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Patients with inflammatory bowel disease are at increased risk of atherothrombotic disease: A systematic review with meta-analysis

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ABSTRACT

Aims: Patients with inflammatory bowel disease (IBD) are known to be at increased risk for venous thrombosis, while their risk for arterial ischemic events is debated. The purpose of this study was to conduct a systematic review of the published literature on the risk of myocardial infarction (MI) in IBD patients and to identify any potential risk factors.

Methods: The present study was performed according to PRISMA, with a systematic search on PubMed, Cochrane, and Google Scholar. Risk of MI was the primary end point, while all causes of death and stroke were secondary endpoints. Both univariate and multivariate pooled analysis were performed.

Results: An overall population of 515,455 controls and 77,140 persons with IBD (26,852, 34.8% Crohn's disease, CD and 50,288, 65.2% ulcerative colitis, UC) was included. Mean age was similar across controls and IBD. Persons with CD and UC had lower rates of hypertension (14.5% vs. 14.6% vs. 25%), diabetes (2.9% vs. 5.2% vs. 9.2%) and dyslipidaemia (3.3% vs. 6.5% vs. 16.1%) compared to controls. Smoking did not significantly differ (17% vs. 17.5% vs. 10.6%). Pooled results of multivariate adjustment showed that, after a 5 years-follow-up, both CD and UC were at increased risk of MI (respectively HR 1.36 [1.12–1.64] and HR 1.24 [1.05–1.46]), of death (HR 1.55 [1.27–1.90] and HR 1.29 [1.01–1.64]), and of other CV disease as stroke (HR 1.22 [1.01–1.49] and HR 1.09 [1.03–1.15], all 95% CI).

Conclusions: Persons with IBD are at increased risk of MI, despite a lower prevalence of the classic risk factors for MI (hypertension, diabetes, dyslipidemia).

1. Introduction

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases that involve not only the intestine but also extraintestinal sites, including joints, skin, eyes, and liver [1]. Their peak age of incidence is around the third decade of life and last a lifetime [2].

Venous thrombotic events are among the most feared complications of IBD and are associated mostly but not exclusively with periods of greater inflammatory activity [3].

Regarding the risk of arterial thrombotic events, the data in the literature are conflicting [4,5]. On one hand, these patients are characterized by a lower average age than most other chronic diseases and have a lower prevalence of classic risk factors for arterial ischemic events (such as hypertension, type 2 diabetes, hypercholesterolemia) [6]. On the other hand, chronic systemic inflammation promotes endothelial dysfunction, plaque formation, and platelet activation and aggregation, all of which are risk factors for both atherosclerosis and atherothrombotic events [7]. Chronic inflammatory illnesses including rheumatoid arthritis and systemic lupus erythematosus have been linked to early atherosclerosis and an elevated risk of cardiovascular morbidity [8] and death in epidemiologic studies [9,10]. Patients with IBD have an

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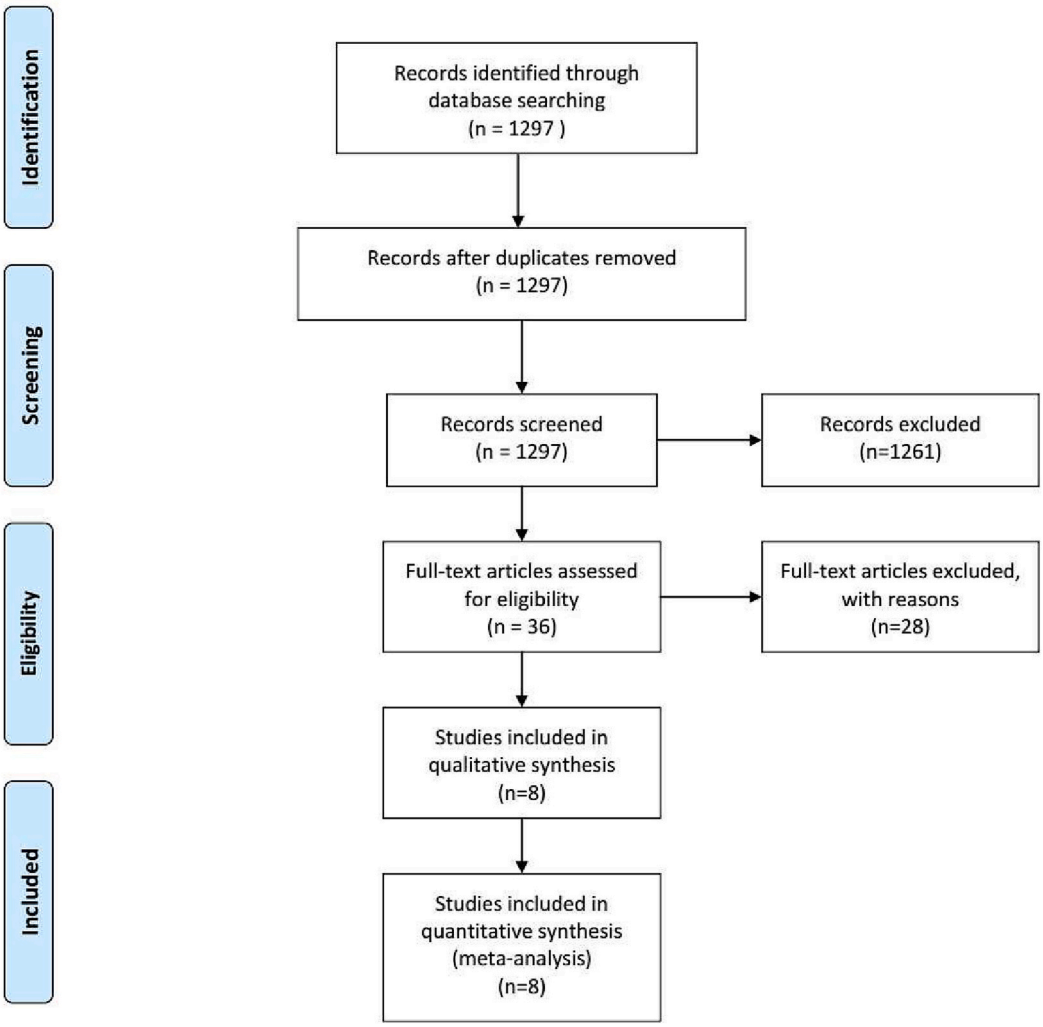

Fig. 1. Prisma flow diagram.

Table 1
Baseline features according to disease*.

	Controls ($n = 515,455$)	CD ($n = 26,852$)	UC ($n = 50,288$)
Age (years)	45 (43–50)	43 (38–45.3)	47 (43.5–50)
Female	55% (52–58)	57% (53–59)	53% (45–60)
Caucasian	63% (57–64)	63% (63–63)	60% (58–67)
Hypertension	25% (13–31)	15% (7–23)	15% (11–30)
Diabetes	9% (3–13)	3% (2–9)	5.2% (2–11)
Dyslipidemia	16% (6–26)	3% (2–18.)	7% (6–27)
Chronic kidney disease	1% (0−3−3)	5% (3–7)	7% (4–9)
Smoking	17% (12–28%)	18% (10–34)	11% (6–13)
Obesity	12% (8–26)	8% (5–12)	10% (8–12)
BMI	27% (26–28%)	26% (22–29)	28% (23–32)
Steroid Therapy	16% (11–23)	28% (19–33)	28% (21–34)
Antihypertensive drugs	5% (3–8)	15% (9–19)	18% (11-2)
Statin therapy	3% (2–7)	9% (4–21)	8% (3–12)
Alcohol use	2% (1–5)	26% (18–27)	7% (4–12)

increased thickness of the carotid intima-media, which is a measure of atherosclerotic disease burden, similar to other chronic inflammatory disorders [11,12].

Conflicting data have been reported about the incidence of thrombotic coronary and cerebral events in patients with IBD [11] and several papers have been released since the publication of the last previous meta-analysis that have not been synthesised with existing data [13].

The aim of this systematic review and meta-analysis was to search for published literature data on the risk of arterial thrombotic events, especially myocardial infarction (MI) and stroke, in IBD patients and to look for the factors that influence this risk.

2. Material and methods

The present study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [14]. We performed a systematic search on PubMed without MeSH terms from inception to 25 December 2021. Pubmed was searched with the following string ("inflammatory bowel disease*" OR "IBD" OR "ulcerative colitis" OR "Crohn's disease" OR "Crohn's disease") AND ("cardiovascular disease*" OR "myocardial infarction" OR "ischemic heart disease" OR "coronary heart disease" OR "coronary artery disease" OR "arterial thromboembolic disease*" OR "cardiovascular event*" OR "arterial thrombotic event*" OR "atherosclerotic vascular disease"). In addition, Cochrane and Google Scholar were searched for the following terms: "inflammatory bowel disease" or "Crohn's disease" or "ulcerative colitis" and "ischemic heart disease" or "myocardial infarction" by two authors (F.B. and D.G.R.). Inclusion criteria were (i) human studies, (ii) case control studies comparing IBD (CD or UC) vs control patients, (iii) studies with multivariate adjustment. In the case of duplicate reporting, the manuscript with the largest sample of patients or longer follow up was selected.

Table 2
Baseline features of included patients and studies.

Study	Comparison	Time period (years)	Region of interest	Patient number	Follow up (years)	Age (y)	Female (%)	HTN (%)	Hyperlipidemia (%)	DM (%)	Smoking (%)	Obesity (%)	Steroid therapy (%)	Antihypertensive therapy (%)	Statin therapy (%)	CKD (%)	Alcohol (%)
Berstain et al	IBD (CD+ CU)	1984–2003	Canada	4193 (CD) 3879 (CU)	19	36.5 42.4	58.5 51.3	–	–	–	–	–	–	–	–	–	–
	Controls			80,489	19	NA	55	–	–	–	–	–	–	–	–	–	–
Aniwan et al	IBD (CD + CU)	1980–2010	USA	339 (CD)	13.8 (8.3–21.0)	31.2 (21.8–47.4)	48	24.2	21.2	8.8	16.2	–	–	–	–	–	–
				397 (CU)	14.4 (8.3–22.7)	35.6 (25.0–48.1)	51.3	30	22.9	8.6	9.3	–	–	–	–	–	–
	Controls			1472	10.0 (4.4–18.6)	34.1 (24.0–47.8)	55	27.1	29	9.2	17.2	–	–	–	–	–	–
Gill et al	IBD (CD + CU)	2010–2020	USA	9406 (CD) 6658 (CU)	4.4	49 ± 18 53 ± 19	59 57	29 30	23 32	11 13	23 20	– –	– –	– –	– –	– –	– –
	Controls			15,292		51 ± 18	59	31	26	12	21	–	–	–	–	–	–
Dregan et al	IBD (CD + CU)	2002–2013	UK	7628 (CD) 12,203 (CU)	–	42 ± 18 47 ± 18	56 49	17 23	3 5	– –	25 13	12 14	28 28	22 27	9 12	10 14	52 57
	Controls			373,851		47 ± 19	57	26	6	–	22	15	12	27	12	7	61
Choi et al	IBD (CD + CU)	2006–2009	South Korea	10,708 (CD) 26,769 (CU)	8.4 ± 1.7	33 ± 16 44 ± 16	35.7 46.2	7.3 14.2	3.5 6.5	2.9 4.9	– –	– –	– –	– –	– –	– –	– –
	Controls			112,431	8.4 ± 1.6	40 ± 17	43.2	11.5	4.9	4.3	–	–	–	–	–	–	–
Kirchgesnerer et al	IBD (CD + CU)	2008–2013	France	97,708 (CD) 112,454 (CU)	3.4 (1.8–4)	40 (28–53) 49 (36–62)	57.7 50.5	10.7 15	3.6 6	3.8 5.5	9.6 4.4	5.3 5.7	– –	– –	– –	– –	2.4 2.2
Osterman et al	IBD (CD + CU)	1980–2010	USA	9829 (CD) 15,498 (CU)	4.6	44.2 50	59 51.6	14.5 18.5	1.3 2.1	1.9 3.6	37 23.2	8.2 11.1	– –	– –	– –	– –	– –
	Controls			144,605		49.1	52	13.5	1.5	2.1	27.9	10.3	–	–	–	–	–
Kristensen et al	IBD (CD + CU)	1996–2009	Denmark	4732 (CD) 13,622 (CU)	6.04 –	43.8 ± 19	54.5	3.1	4.2	1.8	–	–	–	8.7	4.2	0.5	–
	Controls			199,978	6.17	43.1 ± 19	54.8	1.2	2.7	0.1		–	–	5.2	2.7	0.1	–

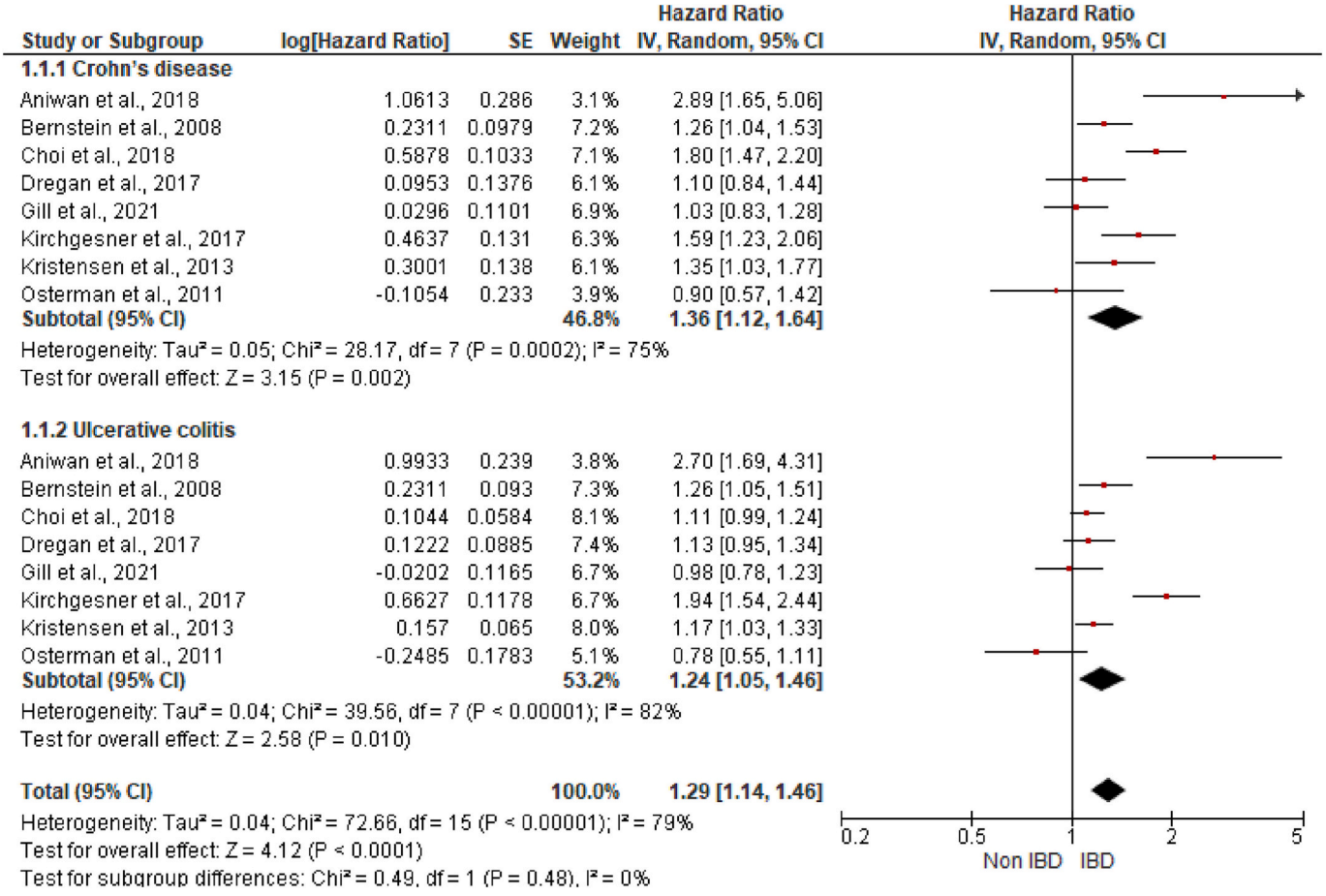

Fig. 2. Adjusted risk of MI.

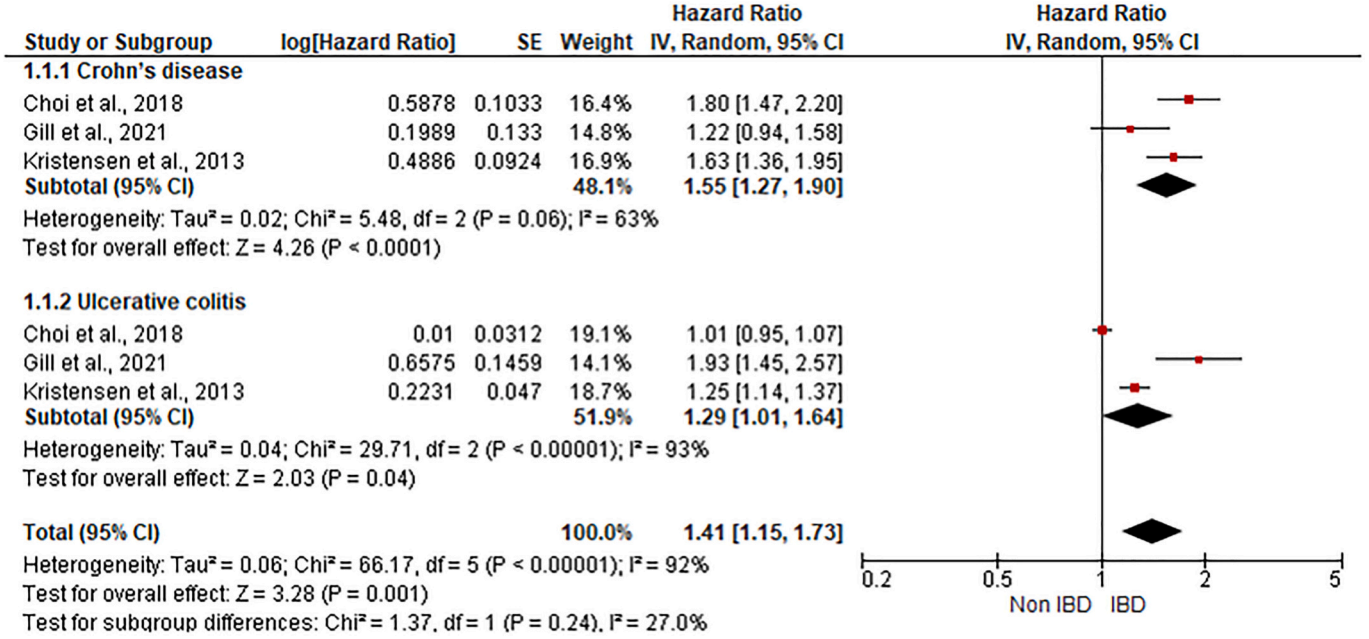

Fig. 3. Adjusted risk of death.

2.1. Data abstraction

Four independent investigators (F.B., D.G.R., A.A., G.G.) assessed titles and abstracts for eligibility. For each eligible study, full texts, supplementary materials, online appendices, and reference lists were examined for inclusion/exclusion criteria. The same authors extracted:

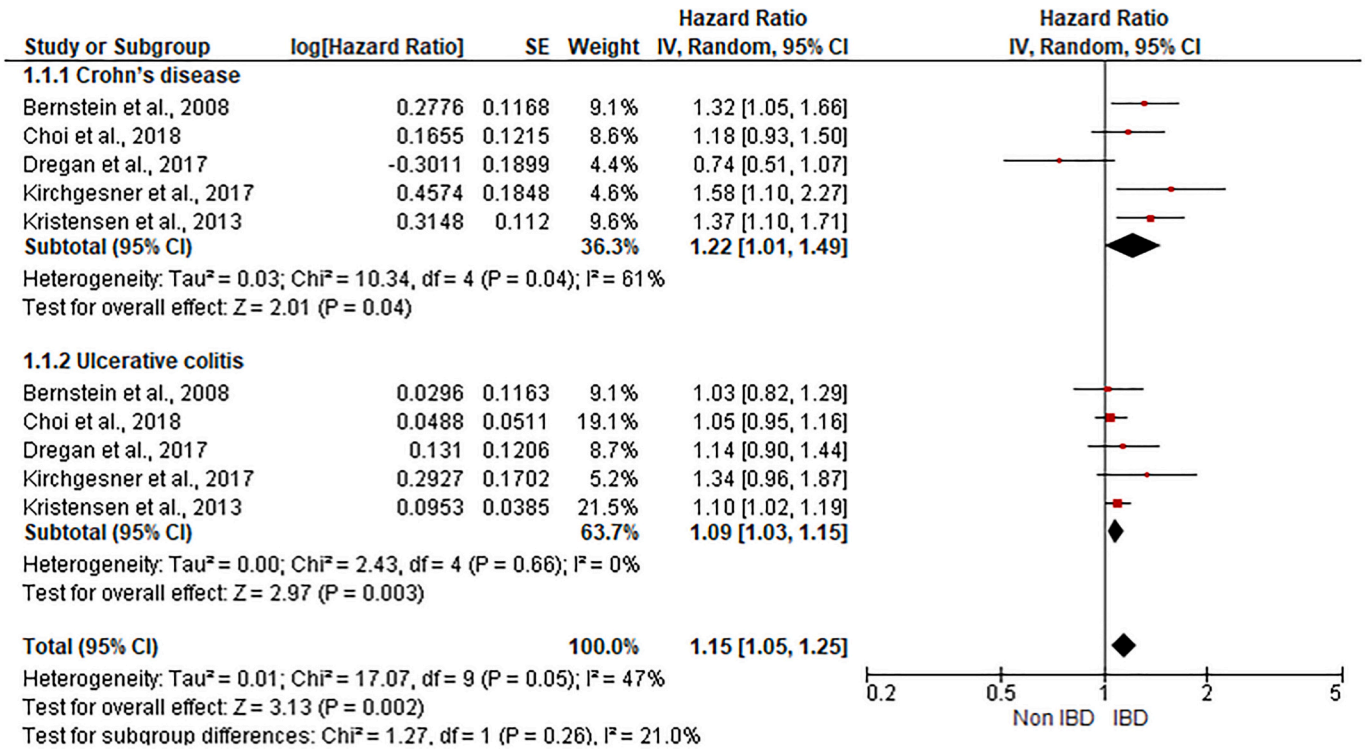

Fig. 4. Adjusted risk of stroke.

i) study characteristics (year of publication, study design, inclusion and exclusion criteria, number of included patients, treatment strategies, number of patients per arm, follow-up duration, primary and secondary endpoints); ii) patients' baseline and procedural characteristics; and iii) outcome measure. All selected studies and abstracted data were finally reviewed by two other authors for their final inclusion (F.D.A, G.T.) and discrepancies were resolved by consensus.

2.2. End points

MI was the primary endpoint, while all causes of death and stroke were secondary endpoints. All events were adjudicated at the longest follow up. Pooled analyses were performed for the incidence of primary and secondary end points and for the impact of UC and CD at multivariate analysis.

2.3. Quality study evaluation

The quality of included studies was independently appraised by four reviewers (A.A., D.G.R., F.B., G.G.), with disagreements resolved by consensus. For each study, we evaluated the risk of bias (low, unclear, or high) for random-sequence generation, allocation concealment, blinding of patients and physicians, blinding during assessment of follow-up, incomplete outcome evaluation, and selective reporting, in keeping with the Cochrane Collaboration approach.

2.4. Statistical analysis

Continuous variables are reported as mean (Standard Deviation) or median (first and third quartile). Categorical variables are expressed as n (%). Statistical pooling for incidence estimates was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals (CIs), using RevMan 5.2 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Small study bias was appraised by graphical inspection of funnel plots. Meta-regression analysis was performed for the primary end point for the more relevant cardiovascular risk factors. Hypothesis testing for superiority was set at the 2-tailed 0.05 level. Hypothesis testing for statistical homogeneity was set at the 2-tailed 0.10 level and based on the Cochran Q test, with I2 values of 25%, 50%, and 75% representing mild, moderate, and severe heterogeneity, respectively. Risk of publication bias was visually evaluated with funnel plot.

The original study protocol was prospectively submitted for registration in PROSPERO and its approval is ongoing.

3. Results

The electronic database searches, from inception to December 2021, identified a total of 1297 studies: 1261 studies were excluded based on title and abstract. Of the potentially eligible 36 remaining studies a total of eight [5,12,15–20] passed a second verification phase and were eventually included in this analysis, for an overall population of 515,455 controls patients and 77,140 IBD patients (26,852 (34.8%) CD and 50.288 (65.2%) UC), Fig. 1 **and** Table 1**.**

3.1. Baseline characteristics

Baseline features are reported in Table 1 **and** Table 2**.**

Mean age was similar across controls and persons with CD and UC. Compared with controls, persons with CD and UC had lower rates of hypertension (25% vs. 14.5% vs. 14.6%), of diabetes (9.2% vs. 2.9% vs.5.2%) and of dyslipidemia (16.1% vs. 3.3% vs. 6.5%). Smoking habits did not differ (10.6% vs.17.0% vs. 17.5%).

3.2. Unadjusted analysis

After a 5.2 years-follow-up (95% Confidence Interval, CI 4.2–9.1), risk of MI was 1.57% [95% CI, 1.07–2.07] for controls, 2.33% [95% CI 1.41–3.25] for patients with UC and 2.35% [1.05–3.66] for patients with CD. Similarly, risk of all-cause death for controls was 2.50% [1.16–3.83], of 4.63% for UC[2.20–7.06] and of 3.66% for CD

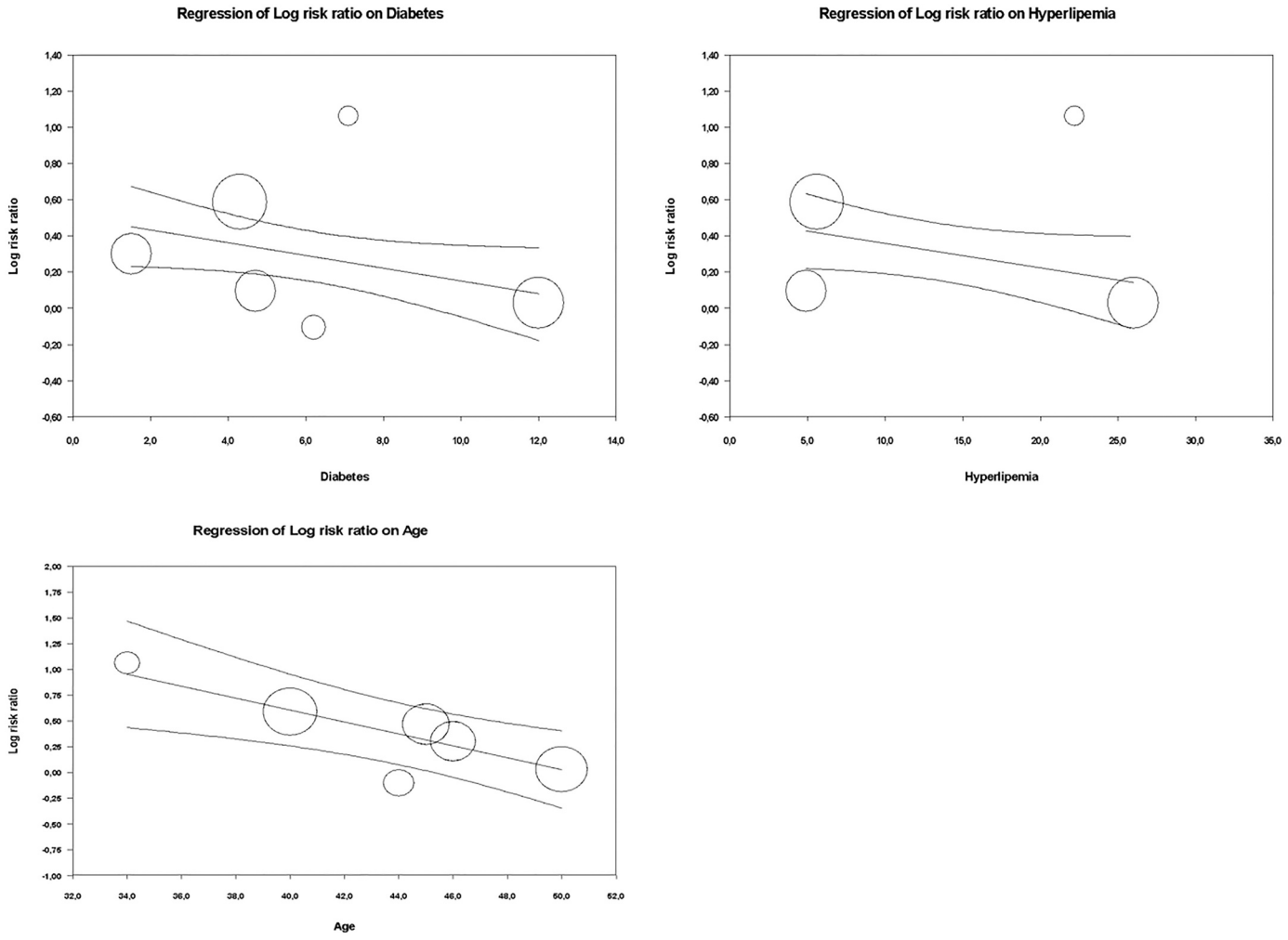

Fig. 5. Meta-regression of MI on diabetes and hyperlidemia and age for CD patients.

[1.31–6.00]. Risk of stroke showed a comparable trend: 1.49% [0.61–2.38] for control, 1.61% [0.99–2.23] for CD, and 2.26% [0.95–3.57] for UC**, see appendix, web only** Figs. 1–3**.**

3.3. Adjusted analysis

Pooled results of multivariate adjustment are reported in Figs. 2–4**.**

There was an increased risk of MI in CD and UC (respectively HR 1.36 [1.12–1.64] and HR 1.24 [1.05–1.46]), of death (HR 1.55 [1.27–1.90] and HR 1.29 [1.01–1.64]), and of stroke (HR 1.22 [1.01–1.49] and HR 1.09 [1.03–1.15]).

3.4. Meta-regression analysis

At meta-regression analysis for UC, smoking showed an effect in reducing the impact of UC on MI (Beta −0.015 [−0.0320:0.0010], p 0.0648), while for CD age, diabetes, and hyperlipidemia significantly reduce the impact of CD on MI (Beta −0.0577 [−0.0901:–0.0253], p 0.001, Beta −0.0355 [−0.0650:-0.0060], p 0.0185, and Beta −0.0135 [−0.0262:-0.0007], p 0.0388, all CI 95%), see Fig. 5**.**

3.5. Funnel plot analysis

Publication bias was explored visually with funnel plots for all adjusted outcomes (MIs, all cause death and stroke) and low risk was visually detected **(see** Fig. 6**).**

4. Discussion

From the results of our meta-analysis, the data seem suggest that:

a) Persons with IBD have approximately a 30% increased risk of MI and 10–20% of stroke
b) Age, diabetes, and hyperlipidaemia reduced the impact of CD on atherothrombotic events, while smoking reduced the impact of UC on atherothrombotic events.

Our results confirm the finding of the previous meta-analysis of Li Z et al. [13] of an increased risk of MI both in the whole IBD group (1.29 in our study, 1.25 in the previous meta-analysis) and in the UC and CD subgroups. The data from our meta-analysis seem to support the fact that, despite having a lower value, the increased risk is true also for cerebrovascular accidents. The additional risk factor given by being affected by IBD has more impact at a young age (which unfortunately is typical of the onset of IBD), as with advancing age there is an increase of prevalence of the typical risk factors of ischemic events (such as hyperlipidemia, diabetes).

Chronic systemic inflammation has been linked to the development of atherosclerosis [21]. Inflammatory cytokines are high in persons with IBD [22]. In addition, earlier research has indicated that individuals with IBD have microvascular endothelial dysfunction, in addition to increased carotid intima-media thickness and arterial stiffness [23]. Moreover, glucocorticoid treatment for IBD resulted in an increased

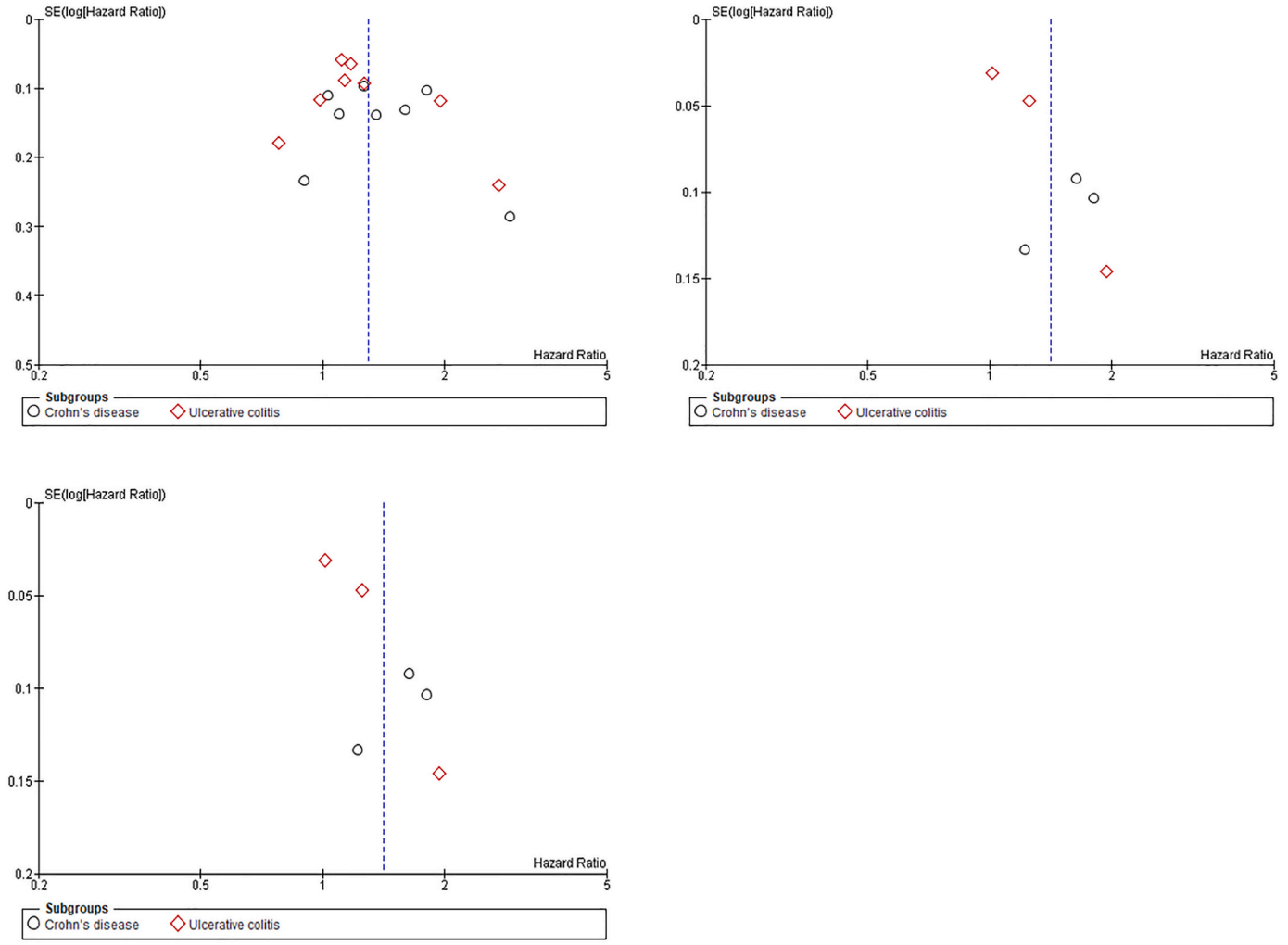

Fig. 6. From above to below, from left to right funnel plot for adjusted risk of MI, of all cause death and of stroke.

burden of cardiovascular disease risk factors, such as obesity, diabetes, and dyslipidemia, as compared to the general population [24]. Another connection between IBD and the risk of MI is tobacco use, which is associated with a higher risk of cardiovascular disease. Smoking has been demonstrated to have opposite effects on the evolution of UC and CD in studies [25]. In fact, smoking is thought to exacerbate the clinical course of CD, increasing the requirement for steroid treatment and the likelihood of early surgery [26], while on the other hand smoking has a preventive impact in UC, resulting in a lower inflammatory burden [27]. Disease severity has a significant impact on the risk of cardiovascular disease [28].

Recently, it has been postulated that genetic factors may have a role in the development of IBD and MI. A previous investigation found that single nucleotide polymorphisms in the NOD2/CARD15 gene were linked to both IBD and coronary artery disease [29]. These pathophysiological pathways could possibly support the link between IBD and the risk of MI.

Regarding the possible influence of drugs on the risk of MI, increased levels of pro-inflammatory cytokines in the bloodstream, such as tumor necrosis factor (TNF)-α, may contribute to endothelial and platelet dysfunction, which can lead to atherosclerosis [30].

Future studies are needed to evaluate whether the use biological agents such as antibodies anti-TNF-α can reduce cardiovascular and cerebrovascular disease risk [31–33].

In the most recent meta-analysis, it was observed that patients with UC and CD had a higher risk of cardiovascular disease. It is worth noting that females were at a substantially higher risk than males, suggesting a possible difference in sex and MI especially in younger patients, already observed in some recent observational registries [34,35]. The risk was consistent across subgroups stratified by coronary artery disease [30]. However, neither UC nor CD had an increased risk of cardiovascular disease-related mortality [36]. Cardiovascular mortality, which can be used as a surrogate for incidence, is less prone to ascertainment bias, although it does not cover the complete spectrum of cardiovascular disease. Mortality from cardiovascular disease is reducing, and hence, there is a reduced risk of mortality, thanks to advances in medical therapy and health care. This could explain why persons with IBD were reported to have a higher risk of cardiovascular disease, as evaluated by cardiovascular disease incidence and not by mortality.

In our up-to-dated systematic review with meta-analyses, despite no difference in age between cases and controls and a lower presence of risk factors (hypertension, diabetes, dyslipidemia) for MI in the group with IBD and similar prevalence of smoking, persons with IBD seemed to be at greater risk of MI in the adjusted analysis. This was true for the whole IBD group and for both CD and UC. The risk of death seemed to be also higher in IBD than in controls.

When evaluating the findings of our study, there are a few caveats to keep in mind. First, we included retrospective studies from a variety of clinical settings, each with its own diagnostic criteria, enrolment age, risk period, and study methodology. Second, the included studies did not account for all traditional and atypical cardiovascular disease risk variables in the same way. However, there was no significant difference in

the pooled analysis of unadjusted and maximally adjusted data from each study in our analysis, implying that any difference due to different variables for adjustment is likely minor. Third, due to a lack of reporting in individual studies, we were unable to comprehensively investigate whether IBD disease activity or specific anti-inflammatory medicines influence the risk of cardiovascular events. In particular, the protective effect of anti-cytokine drugs is well known (31), but only one (12) of the included studies reported subgroup analysis for treatment with these drugs, consequently limiting the inferential aim of the present study in this setting.

Recall bias is another potential flaw that is particularly relevant to case-control studies analyzing cardiovascular events, although overall risk of bias was low **(see** Table 1, Supplementary **appendix)**. However, because most research used medical diagnostic codes to determine exposure and outcome, the impacts of this are likely to be minor. Moreover, several studies only documented MI episodes that required hospitalization, thus missing chronic stable angina or transient ischemic attack, which do not necessitate hospitalization, and thus underestimated the risk of cardiovascular morbidity in persons with IBD. Finally, publication bias was explored visually with funnel plots for all adjusted outcomes (MIs, all cause death and stroke) and low risk was visually detected (see Fig. 6).

5. Conclusions

Our study seems to support a greater risk of arterial ischemic events (particularly MI) in persons with IBD (in the whole group and in both CD and UC) compared to the general population, despite a lower prevalence of the classic risk factors for MI (hypertension, diabetes, dyslipidemia). This could be related to the presence of non-conventional risk factors for MI (particularly inflammation) that play a key role in IBD patients. More prospective studies are needed to confirm these results and to better describe risk variables in this high-risk population and to evaluate the role of possible primary and secondary prevention anti-inflammatory therapy to reduce the higher burden of cardiovascular disease.

Funding

None to declare.

Authors' contributions

O.D·F., G.G., D.G.R., A.M. and G.T. performed the literature search; D.G.R., and F.D. collected the data; F.D., G.M.D.F, E.B., and D.G.R. designed the study; M.I and F.D. performed the data analysis; D.G.R., A. A., G.T., and F.D. interpreted the data; F.B. and D.G.R. wrote the manuscript; J.K. and C.N.B. revised the paper. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of Competing Interest

Conflict of interest: none declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.02.042.

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