Journal of Obesity & Metabolic Syndrome 2026;35:198-210
https://doi.org/10.7570/jomes25060

Original Article

jomes
pISSN 2508-6235
eISSN 2508-7576

Epidemiology, Comorbidities, and Healthcare Costs of Prader–Willi Syndrome in South Korea Using the Korean National Health Insurance Service Database

Aram Yang[1], Yong Jun Choi[2], Eungu Kang[3], Yong Hee Hong[4], Sochung Chung[5,*]

[1]Department of Pediatrics, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul; [2]Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul; [3]Department of Pediatrics, Korea University Ansan Hospital, Ansan; [4]Department of Pediatrics, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon; [5]Department of Pediatrics, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, Korea

Background: Prader-Willi syndrome (PWS) is a rare genetic disorder associated with substantial comorbidity and early mortality. However, the epidemiologic burden on Asian populations, particularly in South Korea, remains poorly understood. This study evaluates the nationwide incidence, prevalence, mortality, comorbidities, and healthcare costs of PWS in South Korea.

Methods: We conducted a retrospective, population-based cohort study using the Korean National Health Insurance Database from 2005 to 2021. Among 2,553 individuals with PWS-related diagnostic codes, 458 patients were included in the study based on predefined criteria incorporating growth hormone therapy (GHT) or methylation-specific polymerase chain reaction testing. Epidemiologic trends, comorbidities, intensive care unit (ICU) admissions, and healthcare expenditures were analyzed.

Results: The overall birth incidence was 6.8 per 100,000 live births, with a significant increase evident after 2016. The median age at diagnosis was 1.0 years, and GHT was initiated at a median age of 2.0 years. The all-cause mortality rate was 3.5%, with pneumonia being the leading cause of death. ICU admission occurred in 25.5% of patients, often during infancy. Intellectual disability and/or developmental delay was present in 68.6% of patients, and type 2 diabetes mellitus in 15.1%. The mean cumulative healthcare cost per patient exceeded 86 million Korean won. Comorbidity prevalence and annual medical costs increased steadily over time.

Conclusion: This is the first nationwide study to quantify the long-term epidemiological and economic burden of PWS in South Korea. Our findings underscore the need for early diagnosis, integrated care models, and policy support for this complex population.

Key words: Prader-Willi syndrome, Prevalence, Incidence, Mortality, Epidemiology

Received June 17, 2025
Reviewed August 10, 2025
Accepted October 16, 2025

*Corresponding author
Sochung Chung
https://orcid.org/0000-0002-7655-2691

Department of Pediatrics, Konkuk University Medical Center, Konkuk University School of Medicine, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 05030, Korea
Tel: +82-2-2030-7553
Fax: +82-2-2030-7748
E-mail: scchung@kuh.ac.kr

The first two authors contributed equally to this study.

INTRODUCTION

Prader-Willi syndrome (PWS) is a rare, multisystem genetic disorder characterized by neonatal hypotonia, poor feeding in infancy, hyperphagia, obesity, intellectual disability, and various endocrinopathies. It is most commonly caused by a lack of expression of paternally inherited genes on chromosome 15q11–q13, due to paternal deletion, maternal uniparental disomy, or imprinting defects.[1,2] The estimated prevalence ranges from 1 in 8,290 to 1 in 30,000 individuals, with a global estimate of approximately 400,000 affected individuals, including approximately 20,000 in the United States.[3-7] PWS occurs equally in both sexes and across all racial and ethnic groups, with most cases arising sporadically.[8]

Due to its complex endocrine and neurodevelopmental manifes-

tations, PWS requires early diagnosis and coordinated multidisciplinary care. Growth hormone therapy (GHT), in particular, plays a central role in mitigating comorbidities and improving long-term outcomes.[9-12]

Despite these clinical advances, epidemiologic evidence remains limited. In addition, global studies have underscored the clinical and socioeconomic burden of PWS, most available data are derived from patient registries in Western countries or regional screening efforts,[13,14] resulting in a significant knowledge gap regarding the disease burden in Asian populations.

Moreover, PWS is associated with a significantly reduced life expectancy compared with the general population. Historically, only a minority of individuals reached the age of 40, with an annual mortality rate of approximately 3%, compared to 1% in the general population.[15] These outcomes underscore the importance of large-scale epidemiologic data to better understand the natural history and healthcare needs of PWS.

In South Korea, the National Health Insurance System (NHIS) and Rare Incurable Disease Registry offer a unique infrastructure by using standardized diagnostic codes and insurance claims to identify and follow patients with PWS.[16] These systems offer comprehensive coverage and enable longitudinal follow-up of rare disease cohorts. Since the approval of somatropin to treat PWS in South Korea in March 2004, GHT has been reimbursed for patients aged 2 years and older.[17]

Although several studies in South Korea have described clinical features of PWS, most are based on single-center experiences, limiting their generalizability.[15,18] Given the chronic and evolving nature of PWS, comprehensive nationwide data are needed to capture its full clinical and economic impacts. This study was designed to evaluate the nationwide incidence, prevalence, mortality, and comorbidities of PWS in South Korea, along with associated healthcare utilization and costs.

METHODS

Data source and study design

This retrospective and population-based cohort study used data from the Korean National Health Insurance Database (NHID), which includes healthcare utilization and screening information for approximately 97% of the South Korean population. The NHID is linked to the National Death Registry, National Health Screening Program, and Rare Incurable Disease Registry.[19] These datasets include demographic information, diagnostic codes from the 10th revision of the International Classification of Diseases (ICD-10), prescription records, procedure codes, and mortality data.

Under the Rare Disease Management Act, a 'rare incurable disease' in South Korea is defined as one affecting fewer than 20,000 individuals or presenting diagnostic challenges due to uncertain numbers of patients. Classification is determined through expert consultation, and patients meeting criteria have been eligible for financial support from the NHIS since 2009.[19] Upon meeting these conditions, patients receive a special reimbursement code that registers them in the Rare Incurable Disease Registry and provides substantial coverage for related medical expenses.[16]

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Study period and follow-up

We analyzed data from January 1, 2005, to December 31, 2021. A 1-year washout period was applied after GHT coverage began in 2004, to ensure accurate identification of incident cases (n = 80 excluded). Mortality follow-up continued until the end of the study period or the date of death.

Case definitions and cohort identification

PWS cases were identified based on three criteria: (1) ICD-10 diagnostic code Q87.1; (2) rare disease reimbursement code V158; and (3) evidence of either GHT for PWS or methylation-specific polymerase chain reaction (PCR) testing. GHT as a treatment for PWS has been reimbursed since 2004 and methylation PCR since 2016, both traceable via insurance claims. Patients who did not meet all three criteria were excluded to minimize misclassification. To ensure specificity, only those treated with somatropin approved for PWS were included. Approved agents during the study period were Genotropin (Pfizer), Eutropin (LG Chem), and SciTropin (SciGen Korea). The patient selection process and application of inclusion and exclusion criteria are detailed in Supplementary Fig. 1.

Prevalence was defined as the number of PWS patients alive and registered in the cohort during the study period. Overall birth inci-

dence was the number of newly identified PWS cases divided by the total number of live births between 2005 and 2021. Annual birth incidence was calculated yearly using the number of new PWS diagnoses and corresponding live births in each year. Mortality was identified using the linked death registry; however, detailed causes of death were not available. As linkage with the Statistics Korea mortality database was not feasible due to the rarity of the disease and small size of the disease cohort, causes of death were instead determined from the principal diagnoses and up to four additional diagnoses recorded on the insurance claim at the time of death and classified according to the criteria of the World Health Organization Mortality Database.[20]

Comorbidities are defined in Supplementary Table 1.

Statistical analysis

Categorical variables were summarized as frequencies and percentages and compared using chi-square or Fisher's exact tests. Continuous variables were expressed as means ± standard deviations or medians with interquartile ranges (IQRs) and compared using a Student's t-test or the Wilcoxon rank-sum test, as appropriate. Kaplan-Meier survival analyses and Cox proportional hazards models were used to evaluate mortality outcomes. Hazard ratios and 95% confidence intervals (CIs) were reported. All statistical analyses were performed using SAS version 9.4 (SAS Institute) and R software version 3.6.1 (R Foundation for Statistical Computing), and applying the 'survival' and 'survminer' packages. A two-sided *P*-value < 0.05 was considered statistically significant.

Ethical approval and patient consent statement

The Institutional Review Board of Kangbuk Samsung Hospital approved the study protocol (KBSMC 2023-07-036). The requirement for informed consent was waived due to the use of anonymized data.

RESULTS

Annual incidence and prevalence of PWS in South Korea

Over a period of 17 years, a total of 458 patients with PWS were

Table 1. Baseline characteristics of patients with Prader-Willi syndrome

Characteristic	Total (n = 458)	Male (n = 241)	Female (n = 217)	*P*
Age at diagnosis (yr)	1.0 (0.0–3.0)	1.0 (0.0–4.0)	1.0 (0.0–3.0)	0.122
Diagnosis age group (yr)				0.309
0–2	326 (71.2)	164 (68.0)	162 (74.7)	
2–5	44 (9.6)	28 (11.6)	16 (7.4)	
5–8	28 (6.1)	17 (7.1)	11 (5.1)	
>8	60 (13.1)	32 (13.3)	28 (12.9)	
Age at initiation of GHT (yr)	2.0 (2.0–5.0)	2.0 (2.0– 5.0)	2.0 (2.0– 4.0)	0.284
Duration of GHT (day)	1,697.0 (931.0–3,045.0)	1,731.5 (1,012.0–3,172.5)	1,616.0 (880.0–2,746.0)	0.017
Comorbidities				
CCI score	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.301
MI	12 (2.6)	6 (2.5)	6 (2.8)	1.000
CHF	17 (3.7)	9 (3.7)	8 (3.7)	1.000
PVD	3 (0.7)	2 (0.8)	1 (0.5)	1.000
CVD	11 (2.4)	4 (1.7)	7 (3.2)	0.431
RD	1 (0.2)	0	1 (0.5)	0.958
PUD	18 (3.9)	8 (3.3)	10 (4.6)	0.640
LD (mild to severe)	53 (11.6)	33 (13.7)	20 (9.2)	0.157
Renal disease	2 (0.4)	2 (0.8)	0	0.525
Tumor	1 (0.2)	1 (0.4)	0	1.000
T2DM	19 (4.1)	10 (4.1)	9 (4.1)	1.000

Values are presented as median (interquartile range) or number (%).
GHT, growth hormone therapy; CCI, Charlston comorbidity index; MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; CVD, cardiovascular disease; RD, rheumatic disease; PUD, peptic ulcer disease; LD, liver disease; T2DM, type 2 diabetes mellitus.

included in the study, and their baseline characteristics are presented in Table 1. The study population comprised 241 males (52.6%) and 217 females (47.4%), with a median age at diagnosis of 1.0 years (IQR, 0.0 to 3.0) and a median age at GHT initiation of 2.0 years (IQR, 2.0 to 5.0). The majority of patients (71.2%) were diagnosed before the age of 2 years, followed by 9.6% between 2 and 5 years, 6.1% between 5 and 8 years, and 13.1% at later ages. The median duration of GHT was 1,697 days, corresponding to approximately 4.6 years (IQR, 931 to 3,045 days).

The overall birth incidence was 6.8 per 100,000 births. Importantly, the mean annual birth incidence after 2016 showed a statistically significant increase compared with before 2016 (8.7 ± 1.8 vs. 5.8 ± 1.4, $P = 0.002$) (Fig. 1A). The overall incidence in the South Korean population was 0.053 per 100,000 person-years. No statistically significant difference was evident in the mean annual incidence before and after 2016 (0.05 ± 0.01 vs. 0.06 ± 0.02, $P = 0.743$) (Fig. 1B). However, the prevalence of PWS in the South Korean population was 0.64% and exhibited a steady upward trend (Fig. 1C). Fig. 1D illustrates the mean age at diagnosis and the age at GHT initiation for newly diagnosed patients each year. Both ages tended to decrease over time (age at diagnosis–coefficient = –0.129, $P = 0.005$; and age at GHT initiation–coefficient = –0.223, $P = 0.014$).

All-cause mortality and critical care

Over the 17-year period, 16 all-cause mortality cases were recorded, with a mean age at death of 22.0 ± 8.3 years (Table 2). The most common cause of death was respiratory disease (seven cases, 43.8%), followed by circulatory disease (five cases, 31.3%). Pneumonia-related deaths accounted for four cases (25.0% of total deaths and 57.1% of respiratory disease-related deaths). Compared with the general population, patients with PWS had a significantly elevated standardized mortality ratio (SMR) of 6.4 (95% CI, 3.7 to 10.4), based on an expectation of 2.5 deaths over the same period.

During the observation period, 117 patients with PWS (25.5%) were admitted to an intensive care unit (ICU), an event that was significantly more common in females than in males (30.4% vs. 21.2%, $P = 0.031$). Female sex was associated with ICU admission in a univariate analysis (odds ratio [OR], 1.5; 95% CI, 1.0 to 2.2; $P = 0.036$) but not after adjusting for age and intubation history (adjusted OR, 1.8; 95% CI, 0.9 to 3.7; $P = 0.114$). The first ICU admission typically occurred during the neonatal or infantile period (median age 0.0 years [IQR, 0.0 to 3.0]).

Comorbidities

Among major comorbidities, intellectual disability and/or developmental delay (ID/DD) was the most prevalent, occurring in 68.6% of patients (Table 3). ID/DD was diagnosed more frequently in males than in females (73.4% vs. 63.1%, $P = 0.023$), and at a later age (median 4.0 years [IQR, 2.0 to 8.0] vs. 3.0 years [IQR, 1.0 to 6.0], $P = 0.042$). Skeletal disorders (e.g., congenital musculoskeletal or thoracic deformities) were observed in 45.6% of patients, with scoliosis being the most common, occurring in 41.9%. The median age at initial diagnosis of scoliosis was 6.0 years (IQR, 3.0 to 11.0).

Behavioral disorders were identified in 26.2% of patients, with a median age at diagnosis of 10.0 years (IQR, 7.0 to 16.0). The prevalence was significantly higher in males than in females (31.1% vs. 20.7%, $P = 0.016$). Attention-deficit/hyperactivity disorder (ADHD) was diagnosed in 17.9% of patients, with a median age at diagnosis of 9.5 years (IQR, 7.0 to 12.0). Similar to behavioral disorders, ADHD was significantly more prevalent in males than in females (22.8% vs. 12.4%, $P = 0.006$). Depression was diagnosed in 13.1% of patients, with a median age at diagnosis of 12.0 years (IQR, 10.0 to 20.0).

At cohort entry, 4.1% of patients had type 2 diabetes mellitus (T2DM). During follow-up, the cumulative prevalence increased to 15.1% (69 patients). There was no significant difference in prevalence between males and females (16.6% vs. 13.4%, $P = 0.404$), but females were diagnosed at a younger age compared with males (median 13.0 years [IQR, 12.0 to 15.0] vs. 16.0 years [IQR, 13.0 to 18.0], $P = 0.019$). A sensitivity analysis using a stricter definition of T2DM (≥ 2 prescriptions within 1 year) showed consistent annual prevalence trends (Supplementary Fig. 2). Hypothyroidism was observed in 14.0% of patients and was significantly more common in males than in females (17.8% vs. 9.7%, $P = 0.017$). The median age at diagnosis was 1.0 years (IQR, 1.0 to 4.0).

Annual prevalence trends of comorbidities are illustrated in Fig. 2. Over the past decade, with the exception of ID/DD (Fig. 2A), the prevalence of all other conditions—including scoliosis, behavioral disorders, ADHD, T2DM, hypothyroidism, and depression—

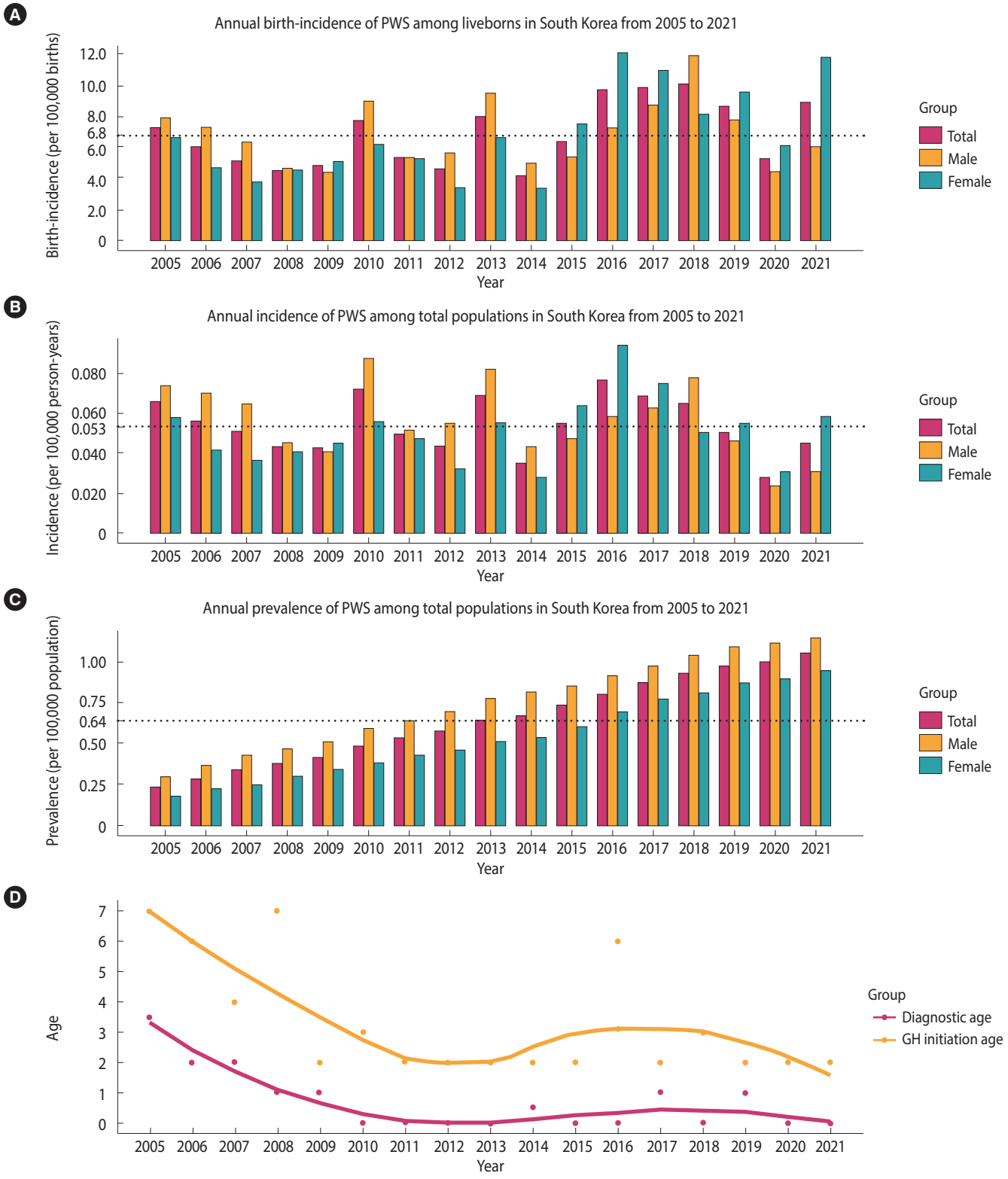

Figure 1. Trends in epidemiology and clinical management of Prader-Willi syndrome (PWS) in South Korea, 2005–2021. (A) Annual birth incidence of PWS among live-borns (per 100,000 births), stratified by sex. (B) Annual incidence of PWS in the total population (per 100,000 person-years), stratified by sex. (C) Annual prevalence of PWS in the total population (per 100,000 persons), stratified by sex. (D) Trends in median diagnostic age and growth hormone (GH) therapy initiation age over time (years).

Table 2. Clinical outcomes of patients with Prader-Willi syndrome

Variable	Total (n=458)	Male (n=241)	Female (n=217)	*P*
All-cause mortality	16 (3.5)	8 (3.3)	8 (3.7)	1.000
Age at death (yr)	22.0±8.3	25.8±7.7	18.2±7.4	0.068
CPR	9 (2.0)	6 (2.5)	3 (1.4)	0.606
Age at CPR (yr)	8.0 (0.0–25.0)	14.0 (0.0–25.0)	6.0 (3.0–16.0)	0.896
ICU admission	117 (25.5)	51 (21.2)	66 (30.4)	0.031
Age at ICU admission (yr)	0.0 (0.0–3.0)	0.0 (0.0–4.5)	0.0 (0.0–3.0)	0.494
Intubation	81 (17.7)	42 (17.4)	39 (18.0)	0.976
Age at intubation (yr)	0.0 (0.0–5.0)	0.0 (0.0–8.0)	0.0 (0.0–1.5)	0.507
Total medical cost (KRW)	86,082,258.7±67,979,238.1	97,719,107.3±82,633,257.5	73,158,385.4±43,259,364.2	0.000
NHIS coverage (KRW)	77,137,443.8±61,629,705.0	87,624,999.2±74,996,947.0	65,489,974.5±39,083,860.1	0.000
OOPE (KRW)	8,944,814.9±8,379,748.1	10,094,108.2±9,868,944.3	7,668,410.9±6,102,404.6	0.001

Values are presented as number (%), mean±standard deviation, or median (interquartile range).
CPR, cardiopulmonary resuscitation; ICU, intensive care unit; KRW, Korean won; NHIS, National Health Insurance Service; OOPE, out-of-pocket expense.

Table 3. Comorbidities at last follow-up among patients with Prader-Willi syndrome

Variable	Total (n=458)	Male (n=241)	Female (n=217)	*P*
ID/DD	314 (68.6)	177 (73.4)	137 (63.1)	0.023
Age at ID/DD diagnosis (yr)	4.0 (1.0–7.0)	4.0 (2.0–8.0)	3.0 (1.0–6.0)	0.042
Scoliosis	192 (41.9)	100 (41.5)	92 (42.4)	0.920
Age at scoliosis diagnosis (yr)	6.0 (3.0–11.0)	6.0 (3.0–11.0)	5.5 (3.0–10.0)	0.771
Behavior disorder	120 (26.2)	75 (31.1)	45 (20.7)	0.016
Age at behavior disorder diagnosis (yr)	10.0 (7.0–16.0)	11.0 (8.0–16.0)	9.0 (7.0–16.0)	0.274
ADHD	82 (17.9)	55 (22.8)	27 (12.4)	0.006
Age at ADHD diagnosis (yr)	9.5 (7.0–12.0)	10.0 (7.5–12.0)	8.0 (7.0–11.0)	0.344
T2DM	69 (15.1)	40 (16.6)	29 (13.4)	0.404
Age at T2DM diagnosis (yr)	15.0 (12.0–17.0)	16.0 (13.0–18.0)	13.0 (12.0–15.0)	0.019
Hypothyroidism	64 (14.0)	43 (17.8)	21 (9.7)	0.017
Age at hypothyroidism diagnosis (yr)	1.0 (1.0–4.0)	2.0 (1.0–4.0)	1.0 (1.0–2.0)	0.183
AED medication	60 (13.1)	42 (17.4)	18 (8.3)	0.006
Age at initiation of AED therapy (yr)	12.5 (4.0–19.0)	14.0 (6.0–21.0)	5.5 (2.0–18.0)	0.032
Depression	60 (13.1)	34 (14.1)	26 (12.0)	0.593
Age at depression diagnosis (yr)	12.0 (10.0–20.0)	13.0 (11.0–20.0)	11.0 (9.0–19.0)	0.265
OSA	58 (12.7)	30 (12.4)	28 (12.9)	0.996
Age at OSA diagnosis	6.0 (2.0–12.0)	5.5 (2.0–15.0)	6.0 (2.0–10.5)	0.623
Adenotonsillectomy	38 (8.3)	26 (10.8)	12 (5.5)	0.062
Age at adenotonsillectomy (yr)	5.0 (4.0–6.0)	5.0 (4.0–6.0)	5.5 (4.0–8.0)	0.267
CCI score	2.0 (1.0–3.0)	2.0 (1.0–4.0)	2.0 (1.0–3.0)	0.073

Values are presented as number (%) or median (interquartile range).
ID/DD, intellectual disability/developmental delay; ADHD, attention-deficit/hyperactivity disorder; T2DM, type 2 diabetes mellitus; AED, anti-epileptic drug; OSA, obstructive sleep apnea; CCI, Charlson comorbidity index.

showed a steady increase over time (Fig. 2B-G). Age-standardized versions of these trends, using the 2021 study population as the reference, are presented in Supplementary Fig. 3.

At the last follow-up, the most commonly observed comorbidities were ID/DD (68.6%), scoliosis (41.9%), behavioral disorders (26.2%), ADHD (17.9%), and T2DM (15.1%). Other conditions included hypothyroidism (14.0%), obstructive sleep apnea (12.7%), epilepsy requiring anti-epileptic drugs (13.1%), and de-

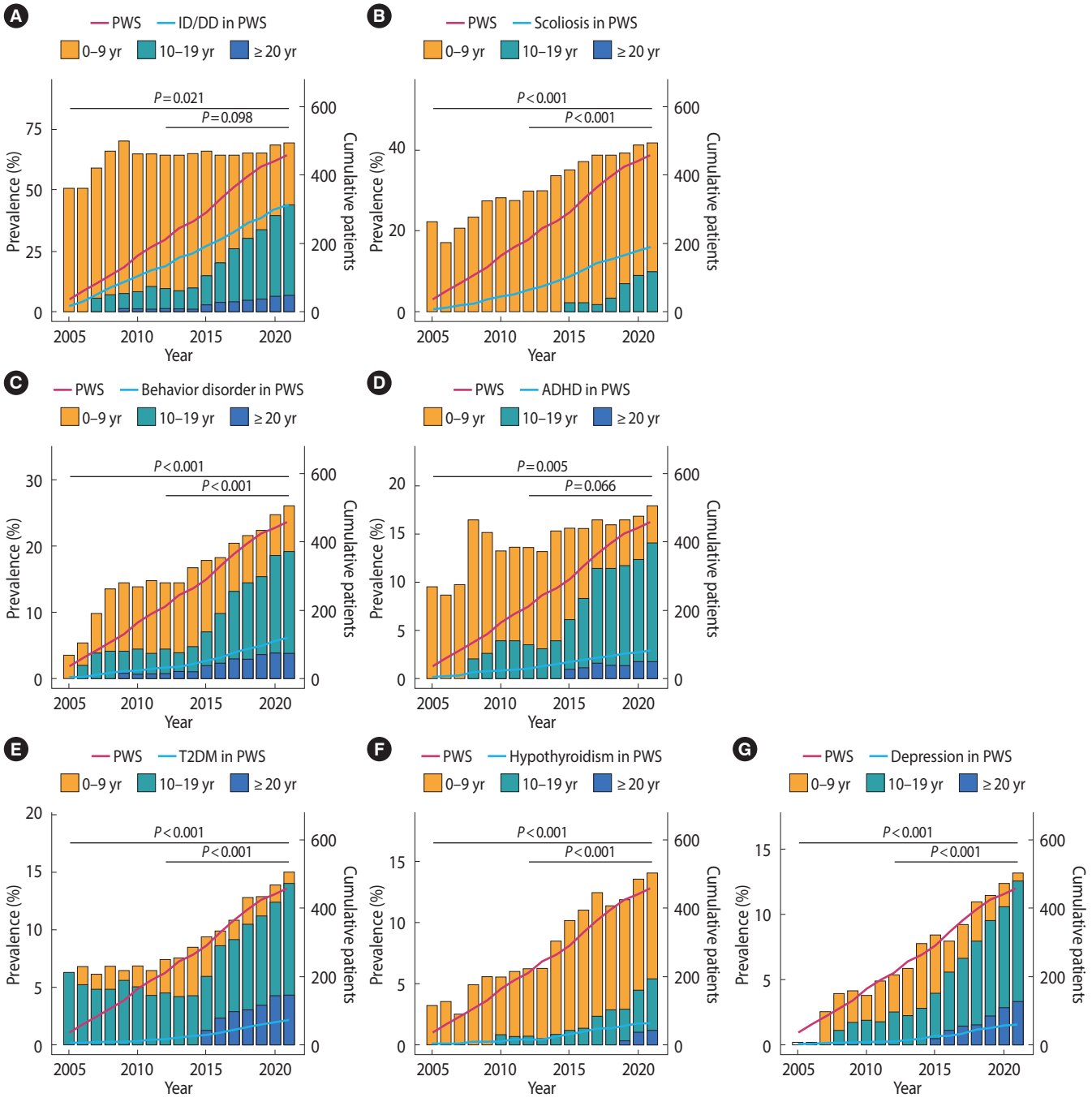

Figure 2. Annual prevalence of comorbidities in patients with Prader-Willi syndrome (PWS) in South Korea from 2005 to 2021. (A) Intellectual and developmental disabilities (ID/DD). (B) Scoliosis. (C) Behavioral disorders. (D) Attention-deficit/hyperactivity disorder (ADHD). (E) Type 2 diabetes mellitus (T2DM). (F) Hypothyroidism. (G) Depression. Each panel shows the annual prevalence (%) on the left Y-axis and cumulative number of affected PWS patients on the right Y-axis. Statistical significance was assessed for trends using *P*-values indicated above each panel.

pression (13.1%). Surgical interventions such as adenotonsillectomy were performed in 8.3% of patients. The median Charlson comorbidity index score was 2.0 (IQR, 1.0 to 3.0). These findings represent the cumulative disease burden at the last follow-up and are summarized in Table 3.

Medical costs

During the observation period, the mean medical cost per patient

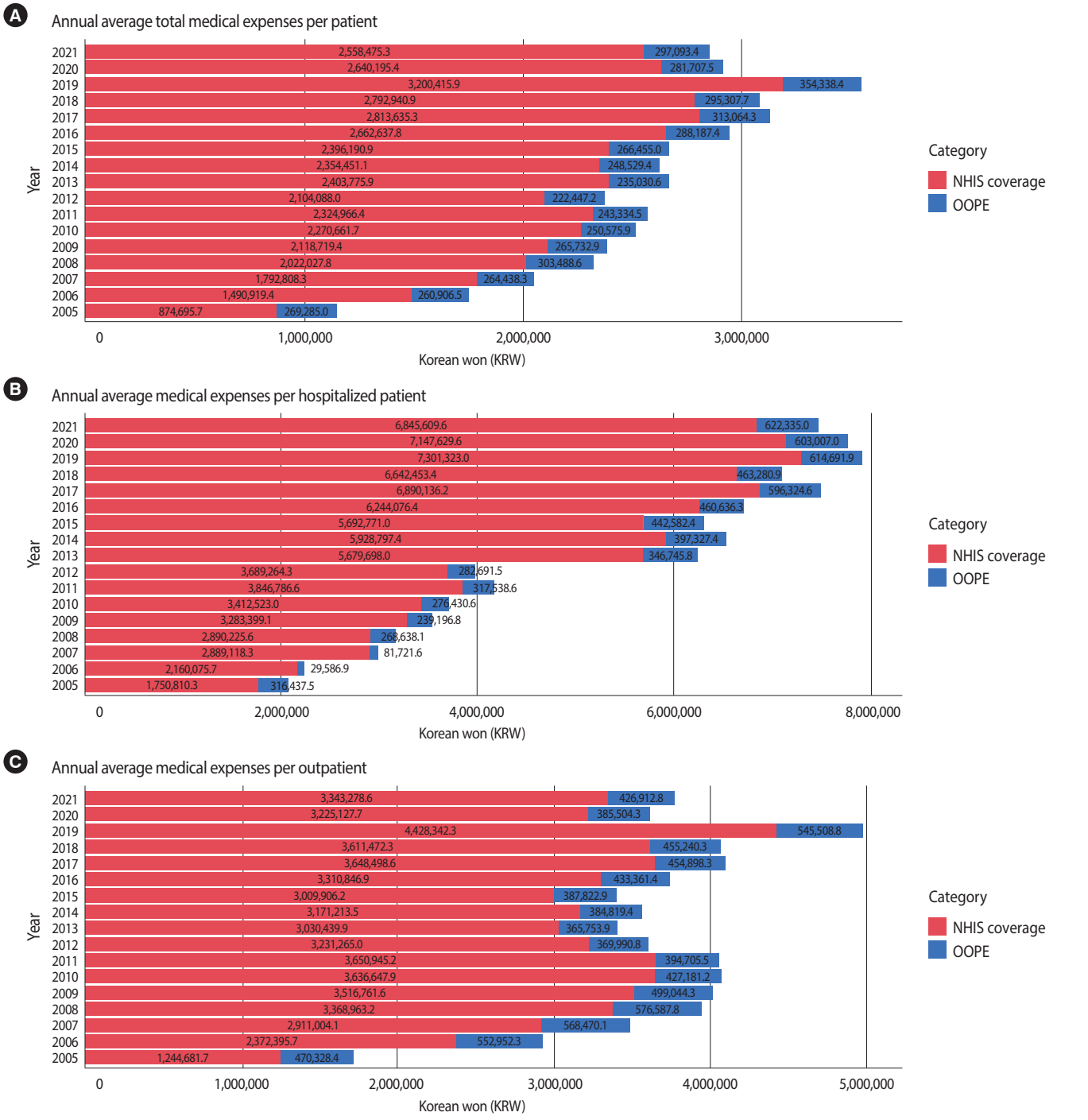

Figure 3. Annual average medical expenditures among patients with Prader-Willi syndrome (PWS) in South Korea from 2005 to 2021.(A) Average total medical expenses per patient. (B) Average medical expenses per hospitalized patient. (C) Average medical expenses per outpatient. Expenses are separated into National Health Insurance Service coverage and out-of-pocket expense (OOPE). All costs are presented in 2005 constant Korean won (KRW), adjusted using the healthcare price index from Statistics Korea.

was 86,082,258.7 ± 67,979,238.1 Korean won (KRW) (Table 2). Of this, out-of-pocket expenses (OOPE) accounted for 8,944,814.9 ± 8,379,748.1 KRW, and NHIS coverage accounted for 77,137,443.8 ± 61,629,705.0 KRW (Table 2). The mean annual healthcare expenditure per patient was 2,557,737 ± 560,814.7 KRW, comprising 274,113.1 ± 32,425.1 KRW in OOPE and 2,283,624.0 ± 544,482.6

KRW in NHIS-covered costs, adjusted to 2005 constant KRW using the healthcare price index (Supplementary Fig. 4A). The mean annual healthcare expenditure increased steadily by 96,580 KRW per year ($P < 0.001$) (Fig. 3A), with a greater contribution from inpatient care (398,864.6 KRW/year; $P < 0.001$) (Fig. 3B) compared with outpatient services (70,737 KRW/year; $P = 0.027$) (Fig. 3C). The medical expenditures in the pediatrics department compared with other departments are shown in Supplementary Fig. 4. Hospitalization costs increased significantly over time in both pediatric patients (280,908.1 KRW/year; $P < 0.001$) (Supplementary Fig. 4B) and non-pediatric departments (375,406.5 KRW/year; $P < 0.001$) (Supplementary Fig. 4C). Outpatient costs increased by 36,665.5 KRW per year in the pediatric departments without statistical significance ($P = 0.186$) (Supplementary Fig. 4D), whereas those in non-pediatric departments showed a significant annual rise of 40,333.6 KRW ($P < 0.001$) (Supplementary Fig. 4E).

DISCUSSION

This study includes all individuals diagnosed with PWS in South Korea over a 17-year period, based on nationwide health insurance and rare disease registry data. The apparent birth incidence was 6.8 per 100,000 live births, with a significant increase in annual incidence. Both median age at diagnosis and GHT initiation decreased over time, reflecting earlier detection and intervention in more recent years. All-cause mortality remained elevated, with a mean age at death of 22 years, and infections, particularly pneumonia, being the most common cause.

To our knowledge, this is the first population-based study in Asia to comprehensively evaluate the incidence, prevalence, mortality, and longitudinal trends in healthcare utilization among patients with PWS, and to include real-world data on psychiatric and metabolic comorbidities throughout the life course.

The overall birth incidence in our study aligns with previous estimates from Western populations (1 in 10,000–30,000).[4,21] Birth incidence increased notably after 2016, likely due to improved molecular diagnostics and greater clinical awareness following reimbursement of methylation-specific PCR testing in South Korea. This suggests that early-period incidence was likely underestimated. In contrast, our recent estimates are similar to those from a Australian newborn screening study (one in 8,290),[6] implying that the true birth incidence may be relatively consistent across populations when diagnostic access is adequate.

The observed rise in annual prevalence and decrease in diagnostic age over time highlight a shift toward earlier recognition and long-term disease management. Both the median age at diagnosis (1.0 years) and GHT initiation (2.0 years) decreased over the study period, indicating that policy changes and improved clinical insight may have allowed for timely intervention. These temporal improvements mirror trends seen in other rare diseases following expanded screening programs and insurance coverage.

Despite these advances, substantial morbidity and mortality persist. The all-cause mortality rate in our cohort was 3.5%, which is similar to prior reports of 1% to 4%.[22,23] The SMR was 6.4, indicating a markedly elevated mortality risk compared with the general population. This value is higher than the 3-fold excess mortality reported in United States claims data[24] but lower than the 11-fold risk observed in a Danish cohort,[25] likely reflecting the younger age distribution and the inclusion of earlier study years in our cohort. A systematic review reported an average age at death of 22.1 years, with infections (35.0%) and cardiovascular diseases (16.8%) the leading causes, and sudden death reported in 4.2% of cases.[26] Our findings align with those of international studies[5,23] indicating increased mortality due to respiratory, cardiovascular, and infectious causes, particularly pneumonia, which accounted for 25.0% of deaths in our study. Nearly one-quarter of patients required admission to an ICU, often during infancy, reflecting the early-life vulnerability of individuals with PWS.

The comorbidity burden was considerable. ID/DD was diagnosed in nearly 70% of patients, with higher prevalence and later diagnosis in males. Previous studies reported delayed motor development in 90%–100% of children with PWS, with milestones achieved at approximately twice the normal age.[21] Most individuals fall within the mild-intellectual-disability range (a mean intelligence quotient of 60–70), although approximately 40% have borderline or low-to-normal intelligence and 20% show moderate impairment.[27] In this study, The median age at ID/DD diagnosis (4.0 years) was later than GHT initiation (2.0 years), likely reflecting the time needed for longitudinal developmental assessment. Neuropsychiatric conditions such as behavioral disorders and ADHD

were also common, particularly in males, consistent with known sex differences in neurodevelopmental expression.[28,29]

Metabolic and endocrine disorders were prevalent. T2DM affected over 15% of our PWS cohorts—similar to previous reports from Sweden (16%)[30] and the Netherlands (17%),[31] and higher than the 9% reported in a Danish cohort.[25] No significant sex difference was observed, consistent with earlier studies.[18,32] Hypothyroidism was found in 14% of patients, with a higher prevalence in males. Although the reported prevalence of hypothyroidism in PWS ranges widely from 2% to 72%,[33] the influence of sex remains unclear. Some studies found no significant sex difference, while others reported greater prevalence in males.[34]

Scoliosis was diagnosed in 42% of patients, with a median age of 6 years at diagnosis, indicating the need for early spinal screening. This aligns with previous findings showing scoliosis in 39%–44% of PWS patients, with a median diagnosis age of 4.5–6.3 years.[35,36]

The annual prevalence of nearly all comorbidities, including scoliosis, behavioral disorders, ADHD, depression, T2DM, and hypothyroidism, increased over time. Previous studies have shown that, as individuals with PWS live longer, the risk of developing comorbidities increases.[30,37] These trends reinforce the progressive nature of PWS and highlight the need for anticipatory, multidisciplinary care.

Healthcare utilization and economic burdens among patients in our study were substantial. The average cumulative cost per patient exceeded 86 million KRW (approximately 65,000 United States dollar), with annual spending increasing over time, particularly for inpatient services. Cost increased across both pediatric and nonpediatric departments, reflecting the chronic and multisystemic nature of the disorder. Prior studies also noted high unmet medical needs in adults with PWS and emphasized the need for systematic screening.[31,38,39] One United States study reported that PWS patients incurred annual medical costs 8.8 times higher than those of controls ($14,907 vs. $819), underscoring the broader financial impact on families and the healthcare system.[39] These findings highlight the need for stronger policy support and coordinated care. While PWS is not part of Korea's national newborn screening regime, reimbursed genetic testing enables earlier, more accurate diagnosis.[40]

Future research should investigate genotype-phenotype correlations, longitudinal quality-of-life outcomes, and caregiver burdens. Integrating patient-reported outcomes and genetic subtype data into national cohorts may support more tailored and value-based care models.

This study has limitations. First, reliance on administrative claims data may lead to underreporting or misclassification. Behavioral and psychiatric outcomes defined by Anatomical Therapeutic Chemical codes may also include off-label use, leading to potential misclassification. In addition, although we applied a strict case definition incorporating diagnostic, reimbursement, and treatment codes, detailed clinical data such as genotype or body mass index were unavailable. Given this operational definition, we acknowledge the possibility of selection bias. To assess this, we conducted a sensitivity analysis using broader and narrower definitions (Supplementary Fig. 5). Although the number of identified cases varied across definitions, our selected definition showed the most reasonable alignment with incidence and prevalence estimates reported in international studies, supporting the robustness of our approach. Second, certain early or self-paid treatments may have been missed, although inclusion of methylation PCR data helped mitigate underascertainment. Moreover, individual-level treatment timelines such as switching or discontinuation could not be evaluated due to data granularity limitations. However, the observed birth incidence in our cohort closely matches those of international reports, suggesting a reasonable degree of cohort validity. Despite these limitations, the study is strengthened by its use of a nationwide dataset, rigorous inclusion criteria, and comprehensive longitudinal follow-up.

In conclusion, this study provides robust evidence of increasing PWS recognition, high comorbidity burden, and substantial healthcare costs in South Korea. While earlier diagnosis and treatment have improved, ongoing challenges remain, particularly in managing neurodevelopmental and metabolic complications. These findings support the need for integrated care models and targeted health policy efforts to address the complex, lifelong needs of individuals with PWS.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found online at https://doi.org/10.7570/jomes25060.

CONFLICTS OF INTEREST

Sochung Chung and Yong Hee Hong are editorial board members of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. There are no other potential conflicts.

ACKNOWLEDGMENTS

This study was supported by the 2022 *Journal of Obesity & Metabolic Syndrome* Research Grant of the Korean Society for the Study of Obesity (Grant No. KSSO-J-2023001).

AUTHOR CONTRIBUTIONS

Study concept and design: AY and SC; acquisition of data: AY, YJC, EK, and YHH; analysis and interpretation of data: AY, YJC, EK, and YHH; drafting of the manuscript: AY and YJC; critical revision of the manuscript: AY and SC; statistical analysis: YJC; obtained funding: AY and SC; administrative, technical, or material support: AY and SC; and study supervision: SC.

DATA AVAILABILITY

Data were obtained from the Korean National Health Insurance Service (NHIS; https://nhiss.nhis.or.kr) under institutional approvals (REQ202302538-047 [NHIS-2024-1-220] and REQ202508 0402-001 [NHIS-2025-09-1-066]). The latter dataset was re-extracted under identical conditions for revision analyses. Due to data-sharing restrictions, NHIS data are not publicly available; however, operational definitions and code lists are provided in Supplementary Table 1 to support reproducibility.

REFERENCES

1. Chung SC, Kim DH, Hong CH. Molecular diagnostic test for Prader-Willi syndrome with SNRPN expression. J Korean Soc Pediatr Endocrinol 1999;4:226-30.
2. Chung SC, Kim DH. A case of mosaicism in Prader-Willi syndrome: detection using fluorescent in situ hybridization. J Korean Soc Pediatr Endocrinol 2000;5:121-6.
3. Vogels A, Van Den Ende J, Keymolen K, Mortier G, Devriendt K, Legius E, et al. Minimum prevalence, birth incidence and cause of death for Prader-Willi syndrome in Flanders. Eur J Hum Genet 2004;12:238-40.
4. Lionti T, Reid SM, White SM, Rowell MM. A population-based profile of 160 Australians with Prader-Willi syndrome: trends in diagnosis, birth prevalence and birth characteristics. Am J Med Genet A 2015;167A:371-8.
5. Pacoricona Alfaro DL, Lemoine P, Ehlinger V, Molinas C, Diene G, Valette M, et al. Causes of death in Prader-Willi syndrome: lessons from 11 years' experience of a national reference center. Orphanet J Rare Dis 2019;14:238.
6. Godler DE, Ling L, Gamage D, Baker EK, Bui M, Field MJ, et al. Feasibility of screening for chromosome 15 imprinting disorders in 16,579 newborns by using a novel genomic workflow. JAMA Netw Open 2022;5:e2141911.
7. Butler MG. Prader-Willi syndrome: current understanding of cause and diagnosis. Am J Med Genet 1990;35:319-32.
8. Driscoll DJ, Miller JL, Cassidy SB. Prader-Willi syndrome. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews [Internet]. University of Washington, Seattle; 1993-2026 [cited 2026 Mar 24]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1330
9. Daley SF, Fermin Gutierrez MA, Mendez MD. Prader-Willi syndrome. In: StatPearls. StatPearls Publishing; 2026 [cited 2026 Mar 24]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553161
10. Butler MG, Thompson T. Clinical and genetic findings with natural history of Prader-Willi syndrome. In: Butler MG, Lee PDK, Whitman BY, editors. Management of Prader-Willi syndrome. Springer; 2022. p. 3-50.
11. Chung SC. Metabolic effects of growth hormone. J Korean Soc Pediatr Endocrinol 2000;5:23-7.
12. Shin HJ, Kim DH. Effects of growth hormone therapy in Prader-Willi syndrome. J Korean Soc Pediatr Endocrinol 2000;5:52-9.
13. Dumbuya JS, Zeng C, Deng L, Li Y, Chen X, Ahmad B, et al. The impact of rare diseases on the quality of life in paediatric patients: current status. Front Public Health 2025;13:1531583.

14. López-Bastida J, Oliva-Moreno J, Linertová R, Serrano-Aguilar P. Social/economic costs and health-related quality of life in patients with rare diseases in Europe. Eur J Health Econ 2016;17 Suppl 1:1-5.
15. Whittington JE, Holland AJ, Webb T, Butler J, Clarke D, Boer H. Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK Health Region. J Med Genet 2001;38:792-8.
16. Jang J, Choi JK, Kim JY, Choi CH. The progress of designation of rare disease for national management. Jugan Geongang Gwa Jilbyeong 2025;18:305-19.
17. Yang A. Prader-Willi syndrome and growth hormone therapy: exploring the precise management of hypothalamic short stature: a review. Precis Future Med 2023;7:107-16.
18. Yang A, Kim J, Cho SY, Jin DK. Prevalence and risk factors for type 2 diabetes mellitus with Prader-Willi syndrome: a single center experience. Orphanet J Rare Dis 2017;12:146.
19. Lim SJ, Jang SI. Leveraging national health insurance service data for public health research in Korea: structure, applications, and future directions. J Korean Med Sci 2025;40:e111.
20. World Health Organization. WHO mortality database [Internet]. WHO; 2025 [cited 2026 Mar 24]. Available from: https://www.who.int/data/data-collection-tools/who-mortality-database
21. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genet Med 2012;14:10-26.
22. Höybye C, Tauber M. Approach to the patient with Prader-Willi syndrome. J Clin Endocrinol Metab 2022;107:1698-705.
23. Butler MG, Manzardo AM, Heinemann J, Loker C, Loker J. Causes of death in Prader-Willi syndrome: Prader-Willi Syndrome Association (USA) 40-year mortality survey. Genet Med 2017;19:635-42.
24. McCandless SE, Suh M, Yin D, Yeh M, Czado S, Aghsaei S, et al. SUN-604 US prevalence & mortality of Prader-Willi syndrome: a population-based study of medical claims. J Endocr Soc 2020;4(Supplement 1):SUN-604.
25. Hedgeman E, Ulrichsen SP, Carter S, Kreher NC, Malobisky KP, Braun MM, et al. Long-term health outcomes in patients with Prader-Willi Syndrome: a nationwide cohort study in Denmark. Int J Obes (Lond) 2017;41:1531-8.
26. Bellis SA, Kuhn I, Adams S, Mullarkey L, Holland A. The consequences of hyperphagia in people with Prader-Willi Syndrome: a systematic review of studies of morbidity and mortality. Eur J Med Genet 2022;65:104379.
27. Whittington J, Holland A, Webb T, Butler J, Clarke D, Boer H. Academic underachievement by people with Prader-Willi syndrome. J Intellect Disabil Res 2004;48:188-200.
28. Gito M, Ihara H, Ogata H, Sayama M, Murakami N, Nagai T, et al. Gender differences in the behavioral symptom severity of Prader-Willi syndrome. Behav Neurol 2015;2015:294127.
29. Guinovart M, Coronas R, Caixàs A. Psychopathological disorders in Prader-Willi syndrome. Endocrinol Diabetes Nutr (Engl Ed) 2019;66:579-87.
30. Giesecke J, Oskarsson A, Petersson M, Nordenvall AS, Tettamanti G, Nordgren A, et al. Comorbidities, endocrine medications, and mortality in Prader-Willi syndrome: a Swedish register study. J Clin Med 2025;14:1307.
31. Pellikaan K, Rosenberg AG, Kattentidt-Mouravieva AA, Kersseboom R, Bos-Roubos AG, Veen-Roelofs JM, et al. Missed diagnoses and health problems in adults with Prader-Willi syndrome: recommendations for screening and treatment. J Clin Endocrinol Metab 2020;105:e4671-87.
32. Clerc A, Coupaye M, Mosbah H, Pinto G, Laurier V, Mourre F, et al. Diabetes mellitus in Prader-Willi syndrome: natural history during the transition from childhood to adulthood in a cohort of 39 patients. J Clin Med 2021;10:5310.
33. Madeo SF, Zagaroli L, Vandelli S, Calcaterra V, Crinò A, De Sanctis L, et al. Endocrine features of Prader-Willi syndrome: a narrative review focusing on genotype-phenotype correlation. Front Endocrinol (Lausanne) 2024;15:1382583.
34. Iughetti L, Vivi G, Balsamo A, Corrias A, Crinò A, Delvecchio M, et al. Thyroid function in patients with Prader-Willi syndrome: an Italian multicenter study of 339 patients. J Pediatr Endocrinol Metab 2019;32:159-65.
35. Miao M, Zhao GQ, Zhou Q, Chao YQ, Zou CC. Orthopedic manifestations in children with Prader-Willi syndrome. BMC Pediatr 2024;24:118.
36. Crinò A, Armando M, Crostelli M, Mazza O, Bruzzese D, Convertino A, et al. High prevalence of scoliosis in a large co-

hort of patients with Prader-Willi syndrome. J Clin Med 2022;11:1574.

37. Luccarelli J. Demographics and medical comorbidities among hospitalized patients with Prader-Willi syndrome: a National Inpatient Sample analysis. Am J Med Genet A 2022;188:2899-907.
38. Chevreul K, Berg Brigham K, Clément MC, Poitou C, Tauber M. Economic burden and health-related quality of life associated with Prader-Willi syndrome in France. J Intellect Disabil Res 2016;60:879-90.
39. Shoffstall AJ, Gaebler JA, Kreher NC, Niecko T, Douglas D, Strong TV, et al. The high direct medical costs of Prader-Willi syndrome. J Pediatr 2016;175:137-43.
40. Mahmoud R, Singh P, Weiss L, Lakatos A, Oakes M, Hossain W, et al. Newborn screening for Prader-Willi syndrome is feasible: early diagnosis for better outcomes. Am J Med Genet A 2019;179:29-36.