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**Severe adverse events associated with thiopurine therapy in inflammatory bowel disease: A retrospective cohort study from a tertiary centerInflammatory Bowel Disease: A Retrospective Cohort Study from a Tertiary Center**

Authors:
Luís Enrique Frisancho, Eduard Brunet-Mas, Belén García Sagué, Luigi Melcarne, Laura Patricia Llovet Soto, Anna Puy Guillen, María José Ramirez Lázaro, Albert Villoria Ferrer, Xavier Calvet, Sergio Lario

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# Severe Adverse Events Associated with Thiopurine Therapy in Inflammatory Bowel Disease: A Retrospective Cohort Study from a Tertiary Center

## Study population

**We reviewed 722 adult patients with Inflammatory bowel disease (IBD)** who received **thiopurine** therapy.

Those who developed a **severe adverse event (SAE) were included.**

Patients with mild or moderate adverse events were not included.

## Methods

Descriptive, **retrospective** observational **cohort study**. Hospital Parc Taulí in Sabadell, Spain.

Variables included were demographic data, disease characteristics, thiopurine dose and length of treatment, adverse event characteristics and clinical outcomes.

## Outcomes

Eighty-one patients (11.2%) experienced a SAE.

The **most frequent SAE were acute pancreatitis and myelotoxicity**.

**Neoplasias** accounted for **16%** of all SAE **after a median follow-up of 15.2 years,** being lymphoma the most common.

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# Severe adverse events associated with thiopurine therapy in inflammatory bowel disease: A retrospective cohort study from a tertiary center

Luis Enrique Frisancho[a*], Eduard Brunet-Mas[a,b*], Belén García-Sagué[a], Luigi Melcarne[a], Laura Patricia Llovet[a], Anna Puy[a], María José Ramirez-Lazaro[a,b] , Albert Villoria[a,b,c], Xavier Calvet[a,b,c†], Sergio Lario[a,b†]

[a] Servei d'Aparell Digestiu. Parc Taulí Hospital Universitari. Institut d'Investigació i Innovació Parc Taulí (I3PT-CERCA). Sabadell, Catalunya, Department de Medicina, Universitat Autònoma de Barcelona

[b] CIBERehd, Instituto de Salud Carlos III.

[c] Departament de Medicina. Universitat Autònoma de Barcelona.

*Both authors contributed equally to this work.

†Both authors contributed equally as senior authors to this work.

**Address for correspondence:**

Eduard Brunet Mas, MD, PhD.

Servei de Malalties Digestives. Hospital de Sabadell.

Departament de Medicina. Universitat Autònoma de Barcelona.

CIBEREHD – Instituto de Salud Carlos III

Parc Taulí, 1. 08208 Sabadell (Barcelona), Spain

e-mail: eduardbrunet91@gmail.com

**Abbreviations list:** inflammatory bowel disease (IBD), ulcerative colitis (UC), Crohn's disease (CD), azathioprine (AZA), 6-mercaptopurine (6-MP), thiopurine methyltransferase (TPMT), Estudio Nacional en Enfermedad Inflamatoria Intestinal sobre Determinantes Genéticos y Ambientales (ENEIDA), confidence intervals (CI), Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), REporting of studies Conducted using Observational Routinely-collected Data (RECORD).

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**ABSTRACT**

**Background and aim of the study**: Thiopurines are cornerstone immunosuppressants for maintenance therapy in inflammatory bowel disease, but their use is limited by potentially serious adverse events. The aim of this study is to characterize severe adverse events associated with thiopurine therapy in a cohort of inflammatory bowel disease patients treated at a tertiary care center.

**Methods**: A retrospective observational study was conducted including adult inflammatory bowel disease patients who developed clinically significant adverse events while on thiopurine therapy. Demographic, disease-related, treatment, and outcome variables were collected. Quantitative variables were expressed as means and standard deviations; categorical variables as percentages with 95% confidence intervals. Statistical significance was defined as $p < 0.05$.

**Main results**: Among 722 inflammatory bowel disease patients treated with thiopurines, 81 (11.2%) experienced at least one severe adverse event. Of these, 24 (30%) required hospitalization, and 2 deaths (2.5%) were attributed to thiopurine-associated malignancies. The most frequent adverse events were acute pancreatitis in 31 patients (38.3%), myelotoxicity in 19 (23.4%), malignancies in 13 (16.0%), and hepatotoxicity in 6 (7.4%). Infections and fever of unknown origin were less common, with 3 cases each (3.7%). No statistically significant associations were observed between adverse events occurrence and sex ($p = 0.36$), IBD subtype ($p = 0.21$), or thiopurine type (azathioprine vs. 6-mercaptopurine; $p = 0.09$).

**Conclusions**: Thiopurine therapy in inflammatory bowel disease is associated with a notable incidence of severe adverse events, particularly acute pancreatitis and myelotoxicity. No consistent demographic or clinical predictors of toxicity were identified, highlighting the importance of universal monitoring strategies during

thiopurine treatment.

**Keywords***:* Inflammatory bowel disease. Thiopurines. Azathioprine. Adverse events.

## STATEMENT OF INTERESTS

- Eduard Brunet-Mas has served as a speaker and consultant for Janssen and Chiesi, Kern, Takeda and Alfasigma.
- Albert Villoria has served as a speaker and consultant from for MSD and Abbvie.
- Luigi Melcarne has served as a speaker and consultant from for MSD, Abbvie, Janssen, Takeda, Pfizer and Tillots.
- Luis Enrique Frisancho, Belen Garcia-Sagué, Laura-Patricia Llovet, Anna Puy, Sergio Lario and Maria José Ramirez-Lazaro have no conflicts of interest to declare.
- Xavier Calvet has received grants for research from Abbott, MSD, and Vifor, and fees for advisory board services form Abbott, MSD, Takeda and Vifor. He has also given lectures for Abbott, MSD, Takeda, Shire and Allergan.

## DATA AVAILABILITY STATEMENT

Data supporting the study findings are available from the corresponding author upon request

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## INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disease encompassing ulcerative colitis (UC), Crohn's disease (CD), and unclassified IBD. Over recent decades, its incidence has risen sharply in industrialized countries (1).

The primary goal of IBD treatments is to induce and maintain remission, which has been shown to prevent complications and improve patients' quality of life (2). Multiple therapeutic options are available, including immunosuppressive agents. Treatment decisions should be guided by patient characteristics, disease severity, prior therapies, potential adverse effects, and patient preferences (1,3).

Thiopurines—azathioprine (AZA) and 6-mercaptopurine (6-MP)—are purine analogues with immunosuppressive properties. Their effect is mediated through intracellular conversion to 6-thioguanine nucleotides, which interfere with DNA mismatch repair, leading to apoptosis and suppression of lymphocyte proliferation (4,5). Thiopurines have been the most widely used immunosuppressants for maintenance therapy in IBD (6). However, their therapeutic effect may take up to three months to become apparent (4), making them unsuitable for induction therapy (5,7–9). Remission maintenance rates of up to 76% have been reported (9).

The major limitation of thiopurine therapy is its adverse effect profile, both short- and long-term. Adverse effects occur in approximately 15% of patients, ranging from 5% to 30% across studies (6), and lead to treatment discontinuation in up to 10% of cases (4,6). A recent retrospective study from New Zealand reported treatment discontinuation in 25% of patients, with hepatotoxicity (34%) and allergic reactions (25%) being the most common causes (10).

Thiopurine-related toxicity includes idiosyncratic reactions, such as general malaise, gastrointestinal symptoms (nausea, anorexia, abdominal pain), acute pancreatitis, arthralgia (mostly small joints), and cutaneous rash (5); dose-dependent effects**,** due to toxic metabolite accumulation, including myelotoxicity—often associated with

dysfunctional alleles of the thiopurine methyltransferase (TPMT) enzyme—and hepatotoxicity (5,6); and immunosuppression-related complications**,** such as infections and malignancies (5).

The two most frequent adverse effects are leukopenia—occurring in about 5% of Caucasian patients but up to 15–39% in Asian populations (11)—and acute pancreatitis, with reported incidence ranging from 3.8% to 8.9% (12,13). Cytopenia may be severe or even life-threatening in 2–5% of cases (6).

Patients on thiopurines also have a significantly increased risk of malignancy: over twice the risk for non-melanoma skin neoplasia (HR 2.25, 95% CI 1.50–3.45), urinary tract neoplasia (HR 2.82, 95% CI 1.04–7.68), and cervical neoplasia (SIR 2.47, 95% CI 1.54–3.73); and up to five times higher risk for lymphomas (SIR 5.71, 95% CI 3.22–10.10) and myeloid malignancies (SIR 6.98, 95% CI 1.44–20.36) (5).

The aim of this study is to characterize severe adverse effects associated with thiopurine treatment in IBD patients at a tertiary hospital. Specifically, we aim to estimate the incidence of severe adverse events and describe the clinical characteristics of patients affected by these events.

## METHODS

### Study Design and Data Collection

This was a descriptive, retrospective observational study conducted on a cohort of patients from Hospital Parc Taulí in Sabadell, Spain.

### Population

Patients included in the ENEIDA registry (*Estudio Nacional en Enfermedad Inflamatoria Intestinal sobre Determinantes Genéticos y Ambientales*) (14) were screened. Eligible participants were diagnosed with IBD between 1970 and 2024 and received thiopurine therapy at any point during the course of their disease.

From this population, we included patients who developed any severe adverse events.

Severe adverse events were defined as those that fulfilled at least one of the following criteria: (1) required permanent discontinuation of thiopurine therapy or a major treatment modification; (2) resulted in hospital admission; (3) required an invasive diagnostic or therapeutic intervention; (4) were associated with confirmed malignancy; or (5) resulted in death. All other adverse events not meeting these criteria were classified as non-severe and were not included in the present analysis. See Table 1 for details.

Patients who experienced mild-moderate adverse events or only gastrointestinal intolerance were not included.

Exclusion criteria were: (1) age under 18 years, (2) discontinuation of follow-up at our center (e.g., transfer to another hospital), (3) receipt of thiopurines for indications other than IBD, and (4) mild–moderate adverse events or isolated gastrointestinal intolerance.

**Variables**

Collected variables included demographic data (age and sex), disease characteristics (IBD subtype and disease location), thiopurine-related variables (specific agent used, whether used as monotherapy or in combination with a biologic, initial dose, dose at the time of the adverse event, and time from IBD diagnosis to thiopurine initiation), adverse event characteristics (type of adverse event, time from thiopurine initiation to event onset, and duration), and clinical outcomes (length of follow-up, need for hospitalization and its duration, treatment modification, switch to another immunosuppressive agent, and patient mortality).

Thiopurine dosing and monitoring followed standard clinical practice throughout the study period. Initial dosing was weight-based (2–2.5 mg/kg/day for azathioprine and 1–1.5 mg/kg/day for 6-mercaptopurine). Subsequent dose adjustments were not

standardized and were performed at the discretion of the treating physician, according to clinical tolerance, hematologic parameters, and liver function tests. Systematic monitoring of thiopurine metabolites (6-TGN and 6-MMP) was not routinely available in our center and was only performed in a very limited number of patients in the most recent years; therefore, metabolite levels were not included in the analysis. TPMT genotyping/phenotyping was implemented in 2015, and prior to that date dosing decisions relied exclusively on weight and clinical and laboratory monitoring.

Reference values were defined according to institutional laboratory standards: lipase (normal range: 13–60 U/L); leukopenia as a white blood cell count $<4\times10^9$/L; neutropenia as neutrophil count $<2.5\times10^9$/L; anemia as hemoglobin <130 g/L in men or <120 g/L in women; and thrombocytopenia as platelet count $<130\times10^9$/L. Transaminase elevation was defined as AST >64 U/L and/or ALT >62 U/L (i.e., ≥2× the upper limit of normal), and fever was defined as a body temperature >37.5°C.

Age was recorded in years; time intervals (from IBD diagnosis to thiopurine initiation, from thiopurine initiation to adverse event onset, and duration of adverse events) were recorded in months; hospitalization was recorded in days.

**Statistical Analysis**

For continuous variables, mean and standard deviation were calculated. For categorical variables, percentages and 95% confidence intervals (CI) were reported. Pearson's correlation coefficient was used for comparisons between independent variables. Statistical significance was set at $p < 0.05$.

**Ethical Considerations**

Data were collected in an MS Excel database, excluding any personally identifiable information. Investigators had access to a restricted list containing only patient medical record numbers.

Given the retrospective nature of the study and the absence of impact on clinical care, informed consent was not required. The study was reviewed and approved by the local Ethics Committee (CEIM), and conducted in accordance with the principles of the Declaration of Helsinki (15). The results will be reported following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and RECORD (REporting of studies Conducted using Observational Routinely-collected Data) guidelines (16). The checklist is attached as supplementary file 1.

**RESULTS**

A total of 722 patients with IBD received thiopurine therapy at our center, of whom 203 (28%) experienced adverse events. Among them, 81 patients (11.2%) developed severe adverse events related to thiopurine use. Of these, 30 were women (37%). The mean follow-up duration was 15.2 years (2–50 years).

The mean age at IBD diagnosis was 41.8 years (range: 20–78), the mean age at thiopurine initiation was 44.4 years (range: 20–76), and the mean age at the time of adverse event onset was 47.2 years (range: 21–79).

Regarding disease subtype, 22 patients (27.2%) had UC and 59 (72.8%) had CD. Regarding UC, the most frequent disease location was pancolitis (n = 10, 46%), followed by left-sided colitis (n = 8, 36%) and ulcerative proctitis (n = 4, 18%). For CD, ileal involvement was most common (n = 27, 46%), followed by ileocolonic (n = 23, 39%) and colonic disease (n = 9, 15%); 8 patients (14%) had perianal disease.

Of the patients with severe adverse events, 76 (93.8%) were treated with azathioprine and 5 (6.2%) with 6-mercaptopurine. The most frequent severe adverse events were acute pancreatitis (n = 31, 38.3%), myelotoxicity (n = 19, 23.4%), malignancies (n = 13, 16%), and hepatotoxicity (n = 6, 7.4%) (Figure 1). In addition, three cases of infection (3.7%) and three cases of fever of unknown origin (3.7%) were identified.

Among the malignancies reported, there were 2 cases of bladder neoplasia (2.5%), 3 renal neoplasia (3.7%), 1 breast neoplasia (1.2%), 1 cervical neoplasia (1.2%), 5 lymphomas (6.3%), and 1 colorectal neoplasia (1.2%). Median time from the initiation of thiopurines to the diagnosis of cancer was 8.7 ± 6.9 years. All patients were on azathioprine at the time of diagnosis, and the drug was withdrawn in all cases.

No statistically significant differences were observed in the distribution of adverse events according to sex ($p$ = 0.36), IBD subtype (UC vs. CD; $p$ = 0.21), or the type of thiopurine used (azathioprine vs. 6-mercaptopurine; $p$ = 0.09). Similarly, no significant difference was found in the time from thiopurine initiation to adverse event onset between patients with UC and those with CD ($p$ = 0.09).

A total of 24 patients (30%) required hospitalization due to the adverse event. Causes of hospitalization included acute pancreatitis in 9 patients (37.6%), myelotoxicity in 2 (8.3%), malignancies in 7 (29.1%), hepatotoxicity in 1 (4.2%), non-cirrhotic portal hypertension in 1 (4.2%), infections in 2 (8.3%), and fever of unknown origin in 2 (8.3%).

Following the adverse event, treatment was modified in 80 patients (98.8%) ($p$ = 0.008). Specifically, thiopurine dose was reduced in 6 patients (7.5%), the drug was discontinued in 49 (60.5%), switched from AZA to 6-MP in 4 (4.9%), and replaced with methotrexate in 21 (25.9%).

Among the 81 patients, 7 died (8.6%), with 2 deaths attributed directly to the adverse event (renal and bladder neoplasia, respectively).

**DISCUSSION**

In our cohort, 28% of patients treated with thiopurines experienced adverse events, a figure closely aligned with that reported by Chaparro et al., who observed a 26% rate in the large Spanish ENEIDA registry involving 3,931 patients (17). This overlap

confirms the consistency of adverse event rates and toxicity patterns in real-world practice. Our study adds complementary value by providing a detailed characterization of severe adverse events within a single tertiary center, with substantially longer follow-up (mean >15 years) and a broader spectrum of malignancies captured during thiopurine exposure. Together, these data help refine the understanding of serious thiopurine-related toxicity in long-term IBD management.

Malignancies were the fourth most frequent severe adverse event in our study, with lymphoma, non-melanoma skin neoplasia, and renal neoplasia being the most common. This contrasts with the findings of Chaparro et al., where neoplasms were among the least frequently reported adverse effects, with only four cases of lymphoma documented (17). The association between thiopurine therapy and malignancy remains a subject of debate. However, there is established evidence linking thiopurines to an increased risk of non-melanoma skin neoplasia, lymphoproliferative and myeloid malignancies, and urinary tract neoplasia (5).

Our broader inclusion criteria—encompassing all neoplasms diagnosed during thiopurine therapy—may account for the higher observed incidence. This approach aligns with findings from Zheng et al., who reported elevated risks for multiple tumor types during thiopurine treatment, including leukemia (SIR 11.9), ovarian neoplasia (SIR 9.1), laryngeal neoplasia (SIR 8.12), genitourinary neoplasia (SIR 7.79), non-Hodgkin lymphoma (SIR 5.54), and colorectal neoplasia (SIR 4.28) (18). Considering the advanced mean age in our population, the observed neoplasia rates, although notable, may reflect age-related risk more than treatment-specific causality, and likely exceed those reported in younger cohorts (5,17).

We found no clinical predictors for severe adverse events. This is consistent with previous research, which identified few reliable predictors for specific adverse outcomes. For instance, older age has been proposed as a risk factor for myelotoxicity, while predictors of hepatotoxicity remain poorly defined (4,19).

Although acute pancreatitis has been linked in prior studies to factors such as oral budesonide use (13), we found no such associations. Additionally, there was no significant correlation with thiopurine dosing strategy (single vs. split dosing), weight-adjusted dosage, prior cholelithiasis, history of pancreatitis, autoimmune comorbidities, or concurrent medications. These findings reinforce the idiosyncratic nature of many thiopurine-related toxicities.

Differences in thiopurine toxicity profiles across populations should also be considered. Asian cohorts consistently report a higher incidence of thiopurine-induced myelosuppression—up to 15–39%—largely explained by the greater prevalence of TPMT and NUDT15 loss-of-function variants in East Asian populations (11). In contrast, Caucasian populations show much lower frequencies of these variants, leading to substantially lower rates of severe cytopenias, in line with the toxicity profile described in Western studies (5). In our cohort, TPMT testing was only introduced late and performed in a minority of patients, preventing any direct analysis of genotype–toxicity correlations. Nevertheless, the severity and frequency of myelosuppression observed appear consistent with those expected for a predominantly Caucasian population.

This study has several limitations. As a retrospective, single-center study, it was limited by incomplete data on some variables and restricted generalizability. Notably, smoking status—a potential risk factor—could not be adequately evaluated due to missing data. Moreover, we did not assess thiopurine metabolite levels (e.g., 6-thioguanine nucleotides), which could have provided insight into pharmacokinetic contributors to toxicity. The long diagnostic window (1970–2024) inevitably encompasses major changes in diagnostic criteria, dosing strategies, metabolite monitoring, and TPMT testing. In this sense, detailed clinical information regarding the management of severe adverse events (e.g., use of growth factors, pancreatitis severity, or structured causality assessment) was not consistently available across all decades of the study period. Therefore, we did not apply formal causality algorithms, and causal attribution was based on the clinical judgment documented at the time of the event. Despite

these limitations, our findings likely reflect real-world clinical experience in comparable healthcare settings.

In conclusion, thiopurines are associated with a substantial burden of severe adverse events in patients with IBD. Acute pancreatitis and myelotoxicity were the most frequently observed complications. The high prevalence of neoplasia after a long-term follow-up in our study suggest that neoplasia risks might be underestimated in previous series. No consistent demographic or clinical predictors of these events were identified, underscoring the need for close monitoring in all patients receiving thiopurine therapy.

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Luis Enrique Frisancho, Eduard Brunet, Belen García and Xavier Calvet designed the study, analysed data and wrote the manuscript.

Eduard Brunet, Belen Garcia-Sagué, Xavier Calvet, Luigi Melcarne, Laura Llovet, Sergio Lario, Maria José Ramirez-Lazaro, Albert Villoria reviewed the text and provided important intellectual content. All authors definitively approved the submitted version.

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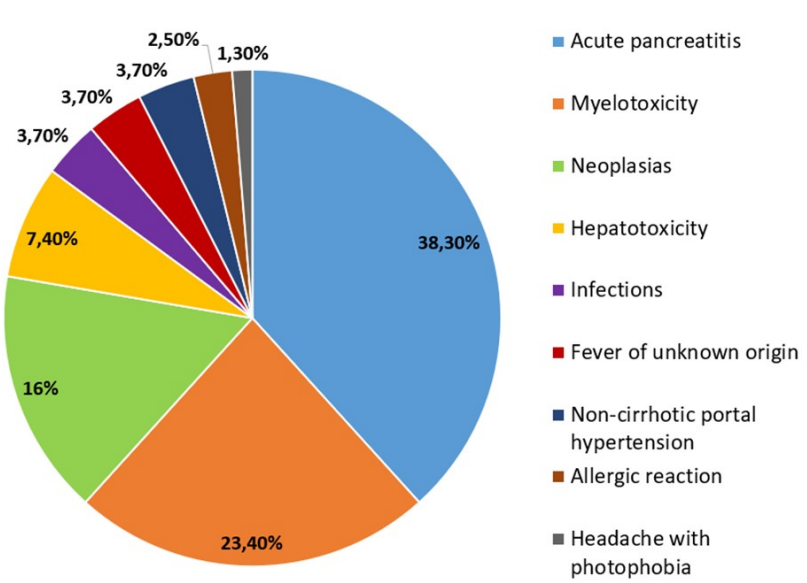


**Figure 1.** Distribution of severe adverse events.

**Table 1.** Definitions and criteria for severe adverse events

| Category of severe adverse event | Criteria applied |
|---|---|
| **Acute pancreatitis** | Lipase elevation ≥3× ULN and characteristic abdominal pain; required hospital admission or led to drug withdrawal |
| **Myelotoxicity (cytopenias)** | Leukopenia $<4\times10^9$/L, neutropenia $<2.5\times10^9$/L, anemia or thrombocytopenia requiring treatment modification or hospitalization |
| **Hepatotoxicity** | AST or ALT ≥2× ULN with need for drug discontinuation, investigation, or hospital monitoring |
| **Malignancies** | Any histologically confirmed neoplasm diagnosed during thiopurine therapy |

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| | |
|---|---|
| **Infections** | Infections requiring antibiotics, intravenous therapy, or hospitalization |
| **Non-cirrhotic portal hypertension** | Radiological or endoscopic diagnosis leading to drug withdrawal or hospitalization |
| **Allergic reactions** | Cutaneous rash, arthralgia requiring drug discontinuation |
| **Fever of unknown origin** | Fever >37.5ºC with no alternative cause and requiring hospital evaluation |
| **Headache with photophobia** | Headache with photophobia requiring drug discontinuation |

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**Supplementary file 1**. STROBE checklist

| | Item No | Recommendation | page |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4-5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 5-6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of | 6 |

| | | | |
|---|---|---|---|
| | | assessment methods if there is more than one group | |
| Bias | 9 | Describe any efforts to address potential sources of bias | 6 |
| Study size | 10 | Explain how the study size was arrived at | 6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 7 |
| | | (*c*) Explain how missing data were addressed | 7 |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | 7 |
| | | (*e*) Describe any sensitivity analyses | 7 |
| **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 | 7 |
| | | (b) Give reasons for non-participation at each stage | 7 |
| | | (c) Consider use of a flow diagram | NA |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg | 7 |

| | | | |
|---|---|---|---|
| | | demographic, clinical, social) and information on exposures and potential confounders | |
| | | (b) Indicate number of participants with missing data for each variable of interest | 7 |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 7-8 |
| 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 | 7-8 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 7-8 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |
| 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 | 9-10 |
| 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 | 10 |
| Interpretation | 20 | Give a cautious overall interpretation of results | 10 |

| | | | |
|---|---|---|---|
| | | considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | |
| 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 | 10 |

*Give information separately for exposed and unexposed groups.