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Comparison of central precocious puberty frequency before and during COVID-19: a systematic review and meta-analysis

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Abstract

Objective The current systematic review and meta-analysis assessed the prevalence of central precocious puberty (CPP) throughout the novel coronavirus disease 2019 (COVID-19) pandemic.

Design A systematic review and meta-analysis were carried out following the principles outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, 2020).

Data sources PubMed, Embase, Web of Science, and WANFANG databases were searched from January 1, 2019, to March 30, 2023.

Eligibility criteria for selecting studies (1) children and adolescents ≤ 15 years; (2) studies with the outcome of frequency of central precocious puberty, measured prior to and throughout the COVID-19 pandemic; (3) a novel CPP diagnosis was created depending on all of the following criteria: girls with a chronological age < 8 years and boys with a chronological age < 9 years at the onset of symptoms, basal luteinizing hormone (LH) levels > 0.3 UI/L, and/or GnRH-stimulated peak LH levels > 5 IU/L.

Data extraction and synthesis The process of extracting data and evaluating the likelihood of bias was carried out by two independent reviewers. The data were pooled employing the generic inverse-variance method and presented as mean differences (MDs) with 95% CIs. The evaluation of heterogeneity was conducted employing the Cochran Q statistic, and the degree of heterogeneity was measured employing the I^2 statistic.

Results This meta-analysis included 17 studies. In contrast to the same period prior to the COVID-19 pandemic, the occurrence of CPP elevated (OR = 2.57; 95% CI, 1.85–3.56). Moreover, body mass index standard deviation score (BMI SDS) differences between CPP patients prior to COVID-19 and throughout the pandemic follow-up was 0.12 (95% CI − 0.01 to 0.25 $P = 0.06$).

Conclusion Overall, CPP frequency significantly elevated throughout the COVID-19 pandemic. Given the restricted number of cohort investigations in this meta-analysis, additional research may be conducted on larger groups of children in order to establish a correlation between the observed rise in precocious puberty and specific pathogenic factors.

Keywords Prevalence, Central Precocious Puberty (CPP), Coronavirus Disease 2019 (COVID-19)

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Introduction

In March 2020, the World Health Organization (WHO) made an official declaration of a pandemic due to the advent of the novel SARS-CoV-2 virus. The COVID-19 pandemic necessitated the implementation of isolation measures, which encompassed educational institutions

and affected children and teenagers who were restricted to their residences and provided with online educational alternatives [1]. The presence of unforeseen and extended disturbances to customary school routines and daily activities, coupled with heightened levels of stress resulting from isolation, constitute major risk factors for the physical and mental well-being of children and adolescents [2, 3]. However, COVID-19 is commonly linked to respiratory disease, and SARS-CoV-2 exhibits various pathophysiological linkages with the endocrine system [4].

Psychological factors, including fear and anxiety, might contribute to the occurrence of precocious puberty by influencing central nervous system (CNS) mediators like N-methyl-D-aspartate (NMDA) and glutamate [5, 6]. Increased anxiety can trigger γ-aminobutyric acid (GABA) activation. The activation of stress pathways that are characteristic of pubertal onset occurs through a receptor in prepubertal subjects [7]. Insufficient data is currently available regarding alterations in CNS mediators in relation to the pandemic, making it difficult to explain the elevation in precocious puberty cases, and further research is needed.

The growing incidence of risk overweight and obesity has been exacerbated by a shift towards a more sedentary lifestyle and the adoption of poorer dietary habits. The levels of fasting glycemia, glucose, and insulin excursion exhibited a significant increase among children throughout the pandemic when contrasted with data obtained from children prior to the pandemic [8]. Childhood obesity has been linked to the secular trend of puberty anticipation, particularly in girls, as evidenced by observations made in recent decades [9, 10]. There exists empirical data supporting a favorable association between hyperinsulinemia, either in isolation or in combination with obesity, insulin resistance, and early puberty [11, 12].

Throughout the COVID-19 pandemic, multiple centers globally indicated a high prevalence of CPP [13]. However, the precise influence of the COVID-19 pandemic on the CPP risk remains uncertain. Therefore, it is imperative to develop an in-depth knowledge and summary of the influence of COVID-19 on the CPP. We aim to investigate the pooled prevalence of CPP and its associated clinical characteristics throughout the COVID-19 pandemic. This investigation additionally offers extensive evidence for academics, practitioners, and clinical endocrinologists to focus on CPP in children throughout the COVID-19 pandemic.

Methods

Literature search

This protocol was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) guidelines, and review findings were reported in line with PRISMA guidance [14]. A systematic search was conducted to find relevant investigations and articles published in four life science databases: PubMed, Embase, Web of Science (Science Citation Index and Social Sciences Citation Index), and WANFANG, from January 1, 2019, to March 30, 2023. Search strategies included the following keywords: "COVID 19," "2019-nCoV Infections," "COVID-19 Virus Disease," "2019 Novel Coronavirus Disease," SARS Coronavirus 2 Infection," "Coronavirus Disease 2019," SARS-CoV-2 Infections," "SARS-CoV-2 Infection," "COVID-19 Virus," "SARS Coronavirus 2," "Wuhan Coronavirus," "Severe Acute Respiratory Syndrome Coronavirus 2," "Puberty, Precocious," "premature pubarche," "premature puberty," "premature thelarche," "puberty praecox," "precocious puberty," "sex precocity," and "sexual precocity," all of which have been compiled from Mesh. There were no restrictions on study type throughout the preliminary search. The reference lists of suitable investigations and prior reviews were systematically investigated in order to find additional investigations that were pertinent to the research topic. We provided a detailed description of our search strategy in Supplementary Table S1.

Eligibility criteria

According to Population-Exposure-Comparison-Outcome framework [15], inclusion criteria were defined as follows: (1) Children and adolescents ≤ 15 years; (2) studies with outcome of frequency of central precocious puberty measured prior and throughout the COVID-19 pandemic; (3) a recent diagnosis of CPP encompassed the presence of the following: the age at which symptoms begin is < 8 years for girls and < 9 years for boys; the levels of basal luteinizing hormone (LH) are > 0.3 UI/L, and/or the peak LH level stimulated by GnRH is > 5 IU/L [16]. No limitations were enforced regarding language or the metrics of impact. The study incorporated various publications that utilized the same study population and conducted measurements at consistent intervals throughout the duration of the pandemic. Individual studies that utilized the same study population and different time points for measuring the pandemic were examined separately. We excluded articles written in languages other than English, publications that did not have English abstracts available, case series, case reports, letters to the editor, literature reviews, book sections, theses, conference proceedings, and preprints from our analysis.

Study selection

The study selection consisted of three stages: (1)the EPPI reviewer program facilitates the importation and automated deduplication of identified studies [17]; (2) two

review authors independently reviewed the titles and/or abstracts of the retrieved papers; (3) the complete text was obtained and evaluated for eligibility by three reviewers, and any disagreements were settled via discussion with an external collaborator. In this meta-analysis, both boys and girls were included to ensure a comprehensive evaluation of CPP during the COVID-19 pandemic. This approach aligns with our inclusion criteria, which specified no gender-based restrictions. However, it is noteworthy that some studies, such as Chioma et al., concentrated primarily on female populations due to the higher incidence of CPP in girls. Despite this, the exclusion of male subjects in these specific studies does not indicate a systematic exclusion in the overall analysis.

Data extraction

Following the acquisition of data from the aforementioned online databases, the elimination of duplicate records was carried out utilizing the 20th iteration of the Endnote software. Subsequently, any remaining duplicate records were manually removed. Throughout the initial round, three authors conducted an independent screening of the studies by evaluating their titles and abstracts. In the subsequent phase, the remaining investigations underwent a comprehensive evaluation by three authors, who assessed their full texts. Throughout all iterations, in the event of a divergence of opinions among the authors, the senior author offered guidance and counsel.

The extracted data encompassed the study's first author, country, publication year, study type, sample size, and precocious puberty status prior to and throughout the COVID-19 pandemic. The Extracted data was systematically arranged utilizing the Excel 2019 software and used for qualitative synthesis.

The main objective was to examine the alterations in the prevalence of central precocious puberty (Table 1). Our secondary aim was to evaluate clinical feature changes of central precocious puberty (Table 2). Table 1 presents the characteristics and frequency of CPP cases before and during the COVID-19 pandemic, whereas Table 2 provides detailed data on the changes in clinical features, such as age at diagnosis and BMI, among CPP patients during these periods. Our secondary aim was to evaluate changes in clinical features of CPP during the pandemic. As detailed in Table 2, the clinical features assessed included the mean age at diagnosis, BA-CA, BMI SDS, and basal LH levels.

Quality assessment

The cross-sectional studies were evaluated using the evaluation tool recommended by the Agency for Healthcare Research and Quality (AHRQ) [18]. The tool comprises a total of 11 items, with a maximum score of 11. 0–3 indicate low quality, 4–7 indicate medium quality, and 8–11 indicate high quality.

Statistical analysis (meta-analysis)

The data were provided utilizing descriptive statistics, specifically (mean ± SD) for continuous variables. On the other hand, frequencies and percentages were employed to represent categorical variables. The dichotomous data were represented using pooled odds ratios (OR) and 95% confidence intervals (95% CI). The calculation of the difference was performed for continuous outcomes using the mean difference (MD) and a 95% CI. A meta-analysis employing random-effects methodology was undertaken to ascertain the pooled effect size for the frequency of CPP, the age at which it is diagnosed, the difference

Table 1 Characteristics of included studies on CPP throughout the COVID-19 pandemic[a]

Author	Year	Country	Study design	Pre-pandemic		Pandemic		AHRQ score
				n	N[b]	n	N[b]	
Peinkhofer M	2022	Italy	A retrospective study	48	24	54	28	6
Chioma L	2022	Italy	A retrospective study	140	37	328	135	8
Trujillo MV	2022	USA	A retrospective study	2340	28	2261	64	5
Mondkar SA	2023	India	A retrospective study	4208	44	3053	136	5
Jimenez ABA	2022	Spain	A retrospective study	598	45	471	87	5
Itani AA	2022	Lebanon	A retrospective study	964	4	416	19	4
Goffredo M	2022	Italy	A retrospective study	1469	34	1063	45	5
Matsubara K	2023	Japan	A retrospective study	248	28	271	51	5

"n" refers to the total number of children evaluated by endocrine providers for potential central precocious puberty (CPP), while "N" represents the number of children who were ultimately diagnosed with CPP. The ratio of 'n' to 'N' varies across studies due to differences in referral patterns, diagnostic criteria, and the prevalence of CPP in the studied populations. For example, in Peinkhofer et al. (2022), the smaller ratio reflects a higher diagnostic yield compared to other studies

[a] *AHRQ* Agency for Healthcare Research and Quality

[b] N represents CPP participants

Table 2 Summary of included studies on CPP throughout the COVID-19 pandemic[a]

Author	Year	Country	AHRQ	N		Age	
				Pre-pandemic	Pandemic	Pre-pandemic	Pandemic
Acinikli KY	2022	Turkey	6	6	22	7.5 ± 1.0	7.5 ± 0.9
Chioma L	2022	Italy	8	37	135	7.58 ± 0.94	7.39 ± 0.84
Umano GR	2022	Italy	5	34	35	7.97 ± 1.11	7.59 ± 0.67
Trujillo MV	2022	USA	5	28	64	7.1 ± 2.1	7.60 ± 1.43
Barberi C	2022	Italy	5	9	17	7.27 ± 0.6	6.99 ± 1.38
Chen Y	2022	China	4	209	191	7.92 ± 0.71	7.95 ± 0.57
Mondkar SA	2023	India	5	44	136	7.8 ± 1.3	8.2 ± 1.2
Acar S	2021	Turkey	6	25	58	7.9 ± 0.8	7.8 ± 0.8
Verzani M	2021	Italy	5	93	224	7.54 ± 1.23	7.37 ± 8.79
Itani AA	2022	Lebanon	4	4	19	6.66 ± 0.78	7.27 ± 0.73
Goffredo M	2022	Italy	5	34	45	/	/
Orman B	2022	Turkey	6	27	30	/	/
Mutlu GY	2022	Turkey	7	214	145	8.6 ± 1.2	8.1 ± 8.1
Matsubara K	2023	Japan	5	33	63	/	/
Stagi S	2020	Italy	6	89	37	7.22 ± 0.48	6.86 ± 0.61

"N" represents the number of children who were ultimately diagnosed with CPP

[a] *AHRQ* Agency for Healthcare Research and Quality

between bone age and chronological age (BA-CA), body mass index standard deviation score (BMI SDS), the basal luteinizing hormone (LH) levels, and the frequency of gonadotropin-releasing hormone agonist (GnRHa) treatment. The heterogeneity among studies was evaluated by employing the I^2 statistic and the P-value derived from Cochran's Q test. In this analysis, a value of $I^2 > 50\%$ and a P-value < 0.05 were deemed to indicate a significant degree of heterogeneity. The publication bias was examined utilizing Begg's test. The statistical analyses were conducted employing Stata software version 16(Stata Corp, College Station, TX, USA).

Ethical approval statement

The analyses conducted in this study were exclusively derived from previously published studies. As a result, it was determined that ethical approval or patient consent was unnecessary. The protocol of this meta-analysis was prospectively registered in the PROSPERO database (Registration No. CRD42024582554).

Results

Search results

A sample size of 10,249 cases prior to and 8,087 cases subsequent to the initiation of the COVID-19 pandemic on the CPP was assessed. Throughout the preliminary investigation, a total of 259 records were discovered across four online databases, following the elimination of duplicate entries (103). Subsequently, in the initial screening process, 110 articles were eliminated depending on their title and abstract. Following this, 46 full-text articles were found and subjected to further evaluation. In conclusion, the qualitative synthesis and meta-analyses were conducted depending on the specified criteria for inclusion, leading to the inclusion of a total of 17 articles (Fig. 1).

All articles were retrospective studies. Seven studies were conducted in Italy, four in Turkey, and one each in the USA, Japan, India, Spain, Lebanon, and China. Four studies were conducted in 2021 and 2023, and the remaining studies were conducted in 2022. The Begg's test ($P = 0.947$) indicated no publication bias (Supplementary Fig. 1).

CPP frequency changes prior to and throughout the COVID-19 pandemic

The pooled data of the eight eligible studies [19–26] reported that CPP frequency was higher throughout the COVID-19 pandemic (OR = 2.57, 95% CI:1.85–3.56, $P < 0.0001$) than prior to the COVID-19 pandemic (Fig. 2). Itani et al. [24] and Peinkhofer et al. [19] reported the highest and lowest CPP frequency changes of 11.49 and 1.08, respectively.

Clinical features changes throughout the COVID-19 pandemic in CPP patients

The analysis comprised a total of 11 investigations [20–22, 24, 27–33]. The mean age at diagnosis differences in CPP patients throughout the pandemic contrasted with

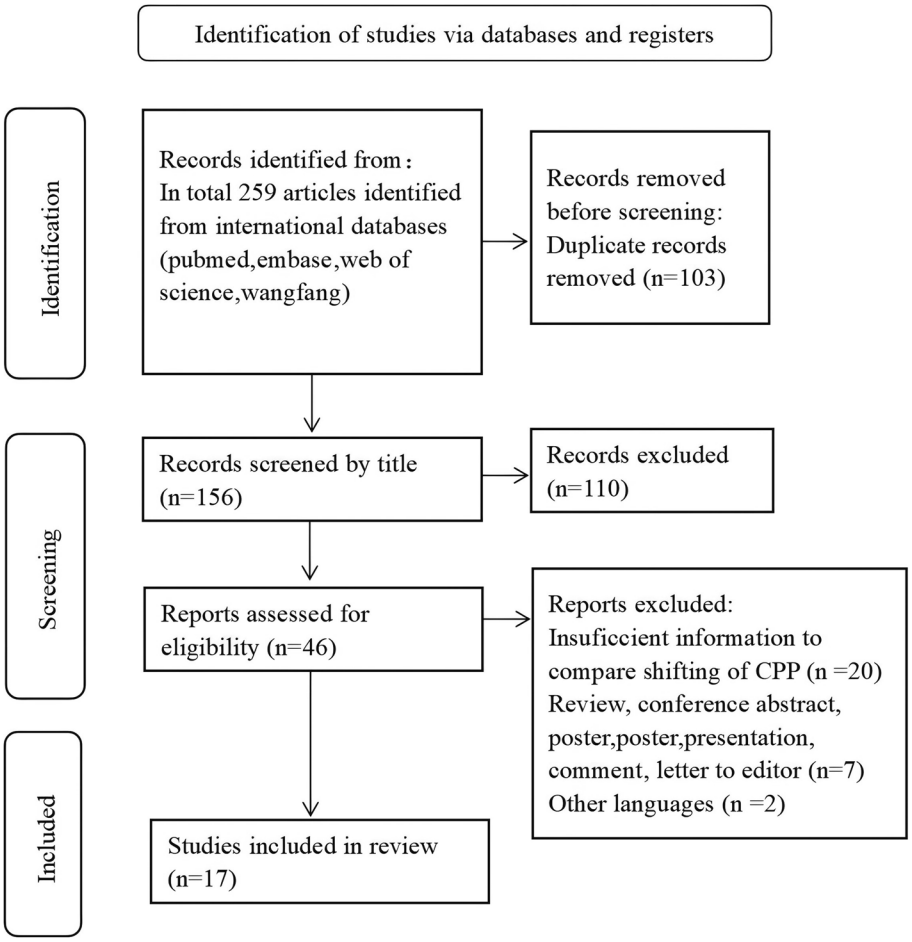

Fig. 1 Flow chart of the literature search

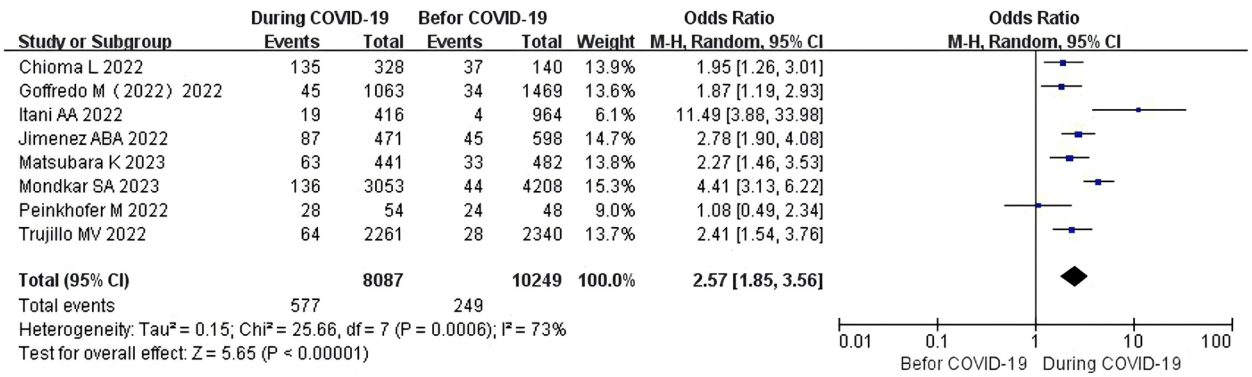

Fig. 2 The pooled risk ratio for CPP frequency changes prior to and throughout the COVID-19 pandemic

before COVID-19 was -0.02D (95% CI: − 0.12 to 0.09, $P = 0.74$), revealing that the mean age at diagnosis was not statistically significant (Fig. 3a).

The calculation of bone age advancement involved determining the discrepancy between chronological age and bone age (BA-CA). Eleven studies evaluated the differences in BA-CA at diagnosis throughout different periods [20–22, 27, 29, 30, 33, 34]. The mean BA-CA differences were not statistically significant throughout

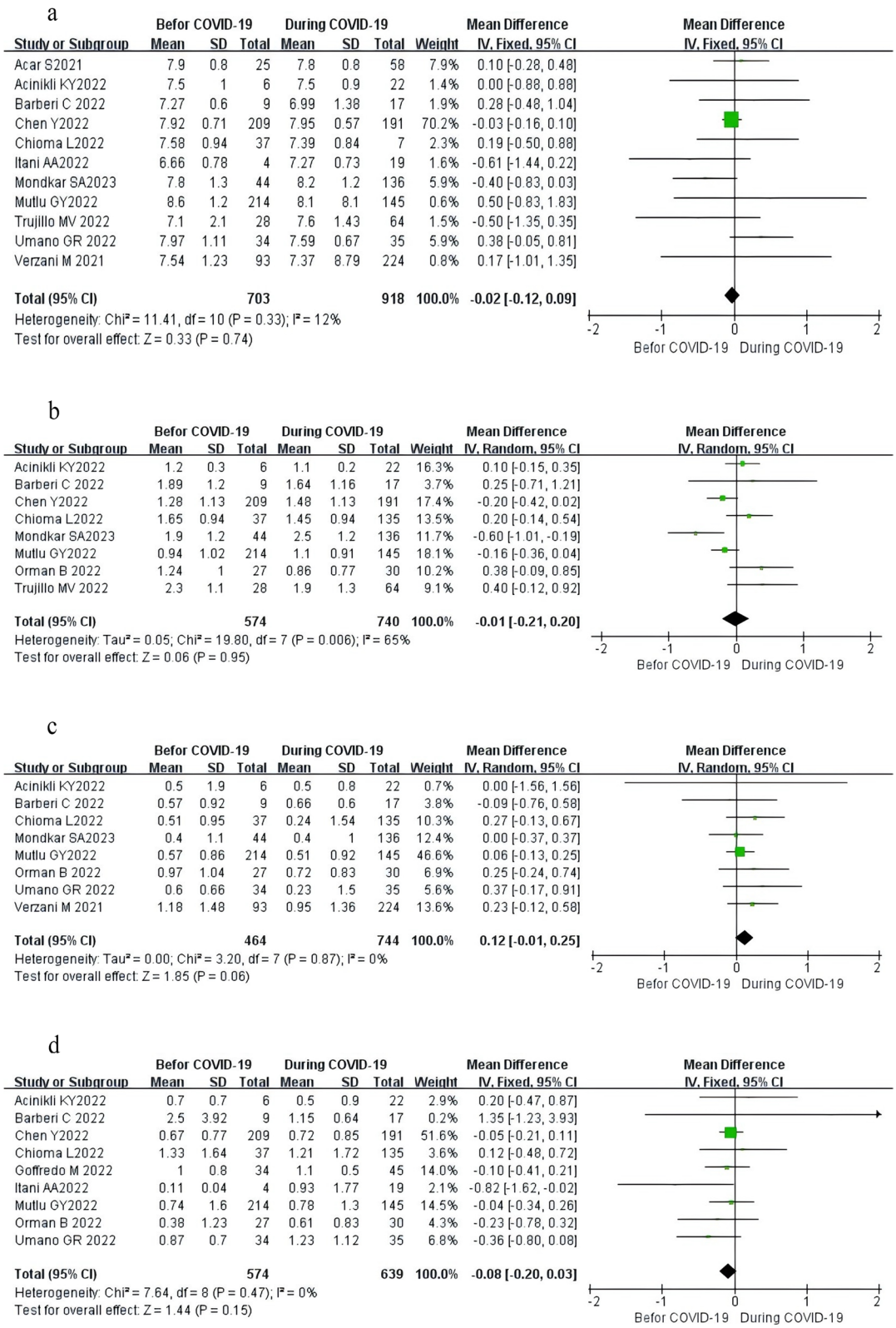

Fig. 3 Clinical features changes throughout the COVID-19 pandemic in CPP patients. (a) Age at diagnosis alterations throughout the COVID-19 pandemic in CPP patients. (b) BA-CA alterations throughout the COVID-19 pandemic in CPP patients. (c) BMI SDS alterations throughout the COVID-19 pandemic in CPP patients. (d) Basal LH alterations throughout the COVID-19 pandemic in CPP patients

the COVID-19 pandemic contrasted to those prior to COVID-19 (95% CI: -0.21 to 0.20, $P=0.95$, Fig. 3b).

Eight studies evaluated the differences in BMI SDA at diagnosis in CPP patients [20, 22, 27–29, 32–34]. Contrasted to before COVID-19, the mean body mass index (BMI SDA differences was 0.12D (95% CI: -0.01 to 0.25, $P=0.06$, Fig. 3c). It was expected that the BMI SDS of the patients was not statistically significant throughout the two different periods.

Serum basal LH levels at diagnosis in CPP patients were found in 9 studies [20, 24, 25, 27–30, 33, 34]. The results showed that the mean basal LH level did not change significantly throughout the COVID-19 pandemic (95% CI: -0.20 to 0.03, $P=0.15$, Fig. 3d). Chioma et al. reported that the basic LH level of children with CPP throughout the epidemic period was higher than that of CPP children before the epidemic [20].

GnRHa treatment frequency changes before and throughout the COVID-19 pandemic.

Not all investigations have investigated or indicated the GnRHa treatment frequency in CPP patients. The pooled data of the three eligible investigations revealed that GnRHa treatment frequency was not different from that before COVID-19 (95% CI: 0.09 to 1.24, $P=0.1$, Supplementary Fig. 2) [22, 24, 33].

Discussion

We present the initial meta-analyses conducted to provide a complete overview of the alterations in CPP throughout the COVID-19 pandemic. The analysis is depended on the examination of existing data published between January 1, 2019, and March 30, 2023. The outcomes of this investigation will offer clinicians valuable insights into the identification of pubertal developmental disorders and the vigilant monitoring of patients with CPP for indications of accelerated pubertal advancement throughout this period of uncertainty.

This study compiled data from 17 unique datasets of 18,336 participants from geologically diverse populations. Throughout the COVID-19 pandemic, several centers globally recorded an elevation in CPP diagnoses [19, 22, 27, 28, 30, 32–36]. Consistent with prior research, a significant rise in the occurrence of CPP was observed throughout the pandemic. Certain studies, including Chioma et al., reported results predominantly for female participants, as the prevalence of CPP was significantly higher in girls compared with boys. This gender disparity in reporting may reflect the demographic distribution of CPP cases, rather than an intentional exclusion of male subjects. In this meta-analysis, all available data that met the inclusion criteria were included, regardless of gender, to avoid any potential bias. We thoroughly reviewed the gender distribution across all included studies to ensure that our analysis remained inclusive and unbiased. Where available, data for both male and female participants were analyzed, and any potential biases arising from gender-specific studies were acknowledged and adjusted for in the overall interpretation of our findings.

Noteworthy, in the present study, the time intervals examined for CPP cases before and during the COVID-19 pandemic varied among the included studies. Most studies compared the number of CPP cases diagnosed in the years immediately preceding the pandemic (e.g., 2018–2019) with those diagnosed during the pandemic years (e.g., 2020–2021). Specific intervals are detailed in Tables 1 and 2. There were no significant variations observed in the age at diagnosis, degree of BA advancement (BA-CA), and basal LH level between the COVID-19 and pre-COVID-19 years. However, the frequency of CPP increases. The data presented indicate that there was no alteration in the characteristics of CPP patients throughout the COVID-19 pandemic despite an observed rise in the proportion of CPP patients. Two potential underlying mechanisms are being considered: 1) a rise in the potential for early identification of CPP, as opposed to a genuine increase in the prevalence of CPP patients, or 2) the effects of environmental factors throughout COVID-19. In our analysis, we aggregated data from multiple studies reporting on CPP frequencies during the COVID-19 pandemic, comparing them with pre-pandemic periods. Although these studies were analyzed collectively to derive a pooled estimate, we acknowledge the importance of examining the characteristics of these studies individually. Each study included in our meta-analysis varied in terms of sample size, geographic location, and methodological approach, which could influence the reported frequency of CPP. To address the concern of whether these factors contributed to the observed increase in CPP frequency during the pandemic, we conducted subgroup analyses where possible. However, due to the heterogeneity in study designs and the limited number of studies, we were unable to perform a detailed analysis of each study's unique characteristics. Future research will concentrate on conducting more granular analyses that account for these variables to better understand the underlying reasons for the observed increase in CPP frequency during the COVID-19 era. It is possible that factors, such as regional differences in public health measures, variations in population demographics, or differences in diagnostic criteria could influence the reported frequencies. These factors will be explored in future studies that separate analyses by study characteristics, which may reveal specific contributors to the increased detection of CPP during the pandemic.

There exists a possibility for early identification of CPP. Increased parental presence following the lifting of the state of emergency could potentially have facilitated the prompt identification of individuals with CPP, thereby enabling more timely medical interventions. It is plausible that physicians were afforded additional time to observe the indicators of early puberty and subsequently refer patients to pediatric endocrinologists due to the diminished patient load of other infectious diseases as a consequence of the COVID-19 pandemic [37].

The timing of puberty is influenced by nutrition and serves as a catalyst for sexual maturation. Furthermore, the presence of obesity has a substantial function in accelerating the initiation of early puberty [38, 39]. Given that the mean age at diagnosis did not differ significantly between pre-pandemic and pandemic periods, it is unlikely that earlier identification of CPP during the pandemic contributed to the observed increase in CPP cases. The BMI SDS values did not change between the pre-pandemic and pandemic cohorts. Although BMI increased throughout the pandemic owing to reduced physical activity, this increase was insignificant. We believe that psychosocial distress, changes in diet and sleep habits, increased screen time, decreased outdoor activities, and/or isolation may have contributed to increased CPP throughout the pandemic.

The initiation of puberty is a multifaceted process that is subject to the influence of various factors. The initiation of puberty is contingent upon the functioning of the hypothalamic-pituitary–gonadal (HPG) axis. Multiple hypothalamic factors have an impact on the secretion of GnRH, while the GnRH pulse generator activity is regulated by both excitatory and inhibitory trans-synaptic neural inputs [40]. Psychological factors, outdoor activity, and overuse of electronic devices affect pubertal timing [41, 42]. The Kisspeptin-Neurokinin-Dynorphin system is the most important system in regulating GnRH secretion, and it is influenced by extrinsic factors, including psychosocial stress. Research has indicated a rise in the prevalence of depression and anxiety symptoms has increased [43]. The impact of psychosocial stress on the hypothalamic–pituitary–adrenal (HPA) axis can result in changes to its response, characterized by initial hyperactivation and then subsequent decrease in the functioning of the stress system in the face of chronic stress. The potential acceleration of pubertal timing may be attributed to the attenuated cortisol profile, as it dampens the stress-related function of the HPA axis. Consequently, this attenuation enables the initiation of a cascade of pubertal hormones through the HPG axis [44].

Throughout the COVID-19 pandemic, there has been a significant decline observed in the duration of time that children allocate to participating in sporting activities [45, 46]. A study in Zhengzhou reported that vitamin D deficiency rates were significantly higher throughout the COVID-19 pandemic control period in 2020 due to decreased outdoor activities [47]. Recent research has revealed a potential link between vitamin D deficiency and the occurrence of precocious puberty, particularly among girls [47, 48].

The rise in instances of precocious puberty may be also associated with exposure to electronic devices. Throughout the COVID-19 pandemic, recreational and educational screen times elevated significantly in Shanghai, which was associated with decreased melatonin levels in children [49]. According to animal and in vitro studies, a physiological decline in melatonin levels occurs prior to the initiation of puberty throughout childhood and may serve as a regulatory element for GnRH neuronal function [50–52]. Moreover, melatonin endogenous circadian rhythms influence glucose tolerance in humans, suggesting that changes in sleep and dietary habits may affect the timing of puberty [53].

Strengths and limitations

The present study possesses multiple strengths. Thorough search strategies were implemented, accompanied by stringent selection criteria and a dual-review process. The available data from the studies provided us with enough information to evaluate changes in CPP frequency.

The present study had several limitations. First, selection bias should be considered because all investigations encompassed in this meta-analysis were retrospective. A quality assessment was conducted to assess the bias risk employing the AHRQ guidelines. The assessment indicated a low likelihood of selection bias. Caution should be exercised in interpreting our findings, as the limited number of studies and events necessitates further investigation. The meta-analysis incorporated cohorts that exhibited geographical diversity. This has the potential to enhance the generalizability of the findings. Second, several factors might influence pubertal timing, including psychological aspects, outdoor activity, sleep habits, and the overuse of electronic devices throughout the COVID-19 pandemic. However, the limited available studies impeded subgroup analysis to explore the influence of the above-mentioned factors.

Conclusion

The outcomes of this systematic review and meta-analysis demonstrate a significant elevation in the frequency of CPP throughout the COVID-19 pandemic. Since the pandemic has ended, the possibility of conducting additional cohort studies to investigate the factors contributing to

the increase in CPP cases is limited. Future research may need to concentrate on retrospective analyses or alternative methods to explore these factors.

Abbreviations

CPP	Central precocious puberty
COVID-19	Coronavirus disease 2019
LH	Luteinizing hormone
MDs	Mean differences
BMI SDS	Body mass index standard deviation score
WHO	World Health Organization
CNS	Central nervous system
NMDA	N-methyl-D-aspartate
GABA	γ-Aminobutyric acid
OR	Odds ratios
BA-CA	Bone age and chronological age
GnRHa	Gonadotropin-releasing hormone agonist
HPG	Hypothalamic-pituitary–gonadal
HPA	Hypothalamic-pituitary-adrenal

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-024-01749-4.

Supplementary Material 1.

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Authors' contributions
The study was conceptualized, and the initial grant protocol was prepared by Jianwei Zhang and Ruoya Wu. Each of the authors made contributions to the initial and subsequent iterations of the manuscript and subsequently provided their approval for the final version to be submitted. Jinliang Xu made significant contributions to the development of the protocol methods and subsequent revisions of the protocol. Xiaoli Tang made significant contributions to the editing of the manuscript.

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Data availability
The data may be made available upon reasonable request from the corresponding authors.

Declarations

Ethics approval and consent to participate
All analyses were based on previously published studies; thus, no ethical approval is required.

Consent for publication
Not required.

Competing interests
The authors declare no competing interests.

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References

1. Alvarez F, Argente D, Lippi F. A Simple Planning Problem for COVID-19 Lockdown. SSRN Electron J. 2020. https://doi.org/10.2139/ssrn.3569911.
2. Ea H, Rc O, Vh P, et al. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. Lancet Psychiatry. 2020;7:547. https://doi.org/10.1016/S2215-0366(20)30168-1.
3. Füzéki E, Groneberg DA, Banzer W. Physical activity ng COVID-19 induced lockdown: recommendations. J Occup Med Toxicol. 2020;15:25. https://doi.org/10.1186/s12995-020-00278-9.
4. Frara S, Allora A, Castellino L, et al. COVID-19 and the pituitary. Pituitary. 2021;24:465–81. https://doi.org/10.1007/s11102-021-01148-1.
5. Stress hormone rapidly tunes synaptic NMDA receptor through membrane dynamics and mineralocorticoid signalling | Scientific Reports. Im Internet: https://www.nature.com/articles/s41598-017-08695-3; Stand: 02.03.2023.
6. Calabrese F, Guidotti G, Molteni R, et al. Stress-induced changes of hippocampal NMDA receptors: modulation by duloxetine treatment. PLoS One. 2012;7:e37916. https://doi.org/10.1371/journal.pone.0037916.
7. Smith SS, Aoki C, Shen H. Puberty, steroids and GABA(A) receptor plasticity. Psychoneuroendocrinology. 2009;34(Suppl 1):S91–103. https://doi.org/10.1016/j.psyneuen.2009.05.011.
8. Giannini C, Polidori N, Chiarelli F, et al. The bad rainbow of COVID-19 time: effects on glucose metabolism in children and adolescents with obesity and overweight. Int J Obes (Lond). 2022;46:1694–702. https://doi.org/10.1038/s41366-022-01164-6.
9. Kaplowitz PB, Slora EJ, Wasserman RC, et al. Earlier onset of puberty in girls: relation to increased body mass index and race. Pediatrics. 2001;108:347–53. https://doi.org/10.1542/peds.108.2.347.
10. Abou El Ella SS, Barseem NF, Tawfik MA, et al. BMI relationship to the onset of puberty: assessment of growth parameters and sexual maturity changes in Egyptian children and adolescents of both sexes. J Pediatr Endocrinol Metab. 2020;33:121–8. https://doi.org/10.1515/jpem-2019-0119.
11. Fl S, Aa J, A T, et al. Hyperinsulinemia induces early and dyssynchronous puberty in lean female mice. J Endocrinol. 2022;254. https://doi.org/10.1530/JOE-21-0447.
12. Jeffery AN, Metcalf BS, Hosking J, et al. Age before stage: insulin resistance rises before the onset of puberty: a 9-year longitudinal study (EarlyBird 26). Diabetes Care. 2012;35:536–41. https://doi.org/10.2337/dc11-1281.
13. Prosperi, S, Chiarelli, F. Early and precocious puberty during the COVID-19 pandemic. Front Endocrinol (Lausanne). 2023;13:1107911. https://doi.org/10.3389/fendo.2022.1107911.
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71.
15. Morgan RL, Whaley P, Thayer KA, et al. Identifying the PECO: a framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environ Int. 2018;121:1027–31. https://doi.org/10.1016/j.envint.2018.07.015.
16. Bangalore Krishna K, Fuqua JS, Rogol AD, et al. Use of Gonadotropin-Releasing Hormone Analogs in Children: Update by an International Consortium. Horm Res Paediatr. 2019;91:357–72. https://doi.org/10.1159/000501336.
17. EPPI-Reviewer: systematic review software. Im Internet: https://eppi.ioe.ac.uk/CMS/Default.aspx?alias=eppi.ioe.ac.uk/cms/er4&; Stand: 15.02.2023.
18. Zhang X, Zhang S, Wu R, et al. Prevalence of autoimmune thyroid disease in patients with psoriasis: a meta-analysis. BMJ Open. 2022;12:e055538. https://doi.org/10.1136/bmjopen-2021-055538.
19. Peinkhofer M, Bossini B, Penco A, et al. Reduction in pediatric growth hormone deficiency and increase in central precocious puberty diagnoses during COVID 19 pandemics. Ital J Pediatr. 2022;48:49. https://doi.org/10.1186/s13052-022-01238-1.
20. Chioma L, Bizzarri C, Verzani M, et al. Sedentary lifestyle and precocious puberty in girls during the COVID-19 pandemic: an Italian experience. Endocr Connect. 2022;11:e210650. https://doi.org/10.1530/EC-21-0650.
21. Trujillo MV, Rungvivatjarus T, Klein KO. Incidence of central precocious puberty more than doubled during COVID-19 pandemic: Single-center retrospective review in the United States. Front Pediatr. 2022;10:1007730. https://doi.org/10.3389/fped.2022.1007730.

22. Mondkar SA, Oza C, Khadilkar V, et al. Impact of COVID-19 lockdown on idiopathic central precocious puberty – experience from an Indian centre. J Pediatr Endocrinol Metab. 2022;35:895–900. https://doi.org/10.1515/jpem-2022-0157.
23. Ariza Jimenez AB, Aguilar Gomez-Cardenas FJ, de la Camara Moraño C. Likely impact of COVID-19 on referrals to pediatric endocrinology: Increased incidence of precocious puberty in a third-level hospital. Endocrinología, Diabetes y Nutrición (English ed). 2022;69:542–4. https://doi.org/10.1016/j.endien.2022.07.002.
24. Itani A, Abou Hamdan A, Zgheib H, et al. Increased incidence of precocious puberty in girls during COVID-19 pandemic: early indicator of the upcoming childhood metabolic syndrome pandemic? Glob Pediatr Health. 2022;9:2333794X2211345. https://doi.org/10.1177/2333794X221134565.
25. Goffredo M, Pilotta A, Parissenti I, et al. Early onset of puberty during COVID-19 pandemic lockdown: experience from two Pediatric Endocrinology Italian Centers. J Pediatr Endocrinol Metab. 2023;36:290–8. https://doi.org/10.1515/jpem-2022-0492.
26. Matsubara K, Higuchi S, Watanabe Y, et al. Increased frequency of central precocious puberty during the coronavirus disease (COVID-19) pandemic at a single center in the Osaka Metropolitan Area of Japan. Clin Pediatr Endocrinol. 2023;32:58–64. https://doi.org/10.1297/cpe.2022-0008.
27. Yüksek Acinikli K, Erbaş İM, Besci Ö, et al. Has the frequency of precocious puberty and rapidly progressive early puberty increased in girls during the COVID-19 pandemic? Jcrpe. 2022;14:302–7. https://doi.org/10.4274/jcrpe.galenos.2022.2022-12-11.
28. Umano GR, Maddaluno I, Riccio S, et al. Central precocious puberty during COVID-19 pandemic and sleep disturbance: an exploratory study. Ital J Pediatr. 2022;48:60. https://doi.org/10.1186/s13052-022-01256-z.
29. Barberi C, Di Natale V, Assirelli V, et al. Implicating factors in the increase in cases of central precocious puberty (CPP) during the COVID-19 pandemic: experience of a tertiary centre of pediatric endocrinology and review of the literature. Front Endocrinol. 2022;13:1032914. https://doi.org/10.3389/fendo.2022.1032914.
30. Chen Y, Chen J, Tang Y, et al. Difference of precocious puberty between before and during the COVID-19 pandemic: a cross-sectional study among Shanghai School-Aged Girls. Front Endocrinol. 2022;13:839895. https://doi.org/10.3389/fendo.2022.839895.
31. Acar S, Özkan B. Increased frequency of idiopathic central precocious puberty in girls during the COVID-19 pandemic: preliminary results of a tertiary center study. J Pediatr Endocrinol Metab. 2022;35:249–51. https://doi.org/10.1515/jpem-2021-0565.
32. Verzani M, Bizzarri C, Chioma L, et al. Impact of COVID-19 pandemic lockdown on early onset of puberty: experience of an Italian tertiary center. Ital J Pediatr. 2021;47:52. https://doi.org/10.1186/s13052-021-01015-6.
33. Yesiltepe Mutlu G, Eviz E, Haliloglu B, et al. The effects of the covid-19 pandemic on puberty: a cross-sectional, multicenter study from Turkey. Ital J Pediatr. 2022;48:144. https://doi.org/10.1186/s13052-022-01337-z.
34. Health Sciences University, Dr Sami Ulus Obstetricsand Gynecology, Children's Health and Disease, Health Implementation and Research Center, Ankara, Turkey, Orman B, Esen S, et al. Status of Central precocious puberty cases at the onset of coronavirus disease 2019 pandemic: a single-center experience. Turk Arch Pediatr. 2022;57:349–53. https://doi.org/10.5152/TurkArchPediatr.2022.2101313.
35. Stagi S, De Masi S, Bencini E, et al. Increased incidence of precocious and accelerated puberty in females during and after the Italian lockdown for the coronavirus 2019 (COVID-19) pandemic. Ital J Pediatr. 2020;46:165. https://doi.org/10.1186/s13052-020-00931-3.
36. Fu D, Li T, Zhang Y, et al. Analysis of the incidence and risk factors of precocious puberty in girls during the COVID-19 pandemic. Int J Endocrinol. 2022;2022:1–9. https://doi.org/10.1155/2022/9229153.
37. Hara T, Furuno K, Yamamura K, et al. Assessment of pediatric admissions for kawasaki disease or infectious disease during the COVID-19 state of emergency in Japan. JAMA Netw Open. 2021;4:e214475. https://doi.org/10.1001/jamanetworkopen.2021.4475.
38. Childhood overweight and obesity and timing of puberty in boys and girls: cohort and sibling-matched analyses. Im Internet: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7394964/; Stand: 07.03.2023.
39. Calcaterra V, Cena H, Regalbuto C, et al. The role of fetal, infant, and childhood nutrition in the timing of sexual maturation. Nutrients. 2021;13:419. https://doi.org/10.3390/nu13020419.
40. Livadas S, Chrousos GP. Molecular and environmental mechanisms regulating puberty initiation: an integrated approach. Front Endocrinol (Lausanne). 2019;10:828. https://doi.org/10.3389/fendo.2019.00828.
41. Sørensen K, Mouritsen A, Aksglaede L, et al. Recent secular trends in pubertal timing: implications for evaluation and diagnosis of precocious puberty. Horm Res Paediatr. 2012;77:137–45. https://doi.org/10.1159/000336325.
42. L Z, D Z, Y S. Adverse childhood experiences and early pubertal timing among girls: a meta-analysis. Int J Environmen Res Public Health. 2019;16. https://doi.org/10.3390/ijerph16162887
43. Xie X, Xue Q, Zhou Y, et al. mental health status among children in home confinement during the coronavirus disease 2019 outbreak in Hubei Province. China JAMA Pediatr. 2020;174:898–900. https://doi.org/10.1001/jamapediatrics.2020.1619.
44. Ruttle PL, Shirtcliff EA, Armstrong JM, et al. Neuroendocrine coupling across adolescence and the longitudinal influence of early life stress. Dev Psychobiol. 2015;57:688–704. https://doi.org/10.1002/dev.21138.
45. Jenssen BP, Kelly MK, Powell M, et al. COVID-19 and Changes in Child Obesity. Pediatrics. 2021;147:e2021050123. https://doi.org/10.1542/peds.2021-050123.
46. Pietrobelli A, Pecoraro L, Ferruzzi A, et al. Effects of COVID-19 lockdown on lifestyle behaviors in children with obesity living in Verona, Italy: a longitudinal study. Obesity (Silver Spring). 2020;28:1382–5. https://doi.org/10.1002/oby.22861.
47. Li T, Li X, Chen N, et al. Influence of the COVID-19 pandemic on the vitamin D status of children: a cross-sectional study. J Med Virol. 2023;95:e28438. https://doi.org/10.1002/jmv.28438.
48. Lee HS, Kim YJ, Shim YS, et al. Associations between serum vitamin D levels and precocious puberty in girls. Ann Pediatr Endocrinol Metab. 2014;19:91. https://doi.org/10.6065/apem.2014.19.2.91.
49. Liu Y, Sun X, Zhang E, et al. Association between types of screen time and weight status during the COVID-19 pandemic: a longitudinal study in children and adolescents. Nutrients. 2023;15:2055. https://doi.org/10.3390/nu15092055.
50. Hadinia SH, Carneiro PRO, Fitzsimmons CJ, et al. Post-photostimulation energy intake accelerated pubertal development in broiler breeder pullets. Poult Sci. 2020;99:2215–29.
51. Roy D, Belsham DD. Melatonin receptor activation regulates GnRH gene expression and secretion in GT1-7 GnRH neurons. Signal transduction mechanisms. J Biol Chem. 2002;277:251–8. https://doi.org/10.1074/jbc.M108890200.
52. Waldhauser F, Weiszenbacher G, Frisch H, et al. Fall in nocturnal serum melatonin during prepuberty and pubescence. Lancet. 1984;1:362–5. https://doi.org/10.1016/s0140-6736(84)90412-4.
53. Rubio-Sastre P, Scheer FAJL, Gómez-Abellán P, et al. Acute Melatonin Administration in Humans Impairs Glucose Tolerance in Both the Morning and Evening. Sleep. 2014;37:1715–9. https://doi.org/10.5665/sleep.4088.

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