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Review of Geographic Variation and Geographic Information Systems (GIS) Applications in Prescription Drug Use Research

Victoria Wangia, PhD¹ and Theresa I. Shireman, PhD, RPh¹

¹University of Kansas Medical Center, Kansas City, Kansas

Abstract

Background—While understanding geography's role in healthcare has been an area of research for over 40 years, the application of geography-based analyses to prescription medication use is limited. The body of literature was reviewed to assess the current state of such studies to demonstrate the scale and scope of projects in order to highlight potential research opportunities.

Objective—To review systematically how researchers have applied geography-based analyses to medication use data.

Methods—Empiric, English language research articles were identified through PubMed and bibliographies. Original research articles were independently reviewed as to the medications or classes studied, data sources, measures of medication exposure, geographic units of analysis, geospatial measures, and statistical approaches.

Results—From 145 publications matching key search terms, forty publications met the inclusion criteria. Cardiovascular and psychotropic classes accounted for the largest proportion of studies. Prescription drug claims were the primary source, and medication exposure was frequently captured as period prevalence. Medication exposure was documented across a variety of geopolitical units such as countries, provinces, regions, states, and postal codes. Most results were descriptive and formal statistical modeling capitalizing on geospatial techniques was rare.

Conclusion—Despite the extensive research on small area variation analysis in healthcare, there are a limited number of studies that have examined geographic variation in medication use. Clearly, there is opportunity to collaborate with geographers and GIS professionals to harness the power of GIS technologies and to strengthen future medication studies by applying more robust geospatial statistical methods.

Keywords

GIS; geographic variation; geospatial; small area variation analyses; medication use

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Dr. Victoria Wangia, University of Kansas Medical Center, School of Nursing and Center for Health Informatics, Mail Stop 4043, 3901 Rainbow Blvd., Kansas City, KS 66160, (913)787-3148, vwangia@kumc.edu.

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BACKGROUND

According to Wennberg, “Geography is destiny”.¹ Location of residence impacts persons’ quality of healthcare received, access to healthcare, and the health resources available to them.^{2,3} Geographic variation is evident throughout the healthcare delivery system. Researchers have found that geographic differences in healthcare utilization are observed even after adjusting for age, disease prevalence, individual health status, insurance coverage, sex and income.⁴ Observed differences are mostly attributed to characteristics of the healthcare system and as such serve as a mechanism to evaluate quality of care.⁵ The challenge, however, is determining the correct “rate” of care, as low rates may signal under-treatment while high rates may signal over-treatment.

Research examining geographic variation in the context of healthcare gained recognition and prominence in the 1970s with the work of John Wennberg and colleagues.⁶ They applied a method known as small area analysis. Small area analysis involves analyzing variation in the use of healthcare in small geographic or demographic areas. Their initial research explored the differences in tonsillectomy rates between Maine and Vermont towns finding tenfold differences.⁶ The field has since expanded extensively to a variety of health services, procedures, settings, populations and geographic regions.^{7–10} Most studies focus on use of medical care or services.¹¹

The first study to examine geographic differences in prescribed medication use was a study of the distribution (sales data) of anti-diabetic agents in three European countries in 1971.¹² It was not until the mid-to late 1990s, however, that more researchers in the United States took up the study of geographic differences in prescription drug use rates.^{4,13,14} In 1996, a group of Canadian researchers laid out a potential research agenda for prescription drug utilization and explicitly indicated the need for research examining geographic differences in prescribing patterns.⁴

OBJECTIVES

To document the current state of knowledge that has been generated through the application of small area analysis to prescription medication use, a literature review was conducted. The aim of the review was to understand what specific medications and disease conditions have been studied, what data sources were commonly used, how medication exposure and geospatial metrics were computed, and which GIS-based techniques were used to analyze the data and lastly, to present a synthesis of the results.

METHODS

A systematic literature review was conducted using PubMed to identify studies of geographic variation in prescription medication use. The electronic search was supplemented by incorporating additional studies from reference lists not identified through the electronic search. The initial search was completed in March 2011 and updated in January 2012.

Search Strategy and Article Selection

In PubMed, the search began with the following search string (Figure 1 details the process and its yield): (“small area analyses” OR “geographic variation” OR “interstate” OR “regional variation” OR “intrastate” OR “GIS” OR “HRR” OR “Geographic Information System”). This search generated 8,860 publications clearly confirming the breadth of research in the area of geography and health. Narrowing the search by adding “AND (“Medication”) quickly reduced the yield to 75 articles. To expand potential medication-related terms, “drug utilization” was added increasing the yield to 104 publications. Adding “pharmaceutical” brought the total to 145 articles.

The search was then limited to *humans* and the *English language*, and returned 121 citations. Abstracts were reviewed first and those that met the following selection criteria were selected: 1) the study had to examine variation in prescription medication use or related issues such as prescribing patterns, quality of prescribing, and drug safety, 2) the study had to include empirical data analysis, and 3) the study had to compare prescription medication use across two or more geographic units of analysis. This limited the list to 38 studies. After reviewing each study, 2 articles noted in the bibliographies but not captured with the electronic search were added. These 40 articles were included in the final review.

Data abstraction

Both authors abstracted information from each study independently using a consistent data abstraction form adapted from the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) criteria.¹⁵ The following information was abstracted from each publication: author/year, country; medication product/class; sample; data source/s; study year; medication exposure measures; geospatial unit of analysis; geospatial measures; GIS data links and technology; and whether geographic variation was observed.

RESULTS

Due to the scope and scale of the review, the presentation is divided into two tables. In Table 1, details about the time period, the country, the medications, the study sample, the data sources, and the medication exposure measures are detailed. In the second table (Table 2), more specific details on the geospatial measures and analyses are included. In the following text, the findings across the “columns” of the tables, highlighting key elements of similarities and differences are discussed. The tables are organized into sections according to the main drug class and by date of publication within the drug class. The order of presentation of the individual studies is the same in Tables 1 and 2.

Prescription Medication Products/Class

The vast majority of studies focused on one of four therapeutic classes: cardiovascular agents, psychotropics, opioids, and antibiotics.^{5,13,14,16–43} Of these, studies of cardiovascular agents were the most common accounting for eleven publications.^{13,17,18,25,26,28,30,32,34,40,41} These studies included a wide variety of agents ranging from aspirin or anti-platelets to renin angiotensin system antagonists.^{13,17,18,25,26,28,30,32,34,40,41} Most of the cardiovascular studies, though, focused

on anti-hypertensives such as angiotensin converting enzyme inhibitors,^{17,18,25,26,28,30} angiotensin receptor blockers,^{17,18,28,30} beta-blockers,^{13,17,18,25,26,28,30,40} calcium channel blockers,^{13,17,18,25,26,40} and diuretics.^{17,28,32,34,40,44}

As with the cardiovascular agents, there was a variety of psychotropic medication subclasses examined in ten studies. Stimulants, in particular, were examined as the targeted class in four studies^{22,24,39,43} and included as part of broader studies in another two^{14,35}. Other psychotropics included antipsychotics,^{5,14,23,29,35} antidepressants,^{5,14,21,35} anticonvulsants,^{5,29,35} and anxiolytics,^{5,14,29,35} Three studies included psychoactive agents along with a variety of other medication classes.^{45–47}

Opioids, which were considered separately from psychotropics in our review, were the focus of five studies^{16,27,37,38,42} and mentioned in an additional three studies^{32,45,46}. Oxycodone, in particular, was the agent in most of these studies.

Interestingly, antibiotics were the focus of study more commonly in Europe^{19,20,31,36} than in the US studies³³. Most took a broad look at antibiotics without selecting subclasses or particular agents. Finally, there were studies that examined multiple classes of medications, sometimes including classes listed above,^{11,45–49} or focused on medications to treat other conditions such as diabetes¹², asthma⁵⁰, dementia⁵¹.

Study Sample

In characterizing the study samples, several features distinguished how people were selected for inclusion: we broadly considered age or age groups, medical conditions, health insurance status, and special surveys or studies.

There were three principal categories of age (children, adults, and older adults), though these were defined differently between studies. Fifteen studies included children.^{5,12,14,19,20,22–24,29,33,35,36,39,43,46,49} Children as young as newborns (age = 0 years) were included in nine studies.^{12,20,22,24,33,35,43,46,49} In general, the upper age cut off for children was 18–19 years.^{12,20,22,24,43,46,49} Several studies included more limited age ranges among children such as 5–14 years,^{14,39} 4–20 years,²³ 2–14 years,⁵² 15 years,²⁹ and under 5 years.³³ There were four studies that stated they included children but did not specify the ages.^{19,31,36,37}

While over half of the studies included adults, the ages were only explicitly stated in ten studies. There were five studies that included 18 year olds and greater.^{16,18,27,38,41} Arlind et al. limited their sample to ages 18–44 years. Four studies targeted “older” adults, with Usher et al., using a lower bound of 45 years, and Hogan et al. and Pilote et al. using a more traditional 65 years plus. Naughton et al. used a slightly higher cut age of 70 years.

A second major factor defining the sample selection was targeting a specific condition or patient population. In accordance with the focus on cardiovascular medications, several studies selected patients after an acute myocardial infarction,^{13,25,30} patients with hypertension,^{18,28,34} and patients with other cardiac conditions.^{26,40,41} In their analysis of opioid exposures, Luo et al. selected persons with backpain and Brownstein et al. selected persons in treatment for substance abuse. There were two studies examining patients with

diabetes,^{12,48} but the majority of studies did not limit the analyses to individuals with any specific condition. Two studies included children within the welfare system and examined psychotropic medication exposures.^{5,29}

Finally, another major source of distinction for the study samples was their enrollment in a health insurance program or a specific survey. For instance, several samples came from registries of people using their national health systems in Sweden,^{17,49,50} Canada,^{43,46} Germany,^{31,36} and England.¹⁹ Within the United States, samples included beneficiaries from Medicare,¹³ Medicaid,^{14,16,34,35} the Veterans Administration,^{11,28} and private insurers.^{37,39,45} Other samples came from national surveys such as the Medical Expenditure Panel Survey,^{27,33,38} the National Survey on Child and Adolescent Well-Being,^{5,29} and the National Addictions Survey.⁴²

Data Sources

The reviewed literature exhibited differences in the sources of data examined. Data sources for prescription medication exposure mostly fell into three categories: administrative claims data, medical records and survey data. Administrative claims data included data from both government and commercial health insurance companies. Medical record data was mainly from chart reviews and registries and, survey data was data collected mainly through national questionnaires.

The US studies that analyzed government health insurance data drew mostly from Medicaid and Medicare data. Five studies utilized Medicaid data.^{14,16,18,34,35} and only two analyzed Medicare data.^{13,38} Commercial health insurance data sources were analyzed in three studies^{37,39,45} and two studies used Veteran Affairs data.^{11,28}

Like the US studies, the main data sources for the non-US studies were government health insurance data for specific countries.^{12,17,20–22,24,25,31,40,43,46,49,50} Sweden's national health insurance data were the most utilized data source, used in three studies.^{17,49,50}

Eight studies examined medical record data drawn from sources such as registries, chart reviews and databases.^{13,19,23,30,41,47,48,50} This included both US and non-US studies. For example, the Swedish prescribed drug register included all out-patient prescriptions dispensed at pharmacies in Sweden from 2005.^{41,50} Chart reviews were retrospective and involved collecting information on the use of medication by clinical indication, region, demographic information, risk behaviors and symptoms.²³ The General Practice Research Database includes diagnosis and prescription data for about five percent of the United Kingdom population.¹⁹ This data was analyzed to assess regional differences in antibiotic prescribing for sore throat, cough and cold.¹⁹

Survey data were collected through interviews and self-administered questionnaires. It was analyzed in nine studies conducted in the US and in other countries.^{5,26,27,29,32,33,36,38,51} National surveys were a common source of data.^{5,27,29,33} For example, the National Survey of Child and Adolescent Wellbeing collects information for US children being investigated for abuse and neglect.^{5,29} Youth, caregivers and welfare workers respond to the surveys.^{5,29} The Medical Expenditure Panel Survey is a national survey that collects longitudinal data on

healthcare use, expenditures, sources of payment and insurance coverage from US households.²⁷ The National Ambulatory Medical Care Survey includes data used to assess use of ambulatory medical care services, and based on patient visits to non-federal employed office-based physicians.³³

Though not national data, other survey data with large sample sizes were used. For example, the multi-center Canadian Health and Aging Study collected data through interviews and surveys from elderly Canadians to understand change in health status and to determine incidence and prevalence of dementia.³²

Medication Exposure Measures

Medication exposure was measured in a variety of ways in the studies. Medication exposure measures examined were prevalence measures, specifically, period prevalence. Period prevalence measured the proportion of the population using a specified drug/s or drug class (one or more) over a specific period of time. Period prevalence was mostly measured on an annual basis,^{5,14,19–24,26,27,29,32,33,37,43,45–48,50,51} and measured monthly in few studies.^{18,25,34,35,49} However, the studies that measured exposure monthly, measured it over different time periods with more studies measuring exposure over a three month period,^{25,34,49} and fewer measuring exposure over a four month period.^{18,35} Medication exposure was also measured hourly.^{30,41} The hourly measurement was based on performance measures of medication use within 24 hours of discharge.³⁰ It also was demonstrated in the measurement of medication use at pre-hospitalization, within 24 hours and after the first 24 hours of discharge.⁴¹

Medication use density or volume was measured by defined daily dose (DDD). This was a common measure across studies and was calculated at specified population levels per day and compared across various geographic units of analysis.^{12,16,21,28,31,36,40} For example, defined daily dose per 1000 inhabitants (DDDs/1000) per day was used as an indicator of the estimated proportion of the population receiving the medication, hence measuring consumption of the medication.⁴⁰

Standardized prescribing/medication ratio was a measure utilized in some studies. It was computed as the observed number of prescriptions divided by the expected number, and compared across geographic units of analysis.^{24,47,48}

Incidence was less common but was studied.^{17,20,50} For example, incidence was compared across counties and measured as the number of individuals who began antihypertensive drugs/1000 patient years calculated from initial dispensing after a wash-out period.¹⁷

Geospatial Units of Analysis

Table 2 shows various geospatial units of analysis examined in the studies. The researchers compared statistics across geographic units of analysis and also included the unit of analysis in regression models as a predictor.

Countries were the most common, largest geographic unit of analysis examined.^{12,20,41} Continents were studied less.⁴¹ US census regions including the Northeast, Midwest, South

and West and comprised of select states were examined,^{27,30,33,38} but states were a more common geographic unit of analysis.^{5,16,18,30,37,39,41,51} A combination of both states and counties were also studied.³⁷ Canadian studies included provinces,^{25,32} and other studies examined smaller areas than provinces and states, and included counties,^{14,18,49,50} zip codes and postal codes.^{22,24,42} Geospatial analysis across cities was not examined in any of the studies but townships were.⁴⁰

Other regions were studied that were not defined by geopolitical units of analysis. For example Veteran Integrated System Networks,^{11,28} hospital referral regions,¹³ local management entities,³⁵ and driving areas for clinical care.³⁴

In some studies, characteristics of the unit of analysis were also linked to allow for comparisons to be made and detail to be drilled down to a smaller area for relationships to be uncovered that could be masked at a higher geographic unit of analysis. These included variables such as residence outside a metropolitan statistical area (MSA), urban, rural and suburban.^{14,38,43} More than one geographic unit of analysis was assessed in some cases, for example, including states and counties; regions and MSA; and regional health authorities and sub-regions.^{37,38,43,46}

The details specifying how regions were created were vague in most studies. One study was very specific about how they mapped zip codes to FIP codes using ZipInfo.com algorithm and aggregated claims to county level.³⁷ Zipinfo.com's algorithm was used in to link patient Zip code to the appropriate county; linking the patient to a region based on US Census regions.³⁷ They specified the exclusion and inclusion criteria noting that counties with less than 100 total claims for prescription drugs were excluded and counties with larger populations were weighted more.³⁷

Analysis

Descriptive methods for measuring variation common in other small area variation analysis studies were common for studying geographic variation of medication use across some of the studies we reviewed. These included the coefficient of variation,^{17,21,35,37,40,45,48} system component variation,^{37,39} extremal quotient,^{16,17,21,32,35,45,48} and interquartile range.^{30,39}

Statistics very specific to geospatial analysis, including risk mapping, cluster detection, spatial scan statistics and local indicators of spatial association (LISA) were also presented.^{40,42} Brownstein et al (2010) used risk mapping to identify hot spots for potential opioid medication abuse.⁴² They also applied spatial detection clustering to identify clusters of medication use/abuse.⁴² Spatial scan statistic enabled the clustering to be identified with statistical significance.⁴² Cheng et al (2011) applied LISA to reduce larger areas into small areas and enable assessment of prescription drug use at a local level, specifically observing local spatial clustering at an individual location.⁴⁰ Spatial clusters were examined because they can be a reflection of inefficiency in healthcare resources and use.⁴⁰ While all studies showed geographic variation in medication use, a minimal number of studies specified use of a specific Geographic Information System (GIS) technology.^{40,42}

Geodata linking

In some studies, one data source was not sufficient to address the study aims and additional data were linked to pharmaceutical data to produce a more comprehensive data set. Linked data allowed for analysis at the geospatial unit of analysis by variables such as race/ethnicity (percent white non-hispanic)³⁵, socioeconomic status (per capita income, percent in poverty^{27,35,39,46}, uninsured (under 18)³⁵, high school graduates (age 25 +)³⁵, population-related factors (population density, rural-urban continuum)^{35,39} and provider availability.^{35,39} These variables were obtained from data sources including, the Area Resource File^{5,37}, the American Medical Association (AMA) data for physician supply data³⁹, census data^{24,35}, US Department of Agriculture data³⁵, North Carolina Health Professions Data System³⁵, data from the Cecil G. Sheps Center for Health Services Research at the University of North Carolina at Chapel Hill³⁵ and Kaiser Family Foundation's State Health Facts⁵.

Maps

Maps may be used as visual representation of spatial data. In studies on medication use, they can be used to display results of the analysis to visualize differences across regions. In the reviewed studies, the measures represented on the maps varied and were dependent on the aims of the study and how medication exposure was measured. Despite the studies being about geography, relatively few included maps.^{11–13,16,18,22,34,37,39,40,42,48} The boundaries represented on the maps were in alignment with the geographic unit of analysis and illustrated variation in medication use observed in the data. However, there were two exceptions where a map was included but no density data was presented.^{12,48}

DISCUSSION

Despite 40 years of small area variation analysis in health care, there is a rather limited application of its techniques to prescription medication exposures (n = 40 studies). As shown in this review, there is a vast degree of variability in the classes of medications or conditions studied to date, the data sources, the study populations, and the measures employed. All of the studies suggest, in one way or another that, as with other health care goods and services, there is substantial variation in prescription medication use in the US and around the world. However, most studies did not perform statistical analyses to test the significance of the variation. The simplest implications of these findings are that patients and providers may lack understanding or consensus as to the optimal use of medications within a given context. These results also suggest a number of avenues for further investigation and development of the joint fields of pharmacoepidemiologic and GIS applications. For example, the range of studies examining psychotropic medication use in children could well be informed through spatial analysis of census tract level data on community level characteristics as well as patient factors. The adoption of new pharmaceutical technologies could be examined in the face of community characteristics and health status. If consensus exists about the appropriate use of medications, small area analyses can highlight geographic units that depart significantly from ideal practices.

Further work, however, must consider more refined analyses. Many of these studies were conducted using broad geopolitical units of analyses, e.g., country or state. While suitable for certain pharmaceutical policy evaluation, smaller geopolitical units are better able to capture local practice variation. There is no consensus on what geographic unit of analysis is appropriate for depicting healthcare. The selection of a geographic unit of analysis can be limited by the data source and often the research question defines the geographic unit of analysis for consideration. There were some common units of analysis across studies such as census regions, states, veteran integrated service networks and counties. The largest geographic unit of analysis examined was a continent and the smallest was at the zip code or postal level. It was common for smaller units of analysis to be aggregated into larger units of analysis. Geopolitical units of analysis were the most common, however, other units of analysis were introduced that were not geopolitical such as hospital referral regions, Veteran Integrated Service Networks and local mental health catchment areas. The geographic units of analysis had different characteristics and in some studies the extent of rural versus urban was introduced. The denominators of medication use prevalence rates were expressed in terms of the populations at the specified geographic unit of analysis.

Further attention also should be given to the medication exposure measures. Medication exposure was classified from simple rates reflecting any versus no use to dosing levels based upon defined daily doses. The decision to prescribe/use a given medication is quite different from the decision to continue use over time. Of course, the selection of the metric should reflect the purpose for the measurement in any given study.

The studies included descriptive statistics commonly used in small area variation analysis to test for excessive variability.⁵² These descriptive statistics include: the coefficient of variation (CV), the system component of variation (SCV), the interquartile range (IR), and the extremal quotient (EQ). The CV, IR and EQ show the distribution of rates and SVC show the differences between observed and expected rates.⁵² Coefficient of variation and extremal quotient provide important information on the degree of variability in exposure in a given area. More inferential approaches may examine factors associated with exposure levels and can include a variety of analytic techniques. The results of this review support the need for expanded research measuring geographic variation across more therapeutic classes than currently demonstrated. The results showed studies examining geographic variation in medication use are few and the focus is narrow. The focus was mostly on four therapeutic classes namely cardiovascular, psychotropic, opioids and antibiotics. Geographic variation for many therapeutic classes remains unexamined.

A strong appeal of geospatial analysis is the ability to link data by geography at the population level.⁵³ Multiple data sources such as the 2000 Census data, the Area Resource File and zip code files were linked to pharmaceutical data to introduce additional spatial and non-spatial variables for the purposes of addressing research objectives and identifying future research questions. A benefit to linking pharmacy claims data and other data sources is the ability to create a more comprehensive data source for analysis. Researchers should continue to explore addressing their study aims by linking to data sources such as the more recent 2010 Census data. In the US both federal and state legislation has led to the rapid adoption of health information technology by healthcare organizations. This creates

opportunity for new more comprehensive data sources researchers can use to explore linking by geography prescription medication claims data and clinical data.

Most studies focused on the presentation of data on maps, hence geospatial visualization. The usefulness of maps remains in their inherent ability to suggest patterns in the phenomena represented on the maps.⁵³ Maps were used in some of the studies to illustrate the observed geographic variation in medication use. They were useful visuals; however, they lacked sophistication. Simple to complex maps can be created with GIS technology,⁵³ and only two studies was explicit about using specific GIS technology to create maps.^{40,42} Therefore, a description of the methods and technology applied to develop the maps was lacking in majority of the studies.

Improved availability and access to geospatial data provides opportunities for researchers to extend beyond visualization and include analyses that distill more relationships in the data and allows for more detailed conclusions. Geospatial analysis includes what happens where, and makes use of geographic information that links features and phenomena to their locations.⁵³ Exploring spatial relationships identifies the linkages or relationships location establishes.⁵³ This is made possible through the application of spatial statistics. Spatial statistics are statistical approaches applied to data with spatial structure.⁵³ Though there were studies that explored some geospatial analysis, the analysis was simple and was limited to comparing prevalence rates across geographic units of analysis. More sophisticated geospatial analysis needs to be introduced to improve the robustness of these studies. For example, spatial autocorrelation assessment is critical in geospatial analysis when close geographic units of analysis are compared, however, only one study examined this.⁴⁰ Spatial autocorrelation is based on the geographical principle that everything is related but the closer things are the more related they are.⁵³ Consequently, spatial autocorrelation tests the strength of the autocorrelation and the assumption of randomness/independence.⁵³ Moran's I is an example of a measure of spatial autocorrelation. Despite the relevance of geospatial analysis, both Moran's I and spatial autocorrelation were only mentioned and examined in one study.⁴⁰ Methods to address clustering effects in geographic units of analysis were also lacking in the studies and were considered in only two studies.^{40,42} Understanding spatial clustering in prescription medication use may indicate inefficiency in healthcare resource allocation and use.⁴⁰

In conclusion, there is enormous opportunity for further application of geospatial statistical methods in the areas of pharmacoepidemiology and pharmaceutical health services research to harness the analytical potential of geospatial methods and the mapping and general visualization and geospatial capabilities of GIS technology designed to handle geographically-referenced data. Utilizing more advanced geospatial methods would increase the validity of study results and generate very interesting hypotheses to test in further studies. Partnering with GIS experts would provide researchers with the expertise needed to identify appropriate geospatial methodology and to generate more sophisticated maps able to more accurately depict relationships in the data.

More recently there is increased attention to pharmaceuticals due to the rising use of prescription medication.⁵⁴ This interest has been further sparked by the realization that

prescription medication use can be a proxy for gauging the performance of health systems.⁵⁴ Though geographic variation in medication use has been explored, the studies are few and the use of GIS technology and geospatial statistics is limited. This literature review contributes to the body of literature by being the first to provide evidence demonstrating the need for future research. The studies are few but it is evident that geographic variation of medication use exists and understanding the reasons for the variation can shed light on health disparities and demonstrate whether health system performance related to for example, quality of care, could explain the geographic variation in medication use and prescribing.

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Figure 1.
Search Strategy and Results

Table 1
Source and Country, Study Period, Medication, Sample, Data Source/s and Medication Measures

Source and Country	Study Period	Rx Class/Class and Products	Study Sample	Data Source	Rx Measures
Cardiovascular					
O'Connor/1999 ¹³ ; US	Feb 1994 – Jul 1995	Calcium Channel Blockers, Angiotensin-Converting Enzyme Inhibitors, Beta Blockers, Aspirin	Adults (age unspecified) Patients with Acute myocardial infarction and Medicare beneficiaries	UB-92 claims form data in the Medicare National Claims History File; Medical records	Rx quality indicators: during hospitalization, at discharge, withheld at discharge if impaired left ventricular function
Hogan, et al./2003 ³² ; Canada	1991 and 1996	Analgesics, Diuretics, Cardiac, Antihypertensive, Antipsychotic, Anxiolytics,	Adults(65+) Participants in the Canadian Study of Health and Aging	Self-report or reported by guardians and chart reviews	Rx "taken as required" recorded based on interview
Budaj et al./2003 ⁴¹ ; Australia, Argentina, Brazil, US, New Zealand, Canada, Europe	Apr 1999 – Mar 2001	Antithrombotic and Antiplatelet	Adults (18+) Patients with Acute Coronary Syndrome admit	Registry (ongoing)	Any use at: prehospitalization, within 24 hrs, after first 24 hrs, at discharge
Lopez et al./2004 ²⁸ ; US	2000–2002 (Federal FY)	Beta Blockers, Angiotensin-Converting Enzyme Inhibitors, Calcium antagonists, Thiazide Diuretic, Angiotensin Receptor Blockers, Diuretic/potassium sparing diuretic combinations, and all other combinations of the above	Adults (age unspecified) Veterans with hypertension	National VA Pharmacy dispensing data	Proportional use: treatment days(1000s); % treatment days
Pilote et al./2004 ²⁵ ; Canada	Apr1997 – Feb 2000	Beta Blockers, Angiotensin-Converting Enzyme Inhibitors, Statins, Calcium Channel Blockers and Nitrates	Adults (65+) Patients admitted for Acute Myocardial Infarction	Canadian provincial data except Nova Scotia (ICONS registry (adds chart data))	Proportions and utilization rates/100 discharges; 90-day post discharge
Muller-Nordhorn et al./2005 ²⁶ ; Germany	Jan – July 1997	Aspirin, Beta Blockers, lipid lowering agents, Angiotensin-Converting Enzyme Inhibitors,	Adults (age unspecified) Inpatient cardiac rehabilitation patients	Physician report and patient self-report	Prescription of medication after 12 months
Laskey et al./2010 ³⁰ ; US	2000–2008	Cardiovascular (ACEI/ARB, BB, Aspirin, Lipid lowering drugs)	Adults (age unspecified) (with acute myocardial infarction)	Get with the guidelines coronary artery disease program data	Rx performance measures: % of Aspirin (ASA) within 24 hr if acute myocardial infarction or angina, % of discharged with ASA, % with left systolic ventricular dysfunction discharged on ACEI/ARB, % discharged on BBs, Low density lipoprotein > 100 receiving lipid lowering drugs
Wettermark, et al./2010 ¹⁷ ; Sweden	2005–2008 Sep–Dec (4 months) each year	Antihypertensive agents– Diuretics, Beta-blockers, Calcium Channel Blockers,	Adults (age unspecified)	Swedish prescribed drug register	% population dispensed drugs before and after

Source and Country	Study Period	Rx Class/Class and Products	Study Sample	Data Source	Rx Measures
Fang et al./2010 ³⁴ , US	1997–1999	Angiotensin-Converting Enzyme Inhibitors, (fixed combinations with thiazides); Angiotensin-Converting Enzyme Inhibitors, (fixed combinations with thiazides); Angiotensin-Converting Enzyme Inhibitors, (fixed combinations with thiazides); Angiotensin-Converting Enzyme Inhibitors, (fixed combinations with thiazides); Angiotensin-Converting Enzyme Inhibitors, (fixed combinations with thiazides);	Adults (age unspecified) (Medicaid enrollees with hypertension)	Angiotensin Receptor Blockers (fixed combinations with thiazides); Angiotensin Receptor Blockers (fixed combinations with thiazides); Angiotensin Receptor Blockers (fixed combinations with thiazides); Angiotensin Receptor Blockers (fixed combinations with thiazides); Angiotensin Receptor Blockers (fixed combinations with thiazides);	Number of prescriptions dispensed per 1000 inhabitants in the 4 months)
Cheng et al./2011 ⁴⁰ , Taiwan	2004	Antihypertensive agent –Thiazide Diuretics	Adults (age unspecified) (Medicaid enrollees with hypertension)	Iowa Medicaid data	Physician local area practice styles for prescribing medication within 90 days of first hypertension diagnosis
Wernmore et al./2011 ¹⁸ , US	Sep 2005 – Dec 2005	Rennin-angiotensin, Beta Blockers, Calcium Channel Blockers,, Diuretics, Antihypertensives	Adults (age unspecified) (with cardiovascular disease)	National health insurance database	1+ medication in 2004; DDD/1000 inhabitants/day
		Antihypertensives-Angiotensin-Converting Enzyme Inhibitors, Beta Blockers and Calcium Channel Blockers	Adults (age unspecified) (long-term dialysis patients and with hypertension and dually eligible for Medicare and Medicaid)	US Renal data System and CMS Medicaid files	First prescription for each person from each class of medication observed over a 4 month period
Psychotropics					
Zito et al./1998 ¹⁴ , US	Jul 1990– Jun 1991	Psychotropic:(psychostimulants, antidepressants, antipsychotic, benzodiazepine and lithium); Nonpsychotropic: (antibiotics; antihistamines;; eye, ear, nose and throat preparations; antitussives; skin preparation) and Mixed Category: (hydroxyzine)	Children (5–14) (seen in ambulatory settings by physicians)	Maryland Medicaid	Use of any of the psychotropic and non-psychotropic and mixed category classes
Brownell and Yogentran/2001 ⁴³ , Canada	Apr 1995 –Mar 1996	Stimulants (drugs unspecified)	Adults and Children (0–19) (with Attention-deficit hypertension disorder (ADHD))	Physician claim files; Drug Claims - Drug Program Information Network (DPHIN); Population Registry (includes information from Census data)	Rate of psychostimulant medication prescribed/ 1000
Roberts and Norris/2001 ²¹ , New Zealand	1993–1997	Anti-depressant (drugs unspecified)	Population unspecified	Health Benefits Limited Rx claims (dispensings)	Dispensings per 1000; days supplied per 1000
Reid et al. 2002 ²² , Australia	1990 – 2000.	Stimulants (methylphenidate, dextroamphetamine)	Adults and Children (0–18) (authorized to receive psychostimulant)	South Australian Health Commission archival records; Australia Bureau of Statistics.	Received authorized psychostimulant during the period 1990–2000
Cox et al./2003 ³⁹ , US	1999	Stimulants (methylphenidate, amphetamines, dextroamphetamine sulfate, pemoline)	Children (5–14) (continuously enrolled)	Express Scripts prescription claims - 1999- Census files	Proportion with at least 1 stimulant use during the study year

Source and Country	Study Period	Rx Class/Class and Products	Study Sample	Data Source	Rx Measures
				1990 & 1998; AMA physician supply – 2001 1990 & 1998; AMA physician supply – 2001 1990 & 1998; AMA physician supply – 2001	
Rawal et al./2004 ²³ ; US	1999–2000	Antipsychotics (drugs unspecified)	Adults and Children (4–20) (Youth with and without psychosis receiving antipsychotic medication in residential treatment facilities)	Retrospective, cross- sectional chart reviews	Rx Used/Not Used – based on chart review
Prosser and Reid/2009 ²⁴ ; Australia	1990 – 2000 and 2001– 2006	Stimulants (drugs unspecified)	Adults and Children (0–18) (authorized to receive psychostimulants in the city of Adelaide)	South Australian Health Commission archival records; Australia Bureau of Statistics.	Received stimulant or Authorized to receive psychostimulant per 1000; Standardized medication ratio
Raghavan et al./2010 ⁵ ; US	2002 – 2004 and 1999 – April	Psychotropic (drugs unspecified)	Children (2–14) (in the child welfare system)	National survey of child and adolescent well-being; Kaiser Family Foundation's State Health Facts File (2009); Area Resource File	Rx for emotional, behavioral, learning, attention or substance- abuse (current use of medications)
Ellis/2010 ³⁵ ; US	2001–2006	Psychotropic (antidepressants, antipsychotics or mood stabilizers, stimulants, anxiolytics and a combination of antipsychotic/antidepressant)	Children (0–4) (Medicaid enrollees who received psychotropic medication)	North Carolina Medicaid data; NC Health Choice enrollees included in 2003 forward	Number of psychotropic drug recipients per 1000 enrollees– on a quarterly basis
Leslie et al./2011 ²⁹ ; US	Oct 1999 – Dec 2000	Psychotropic (specific drugs unspecified)	Children (2–15) (abused or neglected in the welfare system)	National Study on Child and Adolescent Well-being	Receiving medication for emotional, behavioral, attention or substance abuse
Opioids					
Luo et al./2004 ²⁷ ; US	1996–1999	Drugs unspecified	Adults (18+) (with backpain)	Medical Expenditure Panel Survey	1+ medication in the last year
Curtis et al./2006 ³⁷ ; US	2000	Opioids and Controlled Release Oxycodone (Methadone, oxycodone-acetaminophen, oxycodone-aspirin combination, controlled- release oxycodone, codeine phosphate, codeine sulfate, hydromorphone, levorphanol, meperidine, meperidine-promethazine combination)	Adults (age unspecified) (Continuously enrolled outpatient population)	Advance PCS (Caremark RX); Area Resource File; National Survey on Drug Use and Health	1 + medication during the year
Zerzan et al./2006 ¹⁶ ; US	1996–2002	All opiates, methadone, oxycodone	Adults (18+ and 20+)	Medicaid	DDD/1000/D
Craig and Strassels/2010 ³⁸ ; US	1999 –2004	Tramadol, hydrocodone, propoxyphene, codeine, oxycodone, morphine, fentanyl	Adults (18+) (surveyed during study period, residing in community setting and	Medical Expenditure Panel Survey and Medicare Current Beneficiary Survey	Medication price

Source and Country	Study Period	Rx Class/Class and Products	Study Sample	Data Source	Rx Measures
Brownstein et al./2010 ⁴² , US	Oct 2006 – Sep 2008	Hydrocortisone, oxycodone, morphine, oxycontin, vivudin, MS contin	Adults (age unspecified) Patients treated for substance abuse	National Addictions Vigilance Intervention and Prevention Program data; Semi-structured interview conducted upon admission; Retail drug distribution data; Census data	Overall medication abuse. Abuse by medication class, Risk for abuse (overall and by class)
Antibiotics					
Halasa et al./2002 ³³ , US	1993–1999	Antibiotics (penicillin (all types), cephalosporin (all types), erythromycin/lincosamide/macrolides, tetracycline, chloramphenicol derivatives, aminoglycosides, sulfonamides and trimethoprim, miscellaneous antibacterial agents and quinolone/derivatives)	Children (<5) (office-based visits)	National Ambulatory Medical Care Survey; Census data	Annual rate of all antibiotic or specific antibiotic prescriptions per 1000 children
Smith et al./2006 ¹⁹ , UK	1993–2001	Drugs unspecified	Adults and Children (age unspecified) Patients diagnosed for Cough/Cold or Sore throat	General Practice Research Database (GPRD)	Rxs/1000 patients per year for at risk; Regional Rx rates; % episodes with Rx
De With, et al. /2006 ³⁶ , Germany	2003	betalactams, fluoroquinolones, macrolides/clindamycin, aminoglycosides, glycopeptides, and others.	Adults and Children (age unspecified) In-Patients in German acute care hospitals.	Survey data	DDD and RDD per 100 patient days (DDD/100 and RDD/100)
Kern et al./2006 ³¹ , Germany	2003	Antibiotics ("basic" penicillins (oral penicillin or aminopenicillins), extended-spectrum betalactams (oral cephalosporins, anti-staphylococcal penicillins, aminopenicillin/betalactamase inhibitor combinations), broad-spectrum betalactams, newer macrolides (roxithromycin, clarithromycin, azithromycin) vs older macrolides. Quinolones, folate synthesis inhibitors (primarily trimethoprim-sulfamethoxazole), tetracyclines and clindamycin (together with streptogramins and fusidic acid))	Adults and Children (age unspecified) Germans covered by statutory health insurance	Germany health insurance data; Data from Federal and State Bureau of Statistics	DDD/1,000 persons covered by the insurance and day (DID)
Sharland/2007 ²⁰ , UK	Oct 2002– Sep 2005	Drugs unspecified	Children (<18)	National prescribing data; Intercontinental Medical Statistics; UNICEF population data	Number of prescriptions by year for 5 years; Prescription per 1000 person-years (prevalence and incidence)
Others					

Source and Country	Study Period	Rx Class/Class and Products	Study Sample	Data Source	Rx Measures
Dubois et al./2002 ⁴⁵ ; US	1998–1999	Medication for Asthma, Congestive Heart Failure, Rheumatoid/Osteoarthritis and Respiratory Tract Infection (SSRIs, GI drugs, ACE or ACE II inhibitors, Anxiolytics, Narcotics, Brand-name antibiotics (for sinusitis, bronchitis and otitis media), narcotics, inhaled corticosteroids, methotrexate, diuretics, tricyclics, antihistamines, coumadin, Digoxin, New antidepressants, Cox-2 inhibitors)	Adults (age unspecified) (Privately insured health plan members with continuous coverage)	California health plans data	Any prescription for medication during 1998–1999
Kozynskyj/2002 ⁴⁶ ; Canada	1998–1999	Antibiotics, Pain-relief drugs, Iron Supplement and 4 Classes of Psychotropics (oral antibiotics (except tuberculosis drugs), narcotic analgesics and non-steroidal anti-inflammatory drugs; Psychotropics (psycho stimulants, antidepressants, antipsychotics, and anxiolytics))	Adults and Children (0–19) (receiving prescription)	Population Health Research Data Repository: Registration files and Records of prescriptions dispensed in retail pharmacies.	1+ medication in class
Bergman et al./1975 ¹² ; N. Ireland, Norway, Sweden	April–June 1971	Antidiabetic drugs, “supplied” amounts (Metformin, phenformin, chlorpropamide, tolbutamide, carbutamide, glibenclamide, glymidin, acetohexamide, tolazamide, insulin)	Adults and Children (age unspecified) (Country and Within Country (area) Population)	North Ireland - claims data; Norway - sales data; Sweden -sales data	Agreed daily doses/ 1000 inhabitants/day
Usher et al./2005 ⁴⁸ ; Ireland	January– December 2002	Antidiabetics and Cardiovascular Medication used by Diabetics (BB, aspirin, antagonists, ACEI, fibrates)	Adults 45+ (with diabetes)	Primary care prescribing data	Prescribing rates/1000; Standardized Prescribing Ratio (SPR)
Fortinsky/2010 ⁵¹ ; US	2003 for CT and 2004–2005 for ME	All medications for dementia available at the time; Namenda (Maine but not CT); non-prescription therapies included as well such as ginkgo biloba and vitamin E	Adults (age unspecified) (Licensed PCPs in CT and ME)	Survey data	PCP self-reported care practices (prescription medication for patients with memory loss symptoms)
Arnlind et al. 2010 ⁵⁰ ; Sweden	2005 – 2008	Antiasthmatics medications (Respiratory system drugs, Adrenergics inhalants, Selective beta-2-adrenoreceptor agonists, Adrenergics and other drugs for obstructive airway diseases, combinations, Glucocorticoids, Long-acting beta-2-adrenoceptor agonist, Short-acting beta-2-agonists; inhaled corticosteroids; selective and non-selective beta blocking agents)	Adults (18 – 44) (no diagnoses data, but all Swedish citizens)	Swedish National Prescribed Drug register (no diagnoses data)	First time users (Incidence) of medication after a medication free run-in period; Proportion of population for whom medication dispensed during study period(number of users/ 1000 inhabitants); Adherence to quality prescribing g guidelines
Gao and Campbell/2008 ¹¹ ; US	1993	Drugs unspecified	Adults (age unspecified) Veterans	VA pharmaceutical benefits data and Cost Distribution Report (CDR) for total drug cost; National patient care database	logarithm of drug cost

Source and Country	Study Period	Rx Class/Class and Products	Study Sample	Data Source	Rx Measures
Naughton et al./2006 ⁴⁷ ; Ireland	2004	Combination drugs used for a surrogate for chronic diseases (Statins and antiplatelets; antiplatelet and coronary vasodilators; diabetic medications; long acting benzodiazepines; anticholinergic antidepressants)	Adults (70+) (with a specific chronic condition with the 12 month study period)	Irish HSE-Primary care reimbursement services (HSE-PCRS) pharmacy database	3 or more prescription medications associated with a specific chronic condition during the 12 month study period; Cardiovascular disease quality prescribing indicators; Standardized prescribing ratio
Hovstadius, et al./2010 ⁴⁹ ; Sweden	Jul 2006– Sep 2006	All out-patient dispensed prescription drugs	Adults and Children (age unspecified)	Swedish prescribed drug register	Proportion who had more than or equal to 1, 5 or 10 drugs dispensed respectively during a 3-month period.

Table 2
Geospatial Unit of Analysis, Analysis, Data Links; Inclusion of Map; Geographic Variation

Source	Geospatial Unit of Analysis	Analysis (Noting Geospatial)	GIS Data Links	Map
Cardiovascular				
O'Connor/1999	Regions (306 Hospital Referral Regions (HRR))	Mean rates of adherence to quality indicators for the US; 20th and 80th percentiles of age and sex-adjusted rates for each of the 306 HRRs; Correlation between quality indicators by HRR	No	Yes
Hogan et al./2003	Regions (Quebec, Ontario, British Columbia, Atlantic, Prairies)	Descriptive statistics, odds ratios, chi-square testing, and logistic regression analyses (region included); quotient	No	No
Budaj et al./2003	Countries and Continent (Australia, Argentina, Brazil, US, New Zealand, Canada, Europe)	Descriptive statistics; Multivariable stepwise logistic regression (region included)	No	No
Lopez et al./2004	Regions (21 Veteran integrated service network (VISN))	Treatment day equivalents; Quantity/DDD = Number of treatment days; Chi square test, Correlation Analysis	No	No
Pilote et al./2004	Provinces (Nova Scotia, Quebec, Ontario, British Columbia)	Descriptive statistics	No	No
Muller-Nordhorn et al./2005	Regions (East and West Germany)	Logistic regression analyses (region of residence included); t-test and chi-square	No	No
Laskey et al./2010	Regions (US Census Regions - NE, MW, S, W)	Descriptive statistics by region; Pearson tests; Chi square test; Interquartile range; Univariate and Multivariable regression (Association between region and performance measure)	No	No
Wettermark et al./2010	Counties (21 Swedish Counties)	Incidence and Prevalence by County; Chi square test; extremal quotient; coefficient of variation	No	No
Fang et al./2010	Regions (Driving Area for Clinical Care (DACC))	Multivariate linear regression; Instrumental Variables; Area Treatment Ratio; F statistic; Adjusted for patient demographics and clinical characteristics.	Yes	Yes
Cheng et al./2011	Townships	Coefficient of variation; Local indicators of spatial association (LISA)	Yes	Yes
Wetmore et al./2011	States	Descriptive statistics; Chi square test; T-test; Logistic Regression	Yes	Yes
Psychotropics				
Zito et al./1998	Counties (24 counties in Maryland consolidated into 8 regions - according to urban, suburban, or rural)	Logistic Regression (region included)	No	No
Brownell and Yogentran/2001	Regions (4 broad regions of residence (Winnipeg, Brandon, North, Other) (postal and municipal zip codes))	Stimulant rate by region; Logistic Region (region included)	Yes	No
Roberts and Norris/2001	Regions (16 New Zealand regional councils)	Means; weighted coefficient of variation, extremal quotient (no statistical testing)	Yes	No

Source	Geospatial Unit of Analysis	Analysis (Noting Geospatial)	GIS Data Links	Map
Reid et al./2002;	Postcodes (125 postcodes in the Adelaide metropolitan area)	Standardized medication ratio (observed/expected) by postcode	Yes	Yes
Cox et al./2003	States and Regions (50 States and DC; West, Northeast, Midwest and South; Rural/Urban)	Logistic Regression (region included), Prevalence rates per State.; System Component Variation, Interquartile range and Coefficient of Variation	Yes	Yes
Rawal et al./2004	States (Eastern, Large Midwest, Small Midwest and South West States)	Chi-square (to test regional variability); logistic regression; percentages	No	No
Prosser and Reid/2009	Postcodes	Standardized medication ratio by postcode; Chi-square test	Yes	No
Raghavan et al./2010	States – (CA, FL, IL, MI, NY, OH, PA, TX)	Logistic regression (State of residence included)	Yes	No
Ellis/2010	Regions (North Carolina Local Management Entities (LMEs))	Rates; Coefficient of variation; Extremal Quotient; Hierarchical linear model analysis Hierarchical linear model (HLM) analyses and controlled for clustering of observations within LMEs ; proportions; correlation	Yes	No
Leslie et al./2011	Regions (Catchment areas)	Logistic regression; Chi-square; Weighted percentages	Yes	No
Opioids				
Luo et al./2004	Regions (NE, MW, S, W)	Logistic regression (region included); % overall use by region	No	No
Curtis et al./2006	State and County	Regression Models, Weighted Coefficient of Variation., System Component Variation	Yes	Yes
Zerzan et al./2006	States (49 states and DC – No AZ and no TN before 1998)	CV, Mean DDD/1000/Day, Extremal quotient	Yes	Yes
Craig and Strassels/2010	Regions (MW, S, WVS, NE); Rural	2-density gamma mixture model; Frequency; Percentage Coefficients of coverage models	No	No
Brownstein et al./2010	3-digit Zip code	Spatial signal detection, risk mapping, and sensitivity analysis	Yes	Yes
Antibiotics				
Halasa et al./2002	Regions (NE, MW, S, W)	One way analysis of variance or t test; chi square test	No	No
Smith et al./2006	Countries and Regions Scotland, N. Ireland, Wales and 8 English regions comparison	Spread of rates; Spread of proportions	No	No
De With et al./2006	Regions (East, West and South)	Univariate and Multivariate analysis	No	No
Kern et al. 2006; Germany	Regions 23 areas in 16 States (aggregated)	Numbers and rates	Yes.	No
Shatland/2007	Countries (6 Countries (France, Germany, Spain, Italy, UK, USA))	Prescription items per person; Rates	Yes	No

Source	Geospatial Unit of Analysis	Analysis (Noting Geospatial)	GIS Data Links	Map
Others				
Dubois et al./2002	Regions (11 Regions (aggregated counties))	Coefficient of Variation; Extremal Quotient; Rates	Yes	No
Kozyskyj, A. L./2002	Regions (12 Regional Health Authorities in Manitoba, and 12 sub-regions of Winnipeg)	Rates of prescription use by income level, ranked by the premature mortality rate (PMR);	Yes	No
Bergman et al./1975	Countries (Intra- and Inter-) N. Ireland, Norway, Sweden; Within Each Country	Analysis of variance ; Means	Yes	Yes
Usher et al./2005	Regions (North Western, Midland, Southern, North Eastern Mid-Western, Eastern, South Eastern, Western)	Logistic regression (region included); Extremal Quotient ; Coefficient of Variation	No	Yes
Fortinsky/2010	States (Maine and Connecticut)	Pearson correlation coefficients; Regression analysis	No	No
Arnild et al./2010	Counties	Percentages; Rates; Regression analysis of variation (very limited statistics reported)	Yes	No
Gao and Campbell/2008	Regions (Veteran Integrated System Network - Medical center level)	Log linear regression model; hospital characteristics (rural, teaching and psychiatry); Pearson correlation coefficient	Yes	Yes
Naughton et al./2006	Regions (Eastern, Southern, South Eastern, Western, North Eastern, Midwestern, North Western)	Log linear regression model	Yes	No
Hovstadius et al./2010	Counties	Polypharmacy index/region; Weighted polypharmacy index; Binary correlation coefficients between regional prevalence of polypharmacy and regional socioeconomic variables	Yes	No