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Mapping Drug Prescription, Polypharmacy, and Pharmaceutical Spending in Older Adults in Iran: A Multilevel Analysis Based on Claims Data

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Abstract

Background: To date, comprehensive data on drug utilization in Iranian people are lacking. The purpose of this study was to graphically describe drug prescription, polypharmacy, and pharmaceutical spending in > 3 million Iranian elderly people.

Methods: In this multilevel cross-sectional study, using administrative claims data provided by the Iran Health Insurance Organization (IHIO), we assessed drug claims and drug costs in 2018 in >3 million individuals living in Iran and who have been insured with health insurance (Bimeh Salamat). In particular, we analyzed the prevalence of polypharmacy and pharmaceutical spending use according to the annual Report of Iranian Health Insurance Organization. Multilevel ordinal logistic and multilevel beta regression models were used to analyze the data. Significance level was set as $P \leq .05$ and CI at 95%.

Results: Nationally, the mean number of drug prescriptions per patient was 1.46 (SD, 0.81). The mean number of prescribed drugs per patient was 4.32 (SD, = 3.04). The drug cost for each elderly patient was $6.86 (interquartile range (IQR), 12.26), with $4.96 and $1.76 for the insurance and the insured shares, respectively. For elderly women, the odds of polypharmacy (excessive and nonexcessive vs no polypharmacy) were 1.164 (95% CI, 1.142 to 1.186) times that of elderly men. In addition, in the spring season, the odds of polypharmacy were 1.274 (95% CI, 1.241 to 1.309) times that of the winter. Similarly, polypharmacy was strongly higher among patients who had noncommunicable diseases (OR, 2.174; 95% CI, 2.069 to 2.275 ($P < 0.001$)).

Conclusion: The high prevalence of hyper prescription in Iran elderly people may indicate a need for interventions aiming at deprescribing drugs with an unfavorable benefit-risk profile. The best practice guidelines should be developed for improved medical practice in the prescription of medications for such a vulnerable population.

Keywords: Drug Prescription, Polypharmacy, Pharmaceutical Spending, Multilevel, Claim Data

Conflicts of Interest: None declared
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Introduction

Drug therapy is the most commonly used method of any disease treatment in general practice (1). Concomitant use of multiple prescription drugs (polypharmacy) and inappropriate prescribing are important clinical challenges, especially among older patients who often have multiple chronic conditions. Polypharmacy is heterogeneously de-

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↑What is "already known" in this topic:
Concomitant use of multiple prescription drugs (polypharmacy) and inappropriate prescribing are important clinical challenges, especially among older patients who often have multiple chronic conditions.

→What this article adds:
The high prevalence of hyper prescription in Iran elderly people may indicate a need for interventions aiming at deprescribing drugs with an unfavourable benefit-risk profile. Best practice guidelines should be developed for improved medical practice in the prescription of medications for such a vulnerable population.

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fined in studies as the use of multiple medications by the patient, although most studies agree on a threshold of at least 5 medications (2, 3). In Iran, one-quarter of community-dwelling patients aged >65 years self-report taking 5 or more drugs (4), although higher rates have been reported based on claims data (5-7). Demographic transition and population aging are one of the major health challenges in the 21st century. According to official censuses, Iran, like many European countries, is aging. In 1996, about 6.6% of the total population of Iran were people over 60 years old, which reached 7.7% in 2006, and it is projected to reach about 10% of the total population by 2021 (8). This aging process is a multidimensional human, social, economic, cultural, and health issue (9, 10). The elderly are inclined to many diseases because of physiological changes and aging. The incidence of various diseases in the elderly causes these people to take more drugs than other periods of life and, as a result, suffer more drug side effects. Decreased cardiac output, decreasing liver and renal function, hemodynamic changes, along with drug interactions, and the use of over-the-counter medications aggravate the clinical condition of the elderly (11).

Drugs are also expensive and account for 25% of all health care expenditures (12), thus, their rational and efficient use is essential. The appropriate use of medicines can achieve better and safer health care for patients and communities (13, 14). The World Bank estimates that 20% to 50% of health care costs in developing countries are spent on medicines and medical equipment (13). In addition, some studies show that polypharmacy was substantially increased with the increasing insurance share in spending costs (15, 16).

Several studies have reported that polypharmacy is associated with certain risk factors such as increasing age (17-20), female gender (18-20), body mass index (19, 21), and the number of comorbidities (17, 20, 21). Other studies have also shown that polypharmacy is associated with certain noncommunicable diseases (NCDs), such as diabetes mellitus, hypertension, cardiovascular diseases, asthma, and dyslipidemia (20-23).

Studies from different countries have reported varying rates polypharmacy in the elderly, for instance, ranging from 18 % in Brazil, 44% in Sweden, and 86% in South Korea (24-26). In the United States, polypharmacy has tripled over 2 decades to reach 39% (27). One primary reason for this variation may be that there is no clear universal definition for this phenomenon. Studies have used different definitions.

A related phenomenon to the high prevalence rates in polypharmacy is that the elderly population is increasing globally (28). The elderly population in Iran is also increasing due to public health initiatives and improved health care services across the country (29).

Associated with aging is the increasing prevalence of polypharmacy, which necessitates the need for pharmaceutical spending (30, 31). Therefore, investigating the prevalence of polypharmacy and its association with age and sex is crucial to implement measures that promote the rational use of medication. Thus, the objective of this study was to determine and map the drug prescriptions, polypharmacy (>5 drugs), and pharmaceutical spending among elderly patients (≥65 years) and its association with demographic characteristics in more than 3 million elderly Iranian patients using health insurance claim data.

Methods

Study Design and Data Source

We conducted a retrospective descriptive analysis of health insurance claims data covering the years 2018-2019. Data for analysis were extracted using the Electronic Medical Record (EMR) database from a large-scale anonymized health insurance claims database, obtained from National Center for Health Insurance Research (NCHIR) for senior citizens aged ≥65 years, which manages the health insurance program (Bime Salamat) for Iranian residents. Data were obtained from April 2018 to March 2019. As of March 2019 (Esfand 1397 in the Solar Hijri calendar), the insurance program was covering 3,039,629 beneficiaries aged ≥65 years from 429 cities (nested in 31 provinces) in Iran.

The data retrieved from the EMR included patients' demographic and clinical characteristics, such as age, gender, number of drug prescription, number of prescribed drugs, season of drug prescription, total pharmaceutical spending, insurance share, and insured share. Also, the most frequent NCDs in this population were selected. These conditions included each of the following: diabetes, asthma, dyslipidaemia, hypertension, gastrointestinal reflux disease, cardiovascular diseases (ischemic heart disease, heart failure, arrhythmia, and stroke), arthritis (osteoarthritis and rheumatoid arthritis), and mental health conditions (depression, anxiety and dementia).

Definitions

Drug prescription: The number of drug prescription to each patient was quantified by counting the prescriptions that were administered monthly and regularly prescribed for any diseases in an elderly patient setting during the 12-month study period.

Furthermore, the elderly with stable disease conditions might visit outpatient clinics only once every 2 to 3 months. As a result, if only 1 month of data were analyzed, we would overlook elderlies who had no scheduled outpatient visits in that particular month. Consequently, we analyzed 12 months of data to ensure the inclusion of all 3-month prescriptions for elderly patients without monthly clinic visits. Therefore, we categorized prescriptions in three levels: 1 prescription, 2 to 3 prescriptions, and equal to and more than 4 prescriptions.

Polypharmacy: At present, there is no international consensus on the definition of polypharmacy. Based on previous studies (3), we defined polypharmacy as the concomitant prescription of 5 or more drugs in an individual (15). Here, polypharmacy was divided into 3 ordered categories: no polypharmacy (1-4 drugs), nonexcessive polypharmacy (5-9 drugs), and excessive polypharmacy (≥10 drugs) person per month (15, 32, 33).

Pharmaceutical spending: Data for spending in 2018 and prior years come from the NCHIR database, which tracks purchases of medications by each people with "Bi-

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meh Salamt". Information on drug prescription and pharmaceutical spending was extracted manually from the EMR by a trained research assistant and entered into a standardized and pretested case report form. All costs are expressed in US dollars person per month in 2018 prices and exchange rates.

Statistical Analyses

Prevalence was estimated by dividing the number of individuals who received drugs from each group during a 12-month period by the 2018 city population (1-year prevalence). Age- and sex-specific prevalence patterns were explored graphically. Age-standardized or age and sex-standardized prevalence figures were obtained by direct standardization to the entire Iran population (2016 Iran Census) when appropriate. For direct standardization, the entire Iran population (2016 Iran Census) were chosen as a reference or standard population. The observed number of cases calculated in the populations of interest. Then, apply the age (sex)-specific prevalences from the chosen reference population to the populations of interest. The number of people in each age (sex) group of the populations of interest multiplied by the age (sex)-specific prevalence in the comparable age (sex) group of the reference population. Sum the total number of expected cases for each population of interest. Finally, divide the total number of observed cases of the populations of interest by the expected cases.

Categorical variables were calculated as frequencies (%), and continuous variables were presented as the mean and SD or median and interquartile range (IQR). The results of the χ^2-tests were expressed as P values, and the strength of association in the multilevel ordinal logistic regression analyses was expressed as odds ratios (OR) with their corresponding 95% CIs and P values after adjusting for the province and cities clustering effects. In the multilevel ordinal logistic regression (ML-OLR) models, the point estimates, 95% CIs and P values of the factors in both type of univariate and multiple analysis were calculated. Prevalence as a proportional response was estimated from a multilevel beta regression (ML-BR) model. A 2-tailed P < .05 was considered statistically significant. All analyses were performed using R (Version 4.0.3) and SPSS Version 16.0 (IBM Corp). Maps were drawn in Data wrapper. This study was approved by the Research Ethics Committee of Hamadan University of Medical Sciences (Approval no. 16/35/3506). A waiver of patient consent was granted due to the use of anonymized insurance claims data.

Multilevel Ordinal Logistic Regression Model

Explanatory models for ordinal response variable collected during a single time frame have been previously reviewed by Agresti (34), Bender and Benner (35), and O'Connell (36). Such work was adapted to fit the needs of a hierarchical context. To mention a few, Fielding et al (37) and O'Connell, and Doucette (38) presented the application of the generalized multilevel ordinal model to educational data using the distribution of the latent variable. However, the multilevel ordinal model is somewhat of underutilized method in clinical and epidemiological research studies.

When data are collected in clustering format, methodologies for the handling of ordinal outcomes need to be combined with methods that address the multilevel nature of hierarchical data. Thus, event history data have a 3-level hierarchical structure with responses (level 1) nested within cities (level 2) again nested within provinces (level 3). In the current work, a three-level ordinal analysis is applied.

Suppose ordered values, $k = 1, 2, \dots, K$ is assigned to a latent variable Y_{ijk} related with level one unit k nested within level 2 unit j nested within level 3 unit i. The level 3 units consist of patients' characteristics, while levels 2 and 1 units of hierarchically measured factors. The multilevel ordinal logistic models' cumulative probabilities of the response variable (ie, polypharmacy categories) rather than category probabilities using the logit link function are as follows:

$$log\left(\frac{P(Y_{ijk}\leq k)}{P(Y_{ijk}>k)}\right) = logitP\left(Y_{ijk} \leq k\right) = \delta^{(k)} - X'_{ijk}\beta + c_{ij} + p_i \quad (1)$$

Where $k = 1, 2, \dots, K-1$; $\delta^{(k)}$ are the K-1 intercept terms to model the marginal frequencies in the K ordered categories; X'_{ijk} a known matrix associated with the fixed effect β and c_{ij} and p_i are random effects that are assumed to follow a multivariate normal distribution with mean zero vector and variance Σ.

Multilevel Beta Regression Model

Let Y_{ij} be the prevalence of city $j = 1,2, \dots, n_i$ within province $i = 1,2, \dots, I$. The prevalence such that Y_{ij} is a random variable defined in the interval (0, 1). In particular, we assume

$$(Y_{ij}|\mu_{ij}, \varphi) \sim beta(\mu_{ij}, \varphi)$$

follows a beta distribution with mean $\mu_{ij}, 0 < \mu_{ij} < 1$ that represents the prevalence of city j within province i, and φ is a precision parameter, and the greater its value the lesser the variance of Y, assuming φ to be constant. In what follows, we describe the proposed modelling of the μ_{ij}.

Let X_{ij} be a p-dimensional vector of covariates, and β a p-dimensional vector of coefficients, with $x_i = (x_{i1}, \dots, x_{ip})^T$ and $\beta = (\beta_1, \dots, \beta_p)^T$. Also, let Z_{ij} be a q-dimensional vector of covariates with $\boldsymbol{z}_i = (z_{i1}, \dots, z_{ip})^T$, and b_i a q-dimensional vector of random effects. The multilevel beta regression model is as follow:

$$log\left(\frac{\mu_{ij}}{1-\mu_{ij}}\right) = X'_{ij}\beta + Z'_{ij}b_i \quad (2)$$

The model specification is completed by $[b_i|\Sigma] \sim N(0, \Sigma)$, assuming Gaussian random effects.

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Results

Patient Characteristics

The study sample comprised 3,039,629 elderly men and women that nested in 429 cities that nested again within 31 provinces of Iran, whose characteristics are summarized in Table 1. The mean patient age was 73.69 years (SD, 7.12). Among the patients, 48.4% (n = 1,471,180) were men, 36.4% (n = 1,106,425) were between 65-69 years, and 26.3% were prescribed at least 1 drug during the winter season. The mean number of drug prescriptions per patient was 1.46 (SD, 0.81) per month; the median was one (IQR, 1). The mean number of prescribed drugs per patient was 4.32 (SD, 3.04) per month; the median was 4 (IQR, 3.8). Among all elderlies, including those with or without any medications, 57.1% (n = 1,147,439) were prescribed 5 or more drugs during 2018 year.

Prescription expenditures related to elderly patients in Iran during 2018 totaled $59.48 million, with the 49.48% ($29.43 million) spending among old men. Drug cost for each elderly patient was $6.86 (IQR, 12.26) per month, with $4.96 and $1.76 the insurance and the insured shares, respectively.

Drug prescriptions

In this study, the number of drug prescriptions was recorded monthly for each elderly patient during 12-month.

Table 1. Characteristics of older adults aged ≥ 65 years who were prescribed any drug between April 2018 to March 2019 in Iran, (n = 3,039,629)

Characteristics		n	% or mean (SD)
Sex	Female	1,568,448	51.60%
	Male	1,471,181	48.40%
Age, years	Median = 72.0, IQR = 10.0		73.69 (7.12)
Age group	65 – 69 years	1,106,534	36.40%
	70 – 74 years	755,388	24.90%
	75 – 79 years	513,889	16.90%
	80 – 84 years	378,174	12.40%
	85+ years	285,644	9.40%
Season	Spring	724,774	23.80%
	Summer	741,462	24.40%
	Autumn	774,564	25.50%
	Winter	798,829	26.30%
Chronic disease (NCDs)	No	653,520	21.50%
	Yes	2,386,109	78.50%
No. drug prescription, per month	Median = 1.0, IQR = 1.0		1.46 (0.81)
	1 prescription	2,077,410	68.30%
	2 – 3 prescriptions	873,753	28.70%
	≥ 4 prescriptions	88,466	2.90%
No. prescribed drug, per month	Median = 4.0, IQR = 3.8		4.32 (3.04)
no polypharmacy	1 – 4 drugs	1,892,220	62.30%
non-excessive polypharmacy	5 – 9 drugs	965,861	31.70%
excessive polypharmacy	≥ 10 drugs	181,548	6.00%
Total drug cost (US $ per month)	Median = 6.86, IQR = 12.26		19.57 (85.31)
Insurance share (US $ per month)	Median = 4.96, IQR = 9.07		15.74 (72.25)
Insured share (US $ per month)	Median = 1.76, IQR = 3.25		3.83 (15.74)

SD: Standard Deviation; IQR: Interquartile range ($Q_3 - Q_1$).

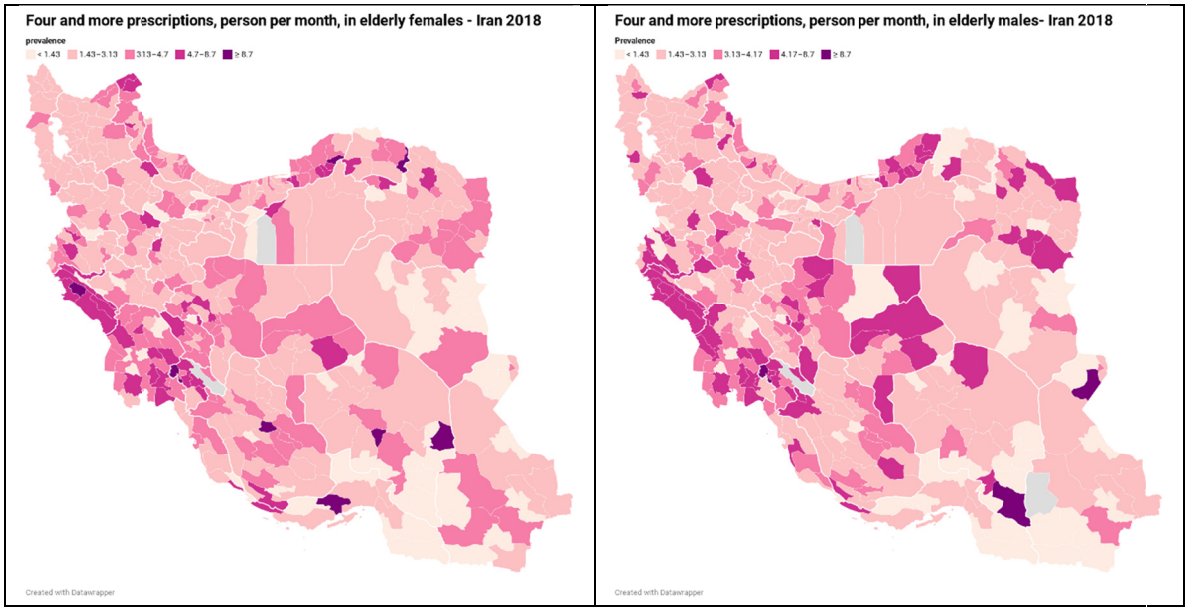

Fig. 1. Prevalence of equal to four and more drug prescriptions, person per month, in elderly patients, Iran 2018

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Based on our findings, in Iran and during 2018, there were 2,295,148 and 2,127,534 drug prescriptions among elderly women and men, respectively. According to mapping results, cities of Tehran, Isfahan, Mashhad, Shiraz, Tabriz, Rasht, Sari, Ahvaz, Kerman, and Karaj were ranked based on the most frequent number of prescriptions in both men and women. The estimated prevalence, for number of drug prescriptions ≥4, ranged between almost zero in Bashagard, a city in Hormozgan province, to 28.57% in Ghaleye-ganj, a city in southeast of Kerman province. In addition, we estimated the prevalence of ≥4 prescriptions per month by sex in all cities of Iran. Results are shown in Figure 1.

In elderly women, Bashagard (0.01%), Deylam (0.03%), Faryab (0.03%), Fanouj (0.06%), and Meshginshahr (0.08%) were 5 cities with the lowest estimated prevalence of ≥4 prescriptions per month; and Malekshahi (15.56%), Khamir (15%), Rabar (12.73%), Fahraj (11.11%), and Faroj (10.39%) were 5 cities with the highest estimated prevalence of ≥4 prescriptions per month (left side of Figure 1). Furthermore, in elderly men, Meshginshahr (0.01%), Eshtehard (0.02%), Dalgan (0.02%), Normashir (0.04%), and Bashagard (0.05%) were 5 cities with the lowest estimated prevalence of ≥4 prescriptions per month; and Ghaleye-ganj (28.57%), Hamoun (11.10%), Bahmai (8.96%), Galikash (7.63%), and Hamidieh (7.14%) were 5 cities with the highest estimated prevalence of ≥4 prescriptions per month (right side of Figure 1).

Polypharmacy

Elderly people in Iran have taken about 13.1 million prescribed drugs during 1 year, which 52.8% (n = 6,938,528) of drug counts related to elderly women. The number of drugs used also decreased with age (Appendix A1 & Appendix A2). More than 13% of prescriptions had 1 drug, and around 37.7% had more than 4 drugs. The maximum of drugs in a prescription was 24.

The estimated number of drug use varied considerably between regions. According to mapping results, cities of Tehran (14.3%), Isfahan (10.1%), Mashhad (5.9%), Shiraz (5.2%), Tabriz (3.2%), Rasht (2.3%), Sari (2.3%), Ahvaz (1.5%), Kerman (1.5%), and Karaj (1.4%) were ranked based on the most frequent number of prescribed drugs in both men and women. Estimated prevalence for number of excessive polypharmacy (≥10 drugs) ranged between almost zero in Arzuiyeh, a city in Kerman province, to 25% in Kavar, a city in southeast of Fars province. We estimated the prevalence of excessive polypharmacy (≥10 drugs) per month by sex in all cities of Iran. Results are presented in Figure 2.

In elderly women, Arzuiyeh (0.01%), Eshtehard (0.01%), Anar (0.02%), Andika (0.03%), and Bastak (0.04%) were 5 cities with the lowest estimated prevalence of excessive polypharmacy per month; and Kavar (25%), Malekshahi (21.74%), Galikash (16.51%), Zirkouh (15.79%), and Rabar (15.38%) were 5 cities with the highest estimated prevalence of excessive polypharmacy per month (left side of Figure 2). Furthermore, in elderly men, Arzuiyeh (0.01%), Eshtehard (0.02%), Anar (0.02%), Andika (.03%), and Eejrud (0.04%) were 5 cities with the lowest estimated prevalence of excessive polypharmacy per month; and Hamidieh (22.22%), Kolaleh (14.98%), Galikash (12.75%), Ghaleye-Ganj (12.50%), and Dashti (12.50%) were 5 cities with the highest estimated prevalence of excessive polypharmacy per month (right side of Figure 2).

Pharmaceutical spending

Expenditures on prescribed drugs amounted to $11.63 million ($3.83 per capita) with more contributed spending ($5.89 million) among elderly women in Iran in 2018,

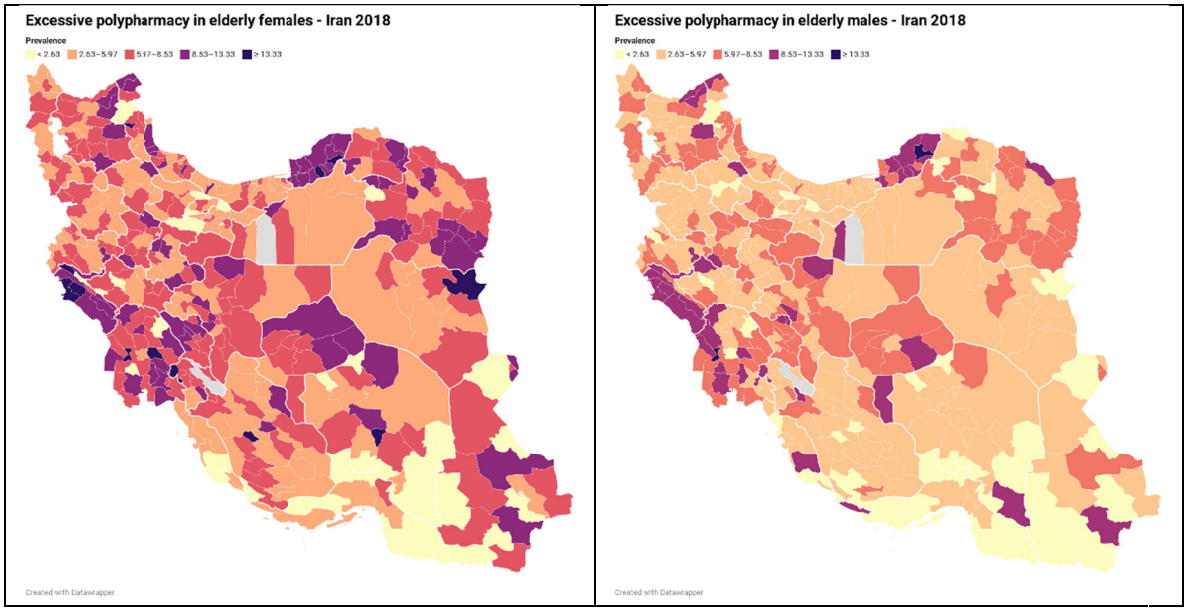

Fig. 2. Prevalence of excessive polypharmacy (≥10 drugs), person per month, in elderly patients, Iran 2018

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Table 2. Associations of patient characteristics with no polypharmacy (1–4 drugs), non-excessive polypharmacy (5–9 drugs) and excessive polypharmacy (≥10 drugs) among older patients aged ≥ 65 years

Variable		No. concomitant drugs, n (%) or median (IQR)			P-value
		1 - 4	5 - 9	≥ 10	
Sex	Female	951,535 (60.7%)	516,461 (32.9%)	100,452 (6.4%)	< 0.001
	Male	940,685 (63.9%)	449,400 (30.5%)	81,096 (5.5%)	
Age group (years)	65 – 69	710,866 (64.2%)	334,993 (30.3%)	60,675 (5.5%)	< 0.001
	70 – 74	469,428 (62.1%)	240,513 (31.8%)	45,447 (6.0%)	
	75 – 79	312,090 (60.7%)	169,257 (32.9%)	32,542 (6.3%)	
	80 – 84	226,730 (60.0%)	126,491 (33.4%)	24,953 (6.6%)	
	85+	173,106 (60.6%)	94,607 (33.1%)	17,931 (6.3%)	
Season	Spring	429,677 (59.3%)	243,880 (33.6%)	51,217 (7.1%)	< 0.001
	Summer	467,627 (63.1%)	232,227 (31.3%)	41,608 (5.6%)	
	Autumn	490,124 (63.3%)	241,117 (31.1%)	43,323 (5.6%)	
	Winter	504,792 (63.2%)	248,637 (31.1%)	45,400 (5.7%)	
Chronic disease (NCDs)	No	409,103 (62.6%)	218,929 (33.5%)	25,488 (3.9%)	< 0.001
	Yes	1,379,171 (57.8%)	816,049 (34.2%)	190,889 (8.0%)	
No. prescription (per month)	1	1,648,458 (79.4%)	424,444 (20.4%)	4,508 (0.2%)	< 0.001
	2 – 3	243,133 (27.8%)	515,371 (59.0%)	115,249 (13.2%)	
	≥ 4	629 (0.7%)	26,046 (29.4%)	61,791 (69.8%)	
Total drug cost (US $ per month)		4.08 (7.19)	11.53 (12.79)	22.74 (30.61)	< 0.001
Insurance share (US $ per month)		2.95 (5.34)	8.29 (9.55)	16.41 (23.39)	< 0.001
Insured share (US $ per month)		1.04 (1.94)	3.16 (3.72)	6.20 (6.84)	< 0.001

Total n = 3,039,629; IQR: Interquartile range ($Q_3 - Q_1$).
P-value conducted from Chi-square (χ^2) test.

excluding insurance rebates (see Tables 1 and 2). In per capita terms, the top province spenders were Tehran ($5.06), Azarbayjan-e-sharqi ($4.62), and Golestan ($4.30), with over $3.68 million, and the lowest province spenders (with complete data) were Fars ($2.29), Mazandaran ($2.34), Ilam ($2.56), and Kohgiluyeh va bowyer ahmad ($2.68), with less than $1.1 thousand during 2018.

In elderly women, Sirik ($0.07), Ghasr-e-gand ($0.1), Normashir ($0.24), Karoun ($0.28), and Doureh ($0.45) were 5 cities with the lowest monthly per capita spenders; and Farsan ($7.52), Bandar-e-gaz ($6.47), Rezvanshahr ($6.11), Rabar ($5.64), and Talesh ($5.63) were 5 cities with the highest monthly per capita spenders (left side of Figure 3). Furthermore, in elderly men, Bashagard ($0.04), Fanouj ($0.06), Kavar ($0.07), Faryab ($0.11), and Jask ($0.24) were 5 cities with the lowest monthly per capita spenders; and Haftgol ($16.32), Bavi ($14.91), Kalat ($10.96), Razo jalgelan ($10.96), and Mobarakeh ($8.18) were 5 cities with the highest monthly per capita spenders in Iran 2018 (right side of Figure 3).

Factors Associated With Polypharmacy

Tables 2 and 3 show the results of the univariate analyses with chi-square tests and multivariate analyses with multilevel ordinal logistic regressions, respectively.

The distribution of polypharmacy (No. concomitant drugs) by variables are shown in Table 2. At the all level of the response (1 to 3), polypharmacy is more frequent (percent) in elderly women, younger age group, spring

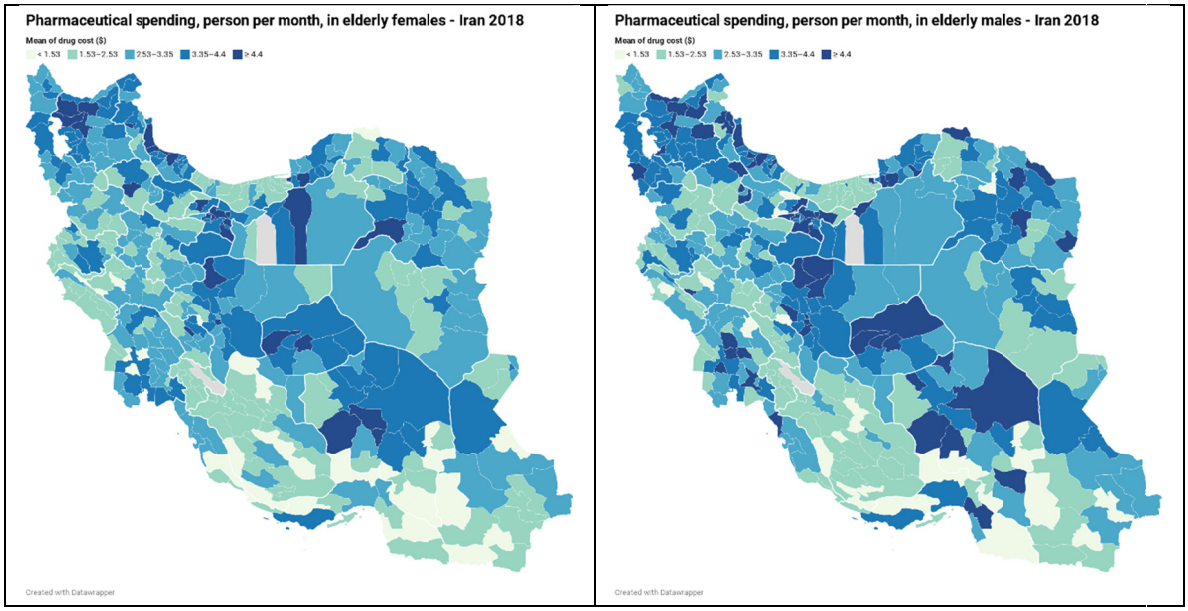

Fig. 3. Mean of pharmaceutical spending, USD $ person per month, in elderly patients, Iran 2018

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season, and elderlies with at least 1 chronic condition (NCDs). However, in relation to number of prescriptions, nonexcessive polypharmacy in level 2 (2-3 prescriptions per month) and excessive polypharmacy in level 3 (>4 prescriptions per month) are more frequent.

The multivariate analyses identified the following factors as being significantly associated with ordered response, in order: 1 = no polypharmacy (1-4 drugs), 2 = nonexcessive polypharmacy (5-9 drugs), and three = excessive polypharmacy (≥10 drugs): age group (reference: 85+ years), sex (reference: male), season (reference: winter), chronic disease (reference: no), drug cost, insurance share, and insured share (all $P < 0.001$).

As can be seen, the variance components of random effects were significant in provinces and cities for the proposed model (multilevel ordinal logistic regression) (Table 3). Therefore, it can be concluded that there was a significant heterogeneity among cities and provinces in terms of the studied response variable. Therefore, all estimates reported and interpreted after adjusting for the province and cities clustering effects.

With increasing age, the chance of higher level of polypharmacy decreased also, so that the odds of higher level of polypharmacy for people in the age group 85+ years are 1.19 (OR, 1/0.841 = 1.19) greater than people in age group 65-69 years, given that all of the other variables in the model are held constant. In addition, odds of higher level of polypharmacy for people in the age group 85+ years are 1.10 (OR, 1/0.841 = 1.10) greater than people in age group 70-74 years, showing a statistically significant effect, $P < 0.001$.

For elderly women, the odds of polypharmacy (excessive and nonexcessive vs no polypharmacy) were 1.164 (95% CI, 1.142-1.186) times that of elderly men. In addition, in the spring, the odds of polypharmacy were 1.274 (95% CI, 1.241-1.309) times that of winter, indicating a statistically significant effect, $P < 0.001$.

Similarly, polypharmacy was strongly higher among patients who had a disease of NCDs (OR, 2.174; 95% CI, 2.069-2.275 ($P < 0.001$)).

In pharmaceutical spending characteristics, an increase in factors of the total drug cost (OR, 1.163; 95% CI, 1.159-1.168), insurance share (OR, 1.009; 95% CI, 1.005-1.009), and insured share (OR, 1.053; 95% CI, 1.048-1.057) also significantly associated with an increase in the odds of higher level of polypharmacy (all $P < 0.001$).

Discussion

The present study mapped and elucidated the drug prescriptions, polypharmacy, and pharmaceutical spending and the factors associated with polypharmacy in >3 million patients aged ≥65 years residing in 429 cities in Iran.

Approximately 4.4 million with a mean of 1.46 per capita drug prescriptions have been distributed to elderly patients during 2018 in Iran. The value of this index is about one-third of the results of other studies. According to data available in the United States, 16% of adults are over 60 years and account for 40% of the prescribed medications, with a mean of 4.5 medicines per person (39).

Approximately, 38% of participants were receiving polypharmacy, showing that polypharmacy in the elderly is currently the norm and not the exception. Concomitant use of multiple prescription drugs ('polypharmacy') is increasingly common, with 10% of the population (39, 40) and 30% of older adults in the United States taking 5 or more drugs simultaneously (39-41). A cross-sectional analysis of the Survey of Health, Aging, and Retirement in Europe (SHARE) database showed that the prevalence of polypharmacy, defined as taking 5 or more medications concurrently in older adults aged 65 years or more, was

Table 3. Factors associated with no monthly polypharmacy (1–4 drugs), non-excessive polypharmacy (5–9 drugs), and excessive polypharmacy (≥10 drugs) among elderly patients aged ≥65 years (multilevel ordinal logistic regression analysis results)

		Multivariable analysis				Univariate analysis			
Parameter		OR	95% CI		P-value	OR	95% CI		P-value
			Lower	Upper			Lower	Upper	
Age group	65 – 69	0.841	0.812	0.870	< 0.001	0.857	0.828	0.886	< 0.001
	70 – 74	0.905	0.873	0.938	< 0.001	0.933	0.901	0.967	< 0.001
	75 – 79	0.950	0.915	0.987	0.009	0.981	0.945	1.019	0.328
	80 – 84	1.007	0.967	1.049	0.726	1.023	0.983	1.064	0.265
	85+¶	1	-	-	-	1	-	-	-
Sex	Female	1.164	1.142	1.186	< 0.001	1.134	1.113	1.156	< 0.001
	Male¶	1	-	-	-	1	-	-	-
Season	Spring	1.274	1.241	1.309	< 0.001	1.210	1.179	1.242	< 0.001
	Summer	1.029	1.002	1.057	0.038	0.996	0.970	1.023	0.791
	Autumn	1.005	.979	1.033	0.692	0.982	0.957	1.008	0.181
	Winter¶	1	-	-	-	1	-	-	-
Chronic disease (NCDs)	Yes	2.174	2.069	2.275	< 0.001	2.149	2.082	2.188	< 0.001
	No¶	1	-	-	-	1	-	-	-
Total cost $		1.163	1.159	1.168	< 0.001	1.007	1.007	1.008	< 0.001
Insurance share $		1.009	1.005	1.013	< 0.001	1.006	1.006	1.006	< 0.001
Insured share $		1.053	1.048	1.057	< 0.001	1.087	1.085	1.090	< 0.001

Variance component from multivariable analysis	Estimate	Standard Error	P-value
Sigma (Province)	0.266	0.040	< 0.001
Sigma (City)	1.461	0.088	< 0.001

-2 log-Likelihood = 268305.044, AIC = 268129.029; BIC = 268250.459
OR: Odds Ratio; CI: Confidence Interval; ¶: Reference level.

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between 26.3% and 39.9% among European countries and Israel (42).

Similar studies using prescribed drug registry data or drug claims data have reported that 44% of Swedes aged ≥70 years (15), 66% of Canadians aged ≥65 years (43), and 77.5% of Qatari elderly patients aged ≥65 years (44) were prescribed 5 or more drugs. It has also been reported that 86% of Koreans aged ≥65 years were prescribed 6 or more drugs (24). Although our estimated prevalence of polypharmacy was between those reported in the European countries and Swedish studies, inherent differences in the definitions of polypharmacy and study settings (eg, data collection methods, healthcare systems, and available drugs) make it difficult to compare results among countries.

The present study showed that 6.5% of all patients aged ≥65 years who were prescribed any drug during the study period were prescribed 10 or more drug types.

The mean cost per prescription was 19.57 US dollars. This was 7.04 US dollars in 2010 (45) and 8.21 US dollars in 2011 (46), which indicated a 3-fold increase in the cost of medicines over the last 5 years. This could be the result of sanctions and a leap in inflation between 2011 and 2018.

Consistent with other studies, the prevalence of polypharmacy in the present study was significantly higher among women (18, 20, 26, 47). In contrast, other studies have reported higher polypharmacy rates in men (17, 24). Such contradictions among study findings could be explained by differences in physicians' prescribing approaches toward genders as well as to differences between genders and their health-seeking behaviors. Consistent with another study in Iran (48, 49), the prevalence of almost all of the NCDs we studied, except for cardiovascular diseases, was higher in women than in men. In addition, polypharmacy showed a stronger association with certain NCDs than others. This is consistent with findings from other studies (17, 21, 22, 24, 27).

A study in Norway (2015) that examined the regular general practitioner role in polypharmacy reported that the risk of polypharmacy in patients increases significantly with the number of prescribers (OR, 2.32; 95% CI, 2.31-2.33) (50). One other factor that could explain such a phenomenon is the high prevalence of NCDs in our study population. Furthermore, a study in Canada showed a significant association between polypharmacy and higher frequency of family physician visits in elderly patients (51). Finally, the provision of medications at lower or no cost to elderly Iranian citizens might make it easier for physicians to prescribe them more.

Finally, in our study, polypharmacy was substantially increased with the increasing insurance share in spending costs. This is consistent with findings from other studies in Sweden (16, 52).

Study Strengths and Limitations

The present study is the first to map the prevalence of polypharmacy and its associated factors among elderly citizens in Iran. The strength of our study lies in its large sample size, which allowed for statistical analysis with sufficient statistical power. Therefore, the findings from this study provide a reliable basis to confirm that high polypharmacy exists in elderly patients in the cities and provinces of Iran. Moreover, the use of standardized estimates, such as the prevalence of polypharmacy and prescription, made the results more valid, reliable, and enabled comparison with other studies.

On the other hand, the lack of a standard definition of number of prescription and polypharmacy across studies made comparisons difficult. Moreover, the calculated prevalence might be overestimated because elderly patients who we extracted might have suffered from multiple health conditions.

Another limitation is that some of the variables (eg, socioeconomic status, marital status, body mass index, or exact NCDs disease) were not consistently recorded for most patients, making us unable to include them in our analysis.

Finally, because of our study design, our findings cannot be generalized to the entire population of interest, but can be only applied to the population included in the study.

Conclusion

This study provided evidence that the prevalence of polypharmacy among Iranian elderly patients is very high, with almost 3 quarters of the study population exposed to it. The study as well demonstrated a significant association between polypharmacy and older age with about 42% of the study participants being older than 75 years. Our findings confirmed the strong relationship between polypharmacy and NCDs, such as hypertension, diabetes mellitus, dyslipidemia, cardiovascular diseases, and asthma. As appropriate care for elderly patients is increasingly challenging, targeted educational programs should be developed for health care professionals to raise their awareness of the magnitude and negative impact of polypharmacy. Furthermore, primary health care centers should establish best practice guidelines for improved medical practice in the prescription of medications for such a vulnerable population.

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Conflict of Interests

The authors declare that they have no competing interests.

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Appendix A1. Number of prescribed drug per month in elderly females by age group and province, Iran 2018

Province	No. prescribed drug per month in elderly females by age group and province - Iran 2018														
	No polypharmacy (1 - 4)					Non-excessive polypharmacy (5 - 9)					Excessive polypharmacy (>= 10)				
	65 to 69	70 to 74	75 to 79	80 to 84	85 +	65 to 69	70 to 74	75 to 79	80 to 84	85 +	65 to 69	70 to 74	75 to 79	80 to 84	85 +
Āẕārbāyjān-e Shārqī	18415	13395	8710	6611	4492	9721	7990	5593	4422	3104	1688	1544	1116	914	606
Āẕārbāyjān-e Ghārbī	11799	7513	5052	4032	2960	5946	4322	3223	2420	1904	1119	818	685	486	317
Ardabīl	4124	2823	2057	1437	1059	2527	1837	1453	1038	736	540	430	292	262	146
Eṣfahān	40129	25282	12876	8150	6721	21765	15884	8921	5561	4408	5063	3874	2061	1271	972
Alborz	7683	4578	2563	1618	953	3259	2223	1313	772	520	509	357	239	152	95
Īlām	2029	1432	829	663	526	1207	886	545	468	305	375	309	208	117	109
Būshehr	3172	1645	1002	800	432	1399	869	514	382	206	243	152	84	84	25
Tehrān	71447	52752	32916	21408	16088	27497	21860	14852	10298	7801	4114	3318	2413	1576	1139
Chahār Mahāl va Bakhtīārī	5039	3472	2253	1443	1344	3116	2378	1694	1086	983	816	594	456	261	208
Khorāsān-e Jonūbī	2951	1616	1282	1000	755	1503	961	834	581	411	226	147	137	100	60
Khorāsān-e Razavī	29810	19582	13297	8657	7075	15136	10901	8230	5730	4474	2857	1995	1596	1135	867
Khorāsān-e Shomālī	2347	1502	961	675	472	1328	997	716	519	319	274	246	161	102	83
Khūzestān	15386	8345	4743	3042	2151	7968	4924	2920	1866	1343	1893	1234	771	548	357
Zanjān	3657	2256	1498	1064	766	1657	1074	804	628	379	287	192	135	119	63
Semnān	4464	2524	1625	1092	800	2309	1599	1001	717	578	354	274	215	138	104
Sīstān va Balūchestān	4141	2138	1236	621	450	2317	1240	805	421	273	475	267	187	79	44
Fārs	29894	17681	10219	8051	6883	14845	9656	6262	5158	4357	2418	1710	1047	873	659
Qazvīn	4127	2713	1673	1111	752	1916	1503	923	704	445	332	284	202	142	84
Qom	2873	1661	1170	760	556	1581	1032	768	505	399	356	207	171	136	81
Kordestān	5839	3392	2055	1328	1116	2824	1742	1252	835	625	462	320	239	185	107
Kermān	12702	7287	4328	3237	2320	6474	4009	2512	1881	1378	1144	742	541	366	226
Kermānshāh	8343	5524	2973	2141	1360	4140	2907	1711	1369	755	793	577	306	247	147
Kohgīlūyeh va Bowyer Ahmad	2480	1667	1068	1150	839	1187	912	554	662	450	274	245	165	161	90
Golestān	7892	5274	3104	2084	1450	5248	3931	2446	1682	1187	1656	1169	760	561	304
Gīlān	19452	12339	7174	5570	4208	10031	7240	4598	3587	2769	1901	1380	1006	825	548
Lorestān	6137	3352	2044	1898	1286	2975	1821	1199	1234	772	515	354	252	223	137
Māzandarān	27967	16954	10399	7363	5162	14291	9694	6223	4553	2955	2192	1693	1135	768	532
Markazī	6275	3480	2315	1747	1372	3012	1988	1447	1152	846	545	407	331	200	187
Hormozgān	3277	1668	910	714	684	1306	695	443	361	319	215	114	73	59	47
Hamadān	7683	4812	3422	2324	1729	3713	2798	2140	1611	1001	780	590	464	298	191
Yazd	6676	3755	2616	1935	2054	3595	2340	1720	1301	1333	729	550	358	280	205

Low

High

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Appendix A2. Number of prescribed drug per month in elderly males by age group and province, Iran 2018

Province	No. prescribed drug per month in elderly males by age group and province - Iran 2018														
	No polypharmacy (1 - 4)					Non-excessive polypharmacy (5 - 9)					Excessive polypharmacy (>= 10)				
	65 to 69	70 to 74	75 to 79	80 to 84	85 +	65 to 69	70 to 74	75 to 79	80 to 84	85 +	65 to 69	70 to 74	75 to 79	80 to 84	85 +
Āzārbāyjān-e Shārqī	16568	12346	9099	7033	5540	7749	6427	4815	3977	3074	1343	1161	855	790	571
Āzārbāyjān-e Ghārbī	12961	8902	5344	4401	3759	6007	4404	2855	2289	1873	1050	859	547	478	378
Ardabīl	4304	2670	1887	1304	1268	2272	1578	1128	819	722	423	282	267	181	167
Eṣfahān	39916	30730	21076	15587	10102	18893	16309	11714	8918	5690	3648	3395	2386	2086	1291
Alborz	5258	3939	2935	2026	1394	1976	1686	1239	984	690	274	237	199	131	99
Īlām	3007	1431	771	601	653	1762	752	477	336	395	493	233	130	101	120
Būshehr	3406	1626	1156	881	557	1369	671	535	339	238	174	112	81	68	26
Tehrān	43658	37929	31091	23468	17411	16264	14585	12531	9533	6935	2488	2082	1813	1376	1036
Chahār Mahāl va Bakhtīārī	4965	3227	2663	1777	1533	2390	1781	1592	1082	971	475	439	295	287	230
Khorāsān-e Jonūbī	3014	2049	1375	877	908	1471	1020	703	474	439	222	146	117	77	66
Khorāsān-e Razavī	25286	17317	13464	9445	7483	11377	8640	7040	5084	3862	1889	1541	1282	984	761
Khorāsān-e Shomālī	2350	1389	924	617	494	1136	719	506	408	282	191	139	106	82	64
Khūzestān	13395	7106	4770	3826	2480	6365	3512	2479	1951	1324	1375	729	564	490	360
Zanjān	4081	2330	1915	1360	1158	1606	977	904	653	562	235	188	137	118	91
Semnān	4988	3370	2276	1522	1468	2389	1847	1438	981	863	352	304	225	190	155
Sīstān va Balūchestān	4904	2718	1520	1008	685	2197	1316	784	521	357	382	248	148	120	58
Fārs	27977	17270	12535	9851	7654	12991	8329	6269	5165	3721	2018	1275	870	805	637
Qazvīn	3233	2304	1689	1353	980	1503	1065	787	650	530	210	185	166	109	101
Qom	3350	2013	1695	1130	902	1870	1075	924	656	543	370	213	196	183	123
Kordestān	5236	3216	2086	1607	1161	2246	1561	1075	756	611	308	251	186	108	87
Kermān	11353	6671	4208	3257	2718	5134	3154	2166	1641	1230	752	481	375	273	206
Kermānshāh	7090	4019	3078	2127	1734	3246	1937	1441	1156	959	572	375	298	230	148
Kohgīlūyeh va Bow-yer Ahmad	3085	1376	943	1055	996	1118	496	385	542	490	183	97	96	144	103
Golestān	7934	4827	2767	2057	1610	4543	2932	1741	1337	1047	1163	728	449	449	366
Gīlān	16727	12212	7632	5872	4218	7399	5870	3634	3103	2406	1243	1010	692	617	515
Lorestān	5215	2862	2520	2090	1596	2553	1372	1240	1117	903	444	249	228	201	171
Māzandarān	26212	17514	11333	8573	6767	10633	7588	5473	4006	2902	1502	1072	925	626	542
Markazī	6552	3760	3242	2598	2176	3093	1865	1673	1386	1219	542	357	274	308	249
Hormozgān	2548	1534	843	866	795	871	583	366	296	293	128	93	42	48	41
Hamadān	6684	4094	3601	2526	2140	2894	1987	1702	1437	1083	502	394	393	344	222
Yazd	7399	4263	3282	2309	1951	3883	2262	2025	1390	1058	579	479	394	281	207

Low

High

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