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Original Article

Incidence of Suicide in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

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Abstract

Background and Aims: Patients with inflammatory bowel disease (IBD) have higher incidence of psychosocial disorders, including depression. As suicide is the most severe manifestation of depression, we sought to identify if patients with IBD have a higher incidence of suicide through a systematic review and meta-analysis.

Methods: Systematic literature searches for articles using EMBASE and MEDLINE using Ovid were conducted to identify studies investigating suicide in IBD. Reference harvesting of the bibliographies of key articles was also performed. We included studies reporting expected number of death or standardized mortality ratio (SMR) for suicide in IBD. Meta-analysis for each IBD condition (Crohn's disease [CD] and ulcerative colitis [UC]) was conducted separately, as well as combined.

Results: Seven cohort studies were identified through our search strategy and included in our systematic review and meta-analysis. In our analysis, the SMR for suicide in patients with IBD for all studies included was 1.20 (95% CI, 0.94–1.54). The overall pooled SMR for CD and UC were 1.36 (95% CI, 0.98–1.88) and 1.16 (95% CI, 0.8–1.69) respectively.

Conclusions: Patients with Crohn's disease and ulcerative colitis may have an increased risk of suicide. These results highlight the importance physicians must place on ensuring the mental health of patients with IBD is both assessed and treated appropriately.

Keywords: *Inflammatory bowel disease; Meta-analysis; Suicide; Systematic review*

Abbreviations:

IBD,	inflammatory bowel disease;
UC,	ulcerative colitis;
CD,	Crohn's disease;
SMR,	standardized mortality ratio;
SR,	systematic review;
MA,	meta-analysis;
CI,	confidence interval;
NOS,	Newcastle-Ottawa Assessment Scale.

Inflammatory bowel disease (IBD) consisting of ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory gastrointestinal disorders, resulting from inappropriate immune response in genetically susceptible individuals (1). There are roughly 330,000 Canadians living with IBD in 2012, and the economic costs of the disease are estimated to be $2.8 billion in 2012 (2). Direct medical costs exceed more than $1.2 billion per annum, and indirect costs (society and patient costs) total $1.6 billion (2). The incidence of IBD appears to be

increasing with time and is the highest in Western nations with an estimated incidence of 20.2 per 100,000 for CD and 19.2 per 100,000 for UC in Canada, which is amongst the highest in the world (3). There is increasing literature that IBD causes significant psychological impairment including depression and decrease in quality of life in affected patients (4–7). Analysis of two Canadian national surveys showed that 17% of patients with IBD suffering from depression had suicidal ideation in the past 12 months (8). The most severe outcome in patients with depression is suicide, but the risk of suicide in patients with IBD is not clear. Considering its relative common prevalence and high economic burden, it would be pertinent to identify if patients with IBD had a higher incidence of suicide. The aims of this study were to determine the incidence of suicide in IBD patients and to determine if patients with IBD were more likely to die from suicide compared with control.

METHODS

This meta-analysis was conducted in accordance with the MOOSE guidelines for observational studies in epidemiology, and a PRISMA flow diagram is provided.

Search Strategy

We searched Medline (1987 to October 1, 2017) and EMBASE (1987 to October 1, 2017) to identify all studies evaluating the incidence of suicide inflammatory bowel disease. The following search strategy was used for MEDLINE on Ovid: 'ulcerative colitis.mp.' or 'crohn* disease*.mp.' or 'exp Enteritis' or 'enteritis.mp. or exp Inflammatory bowel diseases' or 'exp Colitis' or 'Colitis.mp.' and 'suicide.mp.' or 'exp suicide' or 'suicide attempt*.mp.' or 'Suicidal Ideation'. The search strategy for EMBASE on Ovid includes 'ulcerative colitis.mp.' or 'crohn* disease*.mp.' or 'exp enteritis' or 'enteritis.mp.' or 'exp Inflammatory bowel disease' or 'exp Colitis' or 'Colitis.mp.' and 'suicide.mp.' or 'exp suicidal behavior.mp.' or 'suicide attempt*.mp. or 'exp suicidal ideation'. Hand searching bibliographies of relevant reviews, guidelines and included articles and grey-literature search was subsequently performed to identify any further studies for inclusion.

Selection Criteria

Studies had to meet the following criteria for inclusion: (1) population cohort study, (2) published in English, (3) evaluated the standard mortality ratio of suicide (SMR) or expected number of deaths from suicide, (4) study population were above 18 years of age, (5) full manuscript provided and (6) studies published within the last 30 years. Pertinent information was requested from authors if it was felt that would impact study eligibility. If there was a suspicion of overlapping study populations, the larger study population was selected for inclusion. Different patient populations were ascertained from selected studies and verified to exclude overlap.

Data Extraction

Two reviewers (CZ and GB) independently reviewed the gathered citations from the search strategy to identify studies for full-text review. The selected articles were then selected for inclusion, and data was extracted utilizing a standardized data extraction form. Disagreement during the search review were mediated by a third reviewer (BB) and resolved by consensus. Data was extracted for the following variables: year of publication, country of origin, number of deaths from suicide, number of total deaths from all causes, method used to determine cause of death, number of study population, control population selection criteria, study population selection criteria and type and result of statistical analysis.

Assessment of Risk of Bias

The risk of bias was assessed with a funnel plot. Asymmetry of the funnel plot could represent the following: (1) reporting biases, (2) poor methodological quality, (3) true heterogeneity, (4) artifactual and (5) chance (9).

Data Synthesis and Statistical Analysis

Overall pooled estimates of the SMR were obtained using random effects (RE) meta-analysis. The SMR is the ratio between the observed number of deaths to the expected number of deaths (10). It is often used in cohort studies to look at a variety of different causes of death in a study population. The SMR specific for suicide was compiled from each study population. Meta-analysis for each IBD condition (CD and UC) was conducted separately and combined. Natural logarithms of the SMRs were used in the analysis, as it improves the normal approximation (11). Sensitivity analysis was performed in which studies with zero observed events were excluded from the analysis. The reason for the analysis was that the variance of SMR was undefined when it is zero and, therefore, cannot be included in the meta-analysis. We circumvented this by adding 'one' to both the observed deaths and expected deaths for studies with zero deaths and used the adjusted SMR in our analysis. This is analogous to the continuity correction used in meta-analysis of relative risk and odds ratio and is a commonly used ad hoc method in meta-analysis of SMR (12–15).

Gender-specific rates of suicide were investigated due to the known discrepancy rates of depression and suicide in male and female populations. Females have been shown to have higher rates of depression, but males tend to have a higher incidence of completed suicide (16, 17).

Given that the method for calculating the standard error and 95% confidence interval (CI) of SMR varied across studies, instead of using the reported values in each study, we derived the standard error of log SMR using the observed number of suicide (12). The 95% CI for log SMR was then constructed based on normal approximation and back-transformed for interpretation.

Assessment of Heterogeneity

Heterogeneity of the included studies in our analysis was assessed using Cochran's Q (18) and I^2 (19), for both the primary outcome analysis and the sensitivity analysis.

Assessment of Study Quality

We used the Newcastle-Ottawa Assessment Scale (NOS) to assess the methodological quality of included cohort studies (20). Each included study was evaluated based on three main categories including selection population, comparability and outcome. Scores of zero to three points, four to six points and seven to nine points were assessed low, moderate and high-quality studies, respectively.

RESULTS

Of the 508 records identified through our search, seven unique studies were determined eligible for our meta-analysis. A study flow diagram per PRISMA protocol is presented in Figure 1; a summary of all included trials is presented in Table 1.

Risk of Bias

Figure 2 presents the funnel plot for included studies. The funnel plot's scatter plot is symmetrical and suggests that there is minimal bias or between study heterogeneity among included studies (9).

Search Results and Study Description

Five-hundred eight citations were identified from our electronic database, and 10 citations identified from our search of the grey literature and hand searching of bibliographies; 19 citations were selected for full-text review (Figure 1). Following full text review, seven unique studies (21–24) were included for analysis. There were two studies (25, 26) that were excluded because they used odds ratio and hazard ratio instead of SMR. One systematic review (SR) was excluded from our analysis because the included studies did not meet our study criteria including date of publication and lack of reported SMR or expected number of deaths from suicide (27).

Table 1 lists the demographics of the included studies. All included studies looked at patients with IBD in western,

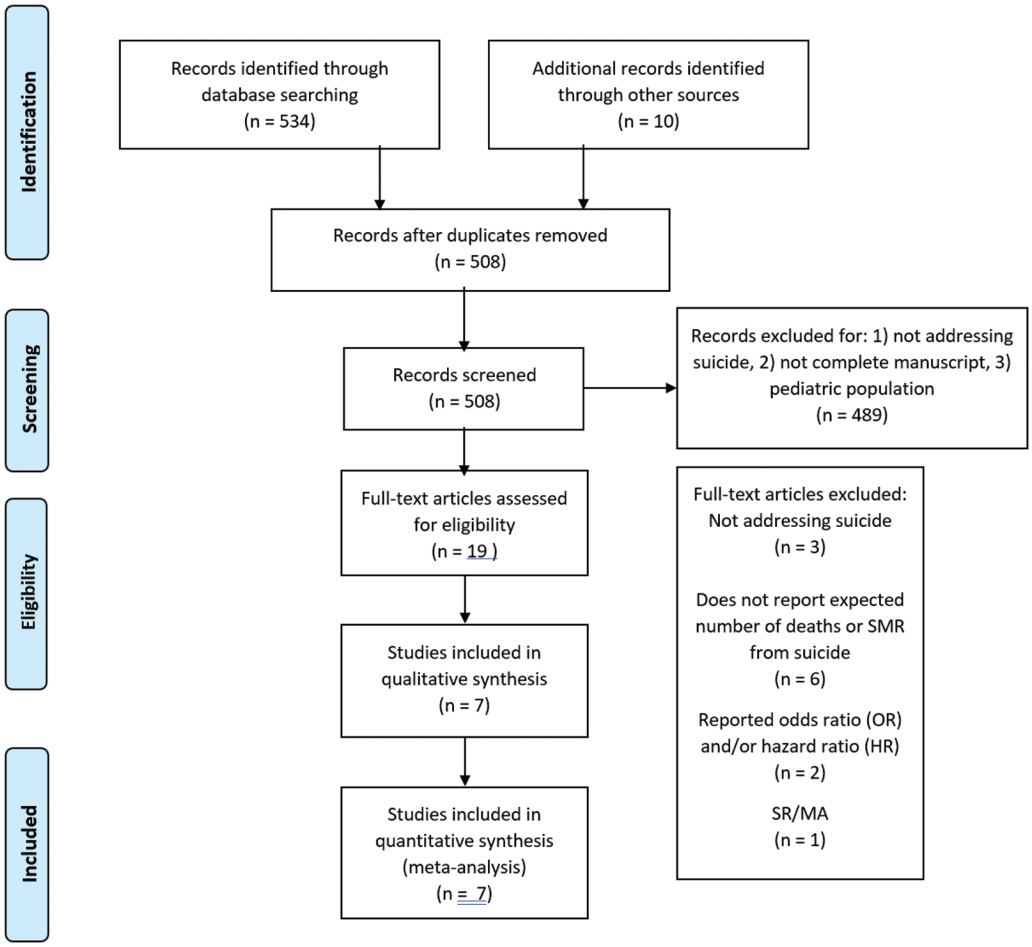

Figure 1. Flow diagram summarizing trial identification and selection.

Table 1. Descriptive statistic for characteristics of included studies

Author	Year	Country	Condition	Gender	Cohort size	No. of overall death	# of suicidal death
Winther et al	2003	Denmark	UC	M	541	145	4
Winther et al	2003	Denmark	UC	F	619	116	6
Jess et al	2006	USA	UC	M	212	36	1
Jess et al	2006	USA	UC	F	166	26	0
Jess et al	2006	USA	CD	M	155	30	0
Jess et al	2006	USA	CD	F	159	26	0
Persson et al	1996	Sweden	CD	M&F	1251	174	9
Persson et al	1996	Sweden	UC	M&F	1547	255	5
Jess et al	2002	Denmark	CD	M	157	39	0
Jess et al	2002	Denmark	CD	F	217	45	1
Ekbom et al	1992	USA	CD	M&F	1469	179	3
Ekbom et al	1992	USA	UC	M&F	2509	505	9
Jussila et al	2014	Finland	UC	M&F	16649	1805	55
Jussila et al	2014	Finland	CD	M&F	5315	439	20
Palli et al	1998	Italy	UC	M&F	689	47	3
Palli et al	1998	Italy	CD	M&F	231	23	1

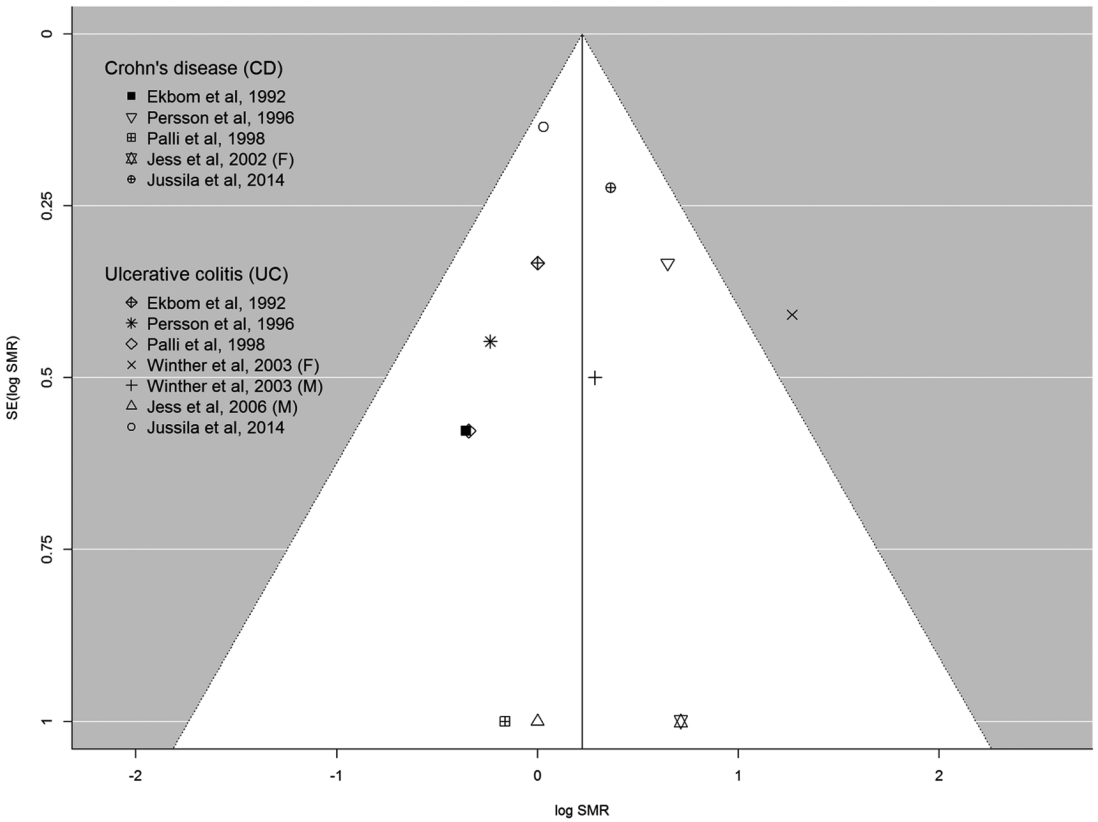

Figure 2. Funnel plot of the studies included in this study. Studies with no events observed were excluded due to undefined standard error. The unshaded area represents the region within which 95% of studies are expected to lie in the absence of both biases and heterogeneity (fixed effect summary log odds ratio ± 1.96 *standard error of summary log odds ratio). The solid vertical line corresponds to the SMR from the random effects model (10).

developed countries with no other ethnic representation from Eastern or developing nations. The control group in included studies were from national representative databases matched for age, ethnic and calendar year but did not include other demographics such as area code, socioeconomic status or underlying psychiatric comorbidities.

Mortality from Suicide

Figure 3 shows the seven included study populations reporting SMRs ranging from 0 (–) (19) to 3.55 (95% CI, 1.59–7.90) (21) for ulcerative colitis and from 0 (–) (22, 24) to 2.04 (95% CI, 0.29–14.48) (24) for Crohn's disease. In this analysis, we found evidence that IBD may be associated with an increased risk of suicide with a SMR for all studies included in this study of 1.20 (95% CI, 0.94–1.54). Three of out of eight study populations in CD reported an SMR greater than one (23, 24, 28), two out of eight study populations in CD reported an SMR less than one (28, 29) and three out of eight study populations in CD reported an SMR of zero (22, 24). The overall pooled SMR for CD showed an SMR of 1.36 (95% CI, 0.98–1.88). Three out of eight study populations in UC reported an SMR greater than one (21, 22, 28), two out of eight study populations in UC reported an SMR of one (23, 30), two out of eight study populations in UC reported a SMR of less than one (22, 28), and one of the eight study populations reported an SMR of zero (23). The overall pooled SMR for UC showed a SMR of 1.16 (95% CI, 0.8–1.69). These results show that the patients with either UC or CD have a tendency for higher risk of death from suicide compared with matched controls, although just short of statistical significance.

Analysis of our seven included studies based on gender was performed. The overall SMR for females with IBD was 2.05 (95% CI, 0.87–4.82). The overall SMR for females with CD from two studies (22, 24) was 1.30 (95% CI, 0.33–5.21). The overall SMR for females with UC from two studies (21, 22) was 2.29 (95% CI, 0.62–8.45). The overall SMR for males in CD was zero from two studies (22, 24) and 1.26 (95% CI, 0.52–3.02) in UC from two studies (21, 22).

Sensitivity Analysis

Figure 4 shows a sensitivity analysis that excluded studies with zero SMR. The overall SMR for CD and UC in our sensitivity analysis was 1.41 (95% CI, 1.01–1.97) and 1.10 (95% CI, 0.81–1.50), respectively. The overall SMR for all included studies was 1.19 (95% CI, 0.94–1.51).

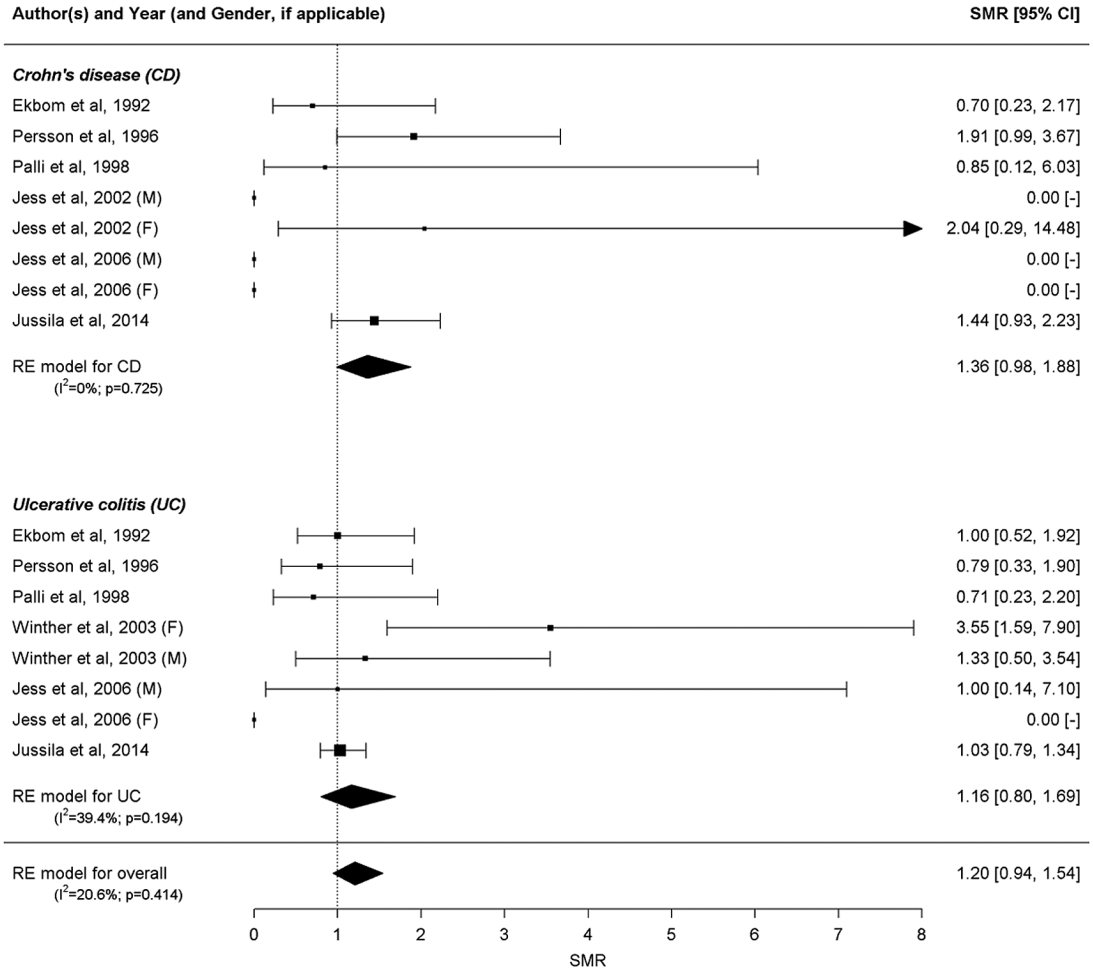

Figure 3. SMR with 95% confidence intervals for all study population, together with the random effects pooled SMR. Heterogeneity testing (I^2, P value from Cochrane's Q) shown for each analysis.

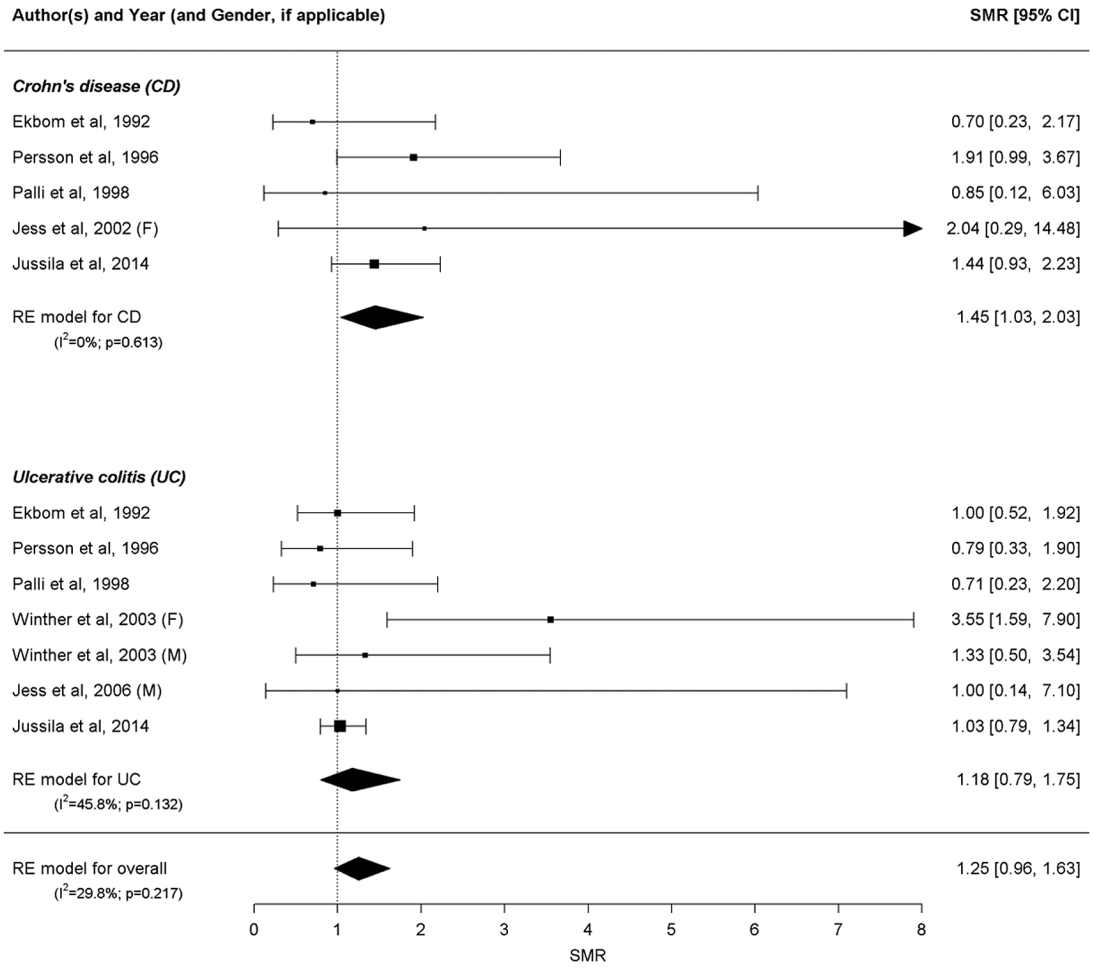

Figure 4. Sensitivity analysis: SMR with 95% confidence intervals for all study population excluding studies with SMR of zero, together with the random effects pooled SMR. Heterogeneity testing (I^2, P value from Cochrane's Q) shown for each analysis.

Heterogeneity Analysis

Figure 3 shows heterogeneity analysis for studies included in our primary analysis for CD and UC. I^2 and the P value from the Cochrane's Q test for CD and UC was I^2=0%, p=0.725 and I^2=39.4% and p=0.194, respectively. Heterogeneity analysis for the both CD and UC showed I^2=20.6%, p=0.414.

In our sensitivity analysis (Figure 4), I^2 and Cochrane's Q (p) for CD and UC was I^2=0%, p=0.613 and I^2=45.8% and p=0.132, respectively. Heterogeneity analysis for the both CD and UC showed I^2=29.8%, p=0.217.

Assessment of Study Quality

The quality of included studies was assessed using the NOS scale. Six of the seven studies scored a seven on the NOS scale, and one of the seven studies scored an eight. An NOS score above six is considered a high-quality study (20). The NOS score was reviewed with both CZ and TL to limit personal bias.

DISCUSSION

This is the first systematic review and meta-analysis to assess the incidence of suicide in IBD. The rate of depression and other psychiatric comorbidities have been identified to be greater in patients with IBD (4–7), but there is scarce literature on suicide in the IBD population. Since IBD is relatively common (3) and has a high economic burden (2), the importance of identifying the prevalence of suicide in patients with IBD is crucial as it is a possible preventable death. Suicide is the second leading cause of mortality among 15- to 24-year old individuals in Canada, and suicide-related behaviors had a cost of 2.4 billion in 2004 (31).

The primary objective in this meta-analysis was to identify if patients with either UC or CD were more likely to die from suicide compared with control. The SMR from included population cohort studies was obtained and analyzed in our study. The SMR for suicide in CD was higher than UC in our study, and both CD and UC had a SMR for suicide greater than one. The 95% confidence interval for SMR in both CD and UC included the null value, implying non-statistical significance. These results indicate that patients with IBD had a trend toward increased mortality from suicide. The 95% confidence intervals were reasonably wide, so the possibility of no association cannot be ruled out, but the possibility of a substantial association also cannot be excluded. This may be due to our study being

underpowered, or there is no real association between IBD and increased suicide. Our sensitivity analysis, which excluded study populations with no suicidal deaths in the IBD groups, did show a significant effect, but this analysis may be biased by specifically excluding studies where there was no evidence of risk in the affected groups.

It is known in the literature that females tend to have higher incidence of depression compared with males (17). However, men have a suicide rate that is 3.0 to 7.5 times that of women (16). Our analysis of gender-specific study population showed that the overall SMR for CD and UC in females was higher compared with men. This suggests that the increased risk of suicide is higher in females suffering from IBD compared with men, but the wide confidence interval cannot allow this conclusion to be certain.

Our study has highlighted the potentially devastating impact that IBD has on the mental health of patients afflicted with the disease. It has been shown in the literature that patients suffering from IBD (5–8, 32–34) suffer from greater rates of depression and other psychiatric disorders compared with the general public. The risk factors identified for increased risk of depression in IBD include female gender, aggressive and active disease, surgery and hospitalization (7, 33).

The quality of the individual cohort population studies was high per their NOS score (20). We have also identified several limitations in the available literature. The death records showing mortality from suicide most likely underestimate the number of suicides as they may be identified as an unknown or other cause. The methods in which suicide was identified among patients with IBD were heterogeneous across the studies since the death records from different countries were unique in terms of the method used to qualify deaths. As all the studies used in this meta-analysis were cohort studies, limitations intrinsic to the study design include absence of data on potential confounding factors, difficulty in identifying an ideal comparison group and lack of identifying temporal relationships. Two case-control studies also investigated the risk of suicide in IBD (25, 26). However, we could not combine the results of the cohort and case-control studies in the same meta-analysis.

The increased incidence of depression in patients with IBD is well established and may affect more than just quality of life. Our study highlights the importance of routine psychiatric assessment in patients suffering from IBD. Screening for and treatment of psychiatric symptoms should be an integral part of the medical assessment in patients with IBD, but recent literature suggests this is not occurring (34). There is evidence that the course of disease in IBD is worse in depressed patients compared with those who are not (35). A recent systematic review/meta-analysis (SR/MA) showed that psychological therapies including cognitive behavioural therapy may have a beneficial effect on depression scores and quality of life in patients with IBD (33). Patients with IBD respond positively to antidepressants (36). Therefore, the importance of identifying psychiatric complaints in patients with IBD is even more important as there may be effective therapies.

In summary, patients with Crohns' disease and ulcerative colitis may have an increased risk of suicide. The increased rate of depression in patients with IBD is well established from the literature, but this is the first SR/MA to investigate the incidence of suicide in IBD patients. Further direction would be collect additional data to more clearly define this apparent association. Lastly, the value for routine psychiatric screening and treatment options in patients with IBD at risk for suicide must be explored.

Supplementary Data

Supplementary data are available at *Journal of the Canadian Association of Gastroenterology* online.

Acknowledgements

BB and CZ contributed to the study concept and design. CZ, GB and DG contributed to the acquisition of data. CZ, TL and BB contributed to the interpretation of data. CZ, TL and BB contributed to the drafting of manuscript. TL and JS contributed to the statistical analyses. All authors commented on and approved the final draft of the manuscript. This study received no financial support.

Conflicts of Interest

Chaoran Zhang, Glynis Byrne, Terry Lee, Joel Singer, Dean Guistini have no conflicts of interest to declare. Brian Bressler is an advisor/speaker for Shire, Pfizer, Merck, Ferring, Janssen, Abbvie, Takeda, Actavis and Genentech; he is an advisor for Pendopharm, Allergan, Amgen, Celgene and has received research support from Janssen, Abbvie, Takeda, Atlantic Pharmaceuticals, GSK, BMS, Amgen, Genentech, Merck, RedHill Biopharm, BI, Qu Biologic, Celgene and Alvine; he has stock options in Qu Biologic.

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