PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between the Chinese famine exposure during infant period and the risk of self-report chronic lung diseases in adulthood: a cross-sectional study
AUTHORS	Wang, Zhenghe; Zou, Zhi-Yong; Yang, Zhongping; Dong, Yanhui; Ma, Jun

VERSION 1 - REVIEW

REVIEWER	Zumin Shi University of Adelaide, Australia
REVIEW RETURNED	19-Dec-2016

GENERAL COMMENTS	Using open access CHARLS data, the authors assessed the association between early life exposure to Chinese famine and chronic lung diseases in adulthood. The study is important and may provide new evidence on the adverse effects of early life famine exposure. The analytical strategy used in the current study is the same as a recent paper of famine exposure and hypertension this group has published. Main concern: 1. The analytical sample size seems problematic to me. It is unlikely that the sample size of the fetal exposure group is larger than non-exposed group, due to the low birth rate during famine. There must be an error in the selection of the sample. Can the authors confirm that all the participants were categorized correctly? Was the date of birth reported using the Chinese lunar calendar transformed correctly? It is also unlikely that the infant-exposed group has a similar sample size as the preschool-exposed group as the age spans are different (1 year vs 2 years). 2. As the age was positively related to chronic lung disease, it is difficult to separate the effect of age from famine exposure. The current findings may be confounded by age. In fact, the group's paper on famine and hypertension suffered from the same problem. Using data from an Australia cohort study, among Australian adults I can find similar ORs for hypertension of age groups similar to the famine exposure groups (reported by the authors). They are obviously not famine related. Minor: 1. Some demographic information (e.g. education, income) is needed in Table 1. 2. As smoking is related to lung problems, a test for interaction between famine exposure and smoking is needed. Could it be that the association in men is in fact due to smoking?

REVIEWER	Li Li
	Department of Nutrition and Food Hygiene, School of Public Health, Anhui Medical University, China
REVIEW RETURNED	31-Dec-2016

GENERAL COMMENTS	In this study, the authors have investigated the associations between prenatal and early postnatal exposure to the Chinese famine and the risk of chronic lung diseases in adulthood. On the whole they have found that the prevalence of chronic lung diseases for the infant-exposed group was significantly higher than the non-exposed group. In addition, after furthermore stratified by gender and famine severity, we found that only infant exposure to the severe famine was associated with the elevated risk of chronic lung diseases among male adults. In conclusion they have reported that severe famine exposure in infant period might increase the risk of chronic lung diseases in male adults. The topic of the manuscript is interesting, but there are several concerns as follows:
	(1) Please give full name for NCDs; "severe" should be "Severe" in Conclusions section of abstract.
	(2) According to literature knowledge, age may be a risk factor of chronic lung diseases in adulthood. In this study, Participants were divided into the non-exposed group and three famine exposed groups (fetus, infant, and preschool-exposed groups). The Chinese famine began in January 1959 and ended in October 1961, and in order to minimize the misclassification of the famine exposure, we defined the participants who were born between October 1, 1962 and September 30, 1964 as the non-exposed group, participants born between October 1, 1959 and September 30, 1961 as the fetal-exposed group, participants born between January 1, 1958 and December 31, 1958 as the infant-exposed group, and defined participants born between January 1, 1956 and December 31, 1957 as the preschool-exposed group. How to clarify the associations between age, exposure to the Chinese famine and the risk of chronic lung diseases in adulthood?
	(3) In multi-variance binary logistics regression models in Table 2, 3, 4, family economic status was the adjusted factors. But in Methods section, there is no information about family economic status. How to get the data? Is family economic status in famine exposure stage? Or in adulthood? And there was no information about family economic status in Results section.

REVIEWER	Dr Priya Parmar
	Auckland University of Technology
	New Zealand
REVIEW RETURNED	25-Jan-2017

GENERAL COMMENTS	Review of Association between the Chinese famine exposure during infant period and the risk of self-report chronic lung diseases in adulthood: a cross-sectional study
	In general yes, the study objective in the abstract was clear but felt this could be stated more clearly. Particularly where it says 'between prenatal and early postnatal [INSERT phase/stage/infant] exposed to the…'
	Statistical analysis review
	How were the covariates for the multivariate logistic regression

	model chosen?
	Was a model selection procedure utilised?
	Please detail this.
	Was there any adjustment for multiple-testing (as the same model repeated for gender-stratified analysis)
	The authors showed no statistical difference in the prevalence between the famine exposed groups (fetus, infant and preschool) and the non-exposed group. Did they find any statistical association between the famine exposed groups (combined) vs. the non-exposed group?
	Is there a supplementary table (for table 4) which shows the full output i.e. the effect of smoking, drinking and family economic status on the prevalence rates of chronic respiratory diseases?

VERSION 1 – AUTHOR RESPONSE

Using open access CHARLS data, the authors assessed the association between early life exposure to Chinese famine and chronic lung diseases in adulthood. The study is important and may provide new evidence on the adverse effects of early life famine exposure. The analytical strategy used in the current study is the same as a recent paper of famine exposure and hypertension this group has published.

Main concern:
1. The analytical sample size seems problematic to me. It is unlikely that the sample size of the fetal exposure group is larger than non-exposed group, due to the low birth rate during famine. There must be an error in the selection of the sample. Can the authors confirm that all the participants were categorized correctly? Was the date of birth reported using the Chinese lunar calendar transformed correctly? It is also unlikely that the infant-exposed group has a similar sample size as the preschool-exposed group as the age spans are different (1 year vs 2 years).

Authors: Thank you for your suggestion. We have again reviewed the database and selected the sample. In the revised manuscript, the sample size of non-exposed group, fetal, infant, and preschool exposed groups was 1,536, 834, 518, and 1,247, respectively. We have renewed all the relevant information throughout the manuscript.

2. As the age was positively related to chronic lung disease, it is difficult to separate the effect of age from famine exposure. The current findings may be confounded by age. In fact, the group's paper on famine and hypertension suffered from the same problem. Using data from an Australia cohort study, among Australian adults I can find similar ORs for hypertension of age groups similar to the famine exposure groups (reported by the authors). They are obviously not famine related.

Authors: Thank you for your suggestion. Age was an important confounder, but we cannot adjust for age in binary logistic regression model, because age and famine exposed cohorts were collinear significantly (Eigenvalue =0.002). We speculate there have two points that support the effect of famine against age. Firstly, the ORs of chronic lung diseases did not increased with age in severely famine-exposed areas. The ORs of chronic lung diseases for fetal, infant, and preschool exposed group were 0.98, 2.57, and 0.75, respectively. Second, we only observed a significantly higher risk (OR=2.57, 95%CI: 1.26, 5.25) of chronic lung diseases for infant exposed group in severely affected areas, but not in fetal or preschool exposed group or in less severely affected areas. Therefore,

severe famine exposure in infant stage could be associated with the elevated risk of chronic lung diseases. However, similar to the published literatures[1-3], age might be also an important confounder in the current study. We have illustrated clearly the confounder in the limitation section. Please refer to Line 266-267, page 13.

Reference:

1. Li YP, Jaddoe VW, Qi L, et al. Exposure to the Chinese famine in early life and the risk of hypertension in adulthood. J Hypertens. 2011;29(6):1085-92.

2. Li YP, Jaddoe VW, Qi L, et al. Exposure to the Chinese Famine in Early Life and the Risk of Metabolic Syndrome in Adulthood. Diabetes Care. 2011;34(4):1014-8.

3. Li YP, Lai JQ, Jaddoe VW, et al. Exposure to the Chinese Famine in Early Life and the Risk of Metabolic Syndrome in Adulthood EDITORIAL COMMENT. Obstet Gynecol Surv. 2011;66(8):465-6.

Minor:

1. Some demographic information (e.g. education, income) is needed in Table 1.

Authors: We have added the family economic status and the highest education attainment in Table 1. Please refer to page 18.

2. As smoking is related to lung problems, a test for interaction between famine exposure and smoking is needed. Could it be that the association in men is in fact due to smoking?

Authors: We have added the interaction between famine exposure and smoking in Table 3. Please refer to page 20. Significant interactions were not observed for males and females (P<0.05), indicating that the significant association in males is not due to smoking.

Reviewer: 2
Reviewer Name: Li Li
Institution and Country: Department of Nutrition and Food Hygiene, School of Public Health, Anhui Medical University, China
Competing Interests: None declared

In this study, the authors have investigated the associations between prenatal and early postnatal exposure to the Chinese famine and the risk of chronic lung diseases in adulthood. On the whole they have found that the prevalence of chronic lung diseases for the infant-exposed group was significantly higher than the non-exposed group. In addition, after furthermore stratified by gender and famine severity, we found that only infant exposure to the severe famine was associated with the elevated risk of chronic lung diseases among male adults. In conclusion they have reported that severe famine exposure in infant period might increase the risk of chronic lung diseases in male adults. The topic of the manuscript is interesting, but there are several concerns as follows:

1. Please give full name for NCDs; "severe" should be "Severe" in Conclusions section of abstract.

Authors: Thank you for your suggestion. We have added the full name for CNDs: (Non-Communicable Diseases). Please refer to Line 62-63, Page 4. We also change "severe" to "Severe" in Conclusions section of abstract. Please refer to Line 40, Page 3.

2. According to literature knowledge, age may be a risk factor of chronic lung diseases in adulthood. In this study, Participants were divided into the non-exposed group and three famine exposed groups (fetus, infant, and preschool-exposed groups). The Chinese famine began in January 1959 and ended in October 1961, and in order to minimize the misclassification of the famine exposure, we defined the participants who were born between October 1, 1962 and September 30, 1964 as the non-exposed group, participants born between October 1, 1959 and September 30, 1961 as the fetal-exposed

group, participants born between January 1, 1958 and December 31, 1958 as the infant-exposed group, and defined participants born between January 1, 1956 and December 31, 1957 as the preschool-exposed group. How to clarify the associations between age, exposure to the Chinese famine and the risk of chronic lung diseases in adulthood?

Authors: Thank you for your suggestion. In deed, age may be a risk factor of chronic lung diseases in adulthood. However, we have not a good method to separate the effect of age from famine exposure. Age could not be adjusted in binary logistic regression model, because age and famine exposed cohorts were collinear significantly (Eigenvalue =0.002) in the current sample. Therefore, similar to previous literatures [1-3], we have not adjusted age in the binary logistic regression model, but illustrated the confounder in the limitation section. Please refer to Line 266-267, page 13.
Reference:
1. Li YP, Jaddoe VW, Qi L, et al. Exposure to the Chinese famine in early life and the risk of hypertension in adulthood. J Hypertens. 2011;29(6):1085-92.
2. Li YP, Jaddoe VW, Qi L, et al. Exposure to the Chinese Famine in Early Life and the Risk of Metabolic Syndrome in Adulthood. Diabetes Care. 2011;34(4):1014-8.
3. Li YP, Lai JQ, Jaddoe VW, et al. Exposure to the Chinese Famine in Early Life and the Risk of Metabolic Syndrome in Adulthood EDITORIAL COMMENT. Obstet Gynecol Surv. 2011;66(8):465-6.

3. In multi-variance binary logistics regression models in Table 2, 3, 4, family economic status was the adjusted factors. But in Methods section, there is no information about family economic status. How to get the data? Is family economic status in famine exposure stage? Or in adulthood? And there was no information about family economic status in Results section.

Authors: Thank you for your suggestion. Family economic status was in adulthood and collected during face-to-face interviews in house by trained interviewers. We have added the information in the Method section. Please refer to Line 147-149, Page 8. Results of family economic status have been added to Table 1 in Results section. Pleased refer to Page 18.

Reviewer: 3 (stats review)
Reviewer Name: Dr Priya Parmar
Institution and Country: Auckland University of Technology, New Zealand
Competing Interests: None declared

1. In general yes, the study objective in the abstract was clear but felt this could be stated more clearly. Particularly where it says 'between prenatal and early postnatal [INSERT phase/stage/infant] exposed to the…'

Authors: Thank you for your suggestion. We have revised the statement of study objective in the abstract. Please refer to Line 20-22, Page 2.

Statistical analysis review
1. How were the covariates for the multivariate logistic regression model chosen?
Was a model selection procedure utilised?
Please detail this.

Authors: Thank you for your suggestion. The method of covariate chooses for multivariate logistic regression was based on literatures and professional knowledge. The objective of the current study was to explore the association of early-life exposed to famine with risk of chronic lung diseases in adulthood, but not to explore the factors of chronic lung diseases. Thus, we adjusted all the factors that were available and related with chronic lung diseases or famine exposure severity in the

multivariate logistic regression model. Such as gender[1, 2], smoking[1, 2], drinking[3], family economic status[4, 5], and the highest education attainment[1].

Reference

1. Alam DS, Chowdhury MA, Siddiquee AT, et al. Prevalence and Determinants of Chronic Obstructive Pulmonary Disease (COPD) in Bangladesh. COPD. 2015;12(6):658-67.

2. Al Ghobain M, Alhamad EH, Alorainy HS, et al. The prevalence of chronic obstructive pulmonary disease in Riyadh, Saudi Arabia: a BOLD study. Int J Tuberc Lung Dis. 2015;19(10):1252-7.

3. Hoth KF, Ford DW, Sandhaus RA, et al. Alcohol use predicts ER visits in individuals with alpha-1 antitrypsin deficiency (AATD) associated COPD. COPD. 2012;9(4):417-25.

4. Jaganath D, Miranda JJ, Gilman RH, et al. Prevalence of chronic obstructive pulmonary disease and variation in risk factors across four geographically diverse resource-limited settings in Peru. Respir Res. 2015;16:40.

5. Burney P, Jithoo A, Kato B, et al. Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty--a BOLD analysis. Thorax. 2014;69(5):465-73.

2. Was there any adjustment for multiple-testing (as the same model repeated for gender-stratified analysis)

Authors: Thank you for your suggestion. We used the Bonferroni method to adjust for multiple testing in gender-stratified analysis. After adjusting, the association between infant exposure to the severe famine and the risk of chronic lung diseases among male adults was still statistical significant (P=0.023, less than significant level: α=0.025).

3. The authors showed no statistical difference in the prevalence between the famine exposed groups (fetus, infant and preschool) and the non-exposed group. Did they find any statistical association between the famine-exposed groups (combined) vs. the non-exposed group?

Authors: Thank you for your suggestion. According your suggestion, we performed the Chi-square test to compare the difference of chronic lung diseased prevalence between famine exposed groups (combined) and non-exposed group. Results showed that there has no statistical difference (χ2=1.19, P=0.276).

4. Is there a supplementary table (for table 4), which shows the full, output i.e. the effect of smoking, drinking and family economic status on the prevalence rates of chronic respiratory diseases?

Authors: Thank you for your suggestion. We have showed the effect of smoking, drinking, family economic status, and the highest education attainment of parents in Supplementary Table 1. Pleased refer to Supplementary Table 1 in Supplementary materials

VERSION 2 – REVIEW

REVIEWER	Zumin Shi University of Adelaide, Australia
REVIEW RETURNED	26-Feb-2017

GENERAL COMMENTS	The responses to my comments are satisfactory. I have some addition concerns: 1. Please check the income. It seems not correct. I don't think the mean individual annual income is 2744 Chinese Yuan. Results from the harmonised CHARLS data suggest a much higher value. 2. Multivariate binary logistic regression and Multi-variance binary logistic regression should be changed to multivariable logistic regression.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Zumin Shi
Institution and Country: University of Adelaide, Australia
Competing Interests: None declared

The responses to my comments are satisfactory. I have some addition concerns:
1. Please check the income. It seems not correct. I don't think the mean individual annual income is 2744 Chinese Yuan. Results from the harmonised CHARLS data suggest a much higher value.
Authors: Thank you for your comments. We have carefully checked the income information. The mean individual annual income is 12,744 Chinese Yuan, and we have corrected the information in the revised manuscript. Please refer to Page 8, Line 147.
2. Multivariate binary logistic regression and Multi-variance binary logistic regression should be changed to multivariable logistic regression.
Authors: We have changed all the multivariate binary logistic regression and multi-variance binary logistic regression to multivariable logistic regression. Please refer to Page 8, Line 157 and 160, Page 19, Line 403, and Page 20, Line 409.

VERSION 3 – REVIEW

REVIEWER	Zumin Shi University of Adelaide
REVIEW RETURNED	31-Mar-2017

GENERAL COMMENTS	The responses and revision are satisfactory.