JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2023;19(1):83-89 / https://doi.org/10.3988/jcn.2023.19.1.83

National Estimates of Narcolepsy in Korea

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Background and Purpose Epidemiological data on narcolepsy are rare in South Korea. We aimed to provide an overview of the burden of narcolepsy and its temporal trend in South Korea.

Methods Patients with narcolepsy were identified by their registration in the Rare and Intractable Disease (RID) register and the Health Insurance Review and Assessment database. Individuals registered in the RID program with the code V234 were considered as having 'definite narcolepsy', while those who claimed health insurance with G47.4 as the primary diagnostic code were considered as having 'probable narcolepsy'. We estimated the annual prevalence, incidence, and medical costs of narcolepsy between 2010 and 2019.

Results The prevalence of definite narcolepsy was 8.4/100,000 in 2019, peaking at 32.0/100,000 in those aged 15–19 years. The prevalence was higher in males, with a relative risk of 1.72. The prevalence has increased over the past 6 years, with an average annual growth rate (AAGR) of 12.2%. The prevalence of probable narcolepsy was 10.7/100,000 in 2019. The incidence of definite narcolepsy increased up to 1.3/100,000 in 2019 with an AAGR of 7.1%. Annual medical expenditure for definite narcolepsy gradually increased up to 4.1 billion KRW in 2019, with a compound annual growth rate of 11.9%.

Conclusions This study has provided the first nationwide estimates for narcolepsy in South Korea. The prevalence of diagnosed narcolepsy in South Korea was at the low end of the range of narcolepsy prevalence rates reported for other countries. However, the prevalence and incidence have been steadily increasing over the past decade.

Keywords narcolepsy; prevalence; incidence; cost.

INTRODUCTION

Narcolepsy is a chronic neurological disorder associated with significant physical and psychosocial impairments.[1-3] It is characterized by excessive daytime sleepiness and cataplexy, as well sleep-related symptoms including hypnagogic hallucinations, sleep paralysis, and disturbed nighttime sleep.[1,4] Previous studies involving general populations found that the prevalence of narcolepsy was 20–50/100,000 persons in North America and Europe.[5-9] Among Asian countries, a study conducted in Hong Kong that used telephone interviews, polysomnography (PSG), and human leukocyte antigen (HLA) typing found a prevalence of 34/100,000 persons.[3] The incidence of narcolepsy was less studied than the prevalence before the H1N1 influenza pandemic in 2009, but numerous observational studies have investigated the changes in narcolepsy type 1 incidence after this pandemic or in association with H1N1 vaccination. The incidence rate of narcolepsy before the 2009 H1N1 pandemic was approximately 1/100,000 persons per year, with the peak of onset in persons aged 10–20 years,[7] and a 2- to 25-fold increase in incidence in children and adolescents was reported following the H1N1 pandemic between 2009 and 2010 in European countries and China.[10-14]

Despite the increase in clinical and social interest in narcolepsy during recent decades,[15]

Received April 11, 2022
Revised July 29, 2022
Accepted July 29, 2022

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epidemiological data on narcolepsy are sparse in South Korea. One study using a screening telephone interview and confirmatory laboratory investigation (PSG, HLA typing) of 20,407 students (14–19 years old) in Seongnam and Yongin found a narcolepsy prevalence of 34/100,000 among South Korean adolescents, but the prevalence rates in other age groups have not been investigated.[16] Another study using the Health Insurance Review and Assessment Service (HIRA) database found that the incidence rate was 1.1–3.8/100,000 person-years for adults and 1.3–2.7/100,000 person-years for children and adolescents between 2006 and 2010, indicating that there was no significant increase associated with the H1N1 pandemic.[17] However, that study solely relied on the HIRA database, which limited its diagnostic accuracy.

This study aimed to assess the prevalence, incidence, and cost of narcolepsy and its temporal trends in South Korea over the last decade (2010–2019) based on representative nationwide data.

METHODS

Data sources

Two national administrative health databases covering the 10-year period from January 2010 to December 2019 were used. The primary resource was the Rare and Intractable Disease (RID) register obtained from the National Health Insurance Service (NHIS). Narcolepsy has been included in the RID program as a target for the copayment assistance policy since 2009, which is supported by the NHIS of South Korea.[15] Patients registered in the RID program make less out-of-pocket payments (10% of the total medical cost) than usual NHIS subscribers (20%–60% of the total cost). To be registered for the RID program, confirmative test results and clinical symptoms must be recorded by physicians and reassessed by administrators. This is therefore a reliable source of epidemiological data for rare diseases.[18] An additional resource was the claims data of national health insurance from the HIRA (https://opendata.hira.or.kr), which was used as a reference. The resident registration data from the Ministry of the Interior and Safety (https://jumin.mois.go.kr/), which includes the total South Korean population and population distributions by age and region, were used for general population data to calculate prevalence and incidence.

Case ascertainment

Narcolepsy was identified in two ways according to the data sources. From the RID register, cases of 'definite narcolepsy' were ascertained using RID code V234 (narcolepsy and cataplexy). We assessed the annual number of patients newly registered with this code between 2010 and 2019 and the annual number of reregistered patients (registration extension) between 2014 and 2019 according to age, sex, and residential area. We assessed the medical cost of narcolepsy by calculating total medical expenses claimed for copayment assistance under the V234 code.

In the HIRA data, cases of 'probable narcolepsy' were ascertained by using the International Classification of Diseases (ICD) code G47.4 (narcolepsy and cataplexy) as the primary diagnostic code to claim any health care utilization. The diagnostic code was designated by the impressions of physicians in regular clinical practice and did not ensure compatible test results. This diagnostic code was therefore considered to be a more-sensitive but less-specific indicator of narcolepsy than the RID code.

Analysis

The annual prevalence of definite narcolepsy per 100,000 individuals in the general population between 2014 and 2019 was calculated based on the RID register. The total number of patients with narcolepsy each year was calculated as the sum of newly registered patients and reregistered patients over the last 5 years, based on the assumption that the narcolepsy less likely to be spontaneously resolved within 5 years. The annual prevalence of probable narcolepsy was calculated based on HIRA data between 2014 and 2019 as a reference.

As an approximate value for annual incidence, we calculated the age-specific annual number of newly registered patients for narcolepsy per 100,000 person-years between 2010 and 2019 based on the RID register. We also investigated the regional distribution of newly registered patients in 2019 and calculated the standardized incidence ratios (SIRs) of 17 administrative districts in South Korea after adjusting for age using the indirect standardization method. SIRs were calculated by dividing the observed number of patients with narcolepsy in each region by the expected number based on the incidence in the general population of South Korea.

For medical expenses, the proportion of medical costs associated with narcolepsy above the national medical expenditure and average cost per patient with narcolepsy were calculated between 2014 and 2019 based on the RID register.

Statistical analyses were performed using MS Excel (Office 365, Microsoft Corp., Redmond, WA, USA) and SPSS (version 26.0, IBM Corp., Armonk, NY, USA). The time trend of annual prevalence with its 95% confidence interval (CI) was estimated using a Poisson regression analysis, and the change in annual medical expenses was analyzed using a gamma regression analysis. Statistical significance was defined as $p<0.05$.

This study was approved by the Institutional Review Board of Kangwon National University (IRB No. 2021-06-024).

RESULTS

The total number of patients registered with narcolepsy in the RID program (code V234) between 2010 and 2019 was 6,811, comprising 5,454 newly registered cases and 1,357 re-registered cases.

Based on the RID register, there were 4,356 patients with definite narcolepsy, with a prevalence of 8.40/100,000 (95% CI=8.15–8.65/100,000) in 2019 (Supplementary Table 1 in the online-only Data Supplement). The prevalence of definite narcolepsy was 1.63 times higher in males (10.40/100,000) than females (6.40/100,000). According to age, the highest prevalence (32/100,000) was observed in both males and females aged 15–19 years, followed by those aged 20–24 and 25–29 years (Fig. 1A). The prevalence increased over time from 2014 to 2019, with an average annual growth rate (AAGR) of 12.2% (95% CI=11.3%–13.1%, $p<0.001$). Both males and females showed significant increases in prevalence between 2014 and 2019 ($p<0.001$) (Fig. 2 and Supplementary Table 1 in the online-only Data Supplement).

The prevalence of probable narcolepsy based on HIRA data was 10.67/100,000 in 2019, and this also showed a significant increasing trend between 2014 and 2019, with an AAGR of 13.6% (95% CI=12.7%–14.4%, $p<0.001$). The prevalence of

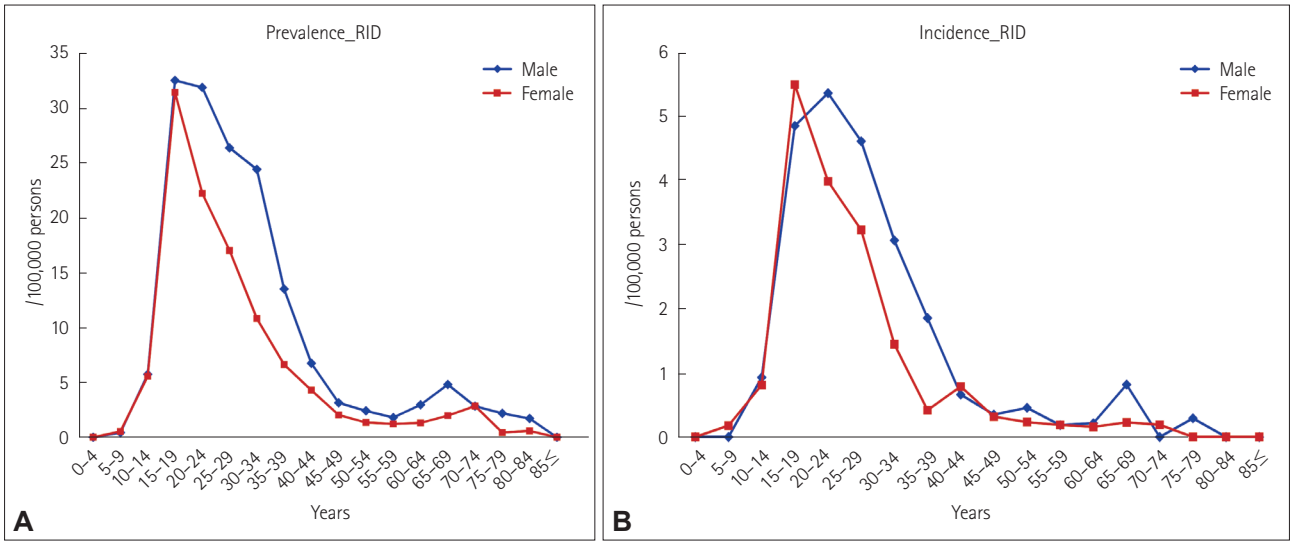

Fig. 1. Prevalence (A) and incidence (B) of definite narcolepsy (per 100,000 persons) according to age and sex in 2019. RID, Rare and Intractable Disease.

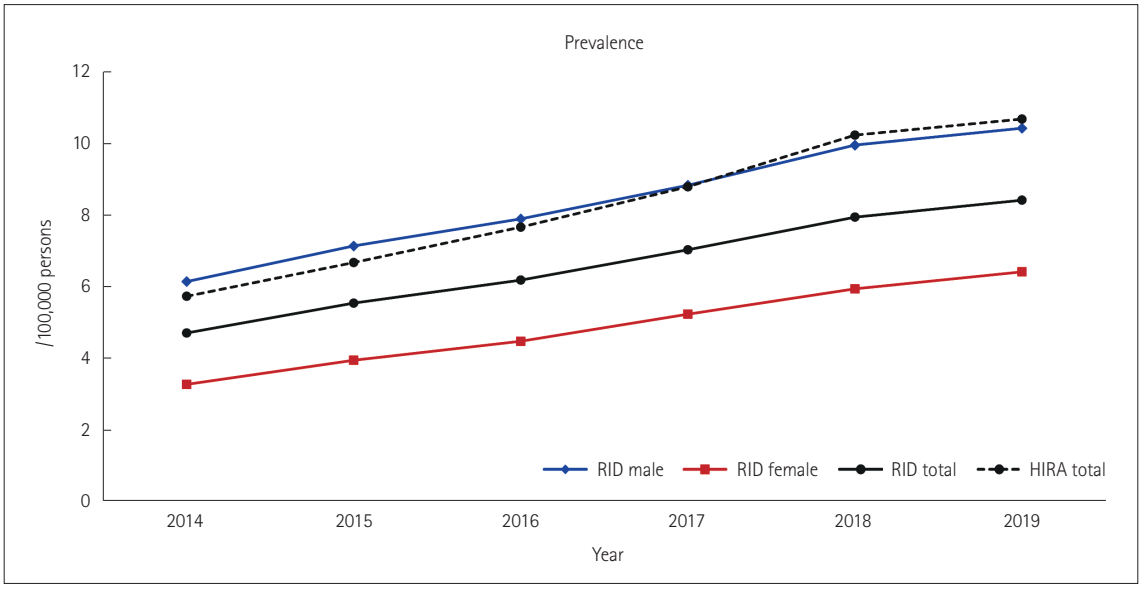

Fig. 2. Annual trends of the prevalence of definite and probable narcolepsy (per 100,000 persons) between 2014 and 2019. RID (solid lines): definite narcolepsy estimated from the RID register. HIRA (dashed line): probable narcolepsy estimated from HIRA data. HIRA, Health Insurance Review and Assessment Service; RID, Rare and Intractable Disease.

Table 1. Annual trend of the incidence of definite narcolepsy between 2010 and 2019

Year	0–9 years	10–19 years	20–29 years	30–39 years	40–49 years	50–59 years	≥60 years	Total
2010	3† (0.06)	116 (1.70)	121(1.76)	85 (1.02)	28(0.32)	20 (0.28)	12 (0.15)	390 (0.77)
2011	5 (0.11)	159 (2.38)	121 (1.80)	81 (0.98)	22 (0.25)	27 (0.36)	14 (0.18)	432 (0.85)
2012	0 (0.00)	141 (2.19)	152 (2.29)	92 (1.13)	36 (0.41)	12 (0.15)	18 (0.21)	457 (0.90)
2013	2 (0.04)	127 (2.04)	133 (2.02)	89 (1.11)	26 (0.29)	16 (0.20)	17 (0.20)	414 (0.81)
2014	0 (0.00)	179 (2.99)	174 (2.62)	91 (1.17)	21 (0.24)	31 (0.38)	39 (0.43)	542 (1.06)
2015	3 (0.07)	172 (3.01)	200 (2.99)	103 (1.34)	24 (0.27)	13 (0.16)	11 (0.11)	532 (1.03)
2016	4 (0.09)	186 (3.39)	210 (3.11)	122 (1.62)	31 (0.35)	17 (0.20)	31 (0.31)	606 (1.17)
2017	2 (0.05)	186 (3.51)	274 (4.02)	142 (1.93)	50 (0.58)	24 (0.28)	35 (0.33)	715 (1.38)
2018	0 (0.00)	188 (3.66)	281 (4.12)	125 (1.72)	45 (0.53)	19 (0.22)	43 (0.38)	704 (1.36)
2019	2 (0.05)	157 (3.17)	294 (4.32)	117 (1.66)	43 (0.51)	23 (0.27)	24 (0.20)	662 (1.28)
AAGR, %‡	−5.9 (−19.2 to 9.5)	7.6 (5.8 to 9.5)	11.6 (9.8 to 13.4)	7.8 (5.5 to 10.1)	8.1 (4.1 to 12.4)	−1.5 (−6.2 to 3.3)	5.7 (1.1 to 10.6)	7.1 (6.1 to 8.1)
p§	0.430	<0.001*	<0.001*	<0.001*	<0.001*	0.530	0.015	<0.001

*p<0.05/7, using Bonferroni correction; †The number of newly registered patients (incidence per 100,000 persons); ‡AAGR values are presented with their 95% confidence intervals; §Poisson analysis.
AAGR, average annual growth rate.

probable narcolepsy was 1.27 times higher than that of definite narcolepsy in 2019 (Fig. 2 and Supplementary Table 1 in the online-only Data Supplement).

The number of newly registered narcolepsy cases in the RID program was 662 in 2019, with an incidence rate of 1.28/100,000 (Table 1). The annual incidence was 1.49 times higher in male than female patients, and peaked in those aged 15–19 years, followed by those aged 20–24, 25–29, 30–34, and 10–14 years (Fig. 1B). The number of newly registered patients with narcolepsy varied among administrative regions in 2019. The incidence rate and SIR adjusted for age were highest in Seoul (SIR=1.65), followed by Gyeonggi (1.16) and Chungbuk (1.12), and were the lowest in Jeonnam (0.33) and Gwangju (0.40) (Fig. 3 and Supplementary Table 2 in the online-only Data Supplement). The incidence of definite narcolepsy showed a significant increasing trend, with an AAGR of 7.1% (95% CI=6.1%–8.1%, p<0.001), particularly in those aged 10–49 years (Table 1). Those aged 20–29 years presented the highest AAGR (11.6%, 95% CI=9.8%–13.4%, p<0.001) (Table 1 and Fig. 4).

The medical costs spent on definite narcolepsy were 4.2 billion KRW in 2019, with an increasing trend and a compound annual growth rate of 11.42% over the last 6 years. The proportion above the total medical expenditure also presented a significant increase, from 0.0035% in 2014 to 0.0043% in 2019 (p<0.001). The average annual medical cost per patient with narcolepsy was 960,833 KRW in 2019, which had not significantly changed since 2014 (Table 2).

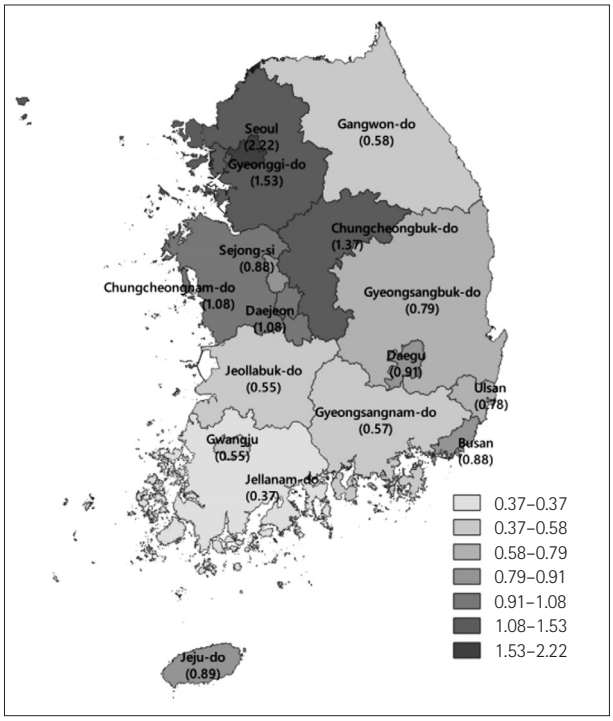

Fig. 3. Regional distribution of newly registered patients with definite narcolepsy (per 100,000 persons) in 2019.

DISCUSSION

This study was the first to estimate the prevalence of narcolepsy across all age groups in South Korea and the largest study on narcolepsy that included the entire population and assessed its nationwide burden. It was enabled by using a national register of rare diseases, which was originally collected for administrative purposes.

The overall prevalence of narcolepsy in South Korea in 2019 was found to be 8.40/100,000 persons, with a peak (32/100,000) in those aged 15–19 years. This was close to that previously reported for those aged 14–19 years in South Korea (34/100,000), which was estimated using a screening survey

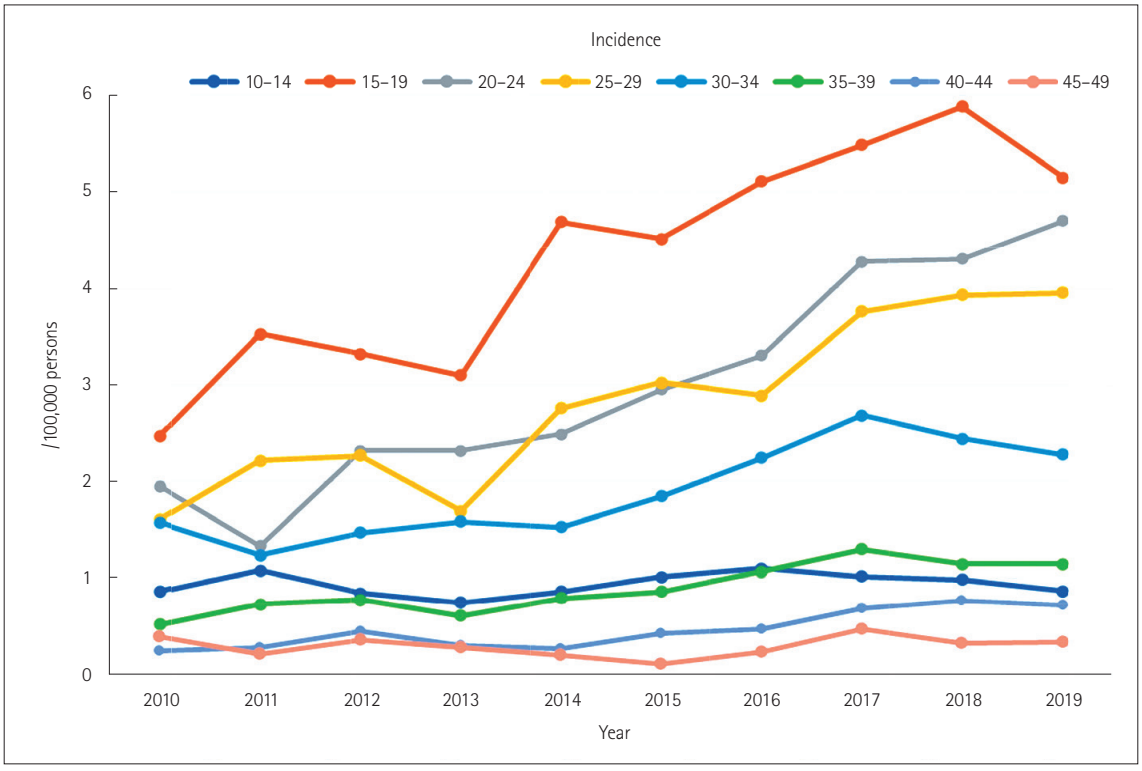

Fig. 4. Annual trend of the incidence of definite narcolepsy (per 100,000 persons), according to per age group, ranged from 10 to 49 years, between 2010 and 2019.

Table 2. Annual trends of medical costs for definite narcolepsy

Year	Total cost, ×1,000 KRW	Proportion of total medical expenditure, %	Average cost per patient
2014	2,188,065	0.0035	907,158
2015	2,396,936	0.0036	841,030
2016	3,069,336	0.0042	961,873
2017	3,203,213	0.0041	881,457
2018	3,740,344	0.0042	910,281
2019	4,185,388	0.0043	960,833
CAGR, %	11.42	3.37	0.96
*p**	<0.001	<0.001	0.217

*Gamma regression analysis.
CAGR, compound annual growth rate.

followed by a confirmatory sleep study.[16] When compared with the prevalence of narcolepsy confirmed by sleep tests (22–34/100,000) in adults excluding elderly individuals reported from population-based studies,[3,5,8] the prevalence in those aged 20–60 years in the present study (10.06/100,000) was lower but within the confidence intervals of those studies.

Racial differences, such as in the HLA type, were suggested to account for the variance in the reported narcolepsy prevalence rates.[19] However, methodological differences cannot be overlooked. Hospital-based studies tend to find lower prevalence rates than population-based studies.[20] The present study covered the entire population of South Korea, but only included those that received medical care associated with narcolepsy. Over the past decade (2010–2019), the public awareness of narcolepsy has increased and accessibility to sleep centers has improved. The increasing trend of newly registered patients over time suggested that the diagnostic gap for narcolepsy is decreasing.

The estimated number of patients with narcolepsy was higher when it was based on HIRA data than on the RID register. The RID register is highly specific but could underestimate the number of patients. National health insurance did not cover PSG until July 2018 and the multiple sleep latency test (MSLT) until December 2021; some probable cases could therefore not undergo diagnostic testing. Even after patients were diagnosed, the registration could have been missing because it was not obligatory. Nevertheless, the false-negative rate might be low, at least in adolescents, based on the proximity between the values estimated from the RID register and from a screening survey followed by confirmative tests in an urban population.[16] The HIRA data could have included false-positive cases because the ICD codes could have been entered based on clinical impression without laboratory confirmation.

Sex and age distributions of narcolepsy were not well known because most epidemiological studies included too few cases.

In the present study, both the incidence and prevalence were higher in males, particularly in those aged 20–40 years. Male predominance was also found in previous large-scale studies, but whether this was due to a referral bias or a true sex effect is still uncertain.[1] Previous studies found that disease onset often occurs in adolescence or early adulthood, and some studies found bimodal distributions with one peak in adolescence and one at 30–39 years old.[1,21] In the present study, age at initial registration in the narcolepsy registry indicated a peak in those aged 15–24 years, and a bimodal distribution was not confirmed. The age at initial registration was slightly higher than that at symptom onset found in previous studies, which might be attributable to diagnostic delay. The time gap between initial diagnosis and symptom onset has been reported to be 8–12 years.[22]

The narcolepsy incidence rates were higher in urban areas, including Seoul and Gyeonggi, even after adjusting for age. Regional variations in narcolepsy incidence have not yet been examined. The regional difference observed in our study may have been associated with several factors: greater recognition of sleep disorders including narcolepsy, accessibility to sleep centers where PSG and MSLT tests are available for people residing in urban areas, and the differences in daily activity patterns or occupational characteristics between rural and urban areas. These differences also support the idea that there are many undiagnosed patients with narcolepsy in South Korea, especially in rural areas.

This study had several limitations. First, the number of patients with definite narcolepsy could have been underestimated since we only included patients who sought health care, although the diagnostic gap seems to be decreasing. Second, we could not acquire detailed clinical information, including the presence of cataplexy or actual disease onset.

In conclusion, this study has provided a current national estimate of narcolepsy in South Korea and information on age, sex, and regional distributions in narcolepsy, which have been rarely reported. The number of patients with narcolepsy increased between 2010 and 2019, which could be attributed to increased recognition of sleep disorders and the availability of a sleep laboratory. This study identified an efficient way to measure the epidemiological parameters of narcolepsy using administrative health databases.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2023.19.1.83.

Availability of Data and Material

The data sets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2021R1G1A1008471).

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