Operative and Non-Operative Management for Intestinal Emergencies: Findings from a Single-Centre Retrospective Cohort Study

Alexander Ross Darbyshire, Ina Kostakis, Paul Meredith, Caroline Kovacs, David Prytherch, Jim Briggs & Simon K. C. Toh

Abstract

Background

Patients with an intestinal emergency who do not have surgery are poorly characterised. This study used electronic healthcare records to provide a rapid insight into the number of patients admitted with an intestinal emergency and compare short-term outcomes for non-operative and operative management.

Methods

A single centre retrospective cohort study was conducted at a tertiary NHS hospital (01/12/2013-31/01/2020). Patients were identified using diagnosis codes for intestinal emergencies, based on the inclusion criteria for the National Emergency Laparotomy Audit. Relevant data was extracted from electronic health care records (n=3 997).

Results

Nearly half of patients admitted with an intestinal emergency received non-operative management (43.7%). Of those who underwent surgery, 63.7% were started laparoscopically. The non-operative group had a shorter hospital (median: 5.4 days vs 8.2 days [started laparoscopically] or 16.8 days [started open]) and fewer unintended intensive care admissions than the surgical group (2.4% vs 8.7 % [started laparoscopically] 21.1% [started open]). However, 30-day mortality for non-operative treatment was double that for surgery (22.4% vs 10.1%). 30-day mortality was found to be even higher for non-operative management (50.3%) compared to surgery (19.5%), in a sub-analysis of patients with admission National Early Warning Score ≥4 (n=683).

Conclusion

The proportion of intestinal emergencies who do not have surgery is greater than expected, and it appears that many respond well to non-operative treatment. However, 30-day mortality for non-operative management was high, and the low number of admissions to intensive care suggests that major invasive treatment was not appropriate for most in this group.

Introduction

Intestinal emergencies are a diverse group of conditions which often require surgery (1). Some of these require urgent transfer to theatre, like perforated peptic ulcers and mesenteric ischaemia (2,3). However, others such as adhesional small bowel obstruction and complex diverticulitis are readily treated by non-operative management, with surgery reserved as second line treatment (4,5). Emergency bowel surgery is now the subject of national audits that monitor outcomes against evidence-based standards of care (1,6). However, a group for which there is little data are patients with an intestinal emergency who may need (but do not have) emergency bowel surgery. This is partly because of the presumption, particularly in cases where urgent surgery is required, that survival is unlikely.

A single-centre cohort study in Scotland has been first to investigate this topic with revealing findings. It identified that a surprising 32% (n=100/314) of patients with an intestinal emergency were declined emergency bowel surgery, with the reason in 74% of cases cited as due to 'poor-fitness' (7). The 30-day mortality rate for patients managed non-operatively was much higher than those who underwent surgery (63% vs 13%). Interestingly, risk-adjusted analysis suggested that 30-day mortality for this group would have been considerably lower (30-40%) if they had undergone surgery (7). While these findings are not definitive, they merit further investigation.

Gathering large amounts of data on patients prospectively can be time consuming and expensive. To quickly get a better understanding of this cohort of patients receiving non-operative management of intestinal emergencies, we decided to use a retrospective approach utilising electronic healthcare records (EHR). The aim of this study was to use EHRs to identify all patients admitted to hospital with an intestinal emergency and compare short-term outcomes for those who were treated with emergency bowel surgery with outcomes for those who were not.

Methods

This study is reported in line with the Reporting of studies Conducted using Observational Routinely-Collected Data (RECORD) statement (checklist in Appendix 1) (8).

Study Design and Setting

This is a single centre retrospective cohort study conducted at Portsmouth Hospitals University NHS Trust (PHU), using data from existing electronic health records between December 2013 and January 2020.

Outcomes

The primary outcome is the number of admissions with intestinal emergencies and the treatment received, be that open or laparoscopic surgery or non-operative management. The secondary outcomes are the rate of conversion to open surgery, 30-day, in-hospital and 1-year mortality, unintended admission to intensive care unit (ICU), length of hospital stay and re-admission within 1 year. Outcomes have been compared between non-operative and operative groups, with the operative group divided into open and laparoscopic surgery.

Participants

The study population was identified using ICD-10* diagnosis codes for intestinal emergencies. Patients aged 16 or older who were admitted with an intestinal emergency were eligible for inclusion. Eligible participants must also have had a full set of vital signs and routine blood tests recorded during admission. Maternity admissions were excluded.

To identify the study population, a comprehensive list of ICD-10 codes was selected based on the inclusion criteria of NELA and clinical expertise. We started with the broadest possible approach to avoid accidentally excluding relevant episodes. This identified far more patients than anticipated and the list was then extensively refined using an iterative process of trial data extractions. Ultimately, ICD-10 codes for only the clear surgical conditions (from the NELA inclusion criteria) as the primary diagnosis for that admission were used.

Data Source

All data on patient demographics, admissions, diagnosis and procedure codes, vital signs, operating theatre and ICU data were extracted from existing EHRs at PHU. The local NELA dataset for the study period was downloaded from the NELA servers.

Variables

National Early Warning Score (NEWS) values were calculated from patient vital signs (9). The score from the first available vital signs observation during an admission was classified as admission NEWS, unless this was recorded after surgery.

Continuous variables were not dichotomised or grouped for analysis. The only exceptions were high NEWS observations which were grouped together for visualisation in plots.

Operative approach was determined using OPCS-4 codes and cross-referenced with the NELA dataset. We opted to define this on an intention to treat basis, so all cases considered as open were

* 10th revision of the International Statistical Classification of Diseases and Related Health Problems.

started as a laparotomy. All laparoscopic cases were started as such and include laparoscopically-assisted and cases converted to open. When calculating the conversion to open rate, laparoscopically-assisted cases were considered as converted to open, as the size/nature of the incision used is not available.

Unintended admission to ICU (UICU) was differentiated from a planned post-operative admission to ICU if it occurred more than 24 hours after the beginning of surgery.

Missing Data

The only missing data items were vital signs/NEWS scores, but this was rare (1.15%). Missingness appeared to be random over time. Patient episodes with missing admission NEWS were therefore omitted from any analysis involving NEWS.

Sample Size

The anticipated sample size was calculated using the known size of the NELA dataset for the study period (n=1 500) and the assumption that an additional 30% of cases who were managed non-operatively would be identified, based on the findings of *McIlveen et al* (7). A sample size of approximately 2 000 cases was felt to be sufficient for this single centre exploratory study, and the largest published to date.

Statistical Analysis

Data were summarised with descriptive statistics including counts and proportions, mean (±SD) and median (IQR) as appropriate.

We investigated the distribution of admission NEWS values, expressed as a proportion of total number of observations, by plotting them against 30-day mortality for each possible value. This allows the thresholds of risk for each possible score to be visualised.

Data analysis was performed in R Studio: R Foundation for Statistical Computing 2020 (Vienna, Austria).

Bias

In this exploratory retrospective study, we provide only descriptive statistics and have not performed a comparative statistical analysis. We recognise that there will be selection bias influencing what treatment patients have received and have interpreted the results accordingly. We have not attempted to control for confounding factors in this paper.

Results

The final study cohort included 3 997 patients. Patient demographics and outcomes are summarised in Table 1. Just under half of patients received non-operative management (43.7%) which is higher than anticipated. Of patients who underwent surgery, laparoscopy was the favoured operative approach (63.7%). The rate of conversion to open surgery for emergency laparoscopy was low
(21.4%, 306/1 432).

Most patients were admitted as an emergency (97.5%) and to a surgical specialty (76.0%). Of the patients admitted under general medicine, the majority received non-operative management. There were few admissions to medicines for older people which seems appropriate given the median age of the cohort. Length of hospital stay was shortest in the non-operative group, followed by laparoscopic and then open surgery. Rates of re-admission to hospital were similar across treatment groups. Patients who received non-operative management had notably few unintended admissions to ICU (2.4%). For cases where surgery was started using an open approach, the rate of unintended admissions to ICU was double that for cases started laparoscopically (21.1% vs 8.7%).

The overall 30-day mortality rate for emergency bowel surgery was comparable to that reported nationally (10.1%) (1). For patients managed non-operatively, 30-day mortality (22.4%) was not as high as we expected based on rates reported in other studies (7). Patients suitable for their surgery to be started laparoscopically were observed to have a much lower 30-day mortality rate than for those who required a laparotomy (4.8% vs 19.5%). 1-year mortality was higher for non-operative management than for surgery (34.7% vs 17.8%).

In Figure 1, the distribution of each admission NEWS value is displayed as a proportion (bars), with the 30-day mortality rate for each value plotted over (points and line). The overall trend is that mortality increases with a rising admission NEWS. There is, however, a notable jump in mortality at a NEWS threshold of 4 for cases managed non-operatively, which is not observed with surgery. We therefore undertook further analysis to look at only cases with an admission NEWS ≥4, with patient demographics and outcomes are summarised for this sub-population in Table 2. Half received non-operative management, with the rest undergoing open or laparoscopic surgery. 30-day mortality increased across all treatment groups but was notably higher for on-operative management compared to surgery (50.3% vs 19.5%).

Discussion

In this paper, we present the findings of the largest UK study to date, investigating patients admitted to hospital with an intestinal emergency who received either operative or non-operative management. By conducting a retrospective analysis of electronic healthcare records, we have been able to provide a rapid report on this poorly studied population. This builds on the findings of McIlveen *et al.* but has also identified some differences within the non-operative group (7).

Just under half of patients received non-operative management, comparably higher than reported by McIlveen *et al* (44% vs 32%), and the 30-day mortality rate was also significantly lower (22% vs 63%) (7). We think this difference is partly explained by our broad inclusion criteria (all conditions which may require emergency bowel surgery), whereas McIlveen focused-on patients who required (but had been declined) surgery. Thus, we have probably captured data on many patients with an intestinal emergency whose condition could reasonably recover without surgery. Analysis of NEWS scores on admission identified a sudden increase in mortality for the non-operative group at a threshold NEWS of 4, which did not occur with surgery. Examination of this subgroup revealed that 30-day mortality for non-operative treatment was more than double that of the total group (50.3% vs 22.4%) and much more comparable to that reported by McIlveen (7).

Emergency bowel surgery was routinely started laparoscopically (63%), with a low rate of conversion to open (21.4%). Notable differences were identified between the open and laparoscopic groups, which may partly explain operative decision making. Patients whose surgery was started laparoscopically were observed to be younger, with a much lower unintended ICU admission, post-operative length of stay, and mortality than open surgery. In addition, patients requiring primarily open surgery were more likely to be unwell pre-operatively with a NEWS >4 (20.3% vs 12.8%). There is now good evidence to demonstrate that emergency bowel surgery performed laparoscopically confers superior outcomes (10). However, in this un-adjusted analysis we cannot say with any certainty that differences we have observed are due to surgical approach alone, rather than the other patient and operative factors.

This study is limited by its retrospective observational design, and we recognise this in our methods and interpretation of the results. There will indeed be unmeasured selection bias influencing what treatment patients have received, which we cannot account for using electronic healthcare records alone. Furthermore, we do not have data on what actual non-operative treatment patients received, such as nasogastric tube decompression, type of antibiotics, or use of parenteral nutrition. There is also no data on why patients did not have surgery, which we feel would be a key outcome for future prospective studies on this topic. Any study using EHRs is also at risk of unknown coding

errors occurring. However, our exploratory data analysis of both diagnosis and procedures codes revealed that the depth of coding was extremely thorough. Furthermore, variables such as vital signs, theatre and ICU data are recorded real-time by the clinical team and likely to be accurate. We also compared data on the operative group with the NELA dataset demonstrating a high-level of agreement.

The strength of this study is that it has provided useful information on a poorly studied patient population and is the largest on this topic to date. The proportion of patients with an intestinal emergency who do not require surgery, is greater than we initially expected (7). It appears that many respond well to non-operative management with a short-associated hospital admission. Nonetheless, the non-operative cohort still has a much higher mortality than those who underwent surgery. While we have not been able to determine why patients did not undergo surgery, the low rate of admission to ICU for the non-operative group suggests that for many of them, major invasive treatment was not appropriate. We have used elevated NEWS scores to reliably identify patients who were unwell on admission, with revealing findings. Only half of patients in this sub-group who received non-operative treatment were alive at 30-days, with a longer-term mortality rate of 60.2%. This information is useful for clinicians in several ways. Firstly, it supports an early discussion of a ward-based ceiling of care with patients who are not suitable for or do not want emergency bowel surgery, particularly if they are unwell. It also provides an estimated short-term mortality rate of 20% to 50% for discussing non-operative management with patients. The observation that patients who are unwell prior to surgery are likely to have a higher post-operative mortality rate is not a novel finding. However, the clear trend between rising admission NEWS and 30-day mortality may prompt clinicians to proceed with urgent surgery, rather than a trial of non-operative management in conditions which would potentially settle with this.

To better understand the differences in patient characteristics and outcomes between those who do and do not undergo emergency bowel surgery, a further condition specific analysis is required. While national audits view this population collectively, the actual underlying conditions and surgical treatments are diverse. For example, adhesional small bowel obstruction is the commonest indication for emergency laparotomy (1). However, only one third of cases require surgery, with the rest resolving with nasogastric decompression (5). Investigating all treatments together may reveal trends such as the superiority of long-term nasogastric drainage and parenteral nutrition, over high-risk laparotomy in a battle-scarred abdomen. Conversely, the laparoscopic approach could be found to have favourable outcomes in older/frail patients, for whom laparotomy carries increased morbidity and mortality (11–13). These examples are theoretical but serve to illustrate how comparing surgery to non-operative management may identify better treatment options.

A prospective study would capture data on why patients were not offered or declined surgery, whether a trial of non-operative treatment was initiated, and investigate the influence (if any) played by other factors like frailty. The decision to proceed with major surgery is a complex one that involves a shared decision-making process with a patient and their family. The second part of the Emergency Laparotomy and Frailty study (ELF-2) is investigating older patients who require but do not undergo emergency bowel surgery due to frailty, which will also hopefully shed further light on this topic (14).

In conclusion, this is the second UK study to compare the use of non-operative management for intestinal emergencies to surgery, and the largest to date. A surprisingly high number of patients do not undergo surgery, however further research is required to investigate why this is the case.

Availability of Data and Materials

The datasets created for this study are not publicly available as they contain confidential patient data. They are subject to the strict data protection rules outlined in the ethical approval for this study and access is restricted to the relevant members of the research team. Access to this data on request would require the approval from the chief investigator of the study and health research authority.

Competing Interests

The authors declare that they have no competing interests.

Funding

Author contributions

ARD and IK contributed equally to this manuscript and are joint first authors. Project initiation: ARD, IK, CK, DP, SKCT and JB. Planning of statistical analysis: all authors. Data extraction: PM and ARD. Cleaning and analysis of data: IK, CK, ARD and PM. Interpretation of results: ARD, IK, CK, DP, SKCT and JB. Drafting of initial manuscript: ARD and IK. Revision of manuscript: ARD, IK, CK, DP, PM, SKCT and JB.

Acknowledgements

We would like to sincerely thank Ms Annabelle Glanville-Hearson for the major contribution she has made to this study as our patient representative. She has played an integral role in the application for funding, set up of the study and discussion of the results with patients. Her poignant and personal insights have been invaluable.

We would also like to thank the Portsmouth Hospital Patient Research Ambassadors for their feedback and advice.

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Tables and Figures

Table 1 - Summary of demographic and admission data and outcomes for patients having open surgery, laparoscopy, and non-operative treatment. Data are presented as counts (%) and median (IQR).

Table 2 - Summary of demographic and admission data and outcomes for patients having open surgery, laparoscopy, and non-operative treatment with an admission NEWS ≥4. Data are presented as counts (%) and median (IQR).

Figure 1 – Plot of the cumulative distribution of each NEWS score as a proportion (bars), with the mortality rate for each score plotted over (points), coloured for each treatment group (see legend).

Table 1

Summary of demographic and admission data and outcomes for patients having open surgery, laparoscopy, and non-operative treatment. Data are presented as counts (%) and median (IQR).

	open	**laparoscopic**	**non-operative**
Admissions, N	817	1,432	1,748
Age [years], median (IQR)	71 (59-80)	61 (44.8-74)	72 (58-82)
Female, N (%)	425 (52.0)	813 (56.8)	945 (54.1)
Type of Admission			
Elective, N (%)	54 (6.6)	46 (3.2)	0 (0.0)
Emergency, N (%)	763 (93.4)	1,386 (96.8)	1,748 (100)
Admission Specialty group			
General Medicine, N (%)	149 (18.2)	168 (11.7)	628 (35.9)
General Surgery, N (%)	667 (81.6)	1,254 (87.6)	1,118 (64)
Medicine for Older People, N (%)	0 (0)	1 (0.1)	6 (0.3)
Included in NELA, N (%)	645 (78.9)	842 (58.8)	0 (0.0)
Palliative care received, N (%)	79 (9.7)	58 (4.1)	171 (9.8)
Outcomes			
Hospital length of stay [days], median (IQR)	16.8 (9.1-34.3)	8.2 (4.5-16.1)	5.4 (2.7-12)
Mortality			
In-hospital, N (%)	132 (16.2)	55 (3.8)	303 (17.3)
30 days, N (%)	159 (19.5)	69 (4.8)	392 (22.4)
1 year, N (%)	242 (29.6)	158 (11.0)	606 (34.7)
Readmission within 1 year, N (%)	293 (35.9)	430 (30.0)	697 (39.9)
Unanticipated ICU admission N (%)	172 (21.1)	125 (8.7)	42 (2.4)
Combined outcome: death or re-admission within 1 year, N (%)	470 (57.5)	519 (36.2)	1,133 (64.8)

Table 2

Summary of demographic and admission data and outcomes for patients having open surgery, laparoscopy, and non-operative treatment with an admission NEWS ≥4. Data are presented as counts (%) and median (IQR).

	open	**laparoscopic**	**non-operative**
Admissions, N	166	183	334
Age [years], median (IQR)	70 (60-78.8)	68 (53-77)	76.5 (66.2-84)
Female, N (%)	91 (54.8)	91 (49.7)	189 (56.6)
Type of Admission			
Elective, N (%)	8 (4.8)	7 (3.8)	0 (0.0)
Emergency, N (%)	158 (95.2)	176 (96.2)	334 (100.0)
Admission Specialty group			
Medicine, N (%)	27 (16.3)	27 (14.8)	146 (43.7)
Surgery, N (%)	139 (83.7)	154 (84.2)	188 (56.3)
Medicine for Older People, N (%)	0 (0.0)	1 (0.5)	1 (0.3)
Included in NELA, N (%)	138 (83.1)	138 (75.4)	0 (0.0)
Palliative care received, N (%)	17 (10.2)	16 (8.7)	62 (18.6)
Outcomes			
Hospital length of stay [days], median (IQR)	17.8 (8.4-35.9)	12.7 (6.7-25.7)	7.7 (2.9-16.4)
Mortality			
In-hospital, N (%)	40 (24.1)	20 (10.9)	136 (40.7)
30 days, N (%)	47 (28.3)	21 (11.5)	168 (50.3)
1 year, N (%)	59 (35.5)	37 (20.2)	201 (60.2)
Readmission within 1 year, N (%)	66 (39.8)	69 (37.7)	101 (30.2)
Unanticipated ICU admission N (%)	47 (28.3)	31 (16.9)	21 (6.3)
Combined outcome: death or re-admission within 1 year, N (%)	113 (68.1)	92 (50.3)	273 (81.7)

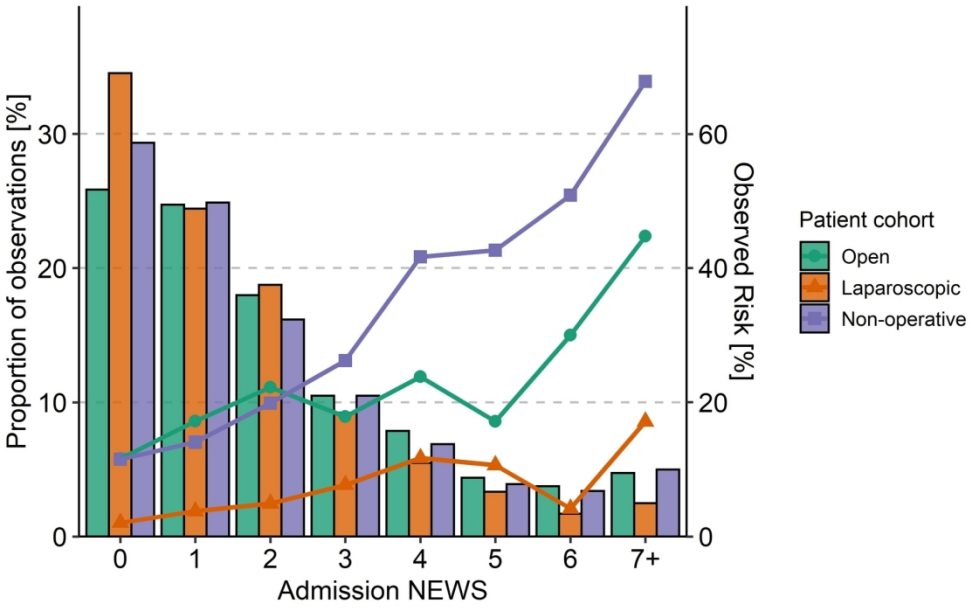

Figure 1 – Plot of the cumulative distribution of each NEWS score as a proportion (bars), with the mortality rate for each score plotted over (points), coloured for each treatment group (see legend).

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The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Page 1-2
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Page 3
Objectives	3	State specific objectives, including any prespecified hypotheses			Page 3
Methods					
Study Design	4	Present key elements of study design early in the paper			Page 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Page 4

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Page 4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 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			Page 5

Bias	9	Describe any efforts to address potential sources of bias			Page 6
Study size	10	Explain how the study size was arrived at			Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Page 6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			Page 6
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Page 6

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Page 6
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Page 7 and 16
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			Page 7 and 16
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure			Page 7, 8 and 16

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			Page 7, 8 and 16
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			NA
Discussion					
Key results	18	Summarise key results with reference to study objectives			Page 9
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		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 10
Interpretation	20	Give a cautious overall interpretation of results considering objectives,			Page 9 to 11

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			Page 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			Page 1
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	NA

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.