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Association between the Chinese famine exposure during infant period and the risk of self-report chronic lung diseases in adulthood: a cross-sectional study

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4 1 **Association between the Chinese famine exposure during**
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6 2 **infant period and the risk of self-report chronic lung diseases**
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8 3 **in adulthood: a cross-sectional study**

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Abstract

Objective This study aimed to examine the associations between prenatal and early postnatal exposed to the Chinese famine and the risk of chronic lung diseases in adulthood.

Design Data analysis from a cross-sectional survey.

Setting and participants 2,603 subjects were enrolled into the study from the China Health and Retirement Longitudinal Study (CHARLS) 2011-2012 baseline survey to analyze the associations between prenatal and early postnatal famine exposure and the risk of chronic lung diseases in adulthood.

Main outcome measures Chronic lung diseases were defined based on the self-report information.

Results The prevalence of self-report chronic lung diseases in fetus-exposed, infant-exposed, preschool-exposed and non-exposed groups was 6.6%, 8.9%, 6.6% and 5.2%, respectively. The prevalence of chronic lung diseases for the infant-exposed group was significantly higher than the non-exposed group. The results of the multi-variance logistics regression analysis indicated that the risk of chronic lung diseases in the infant-exposed group was significantly higher (OR=1.96, 95% CI: 1.14-3.37) than the non-exposed group in severely affected areas, even after adjusting for gender, smoking status, and drinking status (OR=2.03, 95% CI: 1.17-3.52). In addition, after furthermore stratified by gender and famine severity, we found that only infant exposure to the severe

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4 40 famine was associated with the elevated risk of chronic lung diseases among
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6 41 male adults (OR=2.34, 95% CI: 1.05-5.21).
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10 42 **Conclusions** severe famine exposure in infant period might increase the
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12 43 risk of chronic lung diseases in male adults.
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14 44 **Strengths and limitations of this study**

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18 45 ● This study evaluated the associations between prenatal and early
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20 46 postnatal exposure to the Chinese famine and the risk of chronic lung
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22 47 diseases in adulthood, which was unclear in previous studies.
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26 48 ● The present study used the China Health and Retirement Longitudinal
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28 49 Study 2011-2012 baseline survey which covered all geographical regions
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30 50 in China and had broadly representative of entire China mainland found
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32 51 that infant exposure to the severe Chinese famine increased the risk of
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34 52 chronic pulmonary diseases in adulthood.
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39 53 ● Selection bias was unavoidable, because severe famine could eliminate
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41 54 weaker participants, and remain the healthier participants, which may
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43 55 decrease the real effect of famine exposure.
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48 56 ● Self-report information based on doctor diagnosis could lower the real
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50 57 prevalence of chronic pulmonary diseases, and further underestimate the
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52 58 effect of famine exposure.
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4 59 **Key words:** Famine; Developmental Origins of Health and Disease;
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6 60 Chronic Lung Diseases; Infant
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9 61 **Introduction**

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12 62 The chronic lung diseases briefly include chronic obstructive lung diseases
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14 63 (COPDs), chronic bronchitis, bronchial asthma, and lung heart disease
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17 64 (excluding lung tumors and cancer). Global Status Report on NCDs showed
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20 65 that respiratory diseases, including asthma and chronic obstructive lung
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22 66 diseases were the third leading cause of NCDs deaths in 2012 (about 4.0
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25 67 million) [1]. Especially in the developing countries, the burden of chronic lung
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27 68 diseases was heavier than in the developed countries [2].
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31 69 The Development of Health and Disease theory speculated that the fetus in
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33 70 utero would change their growth rate to adapt the supply of nutrients and
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36 71 oxygen. However, several studies had found that these adaptive changes
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38 72 might permanently modify the structure and physiological function of fetus
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41 73 body [3, 4]. The heavier lung diseases burden in the developing countries may
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43 74 be associated with a higher prevalence of low birth weight than in the
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46 75 developed countries. Several studies had found that the low birth weight was a
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48 76 strong factor to predict reduction of forced expiratory vital capacity and forced
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51 77 vital capacity[5-7]. Moreover, although some studies found that the low birth
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53 78 weight increased the risk of asthma[8-12] and the mortality of chronic
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56 79 obstructive lung disease[7], no consistent results was observed in previous
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4 80 studies [13-16]. Due to ethical limitation, we cannot perform the similar
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6 81 research in human beings, but natural historical famines provided us a unique
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8 82 opportunity to examine the DOHaD hypothesis in human beings. The Dutch
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10 83 famine happened in the west of the Netherlands at the end of the World War II
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12 84 that lasted for about six months. Dutch famine study observed that
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14 85 mid-gestation exposure to the famine increased the prevalence of obstructive
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16 86 airways disease in adulthood[17]. Compared with the Dutch famine, the
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18 87 Chinese famine happened in the east of Asia, starting in the end of 1950 and
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20 88 ending in the early of 1960, which lasted for about three years. A majority of
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22 89 studies have found that early-life exposure to the Chinese famine linked with
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24 90 hypertension[18], diabetes[19], metabolic syndrome[20], but the associations
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26 91 with chronic lung diseases are still unclear.
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34 92 In the current study, we used the public data of the China Health and
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36 93 Retirement Longitudinal Study 2011-2012 baseline survey, to examine the
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38 94 associations of varying degrees of famine exposure in early life and chronic
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40 95 lung diseases in adulthood, and explore whether a gender difference exists.
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45 96 **Methods**

47 97 **Sampling and participants**

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49 98 Sampling in the present study was based on a national population-based
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51 99 longitudinal survey in 2011-2012 of China Health and Retirement Longitudinal
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53 100 Study (CHARLS) [21]. A total of 17,708 adults aged above 45 years from
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4 101 10,257 households were randomly selected to receive the household survey
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6 102 among 150 counties, 28 provinces, and autonomous regions of China
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8 103 mainland. 2,751 participants out of 17,708 adults were screened by birthdate
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10 104 into the present study. Finally, 2,603 subjects were enrolled into our final
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12 105 analysis after excluding 148 subjects with information missing of chronic lung
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14 106 diseases.
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19 **Sampling and grouping**

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22 108 Participants were divided into the non-exposed group and three famine
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24 109 exposed groups (fetus, infant, and preschool-exposed groups). The Chinese
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26 110 famine began in January 1959 and ended in October 1961, and in order to
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28 111 minimize the misclassification of the famine exposure, we defined the
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30 112 participants who were born between October 1, 1962 and September 30, 1964
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32 113 as the non-exposed group, participants born between October 1, 1959 and
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34 114 September 30, 1961 as the fetal-exposed group, participants born between
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36 115 January 1, 1958 and December 31, 1958 as the infant-exposed group, and
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38 116 defined participants born between January 1, 1956 and December 31, 1957 as
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40 117 the preschool-exposed group.
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48 **Famine severity**

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51 119 Despite the Chinese famine affected the whole China mainland, the severity
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53 120 was at different levels across provinces due to the difference of regional
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55 121 climate, population density and local food policies. Similar to the previous
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4 122 studies [18, 19], we also used the excess mortality during 1959-1961
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6 123 compared with the 1956-1958 to evaluate of the severity of the famine in the
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9 124 present study, and 50% of the excess mortality was used as the threshold to
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11 125 distinguish the severity of famine exposure. The regions with excess mortality
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13 126 $\geq 50\%$ were categorized as the severe affected areas, and otherwise were
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16 127 divided to the less severe affected areas.

128 **Measurements**

129 **Diagnosis of chronic lung diseases**

130 In this study, data were collected through household survey by investigators
131 who received unified training and passed the examination. The diagnosis of
132 chronic lung diseases was based on the question of "Have you been
133 diagnosed with chronic lung diseases, such as chronic bronchitis, emphysema
134 (excluding tumors, or cancer) by a doctor? ". Subjects answering "Yes" were
135 defined as persons suffering from chronic lung diseases, and subjects
136 answering "No" as those who did not suffer from chronic lung diseases.

137 **Smoking and drinking**

138 The definition of smoking was based on the question of "Have you ever
139 chewed tobacco, smoked a pipe, smoked self-rolled cigarettes, or smoked
140 cigarettes/cigars (by smoking we mean smoking more than 100 cigarettes in
141 life)? ". Subjects answering "Yes" were defined as smoker, and the other as
142 nonsmoker. The definition of drinking was based on the question of "Did you

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4 143 drink any alcoholic beverages, such as beer, wine, or liquor in the past year? "

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6 144 Subjects with answers of "Drink more than once a month" or "Drink but less

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9 145 than once a month" were defined as drinker, and "None of these" as

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11 146 nondrinker.

147 **Analysis**

148 Statistical analyses were performed using IBM SPSS 20.0 (IBM Corporation,

149 Armonk, NY, USA). Continuous and categorical variables were expressed as

150 mean \pm standard deviation and percentage (%), respectively.

151 The Chi square tests were used to compare the difference of chronic lung

152 diseases prevalence between the non-exposed group and famine exposed

153 groups.

154 Univariate and multivariate binary logistic regression models by maximum

155 likelihood method were used to examine the risk of chronic lung diseases

156 among the fetus, infant, and preschool-exposed groups, compared with the

157 non-exposed group, respectively. In multivariate logistic regression model, we

158 adjusted for sex, smoking, drinking. Interactions between famine exposure

159 groups (fetus, infant, or preschool vs. non-exposed) and area (severely

160 affected vs. less severely affected) were tested by adding a multiplicative

161 factor in the binary logistic regression model.

162 In order to explore whether there exists a gender difference, stratified analyses

163 by gender were performed using the same methods. Data were expressed as

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4 164 odds ratio (OR) (95% confidence interval).

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7 165 $P < 0.05$ for two-sided was considered statistically significant for all the
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9 166 analyses.

10 11 12 13 167 **Ethics**

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16 168 Our study is a secondary analysis of the de-identified CHARLS public data.

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18 169 The Medical Ethics Committee of Peking University granted the current study
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21 170 exemption from review. All the subjects were informed and consented for the
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23 171 protocol of study.

24 25 26 172 **Results**

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29 173 The basic characteristics of participants were shown in **Table 1**. A total of
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32 174 2,603 participants were enrolled into the present study. The samples of the
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35 175 non-exposed, fetus, infant, and preschool-exposed groups were 695, 784, 530,
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37 176 and 594, respectively. The prevalence of chronic lung diseases among the
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40 177 non-exposed, fetus, infant, and preschool exposed groups were 5.2%, 6.6%,
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42 178 8.9%, and 6.6%, respectively. However, we did not observe a statistically
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44
45 179 significant difference of prevalence between famine exposed groups (fetus,
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47 180 infant, and preschool) and the non-exposed group.

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50 181 **Table 2** presents the risk of chronic lung diseases among fetus, infant, and
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53 182 preschool famine exposure groups compared with the non-exposed group.
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56 183 Compared with the non-exposed group, the infant-exposed group had a higher
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58 184 risk of chronic lung diseases (OR=1.78; 95% CI: 1.14, 2.79), even after
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4 185 adjusting for gender, smoking, and drinking (OR=1.81; 95% CI: 1.15, 2.85). but
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6 186 the consistent associations were not observed in fetus, and preschool-
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9 187 exposed groups.

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12 188 Stratified analyses by famine severity were showed in **Table 3**. Compared with
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14 189 the non-exposed group, only the prevalence of chronic lung diseases for the
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17 190 infant-exposed group was significantly higher in severely affected area (6.7%
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19 191 vs. 10.1%). Stratified by severity of famine exposure, we found that people in
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22 192 the infant-exposed group were at a higher risk of chronic lung diseases than
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24 193 the non-exposed group in severely affected area (OR=1.96; 95% CI: 1.14,
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27 194 3.37), even after adjusting for gender, smoking, and drinking (OR=2.03; 95%
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29 195 CI: 1.17, 3.52). However, we did not observe the consistent associations in
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32 196 other famine exposed groups and in less severely affected area. We did not
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35 197 observe any significant interactions between famine exposure group (fetus,
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37 198 infant, or preschool vs. non-exposed) and areas (severely affected vs. less
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39 199 severely affected).

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42 200 **Table 4** presents the results of stratified analysis by gender and famine
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45 201 severity. In males, we observed that the infant-exposed group (OR=2.34; 95%
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48 202 CI: 1.05, 5.21) significantly increased the risk of chronic lung diseases in
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51 203 severely affected area, compared with the non-exposed group. The consistent
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53 204 associations were not observed in fetus and preschool-exposed groups and in
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55 205 less severely affected area. In females, we did not observe any significant
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58 206 associations between famine exposed groups and the non-exposed group.
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4 207 Any significant interactions were not observed between famine exposed
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6 208 groups (fetus, infant, or preschool vs. non-exposed) and areas (severely
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9 209 affected vs. less severely affected) neither males nor females.

210 **Discussion**

211 In the current study, we observed that the infant exposure to the Chinese
212 famine significantly increased the risk of chronic lung diseases in later life.
213 After stratifying by gender and famine severity, we found only the infant
214 exposure to severe famine significantly increased the risk of chronic lung
215 diseases in male adults, indicating that the infant period might be a critical
216 period for human lung structure and function development.

217 Several mechanisms could explain the associations. 1) Early-life exposure to
218 the severe famine might perpetually modify the bronchial reactivity during rapid
219 growth. One Dutch famine study found that gestation the famine exposure
220 affected neither the concentrations of total or specific IgE nor lung function
221 values (FEV₁ and FVC), but they observed a significant associations between
222 exposure to famine in mid and early gestation and obstructive airways disease
223 in adulthood[17]. The results indicated that famine exposure might not change
224 the lung function and atopic disease, but could permanently modify the
225 bronchial responsiveness. Though we could not assure the assumption
226 because bronchial reactivity was not measured in this study, this assumption
227 can be one way to explain the mechanism. 2) Severe malnutrition during early

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4 228 life might increase susceptibility to pulmonary injury in later life. Animal model
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6 229 study had found that young animals who were exposed to a low protein
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9 230 maternal diet in fetus were more likely to suffer pulmonary injury than
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11 231 non-exposed young animals, which indicated the programming of the
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13 232 antioxidant defenses and immune system[22]. Another animal study reported
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15 233 fetuses exposed to a low protein diet significantly decreased the binding of
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18 234 dexamethasone to lung receptors[23].
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22 235 The present study further added the new direct evidence in human beings for
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24 236 the fetus origin of diseases. To our knowledge, only one Dutch study explored
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27 237 the associations between the early-life famine exposure and atopy, lung
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29 238 function, and obstructive airways disease, and found that the famine exposure
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31 239 in mid and early gestation might significantly increase the prevalence of
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33 240 obstructive airways disease. Results of the Dutch study were inconsistent with
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36 241 the current study. In this study, we found that only the severe famine exposure
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39 242 in infant stage significantly increased the risk of chronic lung diseases in
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41 243 adulthood. Several reasons could explain the difference. Firstly, race might be
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43 244 a main reason between the two studies. Subjects in the Dutch study came
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46 245 from White European, while subjects in this study were from Asian. Secondly,
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49 246 severity and duration could be another important discrepancy. The Dutch
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51 247 famine only lasted for about six months, while the Chinese famine lasted for
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54 248 about three years. Furthermore, the Chinese famine led to approximately thirty
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57 249 millions premature death[24]. However, the mortality rate during famine period
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4 250 (1945) was more than twice as high as that in 1939, and most of the excess
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6 251 mortality was attributed to severe malnutrition[25].
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10 252 What was interesting is that we observed the severe famine exposure in infant
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12 253 period significantly increased the risk of chronic lung diseases among men, but
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14 254 not among women, which was contradictory to the severity of food shortage.

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17 255 Chinese have held a profound and lasting tradition of “Preferring boys to girls”,
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19 256 and thus boys may have been protected better against the famine by parents.

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22 257 It was inconsistent with metabolic syndrome[26]. We speculated that boy’s
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24 258 lungs development were more sensitive to severely malnutrition in early-life.

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27 259 But the specific mechanisms need to be further explored in future study.
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30 260 There are several limitations in this study. The primary limitation is the
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32 261 selection bias. Severe famine could eliminate weaker participants, and remain
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35 262 the healthier participants, which may decrease the real effect of famine
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37 263 exposure. Secondly, similar to other the Chinese famine studies[18, 19, 27],
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40 264 we also lacked the objective indicators that reflected the severity of famine
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42 265 exposure, e.g. birth weight, birth body length. In addition, because both bad
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45 266 weather and infection in early-life could increase the risk of chronic lung
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47 267 diseases, we could not attribute all the excess mortality rate to the famine
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50 268 exposure. Despite these limitations, the present study used the data of China
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52 269 Health and Retirement Longitudinal Study 2011-2012 baseline survey that has
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55 270 broad representative of entire China mainland, and found that infant exposure
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57 271 to severe famine significantly increased the risk of chronic lung disease among
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4 272 men.
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7 273 **Conclusions**

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10 274 Infant exposure to severe famine could increase the risk of chronic lung
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12 275 diseases in male adults, indicating that the infant stage might be the critical
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14 276 period of lungs development for men.
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17 277 **Footnotes**

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21 278 **Contributors** JM and ZZ were co-investigators and designed the study, ZW,
22
23 279 ZY and YD carried out the initial analysis, and supervised data analysis. All
24
25 280 authors were involved in writing the paper and had final approval of the
26
27 281 submitted and published versions.
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31
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33
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37 284 **Competing interests** The authors declared that they had no competing
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39 285 interests.
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43 286 Our study is a secondary analysis of the de-identified CHARLS public data.
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45 287 The Medical Ethics Committee of Peking University granted the current study
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47 288 exemption from review. All the subjects were informed and consented for the
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49 289 protocol of study.
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51 290 **Consent for publication**

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57 291 Not applicable.
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292 **Availability of data and material**

293 The datasets analyzed in the current study are available in the
294 <http://charls.ccer.edu.cn/zh-CN/page/data/2011-charls-wave1>.

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395 **Table 1** Basic characteristics of study population according to the Chinese famine
 396 exposure

	Non-exposed group	Fetus-exposed group	Infant-exposed group	Preschool-exposed group
N	695	784	530	594
Birth Group	10/1/1962– 9/30/1964	10/1/1959– 9/30/1961	1958/1/1– 12/31/1958	1/1/1956– 12/31/1957
Severely affected area (%)	63.5	62.1	63.4	63.3
Age in 2011(years)	47~49	50~51	53	54~55
Women (%)	53	52	48.1	48.1
Smoking (%)	35.9	37.4	41.4	46.3 [#]
Drinking (%)	15.5	16.5	18.1	18.7
Prevalence chronic respiratory diseases	5.2	6.6	8.9 [#]	6.6

397 [#] Means Chi square tests *P* value <0.05 between preschool exposed group and the
 398 non-exposed group.

Table 2 The risk of Chronic lung diseases among three exposed groups compared with the non-exposed group.

	Non-exposed	Fetus-exposed	Infant-exposed	Preschool-exposed
Self-report prevalence of Chronic respiratory diseases (%)	5.2	6.6	8.9	6.6
<i>P</i> ^a		0.240	0.012	0.290
Odds ratio (95% CI) ^a	Ref.	1.30(0.84-2.02)	1.78(1.14-2.79)	1.29(0.81-2.05)
<i>P</i> ^b		0.201	0.010	0.182
Odds ratio (95% CI) ^b	Ref.	1.33(0.86-2.07)	1.81(1.15-2.85)	1.30(0.81-2.08)

^a Single variance binary logistics regression model

^b Multi-variance binary logistics regression model, adjusted for sex, smoking, drinking and family economic status.

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Table 3 Prevalence of Chronic respiratory diseases by birth group and severity of the Chinese famine area

	Non-exposed	Fetus-exposed	Infant-exposed	Preschool-exposed
Severely affected famine area				
Prevalence (%)	5.4	7.2	10.1	6.1
<i>P</i> ^a		0.278	0.015	0.680
Odds ratio (95% CI) ^a	Ref.	1.35(0.79-2.30)	1.96(1.14-3.37)	1.13(0.63-2.04)
<i>P</i> ^b		0.232	0.012	0.630
Odds ratio (95% CI) ^b	Ref.	1.39(0.81-2.40)	2.03(1.17-3.52)	1.16(0.64-2.11)
Less severely affected famine area				
Prevalence (%)	4.7	5.7	6.7	7.3
<i>P</i> ^a		0.601	0.369	0.234
Odds ratio (95% CI) ^a	Ref.	1.22(0.57-2.61)	1.45(0.65-3.25)	1.60(0.74-3.46)
<i>P</i> ^b		0.549	0.396	0.251
Odds ratio (95% CI) ^b	Ref.	1.26(0.59-2.70)	1.42(0.63-3.20)	1.58(0.73-3.41)
<i>P</i> for interaction between area and group ^a	Ref.	0.426	0.185	0.563
<i>P</i> for interaction between area and group ^b	Ref.	0.469	0.179	0.546

^a Single variance binary logistics regression model.

^b Multi-variance binary logistics regression model, adjusted for sex, smoking, drinking and family economic status.

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Table 4 Prevalence rate of Chronic respiratory diseases by gender, birth group and severity of the Chinese famine area

Variables	Non-exposed groups	Fetus-exposed	Infant-exposed	Preschool-exposed
Female				
Severely affected famine area				
Prevalence (%)	5.9	7.7	9.4	8.7
P^a		0.416	0.178	0.944
Odds ratio (95% CI) ^a	Ref.	1.35(0.66-2.75)	1.67(0.79-3.52)	0.97(0.43-2.19)
P^b		0.323	0.149	0.991
Odds ratio (95% CI) ^b	Ref.	1.35(0.70-3.00)	1.75(0.82-3.76)	1.01(0.44-2.31)
Less severely affected famine area				
Prevalence (%)	3.9	5.0	3.5	5.7
P^a		0.656	0.896	0.143
Odds ratio (95% CI) ^a	Ref.	1.30(0.41-4.06)	0.91(0.21-3.90)	2.36(0.75-7.47)
P^b		0.845	0.845	0.209
Odds ratio (95% CI) ^b	Ref.	1.12(0.35-3.60)	0.86(0.20-3.77)	2.12(0.66-6.80)
P for interaction between area and group ^a	Ref.	0.957	0.465	0.217
P for interaction between area and group ^b	Ref.	0.82	0.437	0.255
Male				
Severely affected famine area				
Prevalence (%)	5.0	6.6	10.8	6.6
P^a		0.453	0.038	0.499
Odds ratio (95% CI) ^a	Ref.	1.37(0.61-3.08)	2.34(1.05-5.21)	1.35(0.57-3.20)
P^b		0.455	0.038	0.499
Odds ratio (95% CI) ^b	Ref.	1.36(0.60-3.08)	2.34(1.05-5.21)	1.35(0.57-3.20)
Less severely affected famine area				
Prevalence (%)	5.6	6.6	9.2	6.3
P^a		0.732	0.298	0.802
Odds ratio (95% CI) ^a	Ref.	1.20(0.43-3.31)	1.70(0.63-4.64)	1.14(0.40-3.25)
P^b		0.698	0.268	0.791
Odds ratio (95% CI) ^b	Ref.	1.22(0.44-3.40)	1.77(0.65-4.86)	1.15(0.40-3.23)
P for interaction between area and group ^a	Ref.	0.841	0.630	0.812
P for interaction between area and group ^b	Ref.	0.864	0.657	0.817

^a Single variance binary logistics regression model

^b multi-variance binary logistics regression model, adjusted smoking, drinking and family economic status.

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BMJ Open

Association between the Chinese famine exposure during infant period and the risk of self-report chronic lung diseases in adulthood: a cross-sectional study

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4 1 **Association between the Chinese famine exposure during**
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6 2 **infant period and the risk of self-report chronic lung diseases**
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8 3 **in adulthood: a cross-sectional study**

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Abstract

Objective This study aimed to examine the associations between early-life exposed to the Chinese famine and the risk of chronic lung diseases in adulthood.

Design Data analysis from a cross-sectional survey.

Setting and participants 4,135 subjects were enrolled into the study from the China Health and Retirement Longitudinal Study (CHARLS) 2011-2012 baseline survey to analyze the associations between prenatal and early postnatal famine exposure and the risk of chronic lung diseases in adulthood.

Main outcome measures Chronic lung diseases were defined based on the self-report information.

Results The prevalence of self-report chronic lung diseases in fetus-exposed, infant-exposed, preschool-exposed and non-exposed groups was 6.1%, 6.5%, 7.9% and 6.8%, respectively. The risk of chronic lung diseases in the infant-exposed group was significantly higher (OR=1.95, 95% CI: 1.10-3.44) than the non-exposed group in severely affected areas, even after adjusting for gender, smoking, and drinking, family economic status, and the highest education attainment of parents (OR=2.57, 95% CI: 1.26-5.25). In addition, after 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 (OR=3.16, 95% CI: 1.17-8.51).

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4 40 **Conclusions** Severe famine exposure in infant period might increase the
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6 41 risk of chronic lung diseases in male adults.
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10 42 **Strengths and limitations of this study**
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13 43 ● This study evaluated the associations between prenatal and early
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15 44 postnatal exposure to the Chinese famine and the risk of chronic lung
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17 45 diseases in adulthood, which were unclear in previous studies.
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21 46 ● The present study using the China Health and Retirement Longitudinal
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23 47 Study 2011-2012 baseline survey that covered all geographical regions in
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25 48 China and had broadly representative of entire China mainland found
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27 49 infant exposure to the severe Chinese famine increased the risk of chronic
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29 50 lung diseases in male adults.
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34 51 ● Selection bias was unavoidable, because severe famine could eliminate
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36 52 the weaker participants, and remain the healthier participants, which may
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38 53 decrease the real effects of famine exposure.
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42 54 ● Self-report prevalence based on doctor diagnosis could be lower than the
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44 55 real prevalence of chronic lung diseases, and could underestimate the
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46 56 effects of famine exposure.
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50 57 **Key words:** Famine; Developmental Origins of Health and Disease;
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52 58 Chronic Lung Diseases; Infant
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56 59 **Introduction**
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4 60 The chronic lung diseases briefly include chronic obstructive lung diseases
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6 61 (COPDs), chronic bronchitis, bronchial asthma, and lung heart disease
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9 62 (excluding lung tumors). Global Status Report on Non-Communicable
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11 63 Diseases (NCDs) showed that respiratory diseases, including asthma and
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13 64 chronic obstructive lung diseases were the third leading cause of NCDs deaths
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15 65 in 2012 (about four million)[1]. Especially in the developing countries, the
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17 66 burden of chronic lung diseases was heavier than that in the developed
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19 67 countries[2].
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24 68 The Development of Health and Disease theory speculated that the fetus in
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26 69 utero would change their growth rate to adapt the condition of nutrients and
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28 70 oxygen. However, several studies had found that these adaptive changes
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30 71 might permanently modify the structure and physiological function of fetus[3, 4].
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33 72 The heavier lung diseases burden in the developing countries might be
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35 73 associated with higher prevalence of low birth weight than that in the
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37 74 developed countries. Several studies had found that the low birth weight was a
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39 75 strong factor to predict reduction of forced expiratory vital capacity and forced
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41 76 vital capacity[5-7]. Moreover, although some studies found that the low birth
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43 77 weight increased the risk of asthma[8-12] and the mortality of chronic
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45 78 obstructive lung disease[7], no consistent results was observed in previous
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47 79 studies[13-16].
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55 80 Due to ethical limitations, we cannot perform the similar research in human
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57 81 beings, but natural historical famines provided us a unique opportunity to
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4 82 examine the DOHaD hypothesis in human beings. The Dutch famine
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6 83 happened in the west of the Netherlands at the end of the World War II, it
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9 84 lasted for about six months. One study observed that mid-gestation exposure
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11 85 to the Dutch famine increased significantly the prevalence of obstructive
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13 86 airways disease in adulthood[17]. Compared with the Dutch famine, the
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16 87 Chinese famine happened in the east of Asia, starting in the end of 1950 and
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19 88 ending in the early of 1960, which lasted for about three years. A majority of
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21 89 studies have found that early-life exposure to the Chinese famine linked with
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23 90 hypertension[18], diabetes[19], metabolic syndrome[20] in adulthood, but the
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26 91 associations with chronic lung diseases are still unclear.
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30 92 In the current study, we used the public data of the China Health and
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32 93 Retirement Longitudinal Study (CHARLS) 2011-2012 baseline survey, to
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34 94 examine the associations between the Chinese famine exposure in early life
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36 95 and the prevalence of chronic lung diseases in adulthood, and further to
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39 96 explore whether the associations were gender-specific.
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42 97 **Methods**

43 98 **Sampling and participants**

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46 99 Sampling in the present study was based on a national population-based
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49 100 longitudinal survey in 2011-2012 of CHARLS[21]. A total of 17,708 adults aged
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52 101 ≥ 45 years old from 10,257 households were randomly selected to receive the
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55 102 household survey among 150 counties, 28 provinces, and autonomous
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4 103 regions of China mainland. 4,182 participants out of 17,708 adults were
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6 104 screened by birthdate into the present study. After excluding 47 subjects with
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9 105 information missing of chronic lung diseases, 4,135 subjects were enrolled into
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11 106 our final analysis (Fig 1).

107 **Sampling and grouping**

108 Participants were divided into the non-exposed group and three
109 famine-exposed groups (fetus, infant, and preschool-exposed groups). The
110 Chinese famine began in January 1959 and ended in October 1961, and in
111 order to minimize the misclassification of the famine exposure, we defined the
112 participants born between October 1, 1962 and September 30, 1964 as the
113 non-exposed group, the participants born between October 1, 1959 and
114 September 30, 1961 as the fetal-exposed group, the participants born between
115 January 1, 1958 and December 31, 1958 as the infant-exposed group, and
116 defined the participants born between January 1, 1956 and December 31,
117 1957 as the preschool-exposed group.

118 **Famine severity**

119 Despite the Chinese famine affected the entire China mainland, the severity
120 was at different levels across provinces due to the difference of regional
121 climate, population density and local food policies. Similar to the previous
122 studies[18, 19], we also used the excess mortality during 1959-1961 compared
123 with the 1956-1958 to evaluate of the severity of the famine in the present

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4 124 study, and 100% was used as the threshold of excess mortality to distinguish
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6 125 the severity of famine exposure. The regions with excess mortality $\geq 100\%$
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9 126 were categorized as the severely affected areas, and otherwise were
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11 127 categorized as the less severely affected areas.

128 **Measurements**

129 **Diagnosis of chronic lung diseases**

130 In this study, data were collected through household survey by investigators
131 who received unified training and passed the examination. The diagnosis of
132 chronic lung diseases was based on the question of "Have you been
133 diagnosed with chronic lung diseases, such as chronic bronchitis, emphysema
134 (excluding tumors, or cancer) by a doctor? ". Subjects answering "Yes" were
135 defined as persons suffering from chronic lung diseases, and subjects
136 answering "No" as those who did not suffer from chronic lung diseases.

137 **Assessment of covariates**

138 The social demographic information, family economic status, the highest
139 education attainment of parents, and lifestyle information including smoking
140 status, drinking status were collected during face-to-face interviews in house
141 by trained interviewers. The highest education attainments of parents was
142 categorized into 4 levels: primary school or below, junior school, senior school,
143 and college or above. Smoking status was classified into never smoking,
144 former smoking, and current smoking (who smoked at least 1 cigarette per day

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4 145 in the last year). Drinking status was classified into never drinking, former
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6 146 drinking, and current drinking (who drunk at least once per week in the last
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9 147 year). The mean level of the present sample (2,744 Chinese Yuan per person
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11 148 per year) was used as cutoff point for family economic status (high vs. low
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14 149 income).

150 **Analysis**

151 Statistical analyses were preformed using IBM SPSS 20.0 (IBM Corporation,
152 Armonk, NY, USA). Continuous and categorical variables were expressed as
153 mean \pm standard deviation and percentage (%), respectively.

154 The Chi-square test was used to compare the difference of chronic lung
155 diseases prevalence between the non-exposed group and famine-exposed
156 group.

157 Univariate and multivariate binary logistic regression models by the maximum
158 likelihood method were used to examine the risk of chronic lung diseases
159 among the fetus, infant, and preschool-exposed groups, compared with the
160 non-exposed group, respectively. In multivariate logistic regression model, we
161 adjusted for gender, smoking, drinking, family economic status, and the
162 highest education attainment of parents. Interactions between famine-exposed
163 groups (fetus, infant, or preschool vs. non-exposed) and areas (severely
164 affected vs. less severely affected) were tested by adding a multiplicative
165 factor in the binary logistic regression model.

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4 166 In order to explore whether there exists a gender difference, stratified analysis
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6 167 by gender was performed using the same methods. Data was expressed as
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9 168 odds ratio (OR) (95% confidence interval).

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12 169 $P < 0.05$ for two-sided was considered statistically significant for all the
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14 170 analysis.

171 **Ethics**

172 Our study is a secondary analysis of the de-identified CHARLS public data.
173 The Medical Ethics Committee of Peking University granted the current study
174 exemption from review. All the subjects were informed and consented for the
175 protocol of study.

176 **Results**

177 The basic characteristics of participants were shown in **Table 1**. A total of
178 4,135 participants were enrolled into the present study. The sample sizes of
179 the non-exposed, fetus, infant, and preschool-exposed groups were 1,536,
180 834, 518, and 1,247, respectively. The prevalence of chronic lung diseases for
181 the non-exposed, fetus, infant, and preschool exposed groups was 6.1%, 6.5%,
182 7.9%, and 6.8%, respectively. we did not observe a statistically significant
183 difference of Chronic lung diseases prevalence among four groups ($P=0.511$).

184 Stratified analysis by famine severity was showed in **Table 2**. Compared with
185 the non-exposed group, only the prevalence of chronic lung diseases for the
186 infant-exposed group was significantly higher in severely affected area (5.6%

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4 187 vs.10.4%). Stratified by severity of famine exposure, we found that subjects in
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6 188 the infant-exposed group were at a higher risk of chronic lung diseases than
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9 189 the non-exposed group in severely affected area (OR=1.95; 95% CI: 1.10,
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11 190 3.44), even after adjusting for gender, smoking, drinking, family economic
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14 191 status, and the highest education attainment (OR=2.57; 95% CI: 1.26, 5.25).
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16 192 However, we did not observe the consistent associations in other
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19 193 famine-exposed groups and in less severely affected areas. In addition, we did
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21 194 not observe any significant interactions between famine exposure groups
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24 195 (fetus, infant, or preschool vs. non-exposed) and areas (severely affected vs.
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26 196 less severely affected).

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29 197 **Table 3** presents the results of stratified analysis by gender and famine
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32 198 severity. In males, we observed that the infant-exposed group (OR=3.16; 95%
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34 199 CI: 1.17, 8.51) significantly increased the risk of chronic lung diseases in
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37 200 severely affected area, compared with the non-exposed group. The consistent
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39 201 associations were not observed in fetal and preschool-exposed groups and in
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42 202 less severely affected area. In females, we did not observe any significant
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44 203 associations between famine exposed groups and the non-exposed group.
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47 204 Any significant interactions were not observed between famine exposed
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49 205 groups (fetus, infant, or preschool vs. non-exposed) and areas (severely
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52 206 affected vs. less severely affected) neither males nor females.

207 **Discussion**

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4 208 In the current study, we observed that the infant exposure to the Chinese
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6 209 famine significantly increased the risk of chronic lung diseases in later life.
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9 210 After stratifying by gender and famine severity, we found only the infant
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11 211 exposure to severe famine significantly increased the risk of chronic lung
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13 212 diseases in male adults, indicating that the infant period might be a critical
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15 213 period for human lung structure and function development.

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19 214 Several mechanisms could explain the associations. 1) Early-life exposure to
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21 215 the severe famine might perpetually modify the bronchial reactivity during rapid
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23 216 growth. One Dutch famine study found that gestation the famine exposure
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25 217 affected neither the concentrations of total or specific IgE nor lung function
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27 218 values (FEV₁ and FVC), but they observed a significant associations between
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29 219 exposure to famine in mid and early gestation and obstructive airways disease
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31 220 in adulthood[17]. The results indicated that famine exposure might not change
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33 221 the lung function and atopic disease, but could permanently modify the
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35 222 bronchial responsiveness. Though we could not assure the assumption
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37 223 because bronchial reactivity was not measured in this study, this assumption
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39 224 can be one way to explain the mechanism. 2) Severe malnutrition during early
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41 225 life might increase susceptibility to pulmonary injury in later life. Animal model
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43 226 study had found that young animals who were exposed to a low protein
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45 227 maternal diet in fetus were more likely to suffer pulmonary injury than
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47 228 non-exposed young animals, which indicated the programming of the
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49 229 antioxidant defenses and immune system[22]. Another animal study reported
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4 230 that fetuses exposed to a low protein diet significantly decreased the binding of
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6 231 dexamethasone to lung receptors[23].
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9 232 The present study further added the new direct evidence in human beings for
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11 233 the fetus origin of diseases. To our knowledge, only one Dutch study explored
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13 234 the associations between the early-life famine exposure and atopy, lung
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15 235 function, and obstructive airways disease, and found that the famine exposure
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17 236 in mid and early gestation might significantly increase the prevalence of
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19 237 obstructive airways disease. Results of the Dutch study were inconsistent with
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21 238 the current study. In this study, we found that only the severe famine exposure
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23 239 in infant stage significantly increased the risk of chronic lung diseases in
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25 240 adulthood. Several reasons could explain the difference. Firstly, race might be
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27 241 a main reason between the two studies. Subjects in the Dutch study came
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29 242 from White European, while subjects in this study were from Asian. Secondly,
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31 243 severity and duration could be another important discrepancy. The Dutch
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33 244 famine only lasted for about six months, while the Chinese famine lasted for
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35 245 about three years. Furthermore, the Chinese famine led to approximately thirty
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37 246 millions premature death[24]. However, the mortality rate during famine period
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39 247 (1945) was more than twice as high as that in 1939, and most of the excess
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41 248 mortality was attributed to severe malnutrition[25].
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53 249 It was interesting that we observed the severe famine exposure in infant period
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55 250 significantly increased the risk of chronic lung diseases among men, but not
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57 251 among women, which seems to be contradictory to the severity of famine
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4 252 exposure. Chinese parents have held a profound and lasting tradition of
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6 253 “Preferring boys to girls”, and thus boys may have been protected better
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9 254 against the famine by parents. It was inconsistent with metabolic syndrome[26].
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11 255 We speculated that boy’s lungs development could be more sensitive to
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13 256 severely malnutrition in early-life. But the specific mechanisms need to be
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15 257 further explored in future study.
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19 258 There are several limitations in this study. The primary limitation is the
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21 259 selection bias. Severe famine could eliminate weaker participants, and remain
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23 260 the healthier participants, which may decrease the real effect of famine
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25 261 exposure. Secondly, similar to other the Chinese famine studies[18, 19, 27],
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27 262 the present study also lacked the objective indicators that reflected the severity
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29 263 of famine exposure, e.g. birth weight, birth body length. Thirdly, because both
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31 264 bad weather and infection in early-life could increase the risk of chronic lung
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33 265 diseases, we could not attribute all the excess mortality rate to the famine
34
35 266 exposure. In addition, we cannot separate the effect of age from famine
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37 267 exposure. Despite these limitations, the present study used the data of China
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39 268 Health and Retirement Longitudinal Study 2011-2012 baseline survey that has
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41 269 broad representative of entire China mainland, and found that infant exposure
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43 270 to severe famine significantly increased the risk of chronic lung disease among
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45 271 men.
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272 **Conclusions**

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4 273 Infant exposure to severe famine could increase the risk of chronic lung
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6 274 diseases in male adults, indicating that the infant stage might be the critical
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9 275 period of lungs development for men.

10 11 12 276 **Footnotes**

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15 277 **Contributors** JM and ZZ were co-investigators and designed the study, ZW,
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17 278 ZY and YD carried out the initial analysis, and supervised data analysis. All
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20 279 authors were involved in writing the paper and had final approval of the
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23 280 submitted and published versions.

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31 283 **Competing interests** The authors declared that they had no competing
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34 284 interests.

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37 285 Our study is a secondary analysis of the de-identified CHARLS public data.
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39 286 The Medical Ethics Committee of Peking University granted the current study
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42 287 exemption from review. All the subjects were informed and consented for the
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45 288 protocol of study.

46 47 48 289 **Consent for publication**

49
50 290 Not applicable.

51 52 53 291 **Availability of data and material**

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57 292 The datasets analyzed in the current study are available in the
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4 293 <http://charls.pku.edu.cn/zh-CN/page/data/2011-charls-wave1>.

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14
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18
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20 299 survey for their cooperation.

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394 **Table 1** Basic characteristics of study population according to the Chinese famine
 395 exposure

Variances	Non-exposed group	Fetal-exposed group	Infant-exposed group	Preschool-exposed group	<i>P</i> value
Birth date	10/1/1962– 9/30/1964	10/1/1959– 9/30/1961	19581/1– 12/31/1958	1/1/1956– 12/31/1957	
N	1,536	834	518	1,247	
Age in 2011(years)	47~49	50~51	53	54~55	
Born in severely affected area, n (%)	657(42.8)	269(32.3)	192(37.1)	482(38.7)	<i>P</i> <0.001
Women, n (%)	801(52.2)	438(52.6)	241(46.5)	614(49.3)	<i>P</i> =0.067
Smoking, n (%)					<i>P</i> =0.014
Never	970(66.4)	519(65.1)	297(61.4)	711(59.8)	
Former	80(5.5)	36(4.5)	28(5.8)	77(6.5)	
Current	410(28.1)	242(30.4)	159(32.9)	400(33.7)	
Drinking, n (%)					<i>P</i> =0.614
Never	948(61.8)	513(61.6)	320(61.9)	787(63.2)	
Less than once per months	155(10.1)	82(9.8)	53(10.3)	100(8.0)	
More than once per months	430(28.0)	238(28.6)	144(27.9)	359(28.8)	
Family income, n (%)					<i>P</i> =0.960
High	199(54.4)	115(53.5)	65(52.4)	143(52.4)	
Low	167(45.6)	100(46.5)	59(47.6)	130(47.6)	
Education, n (%)					<i>P</i> =0.390
Primary school and below	695(89.7)	396(89.8)	246(88.8)	567(92.5)	
Junior school	40(5.2)	27(6.1)	16(5.8)	25(4.1)	
High school	31(4.0)	12(2.7)	10(3.6)	19(3.1)	
College and above	9(1.2)	6(1.4)	5(1.8)	2(0.3)	
Prevalence of chronic lung disease (%)	6.1	6.5	7.9	6.8	<i>P</i> =0.511

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398 **Table 2** The risk of chronic lung diseased among three exposed groups compare with the
 399 non-exposed group.

Variances	Non-exposed group	Fetal-exposed group	Infant-exposed group	Preschool-exposed group
Severely affected famine area				
Prevalence (%)	5.6	5.6	10.4	5.6
P^a		0.973	0.022	0.983
Odds ratio (95% CI) ^a	Ref.	0.99(0.53-1.84)	1.95(1.10-3.44)	0.99(0.60-1.66)
P^b		0.953	0.009	0.437
Odds ratio (95% CI) ^b	Ref.	0.98(0.43-2.20)	2.57(1.26-5.25)	0.75(0.36-1.56)
Less severely affected famine area				
Prevalence (%)	6.4	6.9	6.4	7.6
P^a		0.691	0.964	0.336
Odds ratio (95% CI) ^a	Ref.	1.09(0.71-1.66)	1.01(0.60-1.70)	1.21(0.82-1.76)
P^b		0.254	0.398	0.471
Odds ratio (95% CI) ^b	Ref.	1.38(0.79-2.41)	1.33(0.69-3.56)	1.22(0.71-2.10)
P for interaction between area and group ^a	Ref.	0.468	0.109	0.178
P for interaction between area and group ^b	Ref.	0.421	0.061	0.223

400 ^aSingle variance binary logistics regression model.

401 ^bMulti-variance binary logistics regression model, adjusted for gender, smoking, drinking,
 402 family economic status and the highest education attainment of parents.

403

404 **Table 3** Prevalence rate of chronic lung diseases by gender, birth group and severity of
 405 the Chinese famine area

Variables	Non-exposed group	Fetal-exposed group	Infant-exposed group	Preschool-exposed group
Female				
Severely affected area				
Prevalence (%)	5.0	5.3	7.5	4.7
P^a		0.907	0.359	0.861
Odds ratio (95% CI) ^a	Ref.	1.05(0.44-2.50)	1.53(0.62-3.81)	0.93(0.43-2.03)
P^b		0.514	0.208	0.479
Odds ratio (95% CI) ^b	Ref.	1.39(0.52-3.74)	1.98(0.68-5.72)	0.67(0.23-2.01)
Less severely affected area				
Prevalence (%)	6.9	7.0	4.1	9.4
P^a		0.970	0.218	0.176
Odds ratio (95% CI) ^a	Ref.	1.01(0.57-1.81)	0.57(0.23-1.39)	1.41(0.86-2.32)
P^b		0.238	0.644	0.359
Odds ratio (95% CI) ^b	Ref.	1.55(0.75-3.23)	0.77(0.24-2.39)	1.40(0.68-2.89)
P for interaction between area and group ^a	Ref.	0.498	0.252	0.036
P for interaction between smoking and group ^a	Ref.	0.907	0.003	0.028
P for interaction between area and group ^b	Ref.	0.686	0.179	0.132
P for interaction between smoking and group ^b	Ref.	0.999	0.614	0.0628
Male				
Severely affected area				
Prevalence (%)	6.3	5.9	13.1	6.5
P^a		0.897	0.030	0.930
Odds ratio (95% CI) ^a	Ref.	0.94(0.39-2.29)	2.26(1.08-4.73)	1.03(0.52-3.03)
P^b		0.677	0.023	0.686
Odds ratio (95% CI) ^b	Ref.	0.75(0.20-2.87)	3.16(1.17-8.51)	0.81(0.30-2.22)
Less severely affected area				
Prevalence (%)	5.8	6.9	8.4	5.7
P^a		0.566	0.237	0.974
Odds ratio (95% CI) ^a	Ref.	1.20(0.64-2.24)	1.50(0.77-2.93)	0.99(0.55-1.80)
P^b		0.584	0.178	0.853
Odds ratio (95% CI) ^b	Ref.	1.28(0.53-3.07)	1.82(0.76-4.36)	1.08(0.45-2.60)
P for interaction between area and group ^a	Ref.	0.734	0.217	0.709
P for interaction between smoking and group ^a	Ref.	0.409	0.300	0.207
P for interaction between area and group ^b	Ref.	0.344	0.127	0.887
P for interaction between smoking and group ^b	Ref.	0.950	0.103	0.696

406 ^aSingle variance binary logistics regression model.

407 ^bMulti-variance binary logistics regression model, adjusted for smoking, drinking, family
 408 economic status and the highest education attainment of parents.

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412 **Fig 1.** Flowchart on the sample selecting methods at each step

413 **Figure legends**

414 * Means missing of chronic lung diseases information in raw database.

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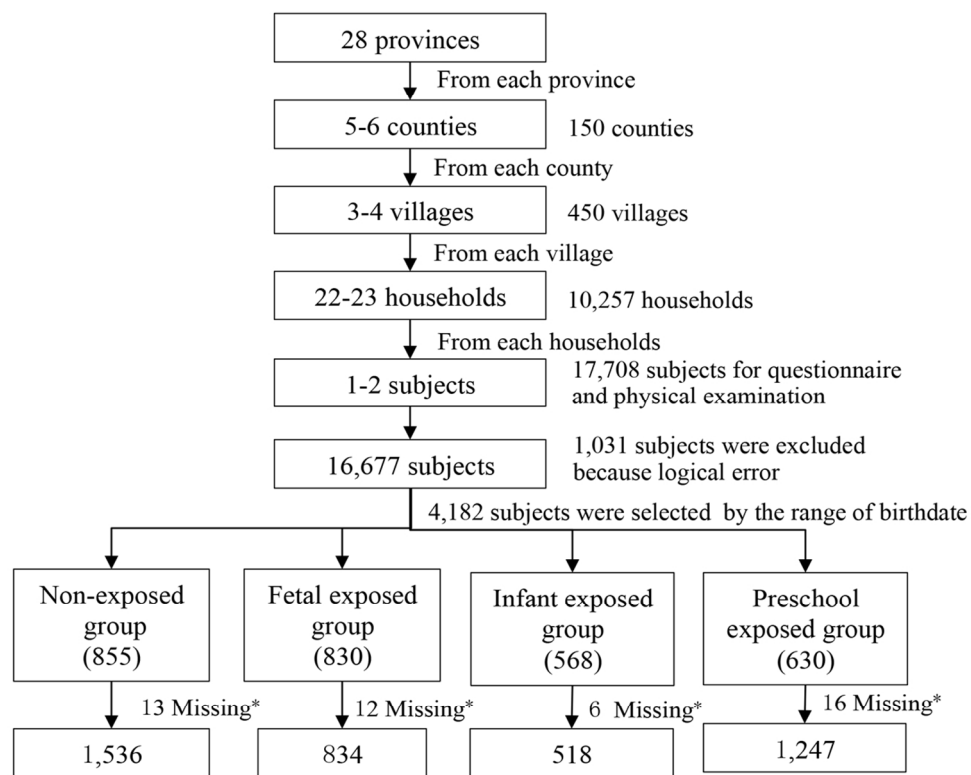


Fig 1. Flowchart on the sample selecting methods at each step

* Means missing of chronic lung diseases information in raw database.

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Only

Supplementary Table 1 The effect of smoking, drinking, family economic status and parents' education attainment on the prevalence rates of chronic lung diseases

Variances	B	S.E.	Wald	df	P	Exp(B)	95% CI.for EXP(B)	
							Lower	Upper
Male								
Less severely affected areas								
Groups			2.157	3	0.54			
Fetal-exposed	0.245	0.447	0.3	1	0.584	1.277	0.532	3.067
Infant-exposed	0.6	0.445	1.815	1	0.178	1.822	0.761	4.362
Preschool-exposed	0.083	0.446	0.034	1	0.853	1.086	0.453	2.603
Smoking	0.141	0.193	0.532	1	0.466	1.151	0.789	1.681
Drinking	-0.124	0.166	0.557	1	0.456	0.883	0.638	1.224
Parents' education attainment	-0.133	0.363	0.134	1	0.714	0.876	0.43	1.783
Family economic status	-0.131	0.347	0.143	1	0.706	0.877	0.444	1.733
Constant	-2.579	0.786	10.779	1	0.001	0.076		
Severely affected areas								
Groups			8.343	3	0.039			
Fetal-exposed	-0.285	0.684	0.174	1	0.677	0.752	0.197	2.872
Infant-exposed	1.15	0.506	5.175	1	0.023	3.158	1.173	8.508
Preschool-exposed	-0.207	0.513	0.163	1	0.686	0.813	0.297	2.221
Smoking	0.188	0.243	0.595	1	0.441	1.206	0.749	1.943
Drinking	-0.192	0.215	0.801	1	0.371	0.825	0.541	1.257
Parents' education attainment	0.217	0.472	0.211	1	0.646	1.242	0.492	3.136
Family economic status	0.306	0.521	0.346	1	0.556	1.359	0.489	3.772
Constant	-3.075	1.028	8.939	1	0.003	0.046		
Female								
Less severely affected areas								
Groups			2.448	3	0.485			
Fetal-exposed	0.44	0.373	1.392	1	0.238	1.553	0.747	3.226
Infant-exposed	-0.268	0.581	0.214	1	0.644	0.765	0.245	2.386
Preschool-exposed	0.339	0.369	0.841	1	0.359	1.403	0.68	2.893
Smoking	0.29	0.259	1.251	1	0.263	1.336	0.804	2.219
Drinking	0.038	0.264	0.02	1	0.886	1.038	0.62	1.741
Parents' education attainment	0.301	0.221	1.842	1	0.175	1.351	0.875	2.085
Family economic status	-0.351	0.401	0.768	1	0.381	0.704	0.321	1.543
Constant	-3.352	0.562	35.558	1	0	0.035		
Severely affected areas								
Groups			3.288	3	0.349			
Fetal-exposed	0.329	0.505	0.425	1	0.514	1.39	0.516	3.742
Infant-exposed	0.682	0.542	1.583	1	0.208	1.977	0.684	5.717
Preschool-exposed	-0.395	0.558	0.501	1	0.479	0.674	0.226	2.011
Smoking	0.337	0.584	0.333	1	0.564	1.401	0.446	4.396
Drinking	-0.38	0.421	0.813	1	0.367	0.684	0.3	1.562
Parents' education attainment	0.224	0.286	0.616	1	0.433	1.252	0.715	2.192
Family economic status	0.355	0.422	0.71	1	0.399	1.427	0.624	3.261
Constant	-3.045	0.895	11.59	1	0.001	0.048		

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found <i>Please see page 1, the title and abstract.</i>
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported <i>Please see page 4-5, the first three paragraphs of the "Introduction" section.</i>
Objectives	3	State specific objectives, including any prespecified hypotheses <i>Please see page 5, the last paragraph of the "Introduction" section.</i>
Methods		
Study design	4	Present key elements of study design early in the paper <i>Please see page 5-6, the "Sampling and participants" section.</i>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection <i>Please see page 5-6, the "Sampling and participants" section.</i>
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants <i>Please see page 6, the "Sampling and grouping" section.</i>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable <i>Please see page 6-7, the "Measurements" section, and the "Famine severity" section.</i>
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group <i>Please see page 6-7, the "Measurements" section, and the "Famine severity" section.</i>
Bias	9	Describe any efforts to address potential sources of bias <i>Please see page 7, the "Diagnosis of chronic lung diseases" section.</i>
Study size	10	Explain how the study size was arrived at <i>Please see page 5-6, the "Sampling and participants" section.</i>
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why <i>Please see page 6-7, the "Assessment of covariates" section.</i>
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding <i>Please see page 8-9, the "Analysis" section.</i> (b) Describe any methods used to examine subgroups and interactions <i>Please see page 8-9, the third paragraph of "Analysis" section.</i> (c) Explain how missing data were addressed <i>N/A.</i> (d) If applicable, describe analytical methods taking account of sampling strategy <i>N/A.</i> (e) Describe any sensitivity analyses <i>N/A.</i>
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially

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eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed

[Please see page 5-6, the “Sampling and participants” section.](#)

(b) Give reasons for non-participation at each stage

N/A.

(c) Consider use of a flow diagram

[Please see page 21. The Fig 1.](#)

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
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[Please see page 18, Table 1.](#)

(b) Indicate number of participants with missing data for each variable of interest

N/A.

Outcome data	15*	Report numbers of outcome events or summary measures
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[Please see page 18, Table 1.](#)

Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
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[Please see page 19-20, Table 2-3.](#)

(b) Report category boundaries when continuous variables were categorized

[Please see page 6-8, the “Famine severity” section, and the “Assessment of covariates” section.](#)

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

N/A.

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
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[Please see page 20, Table 3.](#)

Discussion

Key results	18	Summarise key results with reference to study objectives
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[Please see page 11, the first paragraph of the “Discussion”.](#)

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
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[Please see page 13, the last paragraph of the “Discussion”.](#)

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
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[Please see page 11-13, in the “Discussion”.](#)

Generalisability	21	Discuss the generalisability (external validity) of the study results
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N/A.

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
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[Please see page 14, in the “Funding” section.](#)

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

1
2 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
3 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
4 available at www.strobe-statement.org.
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Association between the Chinese famine exposure during infant period and the risk of self-report chronic lung diseases in adulthood: a cross-sectional study

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4 1 **Association between the Chinese famine exposure during**
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6 2 **infant period and the risk of self-report chronic lung diseases**
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8 3 **in adulthood: a cross-sectional study**

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Abstract

Objective This study aimed to examine the associations between early-life exposed to the Chinese famine and the risk of chronic lung diseases in adulthood.

Design Data analysis from a cross-sectional survey.

Setting and participants 4,135 subjects were enrolled into the study from the China Health and Retirement Longitudinal Study (CHARLS) 2011-2012 baseline survey to analyze the associations between prenatal and early postnatal famine exposure and the risk of chronic lung diseases in adulthood.

Main outcome measures Chronic lung diseases were defined based on the self-report information.

Results The prevalence of self-report chronic lung diseases in fetus-exposed, infant-exposed, preschool-exposed and non-exposed groups was 6.1%, 6.5%, 7.9% and 6.8%, respectively. The risk of chronic lung diseases in the infant-exposed group was significantly higher (OR=1.95, 95% CI: 1.10-3.44) than the non-exposed group in severely affected areas, even after adjusting for gender, smoking, and drinking, family economic status, and the highest education attainment of parents (OR=2.57, 95% CI: 1.26-5.25). In addition, after 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 (OR=3.16, 95% CI: 1.17-8.51).

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4 40 **Conclusions** Severe famine exposure in infant period might increase the
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6 41 risk of chronic lung diseases in male adults.
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10 42 **Strengths and limitations of this study**
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13 43 ● This study evaluated the associations between prenatal and early
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15 44 postnatal exposure to the Chinese famine and the risk of chronic lung
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17 45 diseases in adulthood, which were unclear in previous studies.
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21 46 ● The present study using the China Health and Retirement Longitudinal
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23 47 Study 2011-2012 baseline survey that covered all geographical regions in
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25 48 China and had broadly representative of entire China mainland found
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27 49 infant exposure to the severe Chinese famine increased the risk of chronic
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29 50 lung diseases in male adults.
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34 51 ● Selection bias was unavoidable, because severe famine could eliminate
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36 52 the weaker participants, and remain the healthier participants, which may
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38 53 decrease the real effects of famine exposure.
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42 54 ● Self-report prevalence based on doctor diagnosis could be lower than the
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44 55 real prevalence of chronic lung diseases, and could underestimate the
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46 56 effects of famine exposure.
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50 57 **Key words:** Famine; Developmental Origins of Health and Disease;
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52 58 Chronic Lung Diseases; Infant
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56 59 **Introduction**
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4 60 The chronic lung diseases briefly include chronic obstructive lung diseases
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6 61 (COPDs), chronic bronchitis, bronchial asthma, and lung heart disease
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9 62 (excluding lung tumors). Global Status Report on Non-Communicable
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11 63 Diseases (NCDs) showed that respiratory diseases, including asthma and
12
13 64 chronic obstructive lung diseases were the third leading cause of NCDs deaths
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15 65 in 2012 (about four million)[1]. Especially in the developing countries, the
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17 66 burden of chronic lung diseases was heavier than that in the developed
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19 67 countries[2].
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24 68 The Development of Health and Disease theory speculated that the fetus in
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26 69 utero would change their growth rate to adapt the condition of nutrients and
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28 70 oxygen. However, several studies had found that these adaptive changes
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30 71 might permanently modify the structure and physiological function of fetus[3, 4].
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33 72 The heavier lung diseases burden in the developing countries might be
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35 73 associated with higher prevalence of low birth weight than that in the
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37 74 developed countries. Several studies had found that the low birth weight was a
38
39 75 strong factor to predict reduction of forced expiratory vital capacity(FEV) and
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41 76 forced vital capacity(FVC)[5-7]. Moreover, although some studies found that
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43 77 the low birth weight increased the risk of asthma[8-12] and the mortality of
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45 78 chronic obstructive lung disease[7], no consistent results was observed in
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47 79 previous studies[13-16].
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55 80 Due to ethical limitations, we cannot perform the similar research in human
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57 81 beings, but natural historical famines provided us a unique opportunity to
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4 82 examine the DOHaD hypothesis in human beings. The Dutch famine
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6 83 happened in the west of the Netherlands at the end of the World War II, it
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9 84 lasted for about six months. One study observed that mid-gestation exposure
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11 85 to the Dutch famine increased significantly the prevalence of obstructive
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13 86 airways disease in adulthood[17]. Compared with the Dutch famine, the
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15
16 87 Chinese famine happened in the east of Asia, starting in the end of 1950 and
17
18 88 ending in the early of 1960, which lasted for about three years. A majority of
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20 89 studies have found that early-life exposure to the Chinese famine linked with
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22 90 hypertension[18], diabetes[19], metabolic syndrome[20] in adulthood, but the
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24 91 associations with chronic lung diseases are still unclear.
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29 92 In the current study, we used the public data of the China Health and
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31 93 Retirement Longitudinal Study (CHARLS) 2011-2012 baseline survey, to
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33 94 examine the associations between the Chinese famine exposure in early life
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35 95 and the prevalence of chronic lung diseases in adulthood, and further to
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37 96 explore whether the associations were gender-specific.
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42 97 **Methods**

43 98 **Sampling and participants**

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46 99 Sampling in the present study was based on a national population-based
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49 100 longitudinal survey in 2011-2012 of CHARLS[21]. A total of 17,708 adults aged
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51 101 ≥ 45 years old from 10,257 households were randomly selected to receive the
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54 102 household survey among 150 counties, 28 provinces, and autonomous
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4 103 regions of China mainland. 4,182 participants out of 17,708 adults were
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6 104 screened by birthdate into the present study. After excluding 47 subjects with
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9 105 information missing of chronic lung diseases, 4,135 subjects were enrolled into
10
11 106 our final analysis (Fig 1).

107 **Sampling and grouping**

108 Participants were divided into the non-exposed group and three
109 famine-exposed groups (fetus, infant, and preschool-exposed groups). The
110 Chinese famine began in January 1959 and ended in October 1961, and in
111 order to minimize the misclassification of the famine exposure, we defined the
112 participants born between October 1, 1962 and September 30, 1964 as the
113 non-exposed group, the participants born between October 1, 1959 and
114 September 30, 1961 as the fetal-exposed group, the participants born between
115 January 1, 1958 and December 31, 1958 as the infant-exposed group, and
116 defined the participants born between January 1, 1956 and December 31,
117 1957 as the preschool-exposed group.

118 **Famine severity**

119 Despite the Chinese famine affected the entire China mainland, the severity
120 was at different levels across provinces due to the difference of regional
121 climate, population density and local food policies. Similar to the previous
122 studies[18, 19], we also used the excess mortality during 1959-1961 compared
123 with the 1956-1958 to evaluate of the severity of the famine in the present

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4 124 study, and 100% was used as the threshold of excess mortality to distinguish
5
6 125 the severity of famine exposure. The regions with excess mortality $\geq 100\%$
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9 126 were categorized as the severely affected areas, and otherwise were
10
11 127 categorized as the less severely affected areas.

128 **Measurements**

129 **Diagnosis of chronic lung diseases**

130 In this study, data were collected through household survey by investigators
131 who received unified training and passed the examination. The diagnosis of
132 chronic lung diseases was based on the question of "Have you been
133 diagnosed with chronic lung diseases, such as chronic bronchitis, emphysema
134 (excluding tumors, or cancer) by a doctor? ". Subjects answering "Yes" were
135 defined as persons suffering from chronic lung diseases, and subjects
136 answering "No" as those who did not suffer from chronic lung diseases.

137 **Assessment of covariates**

138 The social demographic information, family economic status, the highest
139 education attainment of parents, and lifestyle information including smoking
140 status, drinking status were collected during face-to-face interviews in house
141 by trained interviewers. The highest education attainments of parents was
142 categorized into 4 levels: primary school or below, junior school, senior school,
143 and college or above. Smoking status was classified into never smoking,
144 former smoking, and current smoking (who smoked at least 1 cigarette per day

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4 145 in the last year). Drinking status was classified into never drinking, former
5
6 146 drinking, and current drinking (who drunk at least once per week in the last
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9 147 year). The mean level of the present sample (12,744 Chinese Yuan per person
10
11 148 per year) was used as cutoff point for family economic status (high vs. low
12
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14 149 income).

150 **Analysis**

151 Statistical analyses were preformed using IBM SPSS 20.0 (IBM Corporation,
152 Armonk, NY, USA). Continuous and categorical variables were expressed as
153 mean \pm standard deviation and percentage (%), respectively.

154 The Chi-square test was used to compare the difference of chronic lung
155 diseases prevalence between the non-exposed group and famine-exposed
156 group.

157 Univariate and multivariable logistic regression models by the maximum
158 likelihood method were used to examine the risk of chronic lung diseases
159 among the fetus, infant, and preschool-exposed groups, compared with the
160 non-exposed group, respectively. In multivariable logistic regression model, we
161 adjusted for gender, smoking, drinking, family economic status, and the
162 highest education attainment of parents. Interactions between famine-exposed
163 groups (fetus, infant, or preschool vs. non-exposed) and areas (severely
164 affected vs. less severely affected) were tested by adding a multiplicative
165 factor in the logistic regression model.

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4 166 In order to explore whether there exists a gender difference, stratified analysis
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6 167 by gender was performed using the same methods. Data was expressed as
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9 168 odds ratio (OR) (95% confidence interval).

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12 169 $P < 0.05$ for two-sided was considered statistically significant for all the
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14 170 analysis.

171 **Ethics**

172 Our study is a secondary analysis of the de-identified CHARLS public data.
173 The Medical Ethics Committee of Peking University granted the current study
174 exemption from review. All the subjects were informed and consented for the
175 protocol of study.

176 **Results**

177 The basic characteristics of participants were shown in **Table 1**. A total of
178 4,135 participants were enrolled into the present study. The sample sizes of
179 the non-exposed, fetus, infant, and preschool-exposed groups were 1,536,
180 834, 518, and 1,247, respectively. The prevalence of chronic lung diseases for
181 the non-exposed, fetus, infant, and preschool exposed groups were 6.1%,
182 6.5%, 7.9%, and 6.8%, respectively. we did not observe a statistically
183 significant difference of Chronic lung diseases prevalence among four groups
184 ($P=0.511$).

185 Stratified analysis by famine severity was showed in **Table 2**. Compared with
186 the non-exposed group, only the prevalence of chronic lung diseases for the

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4 187 infant-exposed group was significantly higher in severely affected area (5.6%
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6 188 vs.10.4%). Stratified by severity of famine exposure, we found that subjects in
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8 189 the infant-exposed group were at a higher risk of chronic lung diseases than
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10 190 the non-exposed group in severely affected area (OR=1.95; 95% CI: 1.10,
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12 191 3.44), even after adjusting for gender, smoking, drinking, family economic
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14 192 status, and the highest education attainment (OR=2.57; 95% CI: 1.26, 5.25).
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16 193 However, we did not observe the consistent associations in other
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18 194 famine-exposed groups and in less severely affected areas. In addition, we did
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20 195 not observe any significant interactions between famine exposure groups
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22 196 (fetus, infant, or preschool vs. non-exposed) and areas (severely affected vs.
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24 197 less severely affected).

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32 198 **Table 3** presents the results of stratified analysis by gender and famine
33
34 199 severity. In males, we observed that the infant-exposed group (OR=3.16; 95%
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36 200 CI: 1.17, 8.51) significantly increased the risk of chronic lung diseases in
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38 201 severely affected area, compared with the non-exposed group. The consistent
39
40 202 associations were not observed in fetal and preschool-exposed groups and in
41
42 203 less severely affected area. In females, we did not observe any significant
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44 204 associations between famine exposed groups and the non-exposed group.
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46 205 Any significant interactions were not observed between famine exposed
47
48 206 groups (fetus, infant, or preschool vs. non-exposed) and areas (severely
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50 207 affected vs. less severely affected) neither males nor females. The effects of
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52 208 main covariates, including smoking, drinking, parents` education attainment,
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4 209 and family economic status on chronic lung diseases were showed in
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6 210 **Supplementary Table 1** stratified by gender and severity.
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9 211 **Discussion**

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12 212 In the current study, we observed that the infant exposure to the Chinese
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14 213 famine significantly increased the risk of chronic lung diseases in later life.
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17 214 After stratifying by gender and famine severity, we found only the infant
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19 215 exposure to severe famine significantly increased the risk of chronic lung
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21 216 diseases in male adults, indicating that the infant period might be a critical
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23 217 period for human lung structure and function development.
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28 218 Several mechanisms could explain the associations. 1) Early-life exposure to
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30 219 the severe famine might perpetually modify the bronchial reactivity during rapid
31
32 220 growth. One Dutch famine study found that gestation the famine exposure
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34 221 affected neither the concentrations of total or specific IgE nor lung function
35
36 222 values (FEV₁ and FVC), but they observed a significant associations between
37
38 223 exposure to famine in mid and early gestation and obstructive airways disease
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40 224 in adulthood[17]. The results indicated that famine exposure might not change
41
42 225 the lung function and atopic disease, but could permanently modify the
43
44 226 bronchial responsiveness. Though we could not assure the assumption
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46 227 because bronchial reactivity was not measured in this study, this assumption
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48 228 can be one way to explain the mechanism. 2) Severe malnutrition during early
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50 229 life might increase susceptibility to pulmonary injury in later life. Animal model
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4 230 study had found that young animals who were exposed to a low protein
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6 231 maternal diet in fetus were more likely to suffer pulmonary injury than
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9 232 non-exposed young animals, which indicated the programming of the
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11 233 antioxidant defenses and immune system[22]. Another animal study reported
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14 234 that fetuses exposed to a low protein diet significantly decreased the binding of
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16 235 dexamethasone to lung receptors[23].
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19 236 The present study further added the new direct evidence in human beings for
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21 237 the fetus origin of diseases. To our knowledge, only one Dutch study explored
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23 238 the associations between the early-life famine exposure and atopy, lung
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25 239 function, and obstructive airways disease, and found that the famine exposure
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27 240 in mid and early gestation might significantly increase the prevalence of
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29 241 obstructive airways disease. Results of the Dutch study were inconsistent with
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31 242 the current study. In this study, we found that only the severe famine exposure
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33 243 in infant stage significantly increased the risk of chronic lung diseases in
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35 244 adulthood. Several reasons could explain the difference. Firstly, race might be
36
37 245 a main reason between the two studies. Subjects in the Dutch study came
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39 246 from White European, while subjects in this study were from Asian. Secondly,
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41 247 severity and duration could be another important discrepancy. The Dutch
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43 248 famine only lasted for about six months, while the Chinese famine lasted for
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45 249 about three years. Furthermore, the Chinese famine led to approximately thirty
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47 250 millions premature death[24]. However, the mortality rate during famine period
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49 251 (1945) was more than twice as high as that in 1939, and most of the excess
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4 252 mortality was attributed to severe malnutrition[25].
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7 253 It was interesting that we observed the severe famine exposure in infant period
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9 254 significantly increased the risk of chronic lung diseases among men, but not
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11 255 among women, which seems to be contradictory to the severity of famine
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13 256 exposure. Chinese parents have held a profound and lasting tradition of
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15 257 “Preferring boys to girls”, and thus boys may have been protected better
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17 258 against the famine by parents. It was inconsistent with metabolic syndrome[26].
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19 259 We speculated that boy’s lungs development could be more sensitive to
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21 260 severely malnutrition in early-life. But the specific mechanisms need to be
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23 261 further explored in future study.
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30 262 There are several limitations in this study. The primary limitation is the
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32 263 selection bias. Severe famine could eliminate weaker participants, and remain
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34 264 the healthier participants, which may decrease the real effect of famine
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36 265 exposure. Secondly, similar to other the Chinese famine studies[18, 19, 27],
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38 266 the present study also lacked the objective indicators that reflected the severity
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40 267 of famine exposure, e.g. birth weight, birth body length. Thirdly, because both
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42 268 bad weather and infection in early-life could increase the risk of chronic lung
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44 269 diseases, we could not attribute all the excess mortality rate to the famine
45
46 270 exposure. In addition, we cannot separate the effect of age from famine
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48 271 exposure. Despite these limitations, the present study used the data of China
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50 272 Health and Retirement Longitudinal Study 2011-2012 baseline survey that has
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52 273 broad representative of entire China mainland, and found that infant exposure
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4 274 to severe famine significantly increased the risk of chronic lung disease among
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6 275 men.
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9 276 **Conclusions**

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12 277 Infant exposure to severe famine could increase the risk of chronic lung
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14 278 diseases in male adults, indicating that the infant stage might be the critical
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17 279 period of lungs development for men.
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20 280 **Footnotes**

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23
24 281 **Contributors** JM and ZW were co-investigators and designed the study, ZW,
25
26 282 ZZ, ZY and YD carried out the initial analysis, and supervised data
27
28
29 283 analysis. All authors were involved in writing the paper and had final approval
30
31 284 of the submitted and published versions.
32
33

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35
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40 287 **Competing interests** The authors declared that they had no competing
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42 288 interests.
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46 289 Our study is a secondary analysis of the de-identified CHARLS public data.
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48 290 The Medical Ethics Committee of Peking University granted the current study
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50 291 exemption from review. All the subjects were informed and consented for the
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52 292 protocol of study.
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55 293 **Consent for publication**

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4 294 Not applicable.
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7 295 **Availability of data and material**
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10 296 The datasets analyzed in the current study are available in the
11
12 297 <http://charls.pku.edu.cn/zh-CN/page/data/2011-charls-wave1>.
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14

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17

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23
24 302 we also acknowledge all the subjects and households that participated in the
25
26 303 survey for their cooperation.
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397 **Table 1** Basic characteristics of study population according to the Chinese
 398 famine exposure

Variances	Non-exposed group	Fetal-exposed group	Infant-exposed group	Preschool-exposed group	<i>P</i> value
Birth date	10/1/1962– 9/30/1964	10/1/1959– 9/30/1961	19581/1– 12/31/1958	1/1/1956– 12/31/1957	
N	1,536	834	518	1,247	
Age in 2011(years)	47~49	50~51	53	54~55	
Born in severely affected area, n (%)	657(42.8)	269(32.3)	192(37.1)	482(38.7)	<i>P</i> <0.001
Women, n (%)	801(52.2)	438(52.6)	241(46.5)	614(49.3)	<i>P</i> =0.067
Smoking, n (%)					<i>P</i> =0.014
Never	970(66.4)	519(65.1)	297(61.4)	711(59.8)	
Former	80(5.5)	36(4.5)	28(5.8)	77(6.5)	
Current	410(28.1)	242(30.4)	159(32.9)	400(33.7)	
Drinking, n (%)					<i>P</i> =0.614
Never	948(61.8)	513(61.6)	320(61.9)	787(63.2)	
Less than once per months	155(10.1)	82(9.8)	53(10.3)	100(8.0)	
More than once per months	430(28.0)	238(28.6)	144(27.9)	359(28.8)	
Family income, n (%)					<i>P</i> =0.960
High	199(54.4)	115(53.5)	65(52.4)	143(52.4)	
Low	167(45.6)	100(46.5)	59(47.6)	130(47.6)	
Education, n (%)					<i>P</i> =0.390
Primary school and below	695(89.7)	396(89.8)	246(88.8)	567(92.5)	
Junior school	40(5.2)	27(6.1)	16(5.8)	25(4.1)	
High school	31(4.0)	12(2.7)	10(3.6)	19(3.1)	
College and above	9(1.2)	6(1.4)	5(1.8)	2(0.3)	
Prevalence of chronic lung disease (%)	6.1	6.5	7.9	6.8	<i>P</i> =0.511

399

400 **Table 2** The risk of chronic lung diseased among three exposed groups compare with the
 401 non-exposed group.

Variances	Non-exposed group	Fetal-exposed group	Infant-exposed group	Preschool-exposed group
Severely affected famine area				
Prevalence (%)	5.6	5.6	10.4	5.6
P^a		0.973	0.022	0.983
Odds ratio (95% CI) ^a	Ref.	0.99(0.53-1.84)	1.95(1.10-3.44)	0.99(0.60-1.66)
P^b		0.953	0.009	0.437
Odds ratio (95% CI) ^b	Ref.	0.98(0.43-2.20)	2.57(1.26-5.25)	0.75(0.36-1.56)
Less severely affected famine area				
Prevalence (%)	6.4	6.9	6.4	7.6
P^a		0.691	0.964	0.336
Odds ratio (95% CI) ^a	Ref.	1.09(0.71-1.66)	1.01(0.60-1.70)	1.21(0.82-1.76)
P^b		0.254	0.398	0.471
Odds ratio (95% CI) ^b	Ref.	1.38(0.79-2.41)	1.33(0.69-3.56)	1.22(0.71-2.10)
P for interaction between area and group ^a	Ref.	0.468	0.109	0.178
P for interaction between area and group ^b	Ref.	0.421	0.061	0.223

402 ^a Single variance binary logistic regression model.

403 ^b Multivariable logistic regression model, adjusted for gender, smoking, drinking, family
 404 economic status and the highest education attainment of parents.

405

406 **Table 3** Prevalence rate of chronic lung diseases by gender, birth group and severity of
 407 the Chinese famine area

Variables	Non-exposed group	Fetal-exposed group	Infant-exposed group	Preschool-exposed group
Female				
Severely affected area				
Prevalence (%)	5.0	5.3	7.5	4.7
P^a		0.907	0.359	0.861
Odds ratio (95% CI) ^a	Ref.	1.05(0.44-2.50)	1.53(0.62-3.81)	0.93(0.43-2.03)
P^b		0.514	0.208	0.479
Odds ratio (95% CI) ^b	Ref.	1.39(0.52-3.74)	1.98(0.68-5.72)	0.67(0.23-2.01)
Less severely affected area				
Prevalence (%)	6.9	7.0	4.1	9.4
P^a		0.970	0.218	0.176
Odds ratio (95% CI) ^a	Ref.	1.01(0.57-1.81)	0.57(0.23-1.39)	1.41(0.86-2.32)
P^b		0.238	0.644	0.359
Odds ratio (95% CI) ^b	Ref.	1.55(0.75-3.23)	0.77(0.24-2.39)	1.40(0.68-2.89)
P for interaction between area and group ^a	Ref.	0.498	0.252	0.036
P for interaction between smoking and group ^a	Ref.	0.907	0.003	0.028
P for interaction between area and group ^b	Ref.	0.686	0.179	0.132
P for interaction between smoking and group ^b	Ref.	0.999	0.614	0.0628
Male				
Severely affected area				
Prevalence (%)	6.3	5.9	13.1	6.5
P^a		0.897	0.030	0.930
Odds ratio (95% CI) ^a	Ref.	0.94(0.39-2.29)	2.26(1.08-4.73)	1.03(0.52-3.03)
P^b		0.677	0.023	0.686
Odds ratio (95% CI) ^b	Ref.	0.75(0.20-2.87)	3.16(1.17-8.51)	0.81(0.30-2.22)
Less severely affected area				
Prevalence (%)	5.8	6.9	8.4	5.7
P^a		0.566	0.237	0.974
Odds ratio (95% CI) ^a	Ref.	1.20(0.64-2.24)	1.50(0.77-2.93)	0.99(0.55-1.80)
P^b		0.584	0.178	0.853
Odds ratio (95% CI) ^b	Ref.	1.28(0.53-3.07)	1.82(0.76-4.36)	1.08(0.45-2.60)
P for interaction between area and group ^a	Ref.	0.734	0.217	0.709
P for interaction between smoking and group ^a	Ref.	0.409	0.300	0.207
P for interaction between area and group ^b	Ref.	0.344	0.127	0.887
P for interaction between smoking and group ^b	Ref.	0.950	0.103	0.696

408 ^a Single variance binary logistic regression model.

409 ^b Multivariable logistic regression model, adjusted for smoking, drinking, family economic
 410 status and the highest education attainment of parents.

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411 **Fig 1.** Flowchart on the sample selecting methods at each step

412 **Figure legends**

413 * Means missing of chronic lung diseases information in raw database.

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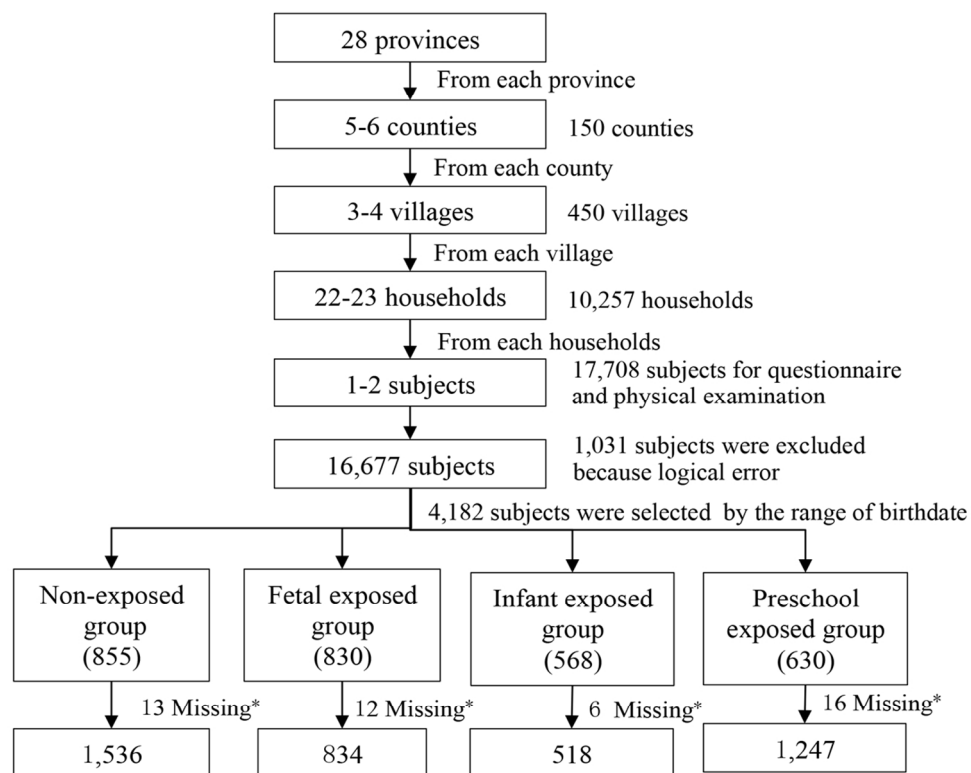


Fig 1. Flowchart on the sample selecting methods at each step

114x93mm (300 x 300 DPI)

Supplementary Table 1 The effects of smoking, drinking, family economic status and parents' education attainment on the prevalence rates of chronic lung diseases

Variances	<i>B</i>	<i>S.E.</i>	<i>Wald</i>	<i>df</i>	<i>P</i>	<i>Exp(B)</i>	95% CI. for EXP (B)	
							Lower	Upper
Male								
Less severely affected areas								
Groups			2.157	3	0.540			
Fetal-exposed	0.245	0.447	0.300	1	0.584	1.277	0.532	3.067
Infant-exposed	0.600	0.445	1.815	1	0.178	1.822	0.761	4.362
Preschool-exposed	0.083	0.446	0.034	1	0.853	1.086	0.453	2.603
Smoking	0.141	0.193	0.532	1	0.466	1.151	0.789	1.681
Drinking	-0.124	0.166	0.557	1	0.456	0.883	0.638	1.224
Parents' education attainment	-0.133	0.363	0.134	1	0.714	0.876	0.430	1.783
Family economic status	-0.131	0.347	0.143	1	0.706	0.877	0.444	1.733
Constant	-2.579	0.786	10.779	1	0.001	0.076		
Severely affected areas								
Groups			8.343	3	0.039			
Fetal-exposed	-0.285	0.684	0.174	1	0.677	0.752	0.197	2.872
Infant-exposed	1.150	0.506	5.175	1	0.023	3.158	1.173	8.508
Preschool-exposed	-0.207	0.513	0.163	1	0.686	0.813	0.297	2.221
Smoking	0.188	0.243	0.595	1	0.441	1.206	0.749	1.943
Drinking	-0.192	0.215	0.801	1	0.371	0.825	0.541	1.257
Parents' education attainment	0.217	0.472	0.211	1	0.646	1.242	0.492	3.136
Family economic status	0.306	0.521	0.346	1	0.556	1.359	0.489	3.772
Constant	-3.075	1.028	8.939	1	0.003	0.046		
Female								
Less severely affected areas								
Groups			2.448	3	0.485			
Fetal-exposed	0.440	0.373	1.392	1	0.238	1.553	0.747	3.226
Infant-exposed	-0.268	0.581	0.214	1	0.644	0.765	0.245	2.386
Preschool-exposed	0.339	0.369	0.841	1	0.359	1.403	0.680	2.893
Smoking	0.290	0.259	1.251	1	0.263	1.336	0.804	2.219
Drinking	0.038	0.264	0.020	1	0.886	1.038	0.620	1.741
Parents' education attainment	0.301	0.221	1.842	1	0.175	1.351	0.875	2.085
Family economic status	-0.351	0.401	0.768	1	0.381	0.704	0.321	1.543
Constant	-3.352	0.562	35.558	1	0	0.035		
Severely affected areas								
Groups			3.288	3	0.349			
Fetal-exposed	0.329	0.505	0.425	1	0.514	1.390	0.516	3.742
Infant-exposed	0.682	0.542	1.583	1	0.208	1.977	0.684	5.717
Preschool-exposed	-0.395	0.558	0.501	1	0.479	0.674	0.226	2.011
Smoking	0.337	0.584	0.333	1	0.564	1.401	0.446	4.396
Drinking	-0.380	0.421	0.813	1	0.367	0.684	0.300	1.562
Parents' education attainment	0.224	0.286	0.616	1	0.433	1.252	0.715	2.192
Family economic status	0.355	0.422	0.710	1	0.399	1.427	0.624	3.261
Constant	-3.045	0.895	11.59	1	0.001	0.048		

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found <i>Please see page 1, the title and abstract.</i>
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported <i>Please see page 4-5, the first three paragraphs of the "Introduction" section.</i>
Objectives	3	State specific objectives, including any prespecified hypotheses <i>Please see page 5, the last paragraph of the "Introduction" section.</i>
Methods		
Study design	4	Present key elements of study design early in the paper <i>Please see page 5-6, the "Sampling and participants" section.</i>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection <i>Please see page 5-6, the "Sampling and participants" section.</i>
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants <i>Please see page 6, the "Sampling and grouping" section.</i>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable <i>Please see page 6-7, the "Measurements" section, and the "Famine severity" section.</i>
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group <i>Please see page 6-7, the "Measurements" section, and the "Famine severity" section.</i>
Bias	9	Describe any efforts to address potential sources of bias <i>Please see page 7, the "Diagnosis of chronic lung diseases" section.</i>
Study size	10	Explain how the study size was arrived at <i>Please see page 5-6, the "Sampling and participants" section.</i>
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why <i>Please see page 6-7, the "Assessment of covariates" section.</i>
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding <i>Please see page 8-9, the "Analysis" section.</i> (b) Describe any methods used to examine subgroups and interactions <i>Please see page 8-9, the third paragraph of "Analysis" section.</i> (c) Explain how missing data were addressed <i>N/A.</i> (d) If applicable, describe analytical methods taking account of sampling strategy <i>N/A.</i> (e) Describe any sensitivity analyses <i>N/A.</i>
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially

		eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Please see page 5-6, the “Sampling and participants” section.
		(b) Give reasons for non-participation at each stage N/A.
		(c) Consider use of a flow diagram Please see page 21. The Fig 1.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Please see page 18, Table 1. (b) Indicate number of participants with missing data for each variable of interest N/A.
Outcome data	15*	Report numbers of outcome events or summary measures Please see page 18, Table 1.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Please see page 19-20, Table 2-3. (b) Report category boundaries when continuous variables were categorized Please see page 6-8, the “Famine severity” section, and the “Assessment of covariates” section. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Please see page 20, Table 3.
Discussion		
Key results	18	Summarise key results with reference to study objectives Please see page 11, the first paragraph of the “Discussion”.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Please see page 13, the last paragraph of the “Discussion”.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Please see page 11-13, in the “Discussion”.
Generalisability	21	Discuss the generalisability (external validity) of the study results N/A.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Please see page 14, in the “Funding” section.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

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2 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
3 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
4 available at www.strobe-statement.org.
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