Multiple Sclerosis incidence rate in southern Iran: A Bayesian epidemiological study

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Abstract

Background: Multiple Sclerosis (MS) remains to be a public health challenge, due to its unknown biological mechanism and clinical impact on young people. The prevalence of this disease in Iran is reported to be 5.3 to 74.28 per 100000 cases. Due to high prevalence of this disease in Fars province, this study aimed to assess the distribution of MS in this region in southern Iran by evaluating its covariates.

Method: Data from 5,468 patients diagnosed with MS were collected, according to the McDonald's criteria, which was reported by the MS Society of Fars from 1991 until 2016. Bayesian spatio-temporal models was also used to describe MS incidence in Fars province. We also investigated the association between overall MS incidence rate and the overall percentage of vitamin D intake, smokers in the population as well as the overall percentage of people with normal BMI as well as alcohol consumption in a population from 1991 until 2016 by Besag, York and Mollie's (BYM) model.

Results: County-level crude incidence rates ranged from 0.22 to 11.31 cases per 100,000 population. The highest relative risk was estimated at 1.8 in the city of Shiraz, the capital of Fars province while the lowest relative risk was estimated at 0.11 in Zarindasht County in southern Fars. The percentages of vitamin D3 intake was significantly associated with the incidence of MS. Although 1% increase in Vitamin D3 intake is associated with 2% decrease in the risk of MS, 1% increase in smoking is associated with 16% increase in the risk of MS, respectively.

Conclusion: Spatial analysis of MS showed low incidence rate of this disease in the south and south east of Fars province, which is due to the effect of different covariates. As suggested by previous studies, vitamin D and smoking among all covaiates might be associated with high incidence of MS.

Background

MS is an autoimmune disorder, in which the central nervous system myelin is attacked. It results in focal lesions and clinical symptoms [1, 2]. In other words, it is a common neurodegenerative inflammatory disease, resulting from myelin and axonal degeneration, predominantly in young adults [1]. The disease is classified into four different courses: a) Relapsing- Remitting (RR) MS, the most common type, which include 85–90% of all cases; b) Secondary Progressive (SP); c) Primary Progressive (PP) MS, accounts for only 10% of the cases; and d) Progressive Relapsing (PR) MS [3]. Worldwide, more than 2.3 million individuals affected by these different type MS [4–6]. The distribution of MS increases retrospectively with distance from the Equator. For example, Canada, Norway, and Sweden have some of the highest prevalence rates of MS in the world, reported in 2013. However, there are exceptions; some countries further away from the equator, such as Russia have low prevalence, whereas other countries closer to the equator, for instance Australia, show a high prevalence [5, 6]. Epidemiological studies based on the geographical region shows that the prevalence ranged from 5.3 to 74.28 per 100,000 individuals in Iran, which is not evenly distributed across different regions [7]. Fars province with 72.1/100,000 (116.5 in

females and 28.3 in males) prevalence rate in 2013 is one of the high risk provinces for this disease. The mean annual incidence rate was 5.2/100,000 from 2002 until 2012 [8].

Environmental risk or lifestyle factors including vitamin D deficiency, obesity, alcohol consumption, and cigarette smoking have been identified. Both low vitamin D levels and cigarette smoking are the strongest risk factors [5, 6, 9, 10]. Although many studies that have investigated the epidemiology of MS and examined the effect of different genetic, environmental and lifestyle factors on this disease [2, 6, 11–21], to the best of our knowledge, there is no study, which has estimated the Spatio-temporal incidence rate of MS in Fars province. Spatio-temporal modeling allows the health outcomes, both in space and time to be simultaneously evolve [22].

This study models the incidence of MS in Fars province in southern Iran over a 26-year period between 1991 to 2016. We also simultaneously investigate the effects of some covariates such as 1) vitamin D3, 2) smoking, 3) BMI, 4) alcohol consumption on the number of multiple sclerosis in 29 Fars province counties, using Besag, York and Mollie's (BYM) spatial-temporal models.

Methods

Study area

Fars province is located in the southwest region of Iran (Figure 1 left) and covers 120,608 km^2 of land. The province is subdivided into 29 counties and has 4.8 million inhabitants (51% males) according to 2016 census report by the Statistical Center of Iran (SCI)[23]. According to census, Fars population in 1996 was 3,817,036 (1,927,415 males and 1,889,621 females), in 2006 was 4,336,878 (2,204,852 males and 2,132,026 females), and in 2016 it reached 4,851,274 (2,461,251 males and 2,390,023 females). To average out, we used 2006 population to estimate the relative risks. The population at risk (i.e. scaled 1/100,000) in 2006 for the 29 counties is shown in Figure 1 (right). As shown in the left figure 1, Shiraz has the highest population at risk.

Data

This is a historical and retrospective cohort study, carried out in MS Society of Fars province from 1991 until 2016. This center is the only MS registry center in Fars province, so the information of almost all MS patients is available in its database. All MS patients who fulfilled the McDonald's criteria [24] from 1991 to 2016 were included in this study. Suspicious cases were referred to the MS committee of Shiraz University of Medical Sciences (SUMS) to a neurologist and were again reevaluated by three expert neurologists to confirm their diagnosis. We excluded all patients from other neighboring provinces that were registered in this longitudinal database. Data of covariates, such as the overall percentage of vitamin D intake, smoking in the population as well as the overall percentage of people with normal BMI and alcohol consumption in the population within the period of 1991-2016 were extracted from the annual health census from the Ministry of Health and medical Education in Fars province, available in SUMS database.

Statistical analysis

In this study, the geographical variation of MS incidence in 29 counties was analyzed. Standardized Incidence Ratio (SIR) was calculated for each county, using the direct method. For the assessment of potential effect of the risk factors on relative risks, data were analyzed, using BYM model, suggested by Besag, York and Mollie's (1991). We applied spatiotemporal model (adapted of BYM model for space–time problems) presented by Bernardinelli et al. (1995) to identify the temporal pattern of MS disease.

The BYM model is one of the most popular full Bayesian models, which is explained in many references with detail (see Blangiardo M, Cameletti M. Spatial and spatio-temporal Bayesian models with R-INLA. John Wiley & Sons; 2015 Jun 2. Page 231). We considered Vitamin D3 intake, smoking, normal BMI, and alcohol consumption as risk factors. The observed number of MS in a geographic unit (county) was assumed to follow a Poisson distribution. In the Bayesian structure, the intercept and fix effects was assumed to follow an improper uniform and normal distribution with zero mean and a small variance as prior. The precision parameters, which control the amount of variability for the random effects, were assumed to follow a gamma distribution (0.5, 0.0005), as suggested by Bernardinelli et al.,1995 (Lawson et al., 2003).OpenBUGS version 3.2.3 [25]was used to estimate parameters and ArcGIS 10.1 [26]was used to display them on maps. We ran two chains with 1000 samples as burn-in and 10000 samples as iteration. Convergence for the chains were confirmed, and the differences between the two chains were very small [27].

Results

We identified 5,468 new MS cases 4344 (79%) women and 1124 (21%) men in Fars province from 1991 to 2016. A total of 3664 patients (67%) were from the city of Shiraz, the capital of Fars province.

Table 1 shows the number of new MS cases in each year, incidence rate per 100,000 population, age, and number of female and male in each year in Fars province during the mentioned 26 years. The highest and lowest incidence rates were observed in 2014 as 11.31(95% CI (10.39, 12.30) per 100,000) and 1992 as 0.22 (95% CI (0.11,0.44) per 100,000). In addition, the highest and lowest age mean were observed in 2014 (32.11±9.40) and 1993 (25.12±8.73). The highest and lowest female/male ratio were observed in 2006 (5.86) and 1991(1.44).

Table 1. Incidence of MS per 100,000 persons in the county levels of Fars province in the south of Iran from 1991 to 2016

Year	No. of cases	Incidence rate (95% CI)	Age at diagnosis (y)		No. of cases Female/male	F/M ratio
			Mean±SD	Min-max		
1991	22	0.61(0.40,0.93)	28.45±8.11	(10-45)	13/9	1.44
1992	8	0.22(0.11,0.44)	30.30±8.08	(22-44)	6/2	3
1993	32	0.86(0.61,1.22)	25.12±8.73	(8-44)	21/11	1.91
1994	28	0.75(0.52,1.08)	26.89±8.25	(11-43)	18/10	1.80
1995	35	0.92(0.66,1.28)	27.32±8.09	(16-46)	29/6	4.83
1996	35	0.91(0.65,1.27)	27.43±8.28	(12-46)	31/4	7.75
1997	26	0.67(0.45,0.98)	25.24±5.89	(14-40)	21/5	4.20
1998	48	1.22(0.92,1.61)	31.51±12.8	(13-77)	39/9	4.33
1999	77	1.93(1.54,2.41)	28.21±8.43	(14-48)	59/18	3.28
2000	77	1.90(1.52,2.38)	29.44±8.77	(9-48)	62/15	4.13
2001	91	2.22(1.81,2.73)	28.01±8.50	(8-55)	77/14	5.50
2002	104	2.51(2.07,3.04)	28.20±8.42	(14-53)	86/18	4.78
2003	119	2.83(2.37,3.39)	29.09±9.03	(11-56)	106/13	8.15
2004	133	3.13(2.64,3.71)	28.58±8.46	(10-59)	101/32	3.16
2005	199	4.63(4.03,5.32)	28.57±8.06	(13-53)	169/30	5.63
2006	199	4.57(3.98,5.26)	28.82±8.62	(12-59)	170/29	5.86
2007	228	5.18(4.55,5.90)	31.23±10.80	(7-86)	186/42	4.43
2008	279	6.27(5.58,7.05)	30.09±8.98	(9-55)	221/58	3.81
2009	288	6.40 (5.70,7.18)	30.47±9.01	(10-56)	237/51	4.65

2010	391	8.59(7.78,9.49)	29.77±8.64	(8-63)	323/68	4.75
2011	438	9.52(8.67,10.46)	31.49±9.45	(5-69)	366/72	5.08
2012	488	10.49(9.60,11.47)	30.26±8.84	(7-64)	405/83	4.88
2013	510	10.85(9.95,11.83)	30.80±9.08	(9-60)	397/113	3.51
2014	537	11.31(10.39,12.30)	32.11±9.40	(11-64)	432/105	4.11
2015	533	11.10(10.20,12.09)	32.09±9.27	(8-62)	415/118	3.52
2016	543	11.20(10.29,12.18)	32.43±8.82	(11-62)	354/189	1.87

Age-specific prevalence rates of MS are shown in Table2. The highest and lowest prevalence rates belonged to 30-40 (26.01 (95% CI, (24.8, 27.3) per 1,000,000) and <20 (95% CI, 4.31 (4.00, 4.64) per1,000,000) age groups. A statistically significant difference was determined between the prevalence of MS amongst men and women (P<0.0001), except age group>60. Highest and lowest values of MS ratio of women to men were observed in <20 (4.65) and >60 (1.5) age groups.

Table 2. Age-specific prevalence rates of MS in the county (per 1,000,000 persons) of Fars province in the south of Iran from 1991 to 2016

Age group	No. of cases	Prevalence	No. of cases Female/male	F/M ratio	P-value F to M
<20	689	4.31(4.00,4.64)	567/122	4.65	<0.0001
20-30	2261	21.71(20.83,22.63)	1797/464	3.87	<0.0001
30-40	1629	26.01(24.8,27.3)	1301/328	3.97	<0.0001
40-50	742	15.89(14.79,17.08)	565/177	3.19	<0.0001
50-60	132	4.54(3.83,5.39)	105/27	3.89	<0.0001
>60	15	4.92(2.96,8.15)	9/6	1.5	0.6056

We generated maps of geographical variations of MS incidence across the 29 counties of Fars province with classic SIR (Fig. 2A), BYM model (Fig. 2B) spatiotemporal model (Fig. 2C), and posterior estimate value of (Figure 2D). shows the difference between the global trend and the area-specific trend , showing that this trend is less steep than the mean trend, whilst shows that the area-specific trend is steeper than the mean trend. The maps should be interpreted by considering that different shades are proportional to the incidence rate value. In other words, the darker the area, the higher the incidence of

MS. The averages of SIRs and relative risks were 0.52 and 0.43, respectively. As can be seen in Figure 2 (A and B), Shiraz is at higher risk than other counties. Shiraz had the highest SIR and relative risk for MS with values of 1.8 and 1.8 (standard deviation= 0.03), respectively. Zarindasht county in southeast of Fars province had the lowest SIR and relative risk, with values of 0.06 and 0.11 (standard deviation= 0.03), respectively. Figure 2C shows the temporal trend of the incidence rate across different regions of Fars province during the period of 1991-2016. The estimated value of time coefficient in this model was 0.0075. The exponential corresponding to the coefficient of time is equal to 1.007 for each successive year. This finding shows that although there is an increasing trend of incidence in Fars, it is very uniform. Figure 2D shows the change of temporal patterns of MS incidence rate. Darker areas show that the trend is steeper for those counties compared with the global trend and brighter areas show that the trend is less steep than the global trend.

Another important point that can be inferred from Figure 2C, is the steady increase of incidence rate of relative risk over time in the northern regions of the province. Figure 2B depicts the average over a period of 26 years, showing higher overall incidence rates in the central regions of Fars. On the other hand, Figure 2C incorporates relative changes over this time period, showing a geographical shift of the incidence rate from the central regions to the northern regions of the province.

Table 3. Summary statistics: posterior mean, posterior standard deviation (SD) and posterior 95% credibility interval for the fixed effects of BYM models in MS incidence

Covariate	Coefficient (SD)	Exp (coefficient)	95% Confidence Interval
% of Vitamin D3 intake	-0.022 (0.005)	0.978	(-.022,-0.008)*
% of smoking	0.149 (0.065)	1.161	(0.032,0.240)*
% of normal BMI	0.021 (0.023)	1.021	(-0.020,0.022)
% of Alcohol consumption	1.012 (0.777)	2.750	(-0.511,2.585)

Table 3 is a summary of the statistics related to different covariates used in BYM model. The fixed effects estimated are presented in Table 3 which shows that the percentages of vitamin D3 intake are significantly associated with MS incidence. Although 1% increase in Vitamin D3 intake is associated with 2% decrease in the risk of MS incidence, 1% increase in smoking is associated with 16% increase in the risk of MS incidence.

Discussion And Conclusion

This study spatially evaluated the MS incidence distribution in Fars province, using Bayesian model. Spatial description of the disease is a useful tool for evaluating the incidence rate data and to generate leads in further public health investigations and interventions [28]. As far as we know, this is the first

study to have estimated the Spatio-temporal incidence rate of MS. This study also investigates the association of vitamin D3, smoking, BMI, and alcohol consumption with MS incidence rate, as well as spatial dependence between the neighboring regions. The findings suggest that further studies are warranted in order to confirm the allocations of health resource across different region.

The results of BYM model describes the low incidence rate of MS in south and southeast of the province. Zarindasht county, located in south with hot and dry climate and high temperature, had the lowest incidence rate. This result is in line with previous studies that showed maintaining adequate levels of vitamin D (as one of the environmental factors) have a protective effect, resulting in lower risk of developing autoimmune diseases including MS[29-31]. The results of this study also showed that larger cities, located in the center of province, especially Shiraz and Abadea in northeast had high MS incidence rates. This is in concordance with previous studies which showed MS to be more common among urban dwellers than rural ones[32]. There is no clear explanation as to why, but higher frequencies in these regions might be due to more accurate diagnosis in these regions which is a result of easier access to healthcare and higher-quality diagnostic procedures. Although, high socioeconomic status (SES) index which includes income, education, ethnicity, job and asset is generally associated with better health outcomes, it seemed that regions with higher SES (i.e. urban areas compared to rural areas) had led to increased risk of MS. However, this is just an association and not a cause, but the reason is unknown [32, 33]. Even though some previous studies were in line with our result, some were contrary and reported no evidence of an association between MS incidence and SES or reported an association with low SES [32-34].

Our results showed that the percentage of Vitamin D3 intake and smoking can be associated with reduced risk of MS incidence, which is in line with previous studies that had suggested maintaining adequate levels of vitamin D can have a protective effect by lowering the risk of developing autoimmune diseases including MS[29-31]. When a person has MS, his or her immune system attacks the coating that protects nerve cells. Research suggests a significant positive effect of vitamin D on the immune system. [29-31, 35]. Smoking as a risk factor can influence the course of MS [16, 36, 37]. Both duration and smoking intensity can contributed independently to the increased risk of MS [38]. Studies amongst MS patients and healthy controls, consistently have provided evidence that both active and passive smoking can result in an increased risk of MS and disease progression. Studies have shown that the risk of MS associated with HLA genotypes is increased by smoking status [36, 39].

According to several studies, obesity is one of the potential risk factors of MS. The growing world-wide obesity epidemic has multiple deleterious effects on public health and has also been associated with an increased risk of MS [40]. Increased obesity leads to lower levels of 25-hydroxyvitamin D, which in turn predisposes to MS [41]. The association between obesity and MS is similar amongst men and women, and the observed trend of higher BMI resulted in a higher risk of developing MS [42]. However, in our study BMI was not associated with the incidence of MS.

Although the impact of alcohol, which might directly suppress various immune responses, on the risk of developing MS has been investigated in different studies, the results were inconsistent. In some studies, researchers found no association between alcohol intake and risk of MS [43], but in some other researchers showed a potential dependency between alcohol consumption and the incidence of MS [10].

Our study had some limitations, which should be taken into consideration in future studies. The major limitation of the present study was that although the MS incidence rate was longitudinal, covariate information was not available per year between 1991 and 2016; hence, we had the overall information of these covariates during this period. Lack of this information prevented us from using these covariates in spatio-temporal model, but investigated their effect on longitudinal mapping. Another limitation was that in this study we focused only on the statistical test results while assessing the effect size gives additional information about the extent of the effected values. Since the incidence and prevalence rates are different in male and female [20], further investigations on the impact of other important covariates, such as climate, sunlight, and air pollution should be conducted [13, 17, 44-48].

Conclusion: Spatial analysis of MS showed low incidence rate of this disease in the south and south-east of Fars province. In addition, large cities also had very high MS incidence rate. Effect of different covariates which were investigated in this study showed that vitamin D and smoking among all covaiates might be associated with the incidence of MS.

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in studies involving human participants were approved by the ethics committee and in accordance with the ethical standards of the Shiraz University of medical science. Written consent was originally obtained by the MS Society of Fars province from participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

NSA and ZSH: designed the study, performed the statistical analyses and interpretation and wrote the manuscript, AM: interpret statistical analysis and wrote the manuscript. RJ, IT, MAB, MA and MJ M: were consulted on the design of the study and reviewed the draft. All authors read and approved the final manuscript.

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Figures

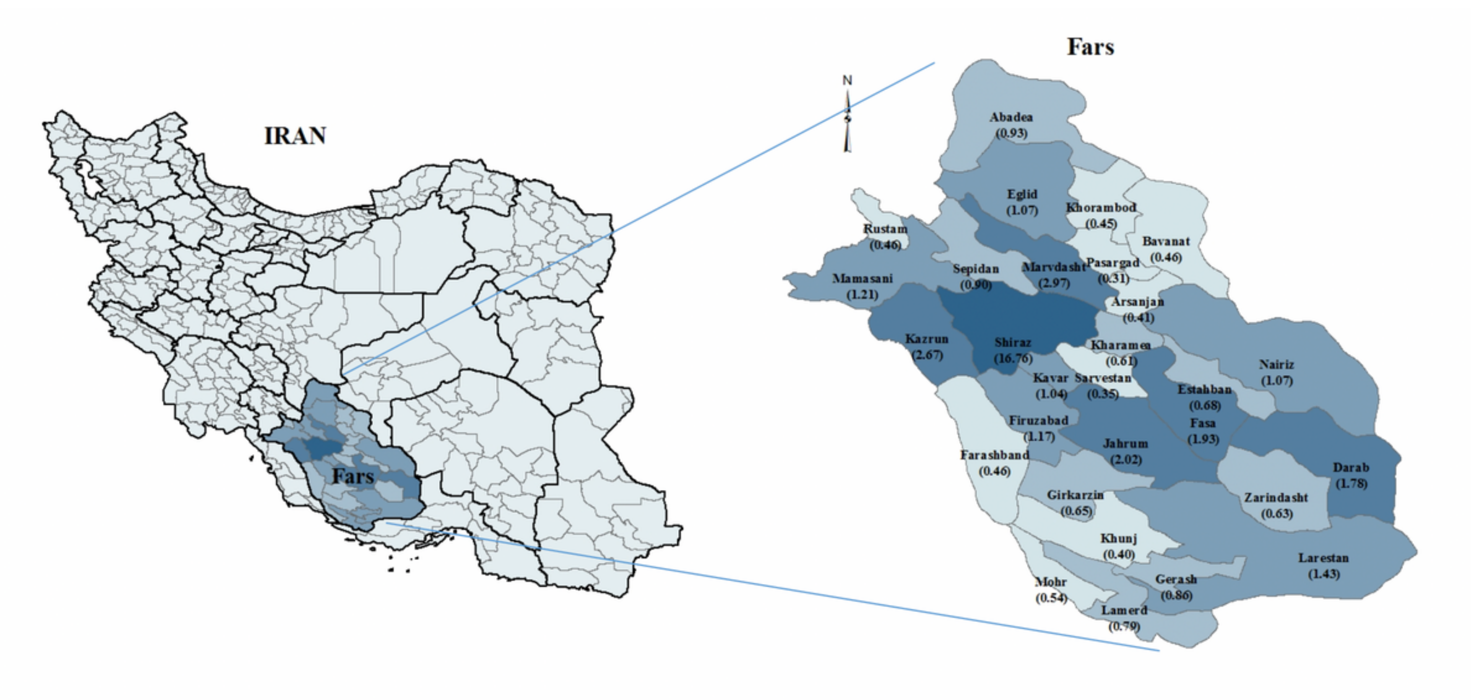

Figure 1

geographical location of Fars province and its counties (created using ArcGIS Desktop: Release 10.1, https://www.esri.com/en-us/arcgis/about-arcgis/overview)

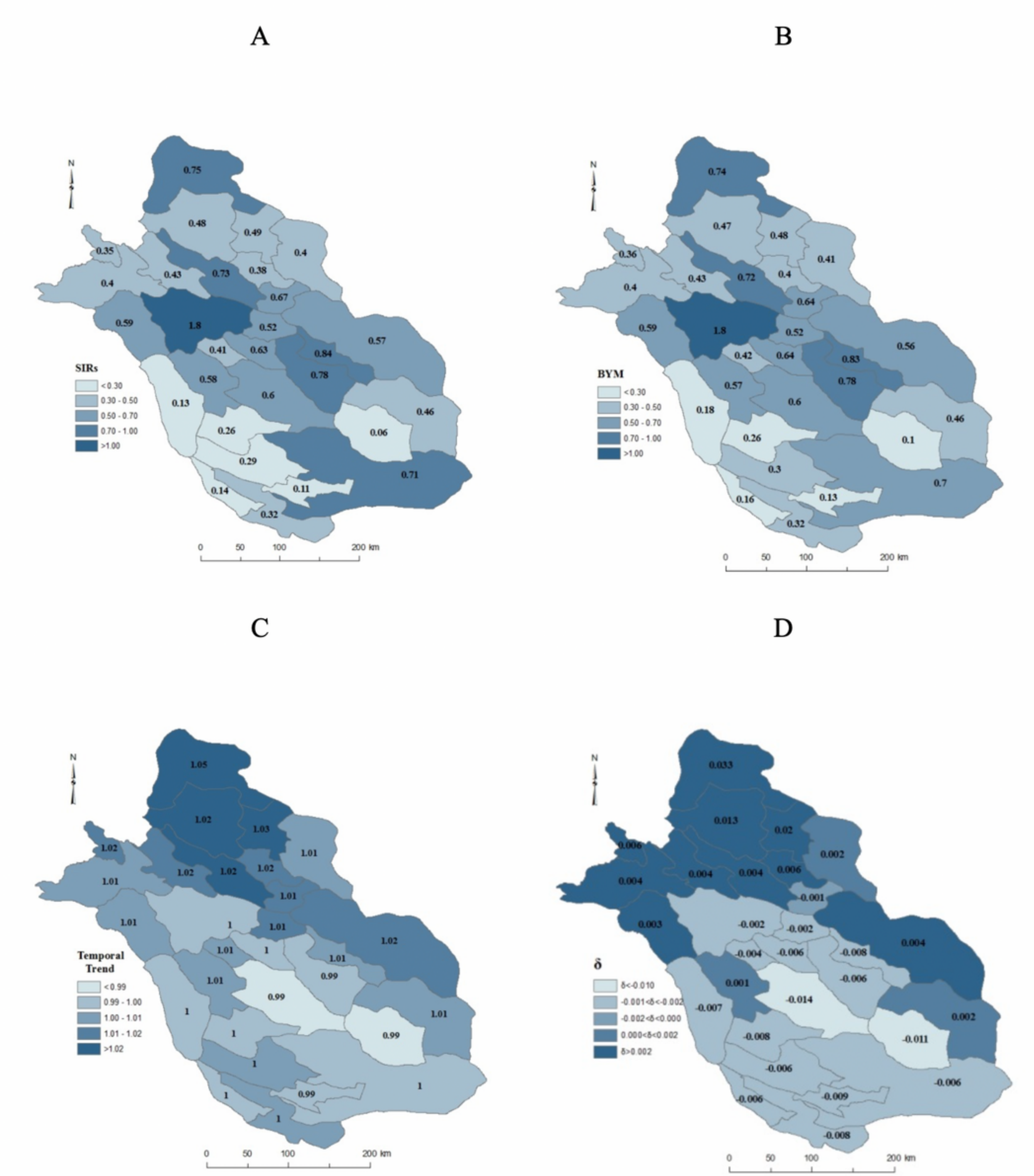

Figure 2

MS incidence rate across the 29 counties of Fars province with classic SIR (A), BYM model (B) spatiotemporal model (C), and posterior estimate value of δ_i (D) (created using ArcGIS Desktop: Release 10.1, https://www.esri.com/en-us/arcgis/about-arcgis/overview)