Drugs (2018) 78:111–121
https://doi.org/10.1007/s40265-017-0846-6

CrossMark

ORIGINAL RESEARCH ARTICLE

Correlation of Opioid Mortality with Prescriptions and Social Determinants: A Cross-sectional Study of Medicare Enrollees

Christos A. Grigoras[1,3] · Styliani Karanika[1,2] · Elpida Velmahos[1] · Michail Alevizakos[1] · Myrto-Eleni Flokas[1] · Christos Kaspiris-Rousellis[3] · Ioannis-Nektarios Evaggelidis[3] · Panagiotis Artelaris[4] · Constantinos I. Siettos[3] · Eleftherios Mylonakis[1]

Published online: 20 November 2017

Abstract
Background The opioid epidemic is an escalating health crisis. We evaluated the impact of opioid prescription rates and socioeconomic determinants on opioid mortality rates, and identified potential differences in prescription patterns by categories of practitioners.
Methods We combined the 2013 and 2014 Medicare Part D data and quantified the opioid prescription rate in a county level cross-sectional study with data from 2710 counties, 468,614 unique prescribers and 46,665,037 beneficiaries. We used the CDC WONDER database to obtain opioid-related mortality data. Socioeconomic characteristics for each county were acquired from the US Census Bureau.
Results The average national opioid prescription rate was 3.86 claims per beneficiary that received a prescription for opioids (95% CI 3.86–3.86). At a county level, overall opioid prescription rates ($p < 0.001$, Coeff $= 0.27$) and especially those provided by emergency medicine ($p < 0.001$, Coeff $= 0.21$), family medicine physicians ($p = 0.11$, Coeff $= 0.008$), internal medicine ($p = 0.018$, Coeff $= 0.1$) and physician assistants ($p = 0.021$, Coeff $= 0.08$) were associated with opioid-related mortality. Demographic factors, such as proportion of white ($p_{\text{white}} < 0.001$, Coeff $= 0.22$), black ($p_{\text{black}} < 0.001$, Coeff $= -0.19$) and male population ($p_{\text{male}} < 0.001$, Coeff $= 0.13$) were associated with opioid prescription rates, while poverty ($p < 0.001$, Coeff $= 0.41$) and proportion of white population ($p_{\text{white}} < 0.001$, Coeff $= 0.27$) were risk factors for opioid-related mortality ($p_{\text{model}} < 0.001$, $R^2 = 0.35$). Notably, the impact of prescribers in the upper quartile was associated with opioid mortality ($p < 0.001$, Coeff $= 0.14$) and was twice that of the remaining 75% of prescribers together ($p < 0.001$, Coeff $= 0.07$) ($p_{\text{model}} = 0.03$, $R^2 = 0.03$).
Conclusions The prescription opioid rate, and especially that by certain categories of prescribers, correlated with opioid-related mortality. Interventions should prioritize providers that have a disproportionate impact and those that care for populations with socioeconomic factors that place them at higher risk.

Christos A. Grigoras and Styliani Karanika contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40265-017-0846-6) contains supplementary material, which is available to authorized users.

✉ Eleftherios Mylonakis
emylonakis@lifespan.org

1 Medical Science, Program on Outcomes Research, Infectious Diseases Division, Rhode Island Hospital, Warren Alpert Medical School of Brown University, 593 Eddy Street, POB, 3rd Floor, Suite 328/330, Providence, Rhode Island 02903, USA

2 General Internal Medicine Section, Boston Medical Center, Boston University School of Medicine, Boston, Massachussets, USA

3 School of Applied Mathematics and Physical Sciences, National Technical University of Athens, Athens, Greece

4 Department of Geography, Harokopio University, Athens, Greece

Key points for Decision Makers

Primary care providers prescribe most opioids. Opioid prescription rate is associated with opioid-related deaths (in total, as well as for each category of opioids and heroin)

Particular specialties' prescription rate is correlated with the opioid-related deaths and practitioners that prescribe more (super-prescribers) are associated disproportionally with opioid-related deaths

Poverty level in the county strengthened the correlation between opioid prescriptions and opioid-related deaths

1 Introduction

More than 650,000 opioid prescriptions are dispensed daily in the USA [1] and 78 people die daily from an opioid-related overdose [2]. The mortality associated with the most commonly prescribed opioids (natural/semisynthetic opioids) represents more than one-third of total overdose deaths [3, 4]. Over the last 15 years, opioid prescriptions and deaths have been moving in parallel, and the experience from the USA and other countries indicates that restrictions in the use of opioids can decrease mortality [5, 6]. However, previous studies reported conflicting data [7, 8] and the size and the fragmented nature of healthcare in the USA create the need to develop local strategies and to prioritize potential interventions to assure significant impact in decrease of mortality.

The association between the opioid prescription rate by different specialties and the opioid-related mortality has not been reported and the impact of different socioeconomic factors has not been documented. The aim of our study was to co-analyze nationwide opioid prescription Medicare part D data (down to individual practitioner) with socioeconomic factors and opioid-related mortality, to evaluate potential connections at a county level.

2 Methods

2.1 Opioid Prescription Data

To estimate the opioid prescription rate, we extracted information on the number of claims, generic drug name, number of Medicare beneficiaries to whom these claims were prescribed, category and specialty of practitioner and ZIP code of each healthcare provider, as reported in the 2013 and 2014 Medicare Part D Opioid Prescriber Summary Files [9]. This database contains annual information for over 30 million patients (that is approximately 60% of the beneficiaries enrolled in the Medicare program) [10]. The search results were classified based on drug class. The first category contained all the claims containing the search term "methadone", while the second included results containing the search term "fentanyl OR meperidin". The final prescription category contained any claim containing the following search terms: "levorph OR morphone OR opium OR oxycodo OR hydromorpho OR butorpha OR oxymorphone OR codein OR morphine OR buprenorphine OR nalbuphine OR tramadol OR tapentadol OR codone OR pentazocine OR alfentanil OR remifentanil OR sufentanil". Both chronic and acute care conditions, as well as long- and short-acting formulations of opioid prescriptions were included in our analysis. Physicians with less than 11 opioid claims per class of drugs (667,294 physicians) were excluded from our study.

We employed the 2010 ZIP Code Tabulation Area (ZCTA) to County Relationship File [11] to assign the opioid claims to the county enclosing each census tract. In case a census tract was contained in more than one county, we assigned the claims to the county that contained the largest proportion of the census tract. Physicians with a unique National Provider Identifier (NPI) were included in the study. The opioid prescription rate was calculated as the total number of opioid claims prescribed per the number of beneficiaries that were prescribed these medications and 95% Poisson confidence intervals (CIs) were estimated. Of note is that nurse practitioners and physician assistants are considered independent prescribers in Medicare, with their own NPI. The District of Columbia was considered as a separate state in all analyses and only data from practitioners with data available from both years were included (113,233 physicians excluded).

Furthermore, we grouped physicians based on the differences both in the mean and variance of prescription rates across prescribers. In order to include the highest number of prescribers, we utilized the most current Medicare Part D dataset of 2014 that includes prescribers who were excluded from our previous analysis due to lack of reporting data for 2013. To examine the potential impact of "super-prescribers", we identified the physicians in the fourth quartile of the opioid prescription rate of each medical specialty. We then separately calculated the prescription rate of all the super-prescribers and all the remaining physicians in a county level and fitted a multivariable linear regression on the total opioid mortality with the prescription rates of the two groups as independent variables. This procedure was repeated for several values of the threshold of the classification as super-prescribers, namely (80, 90, 95, 99%) and the results of the sensitivity analysis were reported in the Supplementary Material.

2.2 Mortality Data

The opioid-related mortality data for each county and state were extracted from the Multiple Cause of Death 1999–2014 dataset published by the Centers for Disease Control and Prevention (CDC) WONDER Online Database [2]. In the ICD-10 coding system, T40.1 encodes heroin-related data, T40.2 natural (morphine, codeine, thebaine) and semi-synthetic (oxycodone, hydrocodone, oxymorphone, hydromorphone, buprenorphine) opioid analgesic-related data (except heroin), T40.3 encodes methadone-related mortality data, and T40.4 synthetic (fentanyl, meperidine) opioid analgesics, except methadone.

We also calculated the total opioid mortality rate as the total opioid-related deaths, summing up all four mortality ICD-10 codes, occurring during 2010–2014, divided by the size of population residing in a county or state. We selected to use aggregate mortality data per county over a 5-year period in order to maximize the number of counties with reported mortality rates. Counties with suppressed mortality data were excluded from our analysis. Similarly, the mortality rate per each opioid class was calculated as the total deaths attributed to each opioid class occurring in the 2010–2014 time-period, divided by the size of population residing in a county or state.

2.3 Socioeconomic Data

We obtained socioeconomic characteristics for each county from the 2010–2014 American Community Survey (ACS) 5-year estimates dataset provided by the US Census Bureau [12]. This dataset is considered to be the most current and most reliable dataset containing information for all counties within the USA [13]. The following explanatory variables were included in our analysis: (1) percentage of people living under the poverty line, (2) percentage of Black, Hispanic or White population, (3) percentage of males, (4) percentage of population aged $\geq$ 65 years, (5) population density, and (6) number of medicare-enrolled opioid prescribing physicians per county population.

2.4 Statistical Analysis

Multivariable linear regression was implemented to predict county opioid-related mortality based on the aggregate opioid prescription rate per county, percentage of people living under poverty line, gender and race distribution in each county. Output of the regression analysis included the *p* value of the model or variable, value of the coefficient of a variable (Coeff) and the coefficient of determination (R^2), which indicates the proportion of variance in the dependent variable that is predictable from the independent variable. To allow comparisons between the effects of each variable, each dependent and independent variable was rescaled to have a mean of zero and standard deviation (SD) of 1. We employed Belsley's test to examine collinearity between independent variables [13, 14]. We performed spatial regression analyses to identify and control for any spatial autocorrelation effect between our variables. Data processing and statistical analyses were performed using MATLAB 2016a (The MathWorks Inc., Natick, MA) and GeoDa (version 1.10). Mortality and prescription rate mappings were created using the Quantum Geographic Information System (QGIS) [15].

3 Results

We analyzed 180,285,363 opioid prescriptions, provided by practitioners with reported data in both 2013 and 2014 Medicare Part D datasets that were prescribed to 46,665,037 beneficiaries. The overall average annual opioid prescription rate was 3.86 claims per beneficiary who received a prescription for opioids (CI 3.86–3.86). Vermont [6.62 opioid claims per beneficiary (CI 6.6–6.65)], Montana [5.18 opioid claims per beneficiary (CI 5.17–5.20)] and Wyoming [5.14 opioid claims per beneficiary (CI 5.11–5.16)] were the states with the highest total opioid prescription rate, while the lowest total opioid prescription rate was noted in New York [3.45 opioid claims per beneficiary (CI 3.44–3.45)], Texas [3.42 opioid claims per beneficiary (CI 3.42–3.42)] and Florida [3.37 opioid claims per beneficiary (CI 3.36–3.37)] (Fig. 1, Table 1 and eTable 1).

At a county level, 14% of the variance of the total opioid-related prescription rate was associated with race (% of white/black population) and gender ($p_{\text{model}} < 0.001$, $R^2 = 0.14$) and an increase of 1 SD in % of white, black or male population resulted in a change of 0.22 SD ($p < 0.001$), -0.19 SD ($p < 0.001$) and 0.13 SD ($p < 0.001$), respectively, in the total opioid prescription rate. Notably, while poverty was discarded from the stepwise selection algorithm multivariable model, a single linear regression yielded that an increase of 1 SD in poverty resulted in a decrease of -0.19 SD ($p < 0.001$) in the opioid prescription rate ($p_{\text{model}} < 0.001$, $R^2 = 0.04$).

The CDC WONDER multiple cause of death database provided the information that in 2010–2014, opioids were associated with 9.72 deaths per 100,000 individuals (CI 9.53–9.83). Methadone was associated with 1.50 deaths/100,000 people (CI 1.29–1.68), natural and semi-synthetic opioid analogues 4.55 deaths/100,000 people (CI

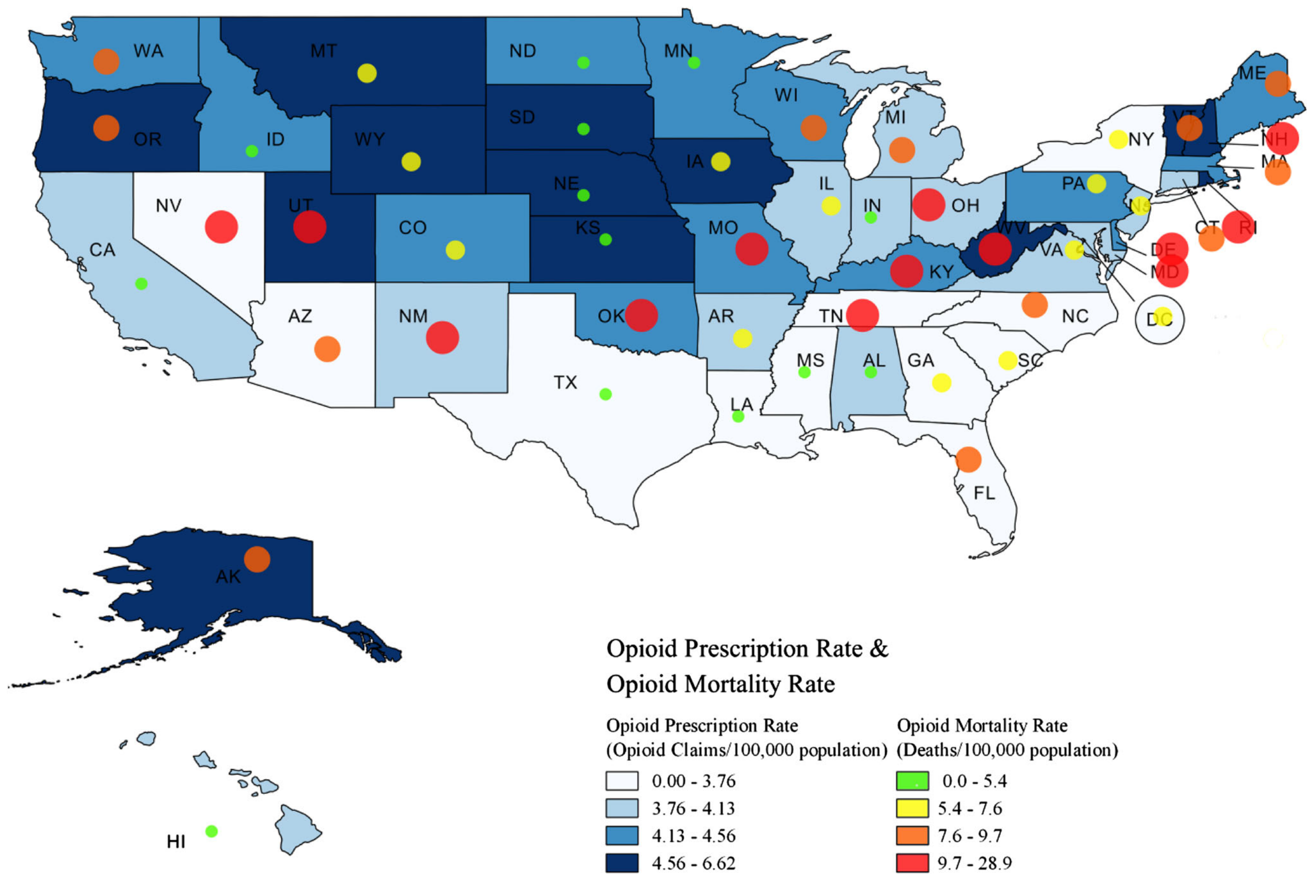

Fig. 1 Opioid prescription and mortality rates. Choropleth map presenting opioid prescription rates per state (2013 and 2014) in blue color progression. Concentric circles represent opioid-related mortality rates per state (2010–2014)

Table 1 Opioid prescription rate in US states

State	Opioid claims per beneficiary	95% confidence interval	Physicians	Beneficiaries	Opioid claims
Top 5 opioid prescription states					
Vermont	6.62	[6.60, 6.65]	463	41,742	276,439
Montana	5.18	[5.17, 5.20]	1062	114,390	593,024
Wyoming	5.14	[5.11, 5.16]	414	37,577	192,967
Alaska	4.89	[4.86, 4.92]	317	25,788	126,121
West Virginia	4.83	[4.83, 4.84]	1945	413,132	1,997,122
Bottom 5 opioid prescription states					
Arizona	3.46	[3.46, 3.47]	5693	987,806	3,421,638
District of Columbia	3.45	[3.43, 3.48]	321	29,810	102,991
New York	3.45	[3.44, 3.45]	12,070	1,464,417	5,045,533
Texas	3.42	[3.42, 3.42]	18,861	3,766,162	12,889,203
Florida	3.37	[3.36, 3.37]	16,549	3,696,917	12,444,407

4.22–4.90), synthetic opioids (except methadone) 1.41 deaths/100,000 people (CI 1.21–1.60) and heroin 2.26 deaths/100,000 people (CI 1.8–2.40). In order to evaluate for a potential association between opioid-related mortality and opioid prescription rate, we used multivariable regression models and took into consideration the effect of the socioeconomic parameters noted above. At a county level, mortality rate attributed to each class of opioids was

Table 2 Multivariable regression models[a]

	Coeff	*p* value	SE	*t* statistic	#	R^2	*p* value (model)
A. Association of total opioid prescription rate with race, gender, physicians/population, age and spatial autocorrelation					2710	0.30	< 0.001
White	0.11	< 0.001	0.02	4.83			
Black	− 0.11	< 0.001	0.02	− 4.79			
Male	0.05	0.003	0.02	2.92			
Physicians	− 0.18	< 0.001	0.02	− 11.52			
Aged > 65 years	0.17	< 0.001	0.02	9.48			
Spatial lag	0.38	< 0.001	0.02	15.94			
B. Association of total opioid mortality rate with opioid prescription rate, poverty, physicians/population, spatial autocorrelation and race					832	0.62	< 0.001
Poverty	0.28	< 0.001	0.03	9.10			
Prescription rate	0.28	< 0.001	0.05	5.06			
White	0.16	< 0.001	0.04	4.23			
Physicians	− 0.07	0.01	0.03	− 2.49			
Spatial lag	0.57	< 0.001	0.03	21.75			
C. Association of mortality related to synthetic opioids with total opioid prescription rate, poverty, physicians/population, spatial autocorrelation and race					181	0.81	< 0.001
Poverty	0.53	< 0.001	0.07	7.86			
White	0.41	< 0.001	0.07	6.12			
Prescription rate	0.32	0.02	0.14	2.37			
Physicians	− 0.32	< 0.001	0.06	− 4.91			
Spatial lag	0.57	< 0.001	0.04	14.69			
D. Association of mortality related to natural and semi-synthetic opioids with total opioid prescription rate, poverty, physicians/population, spatial autocorrelation and race					179	0.8	< 0.001
Poverty	0.37	< 0.001	0.06	5.88			
Prescription rate	0.26	0.05	0.13	1.95			
White	0.21	0.001	0.07	3.21			
Physicians	− 0.22	< 0.001	0.06	− 3.46			
Spatial lag	0.63	< 0.001	0.04	16.6			
E. Association of mortality related to heroin with total opioid prescription rate, poverty, spatial autocorrelation, and race					151	0.49	< 0.001
Poverty	0.42	< 0.001	0.12	8.17			
White	0.37	< 0.001	0.11	3.32			
Prescription rate	0.49	0.03	0.23	2.14			
Spatial lag	0.48	< 0.001	0.06	8.17			
F. Association of mortality related to methadone with total opioid prescription rate, poverty, spatial autocorrelation, and race					124	0.35	< 0.001
Poverty	0.33	< 0.001	0.1	3.3			
White	0.26	0.007	0.1	2.7			
Prescription rate	0.44	0.05	0.22	1.96			
Spatial error	0.42	< 0.001	0.08	5.55			
G. Association of mortality related to opioids with total opioid prescription rate per specialty					794	0.1	< 0.001
Emergency medicine	0.21	< 0.001	0.03	6.13			
Family medicine	0.11	0.008	0.04	2.67			
Internal medicine	0.1	0.018	0.04	2.37			
Physician assistant	0.08	0.021	0.03	2.31			

Table 2 continued

	Coeff	p value	SE	t statistic	#	R^2	p value (model)
H. Association of mortality related to opioids with total opioid prescription rate of prescribers in the 4th quartile (super-prescribers) vs the remaining prescribers					919	0.03	<0.001
Super-prescribers	0.14	<0.001	0.03	4.3			
Remaining	0.07	<0.001	0.03	2.16			

SE standard error, *Coeff* coefficient, # number of counties

[a]The complete regression analyses are presented in Supplementary File 1. The increase in the dependent variable in standard deviations (SD) due to an increase of 1 SD in the respective independent variable

linearly associated with the total opioid prescription rate and 35% of the variance of total opioid-related mortality was correlated with opioid prescription rate ($p_{\text{model}}<0.001$, $R^2 = 0.35$) (Table 2B). This correlation between opioid prescription rate, poverty, % of white population and opioid mortality was consistent with each opioid mortality category [natural/semi-synthetic opioids ($p_{\text{model}}<0.001$, $R^2 = 0.45$) (Table 2D), synthetic opioids ($p_{\text{model}}<0.001$, $R^2 = 0.52$) (Table 2C), heroin ($p_{\text{model}}<0.001$, $R^2 = 0.18$) (Table 2E) and methadone ($p_{\text{model}}<0.001$, $R^2 = 0.35$)] (Table 2F).

The correlation with poverty is particularly interesting, especially since poverty was negatively correlated with the opioid prescription rate. To further examine this correlation, we compared the fitted single linear regression lines of the total opioid mortality to the prescription rate in counties above and below the median poverty level and found that the impact of prescription rate in opioid mortality in counties with high poverty ($p<0.001$, Coeff = 0.51) was higher than in counties with lower poverty ($p<0.001$, Coeff = 0.35). This finding indicates that, even though poverty is negatively correlated with the opioid prescription rate in areas with high poverty, high prescription rate is closely correlated with high opioid-related mortality.

Then, we analyzed data on the prescription patterns among 93 categories of prescribers and found that 10 categories accounted for 90.22% of all opioid claims. Breaking down the opioid prescription per category, family medicine practitioners ranked first, accounting for 31.15% of all opioid claims reported, prescribing 5.32 opioid claims per beneficiary who received an opioid prescription. Internal medicine physicians prescribed 29.04% of all opioid claims reported, with 5.11 opioid claims per beneficiary, while nurse practitioners and physician assistants were accountable for 6.64% of all opioid claims, prescribing 3.81 and 2.74 opioid claims per beneficiary who received an opioid prescription, respectively (Table 3A, eFig. 1, and eTable 2). Because the top 10 medical categories accounted for 9 out of 10 of all opioid claims, we fitted a multivariable linear regression model to examine the impact of the opioid prescription rate of these categories in opioid-related mortality at a county level and we found that overall opioid prescription rates provided by emergency medicine, family medicine physicians, internal medicine and physician assistants were positively associated with opioid-related mortality (Table 2A).

We included the top 25 opioid-prescribing medical specialties accounting for more than 98% of all opioid prescriptions and estimated the mean and the variance of the prescription rate of physicians for each medical specialty and displayed them graphically (Fig. 2). Based on the distribution of the prescription rates, we identified five groups of medical specialties with similar combinations of mean prescription rates and variances, providing potential groups of practitioners who, on average, have similar opioid prescription patterns. The first category consisted mostly of surgical specialties and emergency-medicine physicians, while the second included advanced practice providers (nurse practitioners and physician assistants). The third group included mostly internal and family-medicine practitioners and oncologists. Interestingly, in the last two groups, that were considerably smaller with respect to the number of specialties, we observed both higher variance and mean prescription rates. More specifically, the fourth group consisted of neurologists and infectious diseases practitioners. This difference from the previous groups could be attributed to the variability of clinical practice among the specialists in the same field which reflects the patients' characteristics. Even higher variability was detected in the fifth category, which included the psychiatrists. These findings indicate that regarding opioid policies, educational tools and metrics, one size does not "fit all" and, while some prescribers could be grouped, others should be highly differentiated based on practice characteristics.

Interestingly, we found that a minority of prescribers contributed most prescriptions, and that was particularly characteristic of specific categories of practitioners. For example, the top 25% of physician assistants prescribed more than 55% of the opioids prescribed in this category, while in other categories that are more closely associated with the use of opioid agents (such as hematologists/oncologists) the contribution of these prescribers was more proportionate (Table 3B).The impact of prescribers in the upper quartile on the opioid mortality was associated with opioid-related mortality ($p<0.001$, Coeff = 0.14) and was

Table 3 Opioid prescription rate per medical specialty

A.

Specialty	# of counties	Opioid beneficiaries	Opioid claims	Claims per beneficiary	Proportion of total opioid claims (%)
Family practice	2826	10,549,952	56,158,035	5.32	31.15
Internal medicine	2238	10,237,738	52,354,379	5.11	29.04
Nurse practitioner	2418	3,146,818	11,976,790	3.81	6.64
Physician assistant	1954	3,333,374	9,136,242	2.74	5.07
Orthopedic surgery	1423	3,951,371	9,023,800	2.28	5.01
Interventional pain management	474	1,234,933	5,747,668	4.65	3.19
Anesthesiology	582	1,215,039	5,730,458	4.72	3.18
Emergency medicine	1814	3,847,040	5,132,330	1.33	2.85
Rheumatology	626	785,773	3,957,165	5.04	2.19
Pain management	399	723,269	3,435,111	4.75	1.91
General surgery	1659	1,333,230	2,052,799	1.54	1.14
Neurology	632	345,828	2,034,899	5.88	1.13
Dentist	2011	1,264,041	1,668,344	1.32	0.93
Hematology/oncology	708	286,779	1,436,653	5.01	0.8
Geriatric medicine	309	239,845	1,310,961	5.47	0.73
Urology	979	653,803	960,123	1.47	0.53
Neurosurgery	490	366,319	956,279	2.61	0.53
Oral surgery (dentists only)	754	676,883	814,350	1.2	0.45
Cardiology	448	160,787	622,956	3.87	0.35
Podiatry	934	276,597	605,814	2.19	0.34

B.

Specialty	Proportion of total prescriptions due to physicians in the upper quartile (%)	Proportion of total prescriptions due to physicians in the lower quartile (%)	Mean of prescription rate (claims/beneficiary)	Standard deviation of prescription rate
Physician assistant	55.58	8.03	1.67	0.85
Cardiology	50.00	6.49	2.77	1.42
Nurse practitioner	48.03	5.31	2.79	1.50
Emergency medicine	42.27	8.53	0.99	0.01
Internal medicine	40.23	5.26	3.61	1.53
Family practice	38.56	7.71	3.88	1.47
Anesthesiology	38.52	10.03	3.73	1.34
Geriatric medicine	37.28	12.07	3.80	1.12
Pain management	35.76	13.59	3.88	1.22
Podiatry	35.19	12.69	1.68	0.45

The list contains the top 20 prescribing medical specialties, accountable for 97.16% of all opioid prescriptions. Combined data from Medicare Part D datasets for 2013 and 2014

twice that of the remaining 75% of practitioners ($p < 0.001$, Coeff = 0.07) ($p_{\text{model}} = 0.03$, $R^2 = 0.03$) (Table 3B).

4 Discussion

The USA faces an opioid overdose epidemic [16, 17]. Using the Medicare Part D nationwide database, we found that opioid prescription rates varied widely, and at a county level, the opioid prescription rate was associated with opioid-related mortality (in total, as well as for each category of opioids and heroin). Most opioid prescriptions were provided in the primary/general-care setting and were related to the percent of white and male population in the county. Moreover, opioid-related deaths were correlated with the opioid prescription rate of specific categories of practitioners and they were disproportionally associated with prescribers who belonged to the upper quartile of

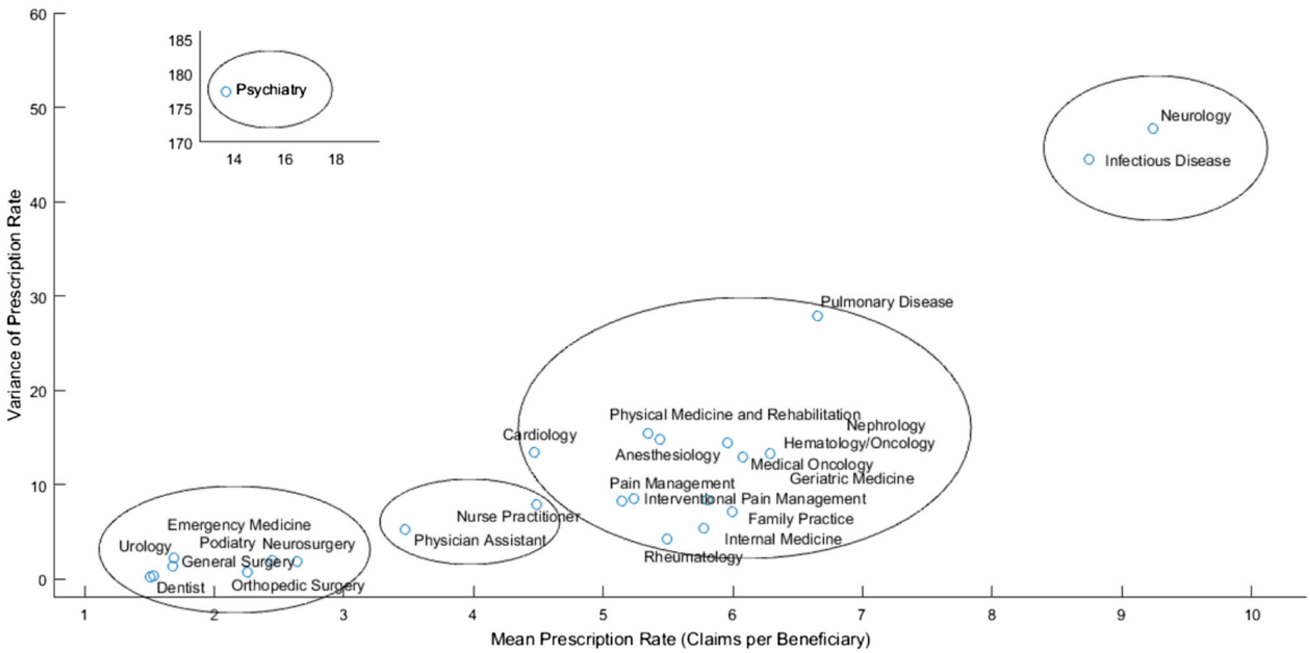

Fig. 2 Mean and variance of opioid prescriptions per specialty. Scatterplot of mean and variance of opioid prescriptions rates of physicians across medical specialties. Data reporting opioid claims per beneficiaries were aggregated for physicians included in the 2014 Medicare Part D dataset

prescribers in their category. Interestingly, most categories of practitioners could be assigned in one of three groups based on similar prescription profiles, while the poverty level in the county was negatively associated with opioid prescriptions, but opioid-related deaths were positively associated with poverty.

In our analysis, most opioid prescriptions were provided by general and primary-care prescribers (family medicine, internal medicine, nurse practitioners and physician assistants). Pain constitutes one of the most prevalent complaints in primary- and emergency-care settings [7] and in a study involving physicians who faced criminal prosecution or charges by medical boards for inappropriate opioid prescribing practices between 1998 and 2006, they found that 39% were either general practitioners or family physicians [18]. Interestingly, prescription behavior has an effect at a county level, as, increased prescription rates by these prescribers was associated with increased opioid-related mortality. The suggested mechanism seems to be multi-factorial. Our working hypothesis is that when providers prescribe more opioids, they become a significant source of diverted opioids [19]. The availability of prescribed opioids inevitably increases not only among direct beneficiaries but also their social environment (diversion) leading to misuse, abuse, overdose and accidental deaths. Of note, 37% of the 44,000 drug-overdose deaths in 2013 was attributable to pharmaceutical opioids, while heroin accounted for an additional 19%, implying that widespread “legal” availability can drive the mortality [20].

Furthermore, we demonstrated patterns in the variability of prescription rates across different medical specialties which could be attributed to the variability of clinical practice. The CDC recently published guidelines on opioid prescribing for primary care providers [19, 20]. Given the direct association between opioid prescription rates by general practitioners and opioid mortality, these guidelines should be expanded and implemented among practitioners (such as internists and rheumatologists) that have similar opioid prescription patterns. However, guidelines, metrics and educational tools for the selection of appropriate treatment should be adjusted for other groups of practitioners that have different prescription patterns, while for some categories of prescribers (such as infectious diseases specialists, neurologists and psychiatrists), there is such variability that the focus should be on sub-groups and should be adjusted based on the clinical practice setting.

Importantly, opioid deaths were associated with physicians at the upper quartile of the opioid prescription rate for their category, suggesting that this subgroup of practitioners should be seen as a separate group and be the primary focus of policies and interventions, as they are associated with a disproportionate part of opioid deaths (twice that of the remaining 75% of practitioners). Notably, previous efforts have focused on interventions targeting super-prescribers [21, 22] but these efforts defined the threshold for intervention arbitrarily. By evaluating different thresholds to define “super-prescribers” (1, 5, 10, 20 and 25%), we found that the impact of this sub-group of prescribers becomes considerably more significant at the 25% threshold. Taken together, these findings support the hypothesis that interventions should prioritize prescribers at the upper end of prescription rate in the category. However, to make a difference, these interventions should take place in real-time and include all prescribers in the upper quartile and prioritize specific categories of prescribers that are disproportionally impacted by super-prescribers.

In addition to categories of prescribers, we identified populations with higher prescription rates, as well as areas where increased prescription rates are more closely correlated with opioid-related deaths. Rural areas appeared to have higher prescription rates along with people aged ≥ 65 years. Also, areas with high opioid prescription rates have increased percentage of white and male population and indeed, previous studies have documented that physicians seem to be more reluctant to prescribe opioids to black patients [23–26]. Poverty was negatively correlated with high opioid prescription rates, but high poverty level in the county strengthened the correlation between high opioid prescription rates and opioid-related deaths. This negative/positive correlation could be attributed to the unavailability of substance use treatment services, inadequate or even lack of access to mental health providers, naloxone restrictions and emergency medical services challenges [26–28].

Regarding study limitations, the method of correlating aggregate mortality data with aggregate opioid prescription data across counties could provide inferior certainty in our conclusions, compared to sampling data from actual cases. Moreover, the Medicare Part D Opioid dataset only includes opioid claims for approximately 60% of the beneficiaries enrolled in the Medicare program and the detailed data are limited to the years 2013–2014, and thus may not accurately represent the whole of Medicare beneficiaries. However, given the convergence of our findings regarding socioeconomic characteristics to previous known results and the necessity of an immediate response to the opioid crisis, this study provides useful directions. Also, we performed all analyses with each data year (2013 and 2014) separately and yielded similar results to the combined database. Notably, the beneficiaries of Medicare (the usual age of eligibility is 65 years) account for approximately 15% of the total US population so the differences may be attributable to differences in insurance coverage and it is unknown if similar deviations in prescription patterns of physicians exist in private insurance programs. In terms of disabled patients who may be included in Medicare population and could have skewed our conclusions, although it could be a limitation of our study since we did not have raw data to stratify per comorbidities and disability, based on published data, they have accounted for less than 10% of Medicare population in 2013 and 2014 [29]. Finally, the variability of the model with super-prescribers has been partially explained with the included predictors. Although it still indicates a true association between the opioid-related mortality and opioid prescription rate by the super-prescribers, more variables should be included to optimize the explanatory power of this model.

5 Conclusion

The opioid epidemic is a complex health crisis demanding immediate action. The rate of opioid prescriptions is associated with opioid deaths, at least among Medicare enrollees, and, as new policies controlling opioid prescriptions are debated and enacted, the initial focus should be on specific categories of prescribers and especially on those at the upper quartile of prescription rates. For most categories of prescribers, policies and educational tools can be grouped based on prescription patterns. Monitoring at a county level can be effective and resources should prioritize to areas where socioeconomic parameters, such as poverty, facilitate the connection between high prescription rates and opioid-related deaths.

Author Contributions *Guarantor of the article*: CAG and EM accept full responsibility for the conduct of the study, have access to the data and have control of the decision to publish.

CAG and EM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CAG: conceptualized and designed the study, performed the literature search, participated in data collection, extraction and interpretation, prepared tables and figures, performed the statistical analysis, drafted the initial manuscript, approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SK: conceptualized and designed the study, performed the literature search, participated in data collection, extraction and interpretation, prepared tables and figures, performed the statistical analysis, wrote and drafted the initial manuscript, approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. EV: participated in literature search, participated in data collection, extraction and interpretation, reviewed and revised the manuscript, approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MA: participated in literature search, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MEF: participated in literature search, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CKR: assisted in designing parts of the study, performed the literature search, participated in data collection, extraction and interpretation, reviewed and revised the manuscript, approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. INE: assisted in designing parts of the study, performed the literature search, participated in data collection, extraction and interpretation, reviewed and revised the manuscript, approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. PA: assisted in designing parts of the study, interpreted the data, prepared tables and figures, performed the statistical analysis, reviewed and revised the manuscript, approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CIS: conceptualized and designed the study, interpreted the data, reviewed and revised the manuscript, approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. EM: Mylonakis conceptualized and designed the study, interpreted the data, reviewed and revised the manuscript, approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with Ethical Standards

Conflict of interest All authors [CAG, SK, EV, MA, MEF, CKR, INE, PA, EM] declare no competing interests

Funding None.

Ethical approval and informed consent N/A.

References

1. Constantino T. IMS Health Study: U.S. Drug Spending Growth Reaches 8.5 Percent in 2015. 2016. http://www.imshealth.com/en/about-us/news/ims-health-study-us-drug-spending-growth-reaches-8.5-percent-in-2015.
2. Statistics CfDCaPNCfH. Multiple Cause of Death 1999–2014 on CDC WONDER Online Database, released 2015. 2016. http://wonder.cdc.gov/mcd-icd10.html.
3. Rudd RA, Seth P, David F, Scholl L. Increases in drug and opioid-involved overdose deaths—United States, 2010–2015. MMWR Morb Mortal Wkly Rep. 2016;65(5051):1445–52.
4. King NB, Fraser V. Untreated pain, narcotics regulation, and global health ideologies. PLoS Med. 2013;10(4):e1001411.
5. Hawton K, Bergen H, Simkin S, Wells C, Kapur N, Gunnell D. Six-year follow-up of impact of co-proxamol withdrawal in England and Wales on prescribing and deaths: time-series study. PLoS Med. 2012;9(5):e1001213.
6. Johnson H, Paulozzi L, Porucznik C, Mack K, Herter B. Decline in drug overdose deaths after state policy changes—Florida, 2010–2012. MMWR Morb Mortal Wkly Rep. 2014;63(26):569–74.
7. Ringwalt C, Gugelmann H, Garrettson M, Dasgupta N, Chung AE, Proescholdbell SK, et al. Differential prescribing of opioid analgesics according to physician specialty for Medicaid patients with chronic noncancer pain diagnoses. Pain Res Manag J Can Pain Soc. 2014;19(4):179–85.
8. Chen JH, Humphreys K, Shah NH, Lembke A. Distribution of opioids by different types of medicare prescribers. JAMA Int Med. 2016;176(2):259–61.
9. Medicare. Medicare part D opioid prescriber summary file. 2016. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/OpioidMap.html.
10. Klees BSWCJ. Brief summaries of Medicare & Medicaid 2013. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/MedicareProgramRatesStats/Downloads/MedicareMedicaidSummaries2013.pdf.
11. Bureau USC. 2010 ZIP code tabulation area (ZCTA) relationship files. https://www.census.gov/geo/maps-data/data/zcta_rel_download.html.
12. Bureau USC. American FactFinder. http://factfinder2.census.gov/.
13. Bureau USC. When to use 1-year, 3-year, or 5-year estimates American Community Survey (ACS) [updated 6 Sep 2016, 18 July 2016]. http://www.census.gov/programs-surveys/acs/guidance/estimates.html.
14. Belsley DA, Kuh E, Welsch RE. Detecting and assessing collinearity. Regression diagnostics. Hoboken: John Wiley & Sons, Inc.; 2005. p. 85–191.
15. Open Source Geospatial Foundation Project 2016. Updated 5 Nov. http://www.qgis.org/en/site/.
16. Popovich N. A deadly crisis: mapping the spread of America's drug overdose epidemic: the Guardian. 2016. https://www.theguardian.com/society/ng-interactive/2016/may/25/opioid-epidemic-overdose-deaths-map.
17. Olsen Y. The CDC guideline on opioid prescribing: rising to the challenge. JAMA. 2016;315(15):1577–9.
18. Goldenbaum DM, Christopher M, Gallagher RM, Fishman S, Payne R, Joranson D, et al. Physicians charged with opioid analgesic-prescribing offenses. Pain Med (Malden, Mass.). 2008;9(6):737–47.
19. Dowell D, Haegerich TM, Chou R. CDc guideline for prescribing opioids for chronic pain—united states, 2016. JAMA. 2016;315(15):1624–45.
20. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep. 2016;65(1):1–49.
21. Bernstein L. Aetna is notifying some doctors about their drug-dispensing habits. The Washington Post. https://www.washingtonpost.com/news/to-your-health/wp/2016/08/03/aetna-is-notifying-some-doctors-about-their-drug-dispensing-habits/?utm_term=.52929125f028.
22. Barnett ML, Olenski AR, Jena AB. Opioid-prescribing patterns of emergency physicians and risk of long-term use. N Engl J Med. 2017;376(7):663–73.
23. Kolata G, Cohen S. Drug overdoses proper rise in mortality rates of young Whites. The New York Times. 2016. [updated 16 Jan 2016]. http://www.nytimes.com/2016/01/17/science/drug-overdoses-propel-rise-in-mortality-rates-of-young-whites.html?_r=0.
24. Becker WC, Starrels JL, Heo M, Li X, Weiner MG, Turner BJ. Racial differences in primary care opioid risk reduction strategies. Ann Fam Med. 2011;9(3):219–25.
25. Cerda M, Ransome Y, Keyes KM, Koenen KC, Tracy M, Tardiff KJ, et al. Prescription opioid mortality trends in New York City, 1990–2006: examining the emergence of an epidemic. Drug Alcohol Depend. 2013;132(1–2):53–62.
26. Gale JA, Schmitz D, Meit M, et al. Rural communities in crisis: strategies to address the opioid crisis 2016. [updated April 2016]. http://www.ruralhealthweb.org/index.cfm?objectid=DB1783C2-DB37-0073-AE5A339A5336A09E.

27. Mack KA, Zhang K, Paulozzi L, Jones C. Prescription practices involving opioid analgesics among Americans with Medicaid, 2010. J Health Care Poor Underserved. 2015;26(1):182–98.
28. CDC. Opioid painkiller prescribing 2016 [updated 1 July 2014]. http://www.cdc.gov/vitalsigns/opioid-prescribing/.
29. SERVICES USDOHAH. 2014 CMS statistics 2014. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/CMS-Statistics-Reference-Booklet/Downloads/CMS_Stats_2014_final.pdf.