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Using drug sales data to evaluate the epidemiology of cardio-metabolic risk factors and their inequality: an ecological study on atorvastatin and total cholesterol in Iran

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Abstract

Background: Statins have been effective medications in lowering serum total cholesterol (TC) concentrations across populations over time. The aim of this study was to estimate national and provincial trends in atorvastatin sales in Iran, to systematically quantify its relationship with socio-economic indicators, and changes in TC level.

Methods: In this retrospective ecological study, conducted in Iran, we examined trends in atorvastatin sales, the wealth index (WI) as a validly-available socio-economic indicator, and TC level between 2004 and 2011. The main outcome variable was mean atorvastatin sold in defined daily dose per 100,000 people per day (DPD). We analyzed the relationship between WI and DPD and between DPD and mean TC across time and space.

Results: At national level, both mean WI and mean DPD showed increasing trend over time, while we observed decreasing trend for TC. Mean WI and DPD in 2011 was nearly 5 and 50 time that of their respective figures in 2004, while the mean TC decreased for nearly 10%. Increases in both WI and DPD had happened in every province, but with different patterns. The maximum and minimum changes in DPD versus WI were seen in Gilan and North Khorasan respectively.

Conclusion: A striking increase occurred in the sales for atorvastatin in Iran from 2004-2012 in most provinces examined. The wealthier a province became, the more sales were seen for atorvastatin. TC optimistically decreased from 2005 to 2011 and its decrease was positively correlated with increasing sales for atorvastatin.

Keywords: Atorvastatin, Socioeconomic status, Hypercholesterolemia, Risk factors, Iran, Epidemiology, Pharmacoepidemiology.

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Introduction

A growing burden of cardio-metabolic risk factors is happening in Iran similar to other developing and developed countries. This will alarmingly lead to greater increases in the burden of non-communicable diseases (NCDs) in the near future (1-5). Provision of trends and estimates for cardio-metabolic risk factors in Iranian population from 1990 to 2013, their distribution at sub-national level, and their effects on the population health is under way in a sub-

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component of the National and Sub-national Burden of Diseases, Injuries, and Risk Factors (NASBOD) study. In the meanwhile, knowledge of the extent of treatment for cardio-metabolic risk factors and its evolution is crucial for planning strategies to proper management in different populations across the country (6).

It has been estimated that high Total Cholesterol (TC) serum level, as an important cardio-metabolic risk factor, is responsible for the death of nearly 4.4 million people every year worldwide (3). Medical management to lower cholesterol is an important and effective intervention which can decrease serum TC concentrations across populations over time (7).

Although different classes of medications have been available to lower cholesterol level, with the increasing availability of statin family in the early 1990s, the use of statins has increasingly been advocated in international clinical practice guidelines (CPGs) for the treatment of high TC (7). However, trends in overall treatment for high TC remains mostly unclear; as it can show to what extent the adoption of guidelines for actual treatment of hypercholesterolemic patients may vary at national or sub-national levels (8). Moreover, little is known about the relationship between socio-economic indicators and use of statins at national and subnational levels across time (9).

Medication sales statistics are one of the best available sources of information about trends in drug therapies, which are currently mostly being used for business purposes by pharmaceutical companies. This sort of data is routinely collected and available in most industrialized countries, but is generally neglected by epidemiologists (10). Our paper focuses on the utilization of drug sales data for epidemiology, here applied to atorvastatin as one of the core medications for treatment of high TC.

Our aim was to estimate trends in atorvastatin sales nationally and in each province, and to systematically quantify its relationship with reliably available socio-economic indicators. Besides, we have identified trends of atorvastatin sales and changes in TC level across time within the country and each province.

Methods

We have investigated the distribution and patterns of sales for atorvastatin between 2004 and 2012 in 31 provinces in Iran – as a proxy to utilization – for which concurrent trend data on sales of various generic and brand forms of atorvastatin could have been obtained. The study rationale is explained in detail in the Appendix 1.

Study design and setting

This was a retrospective ecological study, conducted in Iran, to examine trends in atorvastatin sales, validly-available socio-economic indicators, and TC between 2004 and 2011 at national and provincial levels (Iran's provincial map is included in Appendix 2). We assessed the effects of socio-economic indicators on the sales of atorvastatin (as outcome) utilizing routine administrative and survey data. Comparison of the sales of atorvastatin was also made with mean TC and in relationship with socioeconomic indicators.

Data sources and variables

The main data source was used to estimate the trends in sales of atorvastatin in Iran. The requirements for reliability of this data source is that atorvastatin is available only with a prescription issued by a physician and dispensed by pharmacies, so there is no other way for patients to get the medicine. Also, atorvastatin's main indication of use is for the treatment of hypercholesterolemia which makes it specific for the treatment of the risk factor. More importantly, atorvastatin has been under the coverage of all basic social and medical insurance schemes throughout the nine years of study, so there has been no barriers regarding insurance coverage which might have limited the access to the medication. We did not have access to data form insurance compa-

nies; as there was no need for it in this kind of ecological analysis.

Iran's Food and Drug Administration organization (FDO) under Ministry of Health and Medical Education (MOHME) officially publishes National Drug Sales Statistics (NDSS) on a monthly, quarterly, and yearly basis, using similar methods of data collection all over the country. The data come from statistics on country-wide sales to all retail pharmacies gathered by pharmaceutical distributors and wholesale drug suppliers which hand their statistics over to the FDO. Using the NDSS data, we gathered data on the annual quantity sold for atorvastatin in different districts across Iran from 2004 to 2012, in various dosages (i.e. 10, 20, 40, and 80 mg tablets) under every generic or brand names. The year 2004 was the first year when full data on atorvastatin sales were available.

Dependent variable – sales for atorvastatin: The overall quantities for atorvastatin sold across the country-years were unified using DDD of atorvastatin (i.e. 20mg) to control for variability in dosing between products, without any categorization for sex, age, or demographic variables. Then, the DDD sold in every district of every province was averaged and aggregated at province level. Ideally, medication utilization statistics should be described as numbers of DDDs per 1000 – or per 100,000 – people per day. This will help in providing rough estimates of the proportion of populations treated daily with any medication(s). For this purpose, we used Iran's National Statistics Organization's data from recent demographic surveys and/or censuses to gather the total population for 31 provinces from 2004 to 2012. It should be noted that usually, the general utilization figures for a medication is calculated for the total population of country or province including all age groups. Therefore, we divided the mean DDD in each province-year by its corresponding population in that year and multiplied the result by 100,000. Finally, the result was divided by 365 to form our main outcome variable; i.e. "mean atorvastatin sold in DDD per 100,000 people per day" (hereafter named "DPD").

Independent variable –wealth index (WI) as the validly available indicator of socioeconomic status (SES): Based on the information on asset ownership, the wealth index (WI), as a composite index, was constructed from the Iran's National Statistics Organization's Household Expenditure (HHE) survey to determine the socioeconomic status of the country and its different provinces over nine years of study. The WI is a composite measure which is higher when the SES is high and vice versa. The WI was initially constructed separately for males and females in each province-year in a distinct project at the Non-communicable Diseases Research Center (NCDRC), under Tehran University of Medical Sciences (TUMS). While there were differences in the WI based on gender, it was shown that a combined index (which is not gender-based) performed as well as the separate gender-based indices in all provinces. The advantage of this approach was that this combined single WI was simpler to implement in future research. Therefore, the WI was used independent of sex for analyzing the relationship between SES and sales of atorvastatin. The WI is a unit-less weighted mean of 20-30 variables that are output of principal component analysis (PCA) on HHE data.

Comparison variable – mean TC in province-years: To compare the trends for sales for atorvastatin and TC, we used the results of the TC measurements in 2005, 2007, and 2011 in MOHME's national surveys entitled "Surveillance of Risk Factors of Non-Communicable Diseases". In these surveys, Iranian citizens, aged 15–64 years, gave venous blood samples for serum biochemistry profiling. The mean TC was calculated for each province-year using complex sample survey analysis, based on the clusters of sampling protocol and sample weights. For TC, the measurement unit was

mg/dL and the plausibility range was defined as 67.6-772.2 mg/dL (1.75-20 mmol/L) to address the potential outliers; hypercholesterolemia was defined as TC ≥ 200 mg/dl.

Statistical methods

To address the potential biases, especially in misclassification of exposures and outcomes, the definition of dependent and independent variables was clearly determined prior to study implementation. Standardized protocols for data collection, including training of collaborating personnel, were developed and put into practice to decrease variability in gathering and entering data. Continuous variables were reported as mean±SD. Scatter plots were drawn for sales for atorvastatin versus WI, and also sales of atorvastatin versus mean TC, at all the time points collected. To measure the strength of linear association between variables, the Pearson correlation coefficient was calculated. Linear regression analysis was used to analyze the relationship between WI and sales for atorvastatin. A value of $p<0.05$ was considered significant. Analyses were performed using STATA 13.

Ethical considerations

The original surveys received approval by the relevant ethics review boards based at MOHME. Data sharing agreement had been obtained between NCDRC and MOHME. Secondary analysis of administrative sales data went under approval by a review board composed of members from the NCDRC and FDO. This study was approved by the School of Public Health Research Committee, based at TUMS.

Results

Our final dataset was composed of more than 87,000 medication item in all districts across the whole nine years from 2004-2012. More than 43,000 (49.6%) records were exclusively atorvastatin in its various dosages or generic/brand names.

Table 1 summarizes the national mean (SD) for WI, DPD, and TC from 2004-2012. It also shows the province-years having the lowest and highest figures for the abovementioned variables.

At national level, both mean WI and mean DPD showed increasing trend over time, while we observed decreasing trend for TC. Mean WI in the last year of study was nearly five times that of its figure in 2004. In the meanwhile, the mean DPD showed over 50 times increase during the nine years. In comparison, the mean TC decreased for nearly 10% from 2005 to 2011 (Table 2).

At national level, assessing the relationship between WI and DPD showed moder-

Table 1. Descriptive statistics of WI, DPD, and TC at national level along with their minimum and maximum in respective years, aggregated on nine years from 2004-2012

Variable	Mean	SD	Min	Year	Max	Year
WI*	0.730	0.051	-2.275	2004	2.294	2012
DPD*	0.0083	0.0006	0.0001	2004	0.0712	2012
TC**	192.906	1.227	168.159	2011	223.144	2011

Table 2. Descriptive statistics of WI, DPD, and TC at national level from 2004 to 2012

Year	WI		DPD		TC	
	Mean	SD	Mean	SD	Mean	SD
2004	0.225	0.176	0.0004	0.0001	-	-
2005	0.405	0.157	0.0015	0.0002	202.082	1.370
2006	0.560	0.154	0.0028	0.0004	-	-
2007	0.655	0.150	0.0044	0.0006	191.306	1.784
2008	0.750	0.142	0.0067	0.0008	-	-
2009	0.901	0.133	0.0106	0.0011	-	-
2010	0.945	0.131	0.0103	0.0010	-	-
2011	1.008	0.134	0.0174	0.0018	185.276	1.927
2012	1.118	0.134	0.0206	0.0025	-	-

Table 3. Results of pairwise correlation tests between DPD vs. WI and TC vs. DPD at national level

Pairwise Correlation	Coefficient	p
DPD vs. WI	0.428	<0.001
TC vs. DPD	-0.324	0.002

Table 4. Results of linear regression analysis for DPD as independent vs. WI as dependent variable at national level

DPD	Estimation	SE	t	p
WI	0.0047	0.0006	7.8900	<0.001
Constant	0.0049	0.0007	7.3100	<0.001

Probability > F = 0.0000, R-squared = 0.1833, Adjusted R-squared = 0.1804

ately positive and statistically significant correlation based on pairwise correlation test. The same assessment for DPD and TC showed moderately negative, yet statistically significant results with the same test (Table 3). At national level, in linear regression analysis, DPD showed positive and significant relationship with WI (Table 4).

The scatterplot in Figure 1 visually summarizes the positive correlation and linear association of WI and DPD at national lev-

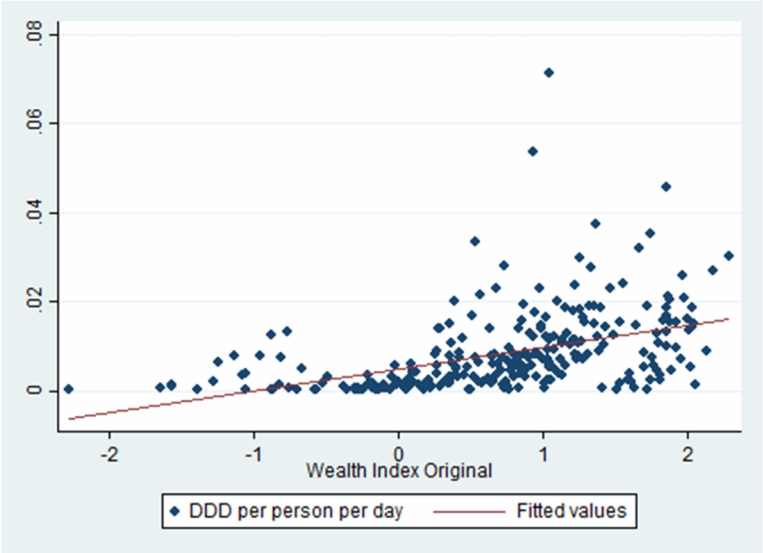

Fig. 1. Scatterplot for WI vs. DPD at national level, with fitted values as liner trend

Fig. 2. Scatterplot for WI vs. DPD at provincial level

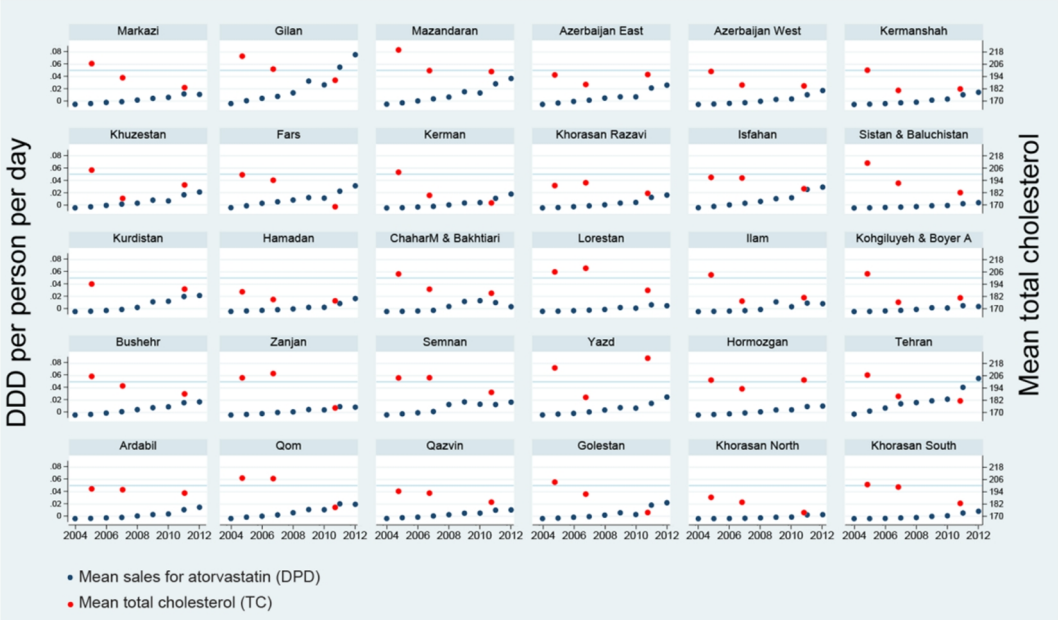

Fig. 3. Scatterplot for TC vs. DPD at provincial level
The light blue line shows the threshold for defining hypercholesterolemia (i.e. TC ≥ 200 mg/dL)
(Note: Alborz province was omitted because it had only one TC measurement in 2011 by the MOHME)

el.

By focusing on province level trends in WI and DPD, scatterplots in Figure 2 show the positive correlation between WI and DPD in 31 provinces. Increase in both WI and DPD has happened in each province, with different slope and speed of change. The highest and lowest changes in DPD versus WI were seen in Gilan and the North Khorasan respectively.

Most importantly, by focusing on province level trends in DPD and TC, scatterplots in Figure 3 show the negative correlation between DPD and WI in 30 provinces. Increase in DPD and decrease in TC happened in many provinces, with different patterns of change.

Discussion

We compared recent national and provincial trends in the sales of atorvastatin for the treatment of hypercholesterolemia along with the WI and TC in Iran, using administrative and survey data. A striking increase occurred in the sales of atorvastatin in Iran over nine years from 2004-2012, and in most provinces examined. This huge increase suggests important changes in the pattern of the use of atorvastatin for treatment of high TC. Moreover, we showed that sale of atorvastatin is related to national and provincial socio-economic status assessed by WI; i.e. generally the wealthier provinces showed more sales for atorvastatin, and also the wealthier a province became, the more sale was seen for atorvastatin, during the nine years of study. Besides, TC optimistically decreased from 2005 to 2011 by nearly 10% and the decrease was positively correlated with increasing sales for atorvastatin.

Validity of this method has been assessed before and the necessary conditions are met in most developed countries; i.e. availability of demographic data, reliability of medication sales statistics by administrative organizations, and supply of medication to any area requiring them (11). Fortunately, these conditions were met in our study, which makes the results of our study ready to be applied for assessment of similar risk factors or diseases.

Sale of atorvastatin to retail pharmacies, like other medications, is a proxy to actual utilization and consumption by patients (12). Some of the sold medication remains as depot within the pharmacies, before being sold to the actual patients. Moreover, not all patients who receive prescriptions

for atorvastatin finally dispense it by going to pharmacies. However, we assumed that for assessing and interpreting trends of sales over time, these challenges cannot interfere with reliable inferences that one can make from the outputs; because the percentage of depots in pharmacies and proportion of people who may not dispense their prescriptions may not differ very much from year-to-year for medications like atorvastatin which experience year-round sales.

The level and trends of atorvastatin sales will reflect not only the burden of hypercholesterolemia but also the rough proportion of patients being treated (13). Ecologically, negative association between sales and hypercholesterolemia means that the medication can show its benefit in decreasing the burden of TC in populations (14). Currently, we can just accept that the increase in sales may be attributable to both increases in diagnosis and in management; both of which are considered scientifically justifiable based on CPGs (8). Nevertheless, the increase in drug sales may also represent an increase in the amount of treatment each patient receives (15). The decreasing trend in mean TC over time and opposing trend for sales for atorvastatin suggest that there is a gap between the actual prevalence of hypercholesterolemia and proper medical management of high TC over these years; i.e. there are still more patients in need of atorvastatin who have not become under treatment.

It is possible that some provinces have a greater prevalence of hypercholesterolemia than others; this would explain some of the increase seen in atorvastatin sales. Surveys which examine the trends in management of hypercholesterolemia with medications can outline the exact situation at national and subnational level. This has not been assessed in the six rounds of MOHME's Surveillance of Risk Factors of Non-Communicable Diseases from 2005-2011 (6).

The WI as an indicator of SES (16) showed interesting relationship with sales for atorvastatin. The steepest rise in sales for atorvastatin has happened in wealthier provinces such as Tehran or Isfahan. In opposite, Sistan and Baluchestan or Khorasan South do not show the same increase of sales, despite their initial levels of high TC in 2005. Almost all provinces in Iran are under coverage of basic social and medical insurance schemes and atorvastatin is subsidized under the available insurance plans. So, the cost of prescriptions to the patient cannot generally be blamed for the inequality seen in sales within different provinces. However, the cost of consultations with physicians may discourage patients from seeking the optimum care and supervision, and consult for their prescriptions (17). Also, the trends in sales of atorvastatin to treat hypercholesterolemia shown here may reflect differences in physicians' prescribing patterns (18); i.e. different members of statin family (apart from atorvastatin) or other classes of cholesterol-lowering drugs may be more popular in worse-off provinces. However, more than 50% of records of data from the FDO belonged to atorvastatin.

In the absence of comparable individual-level data on using atorvastatin for high TC, the interpretation of our findings can only be speculative. Still, we have shown that the dramatic increase in per capita sales of atorvastatin to treat hypercholesterolemia has been accompanied with a reduction in TC levels country-wide and across provinces. However, the speed and slope of changes vary much between provinces which show the possible inequalities in treatment of hypercholesterolemia at subnational levels. Gholami et al. discussed that level of development, level of income, and per capita gross national product (GNP) in different countries have effects on distribution of hypercholesterolemia in various SES categories. They added that increasing access to health care services for societies' disadvantaged groups would reduce the inequalities in the distribution of hypercholesterolemia and its risk factors (19). Galobardes et al. assessed the trends

in risk factors for lifestyle-related diseases by socioeconomic position from 1993–2000 in Geneva, Switzerland. They highlighted that the prevalence of hypercholesterolemia treatment for men in low and high SES categories has increased significantly (20).

Limitations

Our methodology, as an ecological study, shows the overall trends of sales for atorvastatin, WI and TC over space and time for large populations. Demonstrated relationships cannot be interpreted at individual level; as the actual usage of atorvastatin and decrease in TC level for each individual may not necessarily be related to the SES or WI of that individual person. This method is also inadequate for detecting undiagnosed hypercholesterolemia. Thus, our objective was not to assess the burden of high TC in the country or in each province.

The age and sex distribution is not available in NDSS dataset from the FDO. Therefore, we were unable to provide age-specific or sex-specific trends for sales for atorvastatin. For logical interpretation of the inequality between provinces, we should take into account the differences of age in their corresponding general populations.

Our proposed approach, while showing overall therapeutic trends over space and time in an inexpensive and practical way, will not replace field surveys. The classical approach through surveys on random population samples can be feasible, yet expensive alternative.

Conclusion

Our methodology based on drug sales data could be appropriate for other risk factors and/or diseases, in particular for detecting variations over time.

Over the last nine years, we have shown good evidence that increased sales for atorvastatin have been associated with a decline in mean TC at national and provincial levels. This is consistently in accordance with the advice from CPGs which promote the increasing use of statins for hypercholesterolemia (8). However, other explanations should also be assessed in future research projects.

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Conflicts of interest

There is no conflict of interest.

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Appendix 1
Study rationale

Medical management of high TC often needs prescribing a daily treatment to be taken continuously all year long. The medication is usually specific to this risk factor; however, the exact choice of medication(s) may be influenced by various factors, including but not limited to, individuals' risk factor profile, age, health status and probable side effects of medications.

Common classes of cholesterol-lowering drugs include statins, bile-acid-binding resins, cholesterol absorption inhibitors, and combination cholesterol absorption inhibitor and statin. In this area, statin family are among the most commonly prescribed medications and their generic members include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. They are becoming progressively more prescribed for controlling high TC and this is supported by various international CPGs. Atorvastatin is the most popular member of the family, in terms of sales. From 1996 to 2012, Lipitor (the trade name for Atorvastatin) became the world's best-selling medication of all time.

Therefore, the pattern and distribution of sales for atorvastatin can largely outline the situation of treatment for high TC. Based on drug sales data, the total amount of atorvastatin sold in 1 year is known with accuracy. Because of this availability, it would be possible to estimate its average daily consumption by patients. The estimation would be valid if (1) the treatment is specific to the risk factor; and (2) the drug is continuously taken daily all year long. If a combination of several drugs is prescribed for some patients, the estimates become a bit complicated, since correction factors should be used to avoid double counting. Nevertheless, this is not the case for high TC, as statins are prescribed individually and not in combination with other classes of cholesterol-lowering drugs. Moreover, two members of the statin family are not prescribed simultaneously for patients. Besides, combination cholesterol absorption inhibitors and statins have not yet been available in Iran's pharmaceutical market.

Although sales data are actually considered a proxy for consumption of medications, by standard modifications proposed by the World Health Organization (WHO), the data can be used for pharmacoepidemiological purposes. To accurately estimate the average daily consumption of atorvastatin, we should know the average daily dose of the drug prescribed in different population having high TC. For this purpose, WHO has described "defined daily dose (DDD)" as a statistical measure of drug consumption. The definition for DDD is "the assumed average maintenance dose per day for a drug used for its main indication in adults". (WHO Collaborating Centre for Drug Statistics Methodology (WHOCC): DDD Definition and general considerations; http://www.whocc.no/ddd/definition_and_general_considera/). It is used to standardize the comparison of drug usage between different drugs of the same family or class or between various health care environments. DDD was developed as a technical unit of measurement with the purpose of enabling epidemiological comparison of drug consumption that was independent of differences in price or package size.

Appendix 2
Iran's provincial map (30 provinces)