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Increased 10-Year Prevalence of Huntington's Disease in South Korea: An Analysis of Medical Expenditure Through the National Healthcare System

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Background and Purpose This study aimed to determine the updated 10-year prevalence of Huntington's disease (HD) in South Korea and the medical and economic burdens across the duration of the disease.

Methods Data from the National Health Insurance database during 2010–2019 were analyzed. We identified HD cases using predefined criteria. Information on age at diagnosis, sex, and common nonneurological comorbidities were collected. We analyzed individual patterns of the use of medical services and yearly medical expenditure. Incidence rates, 10-year prevalence rates, and longitudinal medical expenditure changes were assessed.

Results New patients with HD (average=152.10) were detected every year, with an annual incidence of 0.29 per 100,000. The estimated 10-year prevalence of HD was 2.2 per 100,000. The most common ages at the time of diagnosis were 50–59 years (23.3%). In 2019, 56.4% of patients with HD were followed-up at referral or general hospitals, and 32.2% were managed at long-term-care hospitals. The annual medical cost for an individual was KRW 6,569,341±895,097 (mean±SD) (mean≈USD 5,653). Medical expenditure was the highest in those aged 60–79 years, and lowest in those younger than 30 years. However, in all age groups, the annual medical expenditure was highest during the 9 years following a diagnosis.

Conclusions This study found that the actual prevalence of HD in South Korea was higher than previously thought and that patients are in a situation with high medical expenditure that persists over time.

Keywords Huntington's disease; epidemiology; Health Insurance and Review Assessment; medical expenditure.

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant and intractable neurodegenerative disorder caused by abnormal cytosine-adenine-guanine (CAG) expansion in the huntingtin gene (*HTT*). The number of CAG repeats (*n* in "[CAG]*n*") is the strongest predictor of HD, and clinical manifestation appears in individuals with ≥36 repeats in complete penetrance. Larger (CAG)*n* is associated with earlier onset and rapid clinical progression.[1,2]

A previous meta-analysis indicated an incidence of 0.38 per 100,000 persons per year in Asia.[1] However, the incidence seems to be relatively low in China, with previous studies finding an annual incidence of 0.046/100,000 between 1984 and 1991[3] and of 0.1/100,000 between 2000 and 2007 in Taiwanese people,[4] in contrast to 0.11–0.8/100,000 in Caucasians.[1] The reported worldwide prevalence of HD is 2.71/100,000, with 0.65/100,000 in Japan,[5] 0.37/100,000 in China,[3] and 0.42/100,000 in Taiwan,[4] which are lower than that of

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1.9–12.1 per 100,000 in Caucasians.[1] However, the exact incidence and prevalence of HD in South Korea remain unclear.

The first diagnosis of HD in South Korea was reported in 1988,[6] and a genetic test was officially introduced in 1996.[7] The National Health Insurance System (NHIS) has covered gene tests for HD since August 2005. In July 2009, the South Korean government launched a support system within the NHIS for rare incurable diseases (RIDs), which provides a reduced coinsurance rate for medical expenses. Patients with HD in South Korea are entitled to receive support for an RID via electronic data interchange in medical institutions when their diagnosis is confirmed.[8]

Investigations of epidemiology in South Korea have been restricted by the initial RID registry being very small,[8,9] and there has been no study of the medical burden on South Korean patients with HD. Despite the complete penetrance through family members by a single gene, and the progressive nature of the disease course, explorations of patients with HD have been challenging due to a lack of further systematic support. We therefore designed this study to identify the updated epidemiology of HD in South Korea over the last 10 years using the now well-established NHIS database linked with the RID support system. We also investigated the burdens for each patient by tracing the 10-year medical expenditure.

METHODS

Data source and study population

The NHIS provides healthcare coverage to the entire population of South Korea, and the Health Insurance and Review Assessment Service (HIRA) data is a repository of claims in the NHIS to reimburse healthcare providers.[10] HIRA data are generated from inpatient and outpatient visits to healthcare institutions, including patient data on demographics, diagnoses, and all medical use except for the uncovered services.

Definition of patients and variables

This study analyzed data during 2010–2019 obtained from the HIRA. We identified newly diagnosed patients by defining new registrants under diagnostic code G10 of the International Classification of Disease (10th revision) accompanied by RID registration, which indicated diagnostic confirmation. We applied a washout period of 2 years (during 2008 and 2009) to exclude previously enrolled patients. We collected data on age, sex, age at diagnosis, and medical expenditure for every subject. We also obtained data for comorbidities such as hypertension (codes I10-13), diabetes mellitus (E10-14), dyslipidemia (E78), chronic kidney disease (N18-19), and dementia (F00-03, F06, G30-31, and R418). To determine the pattern of the use of medical services, we collected the number of times that patients with HD visited different categories of institutions, including inpatient and outpatient clinics. To calculate the total medical expenditure of patients with HD, we collected information on all medical services used that were covered by the NIHS. The Institutional Review Board at the Seoul Metropolitan Government-Seoul National University Boramae Medical Center approved this study (IRB No. 07-2020-297). The need to obtain written informed consent was waived because the HIRA only provides anonymized data to researchers due to strict confidentiality guidelines.

Analysis of outcome measures

We first estimated the annual incidence and 10-year prevalence of HD during 2010–2019. The South Korean population data in the same period were obtained from the KOrean Statistical Information Service (http://kosis.kr/). The distribution of the age at diagnosis was also analyzed.

We then assessed the medical expenditure throughout the 10-year period and for each disease year. To calculate the annual medical expenditure of an individual, claim data for the use of all covered medical services were collected. We classified the patients into age groups (10-year intervals) to analyze the trend of medical expenditure by age. Finally, we traced the individual annual expenditure until 2019 to analyze the difference according to the disease duration.

We finally classified medical institutions into five categories: tertiary referral hospitals, general hospitals, primary hospitals, clinics, and long-term-care hospitals. We then calculated the number of patients during the study period. Finally, the prevalence of nonneurological comorbidity was determined. All statistical analyses were conducted using Stata (version 15; StataCorp LP, College Station, TX, USA) and SAS (version 9.3; SAS Institute, Cary, NC, USA) with the significance level set at $p<0.05$.

RESULTS

Incidence and 10-year prevalence of HD in South Korea

The annual number of HD cases in South Korea was 152.10±16.37 (mean±SD, range=139–473), and the incidence rate was 0.29±0.32 (range=0.28–0.34) per 100,000 persons. Table 1 lists the annual incidence, cumulative incidence, and number of patients with HD who used medical services at least once during each year. Based on the cumulative incidence over 10 years, we estimated the 10-year prevalence to be 2.22 per 100,000 persons considering the expected mortality of 25% over 10 years according to the survival data of patients with HD in South Korea.[11] Notably, the follow-up rate after diagnosis seemed to be low despite the survival data suggesting

Table 1. Number of newly registered HD cases in South Korea during 2010–2019

Year	Total population	Number of newly registered patients with HD	Cumulative number of new HD cases	Number of patients with HD who used medical service in each year	Estimated annual incidence (/100,000 persons)	Estimated cumulative incidence (/100,000 persons)
2010	50,515,666	144	144	144	0.29	0.29
2011	50,734,284	173	317	210	0.34	0.63
2012	50,948,272	168	485	230	0.33	0.95
2013	51,141,463	166	651	257	0.32	1.28
2014	51,327,916	150	801	281	0.29	1.57
2015	51,529,338	119	920	284	0.23	1.80
2016	51,696,216	139	1,059	328	0.27	2.07
2017	51,778,544	159	1,218	385	0.31	2.38
2018	51,826,059	143	1,361	414	0.28	2.65
2019	51,849,861	160	1,521	453	0.31	2.96

The total South Korean population was derived from resident registration data (in December of each year). Estimated annual incidence in each year=(new HD registration cases)/10^5×(total South Korean population in each year). Estimated annual cumulative incidence from the beginning to the corresponding year=(total number of new cases during the study period)/10^5×(average total South Korean population). HD, Huntington's disease.

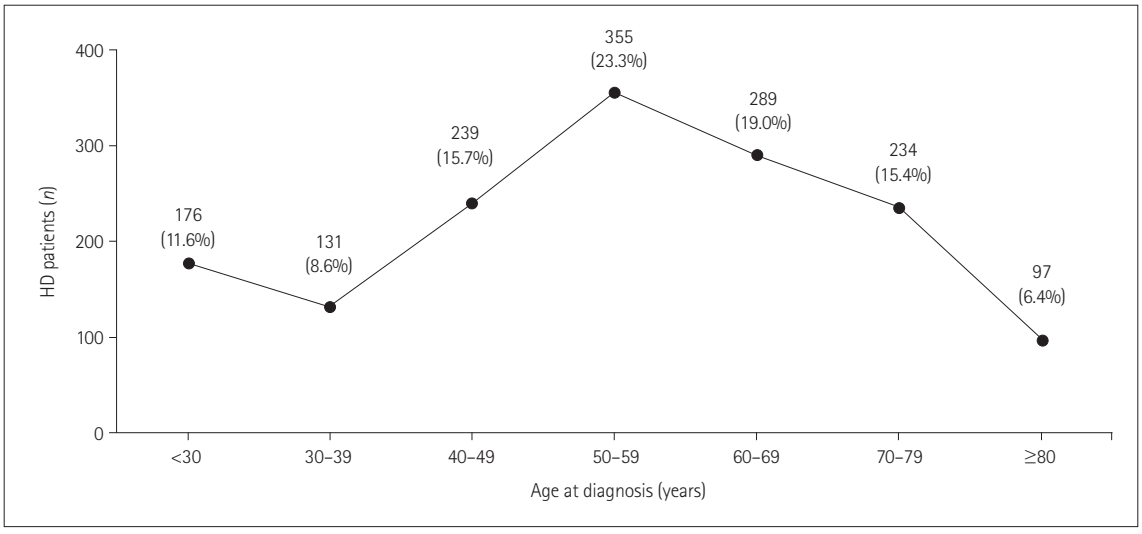

Fig. 1. Distribution of age at diagnosis of HD in South Korea. The peak age range at diagnosis was 50–59 years, followed by 60–69 years. HD, Huntington's disease.

that many were alive. For example, only 453 patients used medical services in 2019, which was 39.7% of the cumulative number of newly diagnosed patients with HD since 2010.

The distribution of age at diagnosis in HD is depicted in Fig. 1. The peak age range at diagnosis was 50–59 years old, with 355 cases (23.3%), followed by 60–69 years with 289 (19.0%). The incidence rates were similar in those aged 40–49 and 70–79 years, at 239 (15.7%) and 234 (15.4%), respectively.

Use of medical services and expenditure of patients with HD in South Korea

The annual number of medical institution visits by all patients with HD was 2524.9±519.3. This number increased 1.83-fold from 1,805 visits in 2010 to 3,302 in 2019. Tertiary and secondary general hospitals were the most frequently visited medical institutions (56.4% in 2019), for which the proportion had increased from 37.1% in 2011. Use of long-term-care hospitals also increased from 18.3% in 2011 to 32.2% in 2019, during which the proportion of clinic or public health center use decreased from 44.6% to 11.4% (Supplementary Table 1 and Supplementary Fig. 1 in the online-only Data Supplement). Tetrabenazine, a selective central monoamine-depleting agent, was the only drug approved in South Korea to treat hyperkinetic movement disorders in HD.[12] Tetrabenazine was prescribed to 133 (8.7%) of 1521 patients over the 10-year analysis period, with 99 cases in tertiary and secondary general hospitals, 22 in specialized clinics, and 12 in long-term-care hospitals.

Table 2. Medical expenses of patients with HD by disease duration and age

Disease duration (years)	Total expenses†	No. of patients with HD	Averaged expenses per patient	Age group (years)							*p*
				<30	30–39	40–49	50–59	60–69	70–79	≥80	
1	10,440,398,539	1,521	6,864,167 [6,299,675–6,864,168]	2,962,623 [2,250,911–3,674,335]	4,936,020 [4,090,746–5,781,293]	5,012,415 [4,376,931–5,647,898]	6,976,338 [6,250,617–7,702,058]	7,654,793 [6,772,240–8,537,345]	10,856,637 [9,465,585–12,247,689]	8,712,402 [6,978,566–10,446,238]	<0.001*
2	8,293,316,661	1,268	6,540,471 [5,987,772–6,540,471]	2,163,267 [1,624,623–2,701,911]	3,650,624 [2,952,346–4,348,902]	4,751,660 [4,089,796–5,413,524]	7,085,294 [6,276,751–7,893,386]	7,271,225 [6,369,875–8,172,576]	11,030,496 [9,487,287–12,582,705]	8,253,265 [6,333,480–10,173,051]	<0.001*
3	7,296,720,220	1,081	6,749,972 [6,189,067–6,749973]	2,600,349 [1,334,128–3,866,570]	4,717,956 [3,748,587–5,687,326]	4,894,140 [4,160,582–5,627,698]	7,336,303 [6,454,661–8,217,946]	7,631,930 [6,594,739–8,669,121]	10,540,853 [8,881,396–12,200,310]	9,094,842 [6,712,757–11,476,927]	<0.001*
4	6,434,108,281	916	7,024,136 [6,381,383–7,024,136]	2,198,173 [1,468,969–2,927,378]	6,724,805 [5,265,223–8,220,388]	5,923,574 [4,952,680–6,894,469]	7,375,021 [6,407,040–8,343,002]	7,304,680 [6,252,060–8,357,299]	10,726,134 [8,814,932–12,637,335]	11,135,781 [7,845,368–14,426,194]	<0.001*
5	5,420,102,175	758	7,150,531 [6,361,841–7,150,531]	2,376,106 [1,598,136–3,154,076]	4,861,644 [3,753,941–5,969,346]	5,785,401 [4,737,075–6,833,728]	7,890,698 [6,747,435–9,033,960]	9,261,029 [7,768,975–10,753,082]	10,374,024 [8,298,787–12,449,261]	9,442,503 [6,268,527–12,616,480]	<0.001*
6	4,292,441,254	627	6,845,999 [6,106,901–6,845,999]	2,465,345 [1,596,695–3,333,994]	3,512,436 [2,616,167–4,408,705]	5,864,677 [4,715,200–7,014,153]	8,747,969 [7,352,645–10,413,292]	8,410,840 [6,918,336–9,903,344]	10,285,761) [8,003,080–12,568,441]	5,235,320 [3,047,619–7,423,021]	<0.001*
7	3,601,481,540	489	7,364,993 [6,357,054–7,364,993]	2,905,390 [1,504,960–4,305,820]	4,321,039 [3,072,318–5,569,759]	6,444,013 [5,057,661–7,830,365]	9,761,899 [7,969,899–11,553,898]	9,499,686 [7,558,481–11,440,891]	9,303,899 [6,909,442–11,698,356]	7,071,358 [3,492,757–10,649,959]	<0.001*
8	2,367,540,863	342	6,922,634 [5,855,685–6,922,634]	2,437,999 [1,559,701–3,316,296]	4,266,139 [2,810,566–5,721,713]	5,125,987 [3,860,192–6,391,781]	9,291,884 [7,216,424–11,367,345]	8,806,778 [6,665,779–10,947,777]	12,044,474 [8,054,134–16,034,813]	5,703,862 [1,751,287–9,656,437]	<0.001*
9	1,278,917,920	214	5,976,252 [4,324,130–5,976,252]	2,370,360 [934,331–3,806,389]	3,403,421 [1,981,222–4,825,619]	4,797,275 [3,251,488–6,343,063]	8,613,785 [6,201,925–11,025,645]	8,071,521 [5,505,149–10,637,894]	8,652,334 [5,036,754–12,267,913]	1,824,456 [-240,110–3,889,022]	<0.001*
10	361,611,729	85	4,254,256 [2,442,626–4,254,256]	1,307,478 [548,328–2,066,646]	3,448,341 [1,497,258–5,399,424]	4,139,042 [1,970,879–6,307,205]	5,759,061 [3,169,472–8,348,650]	6,462,605 [3,295,929–9,629,281]	3,890,561 [1,008,393–6,772,729]	0	0.033*
	*p**			0.103	0.246	0.845	0.462	0.526	0.017*	0.017*	

Data are mean [95% confidence interval] values of medical expenses (in KRW) per patient.
*Significant at $p<0.05$; †Sum of annual medical expenses incurred by all patients with HD following diagnosis for each disease year.
HD, Huntington's disease.

When we estimated the medical expenditure for an individual with HD, the mean yearly cost was KRW 6,569,341± 895,097 per patient (USD 5,737, based on the average exchange rate in 2021 of KRW 1,145=USD 1). The mean annual medical expenditure for an individual ranged from KRW 4,254,256 (USD 3,715) to KRW 7,364,993 (USD 6,432) during the years of follow-up for the disease (Table 2 and Fig. 2A). Among age groups, the highest medical expenditure was observed in those aged 70–79 years, followed by those 80 years or older (Fig. 2B). Tracking the yearly medical expenditure of every individual after diagnosis revealed that this remained similar for the first 9 years after diagnosis and had a decreasing tendency after that. The persistent medical expenditure during the follow-up years was unchanged through all age groups (Supplementary Fig. 2 in the online-only Data Supplement) except in those aged ≥80 years.

In those aged ≥70 years, the medical expenditure was significantly decreased at years 10 and 6 of follow-up compared with the baseline (Supplementary Fig. 2F and G in the online-only Data Supplement; p=0.017 and 0.017, respectively). Regarding the yearly expenditure by disease duration, there was a significant difference among the age groups (p<0.001 during years 1–9, p=0.033 at year 10). The medical expenditure was highest for those aged 70–79 years and lowest for those younger than 30 years. Both those aged 30–39 and 40–49 years had lower medical expenses than those aged ≥50 years (Table 2).

Comorbidities of patients with HD in South Korea

This study also investigated the frequency of dementia and four nonneurological comorbidities between age groups of patients with HD, which may increase the overall medical burden for each patient. Dementia is a significant neurological symptom in HD, and is the most common reason for patients to lose the ability to independently perform activities of daily living and be admitted to a long-term-care hospital or nursing home. The prevalence of dementia in the total population with HD in South Korea was 37.5%, compared with 7.2% in the general elderly population in South Korea (age ≥60 years) according to a report of the National Institute of Dementia in 2019 (www.nid.or.kr). The frequency of dementia in HD increased further in older patients (Fig. 3).

Among the four nonneurological comorbidities, dyslipidemia was the most frequent (47.5%) in patients with HD, followed by hypertension (45.3%) and diabetes mellitus (32.1%), with chronic kidney disease found in only 4.0% of patients (Table 3). Table 3 lists the comorbidity prevalence summary for each age group of patients with HD compared with the data in the corresponding age group of the general population. The comorbidity data of the general South Korean population were obtained from the Korea Health Statistics 2019: the Korea National Health and Nutrition Examination Survey VII-1 (https://knhanes.kdca.go.kr/). Table 3 indicates that compared with the general population, patients with HD had higher prevalence rates of hypertension, diabetes, and dyslipidemia, and a lower prevalence of chronic kidney disease.

DISCUSSION

This study had revealed the updated incidence and prevalence of HD in South Korea using the well-established NHIS database that encompasses the entire South Korean population. Furthermore, this was the first study to estimate the use of medical services and expenditure of patients with HD in South Korea.

During 2010–2019, 1,521 new HD cases were identified in South Korea. The annual incidence estimated from this data was 0.28–0.34 per 100,000 persons. The incidence of HD in South Korea was higher than the data reported for mainland China (0.046)[3] and Taiwan (0.1, range=0.05–0.16).[4] The incidence (per 100,000 persons) seemed to be lower than in countries with high proportions of Caucasians: 0.8 in the United

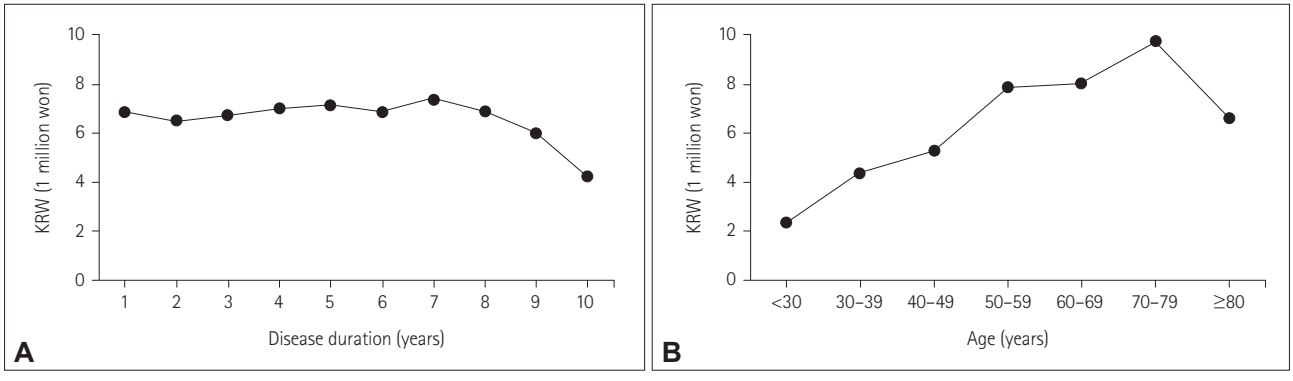

Fig. 2. Medical expenditure of an individual according to disease duration and age at diagnosis. A: Average total medical expenses per patient by disease duration. B: Average medical expenses of an individual patient with Huntington's disease in each age group.

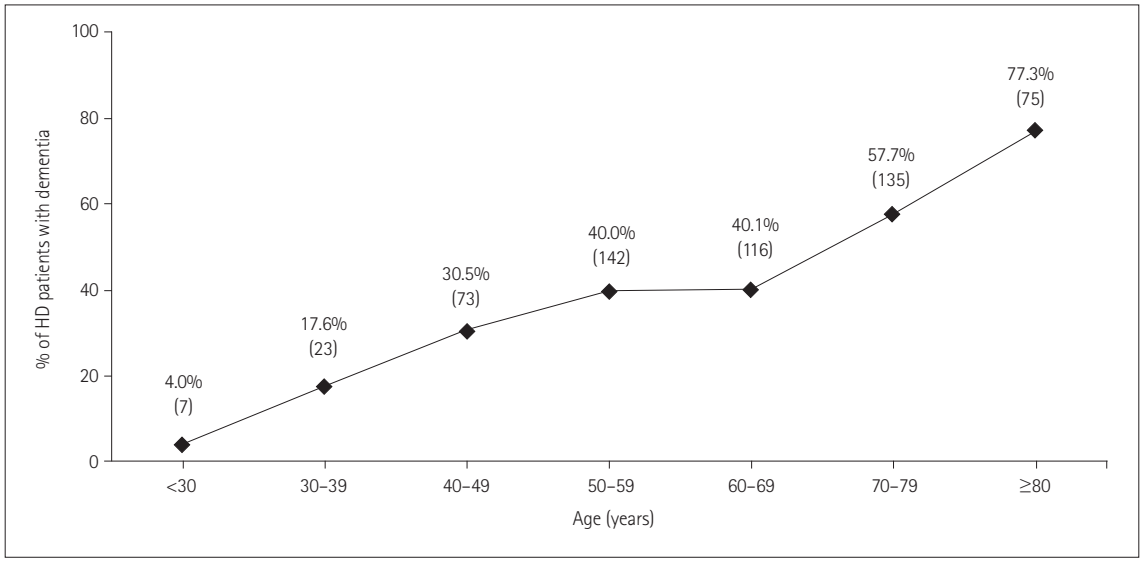

Fig. 3. Dementia and age distribution of patients with HD. The data show the frequency (number) of dementia cases in each age group of patients with HD. HD, Huntington's disease.

Table 3. Common comorbidities and age distribution in patients with HD

Population	Total case	Age group (years)					
		<30	30–39	40–49	50–59	60–69	≥70
Hypertension							
Patients with HD	690 (45.3)	12 (6.8)	22 (16.8)	51 (21.3)	148 (41.7)	189 (65.4)	268 (81)
General population	-	-	9.5	19.0	32.3	51.5	67.2
Diabetes mellitus							
Patients with HD	488 (32.1)	12 (6.8)	15 (11.5)	43 (18)	112 (31.5)	124 (42.9)	182 (55)
General population	-	-	2.7	8.1	14.4	24.4	31.0
Dyslipidemia							
Patients with HD	722 (47.5)	22 (12.5)	31 (23.7)	87 (36.4)	190 (53.5)	186 (64.4)	206 (62.2)
General population	-	-	10.0	16.4	31.2	42.8	35.1
CKD							
Patients with HD	61 (4.0)	1 (0.6)	0 (0)	2 (0.8)	8 (2.3)	17 (5.9)	33 (10)
General population	-	-	4.1	5.0	8.7	16.5	30.8

The case of patient with HD corresponds to this study, and the case of the general population was based on the KNHANES study. Data are *n* (%) values for each comorbidity.
CKD, chronic kidney disease; HD, Huntington's disease; KNHANES, Korea National Health and Nutrition Examination Survey.

Kingdom,[13] 0.47 in Spain,[14] 0.69 in Canada,[15] and 0.65 in Australia.[16]

The current study estimated the prevalence of HD in South Korea to be 2.22 per 100,000 persons. This was higher than a previous preliminary report[8] and also higher than the averaged prevalence of 0.40 per 100,000 (95% confidence interval [CI]=0.26–0.61) in a meta-analysis of studies from Asia.[1] The reported prevalence rates of HD in countries with high proportions of Caucasians were 10.6 in Ireland,[17] 6.29 in Australia,[16] 5.66 in the United Kingdom,[18] and 1.87 in Italy[19] (per 100,000 persons). The pooled prevalence among North America, Europe, and Australia was 5.70 (95% CI=4.42–7.35), and ranged from 1.56 to 12.08 per 100,000 persons.[1] Studies from Latin America indicated wide ranges of 4/100,000 in Mexico city[20] and 0.5/100,000 in Venezuela.[21] Considering the incidence of 0.28–0.34/100,000 and the survival of South Korean patients with HD not differing much from those in Western countries,[11] the prevalence rates found in previous studies from Asia seem to have been underestimated. Our data have therefore revealed that the actual prevalence of HD in South Korea might be tenfold higher than previously thought. This updated epidemiological information should be considered in future HD-related clinical trials.

As presented in Table 1, there was a large difference between the cumulative number of newly registered patients with HD and the number of patients with HD who used medical ser-

vices each year. Although a 25% mortality rate over 10 years was considered,[11] only up to 40% of patients with HD visited medical institutions after their diagnosis. This suggests that physicians did not regularly manage a considerable proportion of the patients with HD in South Korea. The number of patients with HD who used medical services each year therefore cannot represent the actual prevalence of HD, and the prevalence found in the previous study[8] might have been underestimated because it only considered data from those who used medical services. Furthermore, asymptomatic family members of patients with HD with the gene mutation were not considered because they did not use medical services. The same issue should be considered in the studies from China, Taiwan, or Japan if the analyzed databases resulted in only patients who visited medical institutions being considered.

The current study also found that HD diagnosis peaked at 50–59 years old and late-onset cases (in those aged ≥60 years) accounted for 40.1% of the total HD incidence in South Korea. On the other hand, in the United States the peak age range at onset was 40–49 years, and the Enroll-HD database indicated that late-onset cases comprised 512 out of 4,469 patients (11%).[22] Although this discrepancy might be related to a difference between the age at symptom onset (Enroll-HD study) and that at diagnosis (this study), we must also consider the following aspects to explain it. There might be diagnostic delay in South Korean patients with HD because behavioral symptoms can be the initial manifestations of HD, but they might be overlooked in the absence of movement disorders. This is intriguing because late-onset cases have been found to less frequently have behavioral symptoms as the initial manifestations according to a largest cohort data.[22] Further studies are needed to clarify this issue by prospectively investigating the pattern of clinical manifestation in South Korean patients with HD. Another issue was that the high frequency of late-onset cases might have been related to a genetic feature of HD in South Koreans, although this is yet to be identified. Similar to our data, Taiwanese data suggests that the peak age at onset was also 50–59 years.[4] Age at onset is related to the distribution of (CAG)*n* in the population, and the later age at onset in East Asia might therefore be related to the relatively stable (CAG)*n* in this population. Some studies have suggested that CCG interruption of the *HTT* might affect (CAG)*n* stability. The CCG7 polymorphism was shown to be associated with CAG allele expansion in Caucasians,[23] and CCG10 has been shown to be associated with this expansion in Japan.[24] There has been no clear association between CAG instability and CCG polymorphism in the Chinese population.[25] Further research is therefore needed to reveal the genetic difference potentially related to the low prevalence of HD in East Asia.

The use of medical services of patients with HD increased 1.83-fold from 2010 to 2019. The use of medical services also increased 2.5-fold in tertiary and secondary general hospitals from 2010 to 2019. The increase in the use of higher level hospitals might be attributable to the following factors: first, a better knowledge and awareness of HD among physicians, complemented by the availability of gene testing in those hospitals where HD diagnosis can be performed, particularly in older patients and those with no known family history of HD.[26] Second, it is possible that physicians have become more educated about HD diagnosis and so refer suspicious cases to higher-level medical institutions for genetic confirmation.

During the 10-year follow-up period, tetrabenazine was used in only 8.7% of patients, and 74.0% of prescriptions were from tertiary or general hospitals. Tetrabenazine was used in 18.5% of patients with HD in a German study.[27] In order to present the status of accessibility to HD treatment in South Korea, we analyzed the frequency of tetrabenazine prescription as it had been designated as an orphan drug in South Korea, although it was the only one approved for use in the management of Huntington chorea in South Korea. We demonstrated that tetrabenazine usage in South Korea was still uncommon and had been confined to tertiary or general hospitals. We expect that the proportion of prescriptions could increase slightly in the future with the increasing trend of tertiary or secondary general hospital use by patients with HD in South Korea. It is notable that a deuterated isomer of tetrabenazine is unavailable in South Korea, despite being approved in 2017.

HD treatment in South Korea is almost exclusively applied to symptomatic patients, but the overall medical cost was unexpectedly high. The persistent medical expenditure during the follow-up years was unchanged through all age groups (Supplementary Fig. 2A-E in the online-only Data Supplement) except in those aged ≥80 years. Patients with HD might need continuous medical support during the disease course. In those aged 70 years and older, the medical expenditure was decreased at years 10 and 6 of follow-up, which was possibly biased due to the small number of patients in these old age groups who survived.

We also investigated comorbidity patterns in South Korean patients with HD by analyzing the frequencies of hypertension, diabetes, dyslipidemia, and chronic kidney disease. The prevalence of diabetes is known to be high in patients with HD,[28,29] and we also found that the prevalence of diabetes in South Korean patients with HD was higher than that of the general population. Oxidative stress might play an important role in the high frequency of diabetes in HD. Oxidative stress increases phosphorylation of the insulin receptor and the insulin receptor substrate (IRS), which disturb insulin action,[30,31]

and IRS2 signaling has a role in the maintenance of pancreatic β-cell function.[32] In a study of an R6/2 mouse model to express exon 1 of the human mutant *HTT*, an increase in neuronal oxidative stress and aggravation of mitochondrial dysfunction in the brain were observed alongside elevated IRS2.[33] Hypertension can increase the disease burden in neurodegenerative disease,[34] and heart disease has been reported to be the second most common cause of death in HD.[35] Recent studies found higher cardiovascular risk and target organ damage even in individuals with premanifestation HD, emphasizing the importance of blood pressure control in patients with HD.[34,35] However, only a few studies have investigated the cardiovascular burden of HD. We found that the development of hypertension, diabetes, and dyslipidemia was more common in patients with HD in South Korea than in the general population, which could adversely affect the overall disease burden in these patients. Optimal management of these common comorbidities would help to improve their health and reduce the medical burden of patients with HD.

For a patient with dementia in community-based long-term care in South Korea, the mean annual cost was about KRW 21,400,000 (USD 17,859, based on the exchange rate of KRW 1197=USD 1), and the annual direct and indirect costs per patient were about KRW 7,900,000 (USD 6,571) and KRW 13,500,000 (USD 11,288), respectively.[36] Since the current study included the total cost for patients with HD who used medical institutions, our data only reflect the direct cost covered by the NHIS. Even though we did not cover uninsured costs, the medical cost of patients with HD seemed to be higher than that of patients with dementia. Furthermore, the high prevalence of dementia in patients with HD might also contribute to the medical expenditure. The proportion of dementia in patients with HD was higher than 50% in older groups (<70 years old), which might also contribute to the relatively high medical expenditure in these patients.

Furthermore, HD is an autosomal dominant disorder with typical anticipation through generations. Children of patients with HD tend to have worse outcomes when they must actively engage in economic activities because onset occurs earlier and more severely than in their parents. That situation is different from other degenerative diseases in which older patients tend to be cared for by their offspring. The health status therefore might not be efficiently controlled early in the course of HD, which could have contributed to the overall increase in medical expenditure.

There were several limitations in this study. The HIRA claim data did not include data for services such as over-the-counter drugs, or procedures that were not covered by the insurance. The use of medical services or the associated expenditure may therefore have been underestimated in this study. The NHIS is censured by death or other reasons, but we could not identify the specific number or causes of deaths from the HIRA data alone. We tried to improve the accuracy of epidemiology data by capturing the G10 code and the RID registration during the 10-year study period, which were closer to real-world data than previous studies. However, this study was based on claim data, and we therefore might not have detected patients with HD who were not diagnosed or asymptomatic patients who did not visit medical institutions. As a result, the estimated prevalence of HD in this study could have been underestimated. Furthermore, the medical expenditure analysis that used HIRA data only included the medical practices and prescriptions claimed by medical institutions. We therefore could not analyze data for the indirect costs such as expenses of the caregivers employment or secondary losses caused by family member and patients themselves due to the illness and care.

Notwithstanding these limitations, the HIRA contains comprehensive information relating to medical services such as treatment, medication, and procedures that covers 98% of the South Korean population.

In conclusion, this study has performed the first comprehensive analysis of the epidemiology and economic burden of patients with HD in South Korea. The prevalence of HD in South Korea was found to be about 2.22 per 100,000 persons, and medical expenditure was higher in patients with HD than in those with dementia. The current results could serve as a starting point for further research investment in HD in South Korea, which will ultimately improve the health of affected patients.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.0212.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to administrative data of Korean government. but are available from the corresponding author on reasonable request. Data can be available only after applying to the Healthcare Bigdata Hub (https://opendata.hira.or.kr/op/oph/selectCnfcUseAplPrsnt.do) and getting approval from the Health Insurance Review & Assessment Service in South Korea.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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