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ORIGINAL ARTICLE

Recorded diagnosis-based incidence and point prevalence of multiple sclerosis in Azerbaijan between 2013 and 2022: Estimates from a national referral center registry

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ABSTRACT

Objectives: The study aimed to estimate the diagnosis-based incidence of multiple sclerosis (MS) in Azerbaijan between 2013 and 2022 and the recorded point prevalence as of December 31, 2022, using data from the centralized registry of the national referral center and to evaluate differences according to age, sex, and place of residence.

Patients and methods: This registry-based observational study included residents of Azerbaijan who were assessed for suspected MS or reconfirmation of a previous diagnosis between January 1, 2013, and December 31, 2022. Diagnosis or reconfirmation was based on the national clinical protocol aligned with the 2010 and 2017 McDonald criteria. Newly diagnosed patients were included in the recorded diagnosis-based incidence analyses, whereas surviving patients with confirmed or reconfirmed MS on December 31, 2022, were included in the recorded point prevalence analyses. Crude, age-specific, and age-standardized rates were calculated using official population denominators and the world and European standard populations.

Results: Among 2,006 assessed individuals, MS was confirmed or reconfirmed in 1,796 patients; 1,411 (mean age: 34.47 years; range, 15 to 66 years) were newly diagnosed, and 1,753 (mean age: 41.53 years; range, 18 to 73 years) were alive on December 31, 2022. Females accounted for 65.7% of confirmed cases, with a female-to-male ratio of 1.92:1, and 66.4% were urban residents. The mean annual crude recorded diagnosis-based incidence was 1.44 per 100,000 person-years. Recorded incidence peaked at 35 to 39 years. World- and European-standardized recorded incidence rates were 1.33 and 1.22 per 100,000 person-years, respectively; corresponding standardized recorded point prevalence rates were 15.47 and 16.50 per 100,000 persons.

Conclusion: These referral center-based recorded estimates indicate a relatively low recorded MS burden in Azerbaijan, with female predominance and higher recorded rates among urban residents. Since the registry was not population-based and incomplete ascertainment may have influenced the estimates, particularly in rural or underserved areas, these findings should be interpreted as a baseline for strengthening MS surveillance and improving equitable diagnostic access.

Keywords: Azerbaijan, incidence, multiple sclerosis, prevalence, registry.

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disease of the central nervous system characterized by demyelination and neuroinflammation.[1] The disease most commonly begins in young adulthood, particularly between 20 and 50 years of age, and occurs more frequently in females than in males.[2] Multiple sclerosis is a major cause of nontraumatic neurological disability in young adults[2,3] and is associated with substantial clinical and economic burden.[3,4] Therefore, reliable epidemiological data are important for estimating disease burden, planning diagnostic and treatment services, and supporting long-term neurological care.

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The epidemiology of MS varies substantially across geographical regions and populations.[5] Differences in incidence, prevalence, clinical course, and phenotype distribution may reflect interactions between genetic susceptibility, environmental exposures, demographic structure, and health system-related factors, including diagnostic access and case ascertainment.[5] Historically, MS has been reported more frequently in northern Europe and North America; however, an increasing number of cases have also been reported in regions previously considered to have a lower disease burden, including parts of the Middle East, Eastern Europe, the Caucasus, and Central Asia.[2,5]

Azerbaijan is located at the intersection of Eastern Europe and Western Asia and includes diverse climatic and geographical zones, ranging from subtropical lowlands along the Caspian Sea to mountainous areas in the north and west.[6] These geographical, demographic, and healthcare-system characteristics make the assessment of MS epidemiology in Azerbaijan important for national service planning and regional comparisons. Previous Azerbaijani studies have reported MS epidemiological patterns in Baku and in selected regions of the country.[7-11] However, these reports were regional or limited to specific administrative areas, and an integrated national analysis of recorded diagnosis-based MS incidence and point prevalence during the State Program period has not been well established. A national referral center-based estimate may provide useful baseline information for registry development, resource allocation, treatment planning, and future epidemiological surveillance.

This study aimed to estimate the diagnosis-based incidence of MS in Azerbaijan between 2013 and 2022 and the recorded point prevalence as of December 31, 2022, and to evaluate differences according to age, sex, and place of residence.

PATIENTS AND METHODS

This national referral center-based, registry-based observational study was conducted at the Neurology Center of the Ministry of Health of the Republic of Azerbaijan between January 1, 2013, and December 31, 2022. The State Program on the Treatment, Prevention, and Control of Multiple Sclerosis was implemented by Order No. 125 of the Ministry of Health of the Republic of Azerbaijan, which approved a national action plan for MS treatment, prevention, and control. According to this action plan, the creation of a unified electronic registry and database of patients with MS, the implementation of clinical protocols for MS diagnosis and treatment, and the provision of necessary medications were organized within the national health system, with the Neurology Center designated among the responsible institutions. Within this framework, patients with suspected or previously diagnosed MS from regional, public, and private healthcare facilities were referred to the Neurology Center for diagnostic verification, expert assessment, registration, and treatment planning. Since access to disease-modifying therapies within the State Program was linked to expert committee assessment and registration through this centralized pathway, this mechanism was intended to provide broad national coverage of patients requiring specialist confirmation and state-supported treatment. The requirement for written informed consent was waived by the Ethics Committee because the study was based on routinely collected clinical and registry data. The study protocol was approved by the Ethics Committee of the Neurology Center of the Ministry of Health of the Republic of Azerbaijan (Date: December 24, 2012, No: 11/2012). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The source population comprised all individuals who were assessed at the Neurology Center for suspected MS or for reconfirmation of a previous MS diagnosis during the study period. Multiple sclerosis was diagnosed or reconfirmed according to the National Clinical Protocol for the Diagnosis and Treatment of Multiple Sclerosis, approved by the Ministry of Health of the Republic of Azerbaijan, based on the 2010 and 2017 revisions of the McDonald diagnostic criteria.[12,13]

Diagnostic assessment was based on clinical history, neurological examination, magnetic resonance imaging (MRI) findings, laboratory investigations when indicated, and review of available medical documentation. Patients were evaluated by specialist neurologists and, where appropriate, by the expert committee responsible for diagnostic verification and treatment planning.

Case ascertainment was based on the centralized referral, diagnostic verification, registration, and treatment-authorization pathway established through the State Program. During the study period, patients with suspected or previously diagnosed MS from regional hospitals, outpatient

clinics, public healthcare facilities, and private healthcare providers were referred to the Neurology Center, which served as the principal national referral facility for MS. Access to state-supported disease-modifying therapies was linked to expert committee assessment and registration at this center. This mechanism was designed to facilitate broad countrywide referral coverage of diagnosed patients requiring specialist confirmation and state-supported treatment. However, the registry was not based on mandatory linkage with all private diagnostic facilities, MRI centers, disability registries, death registries, insurance databases, or nonreferred outpatient cases. Therefore, complete national case ascertainment cannot be assumed, and missed cases outside this pathway remain possible.

No independent population-based MS registry, nationwide insurance-claims database, disability registry linkage, death-registry linkage, or mandatory reporting system was available to estimate the exact proportion of all MS patients captured by the centralized registry. Therefore, the completeness of case ascertainment could not be quantified directly. The registry should be interpreted as capturing patients who entered the centralized referral, diagnostic verification, registration, and treatment-authorization pathway, rather than all persons with MS in the general population.

Patients were eligible for inclusion if they were residents of Azerbaijan during the study period, had complete and consistent clinical documentation, and had a confirmed or reconfirmed diagnosis of MS according to the diagnostic criteria described above.[12,13] Patients were excluded if their documentation was incomplete or inconsistent, required diagnostic investigations were unavailable, the diagnosis was revised to another neurological or non-neurological condition after diagnostic review, or they were not residents of Azerbaijan.

For incidence analyses, patients were included if MS was newly diagnosed and first confirmed at the Neurology Center between January 1, 2013, and December 31, 2022. Incident cases were assigned to the calendar year of first confirmed MS diagnosis, not to the year of first symptom onset. Therefore, incidence estimates in this study represent recorded diagnosis-based incidence rather than biological disease onset incidence.

For recorded diagnosis-based point prevalence analyses, all patients with confirmed or reconfirmed MS who were alive on December 31, 2022, were included. Patients who died during the study period remained included in the incidence analysis for the calendar year in which MS was first confirmed but were not included in the recorded diagnosis-based point prevalence numerator on December 31, 2022. Survival status was determined using registry follow-up information and clinical documentation available at the Neurology Center, including recorded deaths during the study period.

Individuals living abroad or not resident in Azerbaijan were excluded from the analytical dataset. Military personnel and internally displaced persons were not analyzed as separate categories; if they were residents of Azerbaijan and were assessed at the Neurology Center, they were included according to the documented place of residence available in the registry.

The primary outcomes were recorded diagnosis-based annual MS incidence and point prevalence. Recorded diagnosis-based annual incidence was defined as the number of newly diagnosed MS cases first confirmed in a given calendar year per 100,000 person-years. Recorded point prevalence was defined as the number of surviving patients with confirmed or reconfirmed MS per 100,000 persons on December 31, 2022.

The main variables used in the analyses were year of first confirmed diagnosis, age at diagnosis or prevalence date, sex, place of residence, diagnostic status, and survival status. Age was grouped into five-year age categories for age-specific analyses and direct standardization. Place of residence was classified according to official population statistics.

Clinical and diagnostic data were obtained from the records and registry of the Neurology Center. Population denominators stratified by calendar year, age group, sex, and place of residence were obtained from official publications of the State Statistical Committee of the Republic of Azerbaijan.[6]

Age-standardized recorded diagnosis-based incidence and prevalence rates were calculated by direct standardization using the 2000-2025 world standard population and the 2011-2030 European standard population.[14,15] All crude and standardized rates were expressed per 100,000 persons or person-years with 95% confidence intervals (CIs).

Patients were identified using unique clinical records, personal identification information, date

of birth, sex, and place of residence. Duplicate entries were checked and merged when the same individual appeared in the registry more than once. Diagnostic status was updated when subsequent clinical review changed the initial classification, and non-MS cases were removed from the analytical dataset. Data consistency checks were performed for age, sex, place of residence, year of diagnosis, diagnostic status, and survival status before analysis.

The patient selection process, including individuals assessed at the Neurology Center, patients with confirmed or reconfirmed MS, newly diagnosed cases, reconfirmed previous cases, deaths during follow-up, excluded individuals, and surviving prevalent cases as of December 31, 2022, is summarized in Figure 1.

Several measures were used to reduce potential selection and misclassification bias. Case ascertainment was centralized through the Neurology Center, and diagnoses were established or reconfirmed according to the national clinical protocol and McDonald diagnostic criteria.[12,13] Patients with diagnostically insufficient documentation were excluded as described above.

The variables used in the main recorded diagnosis-based incidence and prevalence analyses, including age, sex, place of residence, year of diagnosis, diagnostic status, and survival status, were complete for all included patients. Therefore, all main analyses were performed using complete cases, and no imputation was required.

Despite the centralized referral and treatment-authorization pathway, the study may not have captured all MS cases in Azerbaijan. Missed cases may have included patients diagnosed or followed outside the Neurology Center, patients without access to specialist neurological services

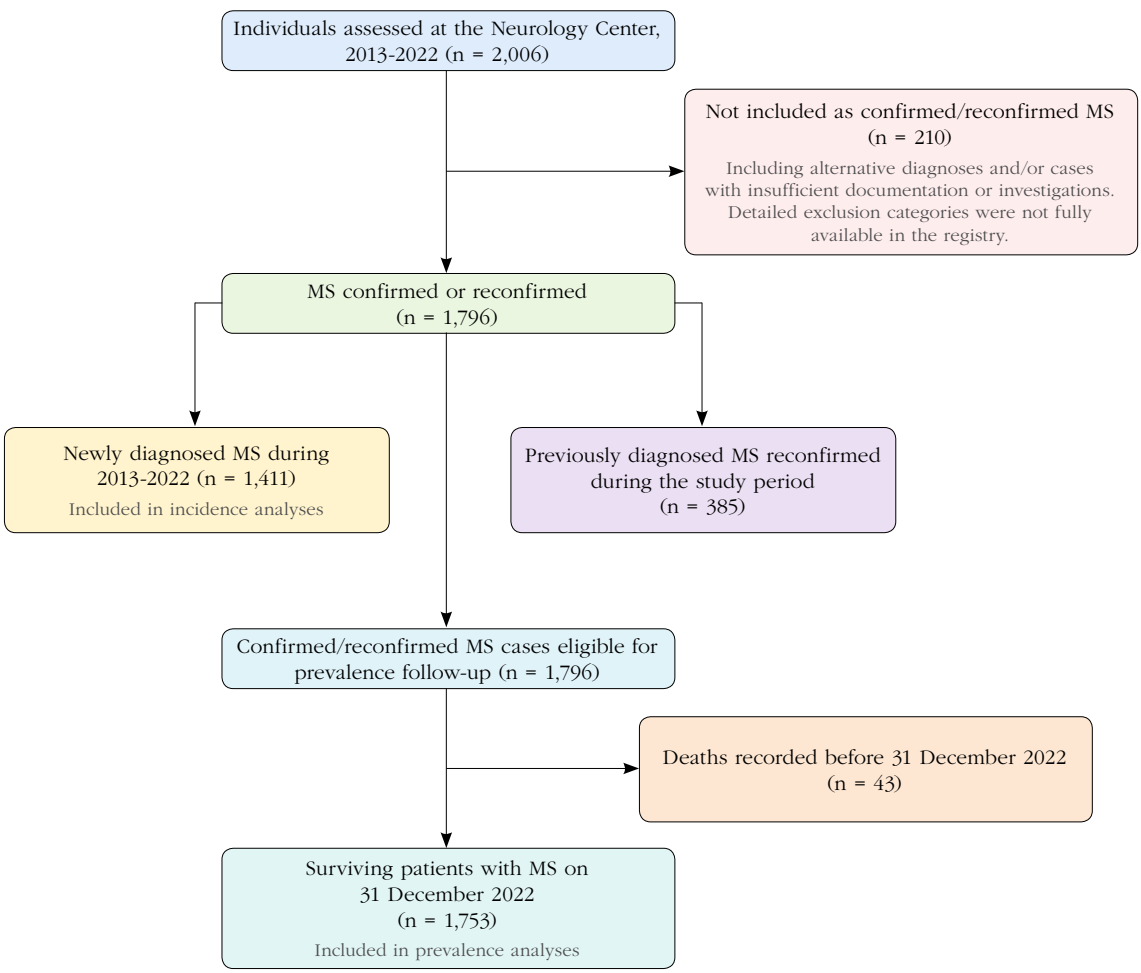

Figure 1. Flow diagram of the study population, case ascertainment, and analytical cohorts.
MS, multiple sclerosis.

or MRI, patients who did not seek state-supported disease-modifying therapies, and nonreferred cases. Therefore, the recorded diagnosis-based incidence and prevalence estimates should be interpreted as national referral center-based estimates and may underestimate the true population burden, particularly in rural or underserved areas.

The year 2020 was included in the primary analyses. Since coronavirus disease 2019 (COVID-19)-related restrictions may have affected access to diagnostic services, hospital attendance, MRI availability, and referral patterns, the possible influence of the pandemic year on recorded diagnosis-based incidence was assessed using sensitivity and segmented analyses. The Poisson trend model was repeated after excluding 2020, and a prespecified COVID-19 year indicator was added to the main Poisson model.

No formal sample size calculation was performed because this was a registry-based observational study. The study size was determined by the number of eligible patients with confirmed or reconfirmed MS who were assessed at the Neurology Center during the 10-year study period.

Statistical analysis

Analyses were performed using IBM SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 2016 software (Microsoft Corp., Redmond, WA, USA). Categorical variables were summarized as frequencies and percentages. Continuous variables, where applicable, were summarized as means with standard deviations or medians with interquartile ranges, depending on their distribution.

Crude annual recorded diagnosis-based incidence, age-specific incidence, point prevalence, and age-specific prevalence were calculated per 100,000 persons or person-years using the corresponding official population denominators. Confidence intervals for crude and age-specific rates were estimated using exact Poisson methods. Age-standardized recorded diagnosis-based incidence and prevalence rates were calculated by direct standardization using the 2000-2025 world standard population and the 2011-2030 European standard population.[14,15] Confidence intervals for age-standardized rates were estimated using gamma-based methods. Age-standardized rates were also calculated separately by sex and place of residence. No separate sex standardization was performed; sex-related differences were presented as sex-specific crude and age-standardized estimates.

Annual trends in recorded diagnosis-based MS incidence were assessed using Poisson regression with a log-link function. The number of newly diagnosed cases was used as the dependent count variable, and the natural logarithm of the corresponding population denominator was included as the offset. Overdispersion was assessed using the Pearson chi-square (χ^2) statistic divided by degrees of freedom and the deviance divided by degrees of freedom. When overdispersion was present, inference was based on Pearson scale-adjusted standard errors. A scale-adjusted Poisson model was retained as the primary analytical approach because the objective was to estimate incidence rate ratios (IRRs) for grouped registry-based case counts using official population denominators. Negative binomial regression was considered an alternative; however, since the study included only 10 annual observations and some stratified models involved sparse age-year cells, the Pearson scale-adjusted Poisson model was considered more appropriate and stable for the main descriptive analyses.

As a supplementary descriptive analysis, annual differences in the distribution of newly diagnosed cases were also examined using Pearson's Chi square test and the Linear-by-Linear Association test. When the overall Chi square test was statistically significant, adjusted standardized residuals were inspected to identify calendar years with observed case counts that differed most from expected counts. These analyses were used only to describe deviations in annual case distribution and were not considered the primary method for estimating incidence trends.

Age-specific recorded incidence was additionally analyzed using Poisson regression with five-year age group as the categorical predictor and the natural logarithm of the population denominator as the offset. The age group with the highest observed national referral center-based incidence was used as the reference category. Bonferroni adjustment was applied for multiple pairwise comparisons where appropriate.

Recorded diagnosis-based point prevalence on December 31, 2022, was calculated using the number of surviving confirmed or reconfirmed cases as the numerator and the corresponding population count as the denominator. Prevalence estimates were calculated overall and according to sex and place of residence. Sex- and residence-specific differences in recorded prevalence were assessed using rate ratios with

95% CIs. These comparisons were reported as differences in recorded rates rather than as direct estimates of underlying disease risk.

Sensitivity and segmented analyses were performed to assess the robustness of the temporal incidence trend. First, the Poisson trend model was repeated after excluding 2020 because COVID-19-related restrictions may have affected diagnostic access and referral patterns. Second, the model was repeated after excluding data from 2013 to 2014 to evaluate the possible influence of early registry maturation and backlog ascertainment. In addition, prespecified segmented Poisson regression models were fitted by adding indicator variables for the year 2020 and for the early registry period from 2013 to 2014 to the main Poisson model. These models were used to assess whether the temporal trend remained consistent after accounting for pandemic-related disruption and possible early registry/backlog effects. Formal joinpoint regression was not performed because the study included only 10 annual observations and the main objective was descriptive. All statistical analyses were two-sided, and a p-value < 0.05 was considered statistically significant.[16]

RESULTS

Between 2013 and 2022, 2,006 individuals were assessed at the Neurology Center (Figure 1). Multiple sclerosis was confirmed or reconfirmed in 1,796 patients, including 1,180 females and 616 males, corresponding to a female-to-male ratio of 1.92:1. Urban and rural residents accounted for 1,192 and 604 patients, respectively. Overall, 210 assessed individuals were not included in the confirmed/reconfirmed MS cohort because MS was not confirmed after diagnostic review or the eligibility criteria were not met. Possible reasons included alternative neurological or nonneurological diagnoses, insufficient or inconsistent documentation, unavailable required diagnostic investigations, or nonresidence in Azerbaijan. However, the registry did not systematically code detailed exclusion reasons for each excluded individual; therefore, a complete numerical breakdown of exclusion categories was not available. Incidence analyses included 1,411 newly diagnosed patients (mean age: 34.47 years; range, 15 to 66 years), whereas prevalence analyses included 1,753 patients with MS (mean age: 41.53 years; range, 18 to 73 years) who were alive on December 31, 2022.

From 2013 to 2022, the mean annual crude recorded diagnosis-based incidence of MS was 1.44 per 100,000 person-years. Recorded incidence was higher among females than males and among urban residents during most years of the study period (Figure 2). The lowest recorded incidence was observed in 2020, followed by a partial increase in 2021 and 2022. The annual crude recorded incidence rates with corresponding case numbers and 95% CIs according to sex and residence are provided in Supplementary Table 1.

In the main age-adjusted Poisson regression model, overdispersion was present, as indicated by Pearson χ^2/df = 2.064 and deviance/df = 2.046. Therefore, inference was based on Pearson scale-adjusted standard errors. After adjustment for five-year age group, calendar year was significantly associated with lower recorded diagnosis-based MS incidence (IRR = 0.942 per year; 95% CI: 0.917-0.967, Wald χ^2 = 19.509, p < 0.001).

The decreasing temporal pattern remained statistically significant after excluding 2020 (IRR = 0.961, 95% CI: 0.938-0.984, p = 0.001) and after excluding the early registry years 2013 to 2014 (IRR = 0.936, 95% CI: 0.900-0.974, p = 0.001). In the model including a COVID-19 year indicator, the year 2020 indicator was independently associated with substantially lower recorded incidence than expected from the underlying temporal trend (IRR = 0.402, 95% CI: 0.285-0.566, p < 0.001). The early-registry indicator for 2013 to 2014 was not significant (IRR = 0.957, 95% CI: 0.745-1.228, p = 0.728). Additional age- and sex-adjusted and age- and residence-adjusted models showed consistent decreasing temporal patterns. Urban residence was associated with higher recorded incidence than rural residence after adjustment for age group and calendar year (IRR = 1.578, 95% CI: 1.363-1.827, p < 0.001). Detailed regression results are provided in Supplementary Table 2.

Age-specific crude incidence peaked in young and middle-aged adults (Table 1). The highest mean annual incidence was observed among individuals ages 35 to 39 years, followed by those ages 30 to 34 years and 25 to 29 years. The recorded incidence was lower among individuals younger than 20 years and those aged 50 years or older.

In the Poisson regression model, using the group aged 35 to 39 years as the reference category, the incidence did not differ significantly

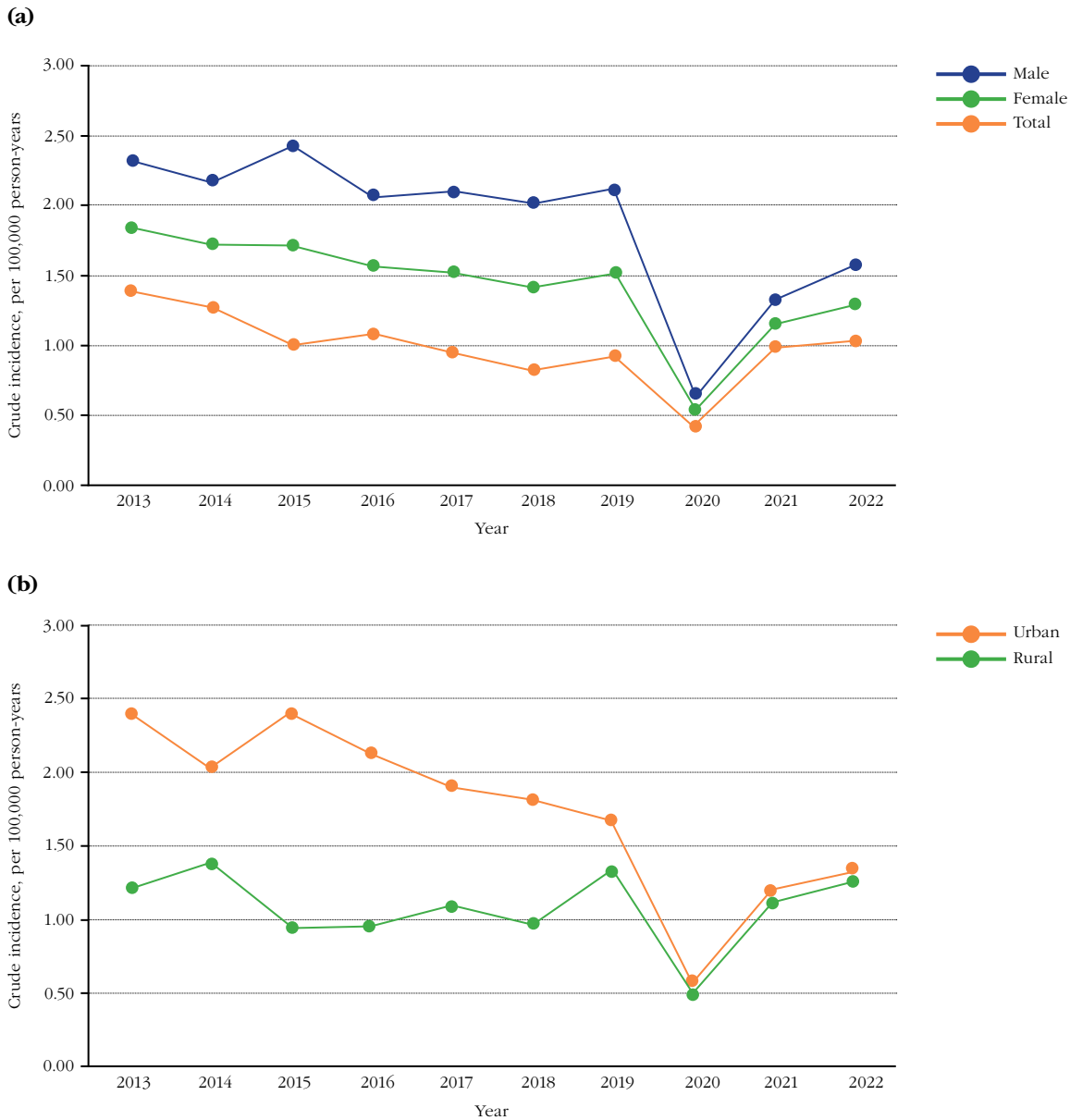

Figure 2. Annual crude recorded diagnosis-based incidence of MS in Azerbaijan from 2013 to 2022: **(a)** overall and by sex and **(b)** by place of residence.

MS, multiple sclerosis.

in the groups aged 25 to 29, 30 to 34, and 40 to 44 years after Bonferroni adjustment. In contrast, the incidence was significantly lower in the groups aged < 20, 20 to 24, 45 to 49, 50 to 54, 55 to 59, 60 to 64, and ≥ 65 years (Table 1). Calendar year was also associated with recorded diagnosis-based incidence in the Poisson models, as summarized in Supplementary Table 2.

As of December 31, 2022, 1,753 surviving patients with MS were registered, corresponding to an overall crude prevalence of 17.31 per 100,000 persons (95% CI: 16.51-18.14). Age-specific recorded diagnosis-based point prevalence increased from young adulthood and reached its highest values in the groups aged 35 to 39, 40 to 44, and 45 to 49 years. The highest total recorded diagnosis-based point prevalence was observed among individuals aged 35 to 39 years (39.83 per 100,000 persons; 95% CI: 35.75-44.24), followed by those aged 45 to 49 years (39.29 per 100,000 persons; 95% CI: 34.45-44.62) and 40 to 44 years (37.71 per 100,000

TABLE 1
Age-specific crude recorded diagnosis-based incidence of multiple sclerosis in Azerbaijan, 2013-2022

Age group (year)	Incident cases (n)	Mean annual incidence per 100,000 person-years	95% CI	IRR	95% CI	*p*
< 20	51	0.18	0.13-0.22	0.05	0.04-0.07	**< 0.001**
20-24	142	1.84	1.53-2.14	0.55	0.44-0.67	**< 0.001**
25-29	261	2.94	2.58-3.29	0.87	0.73-1.04	1.000
30-34	294	3.31	2.94-3.69	0.98	0.83-1.16	1.000
35-39	258	3.37	2.96-3.78	1.00	reference	-
40-44	184	2.80	2.39-3.20	0.83	0.69-1.00	0.547
45-49	148	2.37	1.99-2.76	0.71	0.58-0.86	**0.007**
50-54	51	0.80	0.58-1.02	0.24	0.18-0.32	**< 0.001**
55-59	15	0.25	0.12-0.38	0.08	0.04-0.13	**< 0.001**
60-64	6	0.13	0.03-0.24	0.04	0.02-0.09	**< 0.001**
≥ 65	1	0.01	0.00-0.04	0.00	0.00-0.03	**< 0.001**
Total	1,411	1.43	1.36-1.50	-		-

CI, confidence interval; IRR, incidence rate ratio. Incident cases are totals for 2013-2022. Mean annual incidence was calculated per 100,000 person-years using the sum of yearly population denominators over the study period. IRRs and p values were estimated using a Poisson regression model with log link and the population denominator as offset; those aged 35 to 39 years served as the reference category. Bonferroni-adjusted *p* values were used for pairwise comparisons. Significant *p* values ($p \leq 0.05$) are shown in bold type.

TABLE 2
Crude age-specific prevalence of multiple sclerosis per 100,000 persons with 95% confidence intervals in Azerbaijan on December 31, 2022 (n = 1,753)

	Male		Female		Urban		Rural		Total	
Age group (year)	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI
< 20	0.13	0.02-0.46	0.00		0.13	0.02-0.47	0.00		0.07	0.01-0.25
20-24	2.69	1.23-5.11	8.83	5.82-12.84	8.61	5.77-12.37	2.31	0.93-4.75	5.62	3.94-7.78
25-29	13.65	10.17-17.95	26.40	21.53-32.05	26.68	21.80-32.33	13.24	9.80-17.51	20.14	17.07-23.59
30-34	20.64	16.66-25.29	40.41	34.92-46.51	40.14	34.82-46.04	19.65	15.65-24.36	30.84	27.38-34.62
35-39	29.35	24.45-34.95	49.94	43.59-56.96	45.97	40.19-52.33	31.77	26.34-37.99	39.83	35.75-44.24
40-44	26.95	21.92-32.77	48.46	41.64-56.08	42.47	36.54-49.09	31.12	25.24-37.97	37.71	33.42-42.39
45-49	24.44	19.16-30.73	53.85	45.92-62.75	39.91	33.44-47.27	38.51	31.43-46.70	39.29	34.45-44.62
50-54	24.26	18.87-30.70	40.59	33.76-48.40	38.22	31.74-45.64	26.23	20.48-33.08	32.72	28.26-37.67
55-59	17.06	12.58-22.62	26.94	21.55-33.27	28.35	22.83-34.81	15.37	11.13-20.71	22.31	18.69-26.42
60-64	8.89	5.70-13.23	14.79	10.83-19.73	17.96	13.67-23.16	4.36	2.18-7.80	12.05	9.40-15.23
≥ 65	0.80	0.16-2.33	2.07	0.99-3.80	1.92	0.92-3.54	0.88	0.18-2.58	1.51	0.81-2.59
Total	11.87	10.93-12.86	22.70	21.41-24.05	21.10	19.90-22.34	12.76	11.75-13.84	17.31	16.51-18.14

CI, confidence interval.

persons; 95% CI: 33.42-42.39). The prevalence was lower among individuals aged < 20 years and those aged ≥ 65 years (Table 2).

Recorded diagnosis-based point prevalence was higher among females than males across almost all age groups. Overall, the female prevalence was 22.70 per 100,000 persons (95% CI: 21.41-24.05) compared to 11.87 per 100,000 persons (95% CI: 10.93-12.86; χ^2 (1) = 171.789, $p < 0.001$) in males. The prevalence was also higher among urban residents than among rural residents, with rates of 21.10 per 100,000 persons (95% CI: 19.90-22.34) and 12.76 per 100,000 persons (95% CI: 11.75-13.84), respectively (χ^2 (1) = 100.771, $p < 0.001$; Table 2).

Age-standardized estimates showed a higher national referral center-based incidence and point prevalence among females and urban residents

TABLE 3
Age-standardized incidence and prevalence of multiple sclerosis by sex and residence in Azerbaijan

	Mean annual age-standardized incidence (2013-2022), per 100,000 person-years				Age-standardized prevalence (31 December 2022), per 100,000 population			
	WSt		EuSt		WSt		EuSt	
	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI
Male	0.92	0.84-1.00	0.85	0.78-0.93	10.74	9.89-11.62	11.50	10.57-12.46
Female	1.73	1.62-1.84	1.58	1.48-1.69	20.03	18.88-21.21	21.28	20.04-22.55
Urban	1.60	1.50-1.71	1.46	1.36-1.55	18.58	17.51-19.67	19.71	18.57-20.88
Rural	1.02	0.93-1.11	0.95	0.87-1.04	11.72	10.78-12.69	12.58	11.55-13.63
Total	1.33	1.26-1.40	1.22	1.16-1.29	15.47	14.75-16.21	16.50	15.72-17.30

WSt, World standard population; EuSt, European standard population; CI, confidence interval. Age-standardized incidence is presented as the mean annual rate for 2013-2022; prevalence is presented as the point prevalence on December 31, 2022. Values are estimates (95% CI).

(Table 3). From 2013 to 2022, the mean annual world-standardized incidence was 1.33 per 100,000 person-years (95% CI: 1.26-1.40), whereas the European-standardized incidence was 1.22 per 100,000 person-years (95% CI: 1.16-1.29). Standardized national referral center-based incidence was higher among females than males using both the world standard population (1.73 *vs.* 0.92 per 100,000 person-years) and the European standard population (1.58 *vs.* 0.85 per 100,000 person-years). Urban residents also had a higher standardized national referral center-based incidence than rural residents, with world standardized rates of 1.60 versus 1.02 per 100,000 person-years, and European standardized rates of 1.46 versus 0.95 per 100,000 person-years.

A similar pattern was observed for the age-standardized recorded diagnosis-based point prevalence at the end of 2022. The overall world-standardized prevalence was 15.47 per 100,000 persons (95% CI: 14.75-16.21), and the European-standardized prevalence was 16.50 per 100,000 persons (95% CI: 15.72-17.30). Standardized recorded diagnosis-based point prevalence was higher among females than males using both the world standard population (20.03 *vs.* 10.74 per 100,000 persons) and the European standard population (21.28 *vs.* 11.50 per 100,000 persons). Urban residents also had a higher standardized prevalence than rural residents, with world standardized rates of 18.58 *vs.* 11.72 per 100,000 persons, and European standardized rates of 19.71 versus 12.58 per 100,000 persons (Table 3).

DISCUSSION

This study provides national referral center-based estimates of recorded diagnosis-based incidence and point prevalence of MS in Azerbaijan over a 10-year period. The main findings were a clear female predominance, higher recorded national referral center-based incidence and prevalence among urban residents, and peak recorded national referral center-based incidence in young and middle adulthood.

The interpretation of these estimates should be guided by the structure of the data source. The registry was based on a centralized referral and treatment-authorization pathway within the State Program rather than on complete linkage of all diagnostic, insurance, disability, and mortality databases. Therefore, the estimates should be understood as national referral center-based recorded estimates. They may be conservative, particularly for patients with limited access to specialist neurological care, MRI diagnostics, or referral to the Neurology Center.

Female predominance is one of the most consistently reported epidemiological features of MS.[17-20] In the present study, female patients accounted for 65.7% of the confirmed cases of MS, with a female-to-male ratio of 1.92:1. Both crude and age-standardized estimates showed higher national referral center-based incidence and point prevalence in females than in males. This finding is consistent with the established sex distribution of MS and may reflect the contributions of immunological, hormonal, and epigenetic mechanisms.[21,22] The persistence of female predominance across crude and standardized estimates suggests that sex-related heterogeneity is an important feature of MS epidemiology in Azerbaijan.

Higher recorded MS incidence and point prevalence were observed among urban residents.

In our cohort, 66.4% of the confirmed patients with MS lived in urban areas, and both the crude and age-standardized national referral center-based incidence and point prevalence were higher in urban than in rural populations. A similar urban predominance has been reported in several countries and regions.[23-25] In Bavaria, the prevalence of MS is higher in urban areas than in rural and semirural settlements.[25] However, this pattern is not universal; higher rates have been reported in rural areas of the Telemark region in Norway.[26] Therefore, urban-rural differences in MS epidemiology should be interpreted in relation to local demographic, environmental, and healthcare-related factors.

The higher recorded rates among urban residents in Azerbaijan may reflect differences in diagnostic access and case ascertainment, although true epidemiological differences cannot be excluded. Urbanization, lifestyle-related exposures, environmental factors, and better access to specialized neurological care and MRI diagnostics may contribute to higher recorded rates in urban populations.[23,27-29] Conversely, limited access to neurologists and MRI services in rural areas may delay the diagnosis or reduce case detection. Thus, the lower national referral center-based incidence and point prevalence observed among rural residents may partly reflect residual underascertainment rather than lower underlying disease risk. This interpretation was also supported by the residence-adjusted Poisson model, in which urban residence was associated with higher recorded national referral center-based incidence; however, this association should be viewed as a difference in recorded rates rather than as direct evidence of higher underlying disease risk.

Age-specific national referral center-based incidence showed that MS was most frequently diagnosed in young and middle-aged adults, with the highest national referral center-based incidence in those aged 35 to 39 years, followed by those aged 30 to 34 and 25 to 29 years. This distribution is consistent with the typical age profile of MS, which is most commonly diagnosed in early to middle adult life.[5] International studies have reported variations in age at diagnosis. In rural regions of Türkiye, approximately 85% of patients were diagnosed at ages 15 to 34 years,[23] whereas data from the Danish Multiple Sclerosis Registry indicated that diagnosis occurred more frequently between the ages of 26 and 55 years.[30] The Azerbaijani data fall within this broad international range and support the view that MS primarily affects economically and socially active age groups.

Age-specific recorded diagnosis-based point prevalence patterns differed from incidence patterns. The highest crude prevalence was observed in those aged 35 to 39, 40 to 44, and 45 to 49 years, reflecting both the typical age at disease onset and the accumulation of prevalent cases over time. A lower prevalence in the youngest age group was expected, whereas the decline in older age groups may reflect lower historical incidence, mortality, diagnostic delay in earlier decades, or incomplete ascertainment among older individuals. The persistence of a higher prevalence among females and urban residents across most age groups further supports the sex- and residence-related heterogeneity observed in the national referral center-based incidence analyses.

The age-standardized referral center-based recorded estimates observed in this study were lower than those reported from many high-prevalence regions in Europe, North America, and Australasia but higher than estimates from some lower-prevalence Asian populations.[17-20,23,25,31-34] However, these comparisons should be considered descriptive rather than directly equivalent because many published estimates are derived from population-based registries or administrative data sources, whereas the present study was based on a centralized national referral center registry. Differences between studies may reflect not only true geographical variation in MS burden but also differences in diagnostic criteria, registry completeness, population denominators, age standardization methods, healthcare access, and case ascertainment. In this context, the relatively low recorded diagnosis-based point prevalence estimates in our study may indicate a genuinely lower recorded MS burden, but incomplete case capture, particularly among rural or underserved populations and patients not referred through the centralized pathway, may also have contributed to lower estimates.

The Poisson regression analyses showed a decreasing temporal pattern in recorded diagnosis-based MS incidence between the years 2013 and 2022. However, this finding should be interpreted with caution and should not be considered definitive evidence of a true decline

in the underlying disease risk or biological onset incidence of MS. In this study, incidence was defined according to the calendar year of first confirmed diagnosis at the Neurology Center, rather than the year of first symptom onset. Therefore, temporal changes in recorded incidence may reflect changes in referral patterns, diagnostic access, MRI availability, registry maturation, treatment authorization procedures, and case ascertainment, rather than true changes in MS occurrence.

The sensitivity and segmented analyses were performed to explore whether the observed temporal pattern was influenced by the COVID-19 pandemic or early registry/backlog effects. The decreasing trend in recorded diagnosis-based incidence persisted after excluding 2020 and after excluding the early registry years (2013-2014). In addition, the COVID-19 year indicator showed that recorded incidence in 2020 was substantially lower than expected from the underlying recorded temporal trend, supporting the interpretation that pandemic-related disruption in healthcare access, referral, diagnostic confirmation, and MRI availability contributed to underascertainment in that year. Nevertheless, these analyses cannot fully eliminate the influence of changing referral dynamics, diagnostic access, registry maturation, or incomplete case capture. Accordingly, the temporal trend should be interpreted as a trend in recorded confirmed diagnoses within the centralized referral registry, rather than as direct evidence of a decline in the true population incidence of MS.

Previous Azerbaijani studies provided important regional information on MS epidemiology in Baku and selected administrative regions.[7-11] The present study differs from those reports by integrating recorded cases from all regions of Azerbaijan within the centralized referral and State Program framework and by providing overall national referral center-based estimates of diagnosis-based incidence and point prevalence from 2013 to 2022. Because some previous regional analyses were derived from the same centralized clinical and registry infrastructure, partial overlap with the present dataset is possible. However, the purpose of the current analysis was different: it was designed to estimate the overall recorded national burden and to compare demographic and residence-related patterns at the country level. Thus, the present manuscript should be interpreted as a national-level synthesis and analysis of the centralized referral registry rather than as a duplication of the previous regional reports.

This study had several strengths. It covered a 10-year period and was conducted at the national referral center for MS, which received patients from all regions of Azerbaijan within the framework of the State Program on MS. Diagnosis was based on the national clinical protocol aligned with the McDonald criteria, and recorded incidence and point prevalence were calculated using official population denominators stratified by age, sex, and residence. In addition, both crude and age-standardized estimates were presented, allowing for a more meaningful comparison with international data.

This study also had several limitations. Although the Neurology Center functioned as a national referral center, the study was based on a single-center registry and may not have captured all MS cases in the country, specifically among rural residents or patients with limited access to specialized services. The completeness of case ascertainment could not be quantified because no independent population-based MS registry, nationwide insurance claims database, disability registry linkage, death registry linkage, or mandatory reporting system was available to estimate the proportion of all MS patients captured by the centralized registry. Therefore, the registry should be interpreted as capturing patients who entered the centralized referral, diagnostic verification, registration, and treatment authorization pathway, rather than all persons with MS in the general population. Patients diagnosed or followed outside the Neurology Center, patients managed only in private or regional settings, patients without access to specialist neurological services or MRI, patients who did not seek state-supported disease-modifying therapies, and nonreferred cases may have been missed. As a result, the recorded incidence and point prevalence estimates may underestimate the true population burden, particularly in rural or underserved populations.

Detailed exclusion categories were not systematically coded in the registry, which limited more granular reporting of non-MS cases and exclusions due to alternative diagnoses, insufficient documentation, unavailable diagnostic investigations, or nonresidence. Therefore, excluded individuals were reported according to final confirmed/reconfirmed MS status rather than by detailed exclusion subtype. The COVID-19 pandemic likely caused underascertainment of incident cases in 2020. As incidence was assigned

according to the year of first confirmed diagnosis rather than the year of symptom onset, temporal trends may have been influenced by changes in referral patterns, diagnostic access, MRI availability, registry maturation, and treatment-authorization procedures. In addition, comparisons with other countries should be interpreted cautiously because of differences in case ascertainment, diagnostic criteria, healthcare access, registry quality, age structure, and standardization methods.[33] Direct comparisons are the most meaningful when the same reference population and epidemiological definitions are used.

Overall, the age-standardized recorded incidence and point prevalence of MS in Azerbaijan were lower than those reported from high-prevalence regions of Europe, North America, and Australasia, but higher than those reported from some low-prevalence Asian populations. The patterns observed by sex, residence, and age were broadly consistent with international epidemiological data. These findings provide a referral center-based epidemiological baseline for MS in Azerbaijan and indicate that future MS surveillance should consider demographic and geographic heterogeneity, particularly in relation to diagnostic access and case ascertainment. Further development of registry-based surveillance may improve monitoring of the MS burden and support planning for specialized neurological services.

In conclusion, this 10-year national referral center-based registry study provided recorded diagnosis-based estimates of MS incidence and point prevalence in Azerbaijan during the State Program period. Multiple sclerosis showed a clear female predominance, higher recorded rates among urban residents, and peak recorded incidence in young to middle adulthood. The mean annual age-standardized national referral center-based incidence was 1.33 per 100,000 person-years using the world standard population and 1.22 per 100,000 person-years using the European standard population. By the end of 2022, the age-standardized recorded diagnosis-based point prevalence was 15.47 per 100,000 persons using the world standard population and 16.50 per 100,000 persons using the European standard population. These findings provide a referral center-based epidemiological baseline for Azerbaijan and may inform future registry development, service planning, and strategies to improve equitable access to specialized neurological care.

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