KU LEUVEN **FACULTEIT GENEESKUNDE**

Cardiovasculair risico bij patiënten met inflammatoire darmziekte: een systematic review en meta-analyse

Cardiovascular risk in patients with inflammatory bowel disease: a systematic review and meta-analysis

Masterproef voorgedragen tot het behalen van de graad Master na Master in de huisartsgeneeskunde door

Joren VERBOVEN

Pieter JEHOUL

Afdeling: Academisch Centrum voor Huisartsgeneeskunde

Departement: Public Health and Primary Care

Promotor: Dr. Nathalie CONRAD
Co-promotor: Prof. Dr. Jan VERBAKEL

Leuven, 2020-2022

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Abstract

Background: Some chronic inflammatory diseases have been linked to increased cardiovascular morbidity and mortality. The cardiovascular risk of inflammatory bowel diseases (IBD) however remains unclear. In this systematic review we investigated the association between IBD and cardiovascular diseases, being ischemic heart disease, heart failure, cerebrovascular accidents, peripheral arterial disease and thrombo-embolic events.

Methodology: We performed a systematic review and meta-analysis by searching MEDLine, Web of Science, Embase and the Cochrane Library for cohort and case-control studies that reported incident cardiovascular events in patients with IBD and a non-IBD control population and were published from 01/01/2000 to 31/12/2020. We calculated pooled risk ratios (RR) with 95% confidence intervals (CIs) using random-effect models. Where available preference was given to estimates that were adjusted for known cardiovascular risk factors.

Results: We identified 37 studies with a total of approximately 5 million IBD patients. Analysis stratified by cardiovascular outcome of interest shows a higher risk of ischemic heart disease (pooled RR 1.20 [1.15-1.26]), cerebrovascular accidents (pooled RR 1.22 [1.14-1.31]), heart failure (pooled RR 1.59 [1.09-2.30]), peripheral artery disease (pooled RR 2.02 [1.49-2.75]) and venous thrombo-embolism (pooled RR 1.89 [1.68-2.13]) in IBD patients. Sensitivity analyses restricted to studies with adjusted or unadjusted estimates only, generally led to similar estimates. Atherosclerosis, a prothrombotic state and traditional cardiovascular risk factors are reported to effectuate these effects. Worse disease severity, female gender and younger age in IBD patients affected almost all cardiovascular outcomes negatively.

Conclusion: Patients with inflammatory bowel disease present significantly higher risk of a broad spectrum of cardiovascular disorders even after adjusting for classical cardiovascular risk factors. These findings call for further research on specific cardiovascular risk screening and prevention measures among patients with inflammatory bowel disease, as well as pathophysiological mechanisms underlying these complications.

Keywords: Systematic review, inflammatory bowel disease, cardiovascular morbidity, ischemic heart disease, heart failure, cerebrovascular accidents, peripheral arterial disease, thrombo-embolic events, Crohn's disease, ulcerative colitis.

Abbreviations used

IBD: Inflammatory bowel disease	CVD: Cardiovascular disease	CVA: Cerebrovascular accident
CD: Crohn's disease	IHD: Ischemic heart disease	PAD: Peripheral artery disease
UC: Ulcerative colitis	HF: Heart failure	VTE: Venous thrombo-embolism

Introduction

The effect of chronic inflammatory diseases on cardiovascular health has been subject of medical interest for some time. (1) Some specific inflammatory conditions have already been investigated extensively and have shown significant associations. For instance, psoriasis (2, 3), rheumatoid arthritis (4-7) and lupus erythematosus (5, 6, 8, 9) have been linked to an increased cardiovascular morbidity and mortality.

The cardiovascular risk of inflammatory bowel diseases (IBD) however remains unclear. Studies who do address this issue have shown conflicting results with some studies reporting fewer myocardial infarctions in IBD patients (10) while others reporting opposite trends (1, 11). Similarly, there are studies showing increased numbers of cerebrovascular accidents in IBD patients (1, 12-15), while others did not identify this association (16-19). Even the risk of mortality due to IBD is still under debate. (1, 18, 20-22)

To better understand the association between inflammatory bowel diseases and cardiovascular morbidity, we conducted a systematic review of existing studies investigating the relationship between inflammatory bowel diseases and ischemic heart disease, heart failure, cerebrovascular accidents, peripheral arterial disease and venous thrombo-embolic events.

Methods

The systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) Guidelines (23). The protocol outlined prior to this study was registered in the PROSPERO database (# 242782).

Search strategy

We searched MEDLine, Web Of Science, Embase and Cochrane Library for studies published between 01/01/2000 and 31/12/2020 using a pre-defined search strategy (**appendix**) and conducted secondary referencing by manually reviewing reference lists of key articles. Citation checks and deduplication of results were conducted by Endnote X9 software.(24)

Study selection

Studies were included if they compared incident CVD in a cohort of at least 500 IBD patients and a representative control cohort, and provided estimates of 'hazard ratio', 'incidence rate ratio', 'odds ratio', 'risk ratio' or 'relative risk' with the corresponding 95% confidence interval (CI), or data necessary to calculate these. Study designs were restricted to primary epidemiological observational study designs (i.e. cohort and case-control studies). To best characterize the broad spectrum of cardiovascular disease, we selected five outcomes of interest: (i) ischemic heart disease; (ii) heart failure; (iii) stroke (ischaemic stroke, haemorrhagic stroke, and transient ischaemic attack); (iv) peripheral artery disease; and (v) venous thrombo-embolic events. Only articles written in English were included.

Data extraction

Two researchers (JV and PJ) screened all abstracts identified in the initial search and excluded studies in violation of the inclusion criteria using the reference managing website Rayyan(25). Full-text articles were subsequently reviewed in duplicate and, in cases of disagreement, consensus was achieved through referral to a third reviewer (NC). An electronic data abstraction form was used to record patient and study characteristics, including study design, geographical location, data collection period, sample size, mean age, methods of case identification and diagnostic criteria. The number of events, patient-years-at-risk in each group and the summary statistic were extracted. When the summary statistic was not provided, we calculated RRs from the number of events and person-years at risk. Conversely, if the total number of events was

missing, we estimated it using the summary statistic and its confidence interval. Where available, gender stratified incidence data and trends over time were also recorded.

Risk of bias assessment

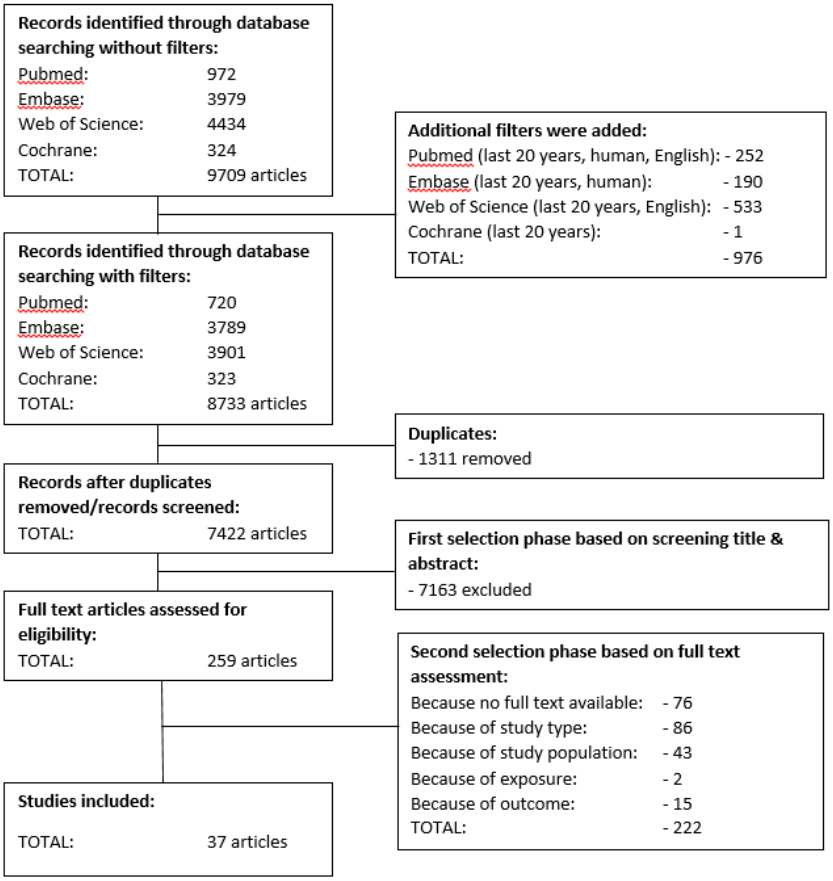
The Newcastle-Ottawa quality assessment scale for nonrandomized studies was used to assess the quality of the included studies.(26) This scale assesses each study in three main areas: the selection process of both cohorts, the similarity and comparability between cohorts and the ascertainment of the outcome of interest. This quality appraisal was performed by the two investigators in conjunction with data extraction, at the study type level.

Statistical analysis

Each IBD-CVD association was studied separately. Where studies provided both crude and adjusted estimates, preference was given to estimates that were adjusted for known cardiovascular risk factors. Crude and adjusted estimates were also investigated separately. Given the rareness of the studied outcome, we considered different risk estimates as rate ratios and calculated pooled estimates and 95% confidence intervals using the inverse variance weighted random effects meta-analysis. We characterized heterogeneity with the I^2 statistic. To illustrate the potential for publication bias and small study effects, funnel plots were drawn to present the effect estimates (horizontal axes) against the standard error (vertical axes) and were interpreted visually (**appendix**).(27) All analyses were completed using Review Manager Software version 5.3.(28)

Results

Figure 1: Study selection flow chart



Using our described search strategy 9709 articles were identified. With additional filtering and removing of duplicates, 8733 articles remained for screening. Assessing just title and abstract, we identified 7163 irrelevant articles to our study. 259 articles were screened for eligibility by full-text reading, of which 222 did not meet eligibility criteria and 37 were included for the final analysis(**figure 1**).

Effect of inflammatory bowel disease on ischemic heart disease

A total of 17 studies investigated the risk of ischemic heart disease (IHD) in IBD patients. Most studies found an increased risk of IHD in IBD patients compared to the general population.(1, 11, 15, 17, 19, 29-37) Out of the fourteen studies supporting this finding, one study saw this increased risk only during active disease stages (29) and another saw this only in female IBD patients over the age of 40.(15) Three out of seventeen studies could not detect a statistically significant difference in IHD risk. (38-40) The pooled estimate for the risk of IHD in IBD patients compared to individuals without IBD was 1.20 [1.15-1.26] (**figure 2**). Sensitivity analyses restricted to studies with adjusted or unadjusted estimates only, led to similar results (**appendix**).

Six studies adjusted for traditional confounding risk factors.(1, 11, 17, 35, 37, 40) All took age, sex, blood pressure and lipid/cholesterol profile into account. Only one didn't take diabetes into account(17) and only 2 did not take smoking status and body weight into account.(1, 37) Other factors such as race(35), alcohol(17), family history of myocardial infarction(11), aspirin use(40), diuretic use(1), vitamin K antagonist use(1) were rarely taken into account.

Six studies further stratified the risk of IHD according to IBD disease severity. (1, 11, 29, 33, 34, 37) Because objectively evaluated disease severity via endoscopy was often not available for study purposes, surrogates were used. Kristensen, et al. (2013) used a combination of surrogates (need for corticosteroid therapy, need for hospitalization, need for anti-TNF therapy) to optimally approximate true disease severity and found that the adjusted relative risk of myocardial infarction rises from 1.17 to 1.49 during flares and even to 2.05 during persistent activity (>120 days). In remission the risk of myocardial infarction was similar in IBD and controls.(1)

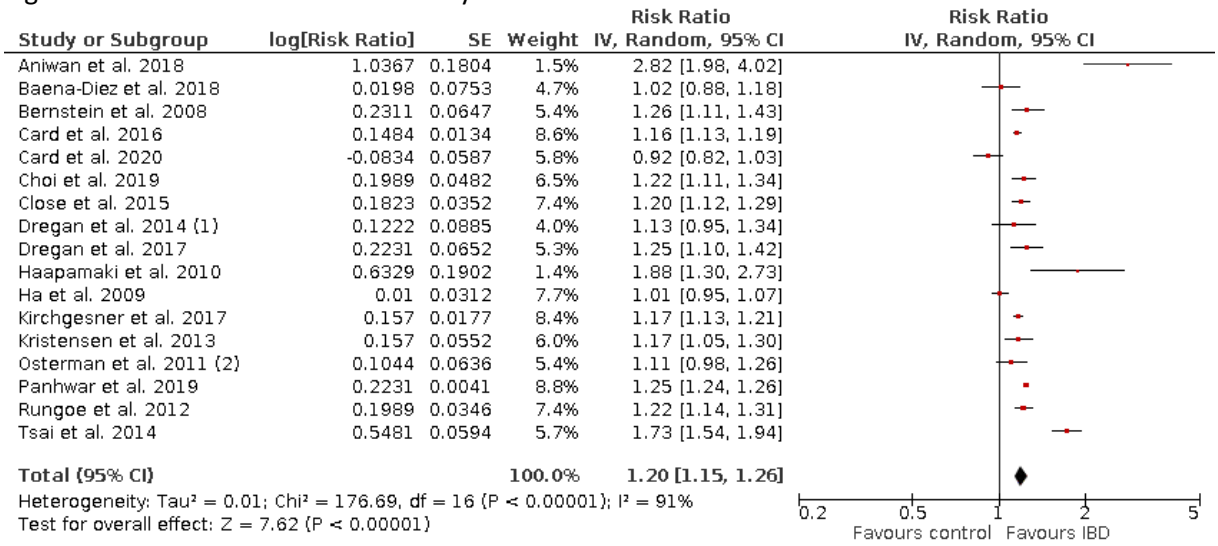
One study, Osterman, et al., stratified the risk of IHD according to IBD duration. They found that UC and CD patients did not suffer a higher risk of myocardial infarction with increasing disease duration. CD patients with >20 years of disease history even had significantly lower risk of myocardial infarction than CD patients with <5 years of disease history.(40)

Five studies further stratified the risk of IHD according to age groups of IBD patients. All conclude that younger IBD patients have an even more accentuated risk of ischemic heart disease compared to older IBD patients with regard to respectively matched peers without IBD. (31, 34-37)

Eight studies further stratified the risk of IHD according to gender. One study shows an increased risk for men after adjusting for traditional cardiovascular risk factors (hypertension, dyslipidemia, diabetes, obesity and smoking).(35) Three other studies did not find any gender related effect.(1, 11, 19) All the other studies reported a significantly higher risk of ischemic heart disease for female IBD patients. (31, 34, 36, 37)

Six studies further stratified the risk of IHD according to IBD subtype. It appears that Crohn's disease is mostly reported to have the biggest effect on the risk of ischemic heart disease.(31, 34, 35, 37) One study could not find a significant risk difference between Crohn and ulcerative colitis.(19) And only one study claimed ulcerative colitis to be the more risky inflammatory bowel disease for developing coronary heart disease.(40)

Figure 2: Pooled effect of inflammatory bowel disease on ischemic heart disease.



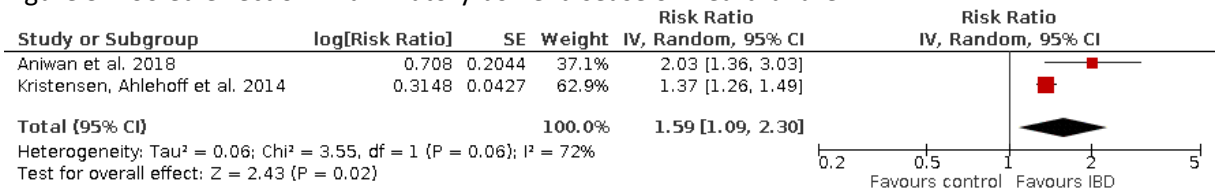
Footnotes
(1) Only UC included
(2) Only UC included

Effect of inflammatory bowel disease on heart failure

Our search of the recent literature resulted in only two studies reporting the effect of IBD on heart failure (HF).(11, 41) Both studies found an increased risk of HF in IBD patients after adjusting for age, sex, blood pressure, diabetes and cholesterol/lipid profile with effects more pronounced in ulcerative colitis than in Crohn's disease.(11) The pooled estimate for the risk of HF in IBD patients compared to individuals without IBD was RR 1.59 [1.09-2.30] (**figure 3**). In sensitivity analyses restricted to studies with unadjusted estimates only, the pooled estimate was not significant (**appendix)**.

The two studies stratified for disease severity, both reporting 2.5 times more risk during flares and persistent activity, while no significant risk was seen during remission.(11, 41) Aniwan, also stratified for IBD subtype, gender and age, but had insufficient HF cases in these subgroups to draw conclusions.(11)

Figure 3: Pooled effect of inflammatory bowel disease on heart failure



Effect of inflammatory bowel disease on cerebrovascular accidents

Fifteen articles concerning cerebrovascular accidents (CVA) were included. Out of these, nine reported an elevated risk in the IBD population (1, 12, 13, 29, 34, 38, 42-44), while the remainder could not find a significant difference between groups.(15-17, 19, 31, 32). The pooled estimate for the risk of CVA in IBD patients compared to individuals without IBD was RR 1.22 [1.14-1.31] (**figure 4**). Sensitivity analyses restricted to studies with adjusted or unadjusted estimates only, led to similar results (**appendix**).

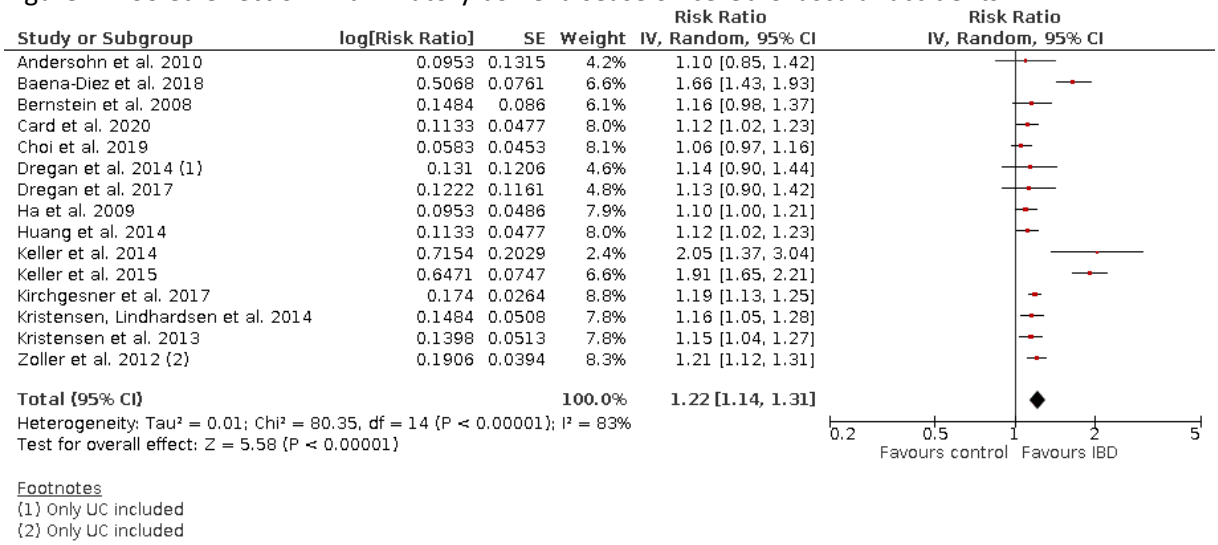
Seven studies adjusted for traditional confounding factors.(1, 12, 13, 16, 17, 42, 43) All accounted for age, sex, blood pressure and lipid/cholesterol profile. Only one did not take diabetes into account.(17) Three studies

did not account for body weight, smoking status or alcohol.(1, 42, 43)

Four studies further stratified the risk of stroke in IBD according to disease severity. All concluded the risk of stroke being greatly raised during flares, while being comparable to the control population in remission. (1, 29, 42, 43)

Four studies further stratified the risk of stroke in IBD according to age groups of IBD patients. Andersohn et al. and Choi et al. concluded younger adults to have higher risk of CVA.(16, 31) Huang et al. and Keller et al. saw elevated risk only in older populations.(12, 13, 42)
Six studies further stratified the risk of stroke in IBD according to gender. Some studies found women with IBD to have increased risk on developing CVA over corresponding men(12, 13, 15), while others did not find a significant interaction with sex.(16, 31, 43)

Figure 4: Pooled effect of inflammatory bowel disease on cerebrovascular accidents



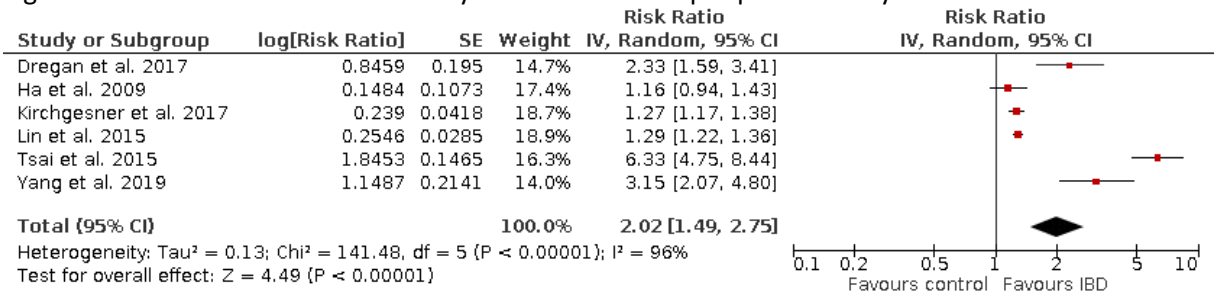
Effect of inflammatory bowel disease on peripheral arterial disease

In our systematic review five out of six studies report an increased risk of peripheral arterial disease (PAD) in patients with IBD.(32, 34, 45-47) Only one study did not find a significant difference between groups.(15)

The pooled estimate for the risk of PAD in IBD patients compared to individuals without IBD was RR 2.02 [1.49-2.75] (**figure 5**). Sensitivity analyses restricted to studies with adjusted or unadjusted estimates only, led to similar results (**appendix**).

Three studies adjusted for cardiovascular risk factors.(45-47) All accounted for age, sex, blood pressure, diabetes and lipid/cholesterol profile. Two studies also took cancer history into account.(45, 47) And one further accounted for body weight.(45)

Figure 5: Pooled effect of inflammatory bowel disease on peripheral artery disease



Effect of inflammatory bowel disease on venous thrombo-embolic events

Out of all twelve studies included in this systematic review, almost all reported increased risk of venous thrombo-embolic events (VTE) in the IBD population. (15, 32, 48-56). One notable exception reported lower VTE risk in the IBD population, but also this study joins the list above when including mesenteric vein thrombosis as a venous trombo-embolic event.(57)

The pooled estimate for the risk of VTE in IBD patients compared to individuals without IBD was RR 1.89 [1.68-2.13] (**figure 6**). Sensitivity analyses restricted to studies with adjusted or unadjusted estimates only, led to similar estimates (**appendix**).

Three studies adjusted for known cardiovascular risk factors(49-51), including age, sex and recent history of any kind of surgery. All but one, also accounted for recent fractures, pregnancy or cancer diagnosis.(49) Kappelman, et al., adjusted for the largest number of risk factors by also including hormone replacement therapy and antipsychotic medication.(50)

Seven studies further stratified the risk of VTE in IBD according to disease severity. (48-54) Because objectively evaluated disease severity via endoscopy was often not available for study purposes, surrogates were used. Three studies used corticosteroid therapy as a surrogate for disease severity (50, 52, 53). Some studies even categorized the duration of corticosteroid need as a flare stage of 120 days and a chronic stage of prolonged use after 120 days. Like this, Chu, et al., and Grainge, et al., report a respective 4 to 8 times higher VTE risk in IBD during a flare compared to controls and a 3.7 to 6 times higher VTE risk in IBD during chronic activity compared to controls. But even in remission (after 120 days without need for corticosteroids) the risk for VTE remained 1.4 to 2 times higher than the general population.(52, 53) Using the frequency of hospitalization as a surrogate for disease severity, Chung, et al, reports a aHR of 1.12 comparing the risk of DVT in IBD patients with one hospitalization per year to the general population. Comparing the risk of DVT in IBD patients with 2 or more hospitalizations per year to the general population resulted in an aHR of 32.9. This increased risk of DVT in IBD compared to controls was also seen for PE, where the adjusted hazard ratio's climbed from 1.23 in those with one hospitalization per year to 24.2 in those with 2 or more per year.(51)

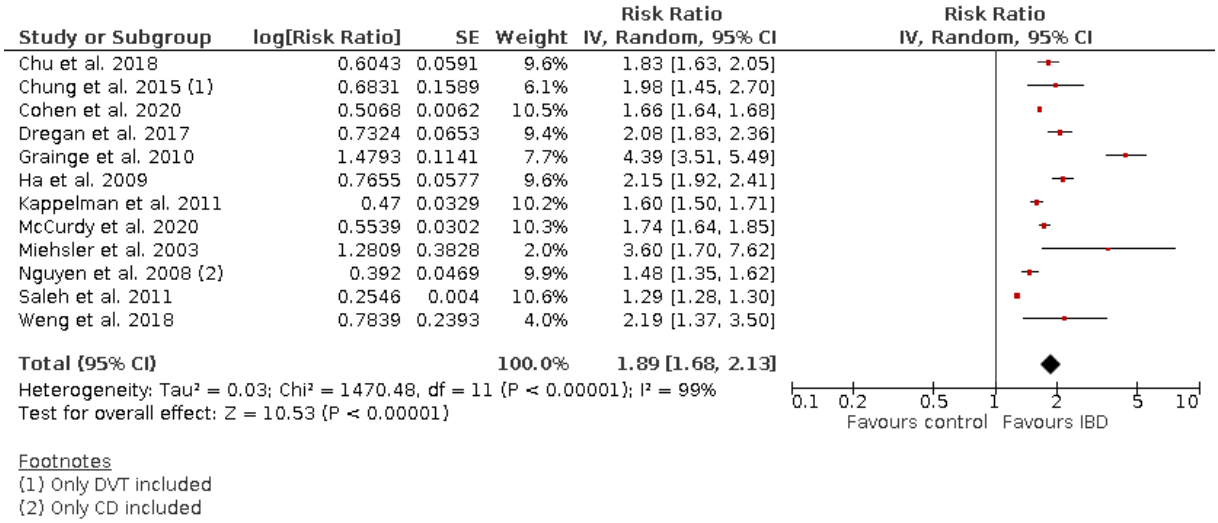
Four studies further stratified the risk of VTE in IBD according to age groups of IBD patients.(49, 50, 55, 58) All show that younger IBD patients have an even more accentuated risk of VTE compared to older IBD patients in regard to respectively matched peers without IBD. When comparing the VTE risk in UC patients below the age of 40 to their age matched controls the resulting OR of 4.31, reported by Nguyen, et al., was strikingly more pronounced than the OR of 1.45 seen when comparing UC patients above the age of 40 to their age matched control group. The same finding is seen in CD patients where the risk of VTE dwindles with age to become insignificantly different from the age matched

controls above the age of 40. (49) Also Kappelman et al., noted that the relative risk found when comparing young IBD patients to their age matched controls is 4 times higher than the relative risk found when comparing older IBD patients to their respective age matched controls. The VTE risk difference thus shrinks, but the absolute risk of VTE keeps increasing with age. (50) Each incremental decade in age is associated with a 20% rise in odds of having a VTE.(49)

Three studies further stratified the risk of VTE in IBD according to gender. Two note a higher risk of VTE in female patients. (51, 58) But one states that there is no statistically significant difference between hospitalized men and women.(56)

Six studies further stratified the risk of VTE in IBD according to IBD subtype. Two studies reported Crohn's disease to have the biggest effect on VTE. (50, 56) Three studies reported ulcerative colitis to have the biggest effect. (49, 55, 58) And one did not find a difference in effect at all. (48)

Figure 6: Pooled effect of inflammatory bowel disease on venous thrombo-embolic events



Footnotes
(1) Only DVT included
(2) Only CD included

Discussion

This systematic review synthesizes the current evidence related to cardiovascular diseases in patients with inflammatory bowel disease. Subsequent meta-analysis concludes that patients with IBD are more susceptible to ischemic heart disease, heart failure, cerebrovascular accidents, peripheral artery disease and thrombo-embolic events.

Interpretation of results

Effect of inflammatory bowel disease on ischemic heart disease

In our meta-analysis the pooled analysis as well as the sensitivity analysis with adjusted and non-adjusted estimates separately, show a similar and significant effect of inflammatory bowel disease on IHD risk. It is however noteworthy that pooling and comparing all included studies was subject to variable outcome definitions (coronary syndrome, ischemic heart disease, myocardial infarction), outcome measures (OR, HR, IRR, RR, SIR), follow-up time and IBD treatment choices. The effect estimates ranged from RR 0.92(29) to RR 2.82(11) and reportedly often being twice as high in the first year after IBD diagnosis.(36) Regarding treatment choices we see that IBD patients treated with 5-ASA and TNF-alfa blockers seem to benefit a risk reduction.(36) Stratifying the risk of IHD in IBD shows a negative effect of disease severity, female gender, younger age and Crohn-type IBD, while longer disease duration appears to have

a positive effect. Our findings are in line with the recent meta-analysis of Feng, W., et al. researching the effect of IBD on IHD, reporting the same findings.(59)

Effect of inflammatory bowel disease on heart failure

In our meta-analysis the pooled analysis as well as the sensitivity analysis with adjusted and non-adjusted estimates separately, show a similar and significant effect of inflammatory bowel disease on HF. It is however noteworthy that only 2 articles investigated this effect and future research is needed. The effect estimates ranged from RR 1.37(41) to RR 2.03(11). Stratifying the risk of HF in IBD shows a negative effect of disease severity.

Effect of inflammatory bowel disease on stroke

In our meta-analysis the pooled analysis as well as the sensitivity analysis with adjusted and non-adjusted estimates separately, show a similar and significant effect of IBD on CVA. It is however noteworthy that pooling and comparing all included studies was subject to variable outcome definitions (stroke, cerebrovascular accident, transient ischemic attack, cerebral infarction), outcome measures (OR, HR, IRR, RR, SIR) and follow-up time. The effect estimates ranged from RR 1.06(31) to RR 2.05(12). Stratifying the risk of stroke in IBD shows a negative effect of disease severity, younger age and female gender.

Effect of inflammatory bowel disease on peripheral artery disease

It is important to mention that some studies included in our analysis only studied a particular subset of PAD. For example, Tsai, et al (2015) only studied arterial disease in the mesenteric vasculature.(46) And Yang, et al., only studied arterial disease in the aorta by looking at aneurysm risk.(47) This might underestimate the prevalence of arterial disease in IBD. Only three studies looked at peripheral artery disease in general(15, 34, 45), of which one could not find a significant effect in inflammatory bowel disease patients.(15) So, once again, like the effect of IBD on heart failure, caution is warranted in interpreting this finding. More future research is needed to fully elucidate the effect of IBD on PAD. Only when pooling all studies together under the umbrella of peripheral artery disease we find a significant effect of IBD on PAD. Our sensitivity analysis using the adjusted and non-adjusted estimates separately both did not confirm this. Effect estimates ranged from 1.16(15) to 6.33(46). Stratifying the risk of PAD in IBD according to age, sex, gender, disease severity and IBD subtype did not detect general trends.

Effect of inflammatory bowel disease on venous thrombo-embolic events

In our meta-analysis the pooled analysis as well as the sensitivity analysis with adjusted and non-adjusted estimates separately, show a similar and significant effect of IBD on VTE. We studied the risk of venous thrombo-embolism as the combined risk of deep vein thrombosis and pulmonary embolism in the IBD population compared to the general population, while accounting for as many known risk factors as possible (fracture, malignancy, surgery, pregnancy, diabetes, heart failure, MI, stroke, use of hormone replacement therapy, use of antipsychotic medication, catheters, BMI, use of oral contraceptives, use of tobacco). Effect estimates ranged from 1.29(55) to 4.39(53). Stratifying the risk of VTE in IBD shows increased risk with disease severity, female gender and younger age in IBD patients. Other interesting predisposing risk factors identified by Weng et al., are a history of bowel surgery, extensive UC, penetrating CD, low Hb, low platelets, low albumin and high CRP.(56) Cohen, et al. adds ports/central venous catheters, long term steroid use, malnutrition and malignancy to the list of risk factors and documents Asian race as a protective factor.(57) To put the IBD related risk of VTE in perspective, we compared it with the effect of other known risk factors. Air travel for example elevates population background risk 1.5 to 3 times, pregnancy and puerperium 3 to 5 times and oral contraceptives 4 to 7 times.(60)

Contribution of our results to the current literature and clinical implications

In the current literature the most recent focus on cardiovascular comorbidities in IBD was carried out by the study group of Sun Hong-Hao and Feng Tian. They made a meta-analysis quantitatively summarizing the evidence of 11 cohort articles reporting cardiovascular disease incidence of coronary heart disease, myocardial infarctions and cerebrovascular accidents in IBD patients compared to controls.(61) Their results were similar to ours, but we broadened the cardiovascular focus by also investigating the effect of IBD on heart failure, peripheral artery disease an venous thrombo-embolic events. This in addition to searching more databases, we were able to include 37 relevant articles encompassing all but one of the articles included by Sun et al. The one article by Yarur, et al. was excluded in our analysis because they reported 356 IBD patients in their study, thereby not meeting our inclusion criteria (>500 IBD patients).(62)

By confirming the negative effect of IBD on cardiovascular health, future research can now focus on effective screening methods and possible prevention measures to benefit IBD patients. Also, by recognizing IBD as a cardiovascular risk factor, it can be used in risk prediction models in routine clinical practice. For now general practitioners could be more attentive for the classic cardiovascular parameters, like blood pressure, cholesterol/lipid profile, weight, physical exercise, smoking status, alcohol use and blood sugar levels to timely detect and treat deviations and temper the already increased cardiovascular risk in these patients.

Reasons for more cardiovascular diseases in IBD

Our meta-analysis shows a negative effect of IBD on all cardiovascular outcomes. Previous studies have suggested this effect is likely to be linked to atherosclerosis, a prothrombotic state and traditional cardiovascular risk factors.

Atherosclerosis

Atherosclerosis is the process of lipid accumulation and endothelial dysfunction at the vessel wall resulting in intimal thickening and subsequent fibrosis with stiffening of arterial walls until the formed atherosclerotic plaque erodes to a thrombosis or ruptures to an embolism.(31) The endothelial dysfunction in this phenomenon was proven in 2009 by Roifman, et al.(63) Next, papa, et al., showed in 2006 that IBD patients have greater values of carotid intima-media thickness compared to healthy controls.(64) And this was confirmed by Wu, et al., in 2017.(65) Stiffening of the arterial wall in IBD was then again documented by Zanoli et al.(66) Together these studies report the stepwise process of atherosclerosis and strengthen the evidence for an increased risk of early atherosclerosis in IBD. The atherosclerotic process in IBD seems to be provoked by systemic inflammation, abnormal lipid metabolism and a prothrombotic state discussed in the next section. Firstly, the systemic inflammation is thought to be an important mediator of atherosclerosis and thrombosis, because of proven similar effects in other chronic inflammatory conditions as rheumatoid arthritis and lupus.(67, 68) Hatoum et al. showed that also in IBD inflammatory cytokines (TNF-alfa, IL6) and CRP expression is increased.(69) The CRP level has been associated with an increased 10-year risk of coronary heart disease regardless of the presence of conventional cardiac risk factors (70) and multiple sources already confirmed this association between inflammation and coronary atherosclerotic disease.(71-74) Next to inflammation, an abnormal lipid metabolism further contributes to the atherosclerotic process, studied by Romanato, et al. and Gris, et al.(75, 76)

Prothrombotic state

A hypercoagulability is established in IBD by platelet activation(77), altered coagulation(78) and impaired fibrinolysis(76) and results in a prothrombotic state predisposing to thrombosis and embolism. Again a key role in the pathogenesis of these prothrombotic aberrations is taken up by inflammation. Active intestinal inflammation will activate the coagulation cascade and upregulate prothrombotic mediators on a local level such as Factors V, VII, and VIII, prothrombin, fibrinogen, and thromboplastin,(79) explaining the witnessed increased risk of localized intestinal platelet aggregation by collins, et al.(80) Hatoum, et al confirms these local effects by angiographically documenting increased microvascular stenosis, abnormal vasa recta and diminished blood flow.(69, 81) Meanwhile an upregulation of pro-inflammatory cytokines such as tumor necrosis factor and interleukin-6 lead to increased tissue factor induction, promoting the pro-coagulant state on a systemic level.(82) Many studies assed whether the prothrombotic state could also be explained by an underlying genetic or acquired thrombophilia (like e.g. Factor V Leiden deficiency, homcysteïne, prothrombine gene mutations, antithrombotic factor III deficiency), but this is not the case.(83-88) Finally it is noteworthy that also vitamin B6 insufficiency has been hinted to play a role in the thrombotic risk. 30% of a 'healthy' non thrombotic IBD cohort is diagnosed with vitamin B6 deficiency.(89) Saibeni, et al., managed to confirm that this insufficiency is associated with a thrombotic risk.(90)

Traditional risk factors

And finally, traditional risk factors for cardiovascular disease should not be overlooked as a negative influence on cardiovascular health in inflammatory bowel disease. A lot of the studies in our systematic review confirm a significantly higher presence of dyslipidemia(15, 31, 35, 37), hypertension(15, 31, 35, 37), diabetes(35, 37), obesity(35) and smoking(35) in IBD patients compared to their control population. Still, traditional risk factors, on their own, do not explain the increased cardiovascular risk in inflammatory bowel disease and could even provide a false sense of safety in those without traditional risk factors. For example, Kristensen (2013) noticed that one in ten of myocardial infarctions in IBD patients happened in the absence of any known cardiovascular risk factor.(1)

Effects of age, sex, IBD subtype, disease duration and disease severity

Our systematic review confirms that several factors influence cardiovascular risk in IBD patients.

Firstly, disease severity has repeatedly been confirmed to have a negative effect on IHD(1, 11, 29, 33, 34, 37), CVA(1, 29, 42, 43) and VTE(48-54). As explained above, this appears to be the result of systemic inflammation and its atherosclerotic and prothrombotic effects.

Secondly, young age in IBD often appears to be a negative influence on the risk of IHD(31, 34-37), CVA(16, 31) and VTE(49, 50, 55, 58). Several reasons were mentioned for this finding. For example, younger IBD patients tend to have higher levels of inflammation,(91) and hence more severe disease course. (92, 93) Increasing overall prevalence of cardiovascular disease in older age-group (due to age or other cardiovascular risk factors) may also explain why excess risk in IBD patients becomes less pronounced with age.(34)

Female gender in IBD was often reported as disadvantageous for the risk of IHD(31, 34, 36, 37), CVA(12, 13, 15) and VTE(51, 58). Multiple theories for this phenomenon have been postulated. Firstly, the role of inflammation appears to be greater in women than in men. Women with IBD have higher levels of CRP (94) and in women the risk of ischemic heart disease directly correlates with increasing levels of CRP independent of traditional risk cardiovascular risk factors. (95) Other hypotheses include female oestrogens (96, 97), menopause (98), smaller caliber

arteries(99) or osteoporosis (100-103), may mediate towards an increased risk of CVD in female IBD patients compared to men.

Finally, Crohn subtype IBD seems to have a negative effect on IHD(31, 34, 35, 37). For other cardiovascular outcomes the effect of subtypes was more balanced. Explanations for this include greater CRP responses and thereby higher degree of systemic inflammation in Crohn patients (104, 105), a common genetic basis via polymorphisms in NOD2/CARD15 that predispose to both Crohn's (106) and atherosclerosis (107) and the increased malabsorption in Crohn's, resulting in hyperhomocysteinaemia and low vitamin B6 plasma levels, which are prothrombotic (90, 108).

Strengths and limitations

Our study has its strengths, but also several limitations that should be considered. Firstly, not all studies adjusted for traditional cardiovascular risk factors when investigating the effect of IBD on cardiovascular diseases. Those that did, often adjusted for a different set of confounders, possibly underestimating their effect.

Secondly, some cardiovascular outcomes of interest like heart failure and peripheral artery disease were poorly represented in the existing literature. Analysis of the effect of IBD on heart failure was based on only two articles. And analysis of the effect of IBD on peripheral artery disease was based on 6 articles. Further investigation concerning these topics is therefore required to consolidate our results.

Next, the limited number of studies did not allow us to quantitatively assess the effect of IBD on each cardiovascular disease by subgroups of age, sex, type of IBD, disease duration or disease severity.

Finally, our study is reliant on observational study designs which are susceptible to bias. Possible selection bias in retrospective cohort studies was mitigated by ensuring that exposure and outcome were not present at the moment of enrollment. However, lower reporting rates of non-significant effects or increased risk due to increased healthcare usage leading to higher rates of diagnosis in individuals regularly followed-up for IBD, cannot be completely excluded.

To contrast these limitations, we emphasize that the big strength of our study is the broad representation of cardiovascular disease over five different outcomes, which provides a unique synoptic view of the cardiovascular consequences of IBD.

Ethical considerations

This research does not involve working directly with IBD patients, but rather with previous research conducted with this population. Therefore, we automatically received permission of the 'Onderwijs-begeleidingscommissie' (OBC) comittee of ethics.

Conflict of interest

None.

Financial gain & funds

None.

Recognition

We would like to thank our promotor and co-promotor for their willingness to repeatedly follow up on our process. In particular we would like to emphasize our appreciation for their support, professional feedback and advice.

Furthermore, we would like to thank Thomas Vandendriessche, Kristel Paque and Krizia Tuand, the biomedical reference librarians of the KU Leuven Libraries – 2Bergen – learning Centre Désiré Collen (Leuven, Belgium), for their help in conducting the systematic literature search.

APPENDIX

Appendix Search string

Our search strategy was constructed around the key concepts of our topic using the FoReST-LOG scheme.(109) The key concepts are: Inflammatory bowel disease (concept 1), Ischemic heart disease (concept 2), Heart failure (concept 3), Cerebrovascular accidents (concept 4), Peripheral vascular disease (concept 5) and Thrombo-embolism (concept 6). The FoReST-LOG scheme implies using other forms of each concept, using related terms of each concept, using synonymous terms and using the ladder of generalization. The eventual search terms were then adjusted to fit the search engine of the different databases inviting MeSH terms and Emtree terms. Help of the 2Bergen Learning Centre was used for optimizing the search string before conducting the final search. To narrow search results additional filters like 'last 20 years', 'human' and 'English' were used.

Final search string:

Embase:
(((Concept1) AND ((Concept2) OR (Concept3) OR (Concept4) OR (Concept5) OR (Concept6))) AND (Concept7)) NOT ('conference abstract':it)

(('inflammatory bowel disease'/exp OR 'inflammatory bowel disease*':ti,ab,kw OR 'ulcerative colitis':ti,ab,kw OR 'idiopathic proctocolitis':ti,ab,kw OR 'colitis gravis':ti,ab,kw OR 'colitis ulcerativa':ti,ab,kw OR 'colitis ulcerosa':ti,ab,kw OR 'ulcerous colitis':ti,ab,kw OR 'ulcerous colon':ti,ab,kw OR 'mucosal colitis':ti,ab,kw OR 'ulcerative colon':ti,ab,kw OR 'ulcerative colorectitis':ti,ab,kw OR 'ulcerative proctorectitis':ti,ab,kw OR 'ulcerative procto rectitis':ti,ab,kw OR 'crohn*':ti,ab,kw OR 'regional enteritis':ti,ab,kw OR 'granulomatous enteritis':ti,ab,kw OR 'ileocolitis':ti,ab,kw OR 'granulomatous colitis':ti,ab,kw OR 'terminal ileitis':ti,ab,kw OR 'regional ileitis':ti,ab,kw OR 'crohn disease*':ti,ab,kw OR 'cleron disease*':ti,ab,kw OR 'enteritis regionalis':ti,ab,kw OR 'morbus crohn':ti,ab,kw OR 'regional enterocolitis':ti,ab,kw) AND (('heart muscle ischemia'/exp OR 'heart muscle isch*mia':ti,ab,kw OR 'myocardial isch*mia*':ti,ab,kw OR 'isch*mic heart disease*':ti,ab,kw OR 'coronary heart disease*':ti,ab,kw OR 'coronary arterial disease*':ti,ab,kw OR 'coronary artery disease*':ti,ab,kw OR 'myocardial infarction*':ti,ab,kw OR 'heart attack*':ti,ab,kw OR 'acute coronary syndrome*':ti,ab,kw OR 'angina pectoris':ti,ab,kw OR 'cardiovascular stroke*':ti,ab,kw OR 'cardiac isch*mia*':ti,ab,kw OR 'cardiac muscle isch*mia*':ti,ab,kw OR 'coronary artery isch*mia*':ti,ab,kw OR 'coronary isch*mia':ti,ab,kw OR 'coronary syndrome*':ti,ab,kw OR 'heart hypoxia*':ti,ab,kw OR 'heart anoxia':ti,ab,kw OR 'heart isch*mia*':ti,ab,kw OR 'heart isch*mic arrest*':ti,ab,kw OR 'heart isch*mic attack*':ti,ab,kw OR 'heart isch*mic time*':ti,ab,kw OR 'heart muscle hypoxia*':ti,ab,kw OR 'heart muscle anoxia':ti,ab,kw OR 'heart transient isch*mic attack*':ti,ab,kw OR 'hypoxic heart*':ti,ab,kw OR 'anoxic heart*':ti,ab,kw OR 'isch*mic heart*':ti,ab,kw OR 'isch*mic myocardium':ti,ab,kw OR 'myocardial anoxia':ti,ab,kw OR 'myocard* hypoxia*':ti,ab,kw OR 'myocard* anoxia':ti,ab,kw OR 'myocard* isch*mia*':ti,ab,kw OR 'subendocardial isch*mia*':ti,ab,kw OR 'cardia* infarct*':ti,ab,kw OR 'heart infarct*':ti,ab,kw OR 'heart muscle infarct*':ti,ab,kw OR 'myocard* infarct*':ti,ab,kw OR 'subendocardial infarct*':ti,ab,kw OR 'isch*mic cardiopath*':ti,ab,kw OR 'coronary insufficienc*':ti,ab,kw OR 'coronary artery insufficienc*':ti,ab,kw OR 'coronary artery occlusive disease*':ti,ab,kw OR 'coronary occlusive disease*':ti,ab,kw OR 'heart disease*':ti,ab,kw OR 'isch*mic cardia* disease*':ti,ab,kw OR 'cardiomyopath*':ti,ab,kw OR 'heart myopath*':ti,ab,kw OR 'myocardiopath*':ti,ab,kw OR 'primary myocardial disease*':ti,ab,kw) OR ('heart failure'/exp OR 'heart failure*':ti,ab,kw OR 'cardiac failure*':ti,ab,kw OR 'heart decompensation*':ti,ab,kw OR 'myocardial failure*':ti,ab,kw OR 'cardia* decompensation*':ti,ab,kw OR 'cardia* incompetenc*':ti,ab,kw OR 'cardia* insufficien*':ti,ab,kw OR

'cardiac stand still':ti,ab,kw OR 'decompensatio cordis':ti,ab,kw OR 'heart incompetenc*':ti,ab,kw OR 'heart insufficien*':ti,ab,kw OR 'insufficientia cardis':ti,ab,kw OR 'myocardial insufficien*':ti,ab,kw OR 'cardiogenic shock*':ti,ab,kw OR 'cardiac shock*':ti,ab,kw OR 'cardiovascular shock*':ti,ab,kw OR 'heart shock*':ti,ab,kw OR 'ventricle failure*':ti,ab,kw OR 'ventricle overload*':ti,ab,kw) OR ('cerebrovascular accident'/exp OR 'cerebrovascular accident*':ti,ab,kw OR 'cva':ti,ab,kw OR 'cerebrovascular lesion*':ti,ab,kw OR 'stroke*':ti,ab,kw OR 'brain vascular accident*':ti,ab,kw OR 'intracranial embolism*':ti,ab,kw OR 'intracranial thrombosis':ti,ab,kw OR 'intracranial arteriosclerosis':ti,ab,kw OR 'brain infarct*':ti,ab,kw OR 'intracranial atherosclerosis':ti,ab,kw OR 'cerebr* vascular accident*':ti,ab,kw OR 'focal cerebral vasculopath*':ti,ab,kw OR 'cerebral apoplex*':ti,ab,kw OR 'brain blood flow disturbance*':ti,ab,kw OR 'brain accident*':ti,ab,kw OR 'brain attack*':ti,ab,kw OR 'brain insult*':ti,ab,kw OR 'brain isch*mic attack*':ti,ab,kw OR 'cerebral insult*':ti,ab,kw OR 'cerebral vascular insufficien*':ti,ab,kw OR 'cerebrovascular arrest*':ti,ab,kw OR 'cerebrovascular failure*':ti,ab,kw OR 'cerebrovascular injur*':ti,ab,kw OR 'cerebrovascular insufficien*':ti,ab,kw OR 'cerebrovascular insult*':ti,ab,kw OR 'isch*mic cerebral attack*':ti,ab,kw OR 'isch*mic seizure*':ti,ab,kw OR 'cerebral artery occlusion*':ti,ab,kw OR 'vertebral artery stenosis*':ti,ab,kw OR 'basilar artery obstruction*':ti,ab,kw OR 'occlusive cerebrovascular disease':ti,ab,kw) OR ('peripheral vascular disease'/exp OR 'peripheral angiopath*':ti,ab,kw OR 'phlebiti*':ti,ab,kw OR 'peripheral arterial disease*':ti,ab,kw OR 'peripheral occlusive artery disease'/exp OR 'peripheral occlusive artery disease*':ti,ab,kw OR 'atherosclerosis':ti,ab,kw OR 'atherosclerotic disease*':ti,ab,kw OR 'arterial occlusive disease*':ti,ab,kw OR 'artery occlusion*':ti,ab,kw OR 'blood vessel occlusion*':ti,ab,kw OR 'claudication*':ti,ab,kw OR 'arteriosclerosis'/exp OR 'arteriosclerosis':ti,ab,kw OR 'arter* disease*':ti,ab,kw OR 'blood vessel calcification*':ti,ab,kw OR 'microangiopath*':ti,ab,kw OR 'macroangiopath*':ti,ab,kw OR 'vasculitis':ti,ab,kw OR 'peripheral arteriopath*':ti,ab,kw OR 'peripheral blood vessel disease*':ti,ab,kw OR 'peripheral vascular disease*':ti,ab,kw OR 'peripheral vascular disorder*':ti,ab,kw OR 'peripheral vasculopath*':ti,ab,kw OR 'peripheral vessel disease*':ti,ab,kw OR 'hemangiopath*':ti,ab,kw OR 'isch*mic vasculopath*':ti,ab,kw OR 'thrombophlebitis':ti,ab,kw OR 'deep venous thrombus':ti,ab,kw OR 'vascular disease*':ti,ab,kw OR 'vascular disorder*':ti,ab,kw OR 'vascular disturbance*':ti,ab,kw OR 'vascular path*':ti,ab,kw OR 'vasculopath*':ti,ab,kw OR 'artery disease*':ti,ab,kw) OR ('thromboembolism'/exp OR 'thromboemboli*':ti,ab,kw OR 'thrombosis':ti,ab,kw OR 'thrombotic event*':ti,ab,kw OR 'thrombo occlusive disease*':ti,ab,kw OR 'thrombotic disease*':ti,ab,kw OR 'thrombotic occlusion*':ti,ab,kw OR 'embolism*':ti,ab,kw OR 'thrombo embol*':ti,ab,kw OR 'atherothrombosis':ti,ab,kw OR 'thrombo obliterative disease*':ti,ab,kw))) AND ('clinical trial'/exp OR 'trial*':ti,ab,kw OR 'intervention stud*':ti,ab,kw OR 'randomized*':ti,ab,kw OR 'randomised*':ti,ab,kw OR 'epidemiology'/exp OR 'epidemiology*':ti,ab,kw OR 'cohort*':ti,ab,kw OR 'case-control*':ti,ab,kw OR 'meta analysis'/exp OR 'meta-analysis':ti,ab,kw OR 'systematic review'/exp OR 'systematic review':ti,ab,kw)) NOT (‘conference abstract’:it)

MEDLine:
((Concept1) AND ((Concept2) OR (Concept3) OR (Concept4) OR (Concept5) OR (Concept6))) AND (Concept7)

(("Inflammatory Bowel Diseases"[Mesh] OR inflammatory-bowel-disease*[tiab] OR ulcerative-colitis[tiab] OR idiopathic-proctocolitis[tiab] OR colitis-gravis[tiab] OR colitis-ulcerativa[tiab] OR colitis-ulcerosa[tiab] OR ulcerous-colitis[tiab] OR ulcerous-colon[tiab] OR mucosal-colitis[tiab] OR ulcerative-colon[tiab] OR ulcerative-colorectitis[tiab] OR ulcerative-proctorectitis[tiab] OR ulcerative-procto-rectitis[tiab] OR Crohn*[tiab] OR regional-enteritis[tiab] OR granulomatous-enteritis[tiab] OR

ileocolitis[tiab] OR granulomatous-colitis[tiab] OR terminal-ileitis[tiab] OR regional-ileitis[tiab] OR cleron-disease*[tiab] OR enteritis-regionalis[tiab] OR regional-enterocolitis[tiab]) AND (("Myocardial Ischemia"[Mesh] OR heart-muscle-ischemia*[tiab] OR heart-muscle-ischaemia*[tiab] OR myocardial-ischemia*[tiab] OR myocardial-ischaemia*[tiab] OR coronary-disease*[tiab] OR coronary-arterial-disease*[tiab] OR coronary-artery-disease *[tiab] OR myocardial-infarct*[tiab] OR heart-attack*[tiab] OR angina-pectoris[tiab] OR angor[tiab] OR cardiovascular-stroke*[tiab] OR cardiac-ischemia*[tiab] OR cardiac-ischaemia*[tiab] OR cardiac-muscle-ischemia*[tiab] OR cardiac-muscle-ischaemia*[tiab] OR coronary-artery-ischemia*[tiab] OR coronary-artery-ischaemia*[tiab] OR coronary-ischemia*[tiab] OR coronary-ischaemia*[tiab] OR coronary-syndrome*[tiab] OR heart-hypoxi*[tiab] OR heart-anoxia*[tiab] OR heart-ischemia*[tiab] OR heart-ischaemia*[tiab] OR heart-ischemic-arrest*[tiab] OR heart-ischaemic-arrest*[tiab] OR heart-ischemic-attack*[tiab] OR heart-ischaemic-attack*[tiab] OR heart-ischemic-time*[tiab] OR heart-ischaemic-time*[tiab] OR heart-muscle-hypoxia*[tiab] OR heart-muscle-anoxia*[tiab] OR heart-transient-ischaemic-attack*[tiab] OR heart-transient-ischemic-attack*[tiab] OR hypoxic-heart*[tiab] OR anoxic-heart*[tiab] OR ischaemic-heart*[tiab] OR ischemic-heart*[tiab] OR ischemic-heart-arrest*[tiab] OR ischaemic-heart-arrest*[tiab] OR ischemic-myocard*[tiab] OR ischaemic-myocard*[tiab] OR myocardial-anoxia*[tiab] OR myocardial-hypoxia*[tiab] OR myocardium-hypoxia*[tiab] OR myocardium-anoxia*[tiab] OR myocardium-ischemia*[tiab] OR myocardium-ischaemia*[tiab] OR subendocardial-ischaemia*[tiab] OR subendocardial-ischemia*[tiab] OR cardiac-infarct*[tiab] OR cardial-infarct*[tiab] OR heart-infarct*[tiab] OR heart-muscle-infarct*[tiab] OR myocardial-infarct*[tiab] OR myocardium-infarct*[tiab] OR subendocardial-infarct*[tiab] OR ischemic-cardiopath*[tiab] OR ischaemic-cardiopath*[tiab] OR coronary-insufficienc*[tiab] OR coronary-artery-insufficienc*[tiab] OR coronary-artery-occlusive-disease*[tiab] OR coronary-occlusive-disease*[tiab] OR heart-disease*[tiab] OR ischemic-cardiac-disease*[tiab] OR ischaemic-cardiac-disease*[tiab] OR ischemic-cardial-disease*[tiab] OR ischaemic-cardial-disease*[tiab] OR cardiomyopath*[tiab] OR heart-myopath*[tiab] OR myocardiopath*[tiab] OR primary-myocardial-disease*[tiab]) OR ("Heart Failure"[Mesh] OR heart-failure*[tiab] OR cardiac-failure*[tiab] OR heart-decompensation*[tiab] OR myocardial-failure*[tiab] OR cardiac-decompensation*[tiab] OR cardiac-incompetenc*[tiab] OR cardiac-insufficienc*[tiab] OR cardial-decompensation*[tiab] OR cardial-incompetenc*[tiab] OR cardial-insufficienc*[tiab] OR cardiac-stand-still[tiab] OR heart-insufficienc*[tiab] OR decompensation-cordis[tiab] OR heart-incompetenc*[tiab] OR insufficientia-cardis[tiab] OR myocardial-insufficienc*[tiab]) OR ("Stroke"[Mesh] OR stroke*[tiab] OR cerebrovascular-accident*[tiab] OR cva[tiab] OR cerebrovascular-lesion*[tiab] OR brain-vascular-accident*[tiab] OR intracranial-embolism*[tiab] OR intracranial-thrombosis[tiab] OR intracranial-arteriosclerosis[tiab] OR brain-infarction*[tiab] OR intracranial-atherosclerosis[tiab] OR cerebro-vascular-accident*[tiab] OR focal-cerebral-vasculopath*[tiab] OR cerebral-apoplex*[tiab] OR brain-blood-flow-disturbance*[tiab] OR brain-accident*[tiab] OR brain-attack*[tiab] OR brain-insult*[tiab] OR brain-ischemic-attack*[tiab] OR brain-ischaemic-attack*[tiab] OR cerebral-insult*[tiab] OR cerebral-vascular-accident*[tiab] OR cerebral-vascular-insufficienc*[tiab] OR cerebrovascular-arrest*[tiab] OR cerebrovascular-failure*[tiab] OR cerebrovascular-injur*[tiab] OR cerebrovascular-insufficienc*[tiab] OR cerebrovascular-insult*[tiab] OR cerebrum-vascular-accident*[tiab] OR ischemic-cerebral-attack*[tiab] OR ischaemic-cerebral-attack*[tiab] OR ischemic-seizure*[tiab] OR ischaemic-seizure*[tiab]) OR ("Peripheral Vascular Diseases"[Mesh] OR peripheral-angiopath*[tiab] OR phlebiti*[tiab] OR peripheral-arterial-disease*[tiab] OR atheroscleros*[tiab] OR atherosclerotic-disease*[tiab] OR arterial-occlusive-disease*[tiab] OR arterioscleros*[tiab] OR "Arteriosclerosis"[Mesh] OR artery-disease*[tiab] OR blood-vessel-calcification*[tiab] OR microangiopath*[tiab] OR macroangiopath*[tiab] OR vasculitis[tiab] OR peripheral-arteriopath*[tiab] OR peripheral-blood-vessel-disease*[tiab] OR peripheral-vasculopath*[tiab] OR peripheral-vessel-

disease*[tiab] OR hemangiopath*[tiab] OR ischemic-vasculopath*[tiab] OR thrombophlebiti*[tiab] OR deep-venous-thrombus[tiab] OR thrombosis[tiab] OR vascular-disease*[tiab] OR vascular-disorder*[tiab] OR vascular-disturbance*[tiab] OR vascular-patholog*[tiab] OR vasculopath*[tiab]) OR ("Thromboembolism"[Mesh] OR thromboembol*[tiab] OR thromboembolic-event*[tiab] OR thrombosis[tiab] OR atherothrombosis[tiab] OR thrombotic-event*[tiab] OR thrombo-occlusive-disease*[tiab] OR thrombotic-disease*[tiab] OR thrombotic-occlusion*[tiab] OR embolism*[tiab] OR thromboembolic-disease*[tiab] OR thrombo-embol*[tiab] OR atherothrombosis[tiab] OR thrombo-obliterative-disease*[tiab]))) AND ("Clinical Trial" [Publication Type] OR trial*[tiab] OR "intervention stud*"[tiab] OR randomized[tiab] OR randomised[tiab] OR "Epidemiologic Studies"[Mesh] OR epidemiologic*[tiab] OR Cohort*[tiab] OR case-control*[tiab] OR "Meta-Analysis" [Publication Type] OR "Systematic Review" [Publication Type])

Web of Science:
(((Concept1) AND ((Concept2) OR (Concept3) OR (Concept4) OR (Concept5) OR (Concept6))) AND (Concept7))

Concept 1:
“inflammatory bowel disease*“ OR “ulcerative colitis“ OR “idiopathic proctocolitis“ OR “colitis gravis“ OR “colitis ulcerativa“ OR “colitis ulcerosa“ OR “ulcerous colitis“ OR “ulcerous colon“ OR “mucosal colitis“ OR “ulcerative colon“ OR “ulcerative colorectitis“ OR “ulcerative proctorectitis“ OR “ulcerative procto rectitis“ OR “crohn*“ OR “regional enteritis“ OR “granulomatous enteritis“ OR “ileocolitis“ OR “granulomatous colitis“ OR “terminal ileitis“ OR “regional ileitis“ OR “crohn disease*“ OR “cleron disease*“ OR “enteritis regionalis“ OR “morbus crohn“ OR “regional enterocolitis“

Concept 2:
“heart muscle isch*mia“ OR “myocardial isch*mia*“ OR “isch*mic heart disease*“ OR “coronary heart disease*“ OR “coronary arterial disease*“ OR “coronary artery disease*“ OR “myocardial infarction*“ OR “heart attack*“ OR “acute coronary syndrome*“ OR “angina pectoris“ OR “cardiovascular stroke*“ OR “cardiac isch*mia*“ OR “cardiac muscle isch*mia*“ OR “coronary artery isch*mia*“ OR “coronary isch*mia“ OR “coronary syndrome*“ OR “heart hypoxia*“ OR “heart anoxia“ OR “heart isch*mia*“ OR “heart isch*mic arrest*“ OR “heart isch*mic attack*“ OR “heart isch*mic time*“ OR “heart muscle hypoxia*“ OR “heart muscle anoxia“ OR “heart transient isch*mic attack*“ OR “hypoxic heart*“ OR “anoxic heart*“ OR “isch*mic heart*“ OR “isch*mic myocardium“ OR “myocardial anoxia“ OR “myocard* hypoxia*“ OR “myocard* anoxia“ OR “myocard* isch*mia*“ OR “subendocardial isch*mia*“ OR “cardia* infarct*“ OR “heart infarct*“ OR “heart muscle infarct*“ OR “myocard* infarct*“ OR “subendocardial infarct*“ OR “isch*mic cardiopath*“ OR “coronary insufficienc*“ OR “coronary artery insufficienc*“ OR “coronary artery occlusive disease*“ OR “coronary occlusive disease*“ OR “heart disease*“ OR “isch*mic cardia* disease*“ OR “cardiomyopath*“ OR “heart myopath*“ OR “myocardiopath*“ OR “primary myocardial disease*“

Concept 3:
“heart failure*“ OR “cardiac failure*“ OR “heart decompensation*“ OR “myocardial failure*“ OR “cardia* decompensation*“ OR “cardia* incompetenc*“ OR “cardia* insufficien*“ OR “cardiac stand still“ OR “decompensatio cordis“ OR “heart incompetenc*“ OR “heart insufficien*“ OR “insufficientia cardis“ OR “myocardial insufficien*“ OR “cardiogenic shock*“ OR “cardiac shock*“ OR “cardiovascular shock*“ OR “heart shock*“ OR “ventricle failure*“ OR “ventricle overload*“

Concept 4:

“cerebrovascular accident*“ OR “cva“ OR “cerebrovascular lesion*“ OR “stroke*“ OR “brain vascular accident*“ OR “intracranial embolism*“ OR “intracranial thrombosis“ OR “intracranial arteriosclerosis“ OR “brain infarct*“ OR “intracranial atherosclerosis“ OR “cerebr* vascular accident*“ OR “focal cerebral vasculopath*“ OR “cerebral apoplex*“ OR “brain blood flow disturbance*“ OR “brain accident*“ OR “brain attack*“ OR “brain insult*“ OR “brain isch*mic attack*“ OR “cerebral insult*“ OR “cerebral vascular insufficien*“ OR “cerebrovascular arrest*“ OR “cerebrovascular failure*“ OR “cerebrovascular injur*“ OR “cerebrovascular insufficien*“ OR “cerebrovascular insult*“ OR “isch*mic cerebral attack*“ OR “isch*mic seizure*“ OR “cerebral artery occlusion*“ OR “vertebral artery stenosis*“ OR “basilar artery obstruction*“ OR “occlusive cerebrovascular disease“

Concept 5:
“peripheral angiopath*“ OR “phlebiti*“ OR “peripheral arterial disease*“ OR “peripheral occlusive artery disease*“ OR “atherosclerosis“ OR “atherosclerotic disease*“ OR “arterial occlusive disease*“ OR “artery occlusion*“ OR “blood vessel occlusion*“ OR “claudication*“ OR “arteriosclerosis“ OR “arter* disease*“ OR “blood vessel calcification*“ OR “microangiopath*“ OR “macroangiopath*“ OR “vasculitis“ OR “peripheral arteriopath*“ OR “peripheral blood vessel disease*“ OR “peripheral vascular disease*“ OR “peripheral vascular disorder*“ OR “peripheral vasculopath*“ OR “peripheral vessel disease*“ OR “hemangiopath*“ OR “isch*mic vasculopath*“ OR “thrombophlebitis“ OR “deep venous thrombus“ OR “vascular disease*“ OR “vascular disorder*“ OR “vascular disturbance*“ OR “vascular path*“ OR “vasculopath*“ OR “artery disease*“

Concept 6:
“thromboemboli*“ OR “thrombosis“ OR “thrombotic event*“ OR “thrombo occlusive disease*“ OR “thrombotic disease*“ OR “thrombotic occlusion*“ OR “embolism*“ OR “thrombo embol*“ OR “atherothrombosis“ OR “thrombo obliterative disease*“

Concept 7:
'clinical trial'/exp OR 'trial*':ti,ab,kw OR 'intervention stud*':ti,ab,kw OR 'randomized*':ti,ab,kw OR 'randomised*':ti,ab,kw OR 'epidemiology'/exp OR 'epidemiology*':ti,ab,kw OR 'cohort*':ti,ab,kw OR 'case-control*':ti,ab,kw OR 'meta analysis'/exp OR 'meta-analysis':ti,ab,kw OR 'systematic review'/exp OR 'systematic review':ti,ab,kw

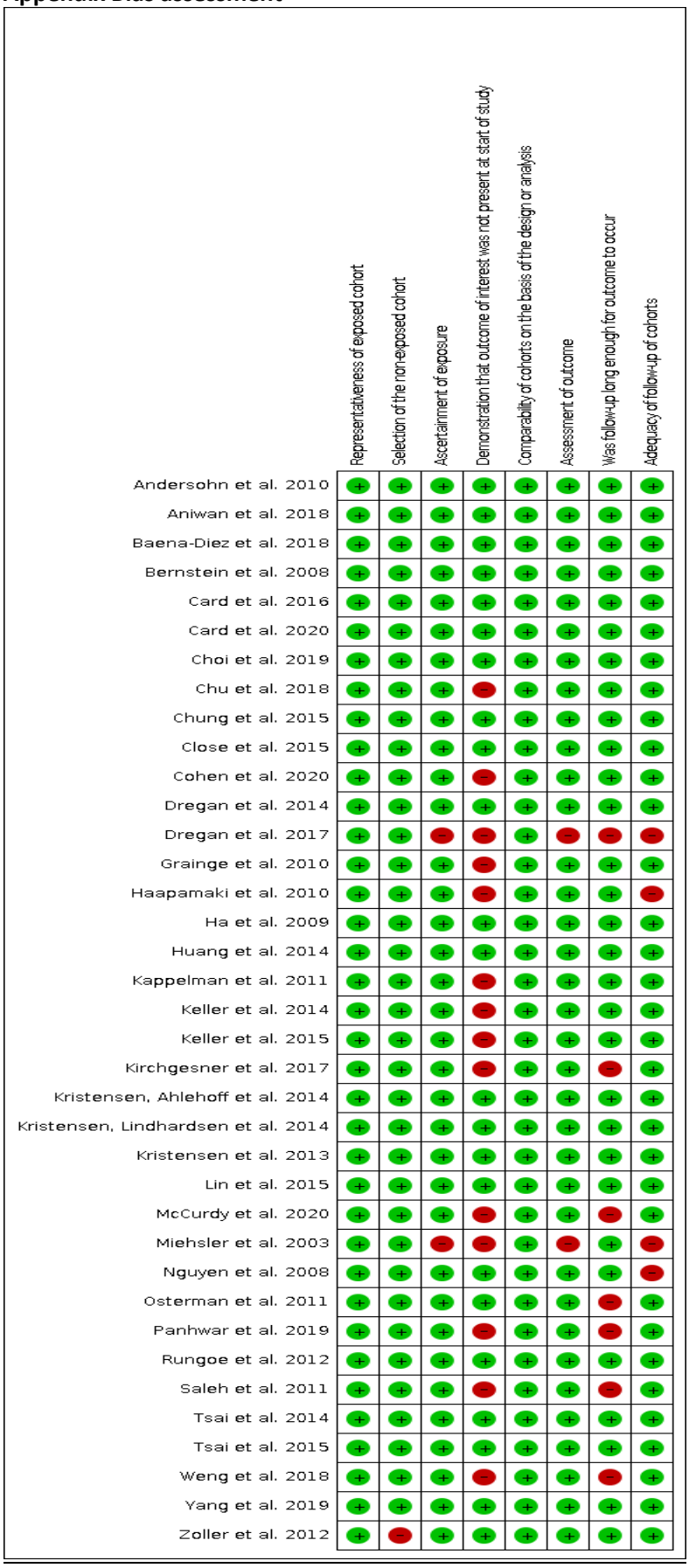
Cochrane:
(((Concept1) AND ((Concept2) OR (Concept3) OR (Concept4) OR (Concept5) OR (Concept6))) AND (Concept7)) NOT (‘conference abstract’:it)

Concept 1:
#1
[mh "inflammatory bowel disease"]
#2
((inflammatory NEXT bowel NEXT disease*) OR (ulcerative NEXT colitis) OR (idiopathic NEXT proctocolitis) OR (colitis NEXT gravis) OR (colitis NEXT ulcerativa) OR (colitis NEXT ulcerosa) OR (ulcerous NEXT colitis) OR (ulcerous NEXT colon) OR (mucosal NEXT colitis) OR (ulcerative NEXT colon) OR (ulcerative NEXT colorectitis) OR (ulcerative NEXT proctorectitis) OR (ulcerative NEXT procto NEXT rectitis) OR (crohn*) OR (regional NEXT enteritis) OR (granulomatous NEXT enteritis) OR (ileocolitis) OR (granulomatous NEXT colitis) OR (terminal NEXT ileitis) OR (regional NEXT ileitis) OR

(crohn NEXT disease*) OR (cleron NEXT disease*) OR (enteritis NEXT regionalis) OR (morbus NEXT crohn) OR (regional NEXT enterocolitis)):ti,ab,kw
#3
#1 OR #2
Concept 2:
#4
[mh "myocardial ischemia"]
#5
((heart NEXT muscle NEXT isch*mia) OR (myocardial NEXT isch*mia*) OR (isch*mic NEXT heart NEXT disease*) OR (coronary NEXT heart NEXT disease*) OR (coronary NEXT arterial NEXT disease*) OR (coronary NEXT artery NEXT disease*) OR (myocardial NEXT infarction*) OR (heart NEXT attack*) OR (acute NEXT coronary NEXT syndrome*) OR (angina NEXT pectoris) OR (cardiovascular NEXT stroke*) OR (cardiac NEXT isch*mia*) OR (cardiac NEXT muscle NEXT isch*mia*) OR (coronary NEXT artery NEXT isch*mia*) OR (coronary NEXT isch*mia) OR (coronary NEXT syndrome*) OR (heart NEXT hypoxia*) OR (heart NEXT anoxia) OR (heart NEXT isch*mia*) OR (heart NEXT isch*mic NEXT arrest*) OR (heart NEXT isch*mic NEXT attack*) OR (heart NEXT isch*mic NEXT time*) OR (heart NEXT muscle NEXT hypoxia*) OR (heart NEXT muscle NEXT anoxia) OR (heart NEXT transient NEXT isch*mic NEXT attack*) OR (hypoxic NEXT heart*) OR (anoxic NEXT heart*) OR (isch*mic NEXT heart*) OR (isch*mic NEXT myocardium) OR (myocardial NEXT anoxia) OR (myocard* NEXT hypoxia*) OR (myocard* NEXT anoxia) OR (myocard* NEXT isch*mia*) OR (subendocardial NEXT isch*mia*) OR (cardia* NEXT infarct*) OR (heart NEXT infarct*) OR (heart NEXT muscle NEXT infarct*) OR (myocard* NEXT infarct*) OR (subendocardial NEXT infarct*) OR (isch*mic NEXT cardiopath*) OR (coronary NEXT insufficienc*) OR (coronary NEXT artery NEXT insufficienc*) OR (coronary NEXT artery NEXT occlusive NEXT disease*) OR (coronary NEXT occlusive NEXT disease*) OR (heart NEXT disease*) OR (isch*mic NEXT cardia* NEXT disease*) OR (cardiomyopath*) OR (heart NEXT myopath*) OR (myocardiopath*) OR (primary NEXT myocardial NEXT disease*)):ti,ab,kw
#6
#4 OR #5
Concept 3:
#7
[mh "heart failure"]
#8
((heart NEXT failure*) OR (cardiac NEXT failure*) OR (heart NEXT decompensation*) OR (myocardial NEXT failure*) OR (cardia* NEXT decompensation*) OR (cardia* NEXT incompetenc*) OR (cardia* NEXT insufficien*) OR (cardiac NEXT stand NEXT still) OR (decompensatio NEXT cordis) OR (heart NEXT incompetenc*) OR (heart NEXT insufficien*) OR (insufficientia NEXT cardis) OR (myocardial NEXT insufficien*) OR (cardiogenic NEXT shock*) OR (cardiac NEXT shock*) OR (cardiovascular NEXT shock*) OR (heart NEXT shock*) OR (ventricle NEXT failure*) OR (ventricle NEXT overload*)):ti,ab,kw
#9
#7 OR #8
Concept 4:
#10
[mh "cerebrovascular accident"]
#11
((cerebrovascular NEXT accident*) OR (cva) OR (cerebrovascular NEXT lesion*) OR (stroke*) OR (brain NEXT vascular NEXT accident*) OR (intracranial NEXT embolism*) OR (intracranial NEXT thrombosis) OR (intracranial NEXT arteriosclerosis) OR (brain NEXT infarct*) OR (intracranial NEXT atherosclerosis) OR (cerebr* NEXT vascular NEXT accident*) OR (focal NEXT cerebral NEXT vasculopath*) OR (cerebral

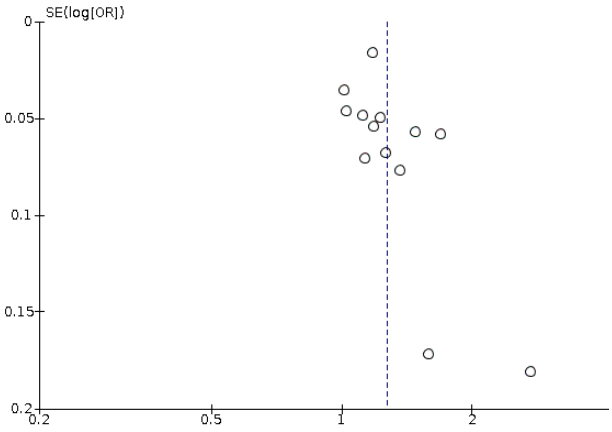
NEXT apoplex*) OR (brain NEXT blood NEXT flow NEXT disturbance*) OR (brain NEXT accident*) OR (brain NEXT attack*) OR (brain NEXT insult*) OR (brain NEXT isch*mic NEXT attack*) OR (cerebral NEXT insult*) OR (cerebral NEXT vascular NEXT insufficien*) OR (cerebrovascular NEXT arrest*) OR (cerebrovascular NEXT failure*) OR (cerebrovascular NEXT injur*) OR (cerebrovascular NEXT insufficien*) OR (cerebrovascular NEXT insult*) OR (isch*mic NEXT cerebral NEXT attack*) OR (isch*mic NEXT seizure*) OR (cerebral NEXT artery NEXT occlusion*) OR (vertebral NEXT artery NEXT stenosis*) OR (basilar NEXT artery NEXT obstruction*) OR (occlusive NEXT cerebrovascular NEXT disease)):ti,ab,kw
#12
#10 OR #11
Concept 5:
#13
[mh "peripheral vascular disease"]
#14
[mh "peripheral occlusive artery disease"]
#15
[mh "arteriosclerosis"]
#16
((peripheral NEXT angiopath*) OR (phlebiti*) OR (peripheral NEXT arterial NEXT disease*) OR (peripheral NEXT occlusive NEXT artery NEXT disease*) OR (atherosclerosis) OR (atherosclerotic NEXT disease*) OR (arterial NEXT occlusive NEXT disease*) OR (artery NEXT occlusion*) OR (blood NEXT vessel NEXT occlusion*) OR (claudication*) OR (arteriosclerosis) OR (arter* NEXT disease*) OR (blood NEXT vessel NEXT calcification*) OR (microangiopath*) OR (macroangiopath*) OR (vasculitis) OR (peripheral NEXT arteriopath*) OR (peripheral NEXT blood NEXT vessel NEXT disease*) OR (peripheral NEXT vascular NEXT disease*) OR (peripheral NEXT vascular NEXT disorder*) OR (peripheral NEXT vasculopath*) OR (peripheral NEXT vessel NEXT disease*) OR (hemangiopath*) OR (isch*mic NEXT vasculopath*) OR (thrombophlebitis) OR (deep NEXT venous NEXT thrombus) OR (vascular NEXT disease*) OR (vascular NEXT disorder*) OR (vascular NEXT disturbance*) OR (vascular NEXT path*) OR (vasculopath*) OR (artery NEXT disease*)):ti,ab,kw
#17
#13 OR #14 OR #15 OR #16
Concept 6:
#18
[mh "thromboembolism"]
#19
((thromboemboli*) OR (thrombosis) OR (thrombotic NEXT event*) OR (thrombo NEXT occlusive NEXT disease*) OR (thrombotic NEXT disease*) OR (thrombotic NEXT occlusion*) OR (embolism*) OR (thrombo NEXT embol*) OR (atherothrombosis) OR (thrombo NEXT obliterative NEXT disease*)):ti,ab,kw
#20
#18 OR #19
COMBINEREN:
#21
#6 OR #9 OR #12 OR #17 OR #20
#22
#3 AND #21

Appendix Bias assessment

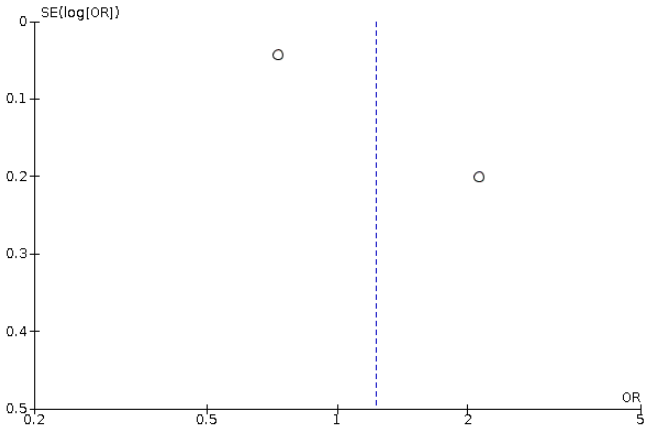


Appendix Funnel plots

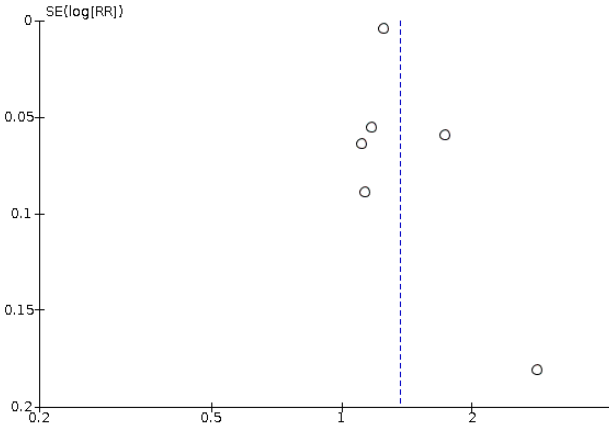
Funnel plot: OR of IHD in IBD



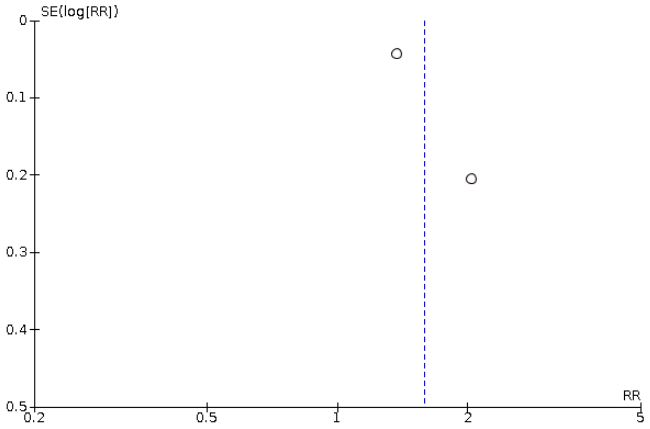
Funnel plot: OR of HF in IBD



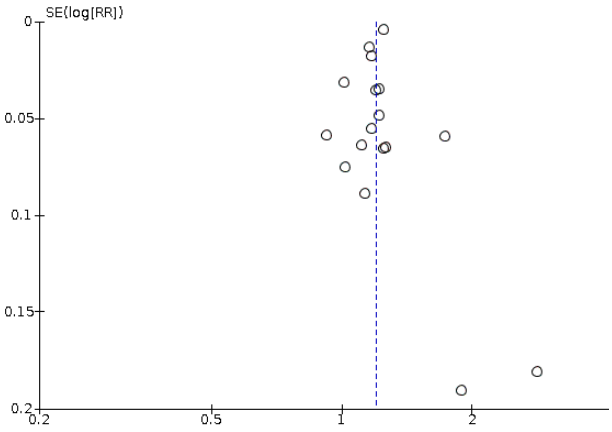
Funnel plot: aRR of IHD in IBD



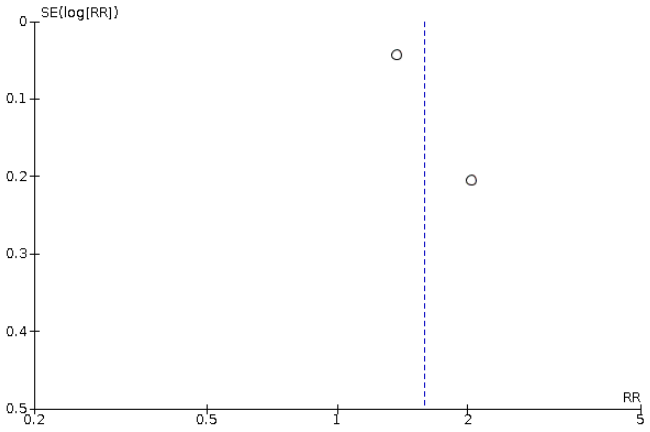
Funnel plot: aRR of HF in IBD



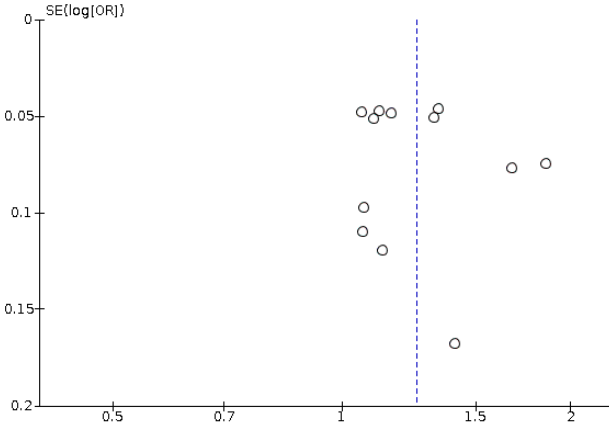
Funnel plot: pooled RR of IHD disease in IBD



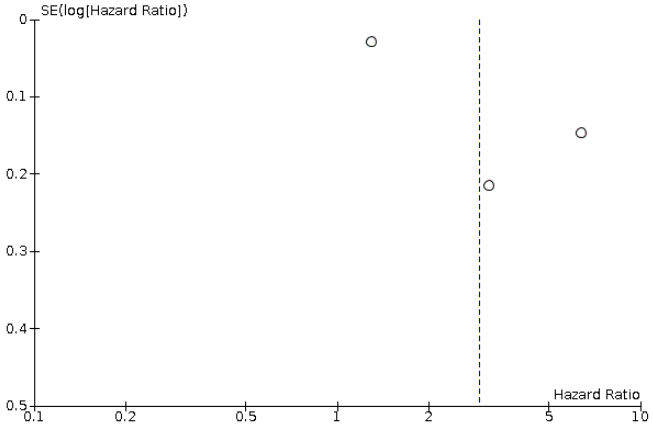
Funnel plot: pooled RR of HF in IBD



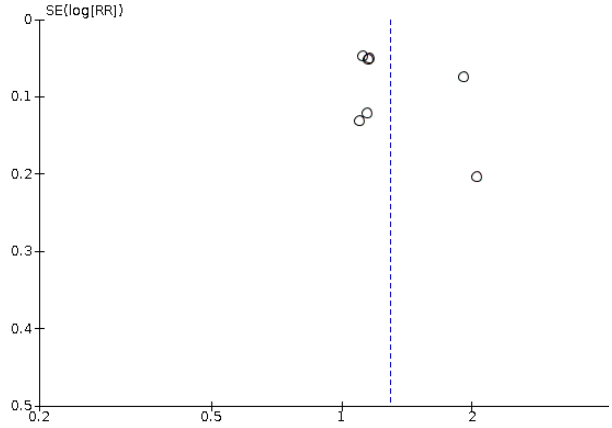
Funnel plot: OR of CVA in IBD



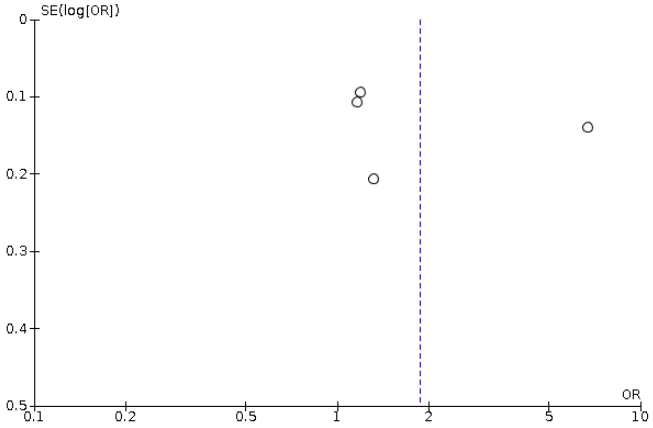
Funnel plot: aHR of PAD in IBD



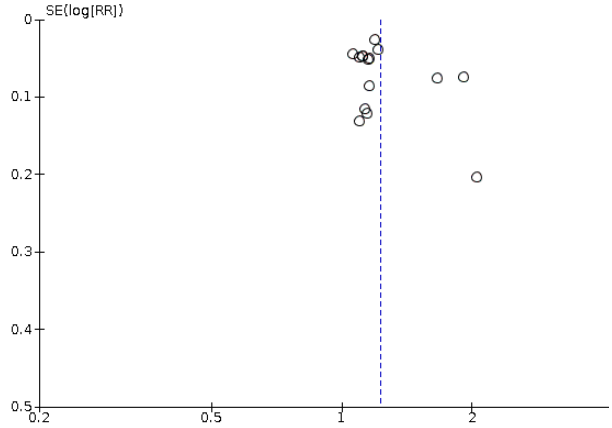
Funnel plot: aRR of CVA in IBD



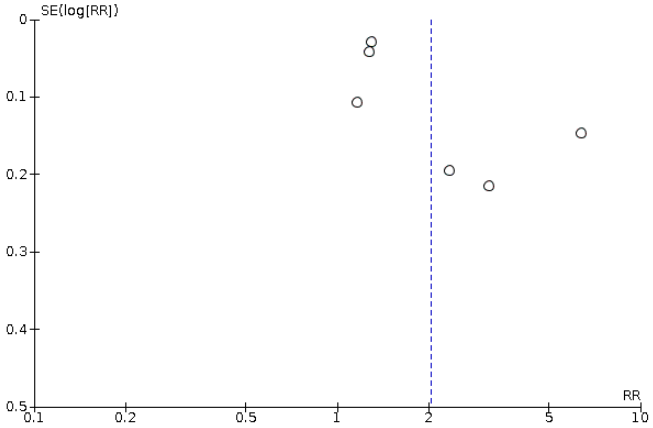
Funnel plot: OR of PAD in IBD



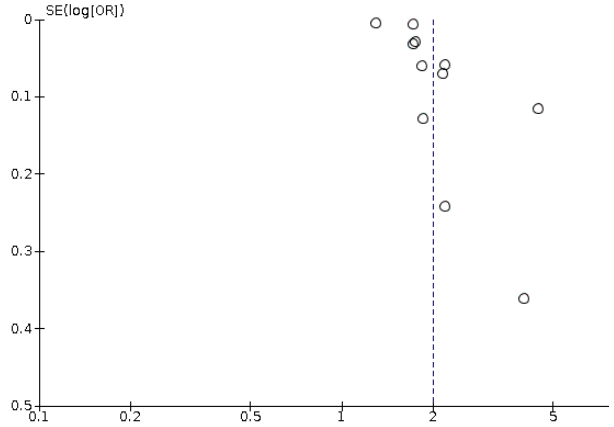
Funnel plot: pooled RR of CVA in IBD



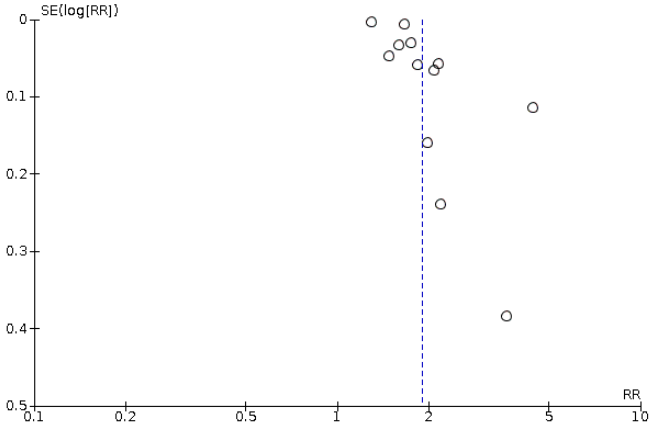
Funnel plot: pooled RR of PAD in IBD



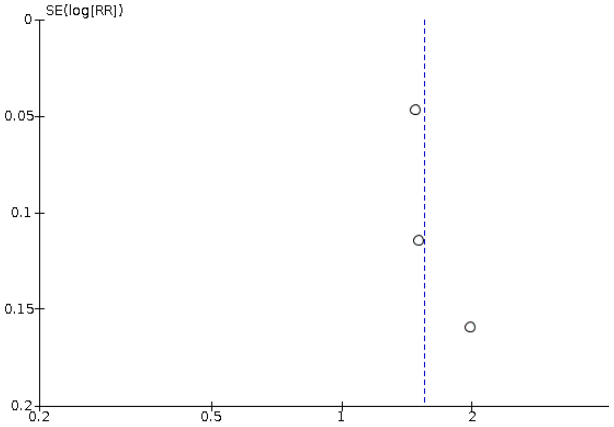
Funnel plot: OR of VTE in IBD



Funnel plot: pooled RR of VTE in IBD



Funnel plot: aRR of VTE in IBD

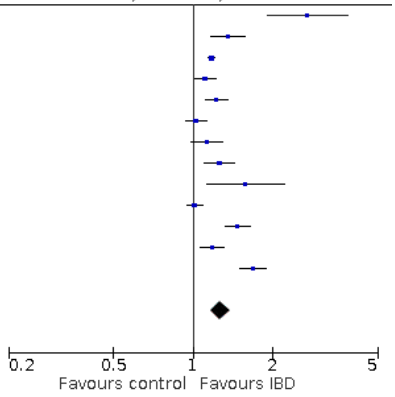


Appendix Sensitivity analyses restricted to studies with adjusted or unadjusted estimates

Unadjusted effect of inflammatory bowel disease on ischemic heart disease.

Study or Subgroup	IBD Events	IBD Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Aniwan et al. 2018	75	736	59	1472	3.6%	2.72 [1.91, 3.87]
Baena-Diez et al. 2018	174	9544	12841	952489	7.4%	1.36 [1.17, 1.58]
Card et al. 2016	5175	56097	22287	280382	9.6%	1.18 [1.14, 1.21]
Card et al. 2020	532	31175	2369	154412	8.7%	1.11 [1.01, 1.23]
Choi et al. 2019	586	37477	1437	112431	8.6%	1.23 [1.11, 1.35]
Close et al. 2015	607	15658	2343	61882	8.7%	1.02 [0.94, 1.12]
Dregan et al. 2014	320	19831	568	39662	7.7%	1.13 [0.98, 1.30]
Dregan et al. 2017	234	4153	21857	483559	7.8%	1.26 [1.10, 1.44]
Haapamaki et al. 2010	62	2831	79	5662	3.8%	1.58 [1.13, 2.21]
Ha et al. 2009	1068	17487	4219	69948	9.1%	1.01 [0.95, 1.09]
Kristensen et al. 2013	365	20795	2389	199978	8.3%	1.48 [1.32, 1.65]
Osterman et al. 2011	390	25327	3096	237592	8.4%	1.18 [1.07, 1.32]
Tsai et al. 2014	434	11822	1045	47288	8.3%	1.69 [1.51, 1.89]
Total (95% CI)		**252933**		**2646757**	**100.0%**	**1.27 [1.17, 1.38]**
Total events	10022		74589			

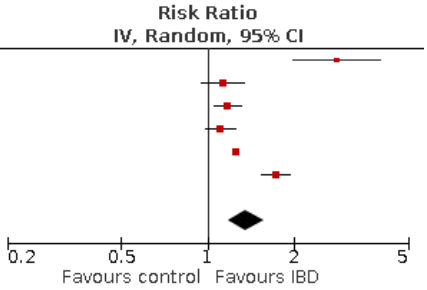
Heterogeneity: Tau² = 0.02; Chi² = 112.38, df = 12 (P < 0.00001); I² = 89%
Test for overall effect: Z = 5.60 (P < 0.00001)



Adjusted effect of inflammatory bowel disease on ischemic heart disease.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Aniwan et al. 2018	1.0367	0.1804	9.1%	2.82 [1.98, 4.02]
Dregan et al. 2014 (1)	0.1222	0.0885	15.8%	1.13 [0.95, 1.34]
Kristensen et al. 2013	0.157	0.0552	18.5%	1.17 [1.05, 1.30]
Osterman et al. 2011 (2)	0.1044	0.0636	17.8%	1.11 [0.98, 1.26]
Panhwar et al. 2019	0.2231	0.0041	20.6%	1.25 [1.24, 1.26]
Tsai et al. 2014	0.5481	0.0594	18.2%	1.73 [1.54, 1.94]
Total (95% CI)			**100.0%**	**1.36 [1.18, 1.57]**

Heterogeneity: Tau² = 0.03; Chi² = 56.45, df = 5 (P < 0.00001); I² = 91%
Test for overall effect: Z = 4.22 (P < 0.0001)

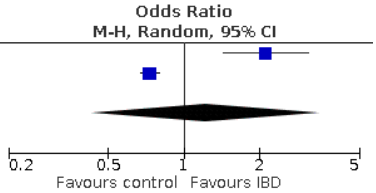


Footnotes
(1) Only UC included
(2) Only UC included

Unadjusted effect of inflammatory bowel disease on heart failure.

Study or Subgroup	IBD Events	IBD Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Aniwan et al. 2018	53	736	52	1472	48.3%	2.12 [1.43, 3.14]
Kristensen, Ahlehoff et al. 2014	553	23681	171405	5412966	51.7%	0.73 [0.67, 0.80]
Total (95% CI)		**24417**		**5414438**	**100.0%**	**1.22 [0.43, 3.47]**
Total events	606		171457			

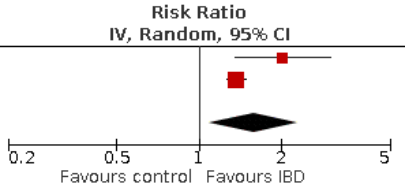
Heterogeneity: Tau² = 0.55; Chi² = 26.90, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 0.38 (P = 0.71)



Adjusted effect of inflammatory bowel disease on heart failure.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Aniwan et al. 2018	0.708	0.2044	37.1%	2.03 [1.36, 3.03]
Kristensen, Ahlehoff et al. 2014	0.3148	0.0427	62.9%	1.37 [1.26, 1.49]
Total (95% CI)			**100.0%**	**1.59 [1.09, 2.30]**

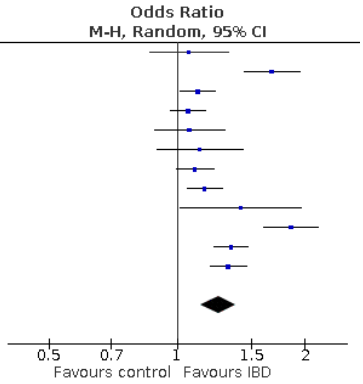
Heterogeneity: Tau² = 0.06; Chi² = 3.55, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 2.43 (P = 0.02)



Unadjusted effect of inflammatory bowel disease on cerebrovascular accidents.

Study or Subgroup	IBD Events	IBD Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Andersohn et al. 2010	89	8054	1670	161078	6.9%	1.07 [0.86, 1.32]
Baena-Diez et al. 2018	177	9544	10665	952489	8.4%	1.67 [1.44, 1.94]
Card et al. 2020	555	31175	2464	154412	9.6%	1.12 [1.02, 1.23]
Choi et al. 2019	595	37477	1681	112431	9.6%	1.06 [0.97, 1.17]
Dregan et al. 2014	164	19831	307	39662	7.5%	1.07 [0.88, 1.29]
Dregan et al. 2017	72	4153	7425	483559	6.5%	1.13 [0.90, 1.43]
Ha et al. 2009	496	17487	1804	69948	9.5%	1.10 [1.00, 1.22]
Huang et al. 2014	568	18392	1965	73568	9.6%	1.16 [1.06, 1.28]
Keller et al. 2014	53	516	155	2063	4.8%	1.41 [1.02, 1.96]
Keller et al. 2015	283	3309	636	13236	8.5%	1.85 [1.60, 2.14]
Kristensen, Lindhardsen et al. 2014	549	24499	3974	236275	9.7%	1.34 [1.22, 1.47]
Kristensen et al. 2013	454	20795	3327	199978	9.5%	1.32 [1.19, 1.46]
Total (95% CI)		**195232**		**2498699**	**100.0%**	**1.25 [1.14, 1.38]**
Total events	4055		36073			

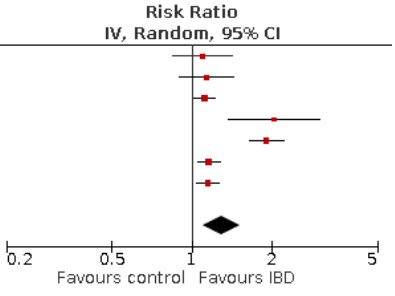
Heterogeneity: Tau² = 0.02; Chi² = 76.05, df = 11 (P < 0.00001); I² = 86%
Test for overall effect: Z = 4.55 (P < 0.00001)



Adjusted effect of inflammatory bowel disease on cerebrovascular accidents

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Andersohn et al. 2010	0.0953	0.1315	12.2%	1.10 [0.85, 1.42]
Dregan et al. 2014 (1)	0.131	0.1206	12.9%	1.14 [0.90, 1.44]
Huang et al. 2014	0.1133	0.0477	17.0%	1.12 [1.02, 1.23]
Keller et al. 2014	0.7154	0.2029	8.4%	2.05 [1.37, 3.04]
Keller et al. 2015	0.6471	0.0747	15.7%	1.91 [1.65, 2.21]
Kristensen, Lindhardsen et al. 2014	0.1484	0.0508	16.9%	1.16 [1.05, 1.28]
Kristensen et al. 2013	0.1398	0.0513	16.9%	1.15 [1.04, 1.27]
Total (95% CI)			**100.0%**	**1.29 [1.11, 1.52]**

Heterogeneity: Tau² = 0.04; Chi² = 48.95, df = 6 (P < 0.00001); I² = 88%
Test for overall effect: Z = 3.20 (P = 0.001)

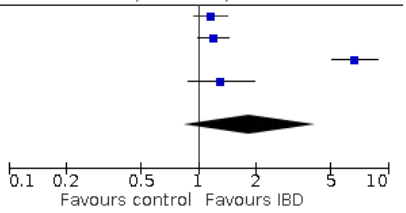


Footnotes
(1) Only UC included

Unadjusted effect of inflammatory bowel disease on peripheral artery disease.

Study or Subgroup	IBD Events	IBD Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Ha et al. 2009	115	17487	397	69948	25.3%	1.16 [0.94, 1.43]
Lin et al. 2015	148	11067	491	43765	25.4%	1.19 [0.99, 1.44]
Tsai et al. 2015	137	9363	83	37452	25.0%	6.69 [5.09, 8.79]
Yang et al. 2019	55	7256	42	7256	24.2%	1.31 [0.88, 1.96]
Total (95% CI)		**45173**		**158421**	**100.0%**	**1.87 [0.84, 4.14]**
Total events	455		1013			

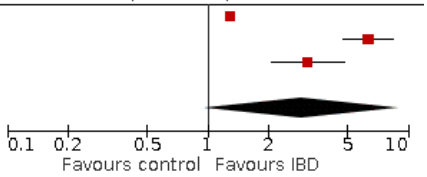
Heterogeneity: Tau² = 0.64; Chi² = 124.54, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.54 (P = 0.12)



Adjusted effect of inflammatory bowel disease on peripheral artery disease.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Lin et al. 2015	0.2546	0.0285	34.1%	1.29 [1.22, 1.36]
Tsai et al. 2015	1.8453	0.1465	33.4%	6.33 [4.75, 8.44]
Yang et al. 2019	1.1487	0.2141	32.6%	3.15 [2.07, 4.80]
Total (95% CI)			**100.0%**	**2.93 [0.95, 9.03]**

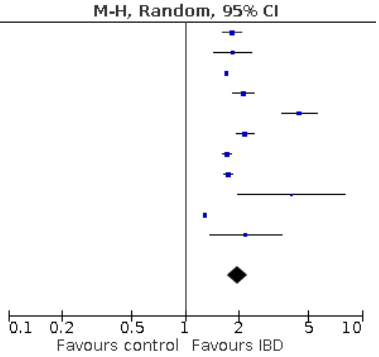
Heterogeneity: Tau² = 0.97; Chi² = 128.59, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.88 (P = 0.06)



Unadjusted effect of inflammatory bowel disease on venous thrombo-embolism risk.

Study or Subgroup	IBD Events	IBD Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Chu et al. 2018	383	23046	970	106795	10.4%	1.84 [1.64, 2.08]
Chung et al. 2015	90	11445	195	45780	8.1%	1.85 [1.44, 2.38]
Cohen et al. 2020	28155	374315	2029915	44748771	11.3%	1.71 [1.69, 1.73]
Dregan et al. 2017	217	4153	12131	483559	10.1%	2.14 [1.87, 2.46]
Grainge et al. 2010	139	13756	165	71672	8.6%	4.42 [3.53, 5.55]
Ha et al. 2009	446	17487	830	69948	10.5%	2.18 [1.94, 2.45]
Kappelman et al. 2011	1181	49799	6646	477504	11.1%	1.72 [1.62, 1.83]
McCurdy et al. 2020	1632	81900	4267	371964	11.1%	1.75 [1.65, 1.86]
Miehsler et al. 2003	38	618	10	618	2.7%	3.98 [1.97, 8.07]
Saleh et al. 2011	43000	2932000	10421000	918570000	11.4%	1.30 [1.28, 1.31]
Weng et al. 2018	21	3178	96	31780	4.7%	2.20 [1.37, 3.53]
Total (95% CI)		**3511697**		**964978391**	**100.0%**	**1.99 [1.74, 2.27]**
Total events	75302		12476225			

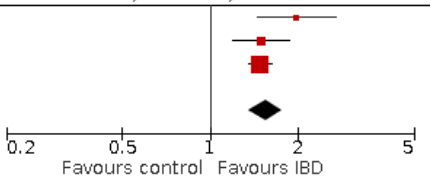
Heterogeneity: Tau² = 0.04; Chi² = 1504.69, df = 10 (P < 0.00001); I² = 99%
Test for overall effect: Z = 10.08 (P < 0.00001)



Adjusted effect of inflammatory bowel disease on venous thrombo-embolic risk.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Chung et al. 2015 (1)	0.6831	0.1589	15.1%	1.98 [1.45, 2.70]
Kappelman et al. 2011	0.4055	0.1139	25.1%	1.50 [1.20, 1.88]
Nguyen et al. 2008 (2)	0.392	0.0469	59.8%	1.48 [1.35, 1.62]
Total (95% CI)			**100.0%**	**1.55 [1.36, 1.77]**

Heterogeneity: Tau² = 0.01; Chi² = 3.09, df = 2 (P = 0.21); I² = 35%
Test for overall effect: Z = 6.44 (P < 0.00001)



Footnotes
(1) Only DVT included
(2) Only CD included

Appendix Personal Reflection Author Pieter Jehoul

Almost three years ago I started my training in becoming a general practitioner. A necessity for graduating was the delivery of a thesis. And so, some months after the start of my program, we had to decide on which subject we would choose and whether we would work together. Since Joren and I knew each other for a long time and could get along well, we decided to collaborate. We picked a subject both of us were interested in and which we deemed useful for our medical field: the association between inflammatory bowel disease and cardiovascular diseases.

Having absolutely no experience in the field of systematic reviews, and in particular the statistics involved in meta-analysis, it was quite a challenge. Looking back, the process was very long.
Luckily we had a good guide in our promotors, who told us step by step what to do and how we could best approach problems. We had regular encounters to discuss progress, initially once every few months, but with the final deadline nearing sometimes only weeks apart.

If I recall correctly, the first meeting we had, was in Leuven, even in person(!). Later on, because of the covid pandemic, we had to rely on Zoom for our communication. This being very convenient because there was no need to travel, although for me it made it harder to express myself in this already difficult matter. It's pitiful we did not meet in person after that anymore, since it brings another dimension in the interaction.

My communication with Joren in this project was very fluent, there was no "barrier" between us. If one of us had any problems, we could easily go to each other with it. Right after each meeting with our promotors, we would typically call each other again to discuss what was said and to make arrangements on how to achieve targets. In my opinion we were both very committed to this project; we divided work equally.

In this reflection note I would also like to give more details on the steps followed for this project. There was put a lot of effort in this thesis, many hours and days went by in the making of it.
After reading some in-depth articles to better understand the subject, we started with the strategy to search for relevant articles. Because we wanted for sure not to miss any interesting study, we used four different databases: Pubmed, Embase, Web of Science and Cochrane. Because each of these required different operator words in their search string, and because we were generally unsure on how to handle this properly, we contacted the 2Bergen-learning centre to guide us on our way. They were very friendly and helpful, even giving us a step-by-step guide for each database.
After acquiring almost 7500 articles doing so, we used the Rayyan website to screen through each article; although the screening went fast, it nonetheless was a big job, as we did this in duplicate. Then, after full-text screening, we extracted all relevant information out of the articles, being a very tedious work, and put it into an excel grid.

From now on, things would become much more interesting, as all these loose numbers would be put in their context with each other. To get to this, it was time to dust off our statistical knowledge. This was the part the two of us were most afraid of, since making a meta-analysis was all new. Statistics were done on Revman, a useful program that requires some practice to work with it, whereafter it actually is quite easy to use.

For this reason we decided I would do the statistics part, whereas Joren would commit more to the writing of the final article. We for sure had some issues with finding the right way to compare outcome measures, as the included studies all used different units for their outcomes. Eventually, I ended up doing the statistics three times, but all worries were forgotten after the view of these beautiful forest plots...
Last step was the writing of the article itself and after multiple proof readings, the both of us were pleased with the result. Also the promotors seemed satisfied.

With this study, we demonstrated that patients with inflammatory bowel disease have a significantly higher risk on developing cardiovascular disorders, and thus it joins the already existing studies claiming so.

I am for sure pleased we could contribute and give something back to the medical field. This study has clinical relevance in the hospital setting, but also in my specialisation field, the general practice, as we encounter this patient group regularly. Although our study did not prove effectiveness of, for example, screening in this population, caution is advised. A more strict surveillance on other risk factors for cardiovascular disorders in the inflammatory bowel disease population might be necessary. To decide on policy plans, further research is definitely needed.

Appendix Personal Reflection Author Joren Verboven

Course of the masterpaper group process:

The course of our masterpaper process was generally slow-moving. Every stage turned out to be more time consuming than originally estimated. Our planning therefore needed to be updated repeatedly. At a certain moment in april 2021 (at the beginning of our last 1.5 year of HAIO training), I feared that the thesis would'nt be ready when the deadline arrived. After expressing my concern to our stagecoördinator, promotor and co-promotor the follow-up appointments were planned faster and more frequent, thereby keeping the project on tracks. Despite the stiff course, the result could be submitted in time.

The reason for the slow-moving and rather stiff course, I believe, lies in a lack of experience. My previous masterpaper was a literature research, while the current thesis consisted of a systematic review and meta-analysis. In other words this was my first encounter with this kind of research.
Our work started on 21/01/2020, when we first visited our promotor and co-promotor. Taking into account that our co-promotor already had experience in the research field of cardiovascular diseases, we chose a topic closely related. We searched the literature for effects of auto-immune diseases and inflammatory diseases on cardiovascular outcomes. Soon we noticed that articles of inflammatory conditions were more numerous than those concerning auto-immune disorders. Diving more deeply into this matter we saw that some inflammatory conditions like rheumatoid arthritis and lupus had already been investigated extensively, both showing a pronounced negative effect on cardiovascular health. Other inflammatory conditions however like Crohn and ulcerative colitis were less studied and showed inconsistent results. We decided to focus on this subject.

Next we concretised our research question (PECO). To start our search strategy, we were pointed to Paque Kristel of the 2Bergen Learning centre, who proved to be essential. Building and optimizing a search strategy was one of the most difficult and most underestimated stages of the process. The MesH terms/Emtree terms, the coding process (AND, OR, NOT, *, “, ‘, [ ]) and the adjustments to be able to fit our search string into different databases were all very labor intensive and time consuming.

At the same time we started working on a protocol. For our promotor as well as co-promotor it was of utmost importance to adhere as much as possible to the generally academically accepted and supported methodology and PRISMA guidelines (preferred reporting items for systematic review and meta-analysis). In this protocol we designed our systematic review and meta-analysis in detail. (Research question, studies of interest, participants, outcomes, inclusion/exclusion criteria, bias assessment, search method, selection process, data extraction, statistics and reporting.) Also this stage required next to the search strategy itself a great effort with a lot of studying, discussing, (re)writing, feedback, questions,… Eventually the protocol could be uploaded in the PROSPERO database around march 2021.

After conducting our search strategy we collected all resulting articles in Endnote X9 (bought via the KU Leuven). Duplicates were removed and the remaining articles were organized in folders. Then the selection process started in 2 phases based on the in- and exclusion criteria captured in the protocol. The first selection phase was based on title and abstract and happened simultaneously by two independent reviewers in the blinded setting of Rayyan. 7422 articles were screened like this before turning of de blinding and discussing discrepancies with our promotor. The same way of working was maintained in the second selection phase based on full article reading of 259 remaining articles. This immense work in combination with school tasks and a full time job were at times challenging to say the least, but we struggled through.

After the selection process the remaining 37 articles were subjected to a bias assessment using the Newcastle Ottawa Quality assessment scale for cohort studies and case-control studies. A flow diagram was set up to present the entire process visually. Then the data extraction could commence. All desired information (as captured by the protocol) was extracted and orderly placed in an excel file. Also this process was surprisingly time consuming. Once all data was collected the part I feared the most could start, statistics. As advised by our promotor we used the program Revman for executing our analysis. This I had never used before. Because statistics are definitely not my friend, my colleague Pieter Jehoul took this for the most part onto his account. For compensation I performed most of the writing when reporting our results in the final article.

Personal share:
In the final result, I as well as Pieter will each have a 50/50 share. A lot of the aforementioned stages we both needed to go through. Just for the part of statistics and writing there were different contributions. Pieter deepened himself into the statistical program and did most of the statistical analysis. This was necessary, because we worked with the desktop version of Revman and not the online version. We therefore could not work simultaneously on the statistical analysis. For compensation I then took most of the reporting, reference managing and finishing (according to the guidelines) onto my account.

Reflecting on the cooperation process, I would describe Pieter as being more of a procrastinator. He delivers most of his work as predetermined deadlines approach, while I like to have everything done quite in advance and according to schedule. This personal difference, may have caused me to harass Pieter sometimes. But generally this did not lead to conflict or a different work load.

Personal vision on the meaning of our work for the general practice:
Recent literature describes a trend where inflammatory conditions are revealed to have a negative effect on cardiovascular health. Patients with lupus and rheumatoid arthritis for example have already proven to be at increased risk for myocard infarction, stroke and thrombosis. With our paper we wanted to check whether patients with an inflammatory bowel disease, like Crohn and colitis ulcerosa, are also at risk and could possibly benefit from cardiovascular prevention.

Cardiovascular prevention is a core business of the general practitioner. Just think how much we concern ourselves with blood pressure, cholesterol medication, tackling of obesity with exercise and diet, sugar controls,… Especially with increasing age or accumulation of morbidity our attention for our core prevention task intensifies. With our research we would like to bring attention to the possible complications of inflammatory bowel disease and direct timely and appropriate preventive care to these patients. Further research is necessary and should investigate which screening methods and preventive measures prove to be efficient.

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