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News & Views

# Prenatal exposure to the SARS epidemic emergency and risk of cognitive impairment in toddlers

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The coronavirus epidemic may affect us far beyond the virus itself. Previously, there was a considerable body of evidence that maternal stress or other limitations caused by adverse events or emergencies, such as natural disasters, did indeed have long-term effects on offspring prenatally exposed to the events [1–2]. However, we did not find any study that evaluated the long-term impact of a severe infectious disease epidemic as a public health emergency on offspring at the population level. We will have to wait to determine these issues regarding coronavirus disease 2019 (COVID-19), but we have a natural experiment from the last important coronavirus epidemic.

Severe acute respiratory syndrome (SARS), the first severe and readily transmissible new infectious disease emerging in the 21st century, wreaked global havoc [3]. We set out to use the natural experiment of the SARS epidemic in 2002–2003 to test the hypothesis that, whatever the cause, prenatal exposure to the epidemic event would have a negative effect on cognitive development in the resultant toddler offspring. These findings will contribute to the existing knowledge pool by providing evidence for the effect of public health emergencies, such as viral epidemics, on offspring for the first time to the best of our knowledge, providing a new perspective to understand the long-term impact of a severe infectious disease epidemic.

The SARS epidemic was used as an event to design a natural experimental study. Individual-level data were obtained from the second China National Sample Survey on Disability (CNSSD), a cross-sectional survey conducted in 2006 (Supplementary Materials online). We restricted our analysis to the child subsample of CNSSD at the age of 2 to 4 years during the survey window that included two undermentioned birth cohorts with different maternal exposures. Additionally, we rested on an exclusion restriction assumption that all toddler participants remained living where their mothers were living at the time of pregnancy and delivery and excluded the migratory samples according to the registration information since the places they were interviewed were different from their birth prefectures. As a result, 67,328 toddlers were included in the final analysis. The derivation of the analytical sample is presented in Fig. 1a.

The outcome variable in this study was whether a child had any cognitive impairment diagnosed by pediatricians and neurologists with more than 5 years of clinical experience at clinics or community health centers. The exposure in our study was any possible prenatal exposure to the event of SARS epidemic in mainland China during the approximately 10 months from periconception to delivery. We measured exposure by both the geographical information about the SARS epidemic of the participants and their birth time relative to the period of the SARS epidemic.

We first implemented a binary variable, "SARS epidemic exposure" (non-SARS epidemic or SARS epidemic), according to whether a sample was living in areas with any SARS cases, depending on the exact cumulative number of cases from the Chinese Center for Disease Control and Prevention. We also implemented an ordinal category of "the severity of SARS epidemic exposure" (non-SARS epidemic, mild epidemic, moderate epidemic, or severe epidemic) according to the SARS epidemic of the samples' living areas reflected by the pattern of local transmission published by the WHO. Then, we generated a binary variable "birth cohort" (before-SARS cohort or SARS cohort) according to the birth time of a sample relative to the period of the SARS epidemic (November 2002 to July 2003). The before-SARS cohort included individuals born between June 2001 and October 2002 (17 months) who were without maternal exposure before or during pregnancy. Individuals born during November 2002 and March 2004 (also 17 months) who were maternally exposed to the SARS epidemic event in the prenatal period were categorized as the SARS cohort. We emphasized once again that the exposure in our study was the event of the SARS epidemic and assumed that none of the children included in any of the groups had been exposed to SARS infection in utero.

We employed the difference-in-differences (DID) method, a quasi-experimental design that obtains an appropriate counterfactual to estimate a causal effect, to estimate the effect of prenatal exposure to the SARS epidemic event on subsequent development of cognitive impairment by comparing variations across birth cohorts between groups with different SARS epidemic exposure. Details of the measurement of the outcome, exposure and other covariates, as well as the statistical analyses, are presented in the Methods section in the Supplementary materials (online).

Among 67,328 toddlers included in the analyses, 487 were diagnosed with cognitive impairment at the time of the survey. The prevalence of cognitive impairment was 0.72% (95% confidential

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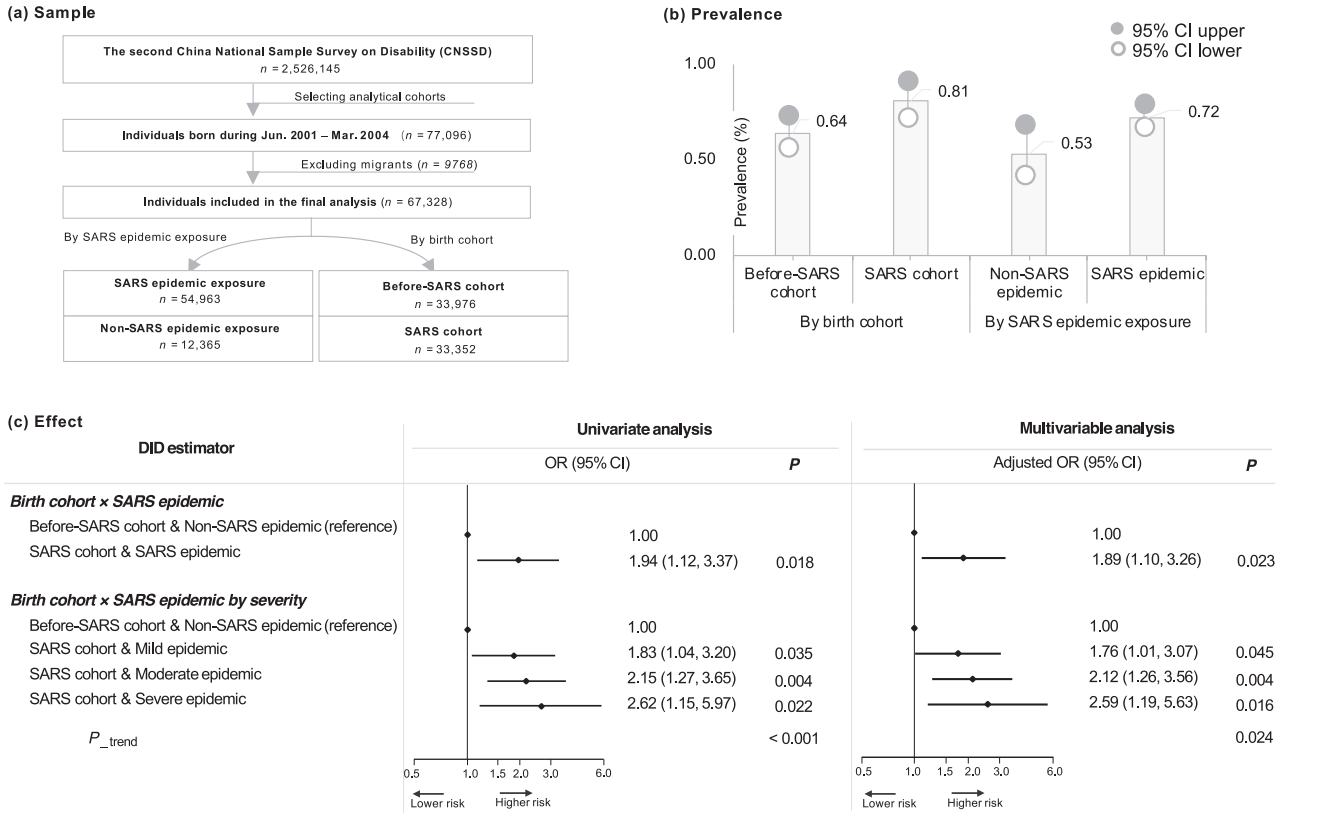


**Fig. 1.** (a) Flowchart of the derivation of the analytical sample. (b) Prevalence of cognitive impairment among toddlers by birth cohort and SARS epidemic group. (c) The effect of prenatal SARS epidemic exposure on cognitive impairment in toddlers. The results of the multivariable analysis were adjusted for age, sex, ethnicity, annual household income per capita, family history of any disability, residence, region, and provincial fixed effects.

interval (CI): 0.66%–0.79%). The SARS cohort exhibited a significantly higher prevalence than the before-SARS cohort, and the prevalence in the group with SARS epidemic exposure was significantly higher than in the group without SARS epidemic exposure (Fig. 1b).

The DID estimates shown in Fig. 1c indicate that prenatal exposure to the SARS epidemic during pregnancy has a long-term adverse effect on the cognition of toddler offspring by significantly increasing the risk of cognitive impairment (odds ratio (OR) = 1.89, 95% CI: 1.10–3.26) in the adjusted model after controlling for multiple covariates.

After further dividing the SARS epidemic exposure by severity, toddlers with mild (OR = 1.76, 95% CI: 1.01–3.07), moderate (OR = 2.12, 95% CI: 1.26–3.56) and severe SARS epidemic event exposure (OR = 2.59, 95% CI: 1.19–5.63) during the prenatal period were all more likely to develop cognitive impairment compared to those without exposure after controlling for covariates (Fig. 1c). The risk increased significantly as the severity of the SARS epidemic exacerbated ($P_{\_trend}$ = 0.024).

The effect was robust based on a series of robustness checks we performed. First, due to data limitations, we did not control for some potential individual confounders, such as the method of delivery, gestational age and environmental risks in early life. To partially address this issue, we used a multilevel model analysis that included some socioeconomic, environmental and maternal health service resource confounders at the province level in addition to covariates at the individual level. A similar significant effect of prenatal exposure to the SARS epidemic event on the risk of cognitive impairment among toddlers was observed (Table S1 online). Then, we conducted two so-called "falsification tests" to check the specificity of our findings in the SARS cohort. In one test, we examined whether the effect would be found if we used the alternative cohort instead of the SARS cohort with the same DID method; we found that there was no significant SARS epidemic event effect in the alternative cohort (Table S2 online). In a further test, we used the alternative cohort instead of the before-SARS cohort as the reference. After controlling for covariates, we still observed a significant effect of prenatal exposure to the SARS epidemic during pregnancy on the risk of cognitive impairment in toddlers (OR = 1.50, 95% CI: 1.03–2.17), and the risk increased with SARS epidemic severity ($P_{\_trend}$ = 0.018) (Table S3 online).

The potential heterogeneity of effects caused by prenatal exposure to the SARS epidemic event across the population was examined by sex (Table S4 online). A significantly marginal SARS epidemic exposure effect by sex interaction was observed wherein the risk of cognitive impairment caused by prenatal exposure to the SARS epidemic event in boys was nearly 4 times that in girls (adjusted OR = 3.98, 95% CI: 1.87–8.46). Probing the interaction showed that the prenatal exposure had a detrimental effect on cognitive impairment for boys (adjusted OR = 3.39, 95% CI: 2.02–5.67), but the effect was not significant for girls ($P \geq 0.05$).

The present study demonstrated for the first time that prenatal exposure to the SARS epidemic event, a public health emergency, has had an enduring deleterious effect on cognitive impairment in toddlers, and the risk increased as the intensification of the severity of SARS epidemic exposure was exacerbated. This is consistent with a previous study in which prenatal flood exposure was associated with cognitive function of toddlers aged 2–3 years, and lower cognitive function was found with increasing levels of stress [4]. Our findings suggest that public health emergencies

could, like other adverse events such as natural disasters, increase the long-term health risk for offspring maternally exposed to such events during pregnancy [1–2,4]. The study of the effect of natural and social events on population health should be one of the contents and methods of the Events Demography, a new interdiscipline of research significance and potential.

A possible pathway through which SARS epidemic event exposure during pregnancy increases the risk of offspring having cognitive impairment is prenatal maternal stress (PNMS), similar to other adverse events in early life. Previous studies have indicated that the outbreak and epidemic of severe infectious diseases can be regarded as a mental health catastrophe, and its consequences include depressive disorders among infected patients [5], stress symptoms among patients' family members, friends, or acquaintances [6], and psychiatric conditions, such as alcohol abuse/dependence in hospital employees [7]. In particular, with the development of social media and the diversity of information acquisition methods, unclear, subjective, and discouraging messages issued by untrusted authorities or individuals may spread on the Internet, leading to not only increased disease spread but also panic [3]. At present, global COVID-19, which has been widely discussed on social media, exhibits an increasing number of infectious and deadly cases that have also fueled the spread of anxiety. For pregnant women, the stress is particularly severe due to the worse clinical course and poorer outcomes compared with non-pregnant women once infected with a new infectious disease, such as SARS or Middle East respiratory syndrome (MERS) [8].

Generally, possible mechanisms by which a PNMS may increase the susceptibility to cognitive impairment of toddler offspring include affecting foetal brain development and postnatal cognitive performance by vertically transferring maternal stress hormones, such as glucocorticoids crossing the placenta [9], altering foetal programming by affecting the hypothalamic–pituitaryadrenal axis [10], and causing epigenetic modification changes such as DNA methylation [11]. A sex disparity of vulnerability was also identified in these mechanisms, that is, the effect appears to be manifested in altered diurnal cortisol secretion in males with increased programmed vulnerability to maternal stressors of the hypothalamic-pituitary-adrenal axis in females [12]. The observed sex effects in our study supported foetal male vulnerability in utero to PNMS and indicated that endocrine mechanisms may play a more important role in the influence shown in the present study. However, the underlying cause of the sex disparity is unclear and needs further study.

Additionally, alternative pathways of influence at the macro and micro levels cannot be fully ruled out. For example, pregnant women may face inadequate access to maternal healthcare services and social support caused by traffic reductions or other restrictions during the epidemic, a poor condition of nutrition required for pregnant women and fetus due to a shortage of fresh vegetables, and changes in the normal or regular lifestyle, including physical activities and outdoor exercise, due to active or passive behavioral strategies to mitigate their risk of contracting infection during the epidemic [13].

In any event, our findings suggest that the long-term consequences of epidemic event exposure during pregnancy will likely be passed on to the next generation through indirect pathways. Nevertheless, we cannot ignore the potential direct effect of the virus on the brain of the fetuses since vertical transmission of SARS-CoV-2 has been demonstrated [14] (even if rare) and the impact of Zika on foetal brain was observed [15]. Fortunately, some measures and efforts that emphasize the importance of dealing with the potential mental health crisis have been taken by governments and hospitals in China. Our findings indicate the need for a better-prepared and comprehensive response plan that includes mental and other specific demands of various high-risk populations, such as pregnant women, in preparation for the next unpredictable public health emergency.

In summary, prenatal exposure to the SARS epidemic event had a long-term adverse effect on the cognitive outcomes of toddler offspring. The effect increased as the epidemic severity exacerbated and was moderated by the sex of the offspring. These findings suggest that policy makers and health professionals, as well as the public, should pay more attention to dissipating the mental pressure and reproductive healthcare limitations caused by the epidemic, especially in pregnant women and other special groups, while carrying out the prevention and control of severe infectious disease outbreaks, such as SARS, COVID-19 or other new infectious diseases.

## Conflict of interest

The authors declare that they have no conflict of interest.

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## Appendix A. Supplementary materials

Supplementary materials to this article can be found online at https://doi.org/10.1016/j.scib.2021.04.011.

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