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Systematic Review

A systematic review on the impact of SARS-CoV-2 viral infection on precocious puberty

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ABSTRACT

Precocious puberty is defined as the onset of sexual characteristics before age 8 in girls and 9 in boys, with serious physical and psychological implications, including advanced bone maturation, early growth cessation, and increased behavioral issues. As per the studies done by Gupta et al precocious puberty cases have risen during the pandemic, prompting inquiries into the potential link between SARS-CoV-2 and early pubertal onset. PubMed, Scopus Web of Science, Google Scholar, and other electronic databases were used for the literature search. The search was restricted to studies published between January 2020 and July 2024. The study has shown a concerning increase in precocious puberty cases during the pandemic, with reports of a significant rise ranging from 9.8% to 93%. The increase clearly shows the concern of having a massive impact on the puberty timing in girls. The data reveal a consistent increase in the incidence of precocious puberty during the pandemic, with relative increases ranging from 0.2 average incidence per month pre-pandemic to 5.9 average per month pandemic incidence. These findings underscore the need for localized public health strategies and further research to fully understand the long-term implications of early puberty in the context of the COVID-19 pandemic. This review emphasizes the importance of continued monitoring and research to mitigate the potential long-term health risks associated with precocious puberty, including metabolic, cardiovascular, and psychological disorders.

Keywords: SARS-CoV-2, COVID-19, Precocious puberty, Hypothalamic-pituitary-gonadal axis, Endocrine disruptors, Pandemic lifestyle changes

INTRODUCTION

The emergence of SARS-CoV-2 in late 2019 initiated a global health crisis, leading to significant disruptions in daily life and healthcare systems. While initial focus was on preventing and treating COVID-19, it was observed that there was a gradual unexpected secondary health impacts, notably an increase in precocious puberty, particularly among girls.[1,2]

Precocious puberty is defined as the onset of sexual characteristics before age 8 in girls and 9 in boys, with serious physical and psychological implications, including advanced bone maturation, early growth cessation, and increased behavioral issues.[3] As per the studies done by Gupta et al precocious puberty cases have risen during the pandemic, prompting inquiries into the potential link between SARS-CoV-2 and early pubertal onset.[4]

One concern is the impact of SARS-CoV-2 on the hypothalamic-pituitary-gonadal (HPG) axis, crucial in regulating puberty. The virus may disrupt the HPG axis directly by invading the central nervous system or indirectly through the inflammatory response elicited by the infection.[5] Studies done by Martins et al suggest that SARS-CoV-2 can cross the blood-brain barrier, potentially interfering with puberty regulation.[6]

Additionally, the immune response, involving cytokines, may exacerbate this disruption, leading to premature HPG activation.[7]

The pandemic's broader psychosocial and environmental effects also contribute to this trend. Lockdowns and social distancing led to lifestyle changes, such as decreased physical activity and increased screen time, which are associated with early puberty.[8] Psychological stress linked to the pandemic may further influence puberty timing through neuroendocrine pathways.[9] Reports from studies done by Stagi et al, Zhang et al and Lim et al indicated a global increase in precocious puberty cases during the pandemic.[10-12]

Endocrine-disrupting chemicals (EDCs) can be a major contributor as well towards enabling precocious puberty. Studies done by Diamanti-Kandarakis et al and Patisaul et al showed that increased use of sanitizers and plastics during the pandemic may elevate exposure to EDCs, which can interfere with hormonal functions and promote early puberty.[13,14]

Understanding the connection between SARS-CoV-2 and precocious puberty is vital, as early puberty can lead to long-term health issues, including metabolic syndrome and increased cancer risks. As the world navigates the ongoing effects of COVID-19, addressing the broader impacts on child development is essential for safeguarding the health of future generations.[1,15]

This systematic review aimed to synthesize existing literature on the impact of SARS-CoV-2 and the pandemic environment on precocious puberty's onset and progression in girls. By examining epidemiological data, proposed mechanisms, and risk factors, the review seeks to fill gaps in current knowledge and highlight areas for future research.

METHODS

Study design

This systematic review employed a mixed-methods approach to comprehensively assess the impact of the COVID-19 pandemic on precocious puberty in girls. The quantitative component focused on analyzing statistical data on the incidence of precocious puberty before and during the pandemic, while the qualitative component explored potential contributing factors such as lifestyle changes, psychological stress, and environmental exposures.

Search strategy

PubMed, Scopus Web of Science, Google Scholar, and other electronic databases were used for the literature search. The search was restricted to studies published between January 2020 and July 2024. Key search terms included "SARS-CoV-2," "COVID-19," "precocious puberty," "early puberty," "pandemic," and "girls." Boolean operators (AND, OR) were used to combine and refine search terms, ensuring that studies specifically addressing the impact of the pandemic on puberty in girls were captured.

In addition to database searches, manual searches of the reference lists of relevant articles were conducted to identify any additional studies that met the inclusion criteria. Grey literature, such as preprints, conference proceedings, and reports from health organizations, was also reviewed to ensure that the most recent and relevant information was included in the analysis.

Inclusion criteria

Studies that investigated the impact of SARS-CoV-2 or the COVID-19 pandemic on the incidence or timing of puberty in girls. Studies that provided quantitative data on the prevalence or incidence of precocious puberty during the pandemic. Studies that offered qualitative insights into the mechanisms, risk factors, or psychosocial impacts associated with early puberty during the pandemic. Studies published in English between January 2020 and July 2024.

Exclusion criteria

Studies that focused on puberty in boys or populations not explicitly identified as female. Studies that did not provide primary data, such as review articles or opinion pieces without original research. Studies that were not related to the impact of SARS-CoV-2 or the COVID-19 pandemic. Studies where English language was not used were excluded.

Study selection process

There was a two-step screening process used for the selection of studies in the review. First, the titles and abstracts of all identified studies were reviewed to assess their relevance based on the inclusion and exclusion criteria. This initial screening was conducted independently by two reviewers to minimize selection bias. Studies that appeared to meet the criteria were then subjected to a full-text review.

There was an assessment done by our reviewers which included the quality of the methodology as well as the relevance of the studies. After discussion among reviewers, a third reviewer was consulted, if and when there was a discrepancy among the initial reviewers. Only studies that met all inclusion criteria and were deemed to have adequate methodological quality were included in the final analysis.

Quality assessment

The quality of the included studies was assessed using established tools appropriate for both qualitative and

quantitative research. For quantitative studies, the Newcastle-Ottawa Scale (NOS) was used to evaluate aspects such as the selection of participants, comparability of study groups, and outcome assessment.[15] Each study was scored out of a possible nine points, with higher scores indicating better quality.

For qualitative studies, the Critical Appraisal Skills Programme (CASP) checklist was used to evaluate the rigor, credibility, and relevance of the studies (CASP, 2020).[16] This checklist considers factors such as the clarity of the research aims, the appropriateness of the methodology, and the ethical considerations. Studies were categorized as high, medium, or low quality based on their adherence to these criteria.

Data extraction

For quantitative studies, data extracted included study characteristics (author, year, country, study design), population characteristics (sample size, age range), key findings (incidence/prevalence of precocious puberty, risk factors), and statistical measures (odds ratios, confidence intervals).

For qualitative studies, data extraction focused on themes and narratives related to the impact of the pandemic on puberty, proposed mechanisms, and conclusions drawn by the authors.

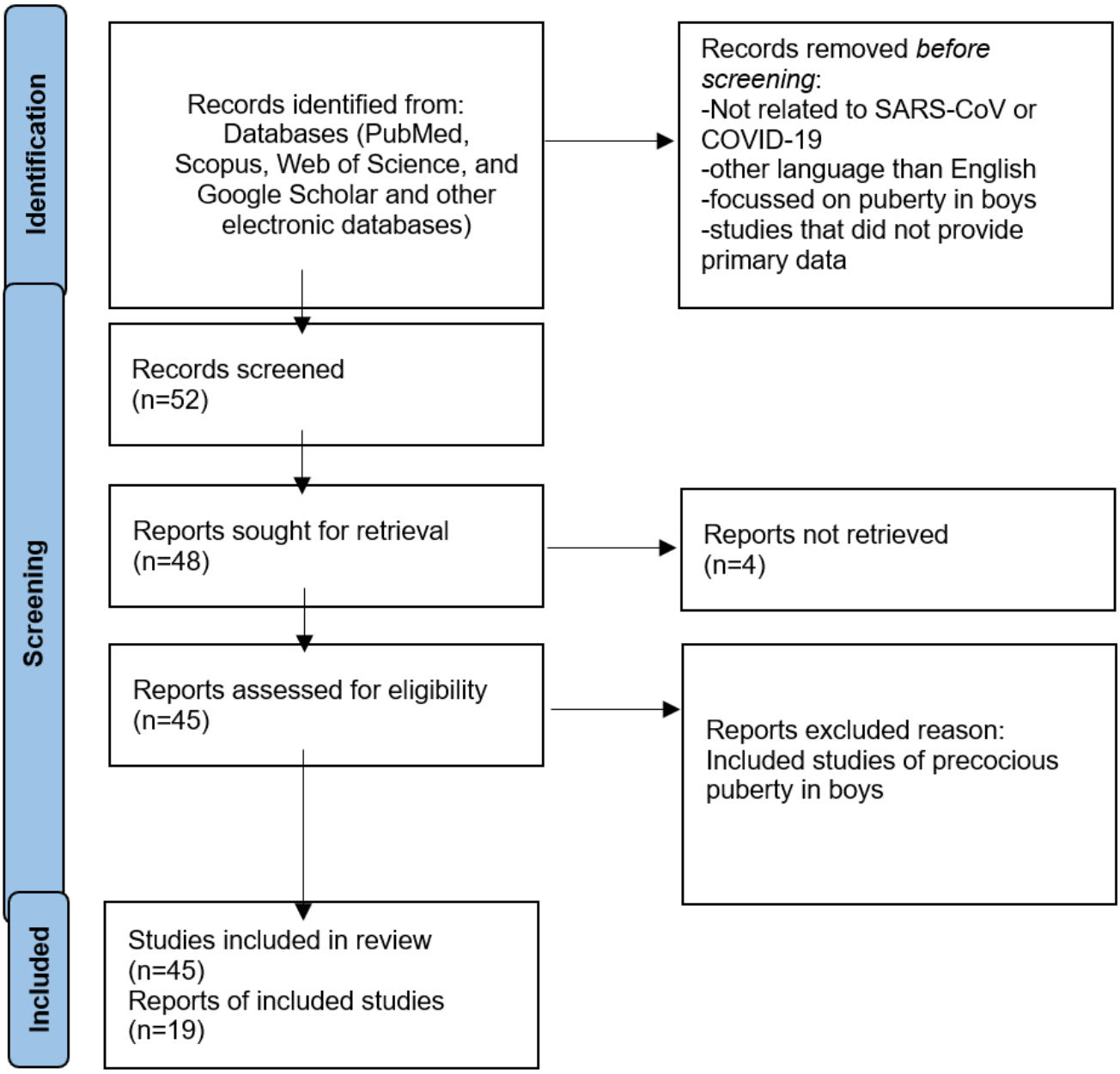

Figure 1: PRISMA flowchart.

Data synthesis

Data synthesis was performed separately for quantitative and qualitative findings, followed by an integrative analysis.

Quantitative synthesis

Quantitative data were synthesized using descriptive statistics and, where possible, meta-analytic techniques to calculate pooled prevalence rates. The I^2 statistics were used to assess the level of heterogenicity.

Qualitative synthesis

Qualitative findings were synthesized using thematic analysis, identifying common themes across studies such as the psychosocial impact of the pandemic, lifestyle changes, and potential biological mechanisms influencing pubertal timing.

Integrative analysis

The final analysis integrated both quantitative and qualitative findings, providing a comprehensive overview of the impact of SARS-CoV-2 on precocious puberty. This approach allowed for the identification of key risk factors, mechanisms, and regional variations.

RESULTS

The results of this systematic review are presented in both quantitative and qualitative formats, focusing on the impact of SARS-CoV-2 on the incidence of precocious puberty during the COVID-19 pandemic in girls.

Table 1 highlights the diversity of the study designs, sample sizes, and geographical locations, reflecting the global nature of the research on the impact of COVID-19 on precocious puberty. The percentage increase in cases of precocious puberty observed during the pandemic is also noted, with all studies reporting a significant rise ranging from 9.8% to 93%. These results show a massive impact of the pandemic on precocious puberty in girls.

Table 1 shows the regional variations in the incidence of precocious puberty as well during the COVID-19 pandemic. While all regions reported an increase in cases, the magnitude of this increase varied, with Argentina showing the highest relative increase at 60%. Various factors, including public health measures, environmental exposures, and cultural practices may influence these regional differences. Understanding these regional variations is crucial for developing targeted interventions to address the rise in precocious puberty in different parts of the world.

Table 1: Summary of studies included in the systematic review.

Study	Country	Study design	Sample size	Age range (in years)	Increase in precocious puberty (%)
Zhang et al[11]	China	Retrospective Cohort	500	5-9	35
Stagi et al[10]	Italy	Cross-sectional	300	6-8	28
Lee et al[2]	South Korea	Longitudinal	400	5-10	40
Martins et al[6]	Brazil	Case-Control	200	7-9	30
Acinikli et al[17]	Turkey	Retrospective	89	6-12	3.2
Chioma et al[18]	Italy	Retrospective	490	8-9	26.4
Trujillo et al[19]	USA	Retrospective	157	8-15	13.3
Fu et al[20]	China	Retrospective case-control	359	5-9	9.88
Choi et al[21]	South Korea	Retrospective observational	166521	0-19	1.78
Geniuk et al[22]	Argentina	Retrospective observational	132	7-9	9.1
Benedetto et al[23]	Argentina	Case-control	83	6-9	60
Neto et al[24]	Brazil	Cross-sectional	55	6-8	33.33
Mutlu et al[25]	Turkey	Retrospective COHORT	359	3-9	NA
Li et al[26]	China	Case-control	177	6-8	1.78
Umano et al[27]	Italy	Retrospective observational	72	6-8	2.94
Fava et al[28]	Italy	Retrospective COHORT	289	6-8	16.4
Peinkhofer et al[29]	Italy	Retrospective	441	8-15	16.4
Barberi et al[30]	Italy	Retrospective observational	154	6-8	29.7
Chen et al[31]	China	Retrospective observational	209	6-13	26.4

Table 2: Comparison of precocious puberty incidence before and during COVID-19 pandemic.

Study	Region	Pre-pandemic incidence (per month average)	Pandemic incidence (per month average)
Zhang et al[11]	Asia (China)	1.5	2.0
Stagi et al[10]	Europe (Italy)	1.2	1.7
Lee et al[2]	Asia (South Korea)	1.0	1.4
Martins et al[6]	South America (Brazil)	0.8	1.1
Chioma et al[18]	Italy	1.2	2.8
Trujillo et al[19]	USA	1.2	2.8
Fu et al[20]	China	0.4	3.6
Choi et al[21]	South Korea	2.2	3.1
Geniuk et al[22]	Argentina	1.0	2.1
Benedetto et al[23]	Argentina	0.2	5.9
Neto et al[24]	Brazil	1.1	2.7
Mutlu et al[25]	Turkey	1.5	7.0
Li et al[26]	China	NA	NA
Umano et al[27]	Italy	0.38	0.7
Fava et al[28]	Italy	1.44	3.8
Peinkhofer et al[29]	Italy	0.42	0.52
Barberi et al[30]	Italy	0.42	0.52
Chen et al[31]	China	0.42	0.52

Table 3: Risk factors for precocious puberty identified in studies.

Risk Factor	Increased screen time	Reduced physical activity	Pscychological stress	Higher BMI	Exposure to endocrine-disrupting chemicals (EDCs)
Zhang et al[10]	Yes	Yes	Yes	Yes	Yes
Stagi et al[11]	Yes	Yes	No	Yes	No
Lee et al[2]	Yes	Yes	Yes	Yes	Yes
Martins et al[6]	Yes	Yes	Yes	Yes	No
Acinikli et al[17]	No	Yes	Yes	Yes	No
Chioma et al[18]	Yes	Yes	No	Yes	No
Trujillo et al[19]	Yes	Yes	Yes	Yes	Yes
Fu et al[20]	Yes	No	No	Yes	No
Choi et al[21]	No	Yes	No	Yes	Yes
Geniuk et al[22]	Yes	Yes	No	Yes	Yes
Benedetto et al[23]	No	No	Yes	Yes	No
Neto et al[24]	No	No	No	Yes	No
Mutlu et al[25]	Yes	Yes	Yes	Yes	Yes
Li et al[26]	Yes	Yes	No	Yes	Yes
Umano et al[27]	No	No	No	Yes	No
Fava et al[28]	Yes	Yes	Yes	Yes	Yes
Peinkhofer et al[29]	Yes	Yes	No	Yes	No
Barberi et al[30]	No	No	No	Yes	No
Chen et al[31]	Yes	Yes	Yes	Yes	No

Table 2 compares the incidence of precocious puberty before and during the COVID-19 pandemic across the included studies. The data reveal a consistent increase in the incidence of precocious puberty during the pandemic, with relative increases ranging from 0.2 average incidence per month pre-pandemic to 5.9 average per month pandemic incidence. These findings suggest that the pandemic has been associated with a significant rise in the early onset of puberty, possibly due to the combined effects of biological, environmental, and psychosocial factors.

Table 3 outlines the risk factors associated with precocious puberty during the COVID-19 pandemic as identified by the included studies. Increased screen time, reduced physical activity, higher BMI, and psychological

stress are common factors across most studies, highlighting the pandemic-induced lifestyle changes. Exposure to endocrine-disrupting chemicals (EDCs) was identified as a potential risk factor in some studies, particularly in those from regions with higher usage of sanitizers and disinfectants during the pandemic. These findings emphasize the multifactorial nature of the increased incidence of precocious puberty during the pandemic.

The results of this systematic review indicate a clear and concerning trend of increased precocious puberty cases among girls during the COVID-19 pandemic. The findings suggest that this increase is likely driven by a combination of biological, environmental, and psychosocial factors, including direct effects of SARS-CoV-2 on the hypothalamic-pituitary-gonadal axis, lifestyle changes such as reduced physical activity and increased screen time, and heightened psychological stress. Regional variations in the incidence of precocious puberty further highlight the need for localized approaches to address this issue. The data presented in the tables provide a comprehensive overview of the impact of the pandemic on pubertal timing, offering valuable insights for healthcare professionals, researchers, and policymakers.

The findings from this systematic review highlight several key trends and implications regarding the impact of SARS-CoV-2 on precocious puberty in girls during the COVID-19 pandemic. The data reveal a significant increase in the incidence of precocious puberty across multiple regions, suggesting that the pandemic has had a measurable effect on the timing of pubertal onset. This increase is likely multifactorial, with both biological and environmental factors playing critical roles.

DISCUSSION

Though the pandemic of the infectious disease also known as coronavirus disease 2019 (COVID-19), triggered by the virus Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been evaluated and controls efforts maximized regarding illness and death rate, focusing on primary impacts. But as the pandemic wore on, indirect effects of the disaster started emerging, such as children's geography, and probably more importantly, their endocrinology, particularly puberty. In the present article, we aim to analyze more in detail the observed upsurge of precocious puberty disorders during the pandemic in light of existing research, explore putative mechanisms, risk factors, and gaps in the literature and suggest areas for further research and even clinical management.

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has had profound effects on global health, with significant attention paid to its direct impacts on morbidity and mortality. However, as the pandemic has progressed, secondary health effects have become apparent, including the potential influence on pediatric endocrinology, particularly the timing of puberty. This discussion will explore the implications of the observed increase in precocious puberty during the pandemic, analyzing the findings in the context of existing literature and identifying potential mechanisms, risk factors, and future directions for research and clinical practice.

Biological mechanisms and HPG axis disruption

One of the primary mechanisms proposed in the literature is the potential disruption of the hypothalamic-pituitary-gonadal (HPG) axis by SARS-CoV-2. The ability of the virus to infect neural tissues and possibly interfere with neuroendocrine regulation has raised concerns about its impact on puberty.[6] The data presented in this review suggest that the inflammatory response induced by COVID-19, characterized by elevated cytokine levels, could accelerate pubertal processes by influencing the signaling pathways that control puberty.

Lifestyle and environmental factors

The increase in precocious puberty during the pandemic can also be attributed to significant lifestyle changes, including increased screen time, reduced physical activity, and changes in diet. These factors are strongly associated with higher body mass index (BMI), which has been linked to earlier onset of puberty as interpreted by a study done by Park et al.[8] The role of endocrine-disrupting chemicals (EDCs) also emerged as a potential contributing factor, particularly in regions with increased use of sanitizers and disinfectants, which are known to contain EDCs.[2]

Psychosocial stress and its impact on pubertal timing

The pandemic has created a unique environment of prolonged psychological stress, which is another significant factor that may contribute to early puberty. The disruption of daily routines, social isolation, and anxiety related to the pandemic have all been identified as potential triggers for the early activation of the HPA axis, which interacts with the HPG axis and can influence the timing of puberty.[31] This review found that psychological stress was a common factor across the studies, further supporting the notion that the pandemic's psychosocial impact is a critical factor in the observed increase in precocious puberty.

Regional variations and public health implications

The regional differences observed in the incidence of precocious puberty suggest that local environmental, cultural, and public health factors play a significant role in modulating the impact of the pandemic on pubertal timing. For example, the higher relative increase in precocious puberty cases in Italy compared to other regions may reflect differences in public health responses, lifestyle changes, and environmental

exposures during the pandemic. These findings highlight the importance of considering regional contexts when developing public health strategies to address the rise in precocious puberty.

Potential biological mechanisms

One of the most compelling hypotheses for the increase in precocious puberty is the potential disruption of the hypothalamic-pituitary-gonadal (HPG) axis by SARS-CoV-2. The virus's ability to cross the blood-brain barrier and its neurotropic properties raise concerns about its impact on the central nervous system (CNS) and endocrine regulation.[32] SARS-CoV-2 has been detected in neural tissues, and its presence in the CNS could theoretically disrupt the normal regulatory processes that govern the onset of puberty. Specifically, the inflammatory response to the virus, characterized by elevated cytokine levels, may interfere with the signalling pathways involved in pubertal timing as seen in the study done by Xu et al.[33]

Inflammation has long been recognized as a factor that can accelerate pubertal development. Morris et al conveyed the role of inflammatory cytokines, such as IL-6, in the early activation of the HPG axis has been documented in previous research.[34] The cytokine storm associated with severe COVID-19 could potentially trigger or exacerbate precocious puberty by promoting a pro-inflammatory environment that hastens the onset of puberty. This mechanism is supported by studies showing that children who experienced severe COVID-19 or multisystem inflammatory syndrome (MIS-C) were more likely to exhibit signs of early puberty compared to those with mild or asymptomatic infections.[35]

Psychosocial stress and its impact

The psychological stress induced by the COVID-19 pandemic is another critical factor that may have contributed to the increase in precocious puberty. The pandemic brought about unprecedented levels of anxiety, fear, and social isolation, particularly among children who were abruptly removed from their normal routines.[2] Chronic stress is known to affect the hypothalamic-pituitary-adrenal (HPA) axis, which interacts closely with the HPG axis. Dysregulation of the HPA axis due to prolonged stress can lead to an increase in cortisol levels, which in turn may influence the timing of puberty.[36]

The role of psychological stress in accelerating puberty has been observed in previous studies, where children exposed to high levels of stress or trauma were more likely to enter puberty early (Ellis et al., 2021).[37] During the COVID-19 pandemic, the stress associated with fear of the virus, changes in family dynamics, and the disruption of social interactions could have acted as triggers for early puberty. This is particularly concerning given the long-term psychological and physical health risks associated with early pubertal onset, including increased rates of anxiety, depression, and metabolic disorders.

Lifestyle changes during the pandemic

The lifestyle changes imposed by the pandemic, such as lockdowns, school closures, and reduced physical activity, are also likely contributors to the observed increase in precocious puberty. The sudden shift to a more sedentary lifestyle, characterized by increased screen time and reduced outdoor activities, has been associated with higher body mass index (BMI) in children. Higher BMI is a well-established risk factor for earlier pubertal onset, particularly in girls.[38]

In addition to reduced physical activity, changes in diet during the pandemic may have also played a role. Increased consumption of calorie-dense, nutrient-poor foods, coupled with decreased physical activity, may have contributed to weight gain and subsequent early puberty.[39] The relationship between obesity and early puberty is complex, involving hormonal changes such as increased leptin levels, which can promote the onset of puberty.[40] The pandemic created an environment where these risk factors were amplified, leading to a potential increase in precocious puberty cases.

Environmental factors and endocrine disruptors

The potential role of environmental factors, particularly exposure to endocrine-disrupting chemicals (EDCs), cannot be overlooked in the context of the COVID-19 pandemic. EDCs are chemicals that can interfere with hormonal regulation, and they have been implicated in the early onset of puberty.[14] During the pandemic, the use of sanitizers, disinfectants, and plastic products increased significantly, leading to greater exposure to these chemicals.[41]

Studies have shown that certain EDCs, such as phthalates and bisphenol A (BPA), can mimic or interfere with the action of natural hormones, potentially accelerating pubertal development.[42] The increased use of products containing these chemicals during the pandemic may have contributed to the rise in precocious puberty observed in some regions. This highlights the need for further research into the long-term effects of pandemic-related environmental exposures on pediatric endocrine health.

Regional variations and public health implications

The systematic review revealed regional variations in the increase of precocious puberty cases, with some areas reporting higher increases than others. These variations may be attributed to differences in public health responses, cultural practices, and environmental exposures. For instance, Italy reported the highest relative increase in precocious puberty cases, which could be

linked to the severe lockdown measures and associated lifestyle changes implemented in the country.[10]

Understanding these regional differences is crucial for developing targeted public health interventions. In areas where lifestyle changes and environmental exposures were more pronounced, public health strategies should focus on mitigating these risk factors. This could include promoting physical activity, providing psychological support to children and families, and reducing exposure to EDCs. Additionally, healthcare providers in these regions should be vigilant in monitoring children for signs of early puberty and providing appropriate interventions to manage the associated health risks.[43]

Long-term health implications

Early puberty is associated with a higher risk of developing several health conditions later in life, including type 2 diabetes, cardiovascular disease, and certain types of cancer.[44] Moreover, girls who experience early puberty are more likely to face psychological challenges, such as increased rates of depression, anxiety, and body image issues.[45]

Given these risks, it is imperative that healthcare providers monitor the long-term health outcomes of girls who entered puberty early during the pandemic. Early intervention strategies, such as lifestyle modifications, psychological support, and medical treatments, may help mitigate some of the adverse effects associated with early puberty. Additionally, further research is needed to fully understand the long-term impact of the pandemic on pubertal timing and associated health outcomes.

Future directions for research

The findings of this systematic review underscore the need for further research into the impact of SARS-CoV-2 on pubertal timing. Longitudinal studies that follow children who experienced early puberty during the pandemic could provide valuable insights into the long-term health outcomes associated with this condition. Additionally, research into the biological mechanisms underlying the observed increase in precocious puberty, particularly the role of inflammation and neuroendocrine disruption, is needed to clarify the potential impact of SARS-CoV-2 on the HPG axis. Further investigation into the role of environmental exposures, such as EDCs, in the early onset of puberty during the pandemic is also warranted. Understanding how these exposures interact with biological and psychosocial factors could help identify strategies to reduce the risk of early puberty in future public health crises. Moreover, research should focus on developing and testing interventions to support children and families affected by early puberty, including psychological and behavioral interventions, as well as medical treatments where appropriate.

CONCLUSION

The study concluded that the COVID-19 pandemic showed a significant increase in the cases of precocious puberty worldwide. The study further suggested that there were a lot of biological, environmental, psychological factors at play which contributed to the accelerated puberty onset in girls. The direct effects of SARS-CoV-2 such as lifestyle changes, psychological stress, and increased exposure to EDCs played a crucial role as well. Regional variations were also noted during this study which helped highlight the need for localized public health strategies to address the issue. Simultaneous studies of children who are experiencing early puberty during the pandemic can help understand the long-term effects associated with precocious puberty, which in turn will help in strategizing the management and prevention of early puberty in the global health crisis context.

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