of these strategies is a pressing research need. Sawyer and Ivers are correct in arguing that improving parent supervision is only one of a suite of public policies needed to reduce crash risks in young people. Much more can and should be done, and the future is filled with possibility.

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Conflict of Interest Disclosures: None reported.


Additional Concerns Regarding Children With Coronavirus Disease 2019

To the Editor We read with interest the review by Castagnoli et al1 summarizing case series of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in 1065 children. The authors report the evidence up to March 3, 2020, and conclude that children with coronavirus disease 2019 (COVID-19) present mostly with mild symptoms, requiring supportive care only, and that no deaths had been reported in the age group younger than 9 years and 1 death in the age group 10 to 19 years. However, such short-term conclusions on an emerging disease where there are limited data available can be precarious. Evidence published since sheds more light on the spectrum of disease and the severity of COVID-19 in children.

For example, a preliminary description of pediatric COVID-19 cases (n = 2572)2 from the US Centers for Disease Control (CDC) between February 12, 2020, and April 2, 2020, showed that 20% received inpatient treatment and 2% required admission to the intensive care unit.2 Further studies report severe and critical cases of children with COVID-19 in up to 11% in the age group of younger than 1 year,3 with requirement of mechanical ventilation. In the CDC report, 3 patients (age not specified) with confirmed SARS-CoV-2 infection had died, with confirmation of cause of death pending. Other reports state 3 deaths in children in China (neonate, aged 10 months, and aged 14 years)4-5 and as of April 25, 2020, national surveillance systems state 2 deaths in Spain (<2 years), 2 in Italy (<9 years), and 1 in Germany (age not specified). Additionally, several deaths in older children have been reported in the media from Belgium, France, Portugal, and the United Kingdom. Furthermore, an ongoing multinational multicenter study in children with COVID-19 conducted by the Paediatric Tuberculosis Network European Trials Group (ptbnet) has captured 4 children with fatal outcome to date (Florian Goetzinger, MD, written communication, April 25, 2020). This confirms that most COVID-19 cases in children are not severe, but severe courses including death can occur in all pediatric age ranges.

While in adults, older age, male sex, cardiovascular disease, hypertension, and chronic respiratory disease have all been associated with severe disease, no definite risk groups have been identified in children. However, children with chronic lung disease (including asthma), cardiovascular disease, and immunosuppression are more often reported to require hospital admission compared with previously healthy children.2 The fact that SARS-CoV-2 can cause severe disease and death in previously healthy neonates and children stresses the need for studies on epidemiology, clinical features, and risk factors of SARS-CoV-2 infection in children.

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Conflict of Interest Disclosures: None reported.


To the Editor We read with great interest the study by Castagnoli et al1 published in JAMA Pediatrics describing the clinical features of coronavirus disease 2019 (COVID-19) in children through a systematic review. We believe that the disease severity of children with COVID-19 was significantly underestimated in the study owing to a lack of crucial studies’ enroll-
ment. Most of the cases included in this review were from reports in the early explosion stage of the COVID-19 outbreak in China; in that stage, children in Hubei province, sick or not, actually were rarely tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).2 Furthermore, the case number in children with critical or severe COVID-19 disease would not increase until the later stage of large community outbreak with an immense disease burden.2 One of the largest pediatric case series3 from the Hubei province in the stage of community outbreak demonstrated that among 171 confirmed cases, there were 8 severe/critical cases (4.6%) and 1 mortality. The case series was not included in the review.3 Severe COVID-19 in children, especially those younger than 1 year, were subsequently reported from other countries with large community outbreaks such as Japan and the United States soon after the World Health Organization declared COVID-19 as a global pandemic.4

With regards to the transmission dynamics, most of the studies showed that early in the outbreak, children usually acquired the infection in the household clusters.1,2 When the epidemic further disseminated without being efficiently contained, the outbreak evolved into an explosion stage, when the school transmission mixed with a wider community spread occurred.2 In most countries, schools were closed during this phase to prevent further intraschool or school-family transmission of the infection.2 Children can be a significant spreader of SARS-CoV-2 if the public health system does not enforce the social distancing policy for children and adolescents (school closure), given the relatively high proportion of mild/asymptomatic infection and prolonged viral shedding in children with COVID-19.5

Because the clinical evidence of COVID-19 in the pediatric population has increased rapidly in recent months, a timely systemic review is needed to reveal a more complete view on the epidemiology of COVID-19 in children and adolescents.

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Conflict of Interest Disclosures: None reported.

To the Editor We read with great interest “Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review” by Castagnoli et al.1 This analysis of 18 studies and 1065 children and adolescents, all from China except one from Singapore, updated to March 3, 2020, showed that coronavirus disease 2019 (COVID-19) affects all ages. Children often present with fatigue, nasal congestion, fever and cough, but severe pneumonia is less common and deaths are extremely rare.1 Castagnoli et al stated that defining the clinical characteristics and severity of the disease in large cohorts of patients is an urgent need. Italian,2 European,3 and US4 reports all have confirmed that few cases (<3%) were among children and adolescents who appeared the least-at-risk population for critical disease in all countries. We consider that interpreting these data and understanding the varied susceptibility of children to SARS-CoV-2 are particularly important to figure out the protective factors in patients of all ages. Resistance to COVID-19 is highly likely to be multifactorial. Preexisting health conditions, including cardiovascular and chronic respiratory diseases, obesity, diabetes, cancer, and immune suppression, have been associated with severe illness and lethality in adult patients and elderly patients.1-4 Data on comorbidities in pediatric COVID-19 were not available in this systematic review4 but need to be fully analyzed in the next large case series to better identify key risk factors in children and potential individual protective and therapeutic strategies. Antigen sequencing of SARS-CoV-2 could also clarify whether cross-immunity with other respiratory viruses or infant vaccinations may occur in different populations. The mechanistic role of angiotensin-converting enzyme 2 receptors in the pathogenesis of severe COVID-19 and its variation according to age still need to be studied. Next, immune senescence and inflammaging include decreased number of naive T cells, impaired phagocytosis, restricted T-cell antigen receptor repertoire, reduced B-cell and T-cell functional responses, and persistent inflammatory molecules, thus predisposing to increased risk of infections and tissue fibrosis.5 Exploring nasopharyngeal and systemic innate and adaptive immunity in pediatric cases is crucial for understanding children’s resistance to SARS-CoV-2, viral transmission, and plausible therapeutic approaches. Anosmia and dysgeusia are reported in many adult patients with COVID-19; the prevalence and importance of these symptoms in children is uncertain. Finally, SARS-CoV-2 antibody tests will reveal whether children were less tested or less exposed to the virus or whether they contracted the infection and expressed mild illness owing to multiple protective mechanisms.

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To the Editor We read with great interest the study by Castagnoli et al that shows mild symptoms, better prognosis, and less severe conditions in children with coronavirus disease 2019 (COVID-19) than adults. Infected children were observed to have recovered within 1 to 2 weeks after disease onset. It is refreshing to note that Castagnoli et al have adopted an optimistic view on the lesser predisposition to or better prognosis for COVID-19 in children than adults. However, considering the limited number of infected children in each individual study, we must hold some reservations about the generalizability of this finding.

In support of the findings by Castagnoli et al, we reason that it is possible that children with enhanced or trained immune systems. We agree that more studies involving neonates (aged 0-28 weeks), because they are in a special condition of not developed or underdeveloped immune systems. We cast doubt on the lower mortality rates of children reported by Castagnoli et al in light of a lower rate of mortality in children with COVID-19 in this systematic review. Yet, this systematic review focused on articles published as of March 3, 2020, reporting only 1 death in 1065 children. Following this cutoff date, articles were published showing 1 pediatric death in China (as of March 19) and 3 in the United States (as of April 2). Hence, time lag bias may have affected the findings of this review, and more concerns are warranted.

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Conflict of Interest Disclosures: None reported.


In Reply We much appreciated the interest aroused by our systematic review, and we thank all the authors for their thoughtful comments about our work. In our analysis, available evidence showed that most children with coronavirus disease 2019 (COVID-19) presented with mild symptoms, if any, and recovered uneventfully. However, 1 infant had a severe presentation and was successfully treated with intensive care, and 1 death was reported.

The research occurred over a brief 3-month period (from December 1, 2019, to March 3, 2020), and the articles were observational designs and came mainly from Chinese reports because European and US studies in children with COVID-19 were not available at the time this review was conducted.

Despite these limitations, accumulating literature confirmed our main findings, showing that children and adolescents appeared the least at-risk population for developing critical disease. Once infected, the risk for a child to develop severe disease requiring hospitalization is 25 times lower than in adults (0.1% vs 2.6%), and the risk of death is 500 times lower than in adults (0.001% vs 0.5%), as based on a French study. Hypotheses regarding the relative resistance of children to COVID-19 include (1) resistance to the infection, (2) more efficient control of the infection, (3) less intense immunopathologic reaction, and (4) better capacity of tissue repair. Bunyavancich et al showed age-dependent nasal gene expression of angiotensin-converting enzyme 2, the receptor that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses for host entry. Lower angiotensin-converting enzyme 2 expression in children relative to adults may help explain why COVID-19 is less prevalent in children.

In addition to reported findings, the unprecedented global research effort to better characterize SARS-CoV-2 infection has shed new light on pediatric COVID-19, adding novel insights to initial evidence. As discussed by Chen and Chiu, Salvatore et al, and Zimmerman et al, although most children with COVID-19 present with mild symptoms, severe cases have been
reported, and death can occur in all pediatric age ranges.\textsuperscript{5} Despite the fact that no definite risk groups have been identified in the pediatric population, comorbidities, including obesity, neurologic condition, chronic lung disease, cardiovascular disease, immunosuppression, and overall medical complexity, have been reported in children with severe COVID-19.\textsuperscript{2} Also, children younger than 1 year are overrepresented in pediatric COVID-19 cohorts, with a higher risk of fatality compared with children older than 1 year;\textsuperscript{3} in this context, as discussed by He and Zhang, further studies need to analyze clinical outcomes in infected neonates.

Moreover, as a confirmation of the broad spectrum of disease caused by SARS-CoV-2, children presenting with a multisystem inflammatory syndrome associated with COVID-19 are also being reported.\textsuperscript{6} This syndrome, with features similar to Kawasaki disease, underscores the need for a better understanding of SARS-CoV-2 infection's pathophysiology in children.

We are working on an updated systematic review of SARS-CoV-2 infection in children and adolescents (PROSPERO, registration number: CRD42020181640) to fully characterize the clinical and immunologic features of pediatric COVID-19.

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Conflict of Interest Disclosures: None reported.

Additional Contributions: We thank Martina Votto, MD, and Ilaria Brambilla, MD, PhD, for their valuable inputs for the preparation of this response letter.


Aggression as a Mediating Behavior in the Association Between Video Game Use and Body Mass Index

To the Editor I read with great pleasure the article titled “Association of Video Game Use With Body Mass Index and Other Energy-Balance Behaviors in Children” by Goodman et al.\textsuperscript{1} The article explores the association between body mass index (BMI) and video game use, identifying physical activity, bedtime regularity, sugar-sweetened beverage consumption, and high-calorie food consumption as potential mediating behaviors.\textsuperscript{1} The authors state that they found a small but not clinically meaningful association.\textsuperscript{1} I believe the authors should have also included aggression as a potential mediating behavior owing to its effect on stress and anxiety levels. Previous studies have demonstrated that video games certainly spike up aggressive behaviors in children,\textsuperscript{2} which can contribute to stress levels in users. This stress from violent video games can not only increase vitals such as heart rate and blood pressure but also increase the release of stress hormones such as epinephrine and norepinephrine. Previous research has also shown that high psychological stress levels can be responsible for contributing to increases in BMI.\textsuperscript{3} When people are stressed, their metabolic rate lowers, resulting in weight gain.

Additionally, the effect of stress on BMI may be worse in people who are already obese. In healthy individuals, experiencing mental stress decreases vascular resistance in skeletal muscle so healthy individuals only experience a moderate increase in blood pressure. However, in individuals who are already obese, mental stress does not decrease the vascular resistance in the skeletal muscle. This means that such individuals experience an enhanced high blood pressure response, which has already demonstrated an association with metabolic rate.\textsuperscript{4} The association of video game use with BMI should be reassessed in children using aggression as a mediating behavior. Video game users should be asked to rate their demonstration of aggressive behavior on a scale of 1 to 10. Perhaps a clinically meaningful association will be found, especially in the case of violent video game use.

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Published Online: November 2, 2020. doi:10.1001/jamapediatrics.2020.2928

Conflict of Interest Disclosures: None reported.


In Reply We read Girkar’s response to our study, “Association of Video Game Use With Body Mass Index and Other Energy-Balance Behaviors in Children,” with great interest and value the points raised. We share her point of view that a number of factors influence body mass index (BMI),\textsuperscript{1} including emotions and stress. The associations between these factors and