# Incidence and Prevalence of Central Precocious Puberty in Korea: An Epidemiologic Study Based on a National Database

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**Objectives** To investigate the prevalence and incidence of central precocious puberty in Korea using claims data provided by the Health Insurance Review and Assessment Service in Korea as the population-based epidemiologic study.

**Study design** In this national registry-based, longitudinal, epidemiologic study, patients who were registered with an *International Classifications of Diseases, Tenth Revision* diagnosis of central precocious puberty (E22.8 according to *International Classifications of Diseases, Tenth Revision*) and treated with gonadotropin-releasing hormone agonist were included. We assessed the age- and sex-specific prevalence and incidence rates of central precocious puberty in Korea from 2008 to 2014.

**Results** A total of 37 890 girls and 1220 boys were newly registered with a diagnosis of central precocious puberty from 2008 to 2014. The overall incidence of central precocious puberty during the study period was 122.8 per 100 000 persons (girls, 262.8; boys, 7.0). The overall prevalence of central precocious puberty during the study period was 193.2 per 100 000 persons (girls, 410.6; boys, 10.9). The incidence and prevalence of central precocious puberty steeply increased during the study period in both girls and boys.

**Conclusions** This epidemiologic study, based on a national registry that included Korean children, demonstrated that the incidence and prevalence rates of central precocious puberty were high and increased steeply during the study period. Further investigations to determine the underlying causes for this rapid increase in central precocious puberty are needed. *(J Pediatr 2019;208:221-8)*.

Precocious puberty is defined as the development of secondary sexual characteristics before 8 years of age in girls and 9 years of age in boys. Over time, earlier sexual maturation has been observed worldwide because of improvements in nutrition and health as a result of improved socioeconomic and sociohygienic conditions.[1] However, in the last few decades European studies have demonstrated that the tendency toward an earlier start of puberty has slowed or stopped in some populations.[2-4] This might indicate that sufficiently improved environmental factors, such as nutrition, hygiene, and health, have allowed the genetic potential for growth and maturation to be fully expressed.[5] In contrast, The Copenhagen Pubertal Study comparing cohorts from 1991 and 2006 found significantly earlier breast development among those girls born more recently.[6] However, this study did not demonstrate an earlier increase in gonadotropin and estradiol levels in girls with early breast development, suggesting that earlier thelarche may have been caused by a gonadotropin-independent phenomenon with increased estrogenic bioavailability or sensitivity rather than true precocious puberty.[7] Two American studies assessing the onset of puberty in girls in the Pediatric Research in Office Settings (PROS), and in boys in the Third National Health and Nutrition Examination Survey reported that puberty started at younger ages than those of currently used norms.[8-10] On the basis of the PROS study, the Lawson Wilkins Pediatric Endocrine Society proposed that the occurrence of either breast or pubic hair development before age 7 years in white girls and before age 6 years in African American girls be considered precocious.[11] However, some question the validity of the PROS study because of selection and observer bias.[7,12,13] Moreover, retrospective studies evaluating the underlying pathology in girls with central precocious puberty have demonstrated that 6%-12% of girls evaluated for central precocious puberty with pubertal onset, even after the age of 6 years, may have been misdiagnosed with intracranial abnormalities or pathologic endocrine disorders.[14-16] Therefore, the occurrence

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| GnRH | Gonadotropin-releasing hormone |
| HIRA | Health Insurance Review and Assessment Service |
| ICD-10 | *International Classifications of Diseases, Tenth Revision* |
| NWT | Northwest Tuscany |
| PROS | Pediatric Research in Office Settings |

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of signs of puberty in 6- to 8-year-old girls should not be considered normal or benign.[15]

Although lowering the age limit for initiating an evaluation of precocious puberty in girls is controversial, a significant increase in the number of girls diagnosed with central precocious puberty based on conventional criteria using the gonadotropin-releasing hormone (GnRH) stimulation test has recently been reported.[17] A Danish study, based on national registries, reported that 0.2% of all Danish girls and <0.05% of Danish boys had some form of precocious pubertal development, and the incidence of precocious puberty was constant during the study period from 1993 to 2001.[18] In addition, a recent study in Korea demonstrated that the annual incidence of central precocious puberty in girls significantly increased by about 15 times from 2004 to 2010.[19] Although several epidemiologic studies of precocious puberty have been reported, it is not clear whether estimates of the prevalence and incidence of precocious puberty are accurate and whether the incidence of precocious puberty is abruptly increasing in some populations.

The present study aimed to investigate the incidence and prevalence of central precocious puberty in Korea using national registry data provided by the Health Insurance Review and Assessment Service (HIRA).

## Methods

This study was conducted as a retrospective population-based study to investigate the incidence and prevalence of central precocious puberty in Korean children by using HIRA claims data from January 1, 2008, to December 31, 2014. Korea has a national health insurance system that provides medical insurance coverage to all its inhabitants, and each individual is registered with a health insurance identification number. All Korean patients who visit a hospital are registered with diagnoses according to the World Health Organization's *International Classifications of Diseases, Tenth Revision* (ICD-10). HIRA conducts reviews for proper diagnosis and management and for assessment of healthcare quality and medical fees. We included girls who were both registered with an ICD-10 diagnosis of central precocious puberty (E22.8 according to ICD-10) before 9 years of age and were treated with GnRH agonist. We included boys who were both registered before 10 years of age and were treated with GnRH agonist. Because there is a lag time of approximately 1.5 years between the first recognition of signs of puberty by parents and the establishment of a diagnosis of central precocious puberty in a hospital,[20] we included only girls who were registered with the diagnosis of central precocious puberty before 9 years of age and boys before 10 years of age for our estimation of the incidence of central precocious puberty. For the estimation of the prevalence of central precocious puberty, we included girls who were registered with the diagnosis of central precocious puberty before 12 years of age and boys who were registered with the diagnosis of central precocious puberty before 13 years of age, the ages at which the national health insurance system allowed treatment for central precocious puberty. The diagnosis of central precocious puberty was made by the following criteria: development of secondary sexual characteristics before 8 years of age in girls (Tanner stage B2 or above) and before 9 years of age in boys (Tanner stage G2 or above, determined as testicular volume >4 mL); advanced bone age; and a peak luteinizing hormone level >5 IU/L after a GnRH stimulation test. HIRA conducted a chart review of all identified medical records of patients with central precocious puberty to confirm the proper diagnosis. This study was approved by the Institutional Review Board of Severance Hospital (No.4-2017-0455).

### Calculation of Incidence and Prevalence

We calculated the incidence of central precocious puberty as the number of children that received a diagnosis of central precocious puberty for the first time during that calendar year divided by the total number of children at risk living in Korea during that calendar year. Incidence is reported using exact CIs, which were calculated using the Ulm formula.[21] In addition, we calculated the prevalence of central precocious puberty as the number of children registered with the diagnosis of central precocious puberty during that calendar year divided by the total number of children living in Korea during that calendar year. The 95% CIs of prevalence with a .05 significance level were also calculated using following formula; $p \pm 1.96\sqrt{\frac{p(1-p)}{n}}$ ($p$, prevalence; $n$, sample size). Sex-specific and age-specific incidence and prevalence calculations of central precocious puberty were performed using population data available from the National Institute of Statistics of Korea.[22] Both incidence and prevalence were calculated per 100 000 inhabitants at that age and sex.

## Results

A total of 37 890 girls and 1220 boys were newly registered with a diagnosis of central precocious puberty from 2008 to 2014. The incidence of central precocious puberty according to sex and calendar year is shown in **Table I** and **Figure 1**. The overall incidence of central precocious puberty during the study period was 122.8 per 100 000 persons (girls, 262.8; boys, 7.0). The incidence of central precocious puberty steeply increased during the study period from 2008 to 2014 both in girls and boys. The incidence of central precocious puberty in girls increased 4.7 times during the study period from 89.4 to 415.3 per 100 000 in girls who were younger than 9 years of age. In boys, the incidence of central precocious puberty increased 9.2 times during the study period from 1.6 to 14.7 per 100 000 in boys who were younger than 10 years of age. Although the incidence in boys was lower than that seen in girls, the rate of the increase in incidence was higher in boys. The incidence of central precocious puberty according to sex and age at diagnosis during the study period is shown in **Figure 2**. The incidence of central precocious puberty

**Table I. Sex-specific annual incidence (per 100 000 persons) of central precocious puberty with CI in Korean children**

| | Girls | | | | Boys | | | | Total | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | No. of cases (n) | Population at risk (n) | Incidence | CI | No. of cases (n) | Population at risk (n) | Incidence | CI | No. of cases (n) | Population at risk (n) | Incidence | CI |
| 2008 | 1956 | 2 187 614 | 89.4 | 85.9-93.9 | 42 | 2 695 506 | 1.6 | 1.1-2.1 | 1998 | 4 883 120 | 40.9 | 39.1-42.8 |
| 2009 | 2878 | 2 108 642 | 136.5 | 131.5-141.6 | 57 | 2 600 690 | 2.2 | 1.7-2.8 | 2935 | 4 709 332 | 62.3 | 60.1-64.6 |
| 2010 | 3646 | 2 044 376 | 178.3 | 172.6-184.2 | 104 | 2 507 717 | 4.1 | 3.4-5.0 | 3750 | 4 552 093 | 82.4 | 79.8-85.1 |
| 2011 | 5965 | 2 022 613 | 294.9 | 287.5-302.5 | 154 | 2 438 991 | 6.3 | 5.4-7.4 | 6119 | 4 461 604 | 137.1 | 133.7-140.6 |
| 2012 | 6793 | 2 021 064 | 336.1 | 110.2-115.5 | 172 | 2 412 106 | 7.1 | 6.1-8.3 | 6965 | 4 433 170 | 157.1 | 153.4-160.8 |
| 2013 | 8286 | 2 016 583 | 410.9 | 402.1-419.8 | 343 | 2 394 894 | 14.3 | 12.8-15.9 | 8629 | 4 411 477 | 195.6 | 191.5-199.8 |
| 2014 | 8366 | 2 014 587 | 415.3 | 406.4-424.3 | 348 | 2 371 865 | 14.7 | 13.2-16.3 | 8714 | 4 386 452 | 198.7 | 1945-202.9 |
| Total | 37 890 | 14 415 479 | 262.8 | 260.2-265.5 | 1220 | 17 421 769 | 7.0 | 6.6-7.4 | 39 110 | 31 837 248 | 122.8 | 121.6-124.1 |

increased with the age at diagnosis in both boys and girls. The most prominent increases in the incidence rate of central precocious puberty were observed in girls age 6-9 years and boys age 8-10 years.

The prevalence of central precocious puberty according to sex and calendar year is shown in Table II and Figure 3. The overall prevalence of central precocious puberty during the study period was 193.2 per 100 000 persons (girls, 410.6; boys, 10.9). The prevalence of central precocious puberty increased steadily both in girls and boys during the study period. The prevalence of central precocious puberty in girls increased 8.6 times from 110.5 to 946.4 per 100 000 in

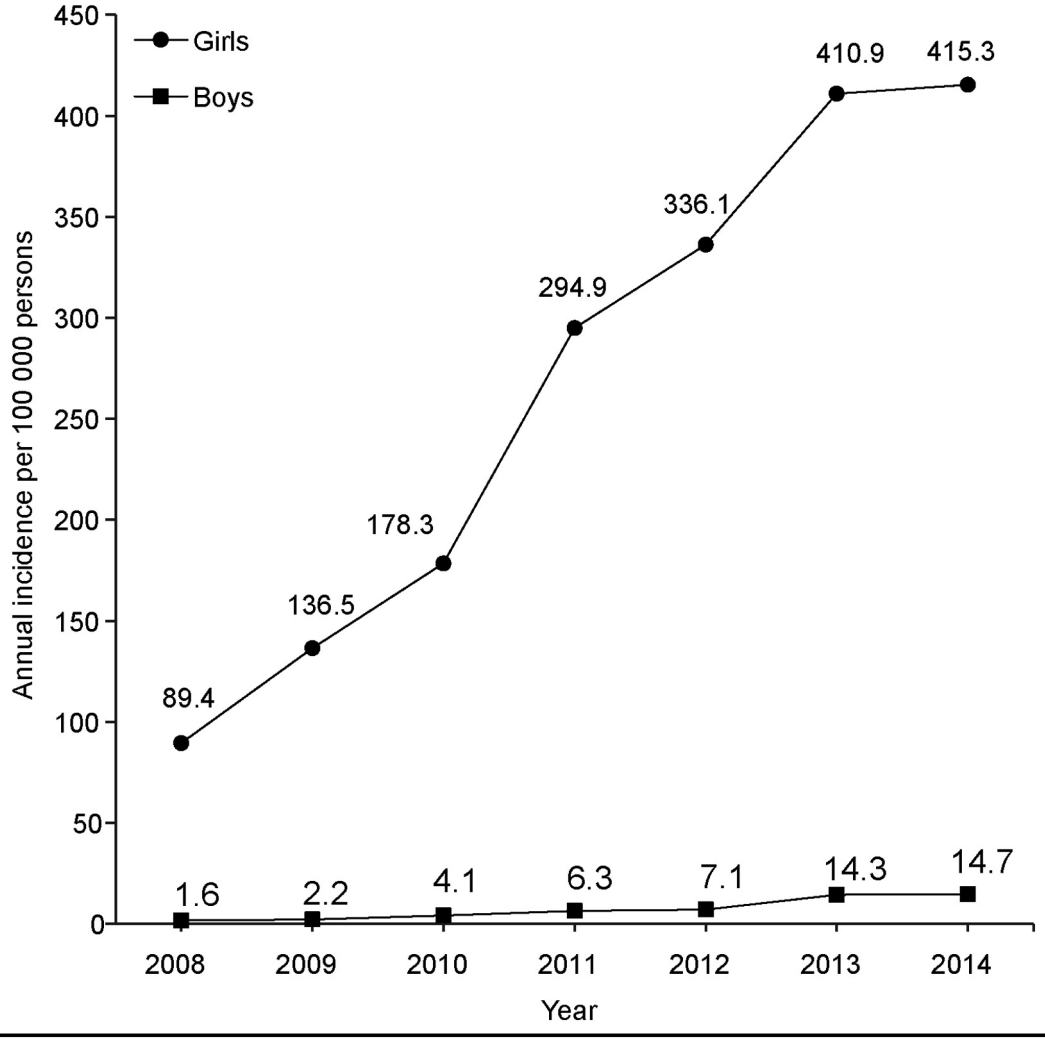


**Figure 1.** Annual incidence of central precocious puberty in Korean children from 2008 to 2014.

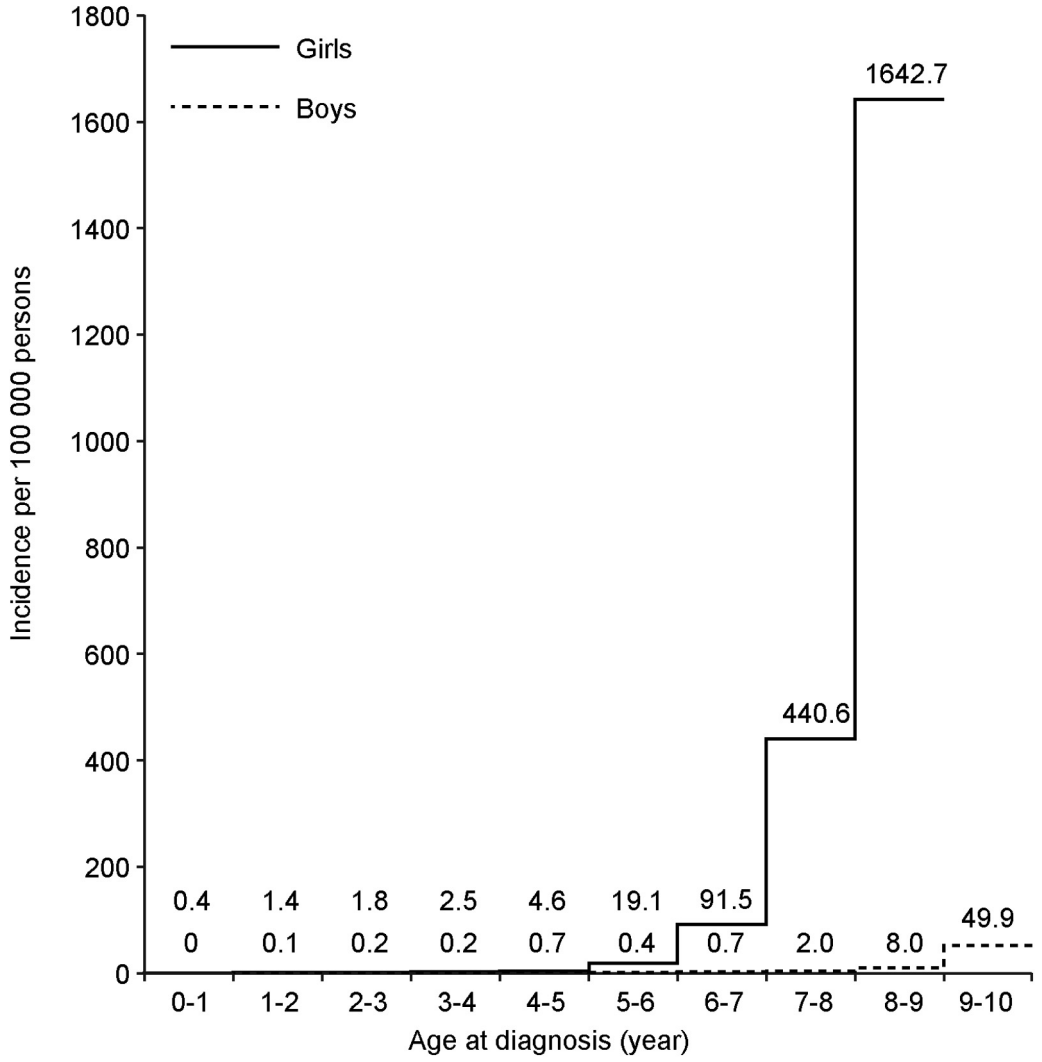


**Figure 2.** Sex-specific incidence of central precocious puberty in Korean children according to the age at diagnosis.

girls who were younger than 12 years old. The prevalence of central precocious puberty in boys increased 10.4 times from 2.9 to 30.1 per 100 000 in boys who were younger than 13 years old. The prevalence was lower in boys, but the increase in the prevalence rate during the study period was similar to that seen in girls.

## Discussion

This study was a retrospective national registry-based epidemiologic study of the incidence and prevalence of central precocious puberty in Korea from 2008 to 2014.

**Table II. Sex-specific annual prevalence (per 100 000 persons) of central precocious puberty in Korean children**

| | Girls | | | | Boys | | | | Total | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | No. of cases (n) | Population (n) | Prevalence | 95% CI | No. of cases (n) | Population (n) | Prevalence | 95% CI | No. of cases (n) | Population (n) | Prevalence | 95% CI |
| 2007 | 1835 | 3 222 751 | 56.9 | 54.3-59.5 | 77 | 3 894 752 | 2.0 | 1.5-2.4 | 1912 | 7 117 503 | 26.9 | 25.7-28.1 |
| 2008 | 3456 | 3 126 699 | 110.5 | 106.8-114.2 | 108 | 3 761 971 | 2.9 | 2.3-3.4 | 3564 | 6 888 670 | 51.7 | 50.0-53.4 |
| 2009 | 5708 | 3 024 022 | 188.8 | 183.9-193.6 | 154 | 3 627 505 | 4.2 | 3.6-4.9 | 5862 | 6 651 527 | 88.1 | 85.9-90.4 |
| 2010 | 8238 | 2 931 773 | 281.0 | 274.9-287.0 | 223 | 3 507 966 | 6.4 | 5.5-7.2 | 8461 | 6 439 739 | 131.4 | 128.6-134.2 |
| 2011 | 12 427 | 2 861 399 | 434.3 | 426.7-441.9 | 340 | 3 409 857 | 10.0 | 8.9-11.0 | 12 767 | 6 271 256 | 203.6 | 200.1-207.1 |
| 2012 | 17 048 | 2 795 923 | 609.7 | 600.6-618.9 | 468 | 3 328 342 | 14.1 | 12.8-15.3 | 17 516 | 6 124 265 | 286.0 | 281.8-290.2 |
| 2013 | 21 803 | 2 737 532 | 796.4 | 785.9-807.0 | 729 | 3 239 479 | 22.5 | 20.9-24.1 | 22 532 | 5 977 011 | 377.0 | 372.1-381.9 |
| 2014 | 25 578 | 2 702 601 | 946.4 | 934.9-958.0 | 948 | 3 154 696 | 30.1 | 28.1-32.0 | 26 526 | 5 857 297 | 452.9 | 447.4-458.3 |
| Total | 96 093 | 23 402 700 | 410.6 | 408.0-413.2 | 3047 | 27 924 568 | 10.9 | 10.5-11.3 | 99 140 | 51 327 268 | 193.2 | 192.0-194.4 |

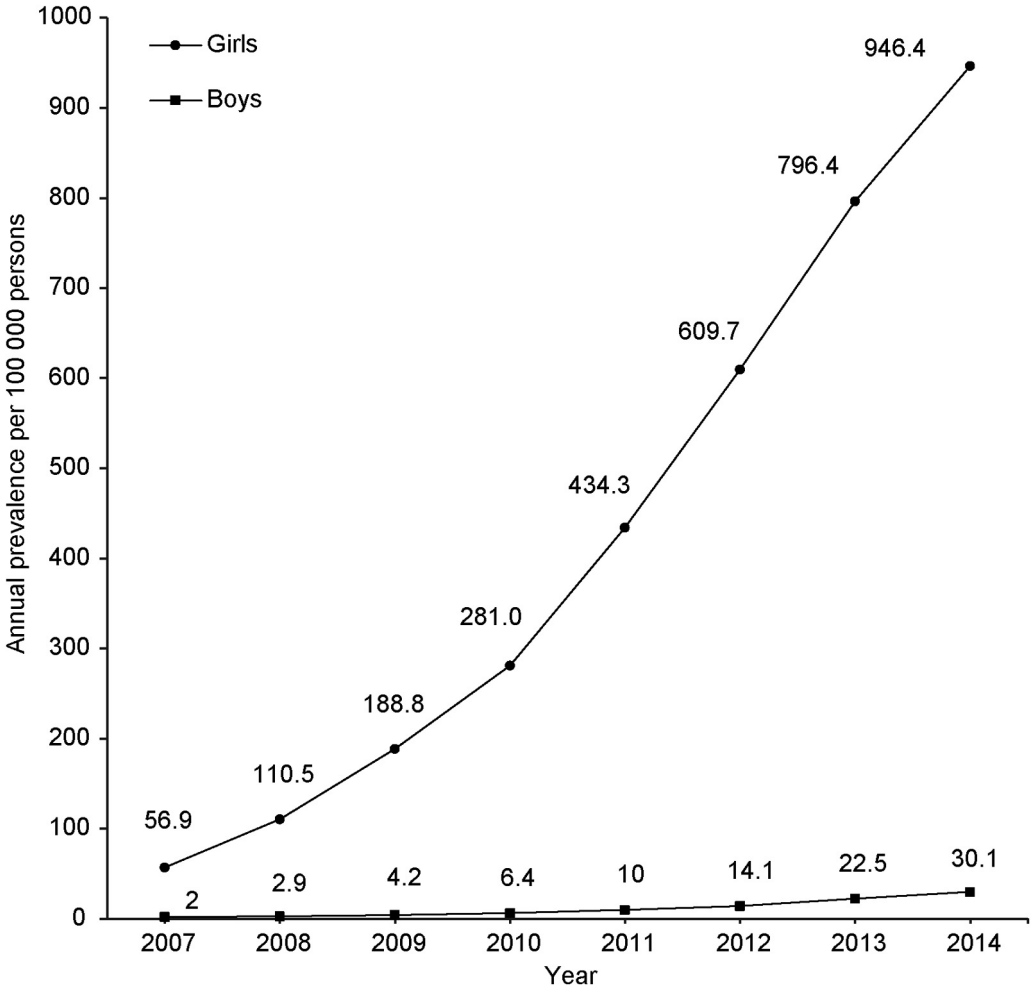


**Figure 3.** Annual prevalence of central precocious puberty in Korean children from 2008 to 2014.

Validation of the central precocious puberty diagnosis was confirmed with a thorough review of the medical records of all cases by HIRA medical personnel. During the study period, we found that the incidence and prevalence of central precocious puberty increased steeply in both girls and boys. The increases were most prominent in girls age 6-9 years and in boys age 8-10 years. The incidence of central precocious puberty in girls younger than 9 years of age increased during the study period from 89.4 to 415.3 per 100 000. In addition, the incidence of central precocious puberty in boys younger than 10 years of age increased from 1.6 to 14.7 per 100 000. The prevalence of central precocious puberty in girls younger than 12 years of age also increased during the study period from 110.5 to 946.4 per 100 000. The prevalence of central precocious puberty in boys younger than 13 years of age increased from 2.9 to 30.1 per 100 000. The incidence and prevalence rates in girls in 2014 were higher than those reported in any previous studies of central precocious puberty.

A limited number of studies have estimated the incidence and prevalence of precocious puberty worldwide. A study from the US in 1982 estimated that the incidence of precocious puberty in the general population was between 1 in 5000 and 1 in 10 000.[23] However, this estimate reflects the sociomedical conditions of the early 1980s and was based on personal experience. In another study from the US, from 1940 to 1984 the crude incidence of precocious puberty was 3.5 per 100 000 person-years in girls between the ages of 6 months and 8 years in Olmsted County, Minnesota.[24] That study investigated the incidence of precocious puberty by reviewing the medical records of girls with any diagnosis referable to breast development or other signs of sexual maturity that developed by the age of 8 years, and the diagnosis of precocious puberty was not confirmed based on hormonal studies such as the GnRH stimulation test. A previous study from Belgium demonstrated that the incidence rate of central precocious puberty in both sexes during the period from 1989 to 1997 was 0.01% of the cumulated population of children, corresponding to 10 per 100 000 persons.[25] However, this study was based on the participation of only 7 Belgian academic pediatric endocrinology units; it was not based on a national registry and was limited by a study

design that only roughly estimated the total Belgian child population. An epidemiologic study of central precocious puberty in Spain from 1997 to 2009 estimated that the overall incidence rate for the population at risk was 0.566 cases per 100 000 person-years at risk.[26] The Spanish study also reported that the annual incidence of central precocious puberty ranged between 0.02 and 1.07 cases per 100 000 persons (girls, 0.13-2.17; boys, 0-0.23). They also reported that the estimated prevalence of central precocious puberty in 2009 was 19 per 100 000 (girls, 37; boys, 0.46). However, that study was based on data gathered from 90% of all tertiary care centers with pediatric endocrinology units, suggesting that of the number of patients with central precocious puberty might be underestimated. Nevertheless, the incidence and prevalence of central precocious puberty in Spain are much lower than those of our study.

A Danish study using data from the Danish National Patient Registry and Statistics from 1993 to 2001 reported that 670 children were newly registered with the diagnosis of precocious puberty from 1993 to 2001, corresponding to 50-70 new cases of precocious puberty per year in Denmark.[18] They estimated a precocious puberty prevalence of 200-230 per 100 000 girls, suggesting that 0.2% of all Danish girls developed precocious puberty before 9 years of age. The incidence was 80 per 100 000 for girls 5-9 years old and 10-20 per 100 000 for boys 5-9 years old; the incidence rate was constant during the study period from 1993 to 2001. However, the calculated prevalence and incidence of precocious puberty in the Danish study may have been overestimated because central precocious puberty was found in only 46% of all cases, and the remaining cases were children with benign variants or early normal pubertal development. Compared with the Danish study, our results show that the incidence and prevalence of central precocious puberty is 2-3 times higher in Korean girls, but much lower in boys. In addition, the incidence rate increased steadily in our study, and the incidence remained constant in the Danish study. A more recent epidemiologic study in Korea from 2004 to 2010 showed high and steadily increasing incidence and prevalence rates, and reported a central precocious puberty prevalence of 55.9 per 100 000 girls and 1.7 per 100 000 boys from 2004 to 2010.[19] They also reported that the overall incidence of central precocious puberty was 15.3 per 100 000 girls and 0.6 per 100 000 boys. These results are much lower than results seen in the Danish study or our study. These differences may be the result of methodological differences between the studies. The Danish study and our study included girls who were registered with the diagnosis with precocious puberty or central precocious puberty, respectively, before 9 years of age and boys who were registered before 10 years of age. On the contrary, the 2004-2010 study from Korea included only girls who were registered with the diagnosis with central precocious puberty before 8 years of age and boys who were registered before 9 years of age. In general, precocious puberty is defined as the occurrence of secondary sexual characteristics first occurring before 8 years of age in girls and 9 years of age in boys. However, because a lag time of 0.56-1.5 years between the first recognition of pubertal development and the establishment of a diagnosis of precocious puberty was reported in previous studies,[17,20,27,28] the application of inclusion criteria used in our study and the Danish study may more closely reflect the true clinical experience.

In our study, the incidence and prevalence rates of central precocious puberty in girls were the highest among the estimates from similar studies and increased every year during the study period. It is not clear why the incidence and prevalence of central precocious puberty are so high and steadily increasing in Korean girls. Factors contributing to the timing of puberty include genetic factors, which involve familial, ethnic, and sex patterns, and environmental factors, such as nutrition, light, stressors, and endocrine disrupting chemicals.[29] Genetic factors play a major role in the timing of puberty, whereas environmental factors play an essentially permissive role in normal conditions. However, environmental signals may play a crucial role in specific conditions, such as precocious puberty in a subset of a population.[29] An Italian study investigated the distribution of central precocious puberty in the northwest Tuscany (NWT) region from 1998 to 2003. Viareggio, one of 5 major cities in NWT, had the highest central precocious puberty prevalence (161 central precocious puberty cases per 100 000 children in Viareggio vs 30.4 per 100 000 children in the other four major cities of NWT).[30] Specifically, they reported that 3 neighborhoods in Viareggio had the highest central precocious puberty frequency (216.1, 393.5, and 274.0 central precocious puberty cases per 100 000 children). Definite variations in the geographic distribution of central precocious puberty in the Italian study suggest that environmental factors, such as estrogen disrupter pollution, could be major central precocious puberty determinants in NWT. In addition, a Belgian study reported an 80-fold higher prevalence of precocious puberty and a higher concentration of p,p'-DDE pesticide in foreign adopted children compared with Belgian natives, thereby suggesting that transient exposure to endocrine disrupters may be related to the development of precocious puberty.[25] In our study, the incidence and prevalence of central precocious puberty increased steeply over a short period of time, suggesting that environmental factors, such as endocrine disrupters, may involve in development of central precocious puberty in Korea. We previously demonstrated that di-(2-ethylhexy) phthalate levels were significantly higher in central precocious puberty patients, suggesting that di-(2-ethylhexy) phthalate, one of the most commonly used plasticizers, may be an etiologic factor for central precocious puberty.[31] An increase in physician awareness of the precocious puberty and resulting increase in evaluation and diagnosis based on societal awareness may be another reason for high incidence and prevalence of central precocious puberty in Korea. An increasing prevalence of obesity in Korean children may also provide a possible explanation for the increasing rate of central precocious puberty. However, because an increase in obesity has been

observed worldwide, this cannot be the sole explanation for the rapid increase in the prevalence of central precocious puberty in Korea. Theoretically, there is a probability that relatively homogeneous genetic background in Korean people may influence high incidence rate of central precocious puberty. However, we have no data or evidence supporting this assumption at this point. In addition, rapidly increasing incidence of central precocious puberty in a short period by the genetic impact might be unlikely. At this time, the exact cause of the steep increase in the incidence and prevalence of central precocious puberty in Korea is unknown, and further studies are needed. In addition, studies regarding the epidemiologic and clinical significance of the effects of endocrine disrupting chemicals on the reproductive system should be performed.

There are some limitations of our data analysis, which should be taken into consideration. First, our estimated prevalence and incidence rates of central precocious puberty may be overestimated because we could not exclude some cases in girls in the 8- to 9-year age range and in boys in the 9- to 10-year age range with early puberty who developed secondary sexual characteristics. In other words, the differences of lag time between the appearance of pubertal sign and diagnosis of precocious puberty in each patient may affect the accuracy of the results. Second, we could not exclude some cases of slowly progressive central precocious puberty, which has a normal timing of menarche and a low risk of a short adult height. Even if the diagnosis of central precocious puberty is established, careful longitudinal observation at least for 6 months should be made to confirm the rapid progression of pubertal development before a treatment decision is reached. However, we could not determine whether the proper observation process was followed in our cases.

In conclusion, we found that the incidence and prevalence of central precocious puberty in Korean children increased rapidly during the period from 2008 to 2014 according to data from HIRA, a nation-based registry. The finding that the incidence and prevalence of central precocious puberty in Korean girls in our study is higher than that of any prior study is noteworthy. An assessment of the risk factors for the development of central precocious puberty in the general population and an effort to elucidate the underlying causes of this steep increase in the incidence and prevalence of central precocious puberty in Korean children are needed. ■

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