A Cross-Sectional Study of Regional Variability in Outpatient Antibiotic Use in Ontario, Canada

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Abstract:	Background: Antimicrobial resistance is an urgent public health crisis. The largest modifiable driver of antimicrobial resistance is antibiotic use. Our objectives were to benchmark outpatient antibiotic use in the province of Ontario and describe the geographic variability. Methods: This was a cross-sectional study of antibiotics dispensed from retail pharmacies in Ontario, Canada between March 2016 and February 2017. We analyzed variability in number of antibiotics dispensed per 1000 population among Ontario's 14 health regions with crude and adjusted Poisson regression models fitted using generalized estimating equations, to account for regional clustering. Multivariable models were adjusted for rurality, physician density, proportion of generalist physicians, proportion of male physicians, and physician career stage. Results: There were 8,352,578 antibiotics dispensed or 621 per 1000 population. The most common antibiotic classes were narrow-spectrum penicillins, macrolides, first generation cephalosporins, and second generation fluoroquinolones, with wide patient age and sex differences

	observed. There was significant geographic variability in total and class specific use. The highest use health region dispensed 778 antibiotics compared to the lowest use region with 533 per 1000 population. The crude and adjusted incidence rate ratios for the highest use region compared to the lowest use region were 1.46 (95%CI 1.07-1.98) and 1.49 (95%CI 1.15-1.93), respectively. Interpretation: We defined baseline antibiotic usage in Ontario over a 12 month period. There was significant variability between health regions that persisted after multivariable adjustment. This variability suggests important opportunities for interventions to optimize antibiotic use and slow the emergence of antimicrobial resistance.

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A Cross-Sectional Study of Regional Variability in Outpatient Antibiotic Use in Ontario, Canada

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Abstract

Background: Antimicrobial resistance is an urgent public health crisis. The largest modifiable driver of antimicrobial resistance is antibiotic use. Our objectives were to benchmark outpatient antibiotic use in the province of Ontario and describe the geographic variability.

Methods: This was a cross-sectional study of antibiotics dispensed from retail pharmacies in Ontario, Canada between March 2016 and February 2017. We analyzed variability in number of antibiotics dispensed per 1000 population among Ontario's 14 health regions with crude and adjusted Poisson regression models fitted using generalized estimating equations, to account for regional clustering. Multivariable models were adjusted for rurality, physician density, proportion of generalist physicians, proportion of male physicians, and physician career stage.

Results: There were 8,352,578 antibiotics dispensed or 621 per 1000 population. The most common antibiotic classes were narrow-spectrum penicillins, macrolides, first generation cephalosporins, and second generation fluoroquinolones, with wide patient age and sex differences observed. There was significant geographic variability in total and class specific use. The highest use health region dispensed 778 antibiotics compared to the lowest use region with 533 per 1000 population. The crude and adjusted incidence rate ratios for the highest use region compared to the lowest use region were 1.46 (95%CI 1.07-1.98) and 1.49 (95%CI 1.15-1.93), respectively.

Interpretation: We defined baseline antibiotic usage in Ontario over a 12 month period. There was significant variability between health regions that persisted after multivariable adjustment. This variability suggests important opportunities for interventions to optimize antibiotic use and slow the emergence of antimicrobial resistance.

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Background

Antimicrobial resistance is an urgent public health threat. A study from the United Kingdom estimates that deaths from drug-resistant infections will surpass cancer by 2050, resulting in 10 million deaths annually in the absence of significant intervention.(1) Antibiotic use is the most important modifiable risk factor promoting the development of antimicrobial resistance at both the individual patient and population levels.(2, 3) In Canada, approximately 92% of antibiotics are used outside of the acute care hospital setting.(4) In the United States it is estimated that 30% of all antibiotics prescribed in the community are unnecessary.(5) A recent study from Canada identified that almost 50% of Ontario seniors with upper respiratory infections inappropriately receive antibiotics, suggesting there are opportunities to reduce community antibiotic use.(6)

Antimicrobial stewardship programs (ASPs) are an Accreditation Canada Required Organizational Practice in hospitals, however there is no comparable requirement to promote appropriate antibiotic use in the community. The most effective ASP interventions in hospitals have involved direct engagement with prescribers to promote behaviour change.(7) Implementation of these strategies is challenging in a community setting. Simply applying the principles of hospital ASPs to the ambulatory setting is not practical because most family physicians work in small groups or solo practices with no administrative oversight, minimal access to real-time infectious disease or antimicrobial stewardship pharmacy consultation, and limited means to collect or analyze prescribing data. Despite an increasing focus on antimicrobial resistance and stewardship, antibiotic utilization rates have not declined over the last decade.(4, 8, 9)

The ability to measure antibiotic use in the community is a critical step in implementing effective stewardship interventions. Using a proprietary population-based Ontario dataset, our objective was to describe the geographical variability of antibiotic use to inform future community-based interventions.

Methods

Setting and Design

We performed a 12 month cross-sectional study analyzing outpatient antibiotic use for the entire population of Ontario, Canada between 1 March 2016 and 28 February 2017. We compared antibiotic variability across Ontario's 14 health regions. The health regions are responsible for planning, integrating, and distributing public healthcare funding in Ontario.

Data Source

The antibiotic use data were obtained from antibiotics dispensed by Ontario pharmacies in the GPM™ database from IQVIA (formerly QuintilesIMS). The dataset consists of aggregated antibiotic prescription counts at the level of the Forward Sortation Area (FSA). The FSA is a geographical unit defined by the first three characters in the Canadian postal code. The IQVIA databases are derived from 64% of Ontario prescriptions. IQVIA uses a validated proprietary geospatial algorithm to project antibiotic prescription counts so that they are representative of 100% of the population.(10) Eligible antibiotics include oral

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systemic antibacterial agents from the J01 class of pharmacologic agents as deemed by the World Health Organization Anatomical Therapeutic Classification System.(11) Total and 13 class specific antibiotic prescription counts were grouped as penicillin without beta-lactamase inhibitors, penicillin with beta-lactamase inhibitors, first generation cephalosporins, second/third generation cephalosporins, second generation fluoroquinolones, third generation fluoroquinolones, macrolides, trimethoprim and/or sulphonamides, tetracyclines, lincosomides, nitrofurantoin, metronidazole, and others.

Covariates

FSAs were assigned to the health regions in which they were located. When FSA boundaries overlapped health region boundaries, FSAs were assigned to the health region that included the main population centre. FSAs without pharmacies were combined with the largest neighbouring FSA. The Xponent™ database from IQVIA was used for physician level covariates including; regional physician density (number of physicians per 1000 population), proportion of generalist physicians (family doctors divided by all physicians), proportion of male physicians, proportion of physicians in early career stage (<11 years), mid-career stage (11-24 years), and late career stage (>24 years). Rural versus urban areas were defined by the middle number in the FSA of the dispensing pharmacy.(12)

Statistical analysis

We presented antibiotic use by number of dispensed prescriptions per 1000 population for total and class specific antibiotics. Patient age and sex differences were evaluated by Chi-Squared tests. Statistical comparisons between health regions were performed using Poisson regression models. Between health region differences were evaluated with incidence rate ratios (IRRs) and 95% confidence intervals (CIs). The lowest using region was set as the reference. For Crude estimates, we used generalized estimating equation (GEE) models with an exchangeable correlation matrix that accounted for clustering amongst FSAs. For the adjusted multivariable models we used GEE including the covariates of rurality, physician density, proportion of generalist physicians, proportion of male physicians, and proportion of early, mid, or late career stage physicians. Counts were offset by the logarithm of the population size. Multivariable models were stratified by antibiotic class as well as patient age and sex (all patients, males <18 years, females <18 years, males 18-64 years, females 18-64 years, males ≥65 years, females ≥65 years). Statistical significance was defined as $p<0.05$. Statistical analyses were performed in SAS Version 9.3 (SAS Institute, Cary, NC). This study has research ethics board approval from Public Health Ontario.

Results

There were 8,352,578 antibiotics dispensed during the 12 month study period, or 621 antibiotics per 1000 population. The population age and sex distribution was similar between health regions (Table 1). Narrow spectrum penicillins, macrolides, first generation cephalosporins, and 2nd generation fluoroquinolones were the most frequently prescribed antibiotic classes. There was significant variability by patient age and sex, with females ≥65 years of age receiving 985 per 1000 population compared to adult males 18-64 years who received 441 antibiotics per 1000 population ($P<0.001$). Approximately 80% of all antibiotics to children <18 years were drugs most commonly used for respiratory indications (most commonly narrow spectrum penicillins and macrolides) while elderly women predominately

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received urinary agents (nitrofurantoin, second generation fluoroquinolones, and trimethoprim and/or sulphonamides). Fluoroquinolones comprised 17%, 20%, 9%, 10%, 0.4%, and 0.2% of all antibiotics in females ≥65 years, males ≥65 years, females 18-64 years, males 18-64 years, females <18 years, and males <18 years, respectively (Figure 1).

We observed significant geographical variability in antibiotic use between health regions. The three highest use regions used 778, 742, and 673 antibiotics per 1000 population, compared to the three lowest using regions with 549, 537, and 534 per 1000 population (Figure 2). There was also substantial variability between the health regions in high-risk antibiotic use, including lincosamides, fluoroquinolones, and 2nd/3rd generation cephalosporins (Figure 3).

In the regression models the highest use region (Erie St. Clair) had a crude and adjusted IRR of 1.46 (95%CI 1.07-1.98) and 1.49 (95%CI 1.15-1.93), respectively. Significant variability persisted in most regions after adjustment for regional differences in physician characteristics, and stratification by patient age and sex (Table 2).

Interpretation

We identified significant geographical variability in antibiotic use amongst Ontario's 14 health regions, which persisted after adjustment for patient and physician factors. This variability was not explained by population differences suggesting opportunities for intervention.

Antibiotic use data in Canada from 1995 to 2010 showed a modest decline suggesting some success in public and provider awareness of rising antimicrobial resistance.(13, 14) However, a recent analysis of antibiotic use in Ontario seniors shows stable usage over the past decade.(9) In the United States similar data have been used to identify substantial inter-state antibiotic use variability. Overall the United States uses 833 antibiotics per 1000 population with some of the Southern states using twice the amount compared to the North West. Ontario uses a similar amount of outpatient antibiotics to the lowest using states,(15) but substantially more than many European countries.(16) It is noteworthy that variability in antibiotic use persists within a province at the smaller health region level. We identified important differences in antibiotic use amongst patient age and sex strata. These differences were partially explained by the higher use of nitrofurantoin, second generation fluoroquinolones, and trimethoprim and/or sulphonamides, likely reflecting antibiotic prescribing for urinary infections. However inter-regional variability persisted in most patient age and sex strata supporting our hypothesis that this variability cannot be explained by population differences. This raises the possibility that this variability could be driven by physician behaviour and amenable to interventions of peer-comparison feedback.

The explanations for variability in antibiotic use are complex. There are a number of potential contributing factors that include patient complexity, patient expectations, socioeconomic status, remoteness, physician access, as well as both patient and physician knowledge. In this study we incorporated some regional variables that account for population and healthcare access differences. A number of studies have suggested that prescriber factors are the key driver of higher antibiotic use. Several Canadian studies have identified physician practice type, practice volume, later career stage, and

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prior prescribing patterns as significant predictors of high or inappropriate antibiotic use.(17-19) Similarly, a study from a large Veteran Affairs population in the United States showed that certain providers tended to prescribe antibiotics for acute respiratory infection visits, while others did not, independent of patient and location factors.(20) Therefore, observed geographical variability may be explained by physician prescribing behaviours being more similar between physicians in close proximity than those in different health regions. Further study evaluating this observation would be of interest.

Overuse of antibiotics has multiple downstream and long-term public health implications. Numerous studies have identified the association of antibiotic use and resistance, at both an ecological and individual patient levels.(2, 3) Studies from the United States have identified the importance of geographic variability of antibiotic use on resistance rates of *Streptococcus pneumoniae* as well as community-associated *Clostridium difficile* infections.(21, 22) Furthermore, it is estimated that there are four emergency department visits for adverse drug events for every 1000 individuals, with antibiotics representing one of the most common culprits.(23) Inappropriate inpatient antibiotic use has been directly associated with adverse patient outcomes, highlighting antimicrobial stewardship as an important patient safety program.(24)

The identification of geographical variability has implications for community interventions. A potential provincial strategy could be to initiate a stewardship program targeting the highest prescribers where the greatest yield is expected.(25) However, overuse of antibiotics is likely by most prescribers in all regions, and there would be expected benefit as a result of population-wide interventions. There was variability in use of high risk antibacterial agents, such as fluoroquinolones. Health Canada recently issued a warning surrounding serious adverse reactions to fluoroquinolones including tendinopathy, peripheral neuropathy, and central nervous system disorders.(26) Targeting a specific high-risk antibiotic class represents another opportunity for quality improvement. However, by targeting only high-risk classes, overall antibiotic use is unlikely to decline due to the *squeezing-of-the-balloon* effect, where use of alternative antibiotics tend to increase.(27) Multiple studies have been published on a variety of interventions for outpatient antibiotic use. The best evidence is for communication skills training, point-of-care diagnostics, and peer-comparison feedback.(25, 28-31) This data supports the need for a province-wide evidence-based antimicrobial stewardship program, with a strong surveillance component, to improve the appropriate use of outpatient antibiotics and slow the emergence of drug resistant infections. Personalized peer-comparison feedback has the greatest potential for significant reduction in unnecessary antibiotic use, however multiple studies have demonstrated the lack of sustained impacts, highlighting that successful programs require ongoing data collection, education, and feedback.(25, 30, 32)

This study is unique by assessing population-level antibiotic use of over 13 million people and demonstrating regional variability after adjustment for regional physician and population differences. This study has some limitations. This data is based on 50% of Ontario's pharmacies and IQVIA extrapolates the data to estimate population use. It is possible that estimated antibiotic use was less precise in certain regions with poorer coverage, however the IQVIA algorithm is a routinely-validated and patented method to extrapolate available data to 100% coverage.(33) Pharmacy dispensing data may not accurately represent antibiotic consumption as patient adherence can vary. Covariates in the

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multivariable models are based on proportions of physician characteristics within a geographic region. We were unable to account for other potentially important predictors of antibiotic variability such as patient expectations. We were also unable to assess appropriateness of antibiotic prescribing from this data as it does not capture patient visits or diagnoses. Other sources of patient-level data will be required to assess appropriateness.

In summary, we have identified significant geographical variability in outpatient antibiotic use among health regions within Ontario. This data provides an important benchmark for expansion of a provincial outpatient antimicrobial stewardship program and highlights opportunities for interventions to optimize antibiotic use.

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Table 1: Population demographics in Ontario by health region

Health region	Total population	< 18 year males (%)	< 18 year females (%)	18-64 year males (%)	18-64 year females (%)	65+ year males (%)	65+ year females (%)
CENTRAL	1,827,890	191,365 (10)	181,065 (10)	562,490 (31)	609,595 (33)	126,235 (7)	157,220 (9)
CENTRAL EAST	1,561,100	158,455 (10)	151,535 (10)	475,115 (30)	502,420 (32)	122,765 (8)	150,585 (10)
CENTRAL WEST	919,600	112,690 (12)	105,375 (11)	288,020 (31)	298,230 (32)	52,995 (6)	62,315 (7)
CHAMPLAIN	1,236,780	125,615 (10)	120,675 (10)	383,865 (31)	400,315 (32)	93,100 (8)	113,355 (9)
ERIE ST. CLAIR	617,100	63,680 (10)	60,450 (10)	186,510 (30)	190,150 (31)	52,670 (9)	63,745 (10)
HAMILTON NIAGARA- HALDIMAND BRANT	1,384,220	137,795 (10)	130,605 (9)	417,155 (30)	433,270 (31)	118,805 (9)	146,625 (11)
MISSISSAUGA HALTON	1,132,555	126,690 (11)	120,365 (11)	353,595 (31)	373,260 (33)	71,240 (6)	87,295 (8)
NORTH EAST	564,460	53,035 (9)	50,275 (9)	170,585 (30)	173,615 (31)	54,510 (10)	62,295 (11)
NORTH SIMCOE MUSKOKA	510,945	52,220 (10)	49,650 (10)	155,810 (30)	160,175 (31)	42,970 (8)	50,075 (10)
NORTH WEST	228,195	24,125 (11)	22,670 (10)	69,975 (31)	70,190 (31)	19,225 (8)	22,005 (10)
SOUTH EAST	547,205	50,530 (9)	48,115 (9)	163,910 (30)	167,095 (31)	54,355 (10)	63,080 (12)
SOUTH WEST	970,240	101,115 (10)	96,455 (10)	290,975 (30)	298,895 (31)	82,750 (9)	100,060 (10)
TORONTO CENTRAL	1,186,530	94,960 (8)	90,475 (8)	409,775 (35)	424,750 (36)	72,005 (6)	94,395 (8)
WATERLOO WELLINGTON	761,815	82,765 (11)	78,790 (10)	240,950 (32)	244,315 (32)	51,905 (7)	62,930 (8)
TOTAL	**13,448,635**	**1,375,040 (10)**	**1,306,500 (10)**	**4,168,730 (31)**	**4,346,275 (32)**	**1,015,530 (8)**	**1,235,980 (9)**

Table2: Regional antibiotic use rate per 1000 population stratified by population age and sex

		Antibiotic use rate per 1000 population						
Health region	**Total number of antibiotics**	**Total**	**< 18 year males**	**< 18 year females**	**18-64 year males**	**18-64 year females**	**65+ year males**	**65+ year females**
CENTRAL	1,143,402	626	540	558	451	692	852	995
CENTRAL EAST	953,269	611	520	546	445	687	773	907
CENTRAL WEST	597,585	650	566	562	489	753	885	1001
CHAMPLAIN	660,223	534	392	420	375	621	737	878
ERIE ST. CLAIR	480,199	778	733	780	540	880	904	1110
HAMILTON NIAGARA- HALDIMAND BRANT	931,476	673	510	552	464	759	878	1108
MISSISSAUGA HALTON	840,333	742	593	617	557	843	1043	1204
NORTH EAST	342,007	606	466	525	426	712	737	912
NORTH SIMCOE MUSKOKA	274,400	537	383	427	363	611	705	925
NORTH WEST	149,335	654	488	574	468	773	784	1022
SOUTH EAST	319,482	584	433	509	392	681	724	882
SOUTH WEST	571,845	589	460	497	394	658	773	1018
TORONTO CENTRAL	671,100	566	503	506	397	646	792	887
WATERLOO WELLINGTON	417,922	549	419	445	388	643	764	920
TOTAL	**8,352,578**	**621**	**508**	**537**	**441**	**706**	**817**	**985**

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Figure 1: Oral antibiotics by drug class per 1000 population in Ontario stratified by patient age and sex

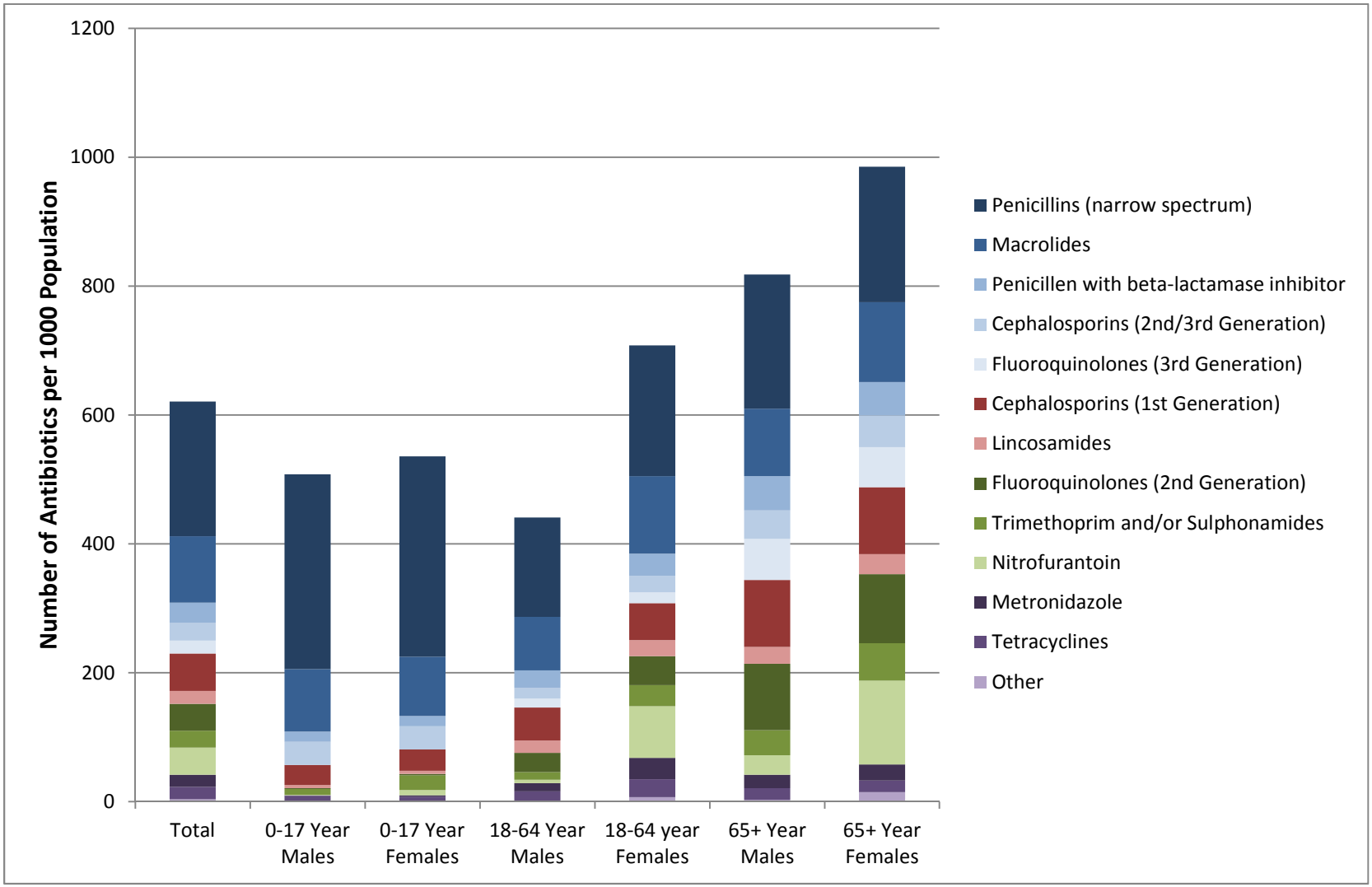

Figure 2: Health region geographic variability in antibiotic use per 1000 population

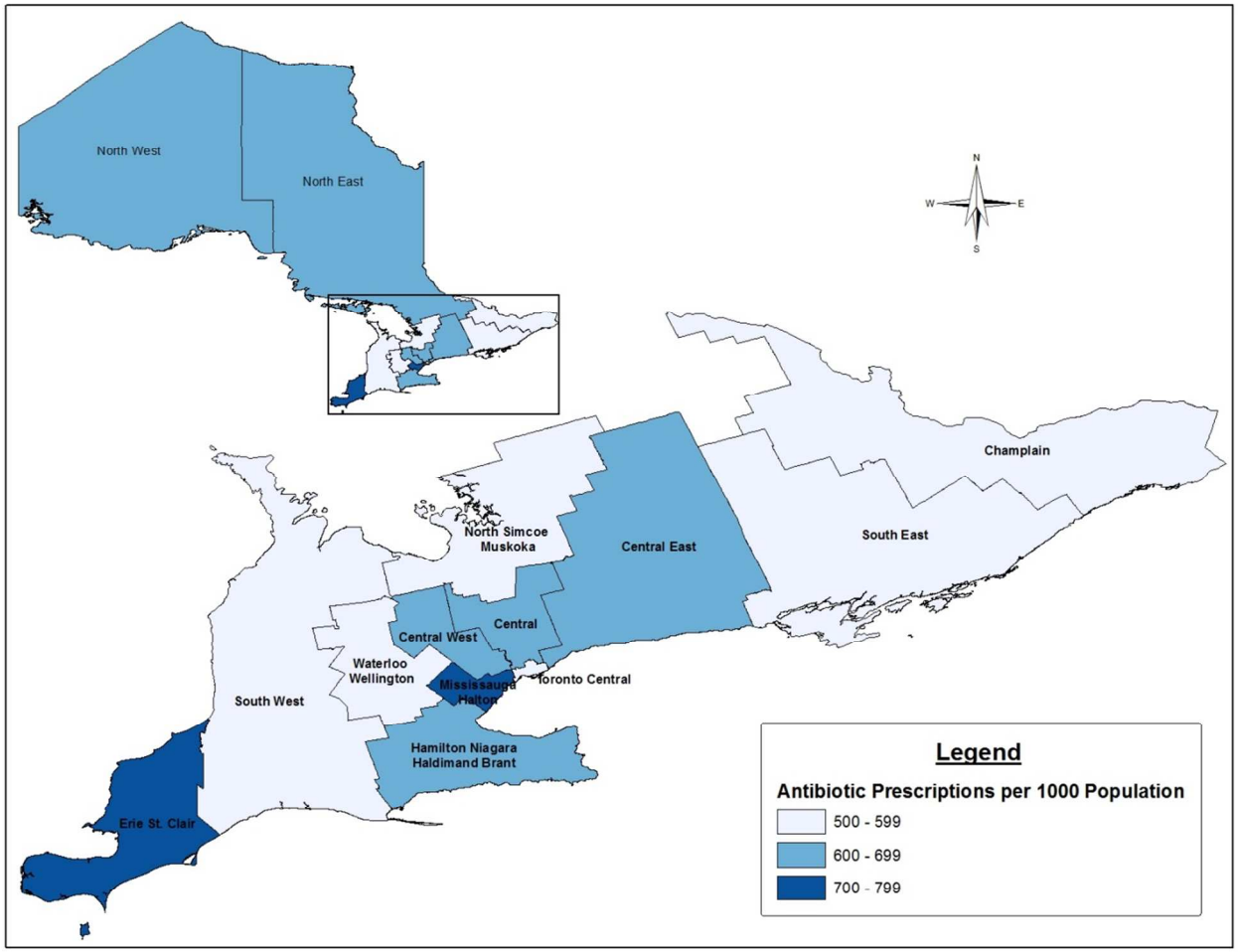

Figure 3: Antibiotic use in each health region separated by drug class

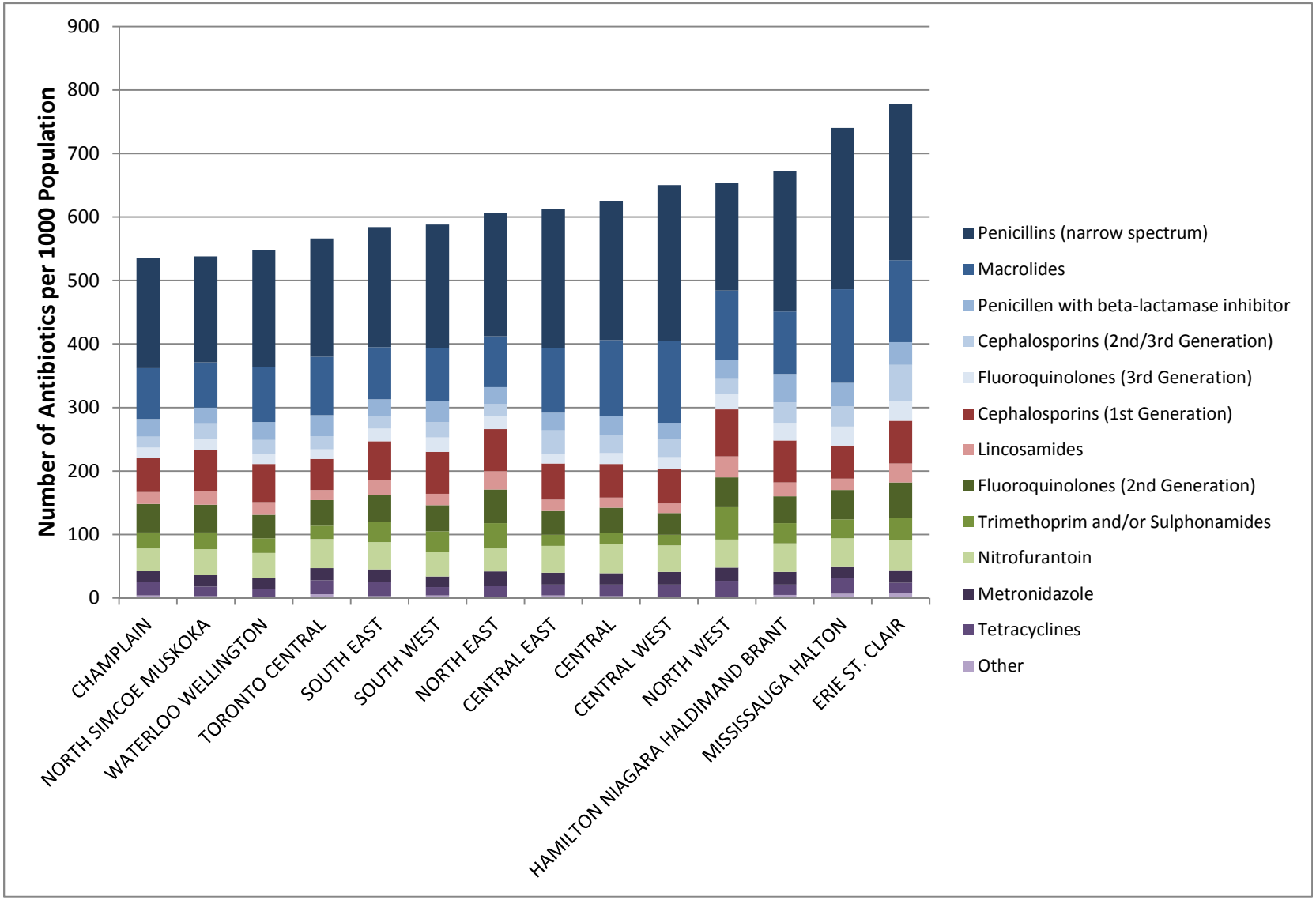

Table 3: Crude and adjusted multivariable Poisson regression models, with generalized estimating equations, of antibiotic use amongst Ontario's 14 health regions and stratified by population age and sex.

Incidence Rate Ratio (95% confidence interval)								
Health Region		**All Patients**	**<18 year males**	**<18 year females**	**18-64 year males**	**18-64 year females**	**65+ year males**	**65+ year females**
CENTRAL	Crude	1.17 (0.96-1.43)	1.38 (1.11-1.71)	1.33 (1.07-1.65)	1.2 (0.98-1.48)	1.11 (0.91-1.37)	1.16 (0.94-1.42)	1.13 (0.91-1.41)
	Adjusted*	1.06 (0.90-1.25)	1.24 (1.03-1.49)	1.20 (0.99-1.45)	1.09 (0.92-1.29)	1.03 (0.87-1.22)	1.03 (0.88-1.22)	1.03 (0.85-1.26)
CENTRAL EAST	Crude	1.14 (0.93-1.41)	1.33 (1.06-1.66)	1.30 (1.03-1.64)	1.19 (0.96-1.47)	1.11 (0.89-1.37)	1.05 (0.85-1.30)	1.03 (0.83-1.29)
	Adjusted*	1.09 (0.92-1.29)	1.23 (1.02-1.5)	1.22 (0.99-1.5)	1.12 (0.95-1.33)	1.07 (0.90-1.28)	1.02 (0.86-1.20)	1.01 (0.83-1.23)
CENTRAL WEST	Crude	1.22 (0.95-1.56)	1.44 (1.12-1.85)	1.34 (1.04-1.72)	1.31 (1.02-1.68)	1.21 (0.95-1.56)	1.20 (0.93-1.55)	1.14 (0.87-1.50)
	Adjusted*	1.09 (0.89-1.35)	1.28 (1.03-1.58)	1.19 (0.95-1.48)	1.17 (0.96-1.44)	1.11 (0.90-1.36)	1.06 (0.85-1.32)	1.02 (0.79-1.31)
CHAMPLAIN	Crude	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Adjusted*	1.00	1.00	1.00	1.00	1.00	1.00	1.00
ERIE ST. CLAIR	Crude	1.46 (1.07-1.98)	1.87 (1.31-2.66)	1.86 (1.32-2.62)	1.44 (1.05-1.97)	1.42 (1.05-1.91)	1.23 (0.91-1.66)	1.26 (0.93-1.72)
	Adjusted*	1.49 (1.15-1.93)	1.94 (1.43-2.63)	1.93 (1.43-2.61)	1.46 (1.13-1.90)	1.46 (1.13-1.88)	1.24 (0.95-1.62)	1.27 (0.95-1.71)
HAMILTON NIAGARA HALDIMAND NORFOLK	Crude	1.26 (1.03-1.55)	1.3 (1.05-1.61)	1.31 (1.07-1.62)	1.24 (1.01-1.52)	1.22 (1.00-1.49)	1.19 (0.95-1.5)	1.26 (0.96-1.65)
	Adjusted*	1.22 (1.04-1.42)	1.26 (1.07-1.49)	1.28 (1.08-1.51)	1.19 (1.02-1.39)	1.19 (1.02-1.38)	1.15 (0.96-1.38)	1.22 (0.95-1.57)
MISSISSAUGA HALTON	Crude	1.39 (1.03-1.87)	1.51 (1.15-1.99)	1.47 (1.11-1.94)	1.49 (1.10-2.02)	1.36 (1.01-1.82)	1.42 (1.02-1.95)	1.37 (0.95-1.97)
	Adjusted*	1.24 (0.95-1.6)	1.31 (1.03-1.68)	1.28 (1.00-1.64)	1.33 (1.02-1.73)	1.23 (0.95-1.6)	1.24 (0.94-1.64)	1.22 (0.88-1.70)

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NORTH EAST	Crude	1.14 (0.85-1.51)	1.18 (0.88-1.59)	1.24 (0.93-1.67)	1.13 (0.84-1.51)	1.14 (0.85-1.53)	0.99 (0.73-1.34)	1.03 (0.77-1.38)
	Adjusted*	1.31 (1.08-1.57)	1.39 (1.13-1.72)	1.46 (1.18-1.81)	1.3 (1.08-1.56)	1.31 (1.08-1.59)	1.13 (0.94-1.36)	1.16 (0.93-1.44)
NORTH SIMCOE MUSKOKA	Crude	1.01 (0.67-1.51)	0.98 (0.64-1.51)	1.02 (0.66-1.59)	0.98 (0.64-1.5)	0.99 (0.66-1.49)	0.97 (0.65-1.44)	1.06 (0.73-1.55)
	Adjusted*	1.06 (0.83-1.35)	1.03 (0.77-1.38)	1.07 (0.79-1.46)	1.03 (0.81-1.31)	1.04 (0.81-1.34)	1.01 (0.8-1.28)	1.09 (0.83-1.43)
NORTH WEST	Crude	1.23 (0.73-2.05)	1.24 (0.64-2.43)	1.37 (0.71-2.62)	1.25 (0.76-2.05)	1.24 (0.77-2.01)	1.06 (0.66-1.72)	1.16 (0.72-1.88)
	Adjusted*	1.31 (0.98-1.76)	1.42 (1.00-2.00)	1.55 (1.08-2.20)	1.33 (1.01-1.75)	1.32 (1.01-1.72)	1.09 (0.8-1.47)	1.19 (0.82-1.73)
SOUTH EAST	Crude	1.09 (0.77-1.55)	1.1 (0.76-1.62)	1.21 (0.82-1.78)	1.05 (0.72-1.52)	1.10 (0.75-1.60)	0.98 (0.71-1.35)	1.01 (0.75-1.36)
	Adjusted*	1.30 (1.08-1.56)	1.34 (1.1-1.64)	1.47 (1.20-1.81)	1.24 (1.02-1.51)	1.29 (1.07-1.56)	1.19 (0.98-1.44)	1.19 (0.95-1.49)
SOUTH WEST	Crude	1.10 (0.85-1.44)	1.17 (0.87-1.58)	1.18 (0.88-1.59)	1.05 (0.81-1.36)	1.06 (0.82-1.37)	1.05 (0.77-1.42)	1.16 (0.82-1.64)
	Adjusted*	1.16 (0.96-1.4)	1.27 (1.04-1.55)	1.29 (1.05-1.58)	1.1 (0.92-1.31)	1.11 (0.93-1.31)	1.11 (0.87-1.43)	1.24 (0.89-1.71)
TORONTO CENTRAL	Crude	1.06 (0.82-1.36)	1.28 (0.93-1.77)	1.21 (0.89-1.64)	1.06 (0.83-1.36)	1.04 (0.80-1.35)	1.08 (0.83-1.39)	1.01 (0.78-1.31)
	Adjusted*	0.88 (0.73-1.05)	1.00 (0.81-1.24)	0.96 (0.77-1.18)	0.88 (0.73-1.06)	0.86 (0.71-1.04)	0.91 (0.74-1.12)	0.89 (0.71-1.12)

*Multivariable models adjusted for health region, rurality, physician density, proportion of family physicians, proportion of male physicians, and proportion of early (<11 years)- vs mid (11-24 years)- vs late (>24 years)-career stage physicians. Reference is the lowest use region (Champlain).

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Location in study
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 2 line 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5 line 5-29
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5 line 32-34
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5 line 41
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5 line 42
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	Page 5 line 42-44
		(*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	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6 line 3-23
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 6 line 14-23
Bias	9	Describe any efforts to address potential sources of bias	Page 6 line 35-50
Study size	10	Explain how the study size was arrived at	Page 5 line 41
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6 line 3-23
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 6 line 25
		(*b*) Describe any methods used to examine subgroups and interactions	Page 6 line 39

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		(*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	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 6 line 47 and table 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	N/A (population-based study)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
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	Page 7 line 9-14 and table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 7 line 16-21 and table 3
		(*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	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure 1 and 3; and Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 7 line 24-27
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	Page 8 line 48- page 9 line 9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 7 line 49 to page 8 line 10

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Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 7 line 29-47
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 3 line 26

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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