Investigating the epidemiology of medication errors in adults in community care settings

A retrospective cohort study in central Saudi Arabia

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ABSTRACT

الأهداف: التحقق من معدل الانتشار الزمني وعوامل الإختطار للأخطاء المهمة سريرياً من ناحية الوصف والمراقبة في إدارة الدواء لدى المرضى البالغين الذين تتم معاينتهم في الرعاية المجتمعية.

الطريقة: استخدمت هذه الدراسة الأترابية بأثر رجعي بيانات السجلات الصحية الإلكترونية (HER). تم اختيار عينة عشوائية تضم 2000 شخص بالغ (18 عاما) في زيارة عيادات طب الأسرة في مستشفى الملك فيصل التخصصي ومركز الأبحاث، الرياض، المملكة العربية السعودية. استغرقت عملية جمع البيانات 3 أشهر (من أول أكتوبر إلى ديسمبر 2017م). قمنا بالتحقق من مدى انتشار وعوامل الخطر المرتبطة بالمرضى المعرضين لخطر الأخطاء الهامة سريرياً. أجريت التحليلات الوصفية ونمذجة التحوف اللوجستي باستخدام برنامج الإحصاء STATA (الإصدار 14).

النتائج: كشفت دراستنا الأترابية أن معدل الانتشار الزمني للأخطاء الدوائية على مدى 15 شهراً هو 8.1% (فاصل ثقة 95% (CI) 6.5–9.7) وعوامل الإختطار المرتبطة بالمرضى المعرضين لخطر الأخطاء الدوائية هي: العمر 65≤ عام، الجنس الذكري، الجنسية السعودية للمريض، واستخدام 5 أو أكثر من الأدوية المتزامنة.

الخاتمة: وجدنا أن الأخطاء المتعلقة بوصف أو مراقبة الأدوية شائعة.

Objectives: To investigate the period prevalence and risk factors for clinically important prescription and monitoring errors among adults managed in community care in Saudi Arabia (SA).

Methods: This retrospective cohort study used electronic health record (HER) data. A random sample comprising of 2,000 adults (≥18 years old) visiting Family Medicine clinics in King Faisal Specialist Hospital and Research Center (KFSH & RC), Riyadh, SA, was selected. Data collection took 3 months (October December 2017). Descriptive analyses and logistic regression modeling were performed using STATA (version 14) statistical software.

Results: The overall period prevalence of medication errors over 15 months was 8.1% (95% confidence interval [CI] 6.5-9.7). Risk factors that significantly predicted overall risk of patients experiencing one or more medication errors were: age ≥65 years, male gender, Saudi nationality, and polypharmacy (defined as the concurrent use of ≥5 drugs).

Conclusions: Clinically important medication errors were commonly observed in relation to both drug prescription and monitoring.

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Patient safety is a public concern in healthcare systems across the world.[1] Medication errors are a major problem across care settings, including home, ambulatory, and primary care (henceforth community) settings.[1] The World Health Organization (WHO) has identified medication errors as key focus areas for the enhancement of patient safety in community settings.[2] A recent systematic review revealed considerable variations in the prevalence rates of medication errors in community settings. This result, at least in part, reflects variations in: i) the definitions of medication errors used in studies, ii) the populations studied, iii) the methodologies employed for error detection, and iv) the outcome measures studied.[3] This systematic review also highlighted the absence of studies focusing on medication errors in community settings in the Kingdom of Saudi Arabia (KSA). The pharmacist-led information technology intervention for medication errors (PINCER) trial is among the world's first randomized studies that aimed to reduce the risk of medication errors in general practice. A validated tool for the measurement of medication errors was developed by Avery et al[4] and was used in the PINCER trial in the United Kingdom (UK). This trial shows that the PINCER intervention is more effective than simple feedback for reduction of the numbers of patients at risk from prescribing and monitoring errors in general practice.

The objectives of this study were to investigate the epidemiology of clinically important errors in medicine management, as defined by the PINCER trial[4] and risk factors for clinically important errors among adults managed in community care in SA.

Methods. The current study was divided into 3 phases: a feasibility phase, pilot retrospective cohort phase, and retrospective cohort study. The feasibility phase involved the identification of sites in SA with ambulatory electronic health record (EHR) data for the investigation of issues pertaining to the accessibility and completeness of data, and which provided the opportunity for the dataset to be used in outcome evaluation (**Table 1**). The PINCER trial focused on a pre-specified list of clinically important errors in prescription and monitoring stages of medicine management.[4]

The pilot phase involved testing: i) sample generation, ii) data extraction, and iii) outcome assessment on a randomly selected sample of 200 patients. This article focuses on the pilot phase and the main retrospective cohort study.

The research protocol, data collection sheet, and waiver of informed consent (in place of individual informed consent) were approved by the Clinical Research Committee and the Research Ethics Committee (REC) of the Office of Research Affairs, King Faisal Specialist Hospital and Research Center (KFSH & RC), Riyadh (project # 2171 060), KSA.

Several ambulatory care centers in Riyadh were contacted for fieldwork selection. Family Medicine clinics in KFSH & RC, Riyadh, SA were selected.

A random sample of patients visiting the Family Medicine clinics in KFSH & RC was generated, and the follow-up was performed retrospectively over the 15 months before data extraction. Data collection took 3 months (October 2017 to December 2017). Electronic records were selected using a random number table that was generated using the "simple random sample without replacement" function in STATA (version 14).

The inclusion criteria were: i) Saudi and non-Saudi adults aged 18 years or older, ii) patients who had been registered with the Family Medicine clinics at KFSH & RC for at least 15 months prior to data extraction, and iii) patients recorded as receiving at least one prescribed or over-the-counter (OTC) medication. These medications were checked against the Saudi Food and Drug Authority (FDA) list of human medications and were subsequently classified into prescription or OTC medications.[5] Patient records were excluded if they did not fulfill the inclusion criteria.

The patients' recorded baseline characteristics were as follows: i) age, ii) gender, iii) nationality (Saudi, non-Saudi), iv) diagnosis or underlying conditions, v) OTC medication use recorded at any point during the 15 months, and vi) polypharmacy (≥5 medications at any point during the 15 months). The exposures of interest were the risk factors, and prescription and/or OTC drug.

The outcome variables were: i) period prevalence of the primary, secondary, composite secondary, and revised updated outcome measures, ii) patient and medication-related risk factors (age, gender, nationality, polypharmacy and OTC medicine use), and iii) physician-related risk factors: age (18-50 years, ≥51 years), gender, nationality (Saudi, non-Saudi), number

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Table 1 - Outcome measures from the Pharmacist-led information technology intervention for medication errors (PINCER) trial and the revised updated PINCER.[7,10]

Outcome measures
Primary outcomes
1. Patients with a history of peptic ulcer who have been prescribed a non-selective, NSAID without co-prescription of a PPI
2. (2a) Patients with asthma who have been prescribed a beta-blocker
3. Patients aged 75 years and older who have been prescribed an ACE, or a loop diuretic long-term, who have not had a computer-recorded check of their renal function and electrolytes in the previous 15 months
Secondary outcomes
(2b) Patients with asthma (and no history of CHD) who had been prescribed a beta-blocker
4. Proportion of women with a past medical history of venous or arterial thrombosis who had been prescribed the combined oral contraceptive pill
5. Patients receiving methotrexate for at least 3 months who had not had a full blood count recorded (5a), or liver function test (5b), in the previous 3 months
6. Patients receiving warfarin for at least 3 months who had not had a recorded check of their INR in the previous 12 weeks
7. Patients receiving lithium for at least 3 months who had not had a recorded check of their lithium concentrations in the previous 3 months
8. Patients receiving amiodarone for at least 6 months who had not had a thyroid function test in the previous 6 months
9. Patients receiving prescriptions of methotrexate without instructions that the drug should be taken every week
10. Patients receiving *prescriptions of amiodarone for at least 1 month who are receiving a dose of more than 200 mg per day*
Composite secondary outcome measures
11. Patients with at least one prescription problem (a combination of outcome measures #1,# 2, or# 4)
12. Patients with at least one monitoring problem (a combination of outcome measures #3, #5, #6, #7, and #8)
Additional revised updated outcome measures
13. Prescription of an oral NSAID, without co-prescription of an ulcer-healing drug, to a patient aged ≥ 65 years
14. Prescription of an anti-platelet drug, without co-prescription of an ulcer-healing drug, to a patient with a history of peptic ulceration
15. Prescription of warfarin or NOAC in combination with an oral NSAID
16. Prescription of warfarin or NOAC and an anti-platelet drug in combination, without co-prescription of an ulcer-healing drug
17. Prescription of aspirin in combination with another anti-platelet drug, without co-prescription of an ulcer-healing drug
18. Prescription of a long-acting beta-2 agonist inhaler (excluding combination products with inhaled corticosteroid) to a patient with asthma who is not also prescribed an inhaled corticosteroid
19. Prescription of an oral NSAID to a patient with heart failure
20. Prescription of antipsychotics for >6 weeks in a patient aged ≥ 65 years with dementia but not psychosis
21. Prescription of an oral NSAID to a patient with eGFR <45
ACE - angiotensin converting, beta-blocker - beta-blocker, CHD - coronary heart disease, eGFR - estimated glomerular filtration rate, INR - international normalized ratio, NOAC - new oral anti-coagulant, NSAID - non-steroidal anti-inflammatory drug, PPI - proton-pump inhibitor, Outcome number 2 has two parts: (2a) and (2b).

of physicians involved in a patient's care (one, more than one), certification (American, British, Canadian, Jordanian, or none), and number of years of experience (1-9 years or ≥10 years). For details on the primary, secondary, composite secondary, and revised updated outcome measures are summarize in **Table 1**.[4,6]

We then compared the results of the cohort study with the baseline results of the UK PINCER trial,[4] which were derived through QResearch database interrogation.[7]

Data sources/measurement. After the selection of a random sample from the Family Medicine clinics, in-depth EHR screening, involving the assessment of diagnostic, medication list, and laboratory data, was conducted.

Development of a data collection tool and process. A paper-based data collection form was used to extract summary descriptions of all the relevant information available in the EHRs to gather each patient's demographics and outcome measures (**Appendix 1**). The information obtained was transferred to an Excel spreadsheet for analysis. The electronic data sheet was stored in a password-protected computer and no patient-identifying information was recorded.

Manual data extraction from the EHRs, involving 200 records, was independently undertaken for the pilot retrospective study. For the main cohort study, data extraction was performed for all 2,000 records, while a second trained reviewer undertook the independent assessment of a random 10% of the sample of records.[8,9] Any discrepancy or disagreement was discussed and resolved through double-checking of records or arbitration if a decision could not be reached.

To reduce the risk of selection bias in sampling, simple random sampling was employed. The independent evaluation of a sample of records was designed to minimize the risk of information bias.[10]

For the cohort study, the largest sample size that was feasible given: i) the time available, ii) resources, iii) research team number, and iv) the manual method employed for data extraction resulted in a total of 2,000 records. A sample size of 10% or more of the major study size is commonly deemed adequate for

pilot studies;[11] thus, 200 patient records were randomly selected for the pilot phase.

Data access and data cleaning methods. Data access and cleaning methods were used as per the PINCER trial protocol.[6,7] The electronic data sheet was checked for errors in data entry, outliers, and missing data. An inventory of medical record numbers and each patient's code number was used to ensure that the same patient was not included in the dataset more than once.

Statistical analysis. Microsoft Excel was used to manage and process data; STATA (version 14) was used to analyze the data.

The overall period prevalence rate of patients with at least one error was calculated as: "the number of patients experiencing one or more medication error at any time during the 15-month period (numerator)/ the total number of patients in the study population (denominator)".[12]

The overall period prevalence rate of medication errors was calculated as follows: "the number of medication errors at any time during the 15-month period (numerator)/the total number of patients in the study population (denominator)".

The prevalence of each outcome measure was described using: i) numerators, ii) denominators, and iii) percentages at patient level, as detailed in the PINCER trial protocol.[6,7] To illustrate patients' demographic characteristics and diagnoses, descriptive statistics in terms of frequency counts and proportions were used. To evaluate the association between the risk factors and outcomes, we performed logistic regression modeling. The results of the regression analysis were presented in terms of odds ratios (OR) with their 95% confidence intervals (CIs). For logistic regression modeling, the dependent variable was defined as the presence/absence of the outcome or, more fully, the presence/absence of patients at risk of clinically important errors. To determine the agreement between the 2 independent data extractors, a Kappa coefficient was calculated. A Kappa score: is a measure of inter-rater agreement for categorical variables.[13] Landis and Koch suggested that a Kappa value lower than 0.40 denotes poor-to-fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement, and 0.81-1.00 almost-perfect agreement.[14]

This study follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist[15] and the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement (**Appendix 2**) for reporting the findings.[16]

Results. Family Medicine clinics in KFSH & RC were selected following the feasibility assessment. Five hundred records meeting the inclusion criteria were reviewed. All the necessary information from each patient's record was available in the Integrated Clinical Information System. In the feasibility study, all the outcomes were observed at least once in a total of 500 patients, except for outcomes 7, 8, and 10 (**Table 1**). However, none of the outcome measures were excluded from the pilot and main studies, because it was considered possible that outcomes 7, 8, and 10 may appear when screening a higher number of records.

The findings from this phase of the research indicated that the pilot study was feasible and likely to provide a random sample, and all the information needed for the outcomes was available in one system. Continuation to the pilot and main phases of the study was therefore initiated without the exclusion of any of the outcome measures.

Pilot retrospective study. In the pilot retrospective study, a random sample of 200 records was selected from the Family Medicine clinics in KFSH & RC. The overall period prevalence rate of patients with at least one medication error over 15 months was 10% (95% CI 5.8-14.2). The overall period prevalence rate of medication errors over 15 months was 16% (95% CI 8.2-23.8). The pilot study suggested that clinically important errors commonly occurred in the medicine management of adults. The highest risk of prescription errors was observed in asthma patients who had been prescribed a ß-blocker. A monitoring error was found in one patient receiving lithium for at least 3 months; the patient did not have a recorded check of their lithium concentrations in the previous 3 months. Risk factors that significantly predicted the overall proportion of patients at the risk of medication errors were age ≥65 years and OTC medication use; however, the obtained data suggested that other factors may be identified in the larger planned follow-up study.

The main retrospective cohort study. A total of 4,398 patients visited the Family Medicine department one month prior to data collection. The required information from 2,000 electronic records was collected after the exclusion of patients who do not meet the inclusion criteria (**Figure 1**).

The percentage of adults in the age range 18-64 years was 83.85% and the percentage of those aged 65 years or older was 16.15%. The majority of the study population was of Saudi nationality (67.2%). **Table 2** summarizes the participants' characteristics. The agreement between the 2 independent data extractors dealing with the 200 EHRs was substantial (Kappa 0.8). All discrepancies

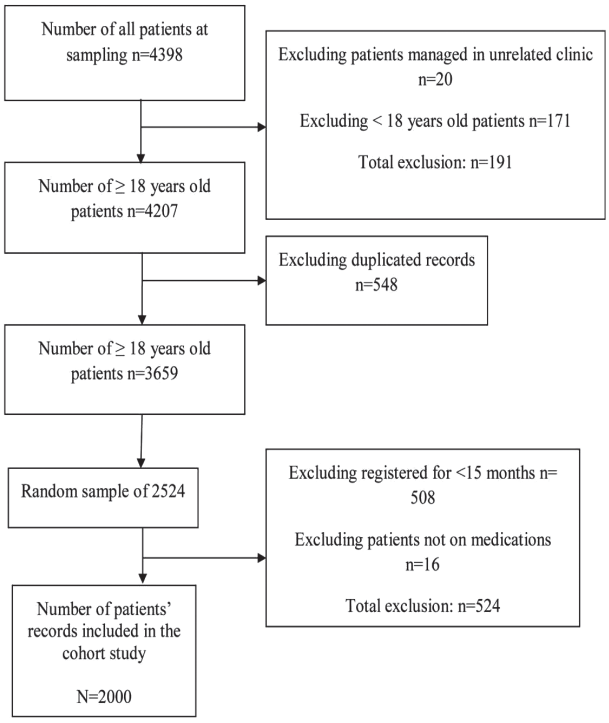

Figure 1 - Cohort study flowchart outlines and sample enrollment.

were resolved by discussion and the double-checking of records.

Table 3 summarizes the prevalence of each outcome measure. A total of 162 prescribing/monitoring errors were found during the study period. The overall period prevalence of patients with at least one medication error over 15 months was 5.85% (95% CI 4.8-6.9), while the overall period prevalence of medication errors over 15 months was 8.1% (95% CI 6.5-9.7).

Risk factors that significantly predicted the overall proportion of patients at risk of experiencing medications errors were: i) age of ≥65 years, ii) male gender, iii) Saudi nationality, and iv) using ≥5 drugs (**Table 4**). Risk factors that significantly predicted the overall proportion of patients who were at risk of experiencing medication errors were physicians' male gender and Saudi nationality (**Table 5**). **Table 5** also summarizes the risk factors for individual errors.

Discussion. Clinically important errors were observed commonly in medicine management. A random sample of 2,000 patient records was selected, resulting in the identification of 162 clinically important errors in medicine management. The overall period prevalence of patients with at least one medication error over 15 months was 5.85% (95% CI 4.8-6.9), while the overall period prevalence of medication errors was 8.1% (95% CI 6.5-9.7). The highest risk of prescription errors was in Outcome 2a: 'patients with asthma who had been prescribed a ß-blocker'. However, for monitoring errors, the highest risk was in Outcome 7: 'patients receiving lithium for at least 3 months, who did not have a recorded check of their lithium concentrations in the previous 3 months'.

Table 2 - Cohort study participants' demographic characteristics.

Variables	n (%)
Age (years)	
18-64	1,677 (83.9)
≥65	323 (16.2)
Mean	49.9
95% confidence intervals	48.2 to 49.6
Gender	
Male	698 (34.9)
Female	1,302 (65.1)
Nationality	
Saudi	1,344 (67.2)
Non-Saudi	656 (32.8)
Polypharmacy	
Yes: ≥5 medications	1,115 (55.8)
No: 1-4 medications	885 (44.3)
OTC medicines	
Yes: using OTC	1,899 (95.0)
No: not using OTC	101 (5.1)
Diagnosis	
Cardiac and vascular disorder	
Cardiac arrhythmias	18 (0.9)
Dyslipidemia	819 (41.0)
Essential hypertension	816 (40.8)
Heart failure	14 (0.7)
Ischemic heart disease	69 (3.5)
Pulmonary disorder	
Asthma	250 (12.5)
COPD	5 (0.3)
Rhinitis	324 (16.2)
Psychiatric disorder	
Depression	164 (8.2)
Dementia	17 (0.9)
Gastrointestinal disorder	
Ulcer	5 (0.3)
Gastritis	90 (4.5)
History of *Helicobacter pylori*	22 (1.1)
Renal disorder	
Chronic kidney disease	60 (3.0)
Arthritic disorder	
Osteoarthritis	180 (9.0)
Osteoporosis	44 (2.2)
Endocrine disorder	
Hypo/hyperthyroidism	353 (17.7)
Diabetes mellitus	595 (29.8)

OTC - over-the-counter (medications), COPD - chronic obstructive pulmonary disease

Table 3 - Cohort study period prevalence of each primary, secondary, composite and revised updated outcome measure described using numerators, denominators, and percentage, at patient level.

Outcome measures	Numerator	Denominator	Proportion of each outcome 95% confidence interval
Primary outcomes			
1. Patients with a history of peptic ulcer who have been prescribed a non-selective NSAID without co-prescription of a PPI	0	4	0
(2a) Patients with asthma who have been prescribed a beta-blocker	7	13	53.8; 95% CI 25.5 to 85.2
3. Patients aged 75 years and older who have been prescribed an ACE inhibitor or a loop diuretic long-term, who have not had a computer-recorded check of their renal function and electrolytes in the previous 15 months	0	11	0
Secondary outcomes			
(2b) Patients with asthma (and no history of CHD) who had been prescribed a beta-blocker	21	241	8.7; 95% CI 5.1 to12.3
4. Proportions of women with a past medical history of venous or arterial thrombosis who had been prescribed the combined oral contraceptive pill	0	4	0
5. Patients receiving methotrexate for at least 3 months who had not had a full blood count recorded (5a), or liver function test (5b), in the previous 3 months	(5a) 0 (5b) 0	(5a) 14 (5b) 14	(5a) 0 (5b) 0
6. Patients receiving warfarin for at least 3 months who had not had a recorded check of their INR in the previous 12 weeks	4	16	25.0; 95% CI 1.2 to 48.8
7. Patients receiving lithium for at least 3 months who had not had a recorded check of their lithium concentrations in the previous 3 months	2	2	100.0; 95% CI 100.0 to 100.0
8. Patients receiving amiodarone for at least 6 months who had not had a thyroid function test in the previous 6 months	0	0	Not calculable
9. Patients receiving prescriptions of methotrexate without instructions that the drug should be taken every week	0	14	0
10. Patients receiving prescriptions of amiodarone for at least 1 month who are receiving a dose of more than 200 mg per day	0	0	Not calculable
Composite secondary outcome measures			
11. Patients with at least one prescription problem (a combination of outcome measures 1, 2, or 4)	28	259	10.8; 95% CI 7.0 to 14.6
12. Patients with at least one monitoring problem (a combination of outcome measures 3, 5, 6, 7, and 8)	6	43	13.95; 95% CI 3.2 to 24.7
Period prevalence	68 total number of errors	2000 total patients	3.4; 95% CI 2.2 to 4.6
Period prevalence	Total of 33 patients with at least one error	2,000 total patients	1.65; 95% CI 1.1 to 2.2
Additional revised updated outcomes measures			
13. Prescription of an oral NSAID, without co-prescription of an ulcer-healing drug, to a patient aged ≥65 years	52	269	19.3; 95% CI 14.6 to 24.1
14. Prescription of an anti-platelet drug without co-prescription of an ulcer-healing drug, to a patient with a history of peptic ulceration	1	4	25.0; 95% CI -54.6 to104.6
15. Prescription of warfarin or NOAC, in combination with an oral NSAID	2	32	6.25; 95% CI -2.6 to 15.1
16. Prescription of warfarin or NOAC and an anti-platelet drug in combination without co-prescription of an ulcer-healing drug	11	22	50.0; 95% CI 27.3 to 72.7
17. Prescription of aspirin in combination with another anti-platelet drug without co-prescription of an ulcer-healing drug	23	344	6.7; 95% CI 4.0 to 9.3
18. Prescription of a long-acting beta-2 agonist inhaler (excluding combination products with inhaled corticosteroid) to a patient with asthma who is not also prescribed an inhaled corticosteroid	0	0	Not calculable
19. Prescription of an oral NSAID to a patient with heart failure	3	14	21.4; 95% CI -3.15 to 46.0
20. Prescription of antipsychotics for >6 weeks in a patient aged ≥65 years with dementia but not psychosis	2	17	11.8; 95% CI -5.3 to 28.8
21. Prescription of an oral NSAID to a patient with eGFR <45	0	38	0
Overall period prevalence	162 total number of errors	2000 total patients	8.1; 95% CI 6.5 to 9.7
Overall period prevalence	Total of 117 patients with at least one error	2,000 total patients	5.85; 95% CI 4.8 to 6.9

ACE - angiotensin converting, CHD - coronary heart disease, eGFR - estimated Glomerular Filtration Rate, INR - international normalized ratio, NOAC - New Oral Anti-coagulant, NSAID - non-steroidal anti-inflammatory drug, PPI - proton-pump inhibitor

Table 4 - Cohort study association between patient and medication-related risk factors and patients at risk of errors outcomes. (Data obtained from logistic regression model).

Outcome number	Age (≥65/18 to 64 years) OR; 95% CI	*P*-value	Gender (male /female) OR; 95% CI	*P*-value	Nationality (Saudi/non-Saudi) OR; 95% CI	*P*-value	Polypharmacy (yes/no) OR; 95% CI	*P*-value	OTC (yes/no) OR; 95% CI	*P*-value
Overall patients at risk of experiencing medications errors										
	27.2; 18.6 to 39.85	0.00	1.9; 1.5 to 2.25	0.00	2.7; 2.2 to 3.3	0.00	4.7; 3.8 to 5.8	0.00	0.8; 0.55 to 1.25	0.38
Number of individual patients at risk outcome										
1	15.7; 1.6 to 151.5	0.02	5.6; 0.6 to 54.1	0.14	1.5; 0.15 to 14.1	0.74	NA	-	NA	-
2a	4.5; 1.5 to 13.5	0.01	2.2; 0.7 to 6.5	0.16	2.7; 0.6 to 12.2	0.19	NA	-	NA	-
2b	1.5; 1.0 to 2.05	0.03	0.9; 0.7 to 1.2	0.46	1.3; 0.9 to 1.8	0.06	2.7; 2.0 to 3.7	0.00	1.4; 0.7 to 2.9	0.32
3	NA	-	1.1; 0.3 to 3.65	0.91	NA	-	3.6; 0.8 to 16.7	0.10	NA	-
4	NA	-	NA	-	NA	-	0.8; 0.1 to 5.6	0.82	NA	-
5a	NA	-	0.5; 0.1 to 1.8	0.29	1.8; 0.5 to 6.5	0.37	2.9; 0.8 to 10.5	0.10	NA	-
5b	NA	-	0.5; 0.1 to 1.8	0.29	1.8; 0.5 to 6.5	0.37	2.9; 0.8 to 10.5	0.10	NA	-
6	5.3; 1.9 to 14.2	0.00	1.45; 0.5 to 3.9	0.46	3.4; 0.8 to 15.2	0.10	5.6; 1.3 to 24.8	0.02	NA	-
7	NA	-	NA	-	NA	-	0.8; 0.1 to 12.7	0.87	0.05; 0.0 to 0.85	0.04
9	NA	-	0.5; 0.1 to 1.8	0.29	1.8; 0.5 to 6.5	0.37	1.9; 0.6 to 6.4	0.25	NA	-
11	1.6; 1.2 to 2.2	0.00	0.95; 0.7 to 1.25	0.74	1.4; 1.1 to 1.9	0.02	2.8; 2.1 to 3.8	0.00	1.55; 0.8 to 3.1	0.22
12	3.9; 2.1 to 7.2	0.00	0.9; 0.5 to 1.7	0.75	2.2; 0.9 to 4.7	0.05	3.55; 1.6 to 7.7	0.00	2.3; 0.3 to 16.6	0.42
13	NA	-	2.2; 1.7 to 2.9	0.00	9.9; 5.9 to 16.9	0.00	3.9; 2.8 to 5.3	0.00	0.8; 0.5 to 1.4	0.47
14	15.7; 1.6 to 151.5	0.02	5.6; 0.6 to 54.1	0.14	1.5; 0.15 to 14.1	0.74	NA	-	NA	-
15	6.2; 3.0 to 12.45	0.00	1.5; 0.7 to 2.95	0.29	2.7; 1.0 to 6.9	0.05	4.4; 1.7 to 11.4	0.00	1.65; 0.2 to 12.3	0.62
16	4.4; 1.9 to 10.3	0.00	1.3; 0.55 to 3.0	0.55	3.1; 0.9 to 10.6	0.07	2.7; 1.0 to 7.4	0.05	1.1; 0.1 to 8.4	0.91
17	4.7; 3.6 to 6.1	0.00	2.3; 1.8 to 2.9	0.00	2.4; 1.8 to 3.25	0.00	5.2; 3.8 to 6.9	0.00	0.6; 0.4 to 0.9	0.02
19	5.3; 1.8 to 15.2	0.00	0.5; 0.1 to 1.8	0.29	6.4; 0.8 to 49.0	0.07	NA	-	NA	-
20	NA	-	2.1; 0.8 to 5.5	0.13	NA	-	3.7; 1.1 to 13.0	0.04	0.4; 0.1 to 1.7	0.22
21	7.6; 3.9 to 14.6	0.00	1.4; 0.7 to 2.6	0.35	5.8; 1.8 to 18.9	0.00	14.7; 3.5 to 61.3	0.00	0.9; 0.2 to 4.0	0.95

NA - no association. OR = 1. Outcome number 2 has 2 parts: (2a) and (2b). Outcome number 5 has 2 parts (5a) and (5b)

Table 5 - Cohort study association between physician-related risk factors and patients at risk of errors outcomes. (Data obtained from logistic regression model).

Outcome number	Age (years) (≥51/18-50) OR; 95% CI	*P*-value	Gender (male/female) OR; 95% CI	*P*-value	Nationality (Saudi/non-Saudi) OR; 95% CI	*P*-value	Certificate (American, British, Canadian, Jordanian certified, or none) OR; 95% CI	*P*-value	Years of experience (≥10/1-9) OR; 95% CI	*P*-value	Number (≥1/1) OR; 95% CI	*P*-value
Overall patients at risk of experiencing medications errors												
	1.0; 0.8 to 1.3	0.84	1.6; 1.3 to 2.1	0.00	1.9; 1.5 to 2.5	0.00	1.0; 0.9 to 1.2	0.49	1.1; 0.9 to 1.4	0.39	0.5; 0.4 to 0.6	0.00
Number of individual patients at risk outcome												
2a	0.6; 0.15 to 2.2	0.42	1.7; 0.45 to 6.55	0.42	2.85; 0.9 to 9.4	0.09	1.3; 0.7 to 2.3	0.41	1.2; 0.35 to 4.2	0.74	0.3; 0.1 to 1.1	0.08
2b	1.4; 0.9 to 1.9	0.06	1.1; 0.8 to 1.5	0.65	0.9; 0.6 to 1.3	0.59	1.05; 0.9 to 1.2	0.49	1.0; 0.75 to 1.4	0.84	1.05; 0.7 to 1.6	0.79
3	1.5; 0.4 to 6.2	0.54	1.1; 0.25 to 4.5	0.92	1.1; 0.2 to 5.6	0.88	1.0; 0.5 to 2.0	0.98	0.7; 0.2 to 2.8	0.62	0.4; 0.1 to 1.55	0.19
4	0.8; 0.1 to 8.5	0.83	0.3; 0.0 to 3.55	0.36	NA	-	0.3; 0.05 to 2.0	0.23	0.35; 0.0 to 3.9	0.39	NA	-
5a	1.9; 0.6 to 6.1	0.31	0.4; 0.1 to 1.25	0.11	1.3; 0.3 to 4.8	0.72	0.7; 0.4 to 1.4	0.33	3.2; 0.7 to 14.8	0.14	0.6; 0.15 to 2.0	0.38
5b	1.9; 0.6 to 6.1	0.31	0.4; 0.1 to 1.25	0.11	1.3; 0.3 to 4.8	0.72	0.7; 0.4 to 1.4	0.33	3.2; 0.7 to 14.8	0.14	0.6; 0.15 to 2.0	0.38
6	0.6; 0.15 to 2.2	0.42	1.1; 0.3 to 3.9	0.85	1.3; 0.3 to 4.8	0.72	0.8; 0.4 to 1.5	0.49	1.2; 0.35 to 4.2	0.74	1.1; 0.2 to 4.8	0.92
7	NA	-	NA	-	NA	-	NA	-	NA	-	0.15; 0.0 to 2.5	0.19
9	1.9; 0.6 to 6.1	0.31	0.5; 0.2 to 1.8	0.30	1.3; 0.3 to 4.8	0.72	0.7; 0.4 to 1.4	0.33	1.9; 0.5 to 7.1	0.35	0.6; 0.15 to 2.0	0.38
11	1.3; 0.9 to 1.7	0.13	1.1; 0.8 to 1.5	0.56	0.9; 0.7 to 1.4	0.83	1.0; 0.9 to 1.2	0.54	1.0; 0.7 to 1.4	0.95	0.9; 0.7 to 1.4	0.95
12	1.1; 0.5 to 2.3	0.76	0.7; 0.3 to 1.4	0.29	1.2; 0.5 to 2.7	0.69	0.7; 0.5 to 1.1	0.13	1.7; 0.8 to 3.8	0.17	0.6; 0.3 to 1.2	0.15
13	0.9; 0.7 to 1.25	0.61	2.6; 1.8 to 3.7	0.00	2.7; 1.9 to 3.7	0.00	1.1; 0.9 to 1.3	0.23	1.4; 1.0 to 1.9	0.04	0.3; 0.2 to 0.4	0.00
15	0.7; 0.3 to 1.6	0.38	1.8; 0.7 to 4.7	0.19	1.5; 0.6 to 3.7	0.38	0.8; 0.55 to 1.3	0.45	1.1; 0.5 to 2.55	0.83	0.45; 0.2 to 1.0	0.06
16	0.6; 0.2 to 1.9	0.41	1.6; 0.5 to 5.2	0.42	1.9; 0.6 to 5.7	0.25	0.9; 0.6 to 1.6	0.87	0.9; 0.3 to 2.7	0.91	0.4; 0.15 to 1.0	0.06
17	0.9; 0.7 to 1.2	0.63	1.7; 1.3 to 2.3	0.00	1.9; 1.45 to 2.7	0.00	0.9; 0.85 to 1.1	0.78	0.9; 0.7 to 1.3	0.91	0.7; 0.5 to 0.9	0.01
19	0.7; 0.2 to 2.6	0.55	5.9; 0.7 to 46.4	0.09	5.2; 1.4 to 18.4	0.01	1.1; 0.6 to 2.0	0.79	1.6; 0.4 to 6.4	0.47	0.6; 0.15 to 2.0	0.38
20	0.8; 0.2 to 2.6	0.67	7.2; 0.9 to 55.8	0.06	1.1; 0.3 to 4.2	0.85	1.05; 0.6 to 1.8	0.86	0.3; 0.1 to 1.2	0.09	0.3; 0.1 to 0.8	0.01
21	0.8; 0.4 to 1.8	0.62	3.6; 1.2 to 10.6	0.02	2.9; 1.4 to 6.5	0.01	1.3; 0.9 to 1.9	0.16	1.9; 0.8 to 4.6	0.14	0.4; 0.2 to 0.75	0.01

NA - no association. OR = 1. Outcome number 2 has 2 parts: (2a) and (2b). Outcome number 5 has 2 parts (5a) and (5b)

Patient and medication-related risk factors that significantly predicted the risk of errors were as follows: i) age ≥65 years, ii) male gender, iii) Saudi nationality, and iv) using ≥5 drugs. Physician-related risk factors that significantly predicted the risk of errors included male gender and Saudi nationality.

Strength. First, the list of clinically important errors in the prescription and monitoring stages that were used in this study was validated and then developed according to a systematic review, with inputs from research studies and experts, and a consensus on the overall burden and severity of iatrogenic harm in primary care, in the PINCER trial.[17-19] Second, data collection of the total pilot study sample and 10% of the sample size of the cohort study was independently undertaken by 2 reviewers, resulting in substantial agreement. Third, patient, medication, and physician-related factors that contribute to the risk of medication error occurrence were considered. Fourth, Outcome 5, methotrexate, was observed more frequently in the cohort study than the pilot study. Fifth, the large, nationally representative cohort of adults was followed-up over a 15-month period. Finally, this is the first epidemiological cohort study to focus on a pre-specified list of clinically important errors in community care settings in SA.

Study limitations. This study has some limitations that should be considered. First, outcomes 8 and 10 were not observed; this could be attributed to the low prescription rate of amiodarone to cardiac arrhythmia patients. Second, data collection was performed manually due to the inability to ensure the accuracy and quality of patients' information gathered electronically. Manual data extraction was also employed to avoid delays associated with the generation of the required anonymized data electronically from the electronic medical records department in KFSH & RC. Third, the results may not be generalizable because the study was conducted in a single community care setting in KSA. Fourth, the actual rates of use of these medications may be unknown as a large number of OTC medications can be brought in from outside the hospital and may not be recorded by physicians. Fifth, there is a risk of information bias, as the investigators relied on only EHR information for the identification and assessment of the outcomes of interest. Finally, there is inconsistency in the precision type between the period prevalence measure in the present cohort (namely, 95% CI) and that in the PINCER trial (namely, IQR); as a result, we compared the proportions alone without precisions.

Interpretation in the light of the wider published literature. Our results were compared to the baseline characteristics of the PINCER trial, as derived from the QRESEARCH database, which is one of the largest aggregate general practice electronic databases worldwide, comprising 487 general practices.[20] The overall period prevalence of the first 12 clinically important errors in medicine management was 3.4% (95% CI 2.2-4.6) in this research, compared to the 0.9% in the PINCER trial.[20]

The distribution of each estimate for the outcome measures is as follows: In this study, higher period prevalence estimates were observed for the following: Outcomes 2a and 2b: asthma and ß-blocker, Outcome 6: warfarin and international normalized ratio, Outcome 7: lithium and lithium level, Outcome 11: at least one prescription error, and Outcome 12: at least one monitoring error. In this study, we could not estimate the rates for the following outcomes, because there were no events: Outcome 1: peptic ulcer and NSAID without an ulcer-healing drug, Outcome 3: ACE inhibitor / diuretics and laboratory test, Outcome 4: venous or arterial thromboembolism and arterial thrombosis and combined oral contraceptives, and Outcomes 5a and 5b: methotrexate and full blood count, and methotrexate and liver function test. For Outcome 8, amiodarone and thyroid function test, we observed no patients on amiodarone. This may reflect both the differences in the healthcare services provided in KSA and the UK and the varied methods of the extraction of data and outcomes between the 2 studies. In the baseline characteristics of the PINCER trial, data were collected prospectively through a computer-recorded method and the level of accuracy and completeness was shown to be high.[20,21] However, in this study, the data were collected retrospectively through manual data extraction. Akbarov et al[22] in a cross-sectional study using linked records in the UK general practices, used 22 medication safety indicators (18 prescribing indicators with an overall prevalence as 5.45% and 4 monitoring indicators with an overall prevalence as 7.65%). In order to compare our study results with the findings from the previous study,[22] it is important to have a consistent definition of numerator and denominator. Only 13 consistent indicators can be compared with the outcome measures employed in this study. The other 9 indicators were not used in our study, so a comparison between the overall outcome measures' estimate and other study[22] overall outcome measures' estimates were not established. This present study found higher period prevalence estimates for the following: Outcome 2a (asthma and ß-blocker), Outcome 6 (warfarin and INR), Outcome 13 (aged ≥65 years using NSAID without an ulcer-healing drug), Outcome

15 (warfarin/NOAC and NSAID), and Outcome 19 (heart failure and NSAID). In this study, we could not estimate the rates for the following outcomes, because there were no events: Outcome 1 (peptic ulcer and NSAID without ulcer-healing drug), Outcome 3 (ACE inhibitor/diuretics and lab test), Outcome 4 (venous or arterial thromboembolism and arterial thrombosis and combined oral contraceptives), Outcomes 5a and 5b (methotrexate and full blood count and methotrexate and liver function test), and Outcome 21 (eGFR <45 and NSAID). For outcome 8 (amiodarone and thyroid function test), no patient in this study was on amiodarone. For (outcome 18: long-acting beta-2 agonist inhaler [excluding combination products with inhaled corticosteroid] to a patient with asthma who is not also prescribed an inhaled corticosteroid), all the study patients were on combination products with the inhaled corticosteroid.

Implications for research, policy, and practice. For healthcare professionals, there is a need for the following: i) training, education, and monitoring with the involvement of medication safety pharmacists in the community, ii) the implementation of computerized prescription with software integration for the detection of clinically important errors in medicine management during prescription entry, iii) the provision of a record of current medication lists for each patient in the community, and vi) empowerment and education among patients and the public, particularly among those with chronic diseases and polypharmacy, to increase the knowledge of medication safety. For patients, tools and technology should be employed, particularly for monitoring and follow-up, as most medication errors occur in this stage due to irregular outpatient visits; there is a need for patients' current medication lists to be shown at each pharmacy visit. Further study is required for the following: i) to replicate the outcome measures in different community care contexts in KSA, to increase the generalizability of our findings and ii) to further explore error-related adverse events, and their causes and prevalence, in community care settings in SA. Consideration should also be given to undertaking interventional studies aimed at reducing the risk of medication errors. A trial based on the PINCER trial could be conducted in the KFSH & RC. Such an initiative would have to be modified to a parallel group design, as opposed to the cluster, randomized control design used in the PINCER trial. A random sample of records of individuals could be selected and randomized to receive either simple feedback or pharmacist intervention. The first challenge would be to identify, by manual or computer-generated methods, those patients who are potentially at risk of clinically important errors in medicine management. In the simple feedback arm of this trial, physicians would be given manual or computer-generated feedback on patients who are at potential risk of clinically important errors, together with brief written educational materials explaining the importance of each type of error. In the pharmacist-intervention arm, pharmacists should provide simple feedback plus educational outreach "academic detailing", while considering the human error theory and provide support in order to correct and prevent medication errors. The choice of manual or computer-generated methods is likely to be challenging, as the computer-generated method has not been used till date in the KFSH & RC. This proposed research initiative should aim to do the following: i) calculate the prevalence of the outcome measures before and after the intervention and ii) decrease the number of clinically important errors as much as possible.

In conclusions, this study shows that clinically important medication errors occur commonly, and such mistakes could potentially harm patients' health. Patient-related risk factors that significantly predicted the overall proportion of patients at risk of experiencing medication errors were as follows: i) age ≥65 years, ii) male gender, iii) Saudi nationality, and iv) using ≥5 drugs. Physician-related risk factors that significantly predicted the overall proportion of patients at risk of errors were male gender and Saudi nationality. Future research should aim to replicate these findings in other community care contexts in SA, to further explore any associated error-related adverse events, and also to develop and evaluate an intervention aimed at decreasing the incidence of clinically important errors in medicine management in SA.

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Appendix 1 - Data collection form of medication errors study.

A) Demographic and basic information

Patient characteristics

Patient code				
Age	Years _____			
Gender	M_____	F _____		
Nationality	Saudi	Non-Saudi		
Diagnosis or past medical history				
	Anaemia		Back pain	
	Allergic rhinitis		Osteoporosis	
	Benign prostatic hypertrophy (BPH)		Osteoarthritis	
	Bronchial asthma		Type 1 diabetes mellitus	
	Chronic obstructive pulmonary disease (COPD)		Type 2 diabetes mellitus	
	Coronary artery disease (CAD)		Vitamin D deficiency	
	Depression		Hypertriglyceridemia	
	Essential primary hypertension (HTN)		Hyperlipidaemia	
	Gastroesophageal reflux disease (GERD)		Other:	
	Heart failure (HF)			
	Hyperthyroidism			
	Hypothyroidism			
Polypharmacy at any point (≥5 medications)			Yes	No
Over-the-counter medication			Yes	No

Physician characteristics

Physician code	
Physician number	

B) outcome measures

	Numerator	Yes/no	Denominator	Yes/no	Comment
Primary, secondary and composite outcome measures					
1	History of peptic ulcer prescribed an non-steroidal anti-inflammatory drug (NSAID) without a proton-pump inhibitor (PPI)		History of peptic ulcer without a PPI		
2a	Asthma prescribed a β-blocker		Asthma		
2b	Asthma and not CHD prescribed a β-blocker		Asthma and not CHD		
3	Aged ≥75 on long term ACE inhibitors or diuretics without urea and electrolyte monitoring in the previous 15 months		Aged ≥75 on long term ACE inhibitors or diuretics		
4	History of venous or arterial thromboembolism and arterial thrombosis prescribed combined oral contraceptives (Female)		History of venous or arterial thromboembolism and arterial thrombosis (female)		
5a	Methotrexate for ≥ 3 months without a full blood count in last 3 months		Methotrexate for ≥3 months		
5b	Methotrexate for ≥ 3 months without an liver function test in last 3 months		Methotrexate for ≥3 months		
6	Warfarin for ≥ 3 months without an international normalised ratio (INR) in last		Warfarin for ≥3 months		
7	Lithium for ≥ 3 months without a lithium level in last 3 months		Lithium for ≥3months		
8	Amiodarone for ≥ 6 months without a thyroid function test in the last 6 months		Amiodarone for ≥6 months		
9	Methotrexate without instructions to take weekly		Patient prescribed methotrexate		
10	Amiodarone for ≥ 1 month at a dose of more than 200mg/day		Amiodarone for ≥1 month		
11	Patients with at least one prescription problem (a combination of outcome measures 1, 2, or 4)				
12	Patients with at least one monitoring problem (a combination of outcome measures 3, 5, 6, 7, and 8)				

Appendix 1 - Data collection form of medication errors study. (continued)

	Numerator	Yes/no	Denominator	Yes/no	Comment
Revised updated outcome measures					
13	Patients aged ≥65 years prescribed an oral NSAID without co-prescription of an ulcer-healing drug		Patients aged ≥65 years without co-prescription of an ulcer-healing drug		
14	History of peptic ulcer prescribed an antiplatelet drug without co-prescription of an ulcer-healing drug		History of peptic ulceration without co-prescription of an ulcer-healing drug		
15	Prescribed warfarin or NOAC in combination with an oral NSAID		Prescribed warfarin or NOAC		
16	Prescribed warfarin or NOAC and an antiplatelet drug in combination without co-prescription of an ulcer-healing drug		Prescribed warfarin or NOAC without co-prescription of an ulcer-healing drug		
17	Prescribed aspirin in combination with another antiplatelet drug without co-prescription of an ulcer-healing drug		Prescribed aspirin without co-prescription of an ulcer-healing drug		
18	Asthma prescribed a long-acting beta-2 agonist inhaler who is not also prescribed an inhaled corticosteroid		Asthma prescribed a long-acting beta-2 agonist inhaler		
19	Heart failure prescribed an oral NSAID		Heart failure		
20	Patients aged ≥65 years with dementia but not psychosis prescribed antipsychotic drugs for >6weeks		Patients aged ≥65 years with dementia but not psychosis		
21	Patients with an eGFR <45 prescribed an oral NSAID		Patients with an eGFR <45		
If the patient had a history of the following:					
Peptic ulcer - see outcome 1 and 14					
Asthma - see outcome 2a, 18					
OR Asthma and <u>not</u> coronary heart disease (CHD) - see outcome 2b, 18					
A female with venous or arterial thromboembolism and arterial thrombosis - see outcome 4					
Patient aged ≥65 years - see outcome 13					
Patient aged ≥65 years with dementia - see outcome 20					
Heart failure - see outcome 19					
eGFR <45 - see outcome 21					
If the patient was on the following medications					
Aged ≥75 years and on angiotensin converting enzyme (ACE) inhibitors or diuretics - see outcome 3					
Methotrexate - see outcome 5a, 5b & 9					
Warfarin - see outcome 6, 15 & 16					
New Oral Anti-Coagulant (NOAC) - see outcome 15 & 16					
Lithium - see outcome 7					
Amiodarone - see outcome 8 &10					
Aspirin - see outcome 17					

ACE - angiotensin converting enzyme, CHD - coronary heart disease, eGFR - estimated glomerular filtration rate, INR - international normalized ratio, NOAC - new oral anti-coagulant, NSAID - non-steroidal anti-inflammatory drug, PPI - proton-pump inhibitor, PINCER - pharmacist-led information technology intervention. Outcome number 5 has 2 parts (5a) and (5b)

Appendix 2 - The RECORD statement-checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data.

Item	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	1	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.	1
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	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	6		
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	6	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.	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	6	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.	
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	7		
Bias	9	Describe any efforts to address potential sources of bias	8		
Study size	10	Explain how the study size was arrived at	8		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	-		

Appendix 2 - Data collection form. (continued)

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	8		
Data access and cleaning methods			8	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	8
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.	-
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	10	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.	-
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)	11		
Outcome data	15	Cohort study - Report numbers of outcome events or summary measures over time Case-control study - Report numbers in each exposure category, or summary measures of exposure Cross-sectional study - Report numbers of outcome events or summary measures	12		
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	11		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	12		

Appendix 2 - Data collection form. (continued)

Discussion					
Key results	18	Summarize key results with reference to study objectives	13		
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	13	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.	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14		
Generalisability	21	Discuss the generalisability (external validity) of the study results	14		
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	17		
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.	-