

**Childhood cognitive impairment after maternal exposure to a public health emergency during pregnancy: a lesson from the SARS epidemic**

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**Backgrounds and theoretical focus**

As a public emergency that nobody can avoid, 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. 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 COVID-19, but we have a natural experiment from the last important coronavirus epidemic.

SARS, as the first severe and readily transmissible new infectious disease emerging in the 21st century, wreaked a global havoc dramatically. We set out to use the natural experiment of the SARS epidemic in 2002–2003 to test the hypothesis that, whatever the cause, maternal exposure to the epidemic event would have a negative effect on cognitive development among the toddler offspring.

**Data and Methods**

The epidemic of SARS was used as an event to design a natural experiment study. Individual-level data were obtained from the second China National Sample Survey on Disability (CNSSD), a cross-sectional survey conducted in 2006 and the most recently released source of individual-level data aimed to investigate the functioning and disability of Chinese household population. A random representative sample, using multistage stratified cluster sampling with probabilities proportional to size, was drawn from 734 counties, 2,980 towns, and 5,964 communities of 31 provinces in mainland China. A total of 2,526,145 subjects were interviewed, representing 2 per 1,000 Chinese residents.

We restricted our analysis to the child subsample of CNSSD born between June 2001 and March 2004 that included two undermentioned birth cohorts with different maternal exposures. Additionally, we rested on an exclusion restriction assumption that all toddler

participants remained were 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 at the age of 2 to 4 years during the survey window were included in the final analysis.

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.

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 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.

### **Expected findings**

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 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 the epidemic exposure.

The DID estimates indicated that maternal exposure to the SARS epidemic significantly increased the risk of cognitive impairment among toddlers (adjusted OR 1.89, 95% CI 1.10–3.26). The effect increased significantly as the severity of the epidemic exacerbated (mild epidemic: 1.76, 1.01–3.07; moderate epidemic: 2.12, 1.26–3.56; severe epidemic: 2.59, 1.19–5.63; P for trend=0.024). Boys appeared more sensitive to the effect with a significantly marginal exposure effect by sex interaction (adjusted OR 3.98, 95% CI 1.87–8.46). The effect was robust based on a series of robustness checks we performed.

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.