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Association between early-life the Great Chinese Famine experience with the risk of poor physical function later in life: A cross-sectional study

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ABSTRACT

Objectives To evaluate the association between early-life exposure to the Great Chinese Famine (1959–1961) and the risk of poor physical function in midlife.

Design A population-based historical-prospective study was performed as part of a wider cross-sectional survey. Exposure to famine was defined by birthdate, and participants were divided into non-exposed group, fetal-exposed group and infant-exposed group.

Setting and Participants A total of 3595 subjects were enrolled into the study from the China Health and Retirement Longitudinal Study (CHARLS) 2015, based on random selection of households which had at least one member who was 45 years old or older in 28 provinces of Chinese Mainland.

Main outcome measures Physical function status was assessed by a six-item self-report on Barthel scale which rated basic activities of daily living (BADL).

Results 743 (20.7 %) out of all participants were exposed to the Great Chinese Famine in their fetal periods, while 1550 (43.1 %) participants were exposed at age of infant. The prevalence of poor physical function in the non-exposed group, fetal period-exposed group, and infant period-exposed group were 12.3, 15.5, and 17.0 %, respectively. In males, after stratification by gender and severity of famine, the risk of poor physical function in fetal period was significantly higher (Odds ratio 2.40, 95 % confidence interval= 1.18 to 4.89, p =0.015) than the non-exposed group in severely affected areas, even after adjusting for number of chronic diseases, place of residence,

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smoking and drinking habits, marital status, educational level, and BMI. A similar association, however, was not observed in female adults.

Conclusionss Males who were exposed to the 1959 – 1961 Great Chinese Famine manifest considerably decreased physical function in later life.

Article Summary

Strengths and limitations of this study

This is the first study that evaluated the association between prenatal and early postnatal exposure to the Great Chinese Famine and the risk of poor physical function in midlife using a nationwide data from China.

The current study used the China Health and Retirement Longitudinal Study 2015 tracking survey from the 28 provinces of Chinese Mainland, and found that exposure to the Great Chinese famine significantly increased the risk of poor physical function in later life, especially fetal exposure in males who had distinctly elevated risk of poor physical function in middle-age life.

Selection bias was inevitable due to excess mortality in early life: this may decrease the real effect of famine exposure on physical function. Self-reported prevalence based on Barthel scale could be lower than the real prevalence of poor physical function.

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INTRODUCTION

The Framework of Life-Course Epidemiology proposes that growth and development taking place during the course of life, including prenatal life and childhood, have long-term effects and consequences on health and functioning in adulthood[1,2]. Within this framework, the Developmental Origins of Health and Disease (DOHaD) supposes that adaptations are responses to early-life (fetal and infant stages). Undernutrition leads to bodily changes in favor of early survival, but may increase the risk of adult chronic disease[3-5], as well as age-related decline in physical function[6]. Impaired physical function is an important manifestation of aging, which is associated with increased morbidity and mortality[7, 8]. Recent literature showed that prenatal undernutrition can lead to poor physical function in later life in men, while prenatal growth was one factor that predicts physical performance in the elderly[9]. Low weight at first postnatal year is associated with a number of ageing markers such as decreased opacity, low muscular strength[10,11], and osteoarthritis in men[12]. Furthermore, childhood development and growth impact on physical performance in midlife[13], and may increase the risk of falls in later life[14]. Poor childhood health status has long-range negative influence on adult health outcomes in terms of self-reported health status, and successful aging[15-17]. These findings indicate that early life malnutrition may increase the risk of poor physical function to a certain extent.

Due to ethical limitations, we cannot perform similar research to examine the DOHaD hypothesis on human beings. However, historical famine provides direct evidence for the hypothesis in humans, and provides a quasi-experimental setting for studying the effect of severe undernutrition in early-life on inverse health outcomes[18]. Due to inclement climatic conditions and radical collectivization movement, extreme food shortage appeared on the entire Mainland China between 1959 and 1961 [19, 20]. Different from the Dutch famine study[21], the Great Chinese Famine caused about 30 million premature deaths, lasted for a longer period, and was more severe[22]. To investigate the association between early life malnutrition and poor physical function in later life in humans, reliable and better evidence can be provided through the Great Chinese Famine study.

In the present study, we used data derived from the China Health and Retirement Longitudinal Study (CHARLS) 2015 to investigate the association between early life exposure to the Great Chinese Famine and the risk of poor physical function in midlife.

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METHODS

Sample and participants

This study was based on nationwide data derived from the China Health and Retirement Longitudinal Study (CHARLS) 2015, which was aimed at providing a high-quality public database with a wide range of information to satisfy the needs of scientific and policy researchers on aging-related issues. The representative samples were obtained through random selection of households with at least one member who was 45 years old or older, from the 28 provinces of Chinese Mainland. The datasets analyzed in the current study are available online (http://charls.pku.edu.cn/zh-CN/page/data/2015-charls-wave4). Details of the sampling procedure and a description of CHARLS are available elsewhere[23]. In the current study, 4667 participants were enrolled into three groups defined by birthdates. After excluding 1072 participants with missing data of BMI or functional limitations, 3595 subjects participated in the study (Figure 1).The Medical Ethics Committee of Peking University granted the present study exemption from review. All the participants were informed and consented to the protocol of the study.

Defining famine groups

Participants were divided into non-exposed group and two famine-exposed groups (fetal- and infant-exposed) on the basis of birthdate. Due to the fact that the exact dates on which the Great Chinese famine started and ended were not clear, and in order to minimize classification bias, participants born between January 1 , 1959 and September 30, 1959; and between October 1, 1961 and September 30, 1962 were excluded[14].The birth dates of the three groups were: 10/01/1962 to 09/30/1964 (non-exposed group); 10/01/1959 to 09/30/1961(fetal stage-exposed group), and 01/01/1956 to 12/31/1958 (infant stage-exposed group).

Famine severity

Due to the fact that different provinces in Chinese Mainland have differences in climate, population density and policies regarding shortage of foods, the severity of famine fluctuated sharply across regions[24]. Excess mortality was used to reflect the severity of famine exposure in the current study, which is consistent with previous studies[14, 24]. The regions with excess

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mortality of 100 % were used to differentiate the severely-affected areas from the mildly-affected areas in the current study[25].

Measurements

Defining poor physical function

Physical function status was assessed through self-reporting on six items on Barthel's scale (BADL)[26], a tool for studying the aging process[27]. The six items were dressing, bathing, feeding, getting in or out of bed, toileting, and control of urination and defecation. There were four responses for each activity: 'no difficulties, 'have some difficulties but still can do without help', 'need help' and 'unable to do'. Poor physical function was identified by the response 'need help' or 'unable to do' in at least one of the six activities.

Assessment of covariates

Covariates such as demographics (birth date, gender, residence place, education, marital status); lifestyles (smoking and drinking), and 14 types self-reported chronic diseases, were collected during face-to-face in-house interviews conducted by trained interviewers, and general obesity (body mass index) was calculated from the height and weight of the biomarker data. Further, Residence place including urban and rural. Educational level was classified into four: primary school or below, middle school, high school, college or above. Marital status was classified into 'living with spouse' (married with spouse present, cohabiting) and 'living without spouse' (married but temporarily not living with spouse for reasons such as work, separated, divorced, widowed, or never married). Smoking status was categorized into 'never smoked' and 'currently smoking' (smoked at least one cigarette per day in the last year). Drinking status was categorized into 'never drank' and 'current drinker'(drank at least once per month in the last year).The diagnosis of 14 types chronic diseases was based on whether the respondents had been diagnosed with any of the following conditions: hypertension, dyslipidemia, diabetes or elevated blood sugar; malignant tumors such as cancer, chronic lung disease, liver disease, heart disease, stroke, kidney disease, stomach disease or digestive system disease; emotional and mental problems, memory-related diseases, arthritis/rheumatism, and asthma. Participants who answered 'yes' were categorized as suffering from the disease diagnosed, while participants who answered 'no' were deemed disease-free. Body mass index (BMI) was categorized as underweight (< 18.5

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kg/m^2), normal (18.5 to 23.9 kg/m^2), overweight (24.0 to 27.9 kg/m^2), or obese (≥28.0 kg/m2) based on Chinese criteria[28].

Statistical analysis

Continuous and categorical variables were expressed as mean ± standard deviation mean (SD) and frequency (percentages), respectively. The χ^2 test was used to compare differences in basic characteristics and the prevalence of poor physical function between the two famine-exposed groups and the non-exposed group.

The association between exposure to famine and poor physical function was determined with binary logistic regression analysis. The unadjusted results and results adjusted for different covariates are presented. Results were adjusted by gender, famine severity, number of chronic diseases, place of residence, smoking, drinking, marital status, educational level and BMI. In consideration of the possibility that severity of famine may affect people differently, and that early life exposure affected men and women differently, severity-stratified famine and sex-stratified analyses were applied.

Data were expressed as OR and 95 % CI. A two-sided p-value ≤ 0.05 was considered statistically significant for all analyses. All statistical analyses were done with IBM SPSS Statistics 17 for Windows (IBM SPSS Inc., Chicago, Illinois, United States).

RESULTS

The basic characteristics of the study population are shown in Table 1. A total of 3595 participants were involved in the study. The results showed that 743 participants (20.7 %) were exposed to the Great Chinese Famine in the fetal period, while 1550 participants (43.1 %) were exposed as infants. The prevalence of poor physical function among individuals in non-exposed group, fetal-exposed group and infant-exposed group were 12.3, 15.5, and 17.0 %, respectively. Compared with unexposed group, the prevalence of poor physical function were significantly higher in fetal period-exposed and the infant-exposed groups (p =0.002).

Table 2 shows the prevalence and risk of poor physical function. The fetal period-exposed (*OR* 1.32, 95 % *CI* = 1.01 to 1.72, p = 0.040), and infant period-exposed (*OR* 1.42, 95 % *CI* = 1.14 to 1.76, p = 0.002) groups had significantly high risk of poor physical function after adjustment

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for gender, severity of famine, number of chronic diseases, place of residence, smoking, drinking, marital status, educational level and BMI, when compared with the non-exposed group. The same procedures were conducted in analyzing the risk of elevated difficulties with dressing, bathing or showering, eating, getting in or out of bed, using the toilet, and control of urination and defecation. Compared with the non-exposed group, it was observed that all the famine-exposed groups had significantly increased risks of elevated difficulty with using the toilet and difficulty with bathing or showering, after adjustment for multiple covariates. The infant-exposed group had significantly higher risks of difficulty with dressing ($p < 0.05$). However, no consistent associations were found with respect to elevated difficulty with eating, getting in or out of bed, and controlling urination and defecation ($p > 0.05$).

Table 3 shows the risk of poor physical function of the exposed groups, relative to the non-exposed group stratified by severity of famine across the entire Mainland China. In less severely affected famine areas, compared with the non-exposed group, only the odds ratio of poor physical function for infant-exposed group was statistically significant (*OR* 1.44, 95 % *CI* = 1.09 to 1.91, $p = 0.010$) even after adjusting for gender, number of chronic diseases, place of residence, smoking, drinking, marital status, educational level and BMI (*OR* 1.41, 95 % *CI* = 1.06 to 1.87, $p = 0.018$). No consistent association in fetal period-exposed group was found in poor physical function ($p > 0.05$). However, in severely affected famine area, the OR of poor physical function for infant-exposed (*OR* 1.55, 95 % *CI* = 1.03 to 2.34, *P*=0.037) and infant groups (*OR* 1.45,95 % *CI* = 1.04 to 2.03, $p = 0.031$) were statistically significant, when compared with the non-exposed group, after adjusting for multiple covariates.

Stratified analysis by gender and severity of famine is shown in Table 4 and Figure 2. In males, when compared with the non-exposed group, exposure at the fetal period (*OR* 2.40, 95 % *CI* = 1.18 to 4.89, $p = 0.015$) significantly increased the risk of poor physical function after adjusting for number of chronic diseases, place of residence, smoking, drinking, marital status, educational level, and BMI in severely affected areas. No consistent associations between fetal and infant-exposed groups were found in less seriously affected famine areas ($p > 0.05$). In

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females, the adjusted risk of poor physical function for two exposed groups showed no statistically significant differences ($p > 0.05$).

DISCUSSION

In the present study, it was observed that early-life exposure to the Great Chinese Famine significantly increased the risk of poor physical function in midlife. After stratifying by gender and famine, it was found that only fetal exposure to severe famine resulted in considerably increased risk of poor physical function in male adults. This is the first study to suggest a relationship between early-life undernutrition and poor physical function using a nationwide data from China.

The current study focused on physical function as the main outcome, and found that fetal exposure to the severe Great Chinese Famine significantly increased the risk of poor physical function in later life. There are no extant studies on direct assessment of the effect of the Great Chinese Famine exposure in early life on physical function in middle-aged. However, a recent study showed that a good childhood health status increases the probability of excellent adult physical function by 14 % (95 % CI: 12–17 %)[29].This implies that early-life stages could be critical periods for physical function in midlife[12]. The development of musculoskeletal system might account for these associations, since protein deficiency due to famine may affect growth to optimal size. Nutrient factors affect the development of an optimal muscle mass which partly determines late life muscle mass and function[6].

In the present study, it was observed that fetal and infant exposure to the Great Chinese Famine significantly increased the risks of elevated difficulty with using the toilet and bathing or showering, while infant exposure significantly increased the risk of difficulty with dressing. However, no consistent results were seen for difficulty with eating, getting in or out of bed, and control of urination and defecation. The results showed that the effects of famine exposure on disability in BADL in late life involved using the toilet, dressing and bathing or showering.

The current study had further added new direct evidence in human beings for the fetal origins hypothesis[30,31]. The findings in this investigation are consistent with the results of the Dutch study which reported that exposure of men to prenatal undernutrition was associated with poor physical function in later life[9]. The poor physical function in later life due to fetal stage exposure was more obvious in male than female survivors. This seemed to be contradictory to the reported effect of severity of famine exposure on the sexes, in which the survival of male children was

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given preference over that of female children due to the tradition of 'preferring boys to girls'[32]. One explanation for the sex-specific effects could be the differences in skeletal muscle metabolism: women have high metabolic flexibility in which substrate oxidation is readily adjusted in accordance with nutrient availability[33]. Another explanation is that when muscle mass is affected, higher relative loss of muscle mass might be seen in men than in women because adult men have greater total lean mass and a lower fat mass than adult women[34]. These gender differences are consistent with the reports of the Dutch famine literature. Furthermore, the same study cohort described the sex-specific effects of prenatal undernutrition[35].

There are some limitations in this study. One major limitation is selection bias which was caused by excess mortality in early life. The Great Chinese Famine might have spared the stronger and healthier subjects and gotten rid of the weaker ones. This selection bias may decrease the real effect of famine exposure on physical function[18]. Secondly, the present study lacks objective indicators of birth characteristic that reflect the severity of famine exposure. Such indicators include birth weight and head circumference which were used in other Chinese famine studies[14, 36]. Thirdly, due to the fact that the Great Chinese Famine lasted for three years (1959–1961), the fetal period-exposed group was separated from the infant-exposed group. Notwithstanding these limitations, this study used national data from CHARLS2015 which had broad representation, and found that early-life exposure to the Great Chinese Famine significantly increased the risk of poor physical function in middle-age life.

CONCLUSION

These results indicate that exposure to the Great Chinese famine significantly increased the risk of poor physical function in later life, especially fetal exposure in males who had distinctly elevated risk of poor physical function in middle-age life.

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Contributors TT and LYD organized the data and performed statistical analysis, while TT, YSL, ZYG and JXM wrote the manuscript. All authors read and approved the final manuscript for publication.

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Ethics approval The Medical Ethics Committee of Peking University.

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Data sharing statement The datasets analyzed in the current study are available online (http://charls.pku.edu.cn/zh-CN/page/data/2015-charls-wave4).

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Figure Legends

Figure 1. Flow chart on the sample selection methods in each step

Figure 2. Differences in risk of poor physical function as determined through stratified analysis by gender and severity of famine

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Table 1. Basic characteristics of the study population

Characteristics	Non-exposed group	Fetal period-exposed group	Infant period-exposed Group	*p*
Birth date	10/1/1962–9/30/1964	10/1/1959–9/30/1961	01/01/1956–12/31/1958	
n	1302	743	1550	
Female, n（%）	708(54.4)	412(55.5)	805(51.9)	0.216
Born in severely affected area n (%)	531(40.8)	252(33.9)	580(37.4)	**0.008**
Urban, n (%)	532(40.9)	279(37.6)	573(37.0)	0.087
Living with spouse, n (%)	1165(89.5)	653(87.9)	1351(87.2)	0.157
Current smoking, n（%）	361(27.7)	214(28.8)	466(30.1)	0.388
Current drinking, n（%）	387(29.7)	213(28.7)	423(27.3)	0.354
Chronic diseases, n（%）				
0	379(29.1)	209(28.1)	440(28.4)	
1	371(28.5)	200(26.9)	422(27.2)	
2	240(18.4)	155(20.9)	307(19.8)	0.694
3	147(11.3)	89(12.0)	177(11.4)	
4	97(7.5)	49(6.6)	98(6.3)	
≥5 (multiple)	68(5.2)	41(5.5)	106(6.8)	
Education level, n (%)				
Primary school or below	602(46.2)	356(47.9)	929(59.9)	
Middle school	488(37.5)	218(29.3)	379(24.5)	
High school	173(13.3)	157(21.1)	224(14.5)	<0.001
College school or above	39(4.61)	12(1.6)	18(1.2)	
General obesity (BMI), n (%)				
Underweight	43(3.3)	22(3.0)	81(5.2)	
Normal weight	557(42.8)	345(46.4)	721(46.5)	0.001
Overweight	473(36.3)	261(35.1)	546(35.2)	
Obese	229(17.6)	115(15.5)	202(13.0)	
Prevalence of poor physical function, n（%）	160(12.3)	115(15.5)	264(17.0)	**0.002**

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Table 2. Comparison of prevalence of poor physical function between famine-exposed groups and non-exposed group#

	Prevalence	Crude Model		Adjusted Model*	
	%	*OR* (95% *CI*)	*p*	*OR* (95% *CI*)	*p*
Difficulty with dressing					
Non-exposed group	34(2.6)	Ref.		Ref.	
Fetal-exposed group	29(3.9)	1.52(0.92 to 2.51)	0.106	1.54(0.93 to 2.56)	0.095
Infant-exposed group	71(4.6)	1.79(1.18 to 2.71)	**0.006**	1.72(1.13 to 2.62)	**0.012**
Difficulty with bathing or showering					
Non-exposed group	35(2.7)	Ref.		Ref.	
Fetal-exposed group	32(4.3)	1.63(1.00 to 2.65)	0.050	1.65(1.01 to 2.70)	**0.046**
Infant-exposed group	77(5.0)	1.89(1.26 to 2.84)	**0.002**	1.74(1.15 to 2.63)	**0.008**
Difficulty with eating					
Non-exposed group	16(1.2)	Ref.		Ref.	
Fetal-exposed group	12(1.6)	1.32(0.62 to 2.80)	0.471	1.32(0.62 to 2.83)	0.469
Infant-exposed group	27(1.7)	1.43(0.76 to 2.66)	0.265	1.17(0.62 to 2.21)	0.622
Difficulty with getting in or out of bed					
Non-exposed group	57(4.4)	Ref.		Ref.	
Fetal-exposed group	37(5.0)	1.15(0.75 to 1.75)	0.532	1.14(0.74 to 1.75)	0.555
Infant-exposed group	76(4.9)	1.13(0.79 to 1.60)	0.508	1.06(0.74 to 1.51)	0.762
Difficulty with using the toilet					
Non-exposed group	94(7.2)	Ref.		Ref.	
Fetal-exposed group	76(10.2)	1.46(1.07 to 2.01)	**0.018**	1.46(1.06 to 2.02)	**0.021**
Infant-exposed group	175(11.3)	1.64(1.26 to 2.13)	**<0.001**	1.61(1.23 to 2.11)	**<0.001**
Difficulty with controlling urination and defecation					
Non-exposed group	32(2.5)	Ref.		Ref.	
Fetal-exposed group	16(2.2)	0.87(0.48 to 1.60)	0.662	0.89(0.48 to 1.63)	0.702
Infant-exposed group	49(3.2)	1.30(0.83 to 2.04)	0.261	1.20(0.76 to 1.90)	0.429
Poor physical function					
Non-exposed group	160(12.3)	Ref.		Ref.	
Fetal-exposed group	115(15.5)	1.31(1.01 to 1.69)	**0.042**	1.32(1.01 to 1.72)	**0.040**
Infant-exposed group	264(17.0)	1.47(1.19 to 1.81)	**<0.001**	1.42(1.14 to 1.76)	**0.002**

Calculations were made using binary logistic regression analysis. Odds ratio represents the ratio of the probability of poor physical function for those who were exposed to famine, when compared with those who were not exposed to famine, at 95 % CIs.

*Adjusted for gender, famine severity, number of chronic diseases, place of residence, smoking, drinking, marital status, educational level and BMI.

(OR: Odds Ratio; CI: Confidence Interval)

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Table 3. Risk of poor physical function in birth groups in the Great Chinese Famine area#

	Prevalence	Crude Model		Adjusted Model*	
	%	*OR* (95% *CI*)	*p*	*OR* (95% *CI*)	*p*
Less severely-affected famine area					
Non-exposed group	91(11.8)	Ref.		Ref.	
Fetal-exposed group	67(13.6)	1.18(0.84 to 1.66)	0.335	1.20(0.85 to 1.69)	0.308
Infant-exposed group	157(16.2)	1.44(1.09 to 1.91)	**0.010**	1.41(1.06 to 1.87)	**0.018**
Severely affected famine area					
Non-exposed group	69(13.0)	Ref.		Ref.	
Fetal-exposed group	48(19.0)	1.58(1.05 to 2.36)	**0.027**	1.55(1.03 to 2.34)	**0.037**
Infant-exposed group	107(18.4)	1.52(1.09 to 2.10)	**0.013**	1.45(1.04 to 2.03)	**0.031**

#Calculations were made using binary logistic regression analysis. Odds ratio represents the ratio of the probability of poor physical function for those who were exposed to famine, when compared with those who were not exposed to famine, at 95 % CIs.
*Adjusted for gender, number of chronic diseases, place of residence, smoking, drinking, marital status, educational level and BMI.
(OR: Odds Ratio; CI: Confidence Interval)

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Table 4. Risk of poor physical function in birth groups by gender and severity of the Great Chinese Famine area#

	Prevalence	Crude Model		Adjusted Model*	
	n (%)	OR (95% CI)	*p*	OR (95% CI)	*p*
Less severely affected famine area					
Male					
Non-exposed group	26(7.6)	Ref.		Ref.	
Fetal period-exposed group	19(8.4)	1.11(0.60 to 2.06)	0.732	1.11(0.60 to 2.08)	0.736
Infant period-exposed group	53(11.3)	1.55(0.95 to 2.53)	0.082	1.45(0.88 to 2.38)	0.145
Female					
Non-exposed group	65(15.2)	Ref.		Ref.	
Fetal period-exposed group	48(18.2)	1.24(0.82 to 1.87)	0.301	1.21(0.79 to 1.83)	0.381
Infant period-exposed group	104(20.8)	1.47(1.05 to 2.07)	**0.027**	1.38(0.97 to 1.95)	0.075
Severely affected famine area					
Male					
Non-exposed group	20(8.0)	Ref.		Ref.	
Fetal period-exposed group	17(16.3)	2.26(1.13 to 4.51)	**0.021**	2.40(1.18 to 4.89)	**0.015**
Infant period-exposed group	37(13.5)	1.80(1.02 to 3.20)	**0.044**	1.66(0.92 to 3.00)	0.095
Female					
Non-exposed group	49(17.5)	Ref.		Ref.	
Fetal period-exposed group	31(20.9)	1.25(0.76 to 2.06)	0.385	1.25(0.75 to 2.08)	0.398
Infant period-exposed group	70(22.9)	1.40(0.93 to 2.10)	0.107	1.35(0.89 to 2.04)	0.161

#Calculations were made using binary logistic regression analysis. Odds ratio represents the ratio of the probability of poor physical function for those who were exposed to famine, when compared with those who were not exposed to famine, at 95 % CIs.
*Adjusted for number of chronic diseases, place of residence, smoking, drinking, marital status, educational level and BMI.
(OR: Odds Ratio; CI: Confidence Interval)

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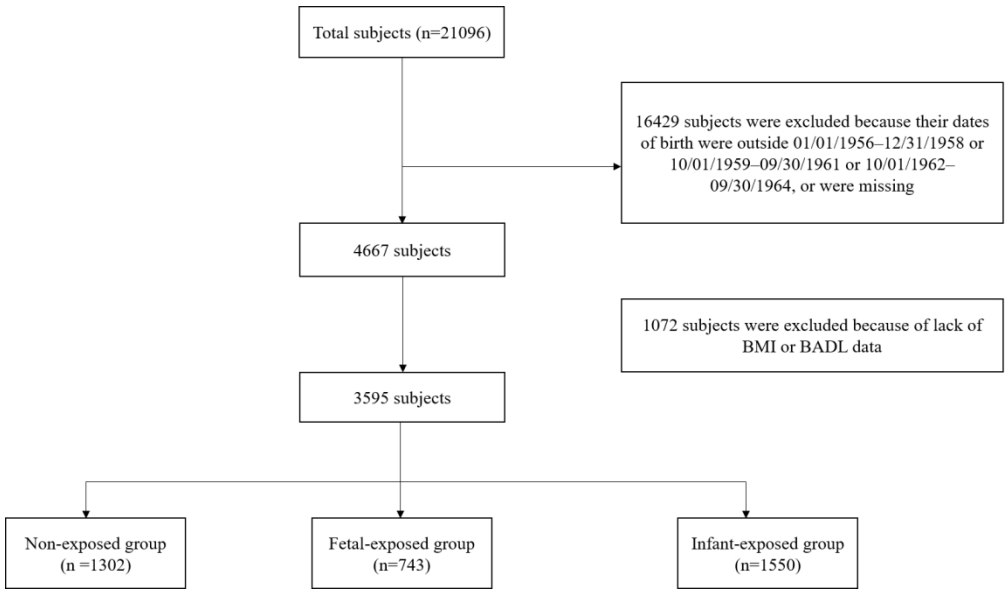

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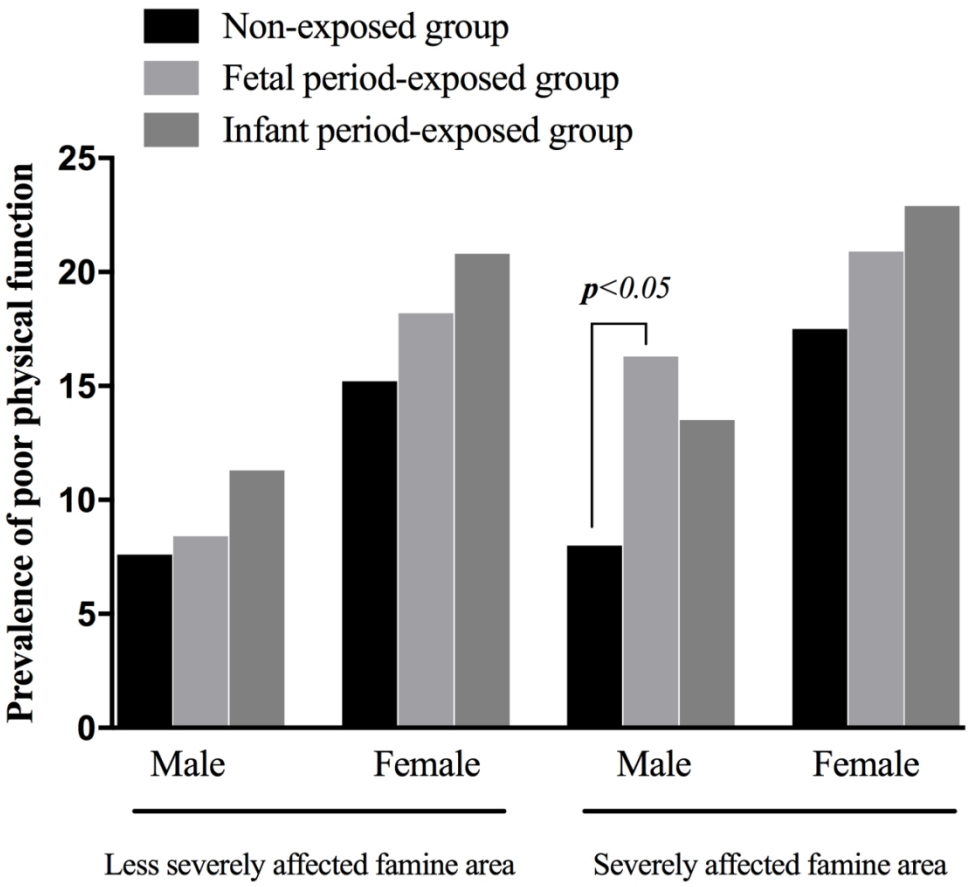

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			**3**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			**3-6**
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
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	*4*
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	5-6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5-6

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		(*e*) Describe any sensitivity analyses	5-6
Results			6-7
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	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	6-7
		Cross-sectional study—Report numbers of outcome events or summary measures	6-7
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	7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-7
Discussion			7-9
Key results	18	Summarise key results with reference to study objectives	7-8
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	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-9
Other information			9-12
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	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
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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The association between early-life exposure to the Great Chinese Famine and poor physical function later in life: a cross-sectional study

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The association between early-life exposure to the Great Chinese Famine and poor physical function later in life: a cross-sectional study

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ABSTRACT

Objectives To evaluate the association between early-life exposure to the Great Chinese Famine (1959–1961) and the prevalence of poor physical function in midlife.

Design A population-based historical-prospective study was performed as part of a wider cross-sectional survey. Exposure to famine was defined by birthdate, and participants were divided into non-exposed group, fetal-exposed group and infant-exposed group.

Setting and Participants A total of 3595 subjects were enrolled into the study from the China Health and Retirement Longitudinal Study (CHARLS) 2015, based on random selection of households which had at least one member aged 45 years old and above in 28 provinces of Mainland China.

Main outcome measures Physical function status was assessed by a six-item self-report on the Barthel scale which rated basic activities of daily living (BADL).

Results 743 (20.7 %) out of all participants were exposed to the Great Chinese Famine in their fetal periods, while 1550 (43.1 %) participants were exposed at the age of an infant. The prevalence of poor physical function in the non-exposed group, fetal period-exposed group, and infant period-exposed group were 12.3, 15.5, and 17.0 %, respectively. Among males, after stratification by gender and severity of famine, the prevalence of poor physical function in the fetal period was significantly higher (Odds ratio 2.40, 95 % confidence interval= 1.18 to 4.89, p =0.015) than the non-exposed group in severely affected areas, even after adjusting for the number of chronic diseases, place of residence, smoking and alcohol drinking habits, marital status, educational level, and Body mass index (BMI). A similar connection between

prenatal and early postnatal exposure to the Great Chinese Famine and the prevalence of poor physical function in midlife, however, was not observed from female adults.

Conclusions Males who were exposed to the Great Chinese Famine (1959 – 1961) present considerably decreased physical function in their later life.

Article Summary

Strengths and limitations of this study

This is the first study that evaluated the association between prenatal and early postnatal exposure to the Great Chinese Famine and the prevalence of poor physical function in midlife, which intends this analysis filled the gap in this range of research.

The study applied the China Health and Retirement Longitudinal Study 2015 tracking survey, which is a nationally representative longitudinal survey.

Stringent quality control measures were applied in every stage of the China Health and Retirement Longitudinal Study (CHARLS) 2015 tracking survey, which ensured the quality of our study.

Selection bias was inevitable due to excess mortality in early life, this might decrease the real effect of famine exposure on physical function.

Self-reported prevalence based on the Barthel scale could be lower than the real prevalence of poor physical function.

INTRODUCTION

The Framework of Life-Course Epidemiology proposes that physical growth and development taking place during the life cycle, including prenatal life and childhood, have long-term effects and consequences on health and function in adulthood[1, 2]. Within this framework, the Developmental Origins of Health and Disease (DOHaD) assumes that physical adaptations are responses to early-life (fetal and infant stages). Undernutrition would lead to bodily changes for early survival, but might increase the prevalence of adult chronic disease[3-5], as well as age-related physical function decline[6]. Impaired physical function is an essential manifestation of aging process, which is associated with increased morbidity and mortality[7, 8]. Recent literature showed that prenatal undernutrition could result in poor physical function in later life among males; meanwhile, prenatal growth was one

factor that predicts physical performance among the elderly[9]. Low weight at first postnatal year is associated with some aging markers such as decreased opacity, low muscular strength[10, 11], and osteoarthritis in men[12].

Furthermore, childhood development and growth have an impact on physical performance in midlife[13], and may increase the prevalence of falls in later life[14]. Poor childhood health status has a long-range negative influence on adult health outcomes in terms of self-reported health status, and successful aging[15-17]. These findings indicate that early life malnutrition may increase the prevalence of poor physical function to a certain extent.

Due to ethical limitations, we cannot perform similar research to examine the DOHaD hypothesis of human beings. However, historical famine provides direct evidence for the hypothesis in humans, and provides a quasi-experimental setting for studying the effect of severe undernutrition in early-life on inverse health outcomes[18]. Due to inclement climatic conditions and radical collectivization movement, extreme food shortage appeared on the entire Mainland China between 1959 and 1961 [19, 20]. Different from the Dutch famine study[21], the Great Chinese Famine caused about 30 million premature deaths, lasted for more extended longer period, and was more severe[22]. To investigate the association between early life malnutrition and poor physical function in later life in humans, reliable and solid evidence could be provided through the Great Chinese Famine study.

In this study, we employed data derived from the China Health and Retirement Longitudinal Study (CHARLS) 2015 to investigate the association between early life exposure to the Great Chinese Famine and the prevalence of poor physical function in midlife.

METHODS

Database

This study was based on nationwide data derived from the China Health and Retirement Longitudinal Study (CHARLS) 2015, which was aimed at providing a high-quality public database with a wide range of information to meet the needs of scientific and policy researchers on aging-related issues. A total number of 21096 individuals from 12235 households were interviewed through a face-to-face questionnaire, and the data collection of the survey was performed from July 2015 to August 2015. The representative samples were collected through a four-staged, stratified, cluster sampling method[22] of households with at least one member who aged 45 years old and above, from the 450 communities, 150 counties,28 provinces of Mainland China. The CHARLS 2015 also collected data on height

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and weight were carried out by trained interviewers. To correct for non-response and sampling frame errors in each step of the CHARLS, the CHARLS team created separate weights for individuals and households. The datasets analyzed in the current study are available online (http://charls.pku.edu.cn/zh-CN/page/data/2015-charls-wave4).[23]

Defining famine groups

Participants were divided into a non-exposed group and two famine-exposed groups (fetal- and infant-exposed) by birthdate. The Great Chinese Famine started in January 1959 and ended in October 1961.Due to the fact that the exact dates on which the Great Chinese famine began and ended were not precise, and in order to minimize classification bias, participants born between January 1 , 1959 and September 30, 1959; and between October 1, 1961 and September 30, 1962 were excluded[14].The birth dates of the three groups were: 10/01/1962 to 09/30/1964 (non-exposed group); 10/01/1959 to 09/30/1961(fetal stage-exposed group), and 01/01/1956 to 12/31/1958 (infant stage-exposed group).

Sample

In the current study, 4667 participants were enrolled into three groups defined by birthdates. After excluding 1072 participants with missing data of BMI or functional limitations, 3595 subjects participated in the study (Figure 1).

Famine severity

Since different provinces in Mainland China vary from climate, population density and policies regarding the shortage of foods, the severity of famine fluctuated sharply across regions[24]. Excess mortality was the change in mortality rate from the average in 1956–1958 to the highest value among the period of 1959–1962 and was used to reflect the severity of famine exposure in the current study, which is consistent with previous studies[14, 24]. The regions with excess mortality of 100 % were conducted to differentiate the severely-affected areas from the mildly-affected areas in this study[25].

Measurements

Defining poor physical function

Physical function status was assessed through self-reporting on six items on Barthel's scale (BADL)[26], a tool for studying the aging process[27]. The six items included dressing, bathing, feeding, getting in or out of bed, toileting, and control of urination and defecation. There

were four possible responses for each activity: 'no difficulties, 'have some difficulties but still can do without help', 'need help' and 'unable to do'. Poor physical function was identified by the response 'have some difficulties but still can do without help', 'need help' or 'unable to do' in at least one of the six activities.

Assessment of covariates

Covariates such as demographics (birth date, gender, residence place, education, marital status); lifestyles (smoking and alcohol drinking), and 14 types self-reported chronic diseases, were collected during face-to-face in-house interviews conducted by trained interviewers, and general obesity (body mass index) was calculated from the height and weight of the biomarker data. Further, residence place included urban and rural areas. Educational level was grouped into four stage: primary school or below, middle school, high school, college or above. Marital status was classified into 'living with spouse' (married with spouse present, cohabiting) and 'living without spouse' (married but temporarily not living with spouse for reasons such as work, separated, divorced, widowed, or never married). Smoking status was characterized into 'never smoked', 'past smoking' and 'currently smoking' (smoked at least one cigarette per day in the last year). Alcohol drinking status was categorized into 'never drank' and 'drinker'(drank at least once per month in the last year).The diagnosis of 14 types of chronic diseases was based on whether the respondents had been diagnosed with any of the following conditions: hypertension, dyslipidemia, diabetes or elevated blood sugar; malignant tumors such as cancer, chronic lung disease, liver disease, heart disease, stroke, kidney disease, stomach disease or digestive system disease; emotional and mental problems, memory-related diseases, arthritis/rheumatism, and asthma. Participants who replied 'yes' were described as suffering from the disease diagnosed, while participants who responded 'no' were deemed disease-free. Body mass index (BMI) was categorized as underweight (< 18.5 kg/m^2), normal (18.5 to 23.9 kg/m^2), overweight (24.0 to 27.9 kg/m^2), or obese (≥28.0 kg/m2) based on Chinese criteria[28].

Ethics

The Medical Ethics Committee of Peking University granted the present study exemption from review. All the participants were informed and consented to the protocol of the study. As the main approach of this study was cross-sectional analysis by collecting data from the China Health and Retirement Longitudinal Study (CHARLS) 2015, there were not many ethical concerns.

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Statistical analysis

Continuous and categorical variables were expressed as mean ± standard deviation mean (*SD*) and frequency (percentages), respectively. The χ^2 test was used to compare differences in basic characteristics and the prevalence of poor physical function between the two famine-exposed groups and the non-exposed group.

The association between exposure to famine and poor physical function was determined with binary logistic regression analysis. The unadjusted results and results adjusted for different covariates are presented. Results were adjusted by gender, famine severity, the number of chronic diseases, place of residence, smoking, alcohol drinking, marital status, educational level and BMI. In consideration of the possibility that severity of famine might affect people differently, and that early life exposure affected men and women differently, severity-stratified famine and sex-stratified analyses were applied. Data were expressed as OR and 95 % CI. A two-sided p-value ≤ 0.05 was considered statistically significant for all analyses. All statistical analyses were conducted with IBM SPSS Statistics 17 for Windows (IBM SPSS Inc., Chicago, Illinois, United States).

Patient and Public Involvement

In present study, we used the data from CHARLS, which is a nationally representative longitudinal survey. Patients or public were not involved.

RESULTS

The basic characteristics of the study population are shown in Table 1. A total of 3595 participants were involved in the study. The results showed that 743 participants (20.7 %) were exposed to the Great Chinese Famine in the fetal period, while 1550 participants (43.1 %) were exposed as infants. The prevalence of poor physical function among individuals in the non-exposed group, fetal-exposed group and infant-exposed group was 12.3, 15.5, and 17.0 %, respectively. Compared with the unexposed group, the prevalence of poor physical function was significantly higher in fetal period-exposed and the infant-exposed groups (p =0.002).

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Table 1. Basic characteristics of the study population

Characteristics	Non-exposed group	Fetal period-exposed group	Infant period-exposed Group	*p*
Birth date	10/1/1962–9/30/1964	10/1/1959–9/30/1961	01/01/1956–12/31/1958	
n	1302	743	1550	
Female, n（%）	708(54.4)	412(55.5)	805(51.9)	0.216
Born in severely affected area n (%)	531(40.8)	252(33.9)	580(37.4)	**0.008**
Urban, n (%)	532(40.9)	279(37.6)	573(37.0)	0.087
Living with spouse, n (%)	1165(89.5)	653(87.9)	1351(87.2)	0.157
Smoking, n（%）				
Never	822(63.1)	445(59.9)	894(57.7)	
Past	119(9.1)	84(11.3)	190(12.3)	**0.024**
Current	361(27.7)	214(28.8)	466(30.1)	
Alcohol drinking, n（%）	387(29.7)	213(28.7)	423(27.3)	0.354
Chronic diseases, n（%）				
0	379(29.1)	209(28.1)	440(28.4)	
1	371(28.5)	200(26.9)	422(27.2)	
2	240(18.4)	155(20.9)	307(19.8)	
3	147(11.3)	89(12.0)	177(11.4)	0.694
4	97(7.5)	49(6.6)	98(6.3)	
≥5 (multiple)	68(5.2)	41(5.5)	106(6.8)	
Education level, n (%)				
Primary school or below	602(46.2)	356(47.9)	929(59.9)	
Middle school	488(37.5)	218(29.3)	379(24.5)	
High school	173(13.3)	157(21.1)	224(14.5)	<0.001
College school or above	39(4.61)	12(1.6)	18(1.2)	
General obesity (BMI), n (%)				
Underweight	43(3.3)	22(3.0)	81(5.2)	
Normal weight	557(42.8)	345(46.4)	721(46.5)	
Overweight	473(36.3)	261(35.1)	546(35.2)	0.001
Obese	229(17.6)	115(15.5)	202(13.0)	
Prevalence of poor physical function, n（%）	160(12.3)	115(15.5)	264(17.0)	**0.002**

Table 2 shows the prevalence and prevalence of poor physical function. The fetal period-exposed (*OR* 1.32, 95 % *CI* = 1.01 to 1.71, *p* = 0.041), and infant period-exposed (*OR* 1.42, 95 % *CI* = 1.14 to 1.76, *p* = 0.002) groups had significantly high prevalence of poor physical

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function after adjustment for gender, severity of famine, number of chronic diseases, place of residence, smoking, alcohol drinking, marital status, educational level and BMI, when compared with the non-exposed group. The same procedures were conducted in analyzing the prevalence of high difficulties with dressing, bathing or showering, eating, getting in or out of bed, using the toilet, and control of urination and defecation. Compared with the non-exposed group, it was observed that all the famine-exposed groups had significantly increased the prevalence of high difficulty with using the toilet and difficulty with bathing or showering, after adjustment for multiple covariates. The infant-exposed group had a significantly higher prevalence of difficulty with dressing ($p < 0.05$). However, no consistent associations were found with concerning high difficulty with eating, getting in or out of bed, and controlling urination and defecation ($p > 0.05$).

Table 2. Comparison of prevalence of poor physical function between famine-exposed groups and non-exposed group#

	Prevalence	**Crude Model**		**Adjusted Model***	
	%	***OR* (95% *CI*)**	***p***	***OR* (95% *CI*)**	***p***
Difficulty with dressing					
Non-exposed group	34(2.6)	Ref.		Ref.	
Fetal-exposed group	29(3.9)	1.52(0.92 to 2.51)	0.106	1.54(0.93 to 2.56)	0.095
Infant-exposed group	71(4.6)	1.79(1.18 to 2.71)	**0.006**	1.72(1.13 to 2.62)	**0.012**
Difficulty with bathing or showering					
Non-exposed group	35(2.7)	Ref.		Ref.	
Fetal-exposed group	32(4.3)	1.63(1.00 to 2.65)	0.050	1.66(1.02 to 2.72)	**0.044**
Infant-exposed group	77(5.0)	1.89(1.26 to 2.84)	**0.002**	1.75(1.16 to 2.65)	**0.008**
Difficulty with eating					
Non-exposed group	16(1.2)	Ref.		Ref.	
Fetal-exposed group	12(1.6)	1.32(0.62 to 2.80)	0.471	1.32(0.62 to 2.83)	0.474
Infant-exposed group	27(1.7)	1.43(0.76 to 2.66)	0.265	1.17(0.62 to 2.20)	0.629
Difficulty with getting in or out of bed					

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Non-exposed group	57(4.4)	Ref.		Ref.	
Fetal-exposed group	37(5.0)	1.15(0.75 to 1.75)	0.532	1.14(0.74 to 1.75)	0.553
Infant-exposed group	76(4.9)	1.13(0.79 to 1.60)	0.508	1.06(0.74 to 1.51)	0.760
Difficulty with using the toilet					
Non-exposed group	94(7.2)	Ref.		Ref.	
Fetal-exposed group	76(10.2)	1.46(1.07 to 2.01)	**0.018**	1.46(1.06 to 2.02)	**0.021**
Infant-exposed group	175(11.3)	1.64(1.26 to 2.13)	**<0.001**	1.61(1.23 to 2.11)	**<0.001**
Difficulty with controlling urination and defecation					
Non-exposed group	32(2.5)	Ref.		Ref.	
Fetal-exposed group	16(2.2)	0.87(0.48 to 1.60)	0.662	0.89(0.48 to 1.63)	0.694
Infant-exposed group	49(3.2)	1.30(0.83 to 2.04)	0.261	1.20(0.76 to 1.90)	0.435
Poor physical function					
Non-exposed group	160(12.3)	Ref.		Ref.	
Fetal-exposed group	115(15.5)	1.31(1.01 to 1.69)	**0.042**	1.32(1.01 to 1.71)	**0.041**
Infant-exposed group	264(17.0)	1.47(1.19 to 1.81)	**<0.001**	1.42(1.14 to 1.76)	**0.002**

Calculations were made using binary logistic regression analysis. Odds ratio represents the ratio of the probability of poor physical function for those who were exposed to famine, when compared with those who were not exposed to famine, at 95 % CIs.
*Adjusted for gender, famine severity, number of chronic diseases, place of residence, smoking, alcohol drinking, marital status, educational level and BMI.
(OR: Odds Ratio; CI: Confidence Interval)

Table 3 presents the prevalence of poor physical function of the exposed groups, relative to the non-exposed group stratified by severity of famine across the entire Mainland China. In less severely affected famine areas, compared with the non-exposed group, only the odds ratio of poor physical function for infant-exposed group was statistically significant (*OR* 1.44, 95 % *CI* = 1.09 to 1.91, $p = 0.010$) even after adjusting for gender, number of chronic diseases, place of residence, smoking, alcohol drinking, marital status, educational level and BMI (*OR* 1.41, 95 % *CI* = 1.06 to 1.87, $p = 0.018$). No consistent association in the fetal period-exposed group was found in poor physical function ($p > 0.05$). However, in severely affected famine area, the OR of poor physical function for infant-exposed (*OR* 1.55, 95 % *CI*

= 1.03 to 2.34, *P*=0.037) and infant groups (*OR* 1.45,95 % *CI* = 1.03 to 2.03, *p* = 0.033) were statistically significant, when compared with the non-exposed group, after adjusting for multiple covariates.

Table 3. Prevalence of poor physical function in birth groups in the Great Chinese Famine area#

	Prevalence	**Crude Model**		**Adjusted Model***	
	%	***OR* (95% *CI*)**	***p***	***OR* (95% *CI*)**	***p***
Less severely-affected famine area					
Non-exposed group	91(11.8)	Ref.		Ref.	
Fetal-exposed group	67(13.6)	1.18(0.84 to 1.66)	0.335	1.20(0.85 to 1.69)	0.309
Infant-exposed group	157(16.2)	1.44(1.09 to 1.91)	**0.010**	1.41(1.06 to 1.87)	**0.018**
Severely affected famine area					
Non-exposed group	69(13.0)	Ref.		Ref.	
Fetal-exposed group	48(19.0)	1.58(1.05 to 2.36)	**0.027**	1.55(1.03 to 2.34)	**0.037**
Infant-exposed group	107(18.4)	1.52(1.09 to 2.10)	**0.013**	1.45(1.03 to 2.03)	**0.033**

#Calculations were made using binary logistic regression analysis. Odds ratio represents the ratio of the probability of poor physical function for those who were exposed to famine, when compared with those who were not exposed to famine, at 95 % CIs.
*Adjusted for gender, number of chronic diseases, place of residence, smoking, alcohol drinking, marital status, educational level and BMI.
(OR: Odds Ratio; CI: Confidence Interval)

Stratified analysis by gender and severity of famine is displayed in Table 4 and Figure 2. Among males, when compared with the non-exposed group, exposure at the fetal period (*OR* 2.43, 95 % *CI* = 1.20 to 4.94, *p* = 0.014) significantly increased the prevalence of poor physical function after adjusting for number of chronic diseases, place of residence, smoking, alcohol drinking, marital status, educational level, and BMI in severely affected areas. No consistent associations between fetal and infant-exposed groups were found in

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less seriously affected famine areas ($p > 0.05$). Among females, the adjusted prevalence of poor physical function for two exposed groups suggested no statistically significant differences ($p > 0.05$).

Table 4. Prevalence of poor physical function in birth groups by gender and severity of the Great Chinese Famine area#

	Prevalence	Crude Model		Adjusted Model*	
	n (%)	OR (95% CI)	*p*	OR (95% CI)	*p*
Less severely affected famine area					
Male					
Non-exposed group	26(7.6)	Ref.		Ref.	
Fetal period-exposed group	19(8.4)	1.11(0.60 to 2.06)	0.732	1.12(0.60 to 2.08)	0.733
Infant period-exposed group	53(11.3)	1.55(0.95 to 2.53)	0.082	1.45(0.88 to 2.38)	0.144
Female					
Non-exposed group	65(15.2)	Ref.		Ref.	
Fetal period-exposed group	48(18.2)	1.24(0.82 to 1.87)	0.301	1.21(0.80 to 1.84)	0.366
Infant period-exposed group	104(20.8)	1.47(1.05 to 2.07)	**0.027**	1.37(0.97 to 1.95)	0.076
Severely affected famine area					
Male					
Non-exposed group	20(8.0)	Ref.		Ref.	
Fetal period-exposed group	17(16.3)	2.26(1.13 to 4.51)	**0.021**	2.43(1.20 to 4.94)	**0.014**
Infant period-exposed group	37(13.5)	1.80(1.02 to 3.20)	**0.044**	1.66(0.92 to 3.00)	0.096
Female					
Non-exposed group	49(17.5)	Ref.		Ref.	
Fetal period-exposed group	31(20.9)	1.25(0.76 to 2.06)	0.385	1.24(0.74 to 2.06)	0.416
Infant period-exposed group	70(22.9)	1.40(0.93 to 2.10)	0.107	1.34(0.88 to 2.03)	0.168

#Calculations were made using binary logistic regression analysis. Odds ratio represents the ratio of the probability of poor physical function for those who were exposed to famine, when compared with those who were not exposed to famine, at 95 % CIs.

*Adjusted for number of chronic diseases, place of residence, smoking, alcohol drinking, marital status, educational level and BMI.

(OR: Odds Ratio; CI: Confidence Interval)

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Figure 2 outlines the absolute prevalence of poor physical function. In females the absolute prevalence of poor physical function is higher compared to males. It is observed in both less-severely and severely Famine affected regions. There is no difference at all for females by exposure severity. with subjects exposed at early infanthood showing the highest prevalence of poor physical function, followed by those exposed in-utero.

DISCUSSION

This is the first study to suggest a relation between early-life undernutrition and poor physical function using national data from China. It was observed that early-life exposure to the Great Chinese Famine significantly increased the prevalence of poor physical function in midlife. After stratifying by gender and famine, it was found that only fetal exposure to severe famine resulted in considerably increased prevalence of poor physical function in male adults. However, the absolute prevalence of poor physical function in females was higher compared to males. It was observed in both less-severely and severely Famine affected regions. These results suggested that early-life poor nutritional might be a critical factor for physical function development in their midlife.

The sensitivity analyses with a different definition of the outcome(two answers or more of "have some difficulties but still can do without help", "needs help" and "unable to do") shows the same result that the fetal period-exposed (*OR* 1.34, 95 % *CI* = 0.89 to 1.99, $p = 0.158$), and infant period-exposed (*OR* 1.48, 95 % *CI* = 1.07 to 2.06, $p = 0.019$) groups had higher prevalence of poor physical function after adjustment for gender, severity of famine, number of chronic diseases, place of residence, smoking, alcohol drinking, marital status, educational level and BMI when compared with the non-exposed group. The definition of the outcome in this study is effective and appropriate.

The current study focused on physical function as the primary outcome, and noticed that fetal exposure to the severe Great Chinese Famine significantly increased the prevalence of poor physical function in later life. There are no existing studies on direct assessment of the effect of the Great Chinese Famine exposure in early life on physical function in middle-aged. However, a recent study explained that a good childhood health status increases the probability of better adult physical function by 14 % (95 % CI: 12–17 %)[29].This implies that early-life stages could be critical periods for physical function in midlife[12]. The development of the musculoskeletal system might account for these associations, since protein deficiency

due to famine may affect growth to optimal size. Nutrient factors affect the development of an optimal muscle mass which partly determines late life muscle mass and function[6].

In the present study, it was observed that fetal and infant exposure to the Great Chinese Famine significantly increased the prevalence of high difficulty with using toilet and bathing or showering, while infant exposure significantly increased the prevalence of difficulty with dressing. However, no consistent results were observed for difficulty with eating, getting in or out of bed, and control of urination and defecation. The results revealed that the effects of famine exposure on disability in BADL in late life involved using the toilet, dressing and bathing or showering.

The current study had combined further direct evidence in human beings for the fetal origins hypothesis[30, 31]. The findings in this investigation are consistent with the results of the Dutch study which reported that exposure to prenatal undernutrition among males was associated with poor physical function in their later life[9]. The poor physical function in later life due to fetal stage exposure was more obvious in male than female survivors. This seemed to be contradictory to the reported effect of severity of famine exposure on the sexes, in which the survival of male children was given preference over that of female children due to the tradition of 'preferring boys to girls'[32]. This was inconsistent with chronic lung diseases[25]. One explanation for the sex-specific effects could be the differences in skeletal muscle metabolism: women have high metabolic flexibility in which substrate oxidation is readily adapted by nutrient availability[33]. Another explanation is that when muscle mass is affected, the higher relative loss of muscle mass might be seen in men than in women because adult men have greater total lean mass and a lower fat mass than adult women[34]. These gender gaps are consistent with the reports of the Dutch famine literature. Besides, the same study cohort described the sex-specific effects of prenatal undernutrition[35].

There are some limitations in this study. One major limitation is selection bias which was caused by excess mortality in early life and "preferring boys to girls" attitude common in China. The Great Chinese Famine might have spared the stronger and healthier subjects and gotten rid of the weaker ones. And the loss of girl participants in the exposed group may add to the explanation of the lack of associations between undernutrition and poor physical function in female in the current study. This selection bias may decrease the real effect of famine exposure on physical function[18], which did relatively reduce the trustworthiness of the study. Secondly, the present study lacks objective indicators of birth characteristic that reflect the severity of famine exposure. Such indicators include birth weight and head circumference which were used in other Chinese famine studies[14, 36]. Thirdly, due to the fact

that the Great Chinese Famine lasted for three years (1959–1961), the fetal period-exposed group was separated from the infant-exposed group. Fourthly, there was a potential information bias which may result from the subjective nature of the outcome variable. Besides, the time lag within the data collection process, the investigation and analysis of data, and the arriving of results is another limitation that needs to be recognized. Notwithstanding these limitations, this study used national data from CHARLS 2015 which had broad representation, and suggested that early-life exposure to the Great Chinese Famine significantly increased the prevalence of poor physical function in middle-age life.

CONCLUSION

These results indicate that exposure to the Great Chinese famine significantly increased the prevalence of poor physical function in later life, especially fetal exposure in males who had a distinctly higher prevalence of poor physical function in middle-age life.

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Provenance and peer review Not commissioned; externally peer reviewed.

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Data sharing statement The datasets analyzed in the current study are available online (http://charls.pku.edu.cn/zh-CN/page/data/2015-charls-wave4).

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Figure Legends

Figure 1. Flow chart on the sample selection methods in each step

Figure 2. Differences in risk of poor physical function as determined through stratified analysis by gender and severity of famine

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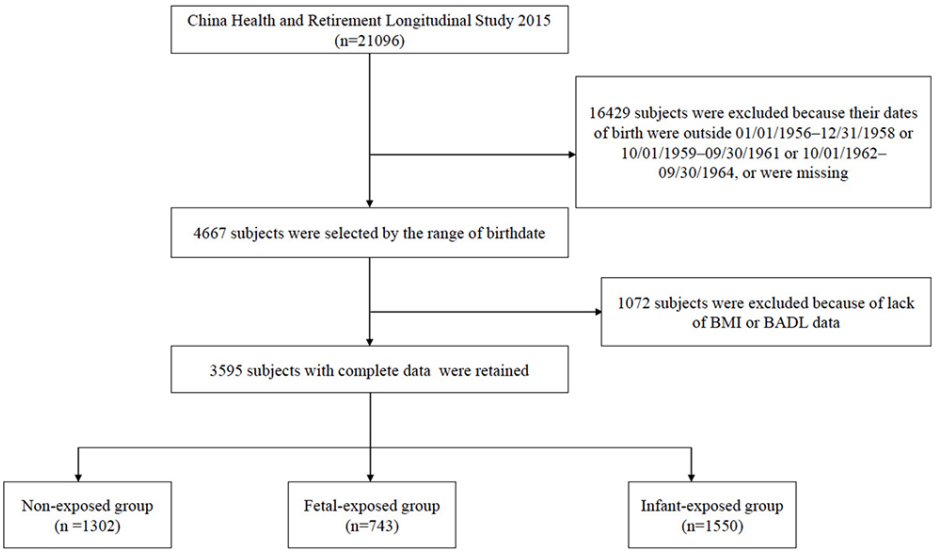

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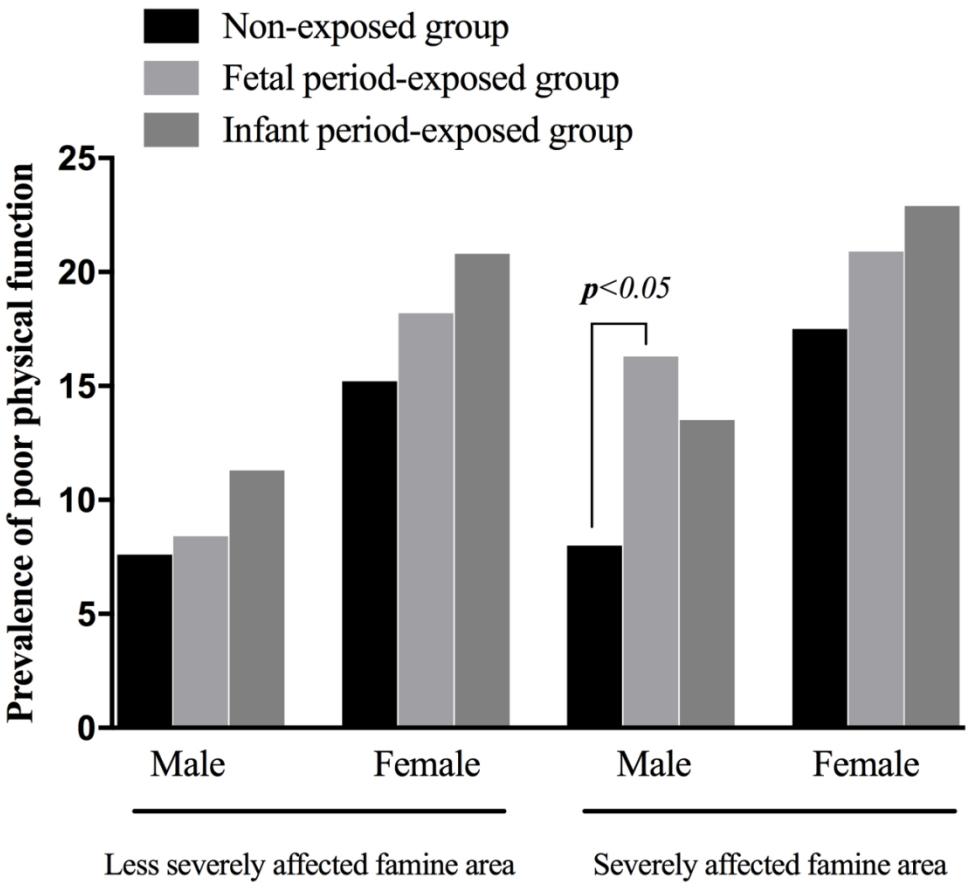

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			**3**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			**3-6**
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
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	*4*
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	5-6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5-6

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		(*e*) Describe any sensitivity analyses	5-6
Results			6-7
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	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	6-7
		Cross-sectional study—Report numbers of outcome events or summary measures	6-7
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	7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-7
Discussion			7-9
Key results	18	Summarise key results with reference to study objectives	7-8
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	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-9
Other information			9-12
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	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
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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