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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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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

famine was associated with the elevated risk of chronic lung diseases among male adults (OR=2.34, 95% CI: 1.05-5.21).

Conclusions severe famine exposure in infant period might increase the risk of chronic lung diseases in male adults.

Strengths and limitations of this study

- This study evaluated the associations between prenatal and early postnatal exposure to the Chinese famine and the risk of chronic lung diseases in adulthood, which was unclear in previous studies.
- The present study used the China Health and Retirement Longitudinal Study 2011-2012 baseline survey which covered all geographical regions in China and had broadly representative of entire China mainland found that infant exposure to the severe Chinese famine increased the risk of chronic pulmonary diseases in adulthood.
- Selection bias was unavoidable, because severe famine could eliminate weaker participants, and remain the healthier participants, which may decrease the real effect of famine exposure.
- Self-report information based on doctor diagnosis could lower the real prevalence of chronic pulmonary diseases, and further underestimate the effect of famine exposure.

Key words: Famine; Developmental Origins of Health and Disease; Chronic Lung Diseases; Infant

Introduction

The chronic lung diseases briefly include chronic obstructive lung diseases (COPDs), chronic bronchitis, bronchial asthma, and lung heart disease (excluding lung tumors and cancer). Global Status Report on NCDs showed that respiratory diseases, including asthma and chronic obstructive lung diseases were the third leading cause of NCDs deaths in 2012 (about 4.0 million) [1]. Especially in the developing countries, the burden of chronic lung diseases was heavier than in the developed countries [2].

The Development of Health and Disease theory speculated that the fetus in utero would change their growth rate to adapt the supply of nutrients and oxygen. However, several studies had found that these adaptive changes might permanently modify the structure and physiological function of fetus body [3, 4]. The heavier lung diseases burden in the developing countries may be associated with a higher prevalence of low birth weight than in the developed countries. Several studies had found that the low birth weight was a strong factor to predict reduction of forced expiratory vital capacity and forced vital capacity[5-7]. Moreover, although some studies found that the low birth weight increased the risk of asthma[8-12] and the mortality of chronic obstructive lung disease[7], no consistent results was observed in previous

studies [13-16]. Due to ethical limitation, we cannot perform the similar research in human beings, but natural historical famines provided us a unique opportunity to examine the DOHaD hypothesis in human beings. The Dutch famine happened in the west of the Netherlands at the end of the World War II that lasted for about six months. Dutch famine study observed that mid-gestation exposure to the famine increased the prevalence of obstructive airways disease in adulthood[17]. Compared with the Dutch famine, the Chinese famine happened in the east of Asia, starting in the end of 1950 and ending in the early of 1960, which lasted for about three years. A majority of studies have found that early-life exposure to the Chinese famine linked with hypertension[18], diabetes[19], metabolic syndrome[20], but the associations with chronic lung diseases are still unclear.

In the current study, we used the public data of the China Health and Retirement Longitudinal Study 2011-2012 baseline survey, to examine the associations of varying degrees of famine exposure in early life and chronic lung diseases in adulthood, and explore whether a gender difference exists.

Methods

Sampling and participants

Sampling in the present study was based on a national population-based longitudinal survey in 2011-2012 of China Health and Retirement Longitudinal Study (CHARLS) [21]. A total of 17,708 adults aged above 45 years from

10,257 households were randomly selected to receive the household survey among 150 counties, 28 provinces, and autonomous regions of China mainland. 2,751 participants out of 17,708 adults were screened by birthdate into the present study. Finally, 2,603 subjects were enrolled into our final analysis after excluding 148 subjects with information missing of chronic lung diseases.

Sampling and grouping

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

Famine severity

Despite the Chinese famine affected the whole China mainland, the severity was at different levels across provinces due to the difference of regional climate, population density and local food policies. Similar to the previous

studies [18, 19], we also used the excess mortality during 1959-1961 compared with the 1956-1958 to evaluate of the severity of the famine in the present study, and 50% of the excess mortality was used as the threshold to distinguish the severity of famine exposure. The regions with excess mortality ≥50% were categorized as the severe affected areas, and otherwise were divided to the less severe affected areas.

Measurements

Diagnosis of chronic lung diseases

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

Smoking and drinking

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

drink any alcoholic beverages, such as beer, wine, or liquor in the past year? " Subjects with answers of "Drink more than once a month" or "Drink but less than once a month" were defined as drinker, and "None of these" as nondrinker.

Analysis

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

The Chi square tests were used to compare the difference of chronic lung diseases prevalence between the non-exposed group and famine exposed groups.

Univariate and multivariate binary logistic regression models by maximum likelihood method were used to examine the risk of chronic lung diseases among the fetus, infant, and preschool-exposed groups, compared with the non-exposed group, respectively. In multivariate logistic regression model, we adjusted for sex, smoking, drinking. Interactions between famine exposure groups (fetus, infant, or preschool vs. non-exposed) and area (severely affected vs. less severely affected) were tested by adding a multiplicative factor in the binary logistic regression model.

In order to explore whether there exists a gender difference, stratified analyses by gender were performed using the same methods. Data were expressed as

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

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

Ethics

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

Results

The basic characteristics of participants were shown in **Table 1**. A total of 2,603 participants were enrolled into the present study. The samples of the non-exposed, fetus, infant, and preschool-exposed groups were 695, 784, 530, and 594, respectively. The prevalence of chronic lung diseases among the non-exposed, fetus, infant, and preschool exposed groups were 5.2%, 6.6%, 8.9%, and 6.6%, respectively. However, we did not observe a statistically significant difference of prevalence between famine exposed groups (fetus, infant, and preschool) and the non-exposed group.

Table 2 presents the risk of chronic lung diseases among fetus, infant, and preschool famine exposure groups compared with the non–exposed group. Compared with the non-exposed group, the infant-exposed group had a higher risk of chronic lung diseases (OR=1.78; 95% CI: 1.14, 2.79), even after

adjusting for gender, smoking, and drinking (OR=1.81; 95% CI: 1.15, 2.85). but the consistent associations were not observed in fetus, and preschool-exposed groups.

Stratified analyses by famine severity were showed in **Table 3**. Compared with the non-exposed group, only the prevalence of chronic lung diseases for the infant-exposed group was significantly higher in severely affected area (6.7% vs. 10.1%). Stratified by severity of famine exposure, we found that people in the infant-exposed group were at a higher risk of chronic lung diseases than the non-exposed group in severely affected area (OR=1.96; 95% CI: 1.14, 3.37), even after adjusting for gender, smoking, and drinking (OR=2.03; 95% CI: 1.17, 3.52). However, we did not observe the consistent associations in other famine exposed groups and in less severely affected area. We did not observe any significant interactions between famine exposure group (fetus, infant, or preschool vs. non-exposed) and areas (severely affected vs. less severely affected).

Table 4 presents the results of stratified analysis by gender and famine severity. In males, we observed that the infant-exposed group (OR=2.34; 95% CI: 1.05, 5.21) significantly increased the risk of chronic lung diseases in severely affected area, compared with the non-exposed group. The consistent associations were not observed in fetus and preschool-exposed groups and in less severely affected area. In females, we did not observe any significant associations between famine exposed groups and the non-exposed group.

Any significant interactions were not observed between famine exposed groups (fetus, infant, or preschool vs. non-exposed) and areas (severely affected vs. less severely affected) neither males nor females.

Discussion

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

Several mechanisms could explain the associations. 1) Early-life exposure to the severe famine might perpetually modify the bronchial reactivity during rapid growth. One Dutch famine study found that gestation the famine exposure affected neither the concentrations of total or specific IgE nor lung function values (FEV_1 and FVC), but they observed a significant associations between exposure to famine in mid and early gestation and obstructive airways disease in adulthood[17]. The results indicated that famine exposure might not change the lung function and atopic disease, but could permanently modify the bronchial responsiveness. Though we could not assure the assumption because bronchial reactivity was not measured in this study, this assumption can be one way to explain the mechanism. 2) Severe malnutrition during early

life might increase susceptibility to pulmonary injury in later life. Animal model study had found that young animals who were exposed to a low protein maternal diet in fetus were more likely to suffer pulmonary injury than non-exposed young animals, which indicated the programming of the antioxidant defenses and immune system[22]. Another animal study reported fetuses exposed to a low protein diet significantly decreased the binding of dexamethasone to lung receptors[23].

The present study further added the new direct evidence in human beings for the fetus origin of diseases. To our knowledge, only one Dutch study explored the associations between the early-life famine exposure and atopy, lung function, and obstructive airways disease, and found that the famine exposure in mid and early gestation might significantly increase the prevalence of obstructive airways disease. Results of the Dutch study were inconsistent with the current study. In this study, we found that only the severe famine exposure in infant stage significantly increased the risk of chronic lung diseases in adulthood. Several reasons could explain the difference. Firstly, race might be a main reason between the two studies. Subjects in the Dutch study came from White European, while subjects in this study were from Asian. Secondly, severity and duration could be another important discrepancy. The Dutch famine only lasted for about six months, while the Chinese famine lasted for about three years. Furthermore, the Chinese famine led to approximately thirty millions premature death[24]. However, the mortality rate during famine period

(1945) was more than twice as high as that in 1939, and most of the excess mortality was attributed to severe malnutrition[25].

What was interesting is that we observed the severe famine exposure in infant period significantly increased the risk of chronic lung diseases among men, but not among women, which was contradictory to the severity of food shortage. Chinese have held a profound and lasting tradition of “Preferring boys to girls”, and thus boys may have been protected better against the famine by parents. It was inconsistent with metabolic syndrome[26]. We speculated that boy’s lungs development were more sensitive to severely malnutrition in early-life. But the specific mechanisms need to be further explored in future study.

There are several limitations in this study. The primary limitation is the selection bias. Severe famine could eliminate weaker participants, and remain the healthier participants, which may decrease the real effect of famine exposure. Secondly, similar to other the Chinese famine studies[18, 19, 27], we also lacked the objective indicators that reflected the severity of famine exposure, e.g. birth weight, birth body length. In addition, because both bad weather and infection in early-life could increase the risk of chronic lung diseases, we could not attribute all the excess mortality rate to the famine exposure. Despite these limitations, the present study used the data of China Health and Retirement Longitudinal Study 2011-2012 baseline survey that has broad representative of entire China mainland, and found that infant exposure to severe famine significantly increased the risk of chronic lung disease among

men.

Conclusions

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

Footnotes

Contributors JM and ZZ were co-investigators and designed the study, ZW，ZY and YD carried out the initial analysis, and supervised data analysis. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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Competing interests The authors declared that they had no competing interests.

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

Consent for publication

Not applicable.

Availability of data and material

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

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Table 1 Basic characteristics of study population according to the Chinese famine 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

Means Chi square tests *P* value <0.05 between preschool exposed group and the 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
P[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)
P[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
P[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)
P[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
P[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)
P[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)
P for interaction between area and group[a]	Ref.	0.426	0.185	0.563
P 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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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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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).

Conclusions Severe famine exposure in infant period might increase the risk of chronic lung diseases in male adults.

Strengths and limitations of this study

- This study evaluated the associations between prenatal and early postnatal exposure to the Chinese famine and the risk of chronic lung diseases in adulthood, which were unclear in previous studies.
- The present study using the China Health and Retirement Longitudinal Study 2011-2012 baseline survey that covered all geographical regions in China and had broadly representative of entire China mainland found infant exposure to the severe Chinese famine increased the risk of chronic lung diseases in male adults.
- Selection bias was unavoidable, because severe famine could eliminate the weaker participants, and remain the healthier participants, which may decrease the real effects of famine exposure.
- Self-report prevalence based on doctor diagnosis could be lower than the real prevalence of chronic lung diseases, and could underestimate the effects of famine exposure.

Key words: Famine; Developmental Origins of Health and Disease; Chronic Lung Diseases; Infant

Introduction

The chronic lung diseases briefly include chronic obstructive lung diseases (COPDs), chronic bronchitis, bronchial asthma, and lung heart disease (excluding lung tumors). Global Status Report on Non-Communicable Diseases (NCDs) showed that respiratory diseases, including asthma and chronic obstructive lung diseases were the third leading cause of NCDs deaths in 2012 (about four million)[1]. Especially in the developing countries, the burden of chronic lung diseases was heavier than that in the developed countries[2].

The Development of Health and Disease theory speculated that the fetus in utero would change their growth rate to adapt the condition of nutrients and oxygen. However, several studies had found that these adaptive changes might permanently modify the structure and physiological function of fetus[3, 4]. The heavier lung diseases burden in the developing countries might be associated with higher prevalence of low birth weight than that in the developed countries. Several studies had found that the low birth weight was a strong factor to predict reduction of forced expiratory vital capacity and forced vital capacity[5-7]. Moreover, although some studies found that the low birth weight increased the risk of asthma[8-12] and the mortality of chronic obstructive lung disease[7], no consistent results was observed in previous studies[13-16].

Due to ethical limitations, we cannot perform the similar research in human beings, but natural historical famines provided us a unique opportunity to

examine the DOHaD hypothesis in human beings. The Dutch famine happened in the west of the Netherlands at the end of the World War II, it lasted for about six months. One study observed that mid-gestation exposure to the Dutch famine increased significantly the prevalence of obstructive airways disease in adulthood[17]. Compared with the Dutch famine, the Chinese famine happened in the east of Asia, starting in the end of 1950 and ending in the early of 1960, which lasted for about three years. A majority of studies have found that early-life exposure to the Chinese famine linked with hypertension[18], diabetes[19], metabolic syndrome[20] in adulthood, but the associations with chronic lung diseases are still unclear.

In the current study, we used the public data of the China Health and Retirement Longitudinal Study (CHARLS) 2011-2012 baseline survey, to examine the associations between the Chinese famine exposure in early life and the prevalence of chronic lung diseases in adulthood, and further to explore whether the associations were gender-specific.

Methods

Sampling and participants

Sampling in the present study was based on a national population-based longitudinal survey in 2011-2012 of CHARLS[21]. A total of 17,708 adults aged ≥45 years old from 10,257 households were randomly selected to receive the household survey among 150 counties, 28 provinces, and autonomous

regions of China mainland. 4,182 participants out of 17,708 adults were screened by birthdate into the present study. After excluding 47 subjects with information missing of chronic lung diseases, 4,135 subjects were enrolled into our final analysis (Fig 1).

Sampling and grouping

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

Famine severity

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

study, and 100% was used as the threshold of excess mortality to distinguish the severity of famine exposure. The regions with excess mortality ≥100% were categorized as the severely affected areas, and otherwise were categorized as the less severely affected areas.

Measurements

Diagnosis of chronic lung diseases

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

Assessment of covariates

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

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

Analysis

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

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

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

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

P <0.05 for two-sided was considered statistically significant for all the analysis.

Ethics

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

Results

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

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

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

Table 3 presents the results of stratified analysis by gender and famine severity. In males, we observed that the infant-exposed group (OR=3.16; 95% CI: 1.17, 8.51) significantly increased the risk of chronic lung diseases in severely affected area, compared with the non-exposed group. The consistent associations were not observed in fetal and preschool-exposed groups and in less severely affected area. In females, we did not observe any significant associations between famine exposed groups and the non-exposed group. Any significant interactions were not observed between famine exposed groups (fetus, infant, or preschool vs. non-exposed) and areas (severely affected vs. less severely affected) neither males nor females.

Discussion

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

Several mechanisms could explain the associations. 1) Early-life exposure to the severe famine might perpetually modify the bronchial reactivity during rapid growth. One Dutch famine study found that gestation the famine exposure affected neither the concentrations of total or specific IgE nor lung function values (FEV_1 and FVC), but they observed a significant associations between exposure to famine in mid and early gestation and obstructive airways disease in adulthood[17]. The results indicated that famine exposure might not change the lung function and atopic disease, but could permanently modify the bronchial responsiveness. Though we could not assure the assumption because bronchial reactivity was not measured in this study, this assumption can be one way to explain the mechanism. 2) Severe malnutrition during early life might increase susceptibility to pulmonary injury in later life. Animal model study had found that young animals who were exposed to a low protein maternal diet in fetus were more likely to suffer pulmonary injury than non-exposed young animals, which indicated the programming of the antioxidant defenses and immune system[22]. Another animal study reported

that fetuses exposed to a low protein diet significantly decreased the binding of dexamethasone to lung receptors[23].

The present study further added the new direct evidence in human beings for the fetus origin of diseases. To our knowledge, only one Dutch study explored the associations between the early-life famine exposure and atopy, lung function, and obstructive airways disease, and found that the famine exposure in mid and early gestation might significantly increase the prevalence of obstructive airways disease. Results of the Dutch study were inconsistent with the current study. In this study, we found that only the severe famine exposure in infant stage significantly increased the risk of chronic lung diseases in adulthood. Several reasons could explain the difference. Firstly, race might be a main reason between the two studies. Subjects in the Dutch study came from White European, while subjects in this study were from Asian. Secondly, severity and duration could be another important discrepancy. The Dutch famine only lasted for about six months, while the Chinese famine lasted for about three years. Furthermore, the Chinese famine led to approximately thirty millions premature death[24]. However, the mortality rate during famine period (1945) was more than twice as high as that in 1939, and most of the excess mortality was attributed to severe malnutrition[25].

It was interesting that we observed the severe famine exposure in infant period significantly increased the risk of chronic lung diseases among men, but not among women, which seems to be contradictory to the severity of famine

exposure. Chinese parents have held a profound and lasting tradition of "Preferring boys to girls", and thus boys may have been protected better against the famine by parents. It was inconsistent with metabolic syndrome[26]. We speculated that boy's lungs development could be more sensitive to severely malnutrition in early-life. But the specific mechanisms need to be further explored in future study.

There are several limitations in this study. The primary limitation is the selection bias. Severe famine could eliminate weaker participants, and remain the healthier participants, which may decrease the real effect of famine exposure. Secondly, similar to other the Chinese famine studies[18, 19, 27], the present study also lacked the objective indicators that reflected the severity of famine exposure, e.g. birth weight, birth body length. Thirdly, because both bad weather and infection in early-life could increase the risk of chronic lung diseases, we could not attribute all the excess mortality rate to the famine exposure. In addition, we cannot separate the effect of age from famine exposure. Despite these limitations, the present study used the data of China Health and Retirement Longitudinal Study 2011-2012 baseline survey that has broad representative of entire China mainland, and found that infant exposure to severe famine significantly increased the risk of chronic lung disease among men.

Conclusions

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

Footnotes

Contributors JM and ZZ were co-investigators and designed the study, ZW，ZY and YD carried out the initial analysis, and supervised data analysis. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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Competing interests The authors declared that they had no competing interests.

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

Consent for publication

Not applicable.

Availability of data and material

The datasets analyzed in the current study are available in the

http://charls.pku.edu.cn/zh-CN/page/data/2011-charls-wave1.

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

Variances	Non-exposed group	Fetal-exposed group	Infant-exposed group	Preschool-exposed group	*P* 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)	*P*<0.001
Women, n (%)	801(52.2)	438(52.6)	241(46.5)	614(49.3)	*P*=0.067
Smoking, n (%)					*P*=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 (%)					*P*=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 (%)					*P*=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 (%)					*P*=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	*P*=0.511

Table 2 The risk of chronic lung diseased among three exposed groups compare with the 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

[a]Single variance binary logistics regression model.

[b]Multi-variance binary logistics regression model, adjusted for gender, smoking, drinking, family economic status and the highest education attainment of parents.

Table 3 Prevalence rate of chronic lung diseases by gender, birth group and severity of 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	0.0.628
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

[a]Single variance binary logistics regression model.

[b]Multi-variance binary logistics regression model, adjusted for smoking, drinking, family economic status and the highest education attainment of parents.

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

Figure legends

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

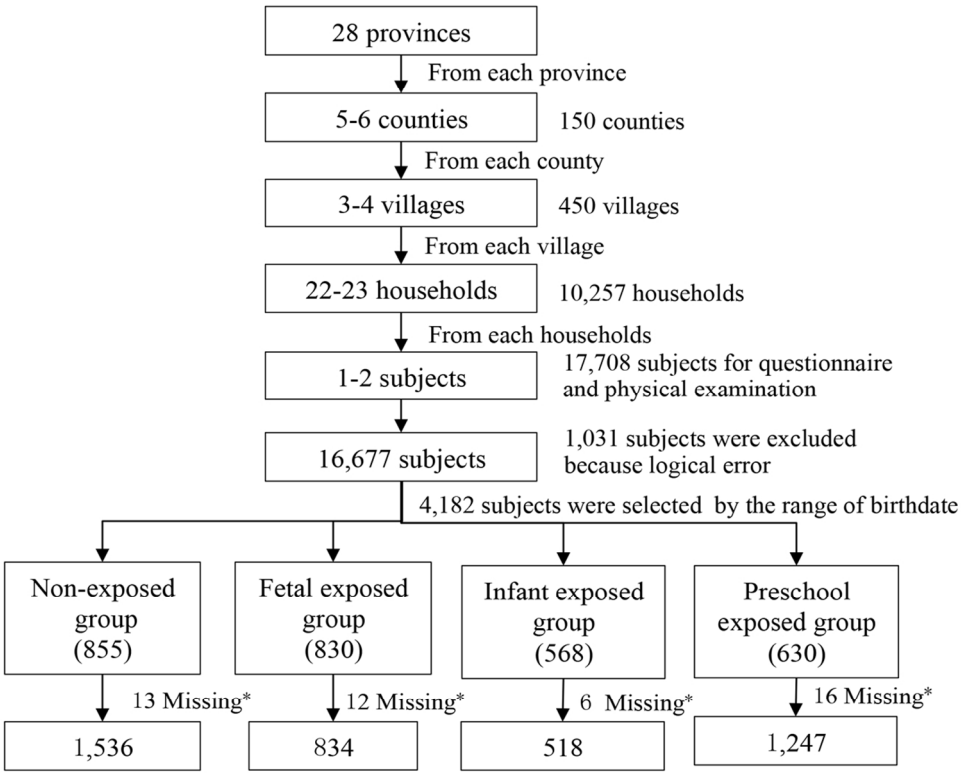

Fig 1. Flowchart on the sample selecting methods at each step

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

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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 Please see page 1, the title and abstract.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Please see page 4-5, the first three paragraphs of the "Introduction" section.
Objectives	3	State specific objectives, including any prespecified hypotheses Please see page 5, the last paragraph of the "Introduction" section.
Methods		
Study design	4	Present key elements of study design early in the paper Please see page 5-6, the "Sampling and participants" section.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Please see page 5-6, the "Sampling and participants" section.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants Please see page 6, the "Sampling and grouping" section.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Please see page 6-7, the "Measurements" section, and the "Famine severity" section.
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 Please see page 6-7, the "Measurements" section, and the "Famine severity" section.
Bias	9	Describe any efforts to address potential sources of bias Please see page 7, the "Diagnosis of chronic lung diseases" section.
Study size	10	Explain how the study size was arrived at Please see page 5-6, the "Sampling and participants" section.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Please see page 6-7, the "Assessment of covariates" section.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Please see page 8-9, the "Analysis" section.
		(*b*) Describe any methods used to examine subgroups and interactions Please see page 8-9, the third paragraph of "Analysis" section.
		(*c*) Explain how missing data were addressed N/A.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy N/A.
		(*e*) Describe any sensitivity analyses N/A.
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

available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is 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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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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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).

Conclusions Severe famine exposure in infant period might increase the risk of chronic lung diseases in male adults.

Strengths and limitations of this study

- This study evaluated the associations between prenatal and early postnatal exposure to the Chinese famine and the risk of chronic lung diseases in adulthood, which were unclear in previous studies.
- The present study using the China Health and Retirement Longitudinal Study 2011-2012 baseline survey that covered all geographical regions in China and had broadly representative of entire China mainland found infant exposure to the severe Chinese famine increased the risk of chronic lung diseases in male adults.
- Selection bias was unavoidable, because severe famine could eliminate the weaker participants, and remain the healthier participants, which may decrease the real effects of famine exposure.
- Self-report prevalence based on doctor diagnosis could be lower than the real prevalence of chronic lung diseases, and could underestimate the effects of famine exposure.

Key words: Famine; Developmental Origins of Health and Disease; Chronic Lung Diseases; Infant

Introduction

The chronic lung diseases briefly include chronic obstructive lung diseases (COPDs), chronic bronchitis, bronchial asthma, and lung heart disease (excluding lung tumors). Global Status Report on Non-Communicable Diseases (NCDs) showed that respiratory diseases, including asthma and chronic obstructive lung diseases were the third leading cause of NCDs deaths in 2012 (about four million)[1]. Especially in the developing countries, the burden of chronic lung diseases was heavier than that in the developed countries[2].

The Development of Health and Disease theory speculated that the fetus in utero would change their growth rate to adapt the condition of nutrients and oxygen. However, several studies had found that these adaptive changes might permanently modify the structure and physiological function of fetus[3, 4]. The heavier lung diseases burden in the developing countries might be associated with higher prevalence of low birth weight than that in the developed countries. Several studies had found that the low birth weight was a strong factor to predict reduction of forced expiratory vital capacity(FEV) and forced vital capacity(FVC)[5-7]. Moreover, although some studies found that the low birth weight increased the risk of asthma[8-12] and the mortality of chronic obstructive lung disease[7], no consistent results was observed in previous studies[13-16].

Due to ethical limitations, we cannot perform the similar research in human beings, but natural historical famines provided us a unique opportunity to

examine the DOHaD hypothesis in human beings. The Dutch famine happened in the west of the Netherlands at the end of the World War Ⅱ, it lasted for about six months. One study observed that mid-gestation exposure to the Dutch famine increased significantly the prevalence of obstructive airways disease in adulthood[17]. Compared with the Dutch famine, the Chinese famine happened in the east of Asia, starting in the end of 1950 and ending in the early of 1960, which lasted for about three years. A majority of studies have found that early-life exposure to the Chinese famine linked with hypertension[18], diabetes[19], metabolic syndrome[20] in adulthood, but the associations with chronic lung diseases are still unclear.

In the current study, we used the public data of the China Health and Retirement Longitudinal Study (CHARLS) 2011-2012 baseline survey, to examine the associations between the Chinese famine exposure in early life and the prevalence of chronic lung diseases in adulthood, and further to explore whether the associations were gender-specific.

Methods

Sampling and participants

Sampling in the present study was based on a national population-based longitudinal survey in 2011-2012 of CHARLS[21]. A total of 17,708 adults aged ≥45 years old from 10,257 households were randomly selected to receive the household survey among 150 counties, 28 provinces, and autonomous

regions of China mainland. 4,182 participants out of 17,708 adults were screened by birthdate into the present study. After excluding 47 subjects with information missing of chronic lung diseases, 4,135 subjects were enrolled into our final analysis (Fig 1).

Sampling and grouping

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

Famine severity

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

study, and 100% was used as the threshold of excess mortality to distinguish the severity of famine exposure. The regions with excess mortality ≥100% were categorized as the severely affected areas, and otherwise were categorized as the less severely affected areas.

Measurements

Diagnosis of chronic lung diseases

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

Assessment of covariates

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

in the last year). Drinking status was classified into never drinking, former drinking, and current drinking (who drunk at least once per week in the last year). The mean level of the present sample (12,744 Chinese Yuan per person per year) was used as cutoff point for family economic status (high vs. low income).

Analysis

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

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

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

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

P <0.05 for two-sided was considered statistically significant for all the analysis.

Ethics

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

Results

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

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

infant-exposed group was significantly higher in severely affected area (5.6% vs.10.4%). Stratified by severity of famine exposure, we found that subjects in the infant-exposed group were at a higher risk of chronic lung diseases than the non-exposed group in severely affected area (OR=1.95; 95% CI: 1.10, 3.44), even after adjusting for gender, smoking, drinking, family economic status, and the highest education attainment (OR=2.57; 95% CI: 1.26, 5.25). However, we did not observe the consistent associations in other famine-exposed groups and in less severely affected areas. In addition, we did not observe any significant interactions between famine exposure groups (fetus, infant, or preschool vs. non-exposed) and areas (severely affected vs. less severely affected).

Table 3 presents the results of stratified analysis by gender and famine severity. In males, we observed that the infant-exposed group (OR=3.16; 95% CI: 1.17, 8.51) significantly increased the risk of chronic lung diseases in severely affected area, compared with the non-exposed group. The consistent associations were not observed in fetal and preschool-exposed groups and in less severely affected area. In females, we did not observe any significant associations between famine exposed groups and the non-exposed group. Any significant interactions were not observed between famine exposed groups (fetus, infant, or preschool vs. non-exposed) and areas (severely affected vs. less severely affected) neither males nor females. The effects of main covariates, including smoking, drinking, parents` education attainment,

and family economic status on chronic lung diseases were showed in **Supplementary Table 1** stratified by gender and severity.

Discussion

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

Several mechanisms could explain the associations. 1) Early-life exposure to the severe famine might perpetually modify the bronchial reactivity during rapid growth. One Dutch famine study found that gestation the famine exposure affected neither the concentrations of total or specific IgE nor lung function values (FEV_1 and FVC), but they observed a significant associations between exposure to famine in mid and early gestation and obstructive airways disease in adulthood[17]. The results indicated that famine exposure might not change the lung function and atopic disease, but could permanently modify the bronchial responsiveness. Though we could not assure the assumption because bronchial reactivity was not measured in this study, this assumption can be one way to explain the mechanism. 2) Severe malnutrition during early life might increase susceptibility to pulmonary injury in later life. Animal model

study had found that young animals who were exposed to a low protein maternal diet in fetus were more likely to suffer pulmonary injury than non-exposed young animals, which indicated the programming of the antioxidant defenses and immune system[22]. Another animal study reported that fetuses exposed to a low protein diet significantly decreased the binding of dexamethasone to lung receptors[23].

The present study further added the new direct evidence in human beings for the fetus origin of diseases. To our knowledge, only one Dutch study explored the associations between the early-life famine exposure and atopy, lung function, and obstructive airways disease, and found that the famine exposure in mid and early gestation might significantly increase the prevalence of obstructive airways disease. Results of the Dutch study were inconsistent with the current study. In this study, we found that only the severe famine exposure in infant stage significantly increased the risk of chronic lung diseases in adulthood. Several reasons could explain the difference. Firstly, race might be a main reason between the two studies. Subjects in the Dutch study came from White European, while subjects in this study were from Asian. Secondly, severity and duration could be another important discrepancy. The Dutch famine only lasted for about six months, while the Chinese famine lasted for about three years. Furthermore, the Chinese famine led to approximately thirty millions premature death[24]. However, the mortality rate during famine period (1945) was more than twice as high as that in 1939, and most of the excess

mortality was attributed to severe malnutrition[25].

It was interesting that we observed the severe famine exposure in infant period significantly increased the risk of chronic lung diseases among men, but not among women, which seems to be contradictory to the severity of famine exposure. Chinese parents have held a profound and lasting tradition of “Preferring boys to girls”, and thus boys may have been protected better against the famine by parents. It was inconsistent with metabolic syndrome[26]. We speculated that boy’s lungs development could be more sensitive to severely malnutrition in early-life. But the specific mechanisms need to be further explored in future study.

There are several limitations in this study. The primary limitation is the selection bias. Severe famine could eliminate weaker participants, and remain the healthier participants, which may decrease the real effect of famine exposure. Secondly, similar to other the Chinese famine studies[18, 19, 27], the present study also lacked the objective indicators that reflected the severity of famine exposure, e.g. birth weight, birth body length. Thirdly, because both bad weather and infection in early-life could increase the risk of chronic lung diseases, we could not attribute all the excess mortality rate to the famine exposure. In addition, we cannot separate the effect of age from famine exposure. Despite these limitations, the present study used the data of China Health and Retirement Longitudinal Study 2011-2012 baseline survey that has broad representative of entire China mainland, and found that infant exposure

to severe famine significantly increased the risk of chronic lung disease among men.

Conclusions

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

Footnotes

Contributors JM and ZW were co-investigators and designed the study, ZW，ZZ, ZY and YD carried out the initial analysis, and supervised data analysis. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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Competing interests The authors declared that they had no competing interests.

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

Consent for publication

Not applicable.

Availability of data and material

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

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

Variances	Non-exposed group	Fetal-exposed group	Infant-exposed group	Preschool-exposed group	*P* 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)	*P*<0.001
Women, n (%)	801(52.2)	438(52.6)	241(46.5)	614(49.3)	*P*=0.067
Smoking, n (%)					*P*=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 (%)					*P*=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 (%)					*P*=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 (%)					*P*=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	*P*=0.511

Table 2 The risk of chronic lung diseased among three exposed groups compare with the 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

[a] Single variance binary logistic regression model.

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

Table 3 Prevalence rate of chronic lung diseases by gender, birth group and severity of 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	0.0.628
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

[a] Single variance binary logistic regression model.

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

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

Figure legends

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

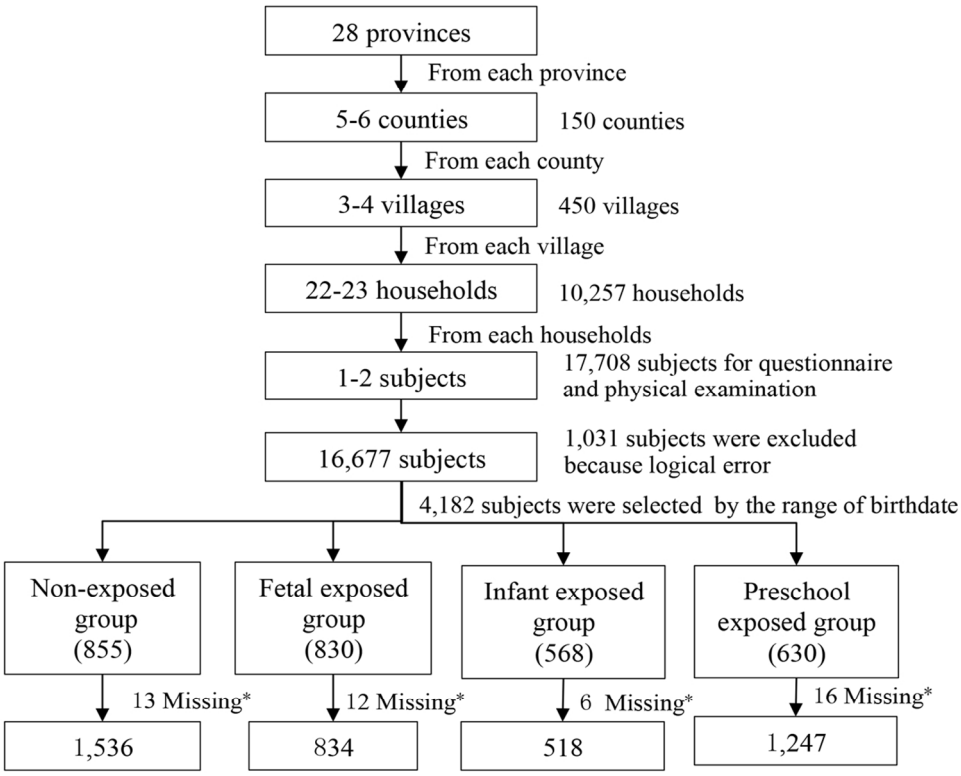

Fig 1. Flowchart on the sample selecting methods at each step

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	*B*	*S.E.*	*Wald*	*df*	*P*	*Exp(B)*	95% CI.for EXP (B)	
							Lower	Upper
Male								
Less severely affected areas								
Groups			2.157	3	0.540			
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 Please see page 1, the title and abstract.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Please see page 4-5, the first three paragraphs of the "Introduction" section.
Objectives	3	State specific objectives, including any prespecified hypotheses Please see page 5, the last paragraph of the "Introduction" section.
Methods		
Study design	4	Present key elements of study design early in the paper Please see page 5-6, the "Sampling and participants" section.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Please see page 5-6, the "Sampling and participants" section.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants Please see page 6, the "Sampling and grouping" section.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Please see page 6-7, the "Measurements" section, and the "Famine severity" section.
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 Please see page 6-7, the "Measurements" section, and the "Famine severity" section.
Bias	9	Describe any efforts to address potential sources of bias Please see page 7, the "Diagnosis of chronic lung diseases" section.
Study size	10	Explain how the study size was arrived at Please see page 5-6, the "Sampling and participants" section.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Please see page 6-7, the "Assessment of covariates" section.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Please see page 8-9, the "Analysis" section.
		(*b*) Describe any methods used to examine subgroups and interactions Please see page 8-9, the third paragraph of "Analysis" section.
		(*c*) Explain how missing data were addressed N/A.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy N/A.
		(*e*) Describe any sensitivity analyses N/A.
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

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