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Early-life famine exposure and rheumatoid arthritis in Chinese adult populations: a retrospective cohort study

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ABSTRACT

Objective This study aimed to explore the association between famine exposure in early life and the odds of rheumatoid arthritis (RA) in adulthood.

Design A population-based retrospective cohort study.

Setting China.

Participants A total of 111 706 participants (1775 with RA) born from 1956 to 1964 were selected from the baseline survey of a large cohort in China.

Primary and secondary outcome measures Four famine exposure groups were generated based on dates of birth, namely prenatal-exposed, infant-exposed, preschool-exposed and non-exposed groups. Logistic regressions were used to explore the association between famine exposure and self-reported RA in adulthood, adjusting for sex, region, monthly income, highest education, alcohol consumption, tobacco use, body mass index (BMI) and metabolic equivalent tasks. Analyses were also performed with stratification for sex (female or male), residing region (urban or rural), famine severity (severe or non-severe) and BMI (≥24 or <24).

Results The study included 1775 (1.59%) RA cases and 109 931 (98.41%) non-RA controls. Among them, 22 413 (20.06%) were prenatal-exposed, 14 899 (13.34%) were infant-exposed and 34 356 (30.76%) were preschool-exposed. Prenatal exposure to famine was not associated with onset of RA in adulthood. Infant-exposed group and preschool-exposed group had significantly elevated odds of getting RA compared with non-exposed group (infant-exposed: OR=1.44, 95% CI 1.24 to 1.67; preschool-exposed: OR=1.38, 95% CI 1.22 to 1.57, p<0.001), and the relationship was stronger among women, urban residents and participants with BMI ≥24. Similar results were additionally observed when an age-balanced control group was used.

Conclusions Exposure to the Great Chinese Famine in early life after birth especially in infancy may be associated with a higher risk of RA in adulthood. Strengthening early-life nutrition could be an implication to prevent future RA.

Strengths and limitations of this study

► This population-based cohort study is the first to explore the association between famine exposure in early life and rheumatoid arthritis in adulthood.
► The large sample was selected with a wide geographical distribution, covering 10 provinces in China.
► The prevalence of rheumatoid arthritis might be misreported using self-reported data.
► Due to its retrospective design, the study lacks individual-level measurements of famine exposure in early life.

INTRODUCTION

Rheumatoid arthritis (RA) is a common chronic systemic inflammatory autoimmune disease causing huge burden in terms of health and financial costs.[1–3] It affects about 1% of the global population and occurs at all ages, mainly prevalent among middle-aged women.[4]

There had been evidence showing that undernutrition during childhood could increase the risk of many chronic diseases in adulthood, including metabolic syndrome (MetS), hypertension, type 2 diabetes and coronary heart disease.[5–7] Inflammatory mediators such as C reactive protein, interleukin 6 and tumour necrosis factor-α are also frequently elevated in patients with these chronic diseases,[8 9] as well as in the sera of patients many years before the clinical onset of RA, suggesting a critical role of the immunopathogenesis of these diseases. Meanwhile, a study showed that early-life malnutrition impacted the development of the immune system.[10] Thus, we had speculation that early-life malnutrition may also be related to the increased risk of RA in adulthood, which had not been studied before.

The Chinese famine of 1959–1961, one of the largest famines in human history with approximately 30 million excess deaths and nearly all provinces in China affected,[11] offers a unique opportunity to test such speculation at the population level. The relationships between early-life malnutrition due to the Chinese famine and later-life diabetes,[12] MetS,[5 13] hypertension,[14] short height[15] and

overweight[16] have been explored. Two previous studies also used this paradigm and demonstrated higher prevalence of arthritis in adulthood among individuals exposed to the Chinese famine during early life.[17 18] However, arthritis was regarded as a single outcome in both studies, while arthritis was actually a mixture of osteoarthritis (40%), RA (17%) and other types of arthritis (43%). Because immune pathways pathogenically drive articular inflammation in RA, but not in osteoarthritis, research as a whole might yield confusing results. Thus, it is necessary to explore RA as a specific outcome.

This study focused on the association between early-life famine exposure and risk of RA in adulthood. We selected participants who were born around the Chinese Great Famine of 1956–1961 from the China Kadoorie Biobank (CKB), a large prospective Chinese cohort,[19] and explored the association between famine exposure and risk of RA in this data set.

PATIENTS AND METHODS
Data source and population
The CKB is a large prospective population-based cohort study on chronic diseases. Data from the baseline survey conducted between 2004 and 2008 were used in the current study.[19] Participants were recruited from five urban regions and five rural regions in ten provinces in China, selected by disease pattern, odds factors, population stability, health register system, and local commitment and capacity.[20] Cluster sampling was applied to recruit participants in each region with units of rural villages or urban residential committees. An interviewer-administered electronic questionnaire survey was used to collect data on demographics, socioeconomic status, lifestyle, medical history and reproductive history. Physical measurements including height and weight, hip and waist circumference, bioimpedance, systolic and diastolic blood pressure (mm Hg), and lung functions were collected at the participants' clinic visit. Finally, data on 515 681 participants were collected, with an overall response rate of about 30% (26%–38% in rural regions and 16%–50% in urban regions). Among 515 681 participants, the study excluded those who withdrew without completion (261, 0.05%), those who attended the survey twice (2208, 0.4%), 1 participant who delivered erroneous data and 320 participants whose age exceeded the study age limitation (between 30 and 79 years old), resulting in 512 891 valid baseline data.[19]

The most common definition of the Chinese famine period from 1 January 1959 to 31 December 1961 was adopted after reviewing previous literature.[11 21 22] Famine exposure of individuals was estimated based on their birth date. This study used nine calendar months as gestation length since the duration of conception was reported shorter than the general 40 weeks during the famine period.[23] Considering the unclear exact start and end of the famine, participants exposed to famine for less than 9 months of the prenatal period, born between

1 January and 30 September in 1959 or 1962, were excluded to ensure the integrity of prenatal exposure. Participants born from 1 January 1956 to 31 December 1957, born from 1 January 1958 to 31 December 1958, born from 1 October 1959 to 31 December 1961, and born from 1 October 1962 to 30 September 1964 were categorised as preschool-exposed group, infant-exposed group, prenatal-exposed group and non-exposed group, respectively. Finally, a total of 111 706 participants whose birth dates matched the four groups were included in this study. Among them, there were two participants with missing values for body weight or height; however, due to the small missing data no analytical adjustments were performed.

Outcomes
History of RA was assessed by the following question: 'Has a doctor ever told you that you had had rheumatoid arthritis? If so, what was the age at first diagnosis?' When answering this question, professional investigators provided participants with identifying information about RA to help them recall accurately.

Covariates
Sociodemographic and lifestyle characteristics were collected, including sex, urban/rural region, residing area, household income, highest level of education, alcohol consumption, tobacco use, body mass index (BMI) and metabolic equivalent of task hours (MET). Household income was categorised as <¥2500 (US$1=¥7.07 in October 2019), 2500–4999, 5000–9999, 10 000–19 999, 20 000–34 999 and ≥35 000. Highest education was categorised into non-formal education or primary school, middle school, and college and above. Tobacco use was classified as 'frequent', 'occasional', 'ex-smoker' and 'non-smoker'. Alcohol consumption was classified as 'weekly', 'reduced intake', 'monthly', 'occasional', 'ex-drinker' and 'non-drinker'. BMI was a variable calculated using the weight and height measured during physical examination and was classified as 'BMI ≥24' and 'BMI <24' based on Chinese overweight standards. MET was measured by the product of the number of hours spent per day participating in each activity during the past year and the MET score (2011 Compendium of Physical Activities) for that activity.[24] Famine severity was categorised by the level of severity in different provinces provided by Peng.[25] Among the 10 provinces of residing areas, Sichuan, Gansu, Henan, Hunan, Shandong and Guangxi were regarded as severe regions, while Heilongjiang, Jiangsu, Hainan and Zhejiang were regarded as non-severe regions.

Statistical analyses
Descriptive analysis was applied to show the distribution of sociodemographic, socioeconomic and lifestyle characteristics of participants in the famine exposure groups. Continuous variables were reported as mean and SD. Categorical variables were presented in numbers and

percentages. Multivariate logistic regressions were used to examine the associations between early-life famine exposure and odds of RA in adulthood. In particular, the strengths of associations were reported using non-exposed group as a reference. To explore the modification effects of sex, residing region, famine severity and BMI on the association between infant famine exposure and RA, analyses were stratified by male/female, rural severe/rural non-severe/urban severe/urban non-severe region and BMI ≥24/BMI <24. Because participants in the exposed groups were older than those in the non-exposed group, the strengths of the associations were reported using both non-exposed and age-balanced groups as a reference, respectively, to minimise the influence of the difference in age. The age-balanced groups were composed of prenatal-exposed and preschool-exposed groups, with the mean age equal to the age of the infant-exposed group (approximately 47 years old). Meanwhile, the age–period–cohort analysis was used as the sensitivity analysis to verify the association excluding the age and period effect; the details of the methods and the results of which are shown in online supplemental file. In subsequent analysis, the differences in sex groups, severity groups and BMI groups were examined by a likelihood ratio test, which compared two models excluding and including the interaction parameters (sex and exposure/severity and exposure/BMI and exposure). For logistic regression models, no covariate was adjusted in model 1. In model 2, region, sex, household income, highest education level, alcohol consumption, tobacco use, BMI and MET were adjusted. OR and 95% CI were reported. The p value threshold was set at 0.05. All statistical analyses were performed using R V.3.6.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

RESULTS

In total, 111 706 individuals born from 1956 to 1964 were analysed in this study, including 1775 (1.59%) RA cases and 109 931 (98.41%) non-RA controls. There were 22 413 (20.06%) people fully exposed to famine in the entire prenatal period, 14 899 (13.34%) participants exposed to famine during the infant period, 34 356 (30.76%) participants exposed to famine during the preschool period and 40 038 (35.84%) participants without famine exposure, among which, respectively, 326 (1.45%), 289 (1.94%), 619 (1.80%) and 541 (1.35%) people reported RA. Participants' average ages (SD) were 45.43 (1.29) years, 47.69 (1.14) years, 49.12 (1.24) years and 42.48 (1.23) years, respectively. Distributions of region, highest education, household income, alcohol consumption and tobacco use were similar across all exposure groups and no significant differences were observed (χ^2 test, p>0.05). Participants in the non-exposed group had the highest

level of average MET (25.83±13.94 hours/day) compared with other groups (analysis of variance, p<0.05). Participants in the infant group had the highest level of average BMI (24.02±3.24) compared with their counterparts (analysis of variance, p<0.05). Detailed demographic, socioeconomic and behavioural characteristics of participants are shown in table 1. The prevalence of RA with age based on all data in the CKB baseline is also shown in online supplemental figure 1 and was consistent with a previous RA study, verifying the validity of our self-reported outcome.[26]

The associations between the different periods of famine exposure and RA in adulthood are presented in table 2. In the two models fitted, the prevalence of RA in adulthood among infant-exposed individuals was significantly higher than the non-exposed individuals (model 1: OR=1.44, 95% CI 1.25 to 1.67; model 2: OR=1.44, 95% CI 1.24 to 1.67; p<0.001). The prevalence of RA in adulthood among preschool-exposed individuals was significantly higher than the non-exposed individuals (model 1: OR=1.34, 95% CI 1.19 to 1.50; model 2: OR=1.38, 95% CI 1.22 to 1.57; p<0.001). However, compared with non-exposed individuals, prenatal-exposed individuals had similar odds of getting RA (model 1: OR=1.08, 95% CI 0.94 to 1.24; model 2: OR=1.06, 95% CI 0.92 to 1.23; p>0.05). The results of the age–period–cohort analysis, provided in online supplemental figure 2, also show an increased relative risk of RA in the 1957–1961 cohort, who were exposed to famine in early life.

As shown in table 3, the strength of the association between infant famine exposure and RA in adulthood diverged by residential region, famine severity, sex and BMI, comparing with non-exposed and age-balanced groups. Stratified by region, urban participants who experienced famine in infancy were more likely to report RA in adulthood compared with the non-exposed and age-balanced groups (non-exposed: OR=1.57, 95% CI 1.28 to 1.93, p<0.001; age-balanced: OR=1.22, 95% CI 1.02 to 1.46, p<0.05). Stratified by famine severity, participants who experienced severe famine in early life had significantly higher odds of RA in adulthood compared with the non-severe group (p value for difference <0.05). Stratified by sex, women who experienced famine in infancy had significantly higher odds of RA in adulthood compared with non-exposed and age-balanced women (non-exposed: OR=1.44, 95% CI 1.20 to 1.72, p<0.001; age-balanced: OR=1.15, 95% CI 1.02 to 1.34, p<0.05). Women who experienced famine in early life had significantly higher odds of RA in adulthood compared with men (p value for difference <0.001). Lastly, when stratified by BMI, infant-exposed participants with BMI ≥24 had a significantly higher likelihood of RA in adulthood compared with their non-exposed and age-balanced counterparts (non-exposed: OR=1.49, 95% CI 1.20 to 1.83, p<0.001; age-balanced: OR=1.28, 95% CI 1.06 to 1.53, p<0.01). Infant-exposed participants with BMI ≥24 had significantly higher odds of RA in adulthood compared

Table 1 Characteristics of the study participants by rheumatoid arthritis (N=111 706)

	Non-exposed (n=40 038)	Prenatal-exposed (n=22 413)	Infant-exposed (n=14 899)	Preschool-exposed (n=34 356)
Age, years, mean±SD	42.48±1.23	45.43±1.29	47.69±1.14	49.12±1.24
RA, n (%)	541 (1.35)	326 (1.45)	289 (1.94)	619 (1.80)
Diagnosis year, mean±SD	31.78±8.92	32.95±9.92	34.74±10.69	34.85±11.01
Region, n (%)				
Urban	22 589 (56.42)	11 307 (50.45)	7076 (47.49)	15 367 (44.73)
Non-severe	13 556 (60.01)	6833 (60.43)	4111 (58.10)	9073 (59.04)
Severe	9033 (39.99)	4474 (39.57)	2965 (41.90)	6294 (40.96)
Rural	17 449 (43.58)	11 106 (49.55)	7823 (52.51)	18 989 (55.27)
Non-severe	3266 (18.72)	2699 (24.30)	1559 (19.93)	4283 (22.56)
Severe	14 183 (81.28)	8407 (75.70)	6264 (80.07)	14 706 (77.44)
Sex, n (%)				
Male	15 182 (37.92)	8723 (38.92)	6021 (40.41)	13 597 (39.58)
Female	24 856 (62.08)	13 690 (61.08)	8878 (59.59)	20 759 (60.42)
Highest education, n (%)				
No formal school	2058 (5.14)	3658 (16.32)	2127 (14.28)	6507 (18.94)
Primary school	7023 (17.54)	5809 (25.92)	3696 (24.81)	9413 (27.40)
Middle school	17 625 (44.02)	6672 (29.77)	4540 (30.47)	9945 (28.95)
High school	10 450 (26.10)	5296 (23.63)	3891 (26.12)	6980 (20.32)
Technical school/college	1894 (4.73)	717 (3.20)	475 (3.19)	1099 (3.20)
University	989 (2.47)	258 (1.15)	170 (1.14)	412 (1.20)
Household income (¥), n (%)				
<2500	320 (0.80)	193 (0.86)	170 (1.14)	392 (1.14)
2500–4999	1634 (4.08)	840 (3.75)	691 (4.64)	1636 (4.76)
5000–9999	7059 (17.63)	3783 (16.88)	2599 (17.44)	5959 (17.34)
10 000–19 999	12 196 (30.46)	7076 (31.57)	4664 (31.30)	10 245 (29.82)
20 000–34 999	11 351 (28.35)	6406 (28.58)	4232 (28.40)	9395 (27.35)
≥35 000	7479 (18.68)	4115 (18.36)	2543 (17.07)	6729 (19.59)
Alcohol consumption, n (%)				
Non-drinker	16 528 (41.28)	8983 (40.08)	6118 (41.06)	14 802 (43.08)
Ex-regular	276 (0.69)	197 (0.88)	174 (1.17)	414 (1.21)
Occasional drinker	14 410 (35.99)	7968 (35.55)	5162 (34.65)	11 522 (33.54)
Monthly	1814 (4.53)	1060 (4.73)	558 (3.75)	1252 (3.64)
Reduced intake	657 (1.64)	408 (1.82)	302 (2.03)	693 (2.02)
Weekly	6354 (15.87)	3797 (16.94)	2585 (17.35)	5673 (16.51)
Tobacco use, n (%)				
Non-smoker	26 141 (65.29)	14 248 (63.57)	9183 (61.64)	21 432 (62.38)
Occasional smoker	2338 (5.84)	1213 (5.41)	789 (5.30)	1724 (5.02)
Ex-smoker	1205 (3.01)	843 (3.76)	646 (4.34)	1502 (4.37)
Frequent smoker	10 358 (25.87)	6110 (27.26)	4281 (28.73)	9698 (28.23)
MET, hours/day	25.83±13.94	24.93±14.03	23.56±14.15	23.86±14.00
BMI, mean±SD	23.81±3.23	23.96±3.20	24.02±3.24	23.95±3.25
BMI <24, n (%)	22 063 (55.11)	11 826 (52.76)	7744 (51.98)	18 106 (52.70)
BMI ≥24, n (%)	17 975 (44.89)	10 587 (47.24)	7155 (48.02)	16 250 (47.30)

BMI, body mass index; MET, metabolic equivalent of task hours; RA, rheumatoid arthritis.

Table 2 OR for getting rheumatoid arthritis in different famine exposure groups

	Non-exposed group	Prenatal-exposed group	Infant-exposed group	Preschool-exposed group
Model 1	1	1.08 (0.94 to 1.24)	1.44 (1.25 to 1.67)***	1.34 (1.19 to 1.50)***
Model 2	1	1.06 (0.92 to 1.23)	1.44 (1.24 to 1.67)***	1.38 (1.22 to 1.57)***

Model 1 did not adjust for any covariate. Model 2 adjusted for sex, region, monthly income, highest education level, alcohol consumption, tobacco use, body mass index and metabolic equivalent of task hours.
****P<0.001.

with infant-exposed participants with BMI <24 (p value for difference <0.001).

DISCUSSION

The results verified our speculation that early-life famine exposure was associated with later-life RA. We further found this association existed for those exposed to famine during the period after birth, especially stronger in infancy, rather than the prenatal period. Moreover, when stratified by sex, residing region, famine severity and BMI, the association was found among urban residents and women and was stronger among participants with BMI ≥24 and in severe famine region.

Our result was consistent with the previous two studies on famine and arthritis. Wang et al[18] and Xu et al[17] reported an OR of 1.50 (1.21–1.85) and 1.656 (1.095–2.505), respectively, among individuals exposed to famine during infancy. However, our findings further indicated infant exposure to famine could be a vital cause specifically of RA, as both studies used arthritis as their outcomes. The findings were further verified by the stronger association between severe famine exposure and RA compared with non-severe famine exposure. RA is associated with most components of the MetS,[27] for instance, body weight changes. The finding that the odds ratio was higher in the group with BMI ≥24 suggested a potentially link between

Table 3 OR for getting rheumatoid arthritis among the infant-exposed group comparing with two reference groups, stratified by region, sex and BMI

Stratified factors	Infant-exposed group (reference: non-exposed group)	Infant-exposed group (reference: age-balanced group†)
	1.44 (1.28 to 1.63)***	1.17 (1.03 to 1.336)*
Region		
Rural	1.31 (1.05 to 1.63)*	1.12 (0.92 to 1.37)
Non-severe	1.20 (0.90 to 1.60)	1.10 (0.84 to 1.42)
Severe	1.40 (0.90 to 2.16)	0.99 (0.67 to 1.44)
P value for difference <0.05		<0.05
Urban	1.57 (1.28 to 1.93)***	1.22 (1.02 to 1.46)*
Non-severe	1.46 (1.09 to 1.94)**	1.19 (0.92 to 1.52)
Severe	1.80 (1.24 to 2.60)**	1.27 (0.92 to 1.74)
P value for difference <0.001		<0.001
Sex		
Male	1.24 (0.98 to 1.57)	1.24 (0.95 to 1.59)
Female	1.44 (1.20 to 1.72)***	1.15 (1.02 to 1.34)*
P value for difference <0.001		<0.001
BMI		
BMI <24	1.40 (1.13 to 1.73)**	1.07 (0.88 to 1.30)
BMI ≥24	1.49 (1.20 to 1.83)***	1.28 (1.06 to 1.53)**
P value for difference <0.001		<0.001

All analyses were adjusted for monthly income, highest education, alcohol consumption, tobacco use, BMI and metabolic equivalent of task hours.
*P<0.05, **P<0.01, ***P<0.001.
†Combined prenatal-exposed and preschool-exposed groups.
BMI, body mass index.

famine and MetS. A study showed that the odds of MetS are significantly higher in infant-exposed individuals rather than fetal-exposed or preschool-exposed groups compared with the non-exposed group,[28] also implying the common underlying pathogenesis of RA and MetS.

The immunopathogenesis of RA could explain the relationship found between famine and RA. RA-specific immune reactions might originate in extra-articular locations, particularly in the mucosal sites such as the intestinal mucosa. Severe acute malnutrition leads to alterations in the gut microbiota.[29] Alterations in compositional diversity and abundance levels of the microbiota, that is, dysbiosis, lead to mucosal disequilibrium in several types of autoimmune and inflammatory diseases, like RA. Through imbalance in T cell subpopulations, this local autoimmunity may progress to systemic disease in some cases.[30] Dysbiosis in mucosal sites may also break in self-tolerance to citrullinated autoantigens,[31] and led to the production of anticitrullinated protein antibody (APCA). APCA, a type of RA-associated antibodies that exist in the blood long before joint inflammation,[32] might be important in the transition from preclinical phase to a clinical expression of RA.

In addition, intestinal microbiota were thought to be the most important source of maturational stimuli for the development of immune system. Gut microbial ecology and function were almost sterile in the fetus, dynamic in infancy, but stabilised in childhood.[10] Especially in the first year, the gut microbiota dramatically change through interactions with the developing immune system, impacting greatly on the development of the host immune system, with the potential to be the main determinant of lifelong health.[10] This may explain why the association between famine exposure and RA was higher in the infant-exposed group and insignificant in the prenatal-exposed group.

The relationship between famine exposure and RA, which was stronger in urban regions than in rural regions, could be explained by the following reasons. First, there was limited availability in healthcare services in rural regions and therefore RA rates might be under-reported due to detection bias. In addition, configurations of the gut microbiome varied across urban and rural populations, as environmental exposures during urbanisation, such as westernisation of diet, increasing antibiotic use and pollution, might affect the gut microbiota.[33] Urban residents, thus, showed a decrease in the diversity and richness of the gut microbiota,[34] which might have a role in the pathogenesis of RA. Furthermore, early-life malnutrition and later-life nutritionally rich environment were related to a higher risk of MetS, which has an established correlation with RA.[35 36] Specifically, people in urban regions consume more meat, sugar and edible oil and fewer crops and vegetables than their rural counterparts,[37] resulting in a higher risk for overload nutrition. Metabolic-triggered inflammation caused by nutrient overload and metabolic surplus consists of components (such as proinflammatory cytokines, adipokines and

vitamin D deficiency) that may contribute to the onset of RA.[38] Moreover, in the past 30 years, there have been waves of huge one-way migration from rural to urban regions. Many people exposed to famine in early life in rural regions migrated to cities, where they experienced overload nutrition, which might also explain the higher odds of RA in urban regions.

Women experiencing famine in early life had higher odds of RA. Among women, a relationship was also found between odds of RA and other famine-related diseases such as obesity, hypertension and cardiovascular disease.[39 40] Women exposed to famine in early life were more likely to have MetS, while similar prevalence was found between men with and without early-life famine experiences.[13 41] Hormones may play an important role in the mechanism because starvation leads to an increase in the secretion of androgen.[42] Brand et al[43] showed that men at the highest tertile of total testosterone had lower odds of incident MetS, while women at the highest tertile of total testosterone had increased odds of incident MetS. Janssen et al[44] and Soriguer et al[45] also noted more androgenic environment was associated with incident MetS in women. Furthermore, sex differences in the gut microbiota composition exist.[46] An interaction exists between the gut microbiota and sex hormones. Whereas the level of 17β-oestradiol was not different between germ-free (GF) and specific pathogen-free (SPF) mice, the level of testosterone was higher in the GF female mice than in the SPF female mice and lower in the GF male mice than in the SPF male mice.[47] Moreover, sex discrimination, where boys are considered to be of greater importance in traditional Chinese culture, may also contribute to the more severe food shortage among girls.[41] Besides, the male mortality was higher than female mortaliy during the Great Famine, leading to a potential survival bias of male participants. Thus, male participants may have better outcomes during adulthood.[41 48]

Our results are in good agreement with previous studies on early predictors of RA. Previous studies showed that breast feeding, a symbol of adequate nutrition in early life, was associated with reduced risk of RA[49]; obesity, MetS and type 2 diabetes, proven to be related to early malnutrition,[5 12 13 50] were risk factors for the development of RA in adulthood.[51 52] Our research provided direct evidence that RA was associated with early malnutrition. Besides, it also indicated that changes in these indicators and diseases may follow the same mechanism chain, which was likely to be an immune response chain, and required further studies.

Strengths and limitations

To our knowledge, this study was the first to explore the association between famine exposure in early life and RA in adulthood. Previous studies examined the association between early-life famine exposure and adult arthritis in general[17 18] and neglected differences in the pathogenesis behind the subtypes of arthritis. Second, the study population had high representativeness of the original

large population, with a wide geographical distribution covering 10 provinces . Third, the interaction between sex and region had been fully considered. Admittedly, some potential limitations of the present study exist. First, RA data were self-reported. Although there were professional investigators who provided information on RA to guide participants, data on RA may be confused with other arthritis. However, the prevalence rate and the average ages of onset of RA in this study were consistent with the characteristics of RA, which indicates the validity of the survey to some degree. Second, the study lacks measurements of famine exposure at the individual level. Individual famine exposure in early life cannot be collected using a self-reported survey questionnaire. Nonetheless, since the Great Chinese Famine was widespread in all provinces in 1959–1961, we assumed that everyone born during this period was affected. Third, current addresses rather than addresses during the famine period were collected. Since the migration rate did not exceed 2% before 1990 and did not exceed 10% after 1990 nationwide, and the migrants were mainly young people with the mean age in the mid-20s, which did not coincide with the age groups of our participants, misclassification bias could be avoided to a large degree.[53]

CONCLUSION

In conclusion, infant famine exposure was associated with higher odds of RA in the adult life, and this effect appeared significant among urban residents and women and stronger in participants with BMI ≥24. The current study showed that malnutrition during infancy may be a risk factor for the aetiology of RA in adult life, and thus infant nutrition should be given more attention to prevent RA in later life. Further studies with precise biological indicators and early predictors of RA should be conducted to confirm the relationship. Future population studies and experimental studies are needed to help establish the underlying biological and physiological mechanisms for the associations between early-life malnutrition and immune diseases such as RA in the present study.

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