interpretation of data and revision of the report. SWH contributed to supervision, statistical analysis, interpretation of the data and revision of the report. CH contributed to conception of the study, supervision, statistical analysis, interpretation of the data and revision of the report. All authors have approved the final draft of the manuscript.

Declaration of Competing Interest

The authors declare that they have no potential conflicts of interest.

Funding

This work was supported by National Natural Science Foundation of China (Grant No. 81741067, 81300279 and 81600260), Science and Technology Program of Guangzhou (Grant No. 201707010419 and 201804010050), High-level Hospital Construction Project (Grant No. DFJH201803, KJ012019099 and DFJH201923). The funders were not involved in the planning, design, analysis, interpretation of study results, preparation of the manuscript, and the submission plan.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.100794.

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