

# Identifying Ontario geographic regions to assess adults who present to hospital with laboratory-defined conditions: a population-based study

Journal:	CMAJ Open
Manuscript ID	CMAJOpen-2019-0065
Manuscript Type:	Cohort (retrospective)
Date Submitted by the Author:	01-May-2019
Complete List of Authors:	Iskander, Carina; Western University, Epidemiology & Biostatistics McArthur, Eric; Institute for Clinical Evaluative Sciences, Nash, Danielle; Institute for Clinical Evaluative Sciences, Gandhi, Sonja; Sanofi Pasteur , Epidemiology and Benefit-Risk Evaluation Weir, Matthew; Western University, Medicine Muanda-Tsobo, Flory; Institute for Clinical Evaluative Sciences, ; Western University, Nephrology Garg, Amit X.; University of Western Ontario, Kidney Clinical Research Unit;
More Detailed Keywords:	
Keywords:	Epidemiology, Health services research
Abstract:	Background: To define geographic regions (forward sortation areas; FSAs) in Ontario, Canada from which people would likely present to a hospital linked to the Ontario Laboratories Information System (OLIS). Collectively, these geographic regions comprise a catchment area to assess adults who present to hospital with laboratory-defined conditions such as acute kidney injury, hyperkalemia and hyponatremia. Methods: This study was descriptive research using administrative data in Ontario, Canada from April 1, 2007 to December 31, 2017. The participants were adults who presented to the emergency department in the National Ambulatory Care Reporting System database for any reason. To assess changes over time, all emergency department visits were divided into fiscal quarters (i.e. April-June, July-September, October-December, January-March). The primary outcome measure was the proportion of people in a given FSA presenting to an emergency department at an OLIS-linked hospital (versus a non OLIS-linked hospital). To be included in the catchment area, at least 90% of all emergency department visits in a given quarter from a given FSA must have occurred at an OLIS-linked hospital. Results: By December 31, 2017, 323 out of 526 Ontario FSAs (61.4%) met the criteria to be in the catchment area. This represents a catchment population of approximately 8.5 million individuals in Ontario.

Interpretation: We successfully identified relevant Ontario geographic
regions to assess adults presenting to hospital with conditions identifie through hospital-based laboratory tests. Studies can now be conducted using these identified areas.
<b>SCHOLARONE</b> <sup>™</sup>
Manuscripts
For Peer Review Only

# Identifying Ontario geographic regions to assess adults who present to hospital with laboratory-defined conditions: a population-based study

Carina Iskander, BMSc<sup>1</sup>; Eric McArthur, MSc<sup>2</sup>; Danielle M Nash, MSc, PhD<sup>1,2</sup>; Sonja Gandhi-Banga, PhD<sup>2,3</sup>; Matthew A Weir, MD, MSc<sup>2,4</sup>; Flory Tsobo Muanda, MD, PhD<sup>1,2</sup>; Amit X Garg, MD, PhD<sup>1,2</sup>

# **Author Affiliations:**

- 1. Department of Epidemiology and Biostatistics, Western University, London, Canada
- 2. ICES, Ontario, Canada
- 3. Epidemiology and Benefit-Risk Evaluation, Sanofi Pasteur, Toronto, Canada
- 4. Department of Medicine, Western University, London, Canada

**Corresponding Author**: Amit X Garg, MD, PhD ICES Western 800 Commissioners Rd. E., Victoria Hospital, Room ELL-215. London, Ontario, Canada N6A 5W9 Tel: 519-685-8502. Email: <u>amit.garg@lhsc.on.ca</u>

Competing interests: None declared.

Word Count: 1,980 (excluding title page, abstract, references, figures & tables) 4,000 word limit

## ABSTRACT

**Background:** To define geographic regions (forward sortation areas; FSAs) in Ontario, Canada from which people would likely present to a hospital linked to the Ontario Laboratories Information System (OLIS). Collectively, these geographic regions comprise a catchment area to assess adults who present to hospital with laboratory-defined conditions such as acute kidney injury, hyperkalemia and hyponatremia.

**Methods:** This study was descriptive research using administrative data in Ontario, Canada from April 1, 2007 to December 31, 2017. The participants were adults who presented to the emergency department in the National Ambulatory Care Reporting System database for any reason. To assess changes over time, all emergency department visits were divided into fiscal quarters (i.e. April-June, July-September, October-December, January-March). The primary outcome measure was the proportion of people in a given FSA presenting to an emergency department at an OLIS-linked hospital (versus a non OLIS-linked hospital). To be included in the catchment area, at least 90% of all emergency department visits in a given quarter from a given FSA must have occurred at an OLIS-linked hospital.

**Results:** By December 31, 2017, 323 out of 526 Ontario FSAs (61.4%) met the criteria to be in the catchment area. This represents a catchment population of approximately 8.5 million individuals in Ontario.

**Interpretation:** We successfully identified relevant Ontario geographic regions to assess adults presenting to hospital with conditions identified through hospital-based laboratory tests. Studies can now be conducted using these identified areas.

#### INTRODUCTION

Health administrative databases are increasingly being used for population-based studies. (1) Typically, outcomes for these studies are assessed using diagnostic codes, which have limited accuracy for the identification of some laboratory-diagnosed conditions. (2–4) This may lead to non-differential outcome misclassification bias which underestimates the true estimate in these studies. (2) In Ontario, Canada, an important improvement in the diagnostic accuracy of laboratory-diagnosed conditions occurred in 2007 with the introduction of the Ontario Laboratories Information System (OLIS), an electronic repository of the province's laboratory test results. (5) This system was implemented to allow healthcare providers timely access to laboratory test results from both community and hospital-based laboratories. The OLIS data has recently been linked to Ontario's other healthcare administrative databases at ICES which provides opportunities for more accurate assessment of laboratory-diagnosed outcomes such as acute kidney injury, hyperkalemia and hyponatremia.

However, although OLIS was initiated in 2007, not all laboratories began submitting their data to OLIS simultaneously. Community laboratories began their contributions to OLIS from the outset, but hospital-based laboratories across the province began their contributions at various times since 2007, and to date, not all contribute. (6) According to eHealth Ontario,134 of the 262 hospital sites across the province were using OLIS, and 13 out of 14 local health integration networks (LHIN) were included, as of December 31, 2017. (6,7) This variation presents a challenge when conducting retrospective population-based studies to assess laboratory-based outcomes during hospital encounters because depending on the date of assessment, the patient's laboratory results may or may not be available in OLIS. We conducted this study to determine the geographic areas in Ontario from which people would likely present

to a hospital with laboratory data included in OLIS, and how these areas changed over time. We used the resulting data to construct a date-dependent look-up table of geographic areas likely to have hospital laboratory data available in OLIS.

#### **METHODS**

#### Study design and research setting

We conducted this descriptive study using health administrative databases, which are linked using unique encoded identifiers and analyzed at ICES in Ontario, Canada. All Ontario residents receive universal access to physician services. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. We have reported this study according to guidelines for observational studies (Appendix 1). (8)

In Canada, geographic regions are defined by postal codes, which help postal operators sort and deliver mail. A postal code is comprised of a combination of six characters that identify a delivery unit. The postal code begins with a forward sortation area (FSA) comprised of the first three characters of a postal code. The first unit represents the postal district, the second unit represents whether the address is urban or rural and the third unit specifies a specific area within a city or town. (9) According to the 2016 Census, Ontario has a total of 516 FSAs. (10)

#### **Data sources**

We conducted this study using six linked datasets: (1) the Ontario Registered Persons Database, which contains demographic information for all residents of Ontario, (2) the Canadian Institute for Health Information Discharge Abstract Database, which contains hospital admission diagnosis information for all persons in Ontario, (3) the National Ambulatory Care Reporting

Page 6 of 26

System Database, which contains information about emergency department visits, (4) the Ontario Laboratories Information System Database, which contains information about laboratory test results within the province, (5) the Ontario Health Insurance Plan Database, which contains health claims information for both inpatient and outpatient physician services, (6) and the Same Day Surgery Database, which contains information on day surgery visits in Ontario.

#### **Cohort assembly**

We assembled a cohort of adults, aged 18 years or older, who presented to the emergency department in the National Ambulatory Care Reporting System database for any reason between April 1, 2007 to December 31, 2017. We divided the cohort into fiscal quarters (April 1-June 30, July 1- September 30, October 1- December 31, January 1- March 31). We excluded multiple emergency department visits by an individual patient within each quarter. As data cleaning steps, we also excluded emergency department visits if there was missing information on the individual's age or sex, if there was a recorded death date on or before the emergency department visit date, or if the individual was a non-Ontario resident.

#### Identifying OLIS-linked versus non-OLIS-linked hospitals over time

Using data from eHealth Ontario, we assembled a list of Ontario hospitals and the fiscal quarter when they started contributing data to OLIS.(6) To more precisely identify the date a contribution began, we searched the OLIS database at ICES for serum creatinine values (a commonly ordered laboratory test) arising from specific hospital laboratories using the unique Canadian Institute for Health Information institution numbers housed at ICES. We categorized hospitals as "OLIS-linked" beginning on the date their laboratory data began to populate the OLIS database and we considered them "non-linked" prior to that date. Hospitals that had not

 contributed data to OLIS prior to December 31, 2017 were considered non-linked hospitals for the entire study period.

#### Identifying the OLIS catchment area

After determining which hospitals contributed to OLIS and when they started doing so, we sought to determine the geographic areas likely to be served by OLIS-linked hospitals (i.e. the catchment area). To determine a hospital's catchment area, we identified the home location of the patients (based on FSA) presenting to their emergency departments. We assigned an FSA to an OLIS-linked hospital if the hospital received 90% or more of the emergency department visits arsing from that FSA in a given fiscal quarter. Using these criteria, we generated a list of all eligible FSAs and the initial date for joining the catchment area. We then produced an interactive Shiny application with a map showing the change in the OLIS catchment area over time using RStudio (RStudio, Inc., Boston, MA) and the leaflet package. All other analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). 

#### RESULTS

A flow diagram describing catchment area ascertainment between 2007 and 2017 in Ontario is shown in Figure 1. As of December 31, 2017, there were 323 out of 526 total FSAs (61.4%) included in the catchment area (see Appendix 2 for a list of all eligible FSAs and the initial date for joining the catchment area). Approximately 8.5 million individuals resided within the FSAs in the catchment area of OLIS-linked hospitals. Baseline characteristics of people residing within the catchment areas of OLIS-linked hospitals are shown in comparison to individuals residing in the catchments of unlinked hospitals (Table 1). On December 31, 2017, the two groups were similar across selected demographic characteristics and comorbidities (Table 1).

	Individuals outside catchment area	Individuals within catchment area	Standardized Difference
	N=4,739,202	N=8,511,875	2
Demographics	, ,	, ,	
Women, N (%)	2,380,493 (50.2%)	4,318,779 (50.7%)	1%
Rural, N (%)	514,721 (10.9%)	883,021 (10.4%)	2%
Age, mean (SD), years	$49.00 \pm 18.52$	$48.35 \pm 18.24$	4%
Age, median (IQR), years	49 (34-62)	48 (33-61)	4%
Age, N (%), years			
18 - <35	1,260,590 (26.6%)	2,309,996 (27.1%)	0%
35 - <45	761,956 (16.1%)	1,457,822 (17.1%)	1%
45 - <55	865,243 (18.3%)	1,599,389 (18.8%)	1%
55- <65	825,632 (17.4%)	1,434,415 (16.9%)	0%
65 - <75	567,124 (12.0%)	948,119 (11.1%)	1%
75 - <85	303,503 (6.4%)	500,634 (5.9%)	1%
85 - <95	132,614 (2.8%)	219,658 (2.6%)	1%
≥95	22,540 (0.5%)	41,842 (0.5%)	0%
Income quintile, N (%)	, , ,	· · · · ·	
1 (lowest)	998,131 (21.1%)	1,539,627 (18.1%)	7%
	944,928 (19.9%)	1,629,030 (19.1%)	2%
2 3	896,788 (18.9%)	1,704,263 (20.0%)	3%
4	929,142 (19.6%)	1,851,508 (21.8%)	5%
5 (highest)	946,006 (20.0%)	1,750,267 (20.6%)	1%
Comorbidities in the	, , ,		
past 5 years, N (%)			
Hypertension	1,084,337 (22.9%)	1,863,194 (21.9%)	2%
Diabetes	541,778 (11.4%)	1,011,328 (11.9%)	1%
Chronic kidney disease	144,924 (3.1%)	243,818 (2.9%)	1%
Congestive heart failure	112,954 (2.4%)	164,019 (1.9%)	3%
Major cancers	201,358 (4.2%)	357,584 (4.2%)	0%

**Table 1.** Baseline characteristics of individuals within the geographic catchment area compared to individuals residing outside the catchment area on December 31, 2017.

<sup>a</sup>Missing rural status was categorized as not rural.

<sup>b</sup>Missing income quintile was imputed into the third quintile.

<sup>c</sup>Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between the groups divided by the pooled SD; a value >10% is interpreted as a meaningful difference between the groups (11).

An interactive map of Ontario is shown at this link: https://ericm.shinyapps.io/olis/. The

geographic catchment area continues to grow and expand across the province as more hospitals

join OLIS. A static map of the OLIS catchment area, as of December 31, 2017, is depicted in

Figure 2.

#### INTERPRETATION

In this study we established the geographic catchment areas of hospitals with laboratory data available through OLIS and determined the temporal changes in these areas. We found over time there was an increase in the number of OLIS-eligible hospitals, with an associated increase in the number of FSAs included in the total OLIS-linked catchment area. It is reassuring that the characteristics of individuals within the catchment area are similar to individuals living outside of it, suggesting results from future studies restricted to the OLIS catchment area should be generalizable to the entire Ontario population. Our study's findings will be a pivotal component of future studies seeking to assess laboratory-diagnosed outcomes among patients admitted to hospital, such as acute kidney injury related to drug exposure. (12)

A strength of this study was our use of emergency department visits to establish hospital catchments, rather than inpatient hospitalizations, which may not represent the local hospital closest to the patient since people may travel further to receive specialized services. This method reduced the risk of outcome misclassification bias, as we likely captured a set of eligible FSAs for a particular hospital that a patient would present to. A limitation to this approach is that we will not capture some individuals who are transferred and admitted to a hospital outside of their local catchment area. The reliability of our findings is supported by the large number of emergency department visits across the entire province to form the basis of catchment area ascertainment. Additionally, there were very few eligibility restrictions, as all adults permanently residing in Ontario were considered for study inclusion.

A limitation of this study was that there were some discrepancies between the fiscal quarter dates provided by the eHealth Ontario website and the dates that the laboratory test results first appeared in OLIS data. Thus, we assumed the correct dates were the dates provided in the OLIS database. Another limitation was that we determined catchment areas if at least 90%

of people from a given FSA with an emergency department visit presented at an OLIS-linked hospital, so not all persons residing in a catchment area visited an OLIS-linked hospital. This introduces the small risk of non-differential outcome misclassification bias for studies that use this catchment area to define their study populations, which may underestimate the true effect. Another consideration is that hospitals within Ontario are continually joining OLIS, thus, updates to this catchment area will be needed in the future.

This study builds on previous work done in Ontario which used common electronic medical laboratory data from 12 hospitals to define geographic catchment regions within Southwestern Ontario (Cerner system). (13) Since the publication of this paper, there have been a number of population-based cohort studies using the defined Cerner catchment area, which assessed the risk for hospitalization with rhabdomyolysis after statin use, the risk of acute kidney injury after co-prescription of clarithromycin compared with azithromycin in individuals taking a calcium-channel blocker, and hyponatremia following the use of antidepressant and antiepileptic drugs. (12,14–16) The results of this study can be used in future research to form the basis of assessing OLIS-linked laboratory outcomes.

#### FUNDING

This study was supported by the ICES Western site. ICES is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). Core funding for ICES Western is provided by the Academic Medical Organization of Southwestern Ontario (AMOSO), the Schulich School of Medicine and Dentistry (SSMD), Western University, and the Lawson Health Research Institute (LHRI). The research was conducted by members of the ICES Kidney, Dialysis and Transplantation team, at the ICES Western facility, who are supported by a grant from the Canadian Institutes of Health Research (CIHR). Dr. Amit Garg was supported by the

Dr. Adam Linton Chair in Kidney Health Analytics and a CIHR Clinician Investigator Award. The opinions, results and conclusions are those of the authors and are independent from the funding sources. No endorsement by ICES, AMOSO, SSMD, LHRI, CIHR, or the MOHLTC is intended or should be inferred.

## CONTRIBUTORS

Carina Iskander, Eric McArthur, Danielle Nash, Sonja Gandhi-Banga and Amit Garg designed the study. Eric McArthur analyzed the data. Carina Iskander wrote the manuscript and all other authors revised it for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work. Additionally, we thank Alexandra Ouedraogo, at ICES Western in London, Ontario, for graphing contributions to this article.

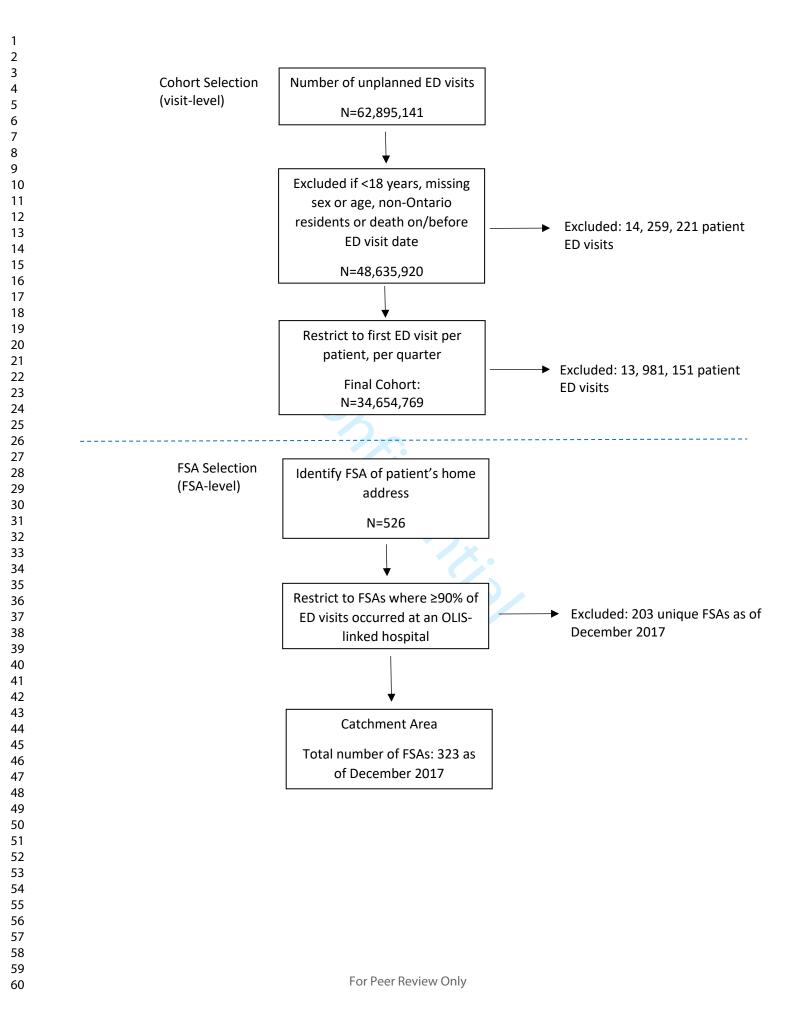
# REFERENCES

- 1. Goel V, Williams J, Anderson G, Blackstien-Hirsch P, Fooks C, Naylor C. Patterns of Health Care in Ontario [Internet]. The ICES Practice Atlas. 1996. Available from: http://www.ices.on.ca/Publications/Atlases-and-Reports/1996/Patterns-of-health-care-2nded
- 2. Hwang YJ, Shariff SZ, Gandhi S, Wald R, Clark E, Fleet JL, et al. Validity of the International Classification of Diseases, Tenth Revision code for acute kidney injury in elderly patients at presentation to the emergency department and at hospital admission. BMJ Open. 2012;2(6).
- 3. Fleet JL, Shariff SZ, Gandhi S, Weir MA, Jain AK, Garg AX. Validity of the International Classification of Diseases 10th revision code for hyperkalaemia in elderly patients at presentation to an emergency department and at hospital admission. BMJ Open. 2012;2(6).
- 4. Gandhi S, Shariff SZ, Fleet JL, Weir MA, Jain AK, Garg AX. Validity of the International Classification of Diseases 10th revision code for hospitalisation with hyponatraemia in elderly patients. BMJ Open. 2012;2(6).
- 5. eHealth Ontario. Ontario Laboratories Information System [Internet]. Available from: https://www.ehealthontario.on.ca/en/for-healthcare-professionals/ontario-laboratoriesinformation-system-olis
- 6. Ontario Laboratories Information System. OLIS Data Contributors. 2018. p. 9–10.
- 7. Ontario Hospital Association. Your Hospitals [Internet]. [cited 2019 Feb 11]. Available from: https://www.oha.com/your-hospitals
- 8. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med. 2015;12(10):e1001885.
- 9. Canada Post. Canada Post: Addressing Guidelines, Forward sortation areas The first segment of the postal code [Internet]. [cited 2018 May 15]. Available from: https://www.canadapost.ca/tools/pg/manual/PGaddress-e.asp#1449304
- 10. Statistics Canada Catalogue. Forward Sortation Area Boundary File, Reference Guide. 2011. p. 1–32.
- 11. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Comput. 2009;38(6):1228–34.
- 12. Patel AM, Shariff S, Bailey DG, Juurlink DN, Gandhi S, Mamdani M, et al. Statin toxicity from macrolide antibiotic coprescription: a population-based cohort study. Ann Intern Med. 2013 Jun;158(12):869–76.
- 13. Gandhi S, Shariff SZ, Beyea MM, Weir MA, Hands T, Kearns G, et al. Identifying geographical regions serviced by hospitals to assess laboratory-based outcomes. BMJ Open. 2013 Jan;3(1).
- 14. Gandhi S, Fleet JL, Bailey DG, McArthur E, Wald R, Rehman F, et al. Calcium-channel blocker-clarithromycin drug interactions and acute kidney injury. JAMA. 2013 Dec;310(23):2544–53.
- 15. Gandhi S, Shariff SZ, Al-Jaishi A, Reiss JP, Mamdani MM, Hackam DG, et al. Second-Generation Antidepressants and Hyponatremia Risk: A Population-Based Cohort Study of Older Adults. Am J Kidney Dis. 2017 Jan;69(1):87–96.

 Gandhi S, McArthur E, Mamdani MM, Hackam DG, McLachlan RS, Weir MA, et al. Antiepileptic drugs and hyponatremia in older adults: Two population-based cohort studies. Epilepsia. 2016 Dec;57(12):2067–79.

**Figure 1.** Flow chart describing catchment ascertainment between April 1, 2007 and December 31, 2017 in Ontario.

**Figure 2.** Representation of all OLIS eligible catchment regions in Ontario by December 31, 2017.



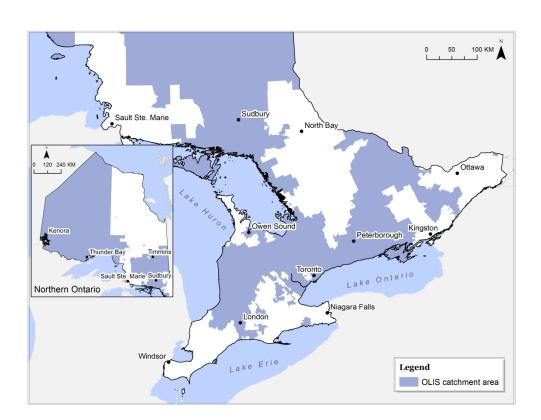


Figure 2. Representation of all OLIS eligible catchment regions in Ontario by December 31, 2017.

279x215mm (300 x 300 DPI)

# Appendix 1. RECORD Checklist

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstra	ct			•	
	1	<ul> <li>(a) Indicate the study's design with a commonly used term in the title or the abstract</li> <li>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</li> </ul>	Abstract Abstract	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	Title
		C		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.	N/A
Introduction			I		
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction		
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction		
Methods					
Study Design	4	Present key elements of study design early in the paper	Methods	ĸ.	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods	9	
Participants	6	( <i>a</i> ) Give the eligibility criteria, and the sources and methods of selection of participants. Describe	Methods	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be	Methods
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A	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	N/A

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
10
20
20 21
21
3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 9 20 21 22 23 24 25 26 27 28 29 30
23
24
25
26
27
28
29
30
21
22
32 33 34 35 36 37 38
34
35
36
37
38
39
40
41
42
43
44
45
45 46
40 47
47 48
40 49
49 50
51
52
53
54
55
56
57
58
59
60

				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.	Methods	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.	Methods
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	Methods		
Bias	9	Describe any efforts to address potential sources of bias	Discussion		
Study size	10	Explain how the study size was arrived at	Methods		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Methods		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods	0	
		(b) Describe any methods used to examine subgroups and interactions	N/A		
		(c) Explain how missing data were addressed	N/A		
		(d) If applicable, explain how loss to follow-up was addressed	N/A		
		(e) Describe any sensitivity analyses	N/A		
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.	Methods
				RECORD 12.2: Authors should provide information on the data	N/A

				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.	Methods
Results					
Participants	13	<ul> <li>(a) Report the numbers of individuals at each stage of the study (<i>e.g.</i>, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)</li> <li>(b) Give reasons for non-participation at each stage.</li> </ul>	Figure 1 Figure 1	RECORD 13.1: Describe in detail the selection of the persons included in the study ( <i>i.e.</i> , 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.	Methods – Figure 1
		(c) Consider use of a flow diagram	Figure 1		
Descriptive data	14	(a) Give characteristics of study participants ( <i>e.g.</i> , demographic, clinical, social) and information on exposures and potential confounders	Table 1		
		<ul><li>(b) Indicate the number of participants with missing data for each variable of interest</li><li>(c) Summarise follow-up</li></ul>	N/A	к. О	
		time ( <i>e.g.</i> , average and total amount)	N/A		
Outcome data	15	Report numbers of outcome events or summary measures over time	Results		
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	N/A		
		(b) Report category boundaries when continuous variables were categorized	N/A		

Other analyses	17	<ul> <li>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period</li> <li>Report other analyses</li> </ul>	N/A N/A		
Onlor undryses	17	done—e.g., analyses of subgroups and interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives	Discussion		
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	Discussion	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.	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion	Κ.	
<b>Other Informatio</b>	on				
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	Funding	9	
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.	N/A

FSA	Eligibility Date
KOG	01-Jan-16
KOJ	01-Jan-16
кок	01-Oct-15
KOL	01-Oct-15
K6A	01-Apr-15
K6T	01-Oct-15
K6V	01-Oct-15
K7A	01-Oct-15
K7C	01-Oct-15
K7H	01-Oct-15
K7R	01-Jan-16
K7S	01-Oct-15
K7V	01-Jan-16
K8A	01-Jul-15
K8B	01-Jul-15
K8H	01-Jul-15
K8N	01-Oct-15
K8P	01-Oct-15
K8R	01-Oct-15
K8V	01-Oct-15
K9A	01-Jul-14
K9H	01-Jul-14
K9J	01-Jul-14
К9К	01-Jul-14
K9L	01-Jul-14
K9V	01-Apr-14
LOA	01-Jul-14
LOB	01-Apr-14
LOC	01-Jul-14
LOE	01-Jul-14
LOG	01-Apr-15
LOH	01-Oct-14
LOJ	01-Oct-15
LOK	01-Apr-16
LOL	01-Apr-16
LOM	01-Jul-16
LON	01-Oct-16
LOP	01-Jan-17
L1A	01-Jul-14
L1B	01-Jul-13
L1C	01-Jan-08
L1E	01-Jan-14
L1G	01-Apr-08

L1H	01-Jul-11	
L1J	01-Apr-12	
L1K	01-Jan-14	
L1L	01-Jan-14	
L1M	01-Oct-14	
L1N	01-Apr-14	
L1P	01-Apr-14	
L1R	01-Apr-14	
L1S	01-Apr-14	
L1T	01-Apr-14	
L1V	01-Apr-14	
L1W	01-Apr-14	
L1X	01-Jul-14	
L1Y	01-Oct-14	
L1Z	01-Apr-14	
L3P	01-Oct-14	
L3R	01-Oct-14	
L3S	01-Oct-14	
L3T	01-Apr-14	
L3V	01-Jan-15	
L3X	01-Apr-13	
L3Y	01-Apr-12	
L3Z	01-Jan-14	
L4A	01-Oct-14	
L4B	01-Apr-14	
L4C	01-Apr-13	
L4E	01-Apr-13	
L4G	01-Apr-13	
L4H	01-Oct-15	
L4J	01-Apr-14	
L4K	01-Oct-15	
L4M	01-Oct-15	
L4N	01-Oct-15	
L4P	01-Apr-13	
L4R	01-Apr-16	
L4S	01-Apr-13	
L4T	01-Apr-14	
L4V	01-Apr-08	
L4W	01-Jul-13	
L4X	01-Jan-14	
L4Y	01-Jul-13	
L4Z	01-Jul-13	
L5A	01-Jul-13	
L5B	01-Jul-13	
L5C	01-Jul-13	
L5E	01-Jan-14	

L5G	01-Jul-13
L5H	01-Apr-14
L5J	01-Jan-15
L5K	01-Jan-15
L5L	01-Jan-14
L5M	01-Jul-13
L5N	01-Jan-15
L5P	01-Jul-07
L5R	01-Jul-13
L5S	01-Apr-13
L5T	01-Jan-14
L5V	01-Jul-13
L5W	01-Jan-14
L6A	01-Jan-15
L6B	01-Oct-14
L6C	01-Oct-14
LGC LGE	01-Oct-14
L6G	01-Oct-14
L6H	01-Jan-15
L6J	01-Jan-15
L6K	01-Jan-15
L6L	01-Jan-15
L6M	01-Jan-15
L6P	01-Apr-14
L6R	01-Jan-14
L6S	01-Apr-14
L6T	01-Jan-14
L6V	01-Apr-14
L6W	01-Apr-14
L6X	01-Jan-15
L6Y	01-Jan-15
L6Z	01-Jan-15
L7A	01-Jan-15
L7B	01-Jul-14
L7C	01-Oct-16
L7E	01-Oct-16
L7G	01-Jan-15
L7J	01-Oct-16
L7K	01-Oct-16
L8B	01-Jul-17
L8P	01-Oct-17
L8R	01-Oct-17
L8S	01-Oct-17
L9E	01-Apr-16
L9H	01-Jan-18
L9J	01-Jan-16
2.25	

L9L	01-Jan-13	
L9M	01-Apr-16	
L9N	01-Apr-12	
L9P	01-Oct-14	
L9R	01-Jan-14	
L9S	01-Oct-15	
L9T	01-Jan-15	
L9V	01-Oct-16	
L9W	01-Oct-16	
L9Y	01-Jul-16	
L9Z	01-Jul-16	
M1B	01-Apr-14	
M1C	01-Apr-14	
M1E	01-Apr-14	
M1G	01-Apr-14	
M1H	01-Apr-14	
M1J	01-Apr-14	
M1K	01-Apr-14	
M1L	01-Jul-14	
M1M	01-Apr-14	
M1N	01-Jul-14	
M1P	01-Apr-14	
M1R	01-Apr-14	
M1S	01-Apr-14	
M1T	01-Apr-14	
M1V	01-Apr-14	
M1W	01-Apr-14	
M1X	01-Oct-14	
M2H	01-Apr-14	
M2J	01-Apr-14	
M2K	01-Jan-14	
M2L	01-Jan-14	
M2M	01-Apr-14	
M2N	01-Jan-14	
M2P	01-Jan-14	
M2R	01-Oct-15	
M3A	01-Apr-14	
M3B	01-Apr-14	
M3C	01-Apr-14	
M3H	01-Oct-15	
M4A	01-Jul-14	
M4B	01-Jul-14	
M4C	01-Jul-14	
M4E	01-Jul-14	
M4G	01-Apr-14	
M4H	01-Jul-14	

M4J	01-Jul-14	
M4K	01-Jul-14	
M4L	01-Jul-14	
M4M	01-Jul-14	
M4N	01-Apr-14	
M4P	01-Apr-14	
M4R	01-Jan-14	
M4S	01-Apr-14	
M4T	01-Apr-14	
M4V	01-Apr-14	
M4W	01-Apr-14	
M4X	01-Apr-14	
M4Y	01-Apr-14	
M5A	01-Apr-14	
M5B	01-Apr-14	
M5C	01-Apr-14	
M5E	01-Apr-14	
M5G	01-Apr-14	
M5H	01-Jul-14	
M5J	01-Apr-14	
M5K	01-Apr-13	
M5L	01-Jul-14	
M5M	01-Apr-14	
M5N	01-Apr-14	
M5P	01-Apr-14	
M5R	01-Apr-14	
M5S	01-Apr-14	
M5T	01-Apr-14	
M5V	01-Apr-14	
M5W	01-Apr-14	
M5X	01-Jul-13	
M6C	01-Apr-14	
M6G	01-Apr-14	
M6H	01-Apr-14	
M6J	01-Apr-14	
M6K	01-Apr-14	
M6P	01-Apr-14	
M6R	01-Apr-14	
M6S	01-Apr-14	
M7A	01-Jan-10	
M8V	01-Apr-14	
M8W	01-Apr-14	
M8X	01-Apr-14	
M8Y	01-Apr-14	
M8Z	01-Apr-14	
M9B	01-Apr-14	

M9C	01-Apr-14	
M9V	01-Oct-15	
NOC	01-Jul-16	
NOG	01-Jan-17	
NOK	01-Jan-15	
NOM	01-Jan-15	
N1A	01-Apr-17	
N1C	01-Jan-17	
N1E	01-Jan-17	
N1G	01-Jan-17	
N1H	01-Jan-17	
N1K	01-Jan-17	
N1L	01-Jan-17	
N1M	01-Jan-17	
N1P	01-Apr-17	
N1R	01-Apr-17	
N1T	01-Apr-17	
N2Z	01-Oct-09	
N3C	01-Apr-17	
N3E	01-Jan-18	
N4G	01-Oct-13	
N4K	01-Jan-08	
N4L	01-Jan-08	
N4N	01-Oct-09	
N4S	01-Oct-13	
N4T	01-Oct-13	
N4V	01-Oct-13	
N4W	01-Oct-14	
N4X	01-Jan-15	
N4Z	01-Jan-15	
N5A	01-Jan-15	
N5C	01-Oct-13	
N5H	01-Oct-13	
N5L	01-Oct-13	
N5P	01-Oct-13	
N5R	01-Oct-13	
N5V	01-Jul-13	
N5W	01-Jul-13	
N5X	01-Jul-13	
N5Y	01-Jul-13	
N5Z	01-Jul-13	
N6A	01-Oct-13	
N6B	01-Jul-13	
N6C	01-Jul-13	
N6E	01-Jul-13	
N6G	01-Jul-13	

N6H	01-Jul-13
N6J	01-Jul-13
N6K	01-Jul-13
N6L	01-Jul-13
N6M	01-Jul-13
N6N	01-Oct-13
N6P	01-Jul-13
N7A	01-Jan-15
N7G	01-Oct-13
POG	01-Jul-15
POJ	01-Jul-14
РОК	01-Jul-14
POM	01-Apr-14
PON	01-Jul-14
POP	01-Jan-14
POT	01-Oct-15
POV	01-Oct-15
POW	01-Oct-15
POX	01-Jan-16
POY	01-Jan-16
P2A	01-Jul-15
P2B	01-Jul-14
P2N	01-Jul-14
P3A	01-Jan-14
P3B	01-Jan-14
P3C	01-Jan-14
P3E	01-Jan-14
P3G	01-Jan-14
P3L	01-Jan-14
P3N	01-Jan-14
P3P	01-Jan-14
P3Y	01-Jan-14
P4N	01-Jul-14
P4P	01-Jul-14
P4R	01-Jul-14
P5A	01-Apr-14
P5E	01-Apr-14
P5N	01-Jul-14
P7A	01-Jan-16
P7B	01-Oct-15
P7C	01-Oct-15
P7E	01-Oct-15
P7G	01-Oct-15
P7J	01-Jan-16
P7K	01-Oct-15
P7L	01-Oct-15

P8N	01-Oct-15
P8T	01-Oct-14
P9A	01-Oct-15
P9N	01-Jan-16