Manuscript Number: DRUGPO-D-17-264R2

Title: Prescription opioids: regional variation and socioeconomic status
- evidence from primary care in England

Article Type: Research Paper

Keywords: Socioeconomic status; dispensed opioid prescriptions; regional
variation; spatial analysis; general practice; England

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Abstract: Background

This study aimed to quantify dispensed opioid prescriptions among 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 had opioid
prescriptions that could be assigned a defined daily dose (DDD) in the
claim-based dispensing database were included. The total amount of
dispensed opioid prescriptions (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
dispensed 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 a variation in prescription opioids dispensed 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.

DRUGPO-D-17-264

Authors' response to the Editors and/or Reviewers

ASSOCIATE EDITOR COMMENTS:

The authors have prepared a revised manuscript that addresses many of the methodologic limitations identified in the original submission. Although this analysis could make a contribution to the scientific literature on socioeconomic marginalization, the manuscript is still marred by many grammatical and spelling mistakes. Further revision is required to remove these errors and, more importantly, ensure the findings are accurately and succinctly expressed. To that end, I would re-emphasize the need for thorough copyediting. Particular attention should be paid to the Introduction and Discussion.

[Reply] Revised as recommended.

We have taken the reviewer and editor's advice to revise sentences in the Introduction section and re-organize the structure of Discussion section. The revised manuscript has been scrutinized for any grammatical and spelling mistakes and proof-read by a senior researcher in the field who are native English speaker. The results of subgroup analyses were summarized, and detail information was moved to the supplementary material to make sure the main findings are succinctly presented.

The authors should strongly consider reporting the subgroup analyses (e.g., lines 239 to 285) in supplementary material to better focus the article.

[Reply] Revised as recommended.

We have taken the advice from the reviewer and editor to shorten the description of the subgroup analysis, and detail information, such as the association between the number of prescription opioids dispensed and registrants' characteristics among the four primary urban areas has been moved to the supplementary material as the Appendix 1.

Further, the authors should pay close attention to comments of the first reviewer about the Discussion, and the need to revise the writing to improve its readability. Currently, the Discussion is poorly structured with new paragraphs appearing haphazardly. I would suggest that the Discussion would improve substantially if shortened to adhere to a standard structure, e.g., a summary of the findings; followed by placing the findings in the context of previously-published literature; followed by implications for policy or practice; study limitations; and conclusion.

[Reply] Revised as recommended.

We have revised the Discussion section to improve the readability of the revised manuscript. The Discussion has been re-organized and structured into four sections with subheadings that signpost readers to the main findings, implications of scientific knowledge and clinical practice, and strengths and limitations.

REVIEWER COMMENTS:

Reviewer #1

General comments:

This is an improved manuscript. The authors have certainly made efforts to improve the methodology of their paper and it does provide granular data for an entire country, which is unique. Below are some general comments and minor comments. I have placed an asterisk next to the comments that I consider major.

Introduction

1. *The readability of the manuscript remains low. Many of the sentences, particularly in the introduction (which should capture the reader's attention), are poorly constructed. For

example, line 29 "Although studies have found that higher deprivation (i.e. lower SES) was associated with higher opioid utilization according to the 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), the generalizability of those finding to different counties is limited due to differing data sources and including different medicines." There are examples of this throughout the text. The messaging is lost. For this manuscript to make it to publication, there needs to be substantial copyediting.

[Reply] Revised as recommended.

We have rewritten some sentences and re-organized the Introduction section to summarize the published literature in order to highlight the knowledge gap. In addition, the revised manuscript has been scrutinized for any typographical and grammar mistakes. It has been proof-read by a pharmacoepidemiology researcher who is also a native English speaker. The revised sentences in the Introduction section are summarized as follows.

[Page 6, line 7]

"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."

[Page 7, line 29]

"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."

[Page 7, line 33]

"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."

[Page 7, line 37]

"Previous studies using aggregate-level data of prescription opioids dispensed in the US and sales data of over-the-counter and prescription opioids in Australia 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."

[Page 8, line 49]

"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."

[Page 8, line 54]

"...in Leeds and Bradford found that higher number of opioid prescribing was associated with lower SES ..."

2. Page 6, line 12: "States" should be changed to "states"

[Reply] Revised as recommended.

[Page 6, line 16] *"...between states with the ..."*

3. P8, line 49: The authors use the terms deprivation and SES interchangeably. Would use reference, as you have, that they are equivalent and then use only one term - probably SES.

[Reply] Revised as recommended.

We have changed the term 'deprived' to 'low SES', and those revised sentences are listed as follows.

[Page 8, line 55] "...was associated with lower SES."

[Page 12, line 131] "It is often used to quantify SES and to inform the implementation ..."

[Page 12, line 136] "...with higher IMD score indicates a lower SES area."

[Page 13, line 138] "...indicates a lower SES area."

[Page 18, line 226] "...found that lower IMD decile (lower SES)"

[Page 18, line 240] "...decile (lower SES), there was..."

[Page 21, line 278] "...located in lower SES areas..."

[Page 23, line 305] "...associated with lower SES which were ..."

[Page 24, line 329] "...lower neighborhood SES was related..."

[Page 27, line 394] "...associated with lower SES when ..."

Methods

1. The authors decided to analyze 1 year of data, likely because of data restrictions, time, etc. However, it may be difficult to draw definitive conclusions about opioid prescribing and SES from one year composite data. Ideally, the authors could look over multiple years to make their conclusions more generalizable. Was 2015 a representative year? Was there higher opioid prescribing among higher SES in previous years?

[Reply] We applied the 2015 data because the UK SES data was only available in 2011 and 2015. Moreover, the primary care practices in England were grouped into Clinical Commissioning Groups in 2012 for the commissioning of healthcare services in a local area (page 9, line 64-66). To inform the relevant issues related to current opioid prescribing, we decided that the most updated information (2015) should be used to identify the association between SES and prescription opioids dispensed. To clarify this reason, we add a sentence in the method section. Moreover, we also acknowledge the limitation due to data restriction and recommend that further studies with more data points are needed to validate the consistency of the association between SES and opioid prescribing.

[Page 9, line 64]

"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."

[Page 26, line 377 to 382]

"Moreover, due to data restriction and the implementation 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. "

2. Please include somewhere in the methods section the scale of IMD score (0 to XX) and whether a lower score represents lower SES or vice versa. In isolation, a median IMD score of 22.4 is meaningless. This is not mentioned until line 216 though I might have missed it elsewhere.

[Reply] The explanation of the IMD score was included in the original manuscript (page 12, line 126). To enhance this information, we revise the description as follows.

[Page 12, line 135]

"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."

3. Pg 10, line 83: "The number of female and registrants over 65 years in each practice were retrieved from NHS Digital"...unclear if this sentence is constructed properly "female and registrants". Please clarify.

[Reply] Revised as recommended.

[Page 10, line 91]

"Within each practice, the number of female registrants and the number of registrants over 65 years were retrieved from NHS Digital."

[Page 14, line 156]

"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."

Results

1. *Subgroup analysis of the 4 primary urban areas. I certainly understand the authors' need to demonstrate consistency, however, I will stress that the extensive discussion in the results detracts from the overall message of the paper. If the author's wish to demonstrate consistency, then I would summarize the findings of this section and put the remainder in the supplemental appendix. For example, "We performed a subgroup sensitivity analysis on 4 primary urban areas to demonstrate consistency of consistency of the association between SES and prescription opioids dispensed. The median opioid utilization varied XXX, XXX, XXX, XXX in Manchester, Newcastle, Birmingham, and London, respectively. In linear regression, we found a negative associated between IMD decile and opioid utilization in all four cities. There were inconsistent associations in these cities in other measures (Supplemental Appendix)." This way the main message of the paper is not lost, you ensure due diligence that you did additional analyses, and those persons from Newcastle can go to the appendix if they so choose to learn more about their city.

[Reply] Revised as recommended.

The results of subgroup analysis have been shortened, and the detail information regarding the inconsistent associations between opioids prescribing and registrants' characteristics among the four primary urban areas have been moved to the supplementary material as Appendix 1.

[Page 19, line 249 to 265]

"In the four primary urban areas, the median opioid utilization varied..... was found between practices in the four cities (Table4) (Appendix 1)."

Discussion

1. Discussion. The discussion section needs further revision since the message is lost on the reader. The main finding of this paper is that there is an association between opioid use and SES. There are factors that certainly influence that (i.e., chronic pain is more common among those with lower SES), however, the message of the paper is diluted by the discussion. The author's should postulate why they think their findings are unique (no one has done this before, there were A LOT of opioid prescriptions, aggregated population data means better generalizability) and robust (validated composite tool to

measure SES, models that were used are appropriate, etc), then discuss some implications to their findings and possible explanations of their findings (lack of training of healthcare providers, chronic pain, etc), then add a limitations section.

[Reply] Revised as recommended

We took the advice recommended by the editor and reviewer to restructure the Discussion into four sections with additional subheadings. We highlight the key message of each section as follows.

[Page 21, line 267 to 285] This section highlights the main finding of this study.

[Page 22, line 287 to 320] This section describes the implication of this study regarding how the study results contributing to the current scientific evidence. We found a consistent result in the association between SES and opioid prescribing when comparing with previous publications.

[Page 24, line 322 to 352] This section indicates the implication of this study for clinical practices. We found there is a need for evidence-based guidance on opioid prescribing.

[Page 25, line 354 to 368] This section outlines the strengths of this study. We emphasized the better generalizability related to the national data sources and the validity due to the official and standardized tool and analytical model.

[Page 26, line 370 to 390] This section discusses the limitations of this study. The natural limitations of using aggregate level dispensing data have been mentioned. The influence of unmeasured characteristics on the association between SES and opioid prescribing was also explained.

[Page 27, line 392 to 396] Conclusion – a summary of key messages.

2. Page 25 line 351: "In this study, the amount of prescription opioids dispend", change word.

[Reply] Revised as recommended

[Page 24, line 324]

"Therefore, the total amount of opioids dispensed in each region ..."

Manuscript submitting to International Journal of Drug Policy

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

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Number of tables and figures: 4 tables and 2 figures and Figure 1 that color should be used in print

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

Keywords: Socioeconomic status; dispensed opioid prescriptions; regional variation; spatial analysis; general practice; England

Abstract

Background

This study aimed to quantify dispensed opioid prescriptions among 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 had opioid prescriptions that could be assigned a defined daily dose (DDD) in the claim-based dispensing database were included. The total amount of dispensed opioid prescriptions (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 dispensed 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 a variation in prescription opioids dispensed 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.

1 **Introduction**

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

12

13 Geographical variation in dispensed opioid prescriptions and over-the-counter opioids
14 have been found in the United States (US) (McDonald et al., 2012; Morden et al.,
15 2014; Zerzan et al., 2006) and Australia (Degenhardt et al., 2016). In the US, there
16 was a 7.3-times variation between states with the highest and lowest number of
17 prescription opioids dispensed (McDonald et al., 2012). In Australia, according to
18 sales data, major cities had lower levels of opioid utilization than remote areas, and
19 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, Jones, & Rehm, 2013b; 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 et al., 2003; Public Health England, 2016a; Shah et al., 2016; Williams &

77 Drinkwater, 2009).

78

79 Monthly practice-level dispensing data from January to December 2015 were used to

80 calculate opioid utilization (NHS Digital, 2015a). In England, the quantity of

81 prescription medicines dispensed is collected monthly by the UK National Health

82 Service (NHS) Digital and stratified by practices (NHS Digital, 2015a). Dispensing

83 data of opioid preparations prescribed for pain relief (excluding those for opioid

84 substitution therapy), including morphine, fentanyl, oxycodone, buprenorphine,

85 hydromorphone, pethidine, tapentadol, tramadol, codeine, dihydrocodeine,

86 dextropropoxyphene and meptazinol, were extracted for analysis based on the British

87 National Formulary classification.

88

89 IMD scores obtained from the Department of Communities and Local Government in

90 2015 (Department for Communities and Local Government, 2015) were used to

91 represent the SES of each practice. Within each practice, the number of female

92 registrants and the number of registrants over 65 years were retrieved from NHS

93 Digital (NHS Digital, 2015b). Other characteristics of registrants were identified from

94 the Quality of Outcomes Framework (QOF) indicators in 2015 (NHS Digital, 2015c).

95 Those aggregate-level data are publicly available and requires no ethical approval.

96

97 <Insert Table 1>

98

99 **Prescription opioid utilization**

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

108

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

113

114 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 and 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 and 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 et al., 2008; Sullivan, Edlund, Zhang, Unutzer, & Wells, 2006).

In this study, the proportion of current smokers, obesity registrants and diagnosed for cancer, depression and mental illness (such as schizophrenia, bipolar affective disorder and other psychoses) was 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

153 health concerns by remunerating general practices for achieving clinical targets (NHS
154 Digital, 2015c), and hence the targets vary each year slightly.

155

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

159

160 **Data analysis**

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

172

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

178

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

184

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

191 interval (95% CI).

192

193 As the cluster effect of CCG was identified by the likelihood-ratio test for all practices
194 in England and practices in London, the random-intercept multilevel mixed-effects
195 linear regression was applied to estimate the association between opioid utilization,
196 IMD deciles and characteristics of registrants. It considered random effects and
197 allowed different intercepts for practices within CCGs, and other variables to be
198 included as fixed-effects. In contrast, as the likelihood-ratio test showed there was no
199 cluster effect from CCGs for practices in Birmingham, Manchester and Newcastle, a
200 multiple linear regression was applied. All analysis was performed using STATA 14
201 (Stata-Corp, Texas, USA, 2015).

202 **Results**

203 **Analysis of practices at the national level**

204 ***Opioid utilization and registrants' characteristics among practices***

205 Of the 7856 practices included from England, the median number of registrants was
206 6565 (IQR: 3974, 9898), and median amount of dispensed opioid prescriptions was
207 36.9 (IQR: 23.1, 52.5) DDD/1000 registrants/day. The median IMD score across the
208 7856 practices in England was 22.4 (IQR: 12.4, 37.0) with a median decile of 4 (IQR:
209 2, 7) (Table 2).

210

211 <Insert Table 2>

212

213 ***Geographical distribution of opioid utilization among CCGs***

214 The 7856 practices were grouped into 209 CCGs in England. The prescription opioids
215 dispensed (DDD/1000 registrants/day) in each CCG ranged from 14.1 to 108.3, with
216 the median of 42.7 (IQR: 32.9, 54.9). CCGs located in northern and eastern areas
217 had higher opioid utilization and more likely to be ranked in the highest third and
218 fourth quartiles of all CCGs. For the majority of CCGs located in London and
219 surrounding areas, the number of prescription opioids dispensed was less than 30
220 DDD/1000 registrants/day, and they were mostly ranked in the lowest quartile (Figure
221 1).

222

223 <Insert Figure 1>

224

225 ***Factors associated with opioid utilization***

226 The simple linear regression found that lower IMD decile (lower SES) were
227 significantly associated with higher opioid utilization in practices across England.

228 Similarly, for individual IMD domains including income, employment, education and
229 skills, health and disability and crime, a significant negative association with opioid
230 utilization was found. Barriers to housing and services and living environment were
231 significantly positively associated with opioid utilization for practices in England. A
232 significant positive association was found between opioid utilization and registrants'
233 demographics and QOF indicators (Table 3).

234

235 <Insert Table 3>

236

237 ***Association between opioid utilization and socioeconomic status***

238 For all practices in England, a significant cluster effect of CCGs was found (variance
239 of the error: 94.2; 95%CI: 76.7, 115.8; $p < 0.0001$). To every decrease in IMD decile
240 (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 the increase in the 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).

<Insert 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 (IQR: 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,

260 0.90) DDD/1000 registrants/day for each decrease in IMD decile. However, IMD
261 decile was not significantly associated with opioid utilization in Newcastle. Although
262 the proportion of registrants aged over 65 years and current smokers were
263 significantly associated with opioid utilization in the four primary urban areas, an
264 inconsistent association between opioid utilization, female gender and other QOF
265 indicators was found between practices in the four cities (Table 4) (Appendix 1).

266 **Discussion**

267 **Main findings**

268 This study found regional variation in opioid utilization and registrant characteristics
269 among practices across England and within the four primary urban areas. The
270 geographical distribution of opioid utilization also varied across CCGs in England.
271 There was a substantial variation in prescription opioids dispensed among practices
272 from Northern and Eastern England to Southern England which mirrors general
273 geographical health inequalities between those from deprived and affluent areas. The
274 highest opioid utilization was 108.3 DDD/1000 registrants/day, equating to
275 approximately 10% of the registrants in the CCGs using 1 DDD of prescription opioid
276 on any given day.

277

278 Aggregate population data demonstrated that practices located in lower SES areas
279 had higher opioid utilization. For every decrease in IMD decile, one more opioid DDD
280 was prescribed and dispensed per 1000 registrants/day. In the subgroup analysis,
281 which considered the variation in demographics, ethnicity and welfare across
282 geographical areas in England, this association was also observed in the top four
283 primary urban areas ranging from 0.6 to 2.7 DDD/1000 registrants/day. In addition to
284 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 (Figure 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 medication (Gebauer, Salas, & Scherrer, 2017).

<Insert Figure 2>

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 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 contract 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 to 2016 were male (Australian Institute of Health and 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 regional 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 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 data 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 and dispensed large quantities of the drug. Furthermore, as the dataset only included dispensing opioid prescriptions at an aggregate-level, the use of illicit opioids, such as heroin use, at an individual patient level was not included in the scope of this study. Moreover, due to data restriction and the implementation of CCGs in 2012, this study used only the most

379 up-to-date information from one calendar year (2015). Ideally, further studies should
380 acquire information from multiple years, including the upcoming calendar years, to
381 validate the consistency of the association between SES and prescription opioids
382 dispensed at the population level.

383

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

391

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

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Figure

Green	First (Lowest): 14.1- 32.9 (DDD/1000 registrants/day)
Yellow	Second: 32.9 – 42.7 (DDD/1000 registrants/day)
Orange	Third: 42.7 – 54.9 (DDD/1000 registrants/day)
Red	Fourth (Upper): 54.9-108.3 (DDD/1000 registrants/day)

Note: DDD: Defined Daily Dose

Figure 1. Opioid utilization among Clinical Commissioning Groups in England

(Note) IMD: Index of Multiple Deprivation, *: Significant factors identified in this study.

Figure 2. Factors related to the regional variation of prescription opioids utilization

Tables

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 and 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

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

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					

Supplementary material

Appendix 1. Association between opioid utilization, socioeconomic status and characteristics of registrants in the four primary urban areas

The median opioid utilization for practices in Manchester, Newcastle, Birmingham and London were 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, and the lowest median IMD score was found in Newcastle (25.9 IOQ: 13.5, 45.2) 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).

In the simple liner regression, a negative association between IMD decile and opioid utilization was found in London, Manchester and Newcastle but not in Birmingham. A significant negative association between individual IMD domains, such as income, employment, education and skills and health and disability and opioid utilization was found in London, Manchester and Newcastle but not in Birmingham. In addition, a significant negative association was found between crime and opioid utilization for practices across London and Newcastle but not in Birmingham or Manchester.

Barriers to housing and services and living environment were significantly positively

associated with opioid utilization in practices in Manchester and Birmingham. However, lower barriers to housing and services decile and higher living environment decile were significantly associated with higher opioid utilization for practices in London. Regarding registrants' demographics and QOF indicators, only current smokers, obesity and depression were consistently associated with opioid utilization in the practices in the four major cities.

After adjusting for registrants' characteristics, SES was significantly associated with opioid utilization in Manchester, Birmingham and London. However, IMD decile was not significantly associated with opioid utilization in Newcastle despite a significant association found in univariate analysis.

In addition, across the cities, opioid utilization significantly increased as the proportion of females increased, except in Manchester. A positive association between opioid utilization and proportion of depression registrants was only found in practices in Birmingham. Furthermore, a negative association between cancer and opioid utilization was only found for practices in Birmingham.

Acknowledgements

The lead author (Teng-Chou Chen) was funded by the Vice-Chancellor's Scholarships for Research Excellence for a PhD studentship at University of Nottingham from 2014 to 2017. Dr Li-Chia Chen was granted the Data Driven Discovery Summer Placement Internship from the University of Nottingham in 2016 that supported the undergraduate student (Miriam Kerry) to work on this project. The funding bodies had no role in the design, collection, analysis, and interpretation of data; in writing the manuscript and in the decision to submit the manuscript for publication.

Figure1
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Figure 2

(Note) IMD: Index of Multiple Deprivation, *: Significant factors identified in this study.

Figure 2. Factors related to the regional variation of prescription opioids utilization

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