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Research Paper

Prescription opioids: Regional variation and socioeconomic status – evidence from primary care in England

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ABSTRACT

Background: This study aimed to quantify opioid prescriptions dispensed from primary care practices throughout England and investigate its association with socioeconomic status (SES).

Methods: This cross-sectional study used publicly available data in 2015, including practice-level dispensing data and characteristics of registrants from the United Kingdom (UK) National Health Service Digital, and Index of Multiple Deprivation (IMD) data from Department of Communities and Local Government. Practices in England which issued opioid prescriptions that could be assigned a defined daily dose (DDD) in the claim-based dispensing database were included. The total amount of opioid prescriptions dispensed (DDD/1000 registrants/day) was calculated for each practice. The association between dispensed opioid prescriptions and IMD was analyzed by multi-level regression and adjusted for registrants' characteristics and the clustered effect of Clinical Commissioning Groups. Subgroup analysis was conducted for practices in London, Birmingham, Manchester and Newcastle.

Results: Of the 7856 included practices in England, the median and interquartile range (IQR) of prescription opioids dispensed was 36.9 (IQR: 23.1, 52.5) DDD/1000 registrants/day. The median opioid utilization (DDD/1000 registrants/day) amongst practices varied between Manchester (53.1; IQR: 36.8, 71.4), Newcastle (48.9; IQR: 38.8, 60.1), Birmingham (35.3; IQR: 23.1, 49.4) and London (13.9; IQR: 8.1, 18.8). Lower SES, increased prevalence of patients aged more than 65 years, female gender, smoking, obesity and depression were significantly associated with increased opioid prescriptions. For every decrease in IMD decile (lower SES), there was a significant increase of opioid utilization by 1.0 (95% confidence interval: 0.89, 1.2, $P < 0.001$) DDD/1000 registrants/day.

Conclusion: There was substantial variation in opioid prescriptions among practices from Northern and Eastern England to Southern England. A significant association between increased opioid prescriptions and greater deprivation at a population level was observed. Further longitudinal studies using individual patient data are needed to validate this association and identify the potential mechanisms.

Introduction

Opioids have been considered the standard care for managing acute severe pain and chronic pain (Rosenblum, Marsch, Joseph, & Portenoy, 2008). In the past decade, there has been a marked increase in opioid-related deaths in several developed countries that coincided with an increasing opioid utilization (Centers for Disease Control & Prevention, 2011; Gladstone, Smolina, & Morgan, 2016; Jauncey, Taylor, & Degenhardt, 2005). At a regional level, drug utilization studies in North America and Australia have also suggested there may be a link between regional opioid utilization, opioid-related harms and socioeconomic status (Degenhardt et al., 2016; Fischer, Jones, & Rehm, 2013; Havens et al., 2007; McDonald, Carlson, & Izrael, 2012; Morden et al., 2014; Zerzan et al., 2006).

Geographical variation in opioid prescriptions and over-the-counter opioids have been found in the United States (US) (McDonald et al., 2012; Morden et al., 2014; Zerzan et al., 2006) and Australia (Degenhardt et al., 2016). In the US, there was a 7.3-times variation

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between states with the highest and lowest number of prescription opioids dispensed (McDonald et al., 2012). In Australia, according to sales data, major cities had lower opioid utilization than remote areas, and there was a 2.5-fold difference between areas with the highest and lowest opioid utilization in 2013 (Degenhardt et al., 2016). Furthermore, higher opioid-related morbidity and mortality have been observed in regions with higher opioid utilization in North America (Fischer et al., 2013; Havens et al., 2007).

A variety of factors may be attributed to the observed variation in opioid prescribing, such as population demographic characteristics (McDonald et al., 2012), prevalence of pain related co-morbidities (Painter, Crofford, & Talbert, 2013), healthcare provider clinical knowledge (Reames, Shubeck, & Birkmeyer, 2014), accessibility of appropriate services (McDonald et al., 2012), insurance coverage and benefit policy (Zerzan et al., 2006). Socioeconomic status (SES) has been identified as a major determinant in the variation of regional opioid utilization as it is associated with chronic pain conditions, persistent opioid utilization and aberrant medication-taking behaviors (Day, Conroy, Lowe, Page, & Dolan, 2006; Department of Health, 2012). Other factors are less important because opioids are classified as controlled substances which are restricted for use in pain management and strict regulations govern prescribing.

Previous studies using aggregate-level data of prescription opioids dispensed in the US (McDonald et al., 2012) and sales data of over-the-counter and prescription opioids in Australia (Degenhardt et al., 2016) found that lower SES was associated with higher opioid utilization. However, the generalizability of these results is limited due to the measure of SES used. Instead of using a validated composite tool to measure SES, published studies only applied selected dimensions, such as income and education to represent SES, and hence may lead to biased conclusions (Banta-Green, Merrill, Doyle, Boudreau, & Calsyn, 2009; Joynt et al., 2013; McDonald et al., 2012; Parsells Kelly et al., 2008; Stover et al., 2006; Svendsen, Fredheim, Romundstad, Borchgrevink, & Skurtveit, 2014; Toblin, Mack, Perveen, & Paulozzi, 2011).

In the United Kingdom (UK), regional variation in health care provision has been identified in several diseases and regarded as an important health equity issue (Lawlor, Bedford, Taylor, & Ebrahim, 2003; Shah et al., 2016; Williams & Drinkwater, 2009). However, research on the variation in opioid utilization and its association with SES remain lacking. Locally, a cross-sectional study conducted in 111 of the 192 practices (780,000 registrants) in Leeds and Bradford found that higher number of opioid prescribing was associated with lower SES (Foy et al., 2016), but this association has not been investigated at the national level. Therefore, this study aimed to examine the association between SES and the number of prescription opioids dispensed in England general practices using a validated composite indicator for SES.

Methods

Study design and data sources

This cross-sectional study used publicly available aggregate-level statistics and datasets from multiple UK government sources. The most up-to-date information on SES (in 2015) was linked with opioid utilization and other population characteristics data by the identifier at practice level (Table 1). Practices in England which had opioid prescriptions dispensed in 2015 with an identifiable number of registrants and Index of Multiple Deprivation (IMD) scores were included as the basic unit for exploring regional variation in this study.

In the UK, primary care practices are the gatekeepers for delivering healthcare in a locality with an average population size of 7139 people in 2015 (NHS Digital, 2016). Most people generally register with one general practice near their home (NHS Choices, 2016). Variation in registrants' characteristics or disease history at a practice-level have been published or are available from Public Health England (Lawlor

Table 1
Summary of aggregated-level statistics and datasets used in this study.

Data source	Dataset	Countries and time	Information retrieved from datasets	Outcome measure used in this study
NHS Digital (NHS Digital, 2015a)	Monthly practice-level dispensing data	England, January to December 2015	Monthly quantity of dispensed opioid preparations for each practice	DDD/1000 inhabitants/day at practice and CCG level
NHS Digital (NHS Digital, 2015b)	Numbers of patients registered at a GP practice	England, January to December 2015	For each practice: Number of registrants Number of females Number of patients aged more than 65 years	DDD/1000 inhabitants/day at practice level Proportion of female gender Proportion of registrants aged more than 65 years
NHS Digital (NHS Digital, 2015c)	Quality and Outcomes Framework - 2014-15	England, 2014	Proportion of registrants with particular characteristics in each practice	Proportion of registrants with particular characteristics
Department of Communities and Local Government (Department for Communities & Local Government, 2015)	All ranks, deciles and scores for the indices of deprivation, and population denominators	England, 2015	Score and decile of IMD and individual domains for each practice	Score and decile of IMD and individual domains
Office for National Statistics (Office for National Statistics, 2015b)	Mid-2014 population estimates for CCGs in England by single year of age and sex	England, 2014	Number of registrants in each CCG	DDD/1000 inhabitants/day at CCG level

(Note) NHS: National Health Service, DDD: Defined Daily Dose, IMD: Index of Multiple Deprivation, CCG: Clinical Commissioning Groups, GP: general practitioner.

et al., 2003; Public Health England, 2016a; Shah et al., 2016; Williams & Drinkwater, 2009).

Monthly practice-level dispensing data from January to December 2015 were used to calculate opioid utilization (NHS Digital, 2015a). In England, the quantity of prescription medicines dispensed is collected monthly by the UK National Health Service (NHS) Digital and stratified by practices (NHS Digital, 2015a). Dispensing data of opioid preparations prescribed for pain relief (excluding those for opioid substitution therapy), including morphine, fentanyl, oxycodone, buprenorphine, hydromorphone, pethidine, tapentadol, tramadol, codeine, dihydrocodeine, dextropropoxyphene and meptazinol, were extracted for analysis based on the British National Formulary classification.

IMD scores obtained from the Department of Communities and Local Government in 2015 (Department for Communities & Local Government, 2015) were used to represent the SES of each practice. Within each practice, the number of female registrants and the number of registrants over 65 years were retrieved from NHS Digital (NHS Digital, 2015b). Other characteristics of registrants were identified from the Quality of Outcomes Framework (QOF) indicators in 2015 (NHS Digital, 2015c). Those aggregate-level data are publicly available and use requires no ethical approval.

Prescription opioid utilization

'Opioid utilization' was measured using the total quantity of prescription opioids dispensed and expressed as the number of Defined Daily Doses (DDDs)/1000 registrants/day for each practice. All opioids dispensed between January and December 2015 that could be assigned a DDD, according to the definitions from World Health Organization (World Health Organization, 2016), were extracted from the NHS Digital monthly practice-level dispensing data. The total amount of each opioid dispensed was calculated by multiplying the strength and quantity retrieved from the database.

For each practice, the sum of the total quantity of each opioid in 2015 was divided by the DDD for each opioid. To derive the number of DDDs/1000 registrants/day of dispensed opioid, the number of DDDs for each opioid were summed, divided by the total number of registrants in the practice, multiplied by 1000, and divided by 365.

From 2012, practices in England were grouped into Clinical Commissioning Groups (CCGs) which are responsible for the planning and commissioning of healthcare services in a local area. In order to study geographical variation in opioid utilization across England, practices were grouped by CCG. The number of DDDs/1000 registrants/day of dispensed opioid for each CCG was derived by dividing the total number of DDDs for each opioid by the number of registrants in the CCGs (Office for National Statistics, 2015b), multiplied by 1000, and divided by 365.

Socioeconomic status

To define the SES of each practice, an IMD score was assigned to each practice through the linkage of practice postcode and Lower-Layer Super Output Areas (LSOA) code, which was retrieved from the UK Office for National Statistics (ONS) (Office for National Statistics, 2015a). LSOA is the unit designed to improve the reporting of small area statistics, such as SES in England and Wales. The mean population size across the 32844 LSOAs was approximately 1500 residents (Office for National Statistics, 2011).

The IMD is the official measure of SES in England. It is often used to quantify SES and to inform the implementation of health-related policy (Department for Communities & Local Government, 2015). IMD scores are calculated using seven individually weighted domains, including income, employment, education, health, crime, barriers to housing and services and living environment. The IMD score ranges from 0 to 100, and a LSOA with higher IMD score indicates a lower SES area. In addition, each LSOA was ranked from the greatest to lowest IMD score, and the IMD rank was categorized into deciles. Therefore, a LSOA with lower IMD decile indicates a lower SES area (Department for Communities & Local Government, 2015).

Characteristics of registrants

Based on published literature, specific characteristics of registrants within practices were retrieved and measured to adjust for potential determinants of opioid utilization (Bauer, Hitchner, Harrison, Gerstenberger, & Steiger, 2016; Foy et al., 2016; Fredheim et al., 2014; Halbert, Davis, & Wee, 2016; Sullivan, Edlund, Zhang, Unutzer, & Wells, 2006; Sullivan et al., 2008).

In this study, the proportion of current smokers, and registrants with obesity, and diagnoses of cancer, depression and mental illness (such as schizophrenia, bipolar affective disorder and other psychoses) were directly extracted from 2015 QOF indicators. QOF indicators are pay-for-performance indicators introduced in 2004 as part of the general practice contract for better management of chronic diseases and major public health concerns by remunerating general practices for achieving clinical targets (NHS Digital, 2015c), and hence the targets vary each year slightly.

The proportion of female registrants and registrants aged over 65 years were calculated by dividing the number of female registrants and registrants aged over 65 years by the total number of registrants within each practice (NHS Digital, 2015b).

Data analysis

Descriptive and regression analyses were applied to all practices in England to explore the association between SES and prescription opioid dispensed at the national level. In addition, subgroup analysis was conducted in practices from the top four primary urban areas, including London, Birmingham, Manchester and Newcastle to examine the consistency of the association at the regional level. The four urban areas were chosen to represent different regions within England that have diverse demographics, ethnicity, immigration, employment and welfare status (Centre for cities, 2011). According to the ONS 2011 census (Office for National Statistics, 2013), the estimated population size in the top four primary urban areas accounted for 30% of the total population in England, and the proportion of the population born outside the UK ranged from 7.3% to 34%.

Descriptive statistics were used to report median and interquartile range (IQR) of opioid utilization, IMD score and registrant characteristics across practices in England and the four urban areas. Each CCG was categorized into a quartile based on opioid utilization and presented graphically to illustration the geographical distribution of opioid utilization.

Simple linear regression was used to measure the correlation between decile in IMD domains, registrant characteristics, and opioid utilization for each practice. Characteristics of registrants included the proportion of females, registrants aged over 65 years, current smokers, obesity registrants and diagnosed for cancer, depression and mental illness.

As healthcare policies and commissioning differ between CCGs, the association between opioid utilization (the dependent variable) and the independent variables, i.e. IMD deciles and characteristics of registrants in each practice, was further analyzed by random-intercept multilevel mixed-effects linear regression with restricted maximum likelihood estimation (Snijders, 2011). The full model included all variables and the regression results were presented as a coefficient and 95% confidence interval (95% CI).

As the cluster effect of CCG was identified by the likelihood-ratio test for all practices in England and practices in London, the random-intercept multilevel mixed-effects linear regression was applied to estimate the association between opioid utilization, IMD deciles and characteristics of registrants. It considered random effects and allowed

Table 2
Opioid utilization and characteristics of registrants in practices in England and the four cities.

	All practices (n = 7,856)	Practices in London (n = 825)	Practices in Birmingham (n = 326)	Practices in Manchester (n = 204)	Practices in Newcastle (n = 175)
Number of registrants	6565 (3974, 9898)	6229 (3827, 9123)	5054 (3054, 8871)	5631 (3557, 8403)	6095 (4295, 9153)
Opioid utilization (DDD/1000 registrants/day)	36.9 (23.1, 52.5)	13.9 (8.1, 18.8)	35.3 (23.1, 49.4)	53.1 (36.8, 71.4)	48.9 (38.8, 60.1)
Socioeconomic status					
IMD score	22.4 (12.4, 37.0)	28.6 (18.7, 37.5)	38.5 (21.6, 52.6)	37.0 (24.8, 51.5)	25.9 (13.5, 45.2)
IMD decile	4 (2, 7)	3 (2, 5)	2 (1, 4)	2 (1, 4)	4 (1, 7)
Income decile	4 (2, 7)	3 (2, 5)	2 (1, 5)	2 (1, 4)	4 (1, 6)
Employment decile	4 (2, 7)	4 (3, 6)	2 (1, 5)	2 (1, 4)	3 (1, 6)
Education and skills decile	5 (3, 7)	7 (5, 9)	3 (1, 5)	3 (2, 6)	4 (2, 8)
Health and disability decile	4 (2, 7)	5 (3, 7)	3 (2, 5)	1 (1, 3)	2 (1, 4)
Crime decile	4 (2, 7)	2 (1, 4)	3 (2, 5)	3 (1, 5)	6 (4, 8)
Barriers to housing and services decile	7 (4, 9)	2 (1, 4)	3 (1, 6)	6 (4, 8.5)	7 (5, 9)
Living environment decile	4 (2, 7)	2 (1, 3)	3 (1, 4)	3 (2, 5)	8 (6, 9)
Proportion of registrant demographics and Quality of Outcomes Framework indicators					
Age over 65 years	17.1 (12.1, 21.2)	9.2 (6.8, 12.2)	14.4 (9.4, 18.4)	12.6 (9.1, 16.7)	18.9 (15.4, 21.7)
Female gender	50.3 (49.0, 51.2)	49.9 (47.9, 51.6)	49.8 (47.5, 50.8)	49.6 (47.6, 50.7)	50.6 (49.0, 51.3)
Current smokers	18.5 (14.6, 22.9)	19.7 (16.2, 22.5)	19.2 (15.4, 23.6)	22.7 (18.8, 28.5)	19.4 (14.5, 23.1)
Obesity	9.0 (6.8, 11.6)	6.9 (4.9, 9.6)	9.4 (7.3, 11.6)	9.3 (7.3, 11.9)	11.8 (9.1, 13.9)
Depression	6.9 (4.9, 9.1)	5.4 (3.7, 7.1)	6.4 (4.4, 9.1)	8.1 (5.4, 10.8)	7.4 (5.1, 9.7)
Mental health diseases	0.83 (0.64, 1.1)	1.2 (0.89, 1.5)	0.92 (0.70, 1.2)	1.0 (0.75, 1.3)	0.85 (0.69, 1.1)
Cancer	2.2 (1.6, 2.8)	1.4 (1.0, 1.8)	1.9 (1.1, 2.5)	1.8 (1.2, 2.3)	2.5 (2.1, 2.9)

(Note) IMD: Index of Multiple Deprivation, DDD: Defined Daily Dose; all statistics are presented in median and interquartile range.

different intercepts for practices within CCGs, and other variables to be included as fixed-effects. In contrast, as the likelihood-ratio test showed there was no cluster effect from CCGs for practices in Birmingham, Manchester and Newcastle, a multiple linear regression was applied. All analysis was performed using STATA 14 (Stata-Corp, Texas, USA, 2015).

Results

Analysis of practices at the national level

Opioid utilization and registrants' characteristics among practices

Of the 7856 practices included from England, the median number of registrants was 6565 (IQR: 3974, 9898), and median amount of prescription opioid dispensed was 36.9 (IQR: 23.1, 52.5) DDD/1000 registrants/day. The median IMD score across the 7856 practices in England was 22.4 (IQR: 12.4, 37.0) with a median decile of 4 (IQR: 2, 7) (Table 2).

Geographical distribution of opioid utilization among CCGs

The 7856 practices were grouped into 209 CCGs in England. The prescription opioids dispensed (DDD/1000 registrants/day) in each CCG ranged from 14.1 to 108.3, with the median of 42.7 (IQR: 32.9, 54.9). CCGs located in northern and eastern areas had higher opioid utilization and more likely to be ranked in the highest third and fourth quartiles of all CCGs. For the majority of CCGs located in London and surrounding areas, the number of prescription opioids dispensed was less than 30 DDD/1000 registrants/day, and they were mostly ranked in the lowest quartile (Fig. 1).

Factors associated with opioid utilization

The simple linear regression found that lower IMD decile (lower SES) were significantly associated with higher opioid utilization in practices across England. Similarly, for individual IMD domains including income, employment, education and skills, health and disability and crime, a significant negative association with opioid utilization was found. Barriers to housing and services and living environment were significantly positively associated with opioid utilization for practices in England. A significant positive association was found between opioid utilization and registrants' demographics and QOF indicators (Table 3).

Association between opioid utilization and socioeconomic status

For all practices in England, a significant cluster effect of CCGs was found (variance of the error: 94.2; 95%CI: 76.7, 115.8; $p < 0.0001$). For every decrease in IMD decile (lower SES), there was a significant increase in opioid utilization of 1.0 (95%CI: 0.89, 1.2, $P < 0.001$) DDD/1000 registrants/day after adjusting for registrants' characteristics. In addition, opioid utilization also significantly increased with a greater proportion of registrants aged over 65 years, female gender, current smokers, obesity and depression. However, the proportion of registrants with mental health diseases was negatively associated with opioid utilization (Table 4).

Subgroup analysis of practices from the top four primary urban areas

In the four primary urban areas, the median opioid utilization varied between 53.1 (IQR: 36.8, 71.4), 48.9 (IQR: 38.8, 60.1), 35.3 (IQR: 23.1, 49.4) and 13.9 (IQR: 8.1, 18.8) DDD/1000 registrants/day for practices in Manchester (n = 204), Newcastle (n = 175), Birmingham (n = 326) and London (n = 825), respectively. The lowest median IMD score was 25.9 (IOQ: 13.5, 45.2) in Newcastle followed by London (28.6, IQR: 18.7, 37.5), Manchester (37.0, IQR: 24.8, 51.5) and Birmingham (38.5, IQR: 21.6, 52.6) (Table 2).

For practices in Manchester, Birmingham and London, opioid utilization significantly increased by 2.7 (95%CI: 1.2, 4.1), 0.82 (95%CI: 0.08, 1.6) and 0.60 (95%CI: 0.31, 0.90) DDD/1000 registrants/day for each decrease in IMD decile. However, IMD decile was not significantly associated with opioid utilization in Newcastle. Although the proportion of registrants aged over 65 years and current smokers were significantly associated with opioid utilization in the four primary urban areas, an inconsistent association between opioid utilization, female gender and other QOF indicators was found between practices in the four cities (Table 4) (Appendix A).

Discussion

Main findings

This study found regional variation in opioid utilization and registrant characteristics among practices across England and within the four primary urban areas. The geographical distribution of opioid utilization also varied across CCGs in England. There was substantial

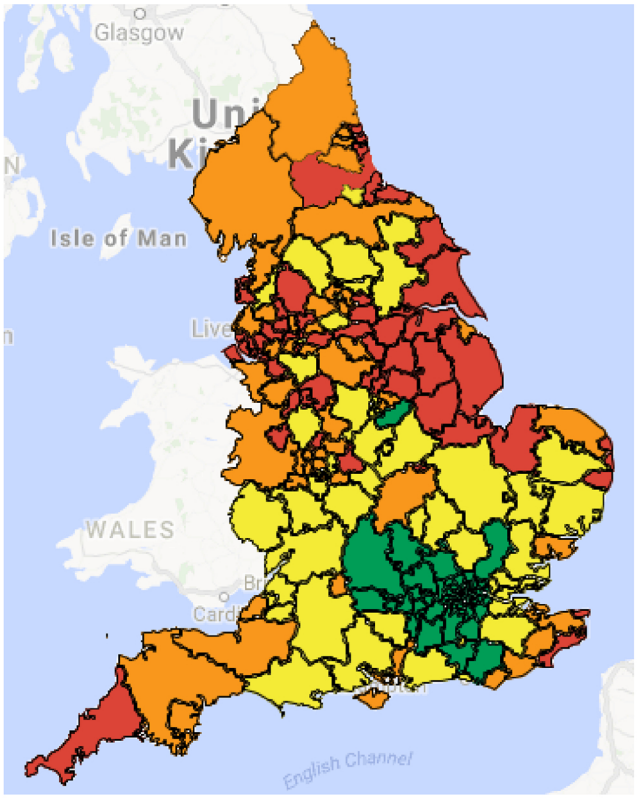

Fig. 1. Opioid utilization among Clinical Commissioning Groups in England.

variation in opioids dispensed among practices from Northern and Eastern England to Southern England which mirrors general geographical health inequalities between those from deprived and affluent areas. The highest opioid utilization was 108.3 DDD/1000 registrants/day, equating to approximately 10% of the registrants in the CCG using 1 DDD of prescription opioid on any given day.

Aggregate population data demonstrated that practices located in lower SES areas had higher opioid utilization. For every decrease in IMD decile, one more opioid DDD was prescribed and dispensed per 1000 registrants/day. In the subgroup analysis, which considered the variation in demographics, ethnicity and welfare across geographical areas in England, this association was also observed in the top four primary urban areas ranging from 0.6 to 2.7 DDD/1000 registrants/day. In addition to IMD, older age, female gender, current smoking, obesity and depression were associated with higher opioid utilization.

Consistent evidence of association between socioeconomic status and opioid utilization

The association between SES and regional variation of opioid utilization involves a complex interaction between social determinants, patients' medicine-taking behavior, pain conditions and physicians' prescribing behavior (Fig. 2). For example, greater physical labor and unemployment led to higher rates of opioid utilization in Australia (Degenhardt et al., 2016) and unemployment was associated with problematic opioid use and dependence (Campbell et al., 2015). In Norway, patients with higher education level were found to be less likely to become persistent opioid users (Svendsen et al., 2014) as they tended to accept a non-opioid analgesic as an effective medicine (Gebauer, Salas, & Scherrer, 2017).

This study used the IMD score to summarise SES and these results were consistent with published cross-sectional studies comparing opioid utilization between counties in the US (McDonald et al., 2012) and Statistical Local Areas in Australia (Degenhardt et al., 2016) which also found that higher opioid utilization was associated with lower SES which were measured by selected dimensions. Furthermore, this study identified a significant association between higher opioid utilization and registrants' characteristics, i.e. current smokers, obesity and depression that have not been found in published studies applied aggregate-level data (Degenhardt et al., 2016; McDonald et al., 2012).

Regarding the population demographics, this study found that female gender was associated with higher opioid utilization. This result is

Table 3
Association between registrant characteristics and opioid utilization in univariate analysis.

	Practices in England	Practices in London	Practices in Birmingham	Practices in Manchester	Practices in Newcastle
Socioeconomic status					
IMD decile	−2.2* (-2.4, -2.1)	−0.87* (-1.1, -0.61)	0.05 (-0.76, 0.53)	−3.0* (-4.6, -1.4)	−2.3* (-3.1, -1.5)
Income decile	−2.3* (-2.5, -2.1)	−0.91* (-1.1, -0.68)	−0.13 (-0.94, 0.69)	−3.7* (-5.2, -2.3)	−2.6* (-3.4, -1.8)
Employment decile	−3.1* (-3.3, -2.9)	−0.77* (-0.99, -0.55)	−0.18 (-0.98, 0.63)	−4.9* (-6.3, -3.4)	−2.8* (-3.6,-2.1)
Education and skills decile	−3.2* (-3.4, -3.0)	−0.84* (-1.1, -0.59)	−0.50 (-1.2, 0.22)	−4.0* (-5.3, -2.7)	−2.2* (-3.0, -1.5)
Health and disability decile	−3.4* (-3.6, -3.3)	−0.96* (-1.2, -0.73)	−0.40 (-1.3, 0.51)	−4.0* (-6.5, -1.5)	−3.1* (-4.1, -2.0)
Crime decile	−0.47*(-0.65, -0.30)	−0.69* (-1.0, -0.36)	−0.41 (-1.4, 0.59)	−0.26 (-1.8, 1.3)	−1.8* (-2.8, -0.86)
Barriers to housing and services decile	2.5* (2.3, 2.6)	−0.44* (-0.73, -0.15)	1.5* (0.78, 2.2)	1.5* (0.17, 2.8)	−0.08 (-1.1, 0.95)
Living environment decile	0.62* (0.44, 0.81)	0.77* (0.33, 1.2)	1.3* (0.43, 2.2)	2.8* (0.89, 4.7)	0.70 (-0.36, 1.75)
Proportion of registrants' demographics					
Age over 65 years	1.1* (1.0, 1.1)	0.28* (0.19, 0.37)	1.3* (1.0, 1.6)	2.3* (1.6, 2.9)	0.36 (-0.11, 0.82)
Female	0.66* (0.49, 0.84)	−0.05 (-0.18, 0.08)	2.1* (1.6, 2.7)	2.2* (0.84, 3.5)	0.37 (-0.83, 1.57)
Proportion of Quality of Outcomes Framework indicators					
Current smokers	1.3* (1.2, 1.4)	0.49* (0.38, 0.59)	1.6* (1.3, 1.8)	2.1* (1.7, 2.6)	1.6* (1.3, 1.4)
Obesity	2.6* (2.5, 2.7)	0.69* (0.53, 0.86)	1.3* (0.72, 1.9)	2.1* (1.2, 3.1)	2.3* (1.6, 3.0)
Depression	2.2* (2.0, 2.3)	0.61* (0.39, 0.83)	2.3* (1.8, 2.8)	2.2* (1.4, 3.0)	1.4* (0.69, 2.1)
Mental health diseases	1.7* (0.88, 2.6)	2.1* (1.5, 2.7)	−0.19 (-4.9, 4.6)	5.9 (-2.4, 14.2)	16.6* (8.4, 24.7)
Cancer	7.1* (6.5, 7.6)	2.5* (1.8, 3.3)	8.6* (6.5, 10.7)	13.3* (8.8, 17.8)	1.8 (-1.9, 5.6)

(Note) * $p < 0.05$, IMD: Index of Multiple Deprivation, all statistics are presented in coefficient and 95% confidence interval.

Table 4
Association between socioeconomic status, registrant characteristics and opioid utilization in the multi-level regression analysis.

	Practices in England	Practices in London	Practices in Birmingham	Practices in Manchester	Practices in Newcastle
Socioeconomic status					
IMD decile	−1.0* (-1.2, -0.89)	−0.60* (-0.90, -0.31)	−0.82* (-1.6, -0.08)	−2.7* (-4.1, -1.2)	−0.16 (-0.98, 0.65)
Proportion of registrant demographics					
Age over 65 years	1.2* (1.1, 1.3)	0.69* (0.50, 0.87)	1.8* (1.3, 2.3)	2.6* (1.7, 3.4)	1.2* (0.53, 1.9)
Female	0.84* (0.71, 0.96)	0.39* (0.24, 0.54)	1.7* (1.1, 2.3)	0.76 (-0.27, 1.8)	1.9* (0.88, 2.8)
Proportion of Quality of Outcomes Framework indicators					
Current smokers	1.3* (1.2, 1.4)	0.49* (0.35, 0.63)	1.4* (1.1, 1.7)	1.9* (1.4, 2.4)	2.3* (1.7, 2.8)
Obesity	0.36* (0.27, 0.46)	0.04 (-0.14, 0.21)	0.38 (-0.03, 0.79)	−0.26 (-1.0, 0.50)	0.23 (-0.43, 0.89)
Depression	0.43* (0.33, 0.53)	0.21 (-0.01, 0.42)	0.69* (0.23, 1.1)	0.64 (-0.03, 1.3)	0.35 (-0.23, 0.92)
Mental health diseases	−2.7* (-3.4, -2.1)	0.71 (-0.06, 1.5)	−1.6 (-5.1, 1.9)	−6.4 (-12.9, 0.13)	−5.3 (-12.9, 2.3)
Cancer	−0.006 (−0.67, 0.66)	0.07 (-1.2, 1.4)	−3.9* (−7.5, −0.39)	0.34 (−5.5, 6.1)	−0.48 (−5.6, 4.6)
Random effects at the CCG level					
The variance of the error[+]	94.2* (76.7, 115.8)	8.5* (4.2, 17.1)	NA	NA	NA

(Note) * p < 0.05, IMD: Index of Multiple Deprivation, CCG: Clinical Commissioning Groups, NA: not applicable, all statistics are presented in coefficient and 95% confidence interval, + presented in variance and 95% confidence interval.

similar to a study exploring variation in opioid prescribing and its associated factors among patients with fibromyalgia (Painter et al., 2013). However, this is in contrast to the study conducted by Degenhardt et al. (2016) in Australia which showed that male gender was related to higher opioid utilization (Degenhardt et al., 2016). The reasons for this discrepancy may be due to the inclusion of methadone in the opioid utilization calculation; it has been reported that more than 65% of patients receiving methadone therapy in Australia between 2007–2016 were male (Australian Institute of Health & Welfare, 2017).

Need for evidence-based guidance on opioid prescribing

In the UK, the use of prescription opioids is required to comply with the strict controlled drug regulations. Therefore, the total amount of opioids dispensed in each region or CCG can also be regarded as an indicator for pain management needs in primary care. The 2011 Health Survey for England suggested that the lower household income is related to higher prevalence of chronic pain conditions (Department of Health, 2012). This finding was consistent with studies conducted in Germany whereby lower neighborhood SES was related to inferior physical health (Voigtlander, Berger, & Razum, 2010), and a US study which indicated an association between neighborhood SES and receipt of opioid among patients with back pain (Gebauer et al., 2017).

Long-term opioid use for chronic non-cancer pain (CNCP) is not supported by current clinical guidance (Hauser et al., 2014; Manchikanti et al., 2012; Public Health England, 2016b), and there is no consensus on duration or dose recommendation for chronic opioid use. In addition, the availability and accessibility of opioids may be influenced by prescribers' clinical training (Linge-Dahl et al., 2015) and health care practitioners' clinical knowledge, and opioid prescribing guidance have been suggested to be associated with regional variation in opioid utilization (Reames et al., 2014). In this study, the significant CCG-related cluster effect implies that the local opioid prescribing policy among CCGs could also contribute to the variation in opioid prescriptions.

To reduce variations in population health outcomes, studies about regional variation in health care delivery in the UK identified areas which may require further policy investigations (Hollingworth et al., 2015). To fully understand the influence of chronic opioid utilization for CNCP on regional variation in opioid utilization and to inform future policy intervention, national studies exploring opioid utilization in patients with CNCP across geographical regions are needed. Moreover, to clarify the relationship between SES and opioid utilization, further longitudinal studies using individual-patient data from practices in England are needed.

Strengths and limitations

This nationwide study showed regional variation in opioid utilization among practices and an association between opioid utilization and SES using aggregated level population data from UK government sources which included all practices and had better generalizability. An

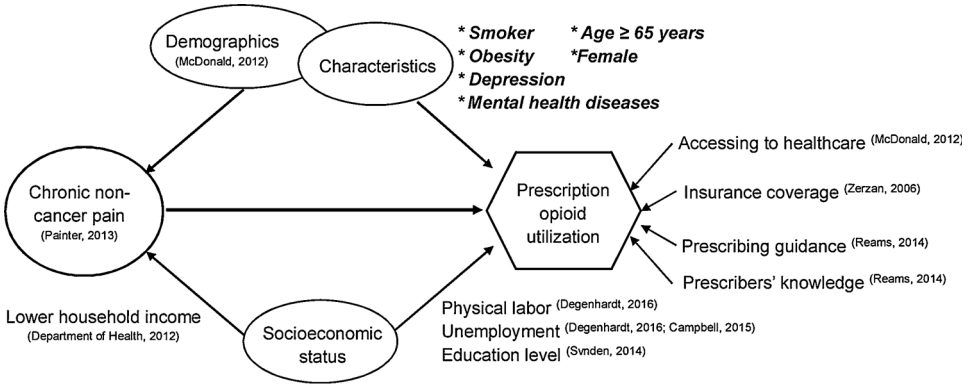

Fig. 2. Factors related to the regional variation of prescription opioids utilization.
(Note) IMD: Index of Multiple Deprivation, *: Significant factors identified in this study.

official and standardized deprivation score was applied to summarise SES, and hence the association was not biased by particular dimensions in SES, a limitation which has affected prior studies.

For unmeasured similarity among practices within CCGs, the cluster effects of CCGs were also considered in the analysis. Furthermore, comparing to previous nationwide studies conducted in other countries (Degenhardt et al., 2016; McDonald et al., 2012), this study used QOF indicator data which is a reliable source for identifying and adjusting for specific patient characteristics and registrant comorbidities as it was introduced in primary cares to remunerate general practices for achieving clinical targets.

The following limitations of this study should be acknowledged. As this study used statistics and datasets collected at an aggregate-level rather than individual level, the variation in demographic characteristics and comorbidities among registrants within practices cannot be measured. It is possible that the estimated opioid utilization was consumed by only a few users who were prescribed large quantities of opioid. . Furthermore, as the dataset only included opioid prescriptions dispensed at an aggregate-level, the use of illicit opioids, such as heroin at an individual patient level was not included in the scope of this study. Moreover, due to data restriction and the creation of CCGs in 2012, this study used only the most up-to-date information from one calendar year (2015). Ideally, further studies should acquire information from multiple years, including the upcoming calendar years, to validate the consistency of the association between SES and prescription opioids dispensed at the population level.

In addition, it is possible that the interaction between SES and the prevalence of chronic pain conditions may have influenced the observed regional variation of prescription opioids dispensed. However, the common CNCP pain conditions, such as low back pain and arthritis, were not targeted as part of the 2015 QOF indicators (NHS Digital, 2015c), hence were not included in the regression analysis. These unmeasured CNCP pain conditions might explain the non-significant association between SES and opioid utilization in Newcastle.

In conclusion, there was marked variation in opioid utilization and characteristics of registrants among practices in England. Higher opioid utilization was associated with lower SES when adjusted demographic characteristics. Individual-level longitudinal studies are needed to explore the association between SES, CNCP and opioid utilization between geographical regions in the UK.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugpo.2018.10.013.

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