Antagonistic effect of early stage zinc on arsenic toxicity induced preterm birth during pregnancy: evidence from a rural Bangladesh birth cohort

Yong-Yue Wei[1,2], Hui Huang[3], Yan-Kai Xia[4], Liang-Min Wei[3], Xin Chen[3], Ru-Yang Zhang[3], Wei-Wei Duan[3], Li Su[5], Mohammad L. Rahman[6], Mahmudur Rahman[7], Md. Golam Mostofa[7], Quazi Qamruzzaman[7], Wen-Hui Guo[4], Xian Sun[4], Hao Yu[3], Hong-Bing Shen[2,8], Zhi-Bin Hu[1,2,8], David C. Christiani[2], Feng Chen[1,2,3]

[1]State Key Laboratory of Reproductive Medicine, Nanjing Medical University, Nanjing, Jiangsu 211166, China;
[2]China International Cooperation Center for Environment and Human Health, Center of Global Health, Nanjing Medical University, Nanjing, Jiangsu 211166, China;
[3]Department of Biostatistics, School of Public Health, Nanjing Medical University, Nanjing, Jiangsu 211166, China;
[4]Key Laboratory of Modern Toxicology of Ministry of Education, School of Public Health, Nanjing Medical University, Nanjing, Jiangsu 211166, China;
[5]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA;
[6]Harvard Medical School, Department of Population Medicine and Harvard Pilgrim Health Care Institute, Boston, MA 02115, USA;
[7]Dhaka Community Hospital Trust, Dhaka, Bangladesh;
[8]Department of Epidemiology, School of Public Health, Nanjing Medical University, Nanjing, Jiangsu 211166, China.

To the Editor: Preterm birth (PTB), defined as livebirth before 37 completed weeks of gestation, is associated with a high degree of immaturity of various organs, and thus are at greater risk of a range of short-term and long-term comorbidities.[1] The estimated PTB prevalence in Bangladesh, already among the highest at 19.1%,[2] is even higher in rural areas in Bangladesh,[3] posing a significant economic and emotional burden to these families and the country. About 22 million residents of Bangladesh are exposed to arsenic (As) at concentrations exceeding 50 parts per billion (ppb), much higher than the World Health Organization's safety limit of 10 ppb. It has been well studied for the As exposure impacts birth outcomes, including PTB. Separately, low maternal zinc (Zn) levels are associated with adverse pregnancy outcomes, including PTB. Although Zn deficiency and As exposure have common pathological symptoms, the mechanisms of interaction between these crucial elements, and how they each impact physiology, is unclear. Animal experiments indicate that As toxicity can be detoxified by Zn supplementation.[4,5] However, there is no evidence from human studies concerning the protective effects of Zn against As-induced PTB.

This study aimed to explore the critical prenatal exposure times in which As and Zn are associated with PTB risk and how maternal serum Zn reduces the effect of As on PTB. We studied 780 pregnant women with available first-trimester serum samples. Of these, 610 participants had second-trimester serum samples available [Supplementary Figure 1, http://links.lww.com/CM9/A391]. Mother-offspring pairs were recruited from a prospective birth cohort in rural Bangladesh (2008–2011). Serum Zn and As were analyzed using an iCAP Qc Inductively Coupled Plasma Mass Spectrometry (iCAP Qc ICP-MS) at the Nanjing Medical University. Limits of detection (LODs) were calculated as three times the average of ten consecutive measurements of the blank diluent. Quality control samples were from Seronorm Trace Elements Serum L-2 (ref. 203113, Sero, Billingstad, Norway) which were analyzed in parallel with study samples (every 20 study samples were analyzed with one standard sample). Metal concentrations below the LOD were imputed by limits of detection (LOD)/2. Relative standard deviations of As and Zn were 14.16% and 17.20%, respectively.

Analyses were conducted using R software Version 3.5.1 (The R Foundation for Statistical Computing). Baseline characteristics of PTB cases and controls were compared using a *t*-test or Mann-Whitney *U* test for continuous variables depending on data distribution and Chi-square test was used for categorical variables. To identify crucial metal exposures for PTB risk, logistic regression models were separately performed for $\log_e$ transformed Zn and As at each trimester and restricted cubic spline was performed for each metal to further explore the non-linear relationship. In addition, by treating PTB as time-to-event

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001241

Yong-Yue Wei and Hui Huang contributed equally to this work.

Correspondence to: Dr. Feng Chen, State Key Laboratory of Reproductive Medicine, Center of Global Health, School of Public Health, Nanjing Medical University, Nanjing, Jiangsu 211166, China
E-Mail: fengchen@njmu.edu.cn

Chinese Medical Journal 2021;134(5)
Received: 30-07-2020 **Edited by:** Xin Chen and Yuan-Yuan Ji

outcome, Cox regression was performed as sensitivity analysis to compare the cumulative PTB rate under high and low levels of metal concentration. Additionally, Zn was dichotomized by median (low-Zn group *vs.* high-Zn group) and As was categorized by tertiles. To evaluate the interaction between Zn and As, strata of the two elements were fully joined and compared to a reference stratus. Non-linear interaction analysis with the incorporation of

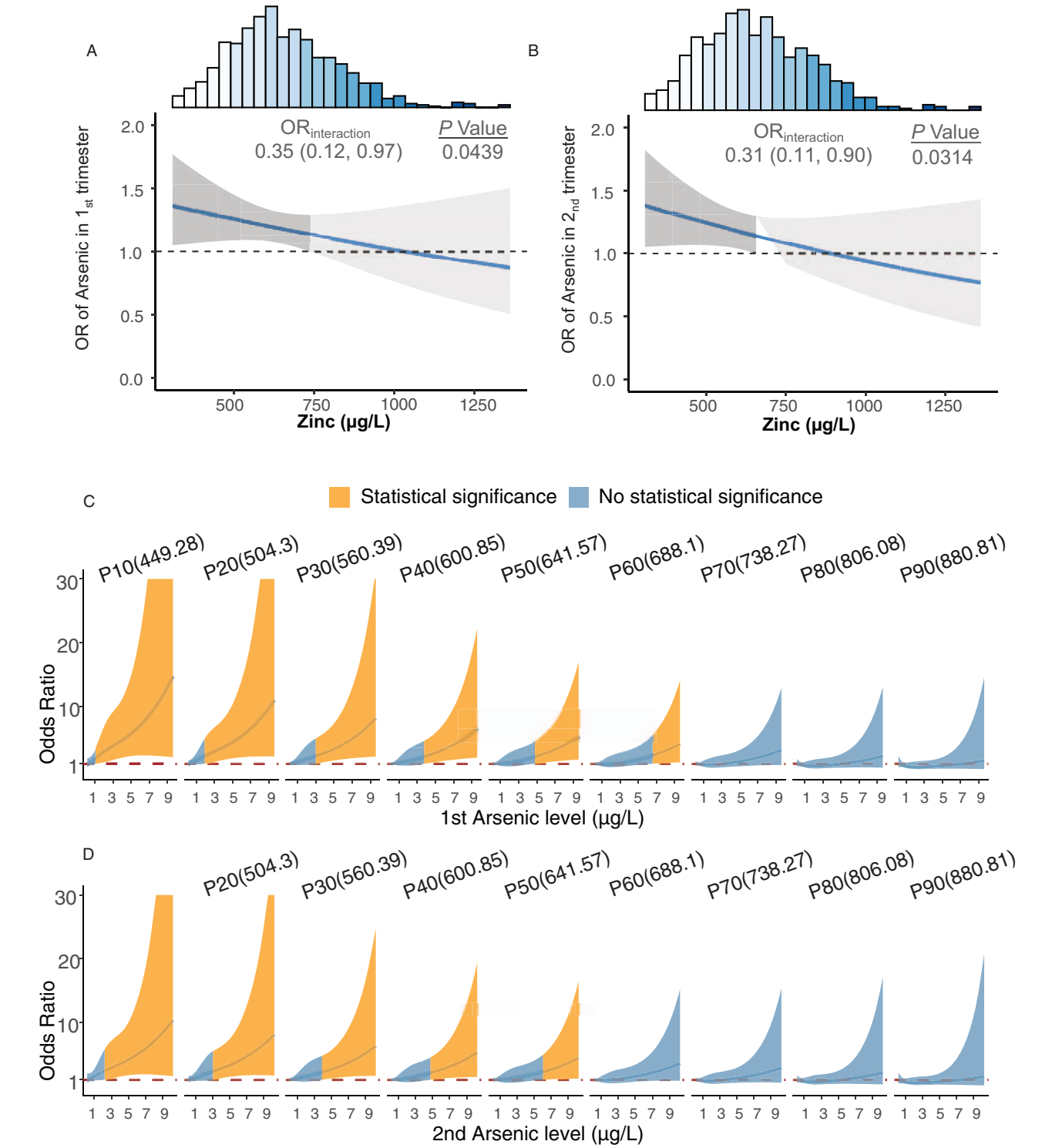

Figure 1: Toxic effect of Arsenic (As) on preterm birth modified by Zinc (Zn) of first trimester. OR of As in first trimester (A) and second trimester (B) on preterm birth modified by serum Zn in the first trimester. The shallow area represents 95% CI, with dark gray indicating areas where the risk is significant, and light gray indicating areas where the risk is not significant. Histogram shows the distribution of serum Zn in the first trimester. The restricted cubic spline for the relationships between As in the first trimester (C) and As in the second trimester (D) and preterm birth in different quantiles of serum Zn in the first trimester. Lines represent adjusted odds ratios based on restricted cubic splines for the log-transformed levels of serum As in the logistic model. Adjustment factors were baseline age, BMI, second-hand smoking status, education, income levels, child marriage, and previous pregnancy. The numbers in parentheses show the serum metal concentrations before log-transformation. BMI: Body mass index; CI: Confidence interval; OR: Odds ratio.

the restricted cubic spline was performed to explore potential non-linear interaction effects.

Of 780 singleton livebirths, 175 (22.4%) were born preterm. Women delivering preterm were more likely to get married before 18 years old and have second-hand smoking exposure, lower maternal weight, lower education level, lower partner education level, and lower income [Supplementary Table 1, http://links.lww.com/CM9/A391]. To determine critical exposure timing, Zn and As concentrations in the first and second trimesters were analyzed using logistic models. Concentrations of serum Zn (odds ratio [OR]: 0.28; 95% confidence interval [CI]: 0.13–0.58; $P = 6.00 \times 10^{-4}$) and As (OR: 1.49; 95% CI: 1.20–1.84; $P = 3.00 \times 10^{-4}$) in the first trimester, and As (OR: 1.35; 95% CI: 1.05–1.74; $P = 0.0205$) in the second trimester were significantly associated with PTB, while Zn in the second trimester did not show significant association with PTB. Non-linear dose-response analysis confirmed these associations [Supplementary Figure 2, http://links.lww.com/CM9/A391]. Stratified analysis was performed by joining Zn and As exposure categories. Notably, serum Zn in the first trimester had a statistically significant interaction with As in the first trimester (OR: 0.35; 95% CI: 0.12–0.97; $P_{interaction} = 0.0439$) and As in the second trimester (OR: 0.31; 95% CI: 0.11–0.90; $P_{interaction} = 0.0314$) in relation to PTB [Figure 1A and 1B]. The non-linear toxic effect of As in either the first or second trimester on PTB risk was fitted under a series of Zn quantiles [Figure 1C and 1D] to demonstrate that As toxicity is attenuated by a high level of serum Zn in the first trimester [Supplementary Table 2, http://links.lww.com/CM9/A391].

This study highlights the protective effect of serum Zn in the first trimester against PTB resulting from As toxicity. This is in line with a recent *in vitro* study illustrating that As exposure significantly reduced the amount of Zn in developing embryos. As competes with Zn to bind to a series of Zn finger proteins recognized as DNA damage repair elements. Interestingly, functional disruptions to Zn finger proteins or to DNA damage repair are associated with PTB risk.[6] In addition, animal studies suggest that As exposure during pregnancy may lead to oxidative stress, suggesting that the application of Zn supplementation reverses oxidative stress indicators and may reduce As toxicity. Prior functional knowledge supports our findings that Zn acts as an antagonist for As toxicity on adverse birth outcome.

In summary, this study identified high maternal serum As during pregnancy is associated with increased PTB risk, which could be attenuated by increased maternal serum Zn during the first trimester. This finding of this study may open up new prospects for supports Zn as a nutritional intervention during pregnancy to against As toxicity and its health implications.

Declaration of patient consent

The authors have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

Funding

This study was supported by grants from the State's Key Project of Research and Development Program (No. 2016YFE0204900), the U.S. National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH) grant (No. R01ES015533), National Natural Science Foundation of China (No. 81530088), the Key International (Regional) Cooperative Research Project (No. 81820108028), National Key Research and Development Program of China (No. 2018YFC0910500), and the Priority Academic Program Development of Jiangsu Higher Education Institutions. Sponsors had no role in the design of the study, the collection and analysis of data, or the preparation of the manuscript.

Conflicts of interest

None.

References

1. Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, *et al*. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health 2019;7:e37–e46. doi: 10.1016/s2214-109x(18)30451-0.
2. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, *et al*. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162–2172. doi: 10.1016/s0140-6736(12)60820-4.
3. Shah R, Mullany LC, Darmstadt GL, Mannan I, Rahman SM, Talukder RR, *et al*. Incidence and risk factors of preterm birth in a rural Bangladeshi cohort. BMC Pediatr 2014;14:112. doi: 10.1186/1471-2431-14-112.
4. Wong CP, Dashner-Titus EJ, Alvarez SC, Chase TT, Hudson LG, Ho E. Zinc deficiency and arsenic exposure can act both independently or cooperatively to affect zinc status, oxidative stress, and inflammatory response. Biol Trace Elem Res 2019;191:370–381. doi: 10.1007/s12011-019-1631-z.
5. Beaver LM, Truong L, Barton CL, Chase TT, Gonnerman GD, Wong CP, *et al*. Combinatorial effects of zinc deficiency and arsenic exposure on zebrafish (Danio rerio) development. PLoS One 2017;12:e0183831. doi: 10.1371/journal.pone.0183831.
6. Norishadkam M, Andishmand S, Zavar Reza J, Zare Sakhvidi MJ, Hachesoo VR. Oxidative stress and DNA damage in the cord blood of preterm infants. Mutat Res 2017;824:20–24. doi: 10.1016/j.mrgentox.2017.10.003.

How to cite this article: Wei YY, Huang H, Xia YK, Wei LM, Chen X, Zhang RY, Duan WW, Su L, Rahman ML, Rahman M, Mostofa MG, Qamruzzaman Q, Guo WH, Sun X, Yu H, Shen HB, Hu ZB, Christiani DC, Chen F. Antagonistic effect of early stage zinc on arsenic toxicity induced preterm birth during pregnancy: evidence from a rural Bangladesh birth cohort. Chin Med J 2021;134:619–621. doi: 10.1097/CM9.0000000000001241