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Anxiety But Not Depression Predicts Poor Outcomes in Inflammatory Bowel Disease

Neeraj Narula MD MPH FRCPC[1]
Maria Ines Pinto-Sanchez MD MSc[1]
Natalia Causada Calo MD[1]
Alexander C. Ford MD[2]
Premsyl Bercik MD PhD[1]
Walter Reinisch MD[3]
Paul Moayyedi MB ChB PhD MPH[1]

[1] Department of Medicine (Division of Gastroenterology) and Farncombe Family Digestive Health Research Institute; McMaster University, Hamilton ON, Canada
[2] Leeds Gastroenterology Institute, St. James's University Hospital, and Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK
[3] Division of Gastroenterology and Hepatology, Medical University of Vienna, Austria.

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Guarantor of the article: Neeraj Narula

Please address correspondence to:
Dr. Neeraj Narula, McMaster University
1280 Main St W, Unit 3V28
Hamilton, ON, L8S 4K1
Canada
Neeraj.narula@medportal.ca

Specific author contributions:
Neeraj Narula - study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; statistical analysis
Maria Ines Pinto-Sanchez – study concept; acquisition of data; drafting of the manuscript
Natalia Causada Calo – study concept; acquisition of data; drafting of the manuscript
Alexander Ford - study concept;acquisition of data; drafting of the manuscript
Premsyl Bercik - study concept, drafting of the manuscript
Walter Reinisch – study concept, design and supervision; drafting of the manuscript
Paul Moayyedi – study concept, design and supervision; drafting of the manuscript

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Abstract

Background and Aims: Patients with inflammatory bowel disease (IBD) have high rates of psychiatric co-morbidities, but it is not clear whether those with co-morbidities are at higher risk of poor outcomes. We aimed to determine whether patients with IBD who have co-existing anxiety and/or depression are more likely to have poor IBD-related outcomes compared with IBD patients without anxiety and/or depression.

Methods: This was a prospective longitudinal follow-up study in Ontario, Canada, from 2008-2016. Patients were asked to complete questionnaires at the time of initial assessment, including the Hospital Anxiety and Depression Scale (HADS). We selected a number of clinical variables at the time of presentation and tested their ability to predict subsequent poor IBD-related outcomes, such as IBD-related hospitalization, emergency room visits, and recurrent courses of corticosteroids over the duration of follow-up. Logistic regression was used for multivariate analysis.

Results: 414 IBD patients completed the baseline questionnaire. Among them, 125 had anxiety and/or depression at baseline. Factors that predicted poor IBD-related outcomes during longitudinal follow-up included increased severity of disease at initial presentation, prior IBD-related surgery, longer duration of follow-up, and elevated C-reactive protein at time of initial presentation. After adjustment for potential covariates, IBD patients with abnormal anxiety sub-scores had poor IBD-related outcomes compared with those without elevated anxiety sub-scores (OR 3.36, 95% CI 1.51-7.48). No difference in IBD-related outcomes were observed in those with abnormal depression sub-scores compared with those without elevated depression scores (OR 0.43, 95% CI 0.14-1.32).

Conclusions: Severe disease, anxiety, and previous IBD-related surgery predict poor IBD-related outcomes in patients in the future. Closer monitoring with regular follow-up may be appropriate for patients with these risk factors.

Keywords: HADS; depression; anxiety; inflammatory bowel disease; Crohn's disease; UC; ulcerative colitis

Background

Inflammatory bowel diseases (IBD) include Crohn's disease (CD) and ulcerative colitis (UC). These are both inflammatory conditions of the gastrointestinal tract characterized by unpredictable periods of relapse and remission. Over 1 million US residents and 2.5 million Europeans are estimated to have IBD [1]. IBD leads to substantial direct and indirect costs to health care systems and society, as it has been associated with higher risks of surgery, hospitalization, cancer, mortality, disability, and work impairment [2]. Half of the total cost of IBD care is driven by approximately 10% of the patients [3], therefore strategies to identify patients at high-risk of poor outcomes, and therefore increased costs, may help clinicians determine where to focus limited resources.

Patients with IBD have higher rates of anxiety and depression compared with the general population [4]. Depression in IBD patients is associated with decreased quality of life [5]. Further, anxiety and/or depression may lead to poor treatment compliance, higher morbidity, and higher mortality in patients with other chronic medical illnesses [6, 7]. We aimed to evaluate whether patients with IBD who have co-existing anxiety and/or depression are more likely to have poor IBD-related outcomes, including hospitalization, emergency room visits, and recurrent use of corticosteroids.

Methods

The sampling frame for this prospective longitudinal follow-up study were patients aged ≥16 years who consulted for the first time for any gastrointestinal indication at the McMaster University Digestive Diseases clinic or St Joseph's Hospital, both in Hamilton, Ontario, Canada between 2008 and 2016. Pediatric patients who will eventually require adult care are referred for transition visits once they reach the age of 16 or 17, so these patients were not discriminated based on age. During this period, 5,978 new patients attended our center. Study participation was offered to all new patients immediately before their consultation with the gastroenterologist. From them, 4,217 (70.5%) patients agreed to participate. Those who expressed their willingness to participate were asked to complete self-administered questionnaires, which collected data on sociodemographics, gastrointestinal symptoms, anxiety, and depression. In order to be able to generalize our results, no exclusion criteria were applied. Results from the current database were published by our group [8-11]. The population used in this study from the database was the subpopulation of patients with an existing diagnosis of IBD at presentation who had $\geq$1 year of follow-up data available.

Patients were asked to complete symptom data using the Rome III diagnostic questionnaire for adult functional GI disorders and the Hospital Anxiety and Depression Scale (HADS)[12, 13]. All questionnaire data were entered into a database by a trained researcher who was not involved with the clinical care of the patient. At the time of the initial assessment, we collected information on the baseline severity of IBD, whether the patient had prior IBD-related surgery, if the C-reactive protein (CRP) was elevated ($\geq$5 mg/L) at the time of initial assessment, and whether the patient was using biologics or immunomodulators. Baseline severity of IBD was determined according to the initial physician assessment of the patient. Physician assessment is based on patient symptom burden, endoscopy, and imaging reports where available. Data on occurrence of poor IBD-related outcomes were collected prospectively by a separate trained researcher who was blinded to the Rome III diagnostic questionnaire and HADS results. Poor IBD-related outcomes were defined as emergency room visits for IBD flares, hospitalization for IBD, or requiring two or more courses of systemic steroids within 1 year of follow-up due to relapse of disease. The Hamilton Health Sciences and St Joseph's Health Care research ethics boards approved the study and all patients signed a study informed consent.

Statistical analysis:

Patient characteristics were described using proportions for categorical variables. Continuous data were presented as mean with standard deviations for parametric distributions, and median with interquartile ranges for non-parametric distributions. A chi-square test was used to compare categorical variables between patients who had abnormal anxiety and/or depression scores at baseline, according to the HADS, compared with those who did not have anxiety or depression. Patients were considered to have an abnormal anxiety score based on the HADS anxiety (HAD-A) subscore of 11 or more or an abnormal depression score based on the HADS depression (HAD-D) subscore of 11 or more [14]. Logistic regression was used for multivariate analysis. All subjects with missing values with respect to the outcome variables were excluded from the analysis. Analysis was done using SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Prior knowledge in combination with forward selection was used to develop a logistic regression model. The significance level for entry into the model was set to 0.05. Variables which were forced into the model included a diagnosis of anxiety based on the HAD-A subscore and depression based on the HAD-D subscore. The correlation coefficient between these two variables was low (r=0.33) so it was decided to

include both variables in the model. The remaining variables selected on prior clinical knowledge for consideration in the forward selection model included age (dichotomized to under age 40 and age 40 and over), smoking status (present vs ex- or never smoker), presence of regular alcohol use, education level (highest accomplished is college or higher vs. secondary school or lower), family history of IBD, baseline severity of IBD according to physician impression (severe, moderate, mild, remission), elevated CRP at baseline ($\geq$5), history of prior IBD related surgery, duration of follow-up (in years), and biologic or immunomodulator use at the time of questionnaire completion. Interaction terms were also explored in case there was a relationship between disease severity and HAD-A subscore or HAD-D subscore . The forward selection model was then applied to determine predictors or confounders that had a significant relationship with poor IBD-related outcomes. Among the variables not selected by the forward selection algorithm (non-candidate variables), each was added into the model one at a time to determine if they showed significance once added back in to the model. Significance was considered to be present when the coefficient p-value was less than 0.05 after insertion back into the model. If the standard error of another variable increased by more than 20% when the non-candidate variable was added, the non-candidate variable was considered to be collinear and was removed from the model. The variables included in the final model are presented along with each beta coefficient, p-value, and the corresponding odds ratios (ORs) for the primary outcome.

Results

Baseline Characteristics

Of the 4127 new patient referrals, 414 (9.8%) had a history of IBD. Of these, 125 (30.2%) had elevated anxiety and/or depression sub-scores at baseline (HADS anxiety or depression subscore$\geq$11). Among these patients, 29 (7%) patients had both elevated anxiety and depression sub-scores at baseline, 79 (19%) patients had only elevated anxiety sub-score, and 17(4%) had only elevated depression sub-score at baseline. The mean age of patients included was 38.2 years (standard deviation (SD) 16.3). The median HADS anxiety subscore was 7 (interquartile range (IQR) 8) and the median HADS depression subscore was 3 (IQR 6). Table 1 details baseline characteristics, which were similar between those who had elevated anxiety and/or depression sub-score at baseline compared with those who did not, with the exception of current smoker status (29.6% among those with elevated anxiety and/or depression sub-score at baseline vs. 14.2% in those without, p=0.0002). The mean duration of follow-up in the group with elevated anxiety and/or depression scores was 4.1 years (SD 2.6) compared to 3.8 years (SD 2.7) in the group without abnormal scores (p=0.35). Table 2 details comparisons between those who

had anxiety only, depression only, or both anxiety and depression. Significant differences were only seen for the proportions with regular alcohol consumption (p=0.03) and higher educational status (p=0.01).

Moderate or severe disease was present in 47.8% of patients at the time of initial assessment according to endoscopy, imaging, and/or physician judgement. The median CRP of IBD patients included was 3 mg/L (IQR 10). Patients with moderate or severe disease at study entry had a trend towards more co-existing psychiatric morbidity at baseline. Moderate to severe anxiety and/or depression was present in 37.1% of patients with moderate or severe disease activity at the index visit compared with 27.1% in patients with mildly active disease or disease in remission (p=0.06).

Predictors of Poor IBD-related Outcomes

The unadjusted OR for subsequent poor IBD-related outcomes for those with elevated anxiety sub-scores at baseline compared with those with normal anxiety sub-scores was 2.46 (95% confidence interval (CI): 1.44-4.19) and for those with elevated depression sub-scores at baseline compared with those with normal depression sub-scores was 1.53 (95% CI: 0.73-3.20). After adjustment for potential covariates, the OR for poor IBD-related outcomes remained significant among those with elevated anxiety sub-scores compared with those without (3.36, 95% CI 1.51-7.48). After adjustment for other covariates, the odds of poor IBD-related outcomes for those with elevated depression sub-scores at time of questionnaire completion was not significantly different than the odds of those with normal depression sub-scores (OR 0.43, 95% CI 0.14-1.32). Table 3 contains a list of all potential confounders included in the final logistic regression model. The forward selection model selected baseline severity of disease, prior IBD-related surgery, longer duration of follow-up, and elevated CRP at baseline as other variables with a significant association with poor IBD-related outcomes, when adjusted for other covariates. Neither of the interaction terms explored was selected by the model.

Among the variables not selected by the forward selection algorithm (non-candidate variables), each was added into the model one at a time to determine if there was any association with poor IBD-related outcomes, once added back in to the model. No variables were found to be significant after this was performed.

Using all predictors selected by the model, as well as anxiety and depression, we examined the association of each of these predictors with each of the poor IBD-related outcomes individually. Results

from this multivariate analysis are presented in Table 4. Prior IBD-related surgery and longer duration of follow-up were significant predictors of both IBD-related hospitalization and one or more ER visits during the course of follow up, when adjusted for other covariates. Baseline elevated CRP was independently associated with recurrent courses of corticosteroids, when adjusted for other covariates. Although there was increased odds of IBD-related hospitalization, ER visits, and recurrent courses of corticosteroids, in those who had elevated anxiety sub-score at baseline, the relationship with any of these outcomes was not significant when examined individually.

In order to determine if poor IBD outcomes were more likely to be seen in patients with increasing anxiety, the HADS anxiety subscore at baseline was divided into equal quartiles. The frequency of patients likely to experience poor IBD outcomes in each quartile is depicted in Figure 1. More patients experienced poor IBD-related outcomes as the quartiles increased (Mantel-Haenszel Chi-Square Test of linear trend p=0.0015). In the highest quartile (HADS score >11), 48.1% of patients experienced a poor IBD-related outcome, which was more than quartile 1 (22.2%), quartile 2 (29.1%), and quartile 3 (30.9%).

Discussion:

In this study, we showed that severity of disease, elevated CRP, previous IBD-related surgery, longer duration of follow-up, and increased anxiety sub-score at baseline were independent predictors of poor IBD-related outcomes during subsequent follow-up. Chronic diseases such as IBD lead to a high burden of care for health care systems and for society [15]. Emergency room visits and hospitalizations are two important drivers of direct costs when it comes to cost of care for patients with IBD [16, 17]. Corticosteroid use has also been significantly associated with future high health care use [18], is an indicator of poor disease control, and early use has been associated with disabling disease and hospitalization in patients with IBD [19, 20]. Predictive factors of patients at high risk of these poor outcomes would be helpful for clinicians to target management strategies towards, in order to direct limited resources to try and limit these costs [21].

Results of this study showed that an elevated anxiety sub-score at baseline is an independent predictor of poor IBD-related outcomes, when adjusted for other covariates. Further, quartile analysis revealed that patients in the highest quartile of baseline anxiety score were significantly more likely to experience poor IBD-related outcomes. Psychiatric illnesses are common in patients with IBD, with a reported

prevalence of depression of 26-30% and anxiety of 21-31% [22-24]. Other studies have demonstrated psychiatric symptoms are more common in patients with active IBD [24]. Our study also found a trend towards more psychiatric co-morbidity in those with moderate or severe IBD. Severity of disease and elevated CRP at baseline were also found to independently predict poor IBD-related outcomes, suggesting that patients with more active disease were more likely to seek emergency room care, require hospitalization, or require multiple courses of corticosteroids subsequently.

Prior IBD-related surgery was found to be a significant predictor of poor IBD-related outcomes. Patients with ulcerative colitis who undergo colectomy often continue to incur disability and require more sick days compared with patients with UC who did not have colectomy, or to the general population [25]. Patients with CD who previously required surgery may have a more severe phenotype, such as fistulizing, penetrating, or perianal disease. There may be some selection bias present in patients with prior IBD-related surgery who are being referred to a tertiary care center for management, as these patients may have developed recurrence or are not responding to conventional therapies. Longer duration of follow-up was also found to be an independent predictor of poor outcomes. Although the average duration of follow-up was similar between the group of patients with and without elevated anxiety and/or depression sub-scores at baseline (table 1), outcomes of interest are more likely to occur in patients who have longer follow-up duration, as has been in observed in other observational studies [26, 27]. As such we included this variable in our multivariate regression to adjust for the impact of increased follow-up duration.

A number of other studies have previously examined the association between psychological co-morbidity and IBD outcomes, but many are limited by being retrospective or cross-sectional [28-30], or are prospective but with only a short duration of follow-up [31]. A large database study suggested an association of mood and IBD recurrence, but was limited by use of clinical disease activity indices as the sole measure of disease activity, and thus may have overestimated the relationship between mood and longitudinal disease activity [32], given than low mood has been shown to influence the future development of functional gastrointestinal disorders [33]. One of the strengths of this study is the prospective collection of certain data at the first patient visit to our tertiary care hospital. This includes use of the HADS questionnaire, which identifies patients with active symptoms of anxiety or depression at the time of assessment, instead of depending on prior history of psychiatric illness, which may be unreliable. The relatively large sample size of this study also allowed us to explore the association of

many predictor variables with the poor IBD-related outcomes, as well as perform quartile analysis for patients based on their anxiety sub-scores. This study also used objective measures of disease activity (i.e. elevated CRP), rather than just reliance on patient-reported symptoms as a measure of severity, which may be present for reasons other than active inflammation [34, 35]. Another strength of this study includes blinding of the researcher who collected and inputted questionnaire data and the researcher who reviewed patient charts in order to judge the occurrence of poor IBD-related outcomes. Lastly, the mean duration of follow-up was approximately 4 years, longer than the only other study of similar design in this field, which also demonstrated a relationship between antecedent psychological co-morbidity and the subsequent development of objective markers of disease activity in patients with IBD [36]. This provided us with the maximum opportunity to examine the association between elevated anxiety or depression scores and poor IBD related outcomes.

Limitations of this study include the fact that assessment of anxiety and depression was based on the HADS score, and did not require a formal assessment by a psychiatric professional. Severity of disease was assessed objectively when possible, i.e. based on endoscopic or imaging severity, but this was not uniformly performed, so required investigator judgement when objective test results were not available. Although we expect most health care utilization to occur within our local health integration network (LHIN), we are limited in the ability to determine utilization that occurred outside of our LHIN, unless it was specifically documented in the provider notes or medical records obtained from outside hospitals, and these were available in the patient charts. In addition, CD and UC were analyzed together as IBD due to the limited sample size, and to enable sufficient power for determining predictors. Further, we did not find a significant relationship between depression and poor IBD-related outcomes, but this may also have been insufficiently powered.

The findings of this study suggest assessment of HADS at baseline should be considered to identify those with anxiety, since these patients may be at higher risk for poor IBD-related outcomes. At a minimum, closer monitoring with regular follow-up may be appropriate for these patients in order to prevent poor outcomes. Consideration should be given to changing our treatment paradigms as a whole, as strategies that only deal with management of inflammation will not deal with all the possible contributing factors to an aggressive disease course and poor outcomes for patients. Further studies are needed to examine whether early psychiatric referral for these patients helps minimize poor outcomes for these patients.

Table 1: Baseline Characteristics of patients			
Variable	**Anxiety and/or Depression at Baseline n=125**	**No Anxiety or Depression n=289**	**P-value**
Male Gender, n (%)	53 (42.4)	129 (44.6)	0.17
Age $\geq$ 40, n (%)	54 (43.2)	118 (40.8)	0.20
Higher Education, n (%)	77 (61.6)	197 (68.2)	0.20
Past Medical History			
Disease Duration, Years (Median, IQR)	4.0 (11.0)	4.0 (12.5)	0.11
Crohn's disease, n (%)	73 (58.1)	154 (53.3)	0.43
Behavior of disease for those with Crohn's disease			0.15
Non-stricturing, non-penetrating (B1) , n (%)	57 (78.1)	114 (74.0)	
Stricturing (B2) , n (%)	13 (17.8)	17 (11.0)	
Penetrating (B3) , n (%)	3 (4.1)	23 (14.9)	
Ulcerative colitis	52 (41.6)	135 (46.7)	0.23
Behavior of disease for those with ulcerative colitis			0.71
proctitis (E1) , n (%)	5 (9.6)	20 (14.8)	
left-sided colitis (E2) , n (%)	15 (28.8)	20 (14.8)	
pancolitis (E3) , n (%)	32 (61.5)	95 (70.4)	
Current Smoker, n (%)	37 (29.6)	41 (14.2)	0.0002
Regular Alcohol Use, n (%)	61 (48.8)	170 (58.8)	0.0581
Family History of IBD, n (%)	48 (38.4)	104 (36.0)	0.64
Disease features			
Previous Luminal Surgery for CD , n (%)	24 (32.9)	40 (26.0)	0.73
Baseline Severity of Disease, n (%)			0.23
Remission	26 (20.8)	39 (13.5)	
Mild	46 (36.8)	95 (32.9)	
Moderate	34 (27.2)	104 (36.0)	
Severe	19 (15.2)	51 (17.6)	
Elevated CRP at initial assessment, n (%)	54 (43.2)	106 (36.7)	0.33
Treatment Regimen			
Currently using biologic therapy, n (%)	18 (14.4)	37 (12.8)	0.66
Currently using immune modulator, n (%)	11 (8.8)	42 (14.5)	0.11

Table 2: Comparison of patients with anxiety and depression, anxiety only, and depression only

Variable	Anxiety and Depression n=29	Anxiety Only n=79	Depression Only n=17	P-value
Male Gender, n (%)	12 (41.4)	34 (43.0)	7 (41.2)	0.62
Age $\geq$ 40, n (%)	14 (48.3)	34 (43.0)	6 (35.3)	0.69
Higher Education, n (%)	18 (62.1)	54 (68.4)	5 (29.4)	0.01
Past Medical History				
Disease Duration, Years (Median, IQR)	3.6 (8.0)	5.0 (11.0)	3.0 (4.0)	0.11
Crohn's disease, n (%)	15 (51.7)	46 (58.2)	12 (70.6)	0.46
Current Smoker, n (%)	8 (27.6)	24 (30.4)	5 (29.4)	0.54
Regular Alcohol Use, n (%)	12 (41.4)	45 (57.0)	4 (23.5)	0.03
Family History of IBD, n (%)	11 (37.9)	30 (38.0)	7 (41.2)	0.58
Disease features				
Previous Luminal Surgery for CD , n (%)	2 (13.3)	15 (32.6)	3 (25.0)	0.31
Baseline Severity of Disease, n (%)				0.07
Remission	8 (27.6)	15 (19.0)	3 (17.6)	
Mild	14 (48.3)	26 (32.9)	6 (35.3)	
Moderate	2 (6.9)	26 (32.9)	6 (35.3)	
Severe	5 (17.2)	12 (15.2)	2 (11.8)	
Elevated CRP at initial assessment, n (%)	12 (41.4)	32 (32.1)	10 (66.7)	0.11
Treatment Regimen				
Currently using biologic therapy, n (%)	7 (24.1)	10 (12.7)	1 (5.9)	0.25
Currently using immune modulator, n (%)	1 (3.4)	6 (7.6)	4 (23.5)	0.15

Table 3: Odds ratios for predictors of poor IBD-related outcomes

Parameter	Unadjusted Odds ratio	Adjusted Odds Ratio	95% Confidence interval for Adjusted Odds Ratio		P-value
Anxiety at baseline	2.46	3.36	1.51	7.48	0.003
Depression at baseline	1.53	0.43	0.14	1.32	0.14
Severity of disease at baseline	1.88	1.46	1.01	2.10	0.04
Prior IBD-related surgery	4.49	5.25	2.49	11.09	<.001
Duration of follow-up	1.32	1.50	1.20	1.88	<.001
Elevated CRP at baseline	2.62	3.23	1.53	6.85	0.002

Table 4: Multivariate analyses of predictors for IBD-related hospitalization, ER visits, or recurrent corticosteroid use

	IBD-related hospitalizations			IBD-related ER visits			Recurrent Courses of corticosteroids		
Predictors	**Odds Ratio**	**95% Confidence interval**		**Odds Ratio**	**95% Confidence interval**		**Odds Ratio**	**95% Confidence interval**	
Anxiety at baseline	1.64	0.53	5.06	1.95	0.60	6.39	1.42	0.51	3.92
Depression at baseline	0.97	0.22	4.25	1.29	0.27	6.24	0.27	0.05	1.37
Severity of disease at baseline	1.17	0.72	1.91	0.98	0.59	1.62	1.49	0.95	2.36
Prior IBD-related surgery	8.66	2.94	25.53	13.93	4.15	46.71	1.03	0.39	2.74
Elevated CRP at baseline	2.64	0.92	7.61	1.63	1.17	2.26	5.68	2.10	15.37
Duration of follow-up	1.77	1.28	2.44	1.63	1.17	2.26	1.29	0.99	1.69

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STROBE Statement—Checklist of items that should be included in reports of **cohort studies**

	Item No	Recommendation	Page reference
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5

		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			

Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.