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Hospital and healthcare insurance system record–based epidemiological study of myasthenia gravis in southern and northern China

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Abstract

Objective This is the first cross-region epidemiological study of myasthenia gravis (MG) in China. We estimated the incidence, prevalence, and medical costs of MG in southern China and explored the differences between the southern and northern Chinese populations.

Methods We collected and analyzed records from 20 hospitals in the southern city, Guangzhou, 13 hospitals in the northern city, Harbin, and two healthcare insurance systems: job based and residence based in Guangzhou during 2000–2017.

Results (1) The estimated annual incidence of MG was 1.55–3.66 per 100,000, and the estimated prevalence of MG was 2.19–11.07 per 100,000 in southern China based on insurance records. (2) The proportion of hospitalized MG patients in the south-based hospital records was three times as high as that in the north-based hospital records. (3) Female MG prevalence was significantly higher than male MG prevalence in Guangzhou, while the similar gender difference in Harbin was not statistically significant due to higher variation in earlier years. (4) The average expense was $35–42 for each outpatient service and $2526–2673 for each hospitalization expense in the south. (5) Contrary to the increase of insurance-based estimate of MG prevalence, the proportion of hospitalized MG patients did not increase over the years, suggesting rising awareness and utilization of health insurance.

Conclusions The southern MG population had a significantly higher prevalence and a lower response threshold to medication than the northern MG population. These results are calling for further investigations on the genetic, cultural, and environmental variations of the Chinese MG populations between north and south.

Keywords Myasthenia gravis · Epidemiology · Southern and northern Chinese population · Hospital records · Health insurance systems · Medical costs

Wei Fang and Yan Li contributed equally to this work.

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Introduction

Myasthenia gravis (MG) is a rare autoimmune disorder caused by an antibody-mediated attack against acetylcholine receptors (AChR) or muscle-specific kinases at neuromuscular junctions [1, 2]. The disease is characterized by fluctuating and fatigable weakness of skeletal muscles and the severity varies from mild ocular symptoms to generalized weakness with bulbar symptoms and respiratory insufficiency [3]. This disease carries a large public and personal health burden due to chronic muscle weakness and fatigue, which leads to high healthcare costs (including long-term treatment and periodic hospitalizations) and indirect costs such as income loss and reduced caregiver productivity [4]. A recent study reported a mean annual cost of $15,675 per MG patient in the US [5]. It is crucial to estimate the incidence and prevalence of MG and compare differences in disease risks among populations from different geographic locations with different genetics and environmental conditions, and social-economic background to deepen our understanding of this rare disease.

Previous epidemiology studies showed that estimated incidence and prevalence rates were highly heterogeneous [6, 7]. For example, studies carried out in Italy, Portugal, Hungary, and Norway reported a prevalence of 240, 111.7, 17.42, and 131 patients per million population, respectively [8–11]. Two population-based epidemiological studies of MG in Korea showed a prevalence of 9.67–10.42 per 100,000 people in 2010 and a steady increase every year to 12.99 per 100,000 in 2014 [12, 13]. A recent systematic review on population-based epidemiological studies showed the range of MG prevalence being 15–179 per million, and the incidence is 1.7–21.3 per million person-years [7]. It is unclear whether this wide range of prevalence and incidence is caused by methodological differences or true differences in disease frequencies based on ethnicity or geographical distribution [14, 15]. Meanwhile, an increasing prevalence with relatively stable incidence has been frequently suggested [7, 15–22]. Advances in therapy with enhanced survival, an aging population as well as improved diagnostic methods might have contributed to the increase [7, 16].

Population-based epidemiological study on rare diseases like MG is costly and often not feasible. China has the largest population in the world with a wide geographical distribution, diverse ethnical background, and environmental conditions, which makes it even more challenging. To fill the gap, we conducted our research at two representative cities: Guangzhou of southern China and Harbin of northern China. The objectives were first to estimate the incidence and prevalence of MG in southern China, and then to compare the epidemiology trend of MG patients between southern and northern China.

Material and methods

Study design

Guangzhou is the capital city of Guangdong—the most southern province of the mainland, with an area of 7,436 km^2 and an estimated 13 million residents. Harbin is the capital city of Heilongjiang—the most northern province of the mainland, with an area of 53,100 km^2 and an estimated 10 million residents according to the 2015 national census (Fig. 1, drawn in ArcGIS 10.0 based on the population density distribution of the Chinese population [23].)

There are two components in the study: (1) prevalence and incidence estimates of MG patients in southern China based on two healthcare insurance systems in Guangzhou and (2) a south-north comparison of epidemiology trends using hospital records.

Healthcare insurance records in Guangzhou

In Guangzhou, over 95% of the population had either job-based insurance (JBI) or residence-based insurance (RBI) which cover physician visits, hospitalizations, and surgical procedures. All available records of patients (2002–2014) with a confirmed diagnosis of acquired autoimmune MG were included.

Hospital records in Guangzhou and Harbin

In China, most hospitals are state-owned public hospitals. Patients with suspected MG are usually referred to a third-grade class A (3A) hospitals (the highest level according to the Chinese ranking system) for final diagnosis and follow-ups with paraclinical tests including antibody test, repetitive nerve stimulation, and single-fiber electromyogram. In this study, records of 20 hospitals in Guangzhou and 18 hospitals in Harbin, all of which were 3A hospitals, were collected and analyzed. The names of all participating hospitals, their locations, and data providers were listed in Supplementary Table 1.

Two of the 20 hospitals in Guangzhou had specialized MG clinics that had attracted large numbers of secondary and tertiary referrals from other hospitals and from neighboring provinces. Their MG patients came from as north as Henan Province, as west as Sichuan and Yunnan Province, and as south as Hainan Province and other parts of Asia such as Indonesia and Burma. Their data were listed in tables and graphs, but not included in the final statistic comparison of hospitalized MG patients between southern and northern hospitals. MG patients of hospitals in Harbin mostly came from the following four provinces: Heilongjiang, Jilin, Liaoning, and Inner Mongolia. Five out of the 18 hospitals in Harbin did not provide their annual numbers of all hospitalized patients, therefore were excluded from our analyses and presentation.

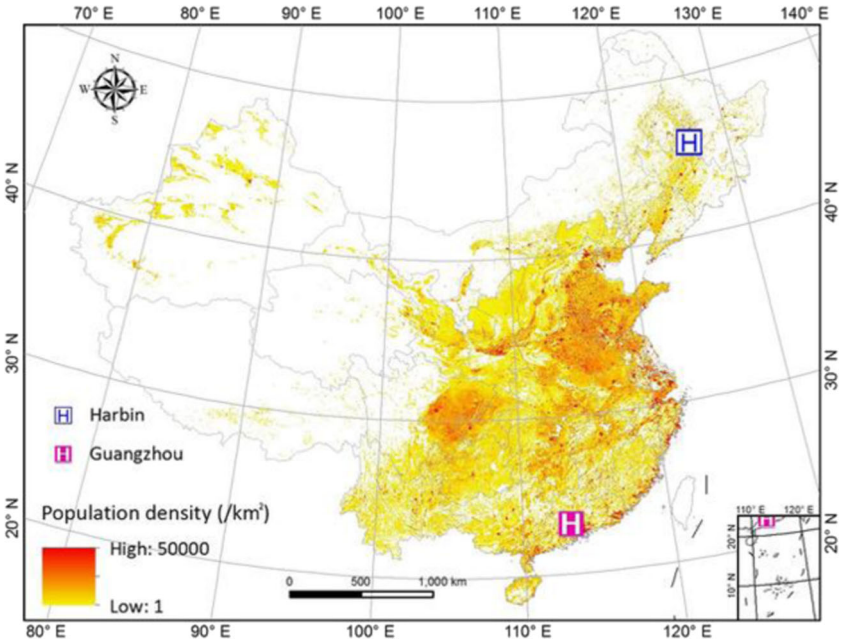

Fig. 1 Population density distribution of the Chinese population. Redrawn in ArcGIS 10.0 based on published data [23]. There were 20 major hospitals in Guangzhou and 13 major hospitals in Harbin included in this study. MG patients in Guangzhou came from the southeast part of China, as north as Henan Province, as west as Sichuan and Yunnan Province, and as south as Hainan Province and other parts of Asia such as Indonesia and Burma. MG patients in Harbin came from the northeast part of China, mostly from four provinces: Heilongjiang, Jilin, Liaoning, and Inner Mongolia

Identification of MG patients

Myasthenia gravis is a rare autoimmune neurological disorder (the ranking of MG in the overall spectrum of the diseases requiring hospitalization was provided by the Statistics and Data Information Center of the First Affiliated Hospital of Sun Yat-sen University in Supplementary Table 2). The majority of the suspected MG patients in China are referred to 3A hospitals that have neurologists for final diagnosis and follow-ups with paraclinical tests including antibody test, repetitive nerve stimulation, and single-fiber electromyogram. The diagnostic criteria of MG in China are consistent with the international standards as follows: (1) typical clinical features of muscle weakness that worsen after repeated activities and improve with rest; (2) positive response to acetylcholinesterase inhibitors; and (3) one or more of the following: (a) decrements of 10% on repetitive nerve stimulation, (b) increased jitter on single-fiber electromyography and (c) positive AChR antibody assay (RSR Ltd., Cardiff, UK). All the MG patients included in the study met the unified and standard diagnostic criteria of MG and have ICD codes [24, 25].

Based on our SYSU Clinical Study 5010 project (2010003), over the period of 2011–2019, the Department of Neurology MG Clinic of the 1st affiliated hospital of Sun Yat-sen University enrolled a total of 207 MG patients for the study and 2 patients with ICD codes were proven falsely diagnosed (in preparation). Therefore, 99.03% of the diagnoses of MG were validated.

Two complementary approaches were used to identify MG patients: (1) a discharge abstract database of the participating hospitals containing diagnostic codes of MG based on the International Classification of Diseases (ICD), i.e., ICD-9 for year 2002 and before (coded as 3580, 35800, or 35801) and ICD-10 after 2002 (coded as G700, G701, or G702). (2) A computerized database of 2 healthcare insurance systems (JBI and RBI) in Guangzhou with the same code for MG. The criteria for inclusion in the MG patient cohort included (1) hospital discharge abstract with MG listed as a primary or secondary diagnosis, (2) three outpatient MG visits within 1 year, or (3) five pyridostigmine prescriptions within 1 year.

It is possible that our assessment of MG prevalence and incidence rates of the southern Chinese population using insurance records could be underestimating the actual rates, as our sample may be biased towards a more severe disease course. In addition, since we do not have accurate information about the population base for hospital MG patients, we can only use the total number of all hospitalized patients as a common denominator to conduct the south-north comparison, denoted as "proportion of hospitalized MG patients." Nevertheless, we were able to obtain several epidemiological parameters of MG, including gender ratio and temporal trend of clinic visits and hospitalizations for this disease over the period of 2000–2017 or as long as the records were available.

Data analyses and presentation

Using insurance records in Guangzhou, prevalence rates were calculated as the ratio of the total number of MG outpatients over the total number of people insured of that year. For incidence, we first established the time (year) of a new MG patient was first diagnosed and treated (either as an outpatient or as an inpatient), then calculated the ratio of the total number of new MG patients over the total number of people insured of that year. *t* tests and pair-wise *t* tests were used to contrast between

insurance types, between genders, and between north and south. Linear regressions were conducted on trends over the years. All statistical analyses were conducted using SPSS version 20.0 for Windows (SPSS Inc., USA).

Ethics approval

Ethics approval was obtained from the ethics committees of the participating hospitals to collect data from all patients. Informed consent was obtained from all patients to access their data whenever applicable.

Results

Estimated prevalence and incidence of MG in southern China

A total of 3328 and 379 MG cases were identified during the study period from JBI and RBI, respectively. This outpatient prevalence can be used to infer the likely range of the population prevalence of MG. Not every patient with MG was hospitalized, thus the overall population prevalence might be even higher.

The estimated annual incidences of MG were 3.66 ± 2.70 and 1.55 ± 0.53 per 100,000, and the estimated prevalence was 11.07 ± 3.67 and 2.19 ± 0.95 per 100,000, based on JBI and RBI respectively (Table 1). Both estimates were much higher for MG patients with JBI than those with RBI ($p < 0.001$).

Comparison between southern and northern Chinese MG populations

The proportion of hospitalized MG patients in the southern Chinese population (66.24 ± 88.64 per 100,000 for all 20 hospitals, or 40.69 ± 27.33 per 100,000 excluding the top two hospitals due to their high likelihood of secondary and tertiary referrals of MG patients) was significantly higher than in the northern population (13.29 ± 8.25 per 100,000) ($p < 0.001$ for the conservative comparison, Figs. 2 and 3b).

Seeing there was a wide range of variations among hospitals, we conducted a second south-north comparison by pooling all hospital records each year to form an overall annual database for the studied regions (Table 2). The proportion of hospitalized MG patients in the south (79.31 ± 8.56 per 100,000 for 2000–2014) was significantly higher than in the northern population (20.11 ± 9.05 per 100,000 for 2002–2017, or 15.77 ± 2.53 per 100,000 for 2006–2017 if we excluded the first 4 years due to their small sample sizes) ($p < 0.001$).

Differential prevalence and incidence of MG patients between men and women

Both from the insurance records in Guangzhou, and hospital records in both south and north, we found significantly more female MG patients than male patients in China (Fig. 3, Tables 1 and 2).

Female MG prevalence in Guangzhou was significantly higher than male ($p = 0.044$), and more so for JBI (4.44 ± 1.59 for male vs 6.65 ± 2.08 for female per 100,000) than for RBI (1.03 ± 0.48 for male vs 1.16 ± 0.48 for female per 100,000) ($p = 0.053$ for gender*insurance type interaction) (Table 1 and Fig. 3a).

Proportion of female MG inpatients was significantly higher than male when we analyzed the data at the regional scale by pooling all hospital records per year (34.85 ± 4.54 for male vs 44.43 ± 5.41 for female per 100,000 for the south, and 8.98 ± 5.88 for male vs 10.85 ± 4.03 for female per 100,000 for the north) (Table 2, Fig. 3b). If the data from all hospitals remained separate, the significant gender difference was only found in the southern population (17.89 ± 13.44 for male vs 22.79 ± 14.49 for female per 100,000, $p < 0.05$), not for the northern population ($0.05 < p < 0.10$) due to wide variations in earlier years. In fact, after removing the first 4 years, *t* test was highly significantly (6.31 ± 1.57 for male vs 9.08 ± 1.74 for female per 100, 000, $p < 0.001$) (Table 2).

Temporal trend of the epidemiology of MG patients in China

The estimated prevalence (4.78 to 14.37/100,000 for JBI, and 1.08 to 3.68/100,000 for RBI) increased steadily over the years (2002–2014) (Fig. 4a, b). Closer observation indicates JBI-based estimates had a significant jump (increase) after 2009 (2009–2012) compared with years before 2008, and then leveled off after 2012. Such an abrupt increase may indicate a policy-related change instead of a real increase in the disease risk.

Meanwhile, the annual proportion of hospitalized MG patients did not increase over the years in the south (2000–2014) and even decreased in the north (2002–2017) partly due to the first 4 years with low sample sizes (Fig. 4c). This indicates that the temporal increase of estimated incidence and prevalence was only an artifact of the increased awareness and usage of health insurance, not due to an actual increase in disease risk.

Medical costs of MG patients between two healthcare systems in southern China

The 3328 patients with JBI utilized 16,589 outpatient services and 802 patients utilized 1148 inpatient services. The average expense was $170.98 for each outpatient, $35.03 for each clinic visit and $3539.27 for each inpatient, $2525.88 for each hospitalization, respectively (all calculations used the RMB: USD exchange rate of 0.14). The 379 patients with RBI

Table 1 The estimated annual incidence and the estimated prevalence of MG per 100,000 based on JBI and RBI respectively

Year	Total number of insured	Number of MG outpatients		Estimated prevalence (/100,000)				Number of new MG outpatients	Estimated incidence (/100,000)
		T	M	F	T	M	F	T	T
Job-based insurance									
2002	1,019,697	--	--	--	--	--	--	NA	NA
2003	1,581,373	--	--	--	--	--	--	27	1.71
2004	1,904,536	--	--	--	--	--	--	17	0.89
2005	2,085,840	--	--	--	--	--	--	30	1.44
2006	3,072,698	--	--	--	--	--	--	25	0.81
2007	3,325,624	--	--	--	--	--	--	42	1.26
2008	3,666,357	--	--	--	--	--	--	38	1.04
2009	3,826,813	183	68	116	4.78	1.78	3.03	167	4.36
2010	4,273,645	378	147	234	8.84	3.44	5.48	241	5.64
2011	4,662,753	530	207	323	11.37	4.44	6.93	338	7.25
2012	5,078,604	683	273	410	13.45	5.38	8.07	375	7.38
2013	5,382,826	732	312	420	13.60	5.8	7.8	311	5.78
2014	5,720,692	822	331	491	14.37	5.79	8.58	364	6.36
Average	4,824,222	555	223	332	11.07	4.44	6.65	299	3.66
Stdev	707,734	241	102	138	3.67	1.59	2.08	81	2.70
Residence-based insurance									
2008	831,684	9	4	5	1.08	0.48	0.6	NA	NA
2009	2,253,505	40	20	20	1.78	0.89	0.89	49	2.17
2010	2,510,022	31	14	17	1.24	0.56	0.68	17	0.68
2011	2,585,729	53	23	30	2.05	0.89	1.16	36	1.39
2012	2,673,576	63	29	34	2.36	1.08	1.27	37	1.38
2013	2,656,104	83	40	43	3.12	1.51	1.62	50	1.88
2014	2,716,767	100	49	51	3.68	1.8	1.88	49	1.80
Average	2,318,198	54	26	29	2.19	1.03	1.16	40	1.55
Stdev	673,500	31	15	16	0.95	0.48	0.48	12.77	0.53

T, total number of MG patients; *M*, male MG patients; *F*, female MG patients

utilized 1892 outpatient services and 93 patients utilized 144 inpatient services. On average, each MG outpatient and inpatient with RBI utilized $209.34 and $4224.08 per year. The average expense was $42.12 for each clinic service and $2672.65 for each hospitalization. The detailed annual expenses and numbers of outpatient visits and hospitalizations are listed in Table 3. The medical expenses only represented MG-related direct costs. Indirect costs, such as time lost from work or disability, were not included.

Discussion

Overall trend and uncertainty of the epidemiological estimates

The estimated prevalence rates in our study were consistent with those of previous studies (15–179 per 100000 people [6, 7, 26]), while estimated incidence rate seemed slightly higher than prior estimated pooled incidence rates (0.17–2.13 per 100,000 person-years [7], or 0.3–3.0 per 100,000 person-years [15]). These marked variations could be attributed to a number of factors: the heterogeneity of populations in terms of ethnicity and geographical region, different methodologies employed by the studies and particularly regarding the ascertainment of MG cases, as cases with minor symptoms, might have been missed in some studies [7, 16, 19]. In addition, we also noticed that the other studies typically used the whole population as the denominator for their calculation of epidemiologic measures, but our study only focused on insured people which was about 95% of the population, this comparison is slightly biased. Further, we analyzed the temporal trends of MG outpatient incidence and prevalence rates. The MG outpatient incidence and prevalence rates in our population tended to significantly increase during the study period. Other studies reported a similar increase of MG prevalence, particularly amongst older patients, over the years [27–29], which might be attributed to the aging of the population,

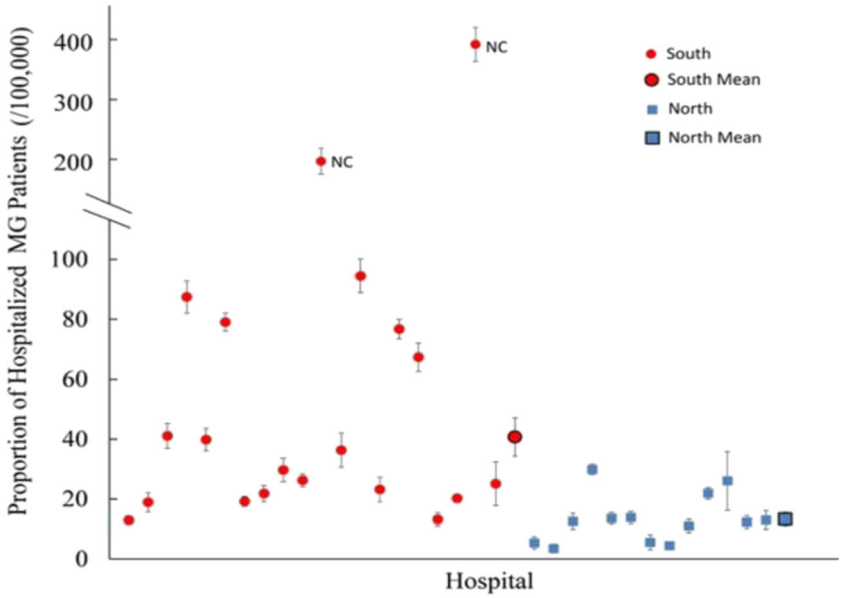

Fig. 2 Proportions of hospitalized MG patients in 20 hospitals in Guangzhou (red circles representing mean ± 1SE over years for each southern hospital) and 13 hospitals in Harbin (blue squares representing mean ± 1SE over years for each northern hospital). Overall average proportion of hospitalized MG patients in south (red circle with black border, 40.69 ± 6.44 per 100,000, mean ± 1SE) was calculated without including two hospitals (NC: not included) that frequently received secondary and tertiary referrals of MG patients from other hospitals and provinces. Overall average proportion of hospitalized MG patients in north (blue square with black border, 13.29 ± 2.29 per 100,000, mean ± 1SE) was calculated over all 13 northern hospitals

improved diagnostic techniques, enhanced awareness of the disease, as well as more complete case-ascertainment [30]. However, our hospital records did not show a similar increase over time for the proportion of hospitalized MG patients. Therefore, it is possible that, either the increase of MG prevalence mostly happened among outpatients, or the increase of MG prevalence was an artifact of patients' awareness and utilization of healthcare insurance.

Over the years, more people got health insurance due to the following three incentives: First, healthcare benefits improved

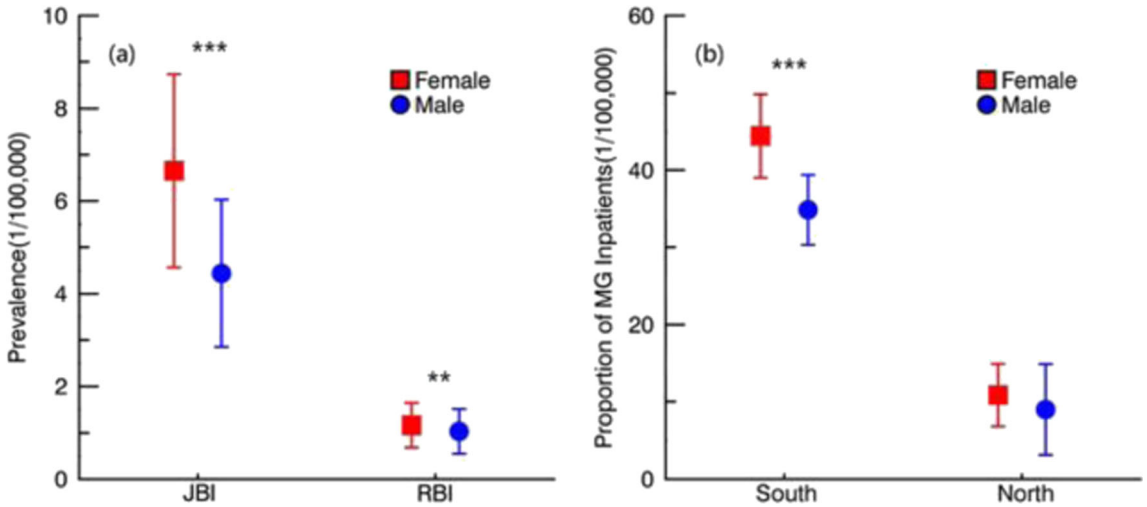

Fig. 3 Gender difference in both insurance-based prevalence estimates (**a**) and hospital-based estimates of the proportion of MG inpatients (**b**). **a** Box plot of estimated prevalence (/100,000) based on two insurance systems in Guangzhou (JBI, job-based insurance; RBI, residence-based insurance) separated with genders. **b** Box plot of the proportion of hospitalized MG inpatients (/100,000) based on hospital records (south: 20 hospitals in Guangzhou; north: 13 hospitals in Harbin) separated with genders. For each box, the asterisk inside the box is the mean and the lines from the bottom to the top are minimum, first quartile, medium, third quartile, and maximum, respectively. A two-factor ANOVA (analysis of variance) showed that JBI prevalence (11.07 ± 3.67 per 100,000) was significantly higher than RBI prevalence (2.19 ± 0.95 per 100,000) ($p < 0.001$), there was a higher MG prevalence in female than in males (6.65 ± 2.08 vs 4.44 ± 1.59 per 100,000 for JBI and 1.16 ± 0.48 vs 1.03 ± 0.48 per 100,000 for RBI) ($p = 0.044$), and the gender difference is more so in JBI than in RBI ($p = 0.053$). Two pairwise t tests on gender effects were conducted independently on JBI data (***$p < 0.001$) and RBI data (**$0.001 < p < 0.01$)

Table 2 Comparison between hospitalized MG patients in southern and northern China

	Year	Number of hospitals	Total number of MG inpatients	Total number of male MG inpatients	Total number of female MG inpatients	Total number of all inpatients	Proportion of hospitalized MG/100,000	Proportion of hospitalized male MG/100,000	Proportion of hospitalized female MG/100,000
North	2002	1	20	12	8	45,267	44.18	26.51	17.67
	2003	2	17	6	11	54,025	31.47	11.11	20.36
	2004	3	23	12	11	65,825	34.94	18.23	16.71
	2005	4	31	17	14	141,413	21.92	12.02	9.90
	2006	7	26	8	18	175,295	14.83	4.56	10.27
	2007	7	32	12	20	200,811	15.94	5.98	9.96
	2008	9	41	16	23	253,682	16.16	6.31	9.07
	2009	10	50	18	29	333,527	14.99	5.40	8.69
	2010	13	73	24	48	383,568	19.03	6.26	12.51
	2010	13	72	33	38	433,563	16.61	7.61	8.76
	2012	17	65	27	35	642,596	10.12	4.20	5.45
	2013	18	156	60	91	829,088	18.82	7.24	10.98
	2014	18	153	62	79	930,561	16.44	6.66	8.49
	2015	13	127	69	58	689,405	18.42	10.01	8.41
	2016	13	112	50	62	749,736	14.94	6.67	8.27
	2017	13	101	38	63	777,341	12.99	4.89	8.10
Mean ± 1SD	2002–2017						20.11 ± 9.05	8.98 ± 5.88	10.85 ± 4.03
Mean ± 1SD	2006–2017						15.77 ± 2.53	6.31 ± 1.57	9.08 ± 1.74
South	2000	9	131	59	72	190,641	68.72	30.95	37.77
	2001	9	162	61	101	210,371	77.01	29.00	48.01
	2002	9	173	73	100	224,474	77.07	32.52	44.55
	2003	13	240	106	134	294,809	81.41	35.96	45.45
	2004	17	284	142	142	409,053	69.43	34.71	34.71
	2005	18	343	168	175	453,766	75.59	37.02	38.57
	2006	18	414	198	216	489,093	84.65	40.48	44.16
	2007	20	467	213	254	556,356	83.94	38.28	45.65
	2008	21	655	300	352	660,557	99.16	45.42	53.29
	2009	21	656	274	382	700,454	93.65	39.12	54.54
	2010	21	667	270	397	811,949	82.15	33.25	48.89
	2011	21	637	269	368	904,745	70.41	29.73	40.67
	2012	21	749	320	429	1,019,452	73.47	31.39	42.08
	2013	21	857	371	486	1,108,601	77.30	33.47	43.84
	2014	20	895	371	524	1,182,192	75.71	31.38	44.32
Mean ± 1SD	2000–2017						79.31 ± 8.56	34.85 ± 4.54	44.43 ± 5.41

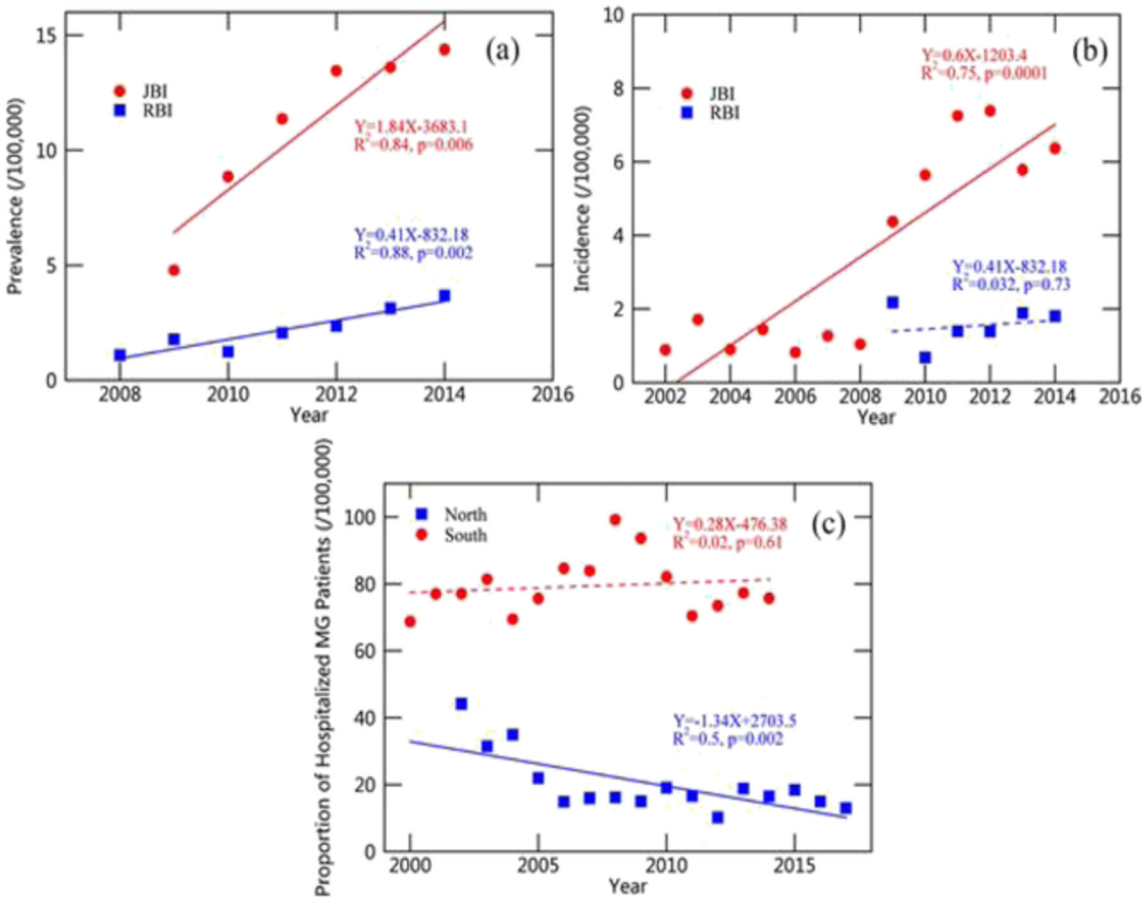

Fig. 4 Temporal fluctuations of estimated prevalence (**a**) and incidence (**b**) based on insurance records in Guangzhou (JBI, job-based insurance; RBI, residence-based insurance), and proportion of hospitalized MG inpatients (**c**) based on hospital records (south: 20 hospitals in Guangzhou; north: 13 hospitals in Harbin) over the study period (2000–2017). Solid lines indicate the regression over time being statistically significant ($p < 0.05$), while dashed lines had a $p \geq 0.0$

drastically in terms of cost coverage for hospitalization and the number of diseases covered for clinic visits (Tables 4 and 5). Second, increasing effort of healthcare outreach resulted in an increasing level of public awareness of insurance coverage. Third, besides JBI and RBI, there was a third type of insurance (NRI-New Rural Cooperative Medical Insurance) for anyone else with minimum premium (about $20/year) and 50% coverage for hospitalization cost. One can imagine that such healthcare policy had contributed to an overall 95% healthcare coverage in Guangzhou. Starting 2015, NRI in Guangzhou merged with RBI, enjoying the improved benefits mentioned in Tables 4 and 5. In 2018, NRI in Harbin merged with RBI.

Gender differences

In addition to finding an increase in the MG outpatient incidence and prevalence during the study period, our study also showed a female predominance distribution, which is noted by other researchers [12]. Based on previously published epidemiology studies in China and this current one, all except one study showed that there are more female MG patients than male MG patients (between 12 and 49% higher) from the south to the north, with no consistent latitudinal trend [31–33] (Table 6). The female predominance has been thought to represent certain effects of sex hormones in autoimmune diseases [34]. A previous animal model study showed that estrogen enhances susceptibility to experimental autoimmune MG through the action on acetylcholine receptor-specific T and B cell responses [35]. Fluctuations in disease activity during pregnancy or menstrual periods also suggest the possible effects of sex hormones on MG [36, 37].

Insurance preferences

Another interesting observation in the current study is higher proportions of MG patients (both outpatients and inpatients) with JBI used their insurance than patients with RBI. An explanation for this phenomenon might be that MG patients with JBI receive better education, higher income, and better medical benefits than those with RBI, and therefore they have more incentives to see doctors.

Table 3 Detailed annual expenses and numbers of outpatient visits and hospitalizations

Year	Total number of insured	Total number of MG outpatients	Total number of MG clinic visits	Total cost of MG outpatients (USD)	Average cost (USD)/MG outpatient	Average Cost (USD) /MG Clinic Visit	Total Number of MG Inpatients	Total Number of MG Hospitalization	Total Cost of MG Inpatients (USD)	Average Cost (USD)/MG Inpatient	Average Cost (USD)/MG Hospitalization
Job-based insurance											
2002	1,019,697	NA	NA	NA	NA	NA	9	10	10,887.70	1209.74	1088.77
2003	1,581,373	NA	NA	NA	NA	NA	27	30	52,523.09	1945.30	1750.77
2004	1,904,536	NA	NA	NA	NA	NA	18	24	65,013.32	3611.85	2708.89
2005	2,085,840	NA	NA	NA	NA	NA	37	44	94,305.25	2548.79	2143.30
2006	3,072,698	NA	NA	NA	NA	NA	32	38	84,305.81	2634.56	2218.57
2007	3,325,624	NA	NA	NA	NA	NA	53	69	132,819.02	2506.02	1924.91
2008	3,666,357	NA	NA	NA	NA	NA	58	85	250,804.72	4324.22	2950.64
2009	3,826,813	183	651	15,914.06	86.96	24.45	63	120	366,185.25	5812.46	3051.54
2010	4,273,645	378	1943	55,626.88	147.16	28.63	63	82	239,760.96	3805.73	2923.91
2011	4,662,753	530	2574	98,168.95	185.22	38.14	90	132	400,675.23	4451.95	3035.42
2012	5,078,604	683	3250	124,916.96	182.89	38.44	133	197	576,040.15	4331.13	2924.06
2013	5,382,826	732	3922	152,014.12	207.67	38.76	99	141	468,379.98	4731.11	3321.84
2014	5,720,692	822	4249	177,520.95	215.96	41.78	120	176	491,719.19	4097.66	2793.86
Average	4,824,222	555	2765	104,026.99	170.98	35.03	62	88	248,724.59	3539.27	2525.88
Stdev	707,734	241	1338	60,467.01	47.63	6.84	39	60	192,467.58	1287.33	648.09
Residence-based insurance											
2008	831,684	9	23	585.91	65.10	25.47	4	5	5,529.77	1,382.44	1,105.95
2009	2,253,505	40	202	7,365.81	184.15	36.46	11	20	61,757.85	5,614.35	3,087.89
2010	2,510,022	31	209	8,467.16	273.13	40.51	9	15	89,668.23	9,963.14	5,977.88
2011	2,585,729	53	261	12,625.45	238.22	48.37	12	17	25,537.07	2,128.09	1,502.18
2012	2,673,576	63	294	13,952.15	221.46	47.46	14	24	40,673.42	2,905.24	1,694.73
2013	2,656,104	83	504	23,746.28	286.10	47.12	14	19	62,504.36	4,464.60	3,289.70
2014	2,716,767	100	399	19,722.42	197.22	49.43	29	44	90,209.90	3,110.69	2,050.22
Average	2,318,198	54	270	12,352.17	209.34	42.12	13	21	53,697.23	4,224.08	2,672.65
Stdev	673,500	31	154	7,801.53	73.63	8.73	8	12	31,760.42	2,897.54	1,665.63

Table 4 Benefits of residence-based healthcare insurance

Year	Premium/year	Maximum cost coverage for hospitalization
2010	$67.20	$19,040.00
2015	$21.28	$26,013.12
2019	$51.24	$33,131.28

Due to their differential economic development conditions, patients in Guangzhou enjoyed significantly better healthcare benefits (Table 7), which may have partially contributed to a higher flood of MG patients, especially in recent years.

Several methodological issues should be addressed regarding the JBI and RBI database utilized in this study. First, we identified MG cases based on diagnostic coding. Clinical information including AChR antibody titer, results of electrodiagnostic and pharmacological tests were not available in JBI and RBI database. Accordingly, there are concerns regarding diagnostic accuracy. For this reason, we used the information on treatment rather than simply relying on the diagnostic code for case identification. Second, not all patients with MG have access to a hospital, and so patients with mild symptoms might have been missed, thereby leading to the incidence and prevalence rates being underestimated. Third, the MG cohort can only capture those patients who access health care resources, and cannot account for the populations who rarely or never access healthcare.

Medical costs

MG is a chronic autoimmune disease, which carries a large public health burden due to the presence of chronic muscle weakness and fatigability. A US study calculated the mean yearly cost of $15,675 per MG patient [5]. Another recently published study from Taiwan reported a $1333 yearly cost per MG patient [20]. Our results are similar to the second study. Expensive treatments such as IVIG or plasma-exchange are not covered by medical insurance in China, and also rarely used during MG treatment. However, we are not able to tell to what extent our cost estimate is biased due to the non-coverage of expensive treatments by insurances.

Geographical differences

Most strikingly, we found the proportion of hospitalized MG patients in the south was three times as high as that in the north, indicating a much higher disease risk. Meanwhile, we found MG patients in the north, in general, were treated with a higher dosage of prednisone and other immunosuppressive agents with little side effects, which would have caused a wide range of side effects among MG patients in the south given the same high dosage (personal observations, detailed study is ongoing). A few possible contributing factors might have contributed to this north-south disparity: (1) Genetic: There are proven north-south genetic differences (e.g., HLA alleles) that have different affinities for peptides from antigens [38], or epigenetic changes induced by environmental factors [39]. We conducted a thorough literature search for published studies on genetic polymorphism among Chinese MG patients in Beijing [40], Tianjin [41, 42], Shanghai [43, 44], and Guangzhou [45]. There are significant genetic differences found between northern and southern Han Chinese. (2) Environmental: Higher temperature and humidity in the tropical and subtropical regions foster more pathogen (bacteria and viruses), parasites, and other causes of inflammation, which in turn may trigger more immune responses in the south. The southern diet, especially the Cantonese, covers extremely diverse sources of food items while the northern

Table 5 Benefits of residence-based healthcare insurance

Year	Premium/year	Maximum cost coverage for hospitalization	Number of diseases covered for clinic visits	Reimbursement rate (%)
2017	$25.48	$25,452.00	32	Tier I: 85% Tier II: 70% Tier III: 55%
2018	$27.86	$30,380.00	48	Tier I: 90% Tier II: 80% Tier III: 60%
2019	$51.24	$33,131.28	58	Tier I: 90% Tier II: 80% Tier III: 70%

Table 6 Prevalence of MG in China between men and women

References	Number of male MG patients	Number of female MG patients	M:F ratio	Name of the hospital	Location	Latitude °N
Wang, et al. 2013 [31]	555	553	1:1	The 309th Hospital of PLA	Beijing	39.9042
Zhang, et al. 2007 [32]	173	215	1:1.2	Tongji Hospital	Wuhan	30.5928
Gao, et al. 2016 [33]	220	258	1:1.17	Multiple general hospitals	Henan Province	28.2282
Huang et al. 2013 [25]	1004	1150	1:1.15	The 1st Affiliated Hospital of Sun Yat-sen University	Guangzhou	23.1291
This study	464	608	1:1.31	18 3A hospitals (2002–2017)	Harbin	45.8038
This study	3195	4132	1:1.29	21 3A hospitals (2000–2017)	Guangzhou	23.1291
This study	1338	1994	1:1.49	Job-based insurance (2009–2014)	As above	As above
This study	179	200	1:1.12	Residence insurance (2008-2014)	As above	As above

diet is much more limited and conservative. Some of these factors are predisposing for MG, such as hormones, vitamin D, diet, and microbiota. Other factors are triggering for MG, such as infections, pollutants, and pharmacological molecules [46]. Food products could be modifiers of immune responses or have a direct impact on gut microbiota that triggers or remediate inflammation and autoimmunity. (3) Social/cultural: a different lifestyle in the south may make MG more noticeable. Paddy rice, a main crop in the south with 2–3 harvests a year, requires an extraordinary amount of work to cultivate and maintain with elaborate irrigation systems, while wheat as a main crop in the north requires a fraction of man-hours [47]. More advanced economic development in the south made life even faster-paced. All these social-economical-cultural differences contributed to a much longer working day in the south, which provided less resting time for MG patients to recover and restore muscle functions. Further investigations are much needed to look into the underlying causes for the north-south disparity of MG epidemiology and treatment responses. (4) Healthcare policy change as discussed earlier.

Although detailed demographic information of the MG patients were not available from the insurance companies, since there are over 95% of population covered by healthcare insurances (JBI, RBI, and NRI) across all age groups, starting from infancy, it is safe to say that the demographic profile of insured people is similar to that of the overall population.

Nevertheless, this is the first regional epidemiological study of MG in China. The methodology developed in this study can be readily applied to other parts of China and the world, yielding thought-provoking patterns and questions. Further investigations on the impact of genetic, environmental, and cultural factors on the diagnosis and effective treatment of MG are much needed.

Conclusions

The estimated prevalence and incidence of MG in southern China were consistent with prior studies from other parts of the world, but with wide variations between genders and between types of insurance. Temporal increase of insurance-based estimate of MG prevalence was likely caused by rising awareness and utilization of health insurance, instead of a real change of MG prevalence. The southern MG population had a significantly higher prevalence and a lower response threshold to medication than the northern MG population, which are calling for further investigation on the contributions of genetic and environmental factors between north and south.

Table 7 Healthcare policy comparison between southern and northern China

	Premium/year	Maximum cost coverage for hospitalization	Insurance coverage for hospitalization
South (Guangzhou)	$51	JBI $82,834 RBI $33,131	JBI 80% RBI students and juniors 80% RBI adults 70%
North (Harbin)	$42	JBI $35,000 RBI $11,200	JBI 90% RBI students and juniors 75% RBI adults tier I 55% RBI adults tier II 50%

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Author contributions Weibin Liu and Wei Fang initiated and oversaw the entire project. WB Liu organized all data collections from Guangzhou and supervised and sponsored data collections from Harbin. LH Wang twice organized data collections from Harbin (in 2015 and 2018). W Fang, H Ran, and WB Liu drafted the manuscript. W Fang and Y Li created the database and performed all analyses in multiple revisions. P. Xu contributed to data analyses and presentations. WB Liu and W Fang are the guarantors of the study who take responsibilities for the integrity of data collection, analyses, and presentation. All other authors actively participated in data collection, results discussion, and multiple revisions of the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical approval was obtained from the ethics committees of the participating hospitals to collect data from all patients.

Informed consent Informed consent was obtained from all patients to access their data whenever applicable.

Abbreviations AChR, acetylcholine receptors; ICD, International Classification of Diseases; JBI, job-based insurance; MG, myasthenia gravis; RBI, residence-based insurance

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