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RESEARCH

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Sex-specific associations of prenatal Chinese famine exposure with cataract risk at age sixty: a cross-sectional study

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Abstract

Background Age-related cataract (ARC) is among the most common blinding eye disorders among the elderly. Prenatal nutrition may cause irreversible damage to the development of the ocular crystalline lens. Nevertheless, the potential association between prenatal malnutrition and age-related cataract has not been thoroughly examined. We investigated the prevalence of cataract at the age of 60 after prenatal exposure to Chinese famine (1959–1961) and particularly evaluated whether there was a disparity in this effect between men and women.

Methods We utilized the health examination medical record system of a large-scale comprehensive hospital to screen individuals born in Chongqing, China and undergoing eye health examinations. Participants were categorized based on their year of birth into the famine-exposed group (1960) and the non-exposed group (1963), with their medical records at age 60 extracted from the database. Univariate and multivariate logistic regression analyses were conducted to investigate the association between famine exposure and the risk of developing ARC by age 60.

Results The prevalence of ARC was significantly higher in the famine-exposed group (60.26%) compared to the non-exposed group (47.90%) ($P < 0.001$). After adjusting for diabetes history, body mass index (BMI), fasting blood glucose (FBG) level, and high-density lipoprotein (HDL) level using multivariate logistic regression analysis, the risk of ARC remained significantly higher in the famine-exposed group (OR:1.63; 95%CI:1.31–2.03). Subgroup analysis by sex indicated that women exposed to famine (OR: 1.77; 95% CI: 1.25–2.52) exhibited a higher risk of ARC compared to men (OR: 1.53; 95% CI: 1.16–2.03).

Conclusions Prenatal exposure to famine might increase the risk of ARC among Chinese adults at age 60, and women exhibit a higher susceptibility than men.

Keywords Age-related cataract, Famine, Prenatal-malnutrition, Sex difference

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Background

Age-related cataract (ARC), characterized by lens opacification, is a leading cause of global vision impairment [1], affecting approximately 95 million individuals [2]. It is projected that by 2020, there will be 36 million blind individuals worldwide, with over 13.5 million cases attributed to ARC [3]. Aging plays a pivotal role in the mechanisms underlying ARC. With declining birth rates and increasing life expectancy in China [4], the aging population has emerged as a significant public health concern requiring immediate attention. Projections indicate that by 2025, over 300 million individuals in China will be aged 60 or older [5]. Therefore, given the association between ARCs and aging, this issue warrants substantial focus within the country. While surgical intervention offers hope for those affected by cataracts, its application is often limited due to postoperative complications, uncertain visual outcomes, and considerable socio-economic burdens [6]. Recent research suggests that although aging remains the primary factor contributing to ARCs' occurrence, specific nutritional deficiencies may also elevate the incidence rate of cataracts. Nutritional interventions during adulthood have demonstrated potential in mitigating ARC risk [7, 8]. However, there exists a notable paucity of studies examining the relationship between early-life nutritional status and the onset of ARCs. Furthermore, such research could enhance our understanding of the nutritional needs of pregnant women—a particularly vulnerable group. In light of aging's irreversibility, nutritional intervention may emerge as a critical strategy for slowing down ARC progression.

Malnutrition during pregnancy not only increases the abortion rate but also affects the fetus's lifelong health and disease status. The theory of "fetal programming" suggests that the fetus adapts its physiological function and metabolic pattern to adverse environments, leading to permanent changes in body structure and function [9, 10]. The " Development origins of health and disease" (DOHaD) theory asserts that individuals react to the maternal environment from gametogenesis to adulthood, influencing disease susceptibility through epigenetic changes [11, 12]. Uterine malnutrition has been linked to increased risks of obesity [13], type 2 diabetes [14, 15], cardiovascular disease [16], metabolic syndrome [17], depressive symptoms [18], cognitive performance [19], and other diseases in adulthood. However, whether uterine famine affects the risk of ARC in adulthood remains unexplored. As the embryonic stage significantly influences crystal formation, both genetic factors and maternal developmental conditions are acknowledged to impact crystal development [20, 21]. Therefore, we hypothesize that inadequate nutrition during pregnancy may contribute to future generations' ARCs occurrence.

It is important to note that experimental research involving human subjects exposed to prenatal malnutrition is both unethical and impractical. The population affected by the three-year famine in China offers a valuable natural experiment to observe the consequences of maternal malnutrition on offspring health. The 1959–1961 famine caused by climate change in China was unprecedented in human history, lasting longer than the Dutch famine, and resulting in the unfortunate demise of over 30 million individuals [22]. Chongqing, severely affected by this catastrophe, has been previously studied, revealing various health issues among those exposed to prenatal famine during this time [23–28]. Therefore, this study focuses on Chongqing as a preliminary investigation site to explore any potential correlation between prenatal famine exposure and ARC occurrence in offspring at age 60. Furthermore, considering the importance of a sexual perspective in public health strategies, we also investigated whether prenatal famine exposure led to sexual differences in ARC incidence.

Methods and materials

Definition of famine and study population

The Chinese famine occurred from 1959 to 1961. To minimize variations in famine exposure considering the varying degrees during these years and potential food supplementation at different stages, individuals born in 1959 and 1961 were excluded. Therefore, individuals born in 1960 were selected as the famine-exposed group. A one-year transition period was implemented to avoid misclassification; hence, individuals born in 1962 were excluded, while those born in 1963 formed the non-exposed group. we compared the incidence rate of ARC between the famine-exposed group and the non-exposed group at the age of 60. We conducted a retrospective extraction of the health examination data of the famine-exposed group (born from January 1, 1960 to December 31, 1960) during the period from January 1, 2020 to December 31, 2020, as well as that of the non-exposed group (born from January 1, 1963 to December 31, 1963) during the period from January 1, 2023 to December 31, 2023.Furthermore, this research excluded the health examination data of non-60-year-old individuals and eliminated the participants who were not born in Chongqing according to the Chinese identity ID numbers. All the data were sourced from the Health Management Center of the Second Affiliated Hospital of Chongqing Medical University. This retrospective study was authorized and approved by the Medical Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University.

Definition of age-related cataract (ARC)

The Lens Opacities Cataract Classification System III (LOCS III) guideline [29] was adopted for ARC assessment. A professional ophthalmologist used a slit lamp to examine the anterior segment of the eye, including the eyelid, cornea, conjunctiva, iris, lens, anterior chamber, and pupils. Reverse lighting of the slit lamp evaluated and classified cataracts, with an indirect ophthalmoscope used for fundus examination, including the optic disc, macular area, retinal blood vessels, etc. ARCs included cortical, nuclear, posterior subcapsular, or mixed types. If both eyes had ARCs, one eye was randomly selected [30]. Subjects were excluded if they had congenital, metabolic, traumatic, and complicated cataracts, previous ophthalmic surgery, or active ocular inflammation.

Measurements and variables

All subjects underwent venous blood collection at least 12 h after fasting from 8 to 10 am. Blood biochemical analyses, including FBG (fasting blood glucose) levels, SBP (systolic blood pressure), DBP (diastolic blood pressure), TG (triglycerides), TC (total cholesterol), HDL (high-density lipoprotein), and LDL (low-density lipoprotein), were conducted using an automatic analyzer (AU5800, Beckman Coulter Ltd., Tokyo, Japan). Physical examinations included height, weight, and blood pressure measurements. Height and weight were measured using the Omron Physical Examination Scale (HNH-318, Omron Ltd, Shenzhen, China). Participants were measured after removing their shoes and hats. Body mass index (BMI) was calculated as the ratio of body weight (kg) to the square of body height (m). Blood pressure was determined by well-trained nurses or physicians utilizing standard mercury sphygmomanometers. Participants rested for at least 10 min in a seated position before measurements. Hypertension was diagnosed based on the following criteria [31]: (1) SBP $\geq$140 mmHg or DBP $\geq$90 mmHg; (2) self-reported previous diagnosis of hypertension by a physician; and (3) the use of known antihypertensive treatments. Diabetes diagnosis was established if participants met any of the following criteria [32]: (1) fasting blood glucose level $\geq$7.0 mmol/L; (2) self-reported diagnosis of diabetes by a physician; and (3) the use of known antidiabetic treatment.

Statistical analysis

The data underwent cross-verification by two individuals and were processed using Excel 2010. Continuous variables are reported as the mean and standard deviation ($\pm$SD), while categorical variables are presented as proportions (%). Independent t-tests were used for continuous variables exhibiting a normal distribution, and chi-square tests were used for categorical variables.

To explore factors associated with ARCs, parameters with $p<0.1$ in univariate logistic regression analysis were incorporated into multivariate unconditional logistic regression analysis. The crude odds ratio (OR) was calculated using Model 1, and Model 2 adjusted for diabetes history to calculate the OR. Additionally, Model 3 factored in BMI, FBG, and HDL to establish the adjusted OR and corresponding 95% confidence interval (CI) in assessing the association between famine exposure and cataract prevalence. Independent dummy variables were generated to decompose the analysis based on sex-specific famine exposure and evaluate its distinct impact on ARC risk. All analyses were conducted using SPSS 22.0 software at a significance level of $p<0.05$.

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Results

Characteristics of the study population

In the medical record database of the Health Management Center at the Second Affiliated Hospital of Chongqing Medical University, targeted screening was conducted in accordance with predefined criteria consistent with the definition of the "study population" outlined above. Following this screening process, a total of 23,283 participants were included. Among them, Among them, the number of individuals who were born in Chongqing City, received eye examinations and were exactly 60 years old at the time of the examination was 7,474. Due to incomplete records on education level, occupational exposure to outdoor environments, smoking and alcohol consumption habits, physical activity levels, as well as a history of hypertension and diabetes, a total of 2,992 participants were excluded from the analysis. Additionally, due to insufficient measurements for BMI, FBG, SBP, DBP, TG, TC, HDL, and LDL levels in some individuals' datasets; a further exclusion of 1,033 participants was necessary. Moreover, those diagnosed with non-ARCs cataract type or other eye diseases resulted in the exclusion of an additional group comprising 1722 participants. Consequently, a final sample size of 1727 participants was included in the study population, with 468 participants belonging to the prenatal famine-exposed group and 1259 participants to the non-exposure group(Fig. 1).

As shown in Table 1, a significant difference was observed between the prenatal famine-exposed group and the non-exposed group regarding their history of diabetes ($p=0.050$). However, no statistically significant differences were found among variables such as outdoor workers, smoking, alcohol consumption, exercise habits, and a history of hypertension.

Measurement value of the study population

Table 2 presents the prevalence of cataracts in the prenatal famine-exposed group and the non-exposed group,

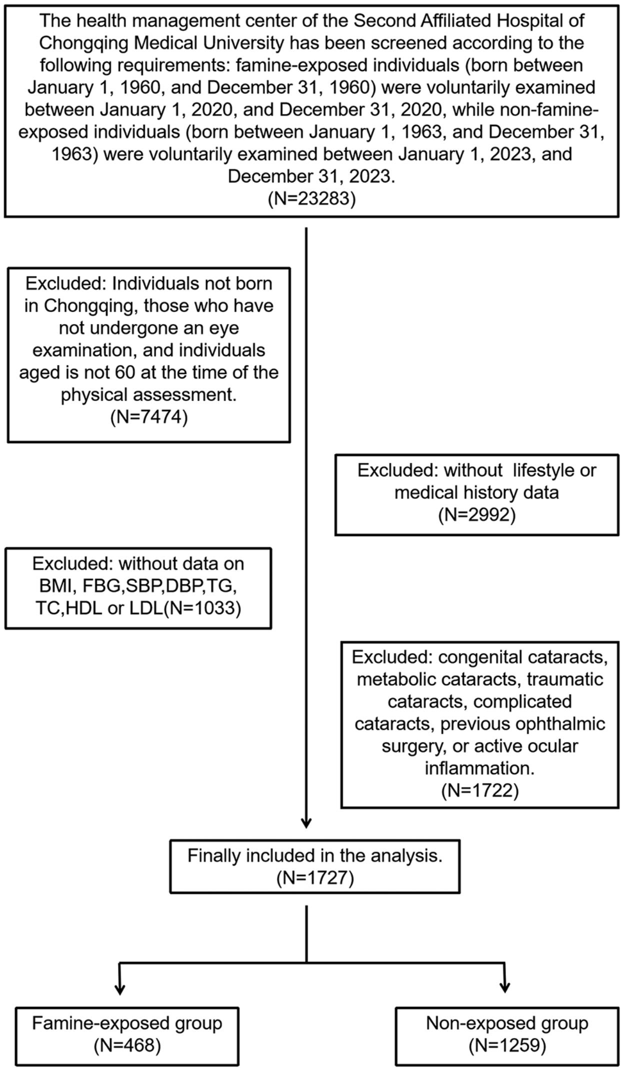

Fig. 1 The flow chart of the participants in the study

Table 1 Basic characteristics of the study participants according to the famine exposure

	famine-exposed	Non-exposed	P^a
Number	468	1259	
Age	60.54 ± 0.31	60.57 ± 0.38	0.506
Sex, n(%)			
Women	193(41.24)	486(38.6)	0.319
Men	275(58.76)	773(61.4)	
Residence			
Urban	256(54.7)	667(53.0)	0.524
Rural	212(45.3)	592(47.0)	
Educational status			
High school and below	377(80.6)	983(78.1)	0.263
College and above	91(19.4)	276(21.9)	
Outdoor workers			
No	349(74.6)	911(72.4)	0.357
Yes	119(25.4)	348(27.6)	
Smoking			
No	265(56.6)	736(58.5)	0.492
Yes	203(43.4)	523(41.5)	
Alcohol drinking			
No	227(48.5)	649(51.5)	0.261
Yes	241(51.5)	610(48.5)	
Exercises habits			
No exercise	239(51.1)	689(54.7)	0.392
Less than regular exercise	117(25.0)	287(22.8)	
Regular exercise	112(23.9)	283(22.5)	
Hypertension, n(%)			
No	318(67.95)	880(69.90)	0.435
Yes	150(32.05)	379(30.10)	
Diabetes, n(%)			
No	384(82.05)	1081(85.86)	0.050
Yes	84(17.95)	178(14.14)	

[a] Pearson's chi-square test

Table 2 The measurement value of the study participants according to famine exposure

	Famine-exposed	Non-exposed	*P*-value
ARCs, n(%)			
No	186(39.74)	656(52.10)	< 0.001
Yes	282(60.26)	603(47.90)	
BMI(kg/m^2)	24.04 ± 3.38	24.46 ± 3.98	0.010
FBG(mmol/L)	5.32 ± 1.16	5.24 ± 0.98	0.012
SBP(mmHg)	126.00 ± 23.00	125.00 ± 24.00	0.245
DBP(mmHg)	77.00 ± 14.00	77.00 ± 16.00	0.319
TG(mmol/L)	1.50 ± 1.21	1.56 ± 1.19	0.470
TC(mmol/L)	5.18 ± 1.23	5.14 ± 1.23	0.548
HDL(mmol/L)	1.42 ± 0.39	1.36 ± 0.38	0.013
LDL(mmol/L)	2.61 ± 0.94	2.64 ± 0.97	0.506

ARCs: Age-related cataracts; BMI: Body mass index; FBG: Fasting blood glucose; SBP: systolic; blood pressure; DBP: diastolic blood pressure; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; P-value: independent t-test for continuous variables or χ2-test for categorical variables

with rates of 282 (60.26%) and 603 (47.90%), respectively. These findings highlight a significantly higher prevalence of cataracts in the prenatal famine-exposure group compared to the non-exposure group ($P<0.001$). Significant differences were observed in BMI, FBG, and HDL between the two groups ($p<0.050$). Specifically, individuals in the prenatal famine exposure group exhibited lower BMI values (24.04±3.38) than those in the non-exposure group (24.46±3.98), while FPG and HDL levels were higher among individuals exposed to prenatal famine (5.32±1.16, 1.42±0.39) compared to their non-exposed counterparts (5.24±0.98、1.36±0.38).

Association of famine exposure and ARCs

In the multivariate logistic regression analysis (Table 3), Model 1 revealed that prenatal famine exposure was significantly associated with an increased risk of ARCs (OR: 1.65; 95%CI: 1.33–2.05), even without adjusting for any confounding factors. Notably, women had a higher risk of ARCs (OR: 1.72; 95%CI: 1.22–2.44) compared to men

Table 3 Association between famine exposure and age-related cataract by multivariate logistic regression analysis

Characteristic	famine-exposed		Women		Men	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Model 1	1.65(1.33,2.05)	< 0.001	1.72(1.22,2.44)	0.002	1.61(1.22,2.12)	0.001
Model 2	1.62(1.31,2.02)	< 0.001	1.74(1.23,2.46)	0.002	1.56(1.18,2.06)	0.002
Model 3	1.63(1.31,2.03)	< 0.001	1.77(1.25,2.52)	0.001	1.53(1.16,2.03)	0.003

Adjusted covariates: Model 1: Crude model; Model 2: Diabetes history; Model 3; Model 2 plus BMI, FBG, HDL

(OR: 1.61; 95%CI: 1.22–2.12). After adjusting for diabetes history, the risk of ARCs in both the prenatal famine-exposure group (OR: 1.62; 95%CI:1.31–2.02) and men subgroup (OR: 1.56; 95%CI:1.18–2.06) decreased, while it increased in women (OR :1.74; 95%CI:1.23–2.46). Furthermore, after further adjustment for diabetes history, BMI, FBG, and HDL levels, the association between prenatal famine exposure and ARCs persisted and remained statistically significant (OR: 1.63; 95%Cl:1.31–2.03). Notably, women (OR: 1.77; 95%Cl:1.25–2.52) exposed to prenatal famine exhibited a higher risk of ARCs than men (OR:1.53;95%Cl:1.16–2.03).

Discussion

Our investigation demonstrated a significant association between prenatal famine exposure and an increased risk of ARC at age 60, with a notable sex-specific trend wherein women exhibited a higher susceptibility compared to men.

Prenatal exposure to famine has been linked to elevated susceptibility to various adult-onset diseases, most of which are age-related conditions [13–17]. This suggests that prenatal famine exposure may induce changes in fundamental biological processes, including cellular aging, metabolism, and inflammation, ultimately accelerating the aging process. ARCs represent one manifestation of aging in the ocular system. The development of the eye initiates during the early stages of pregnancy, marked by the emergence of morphological features in the embryonic lens approximately 28 days after conception. Subsequently, lens development continues throughout gestation. To maintain lens transparency, lens fibroblasts lack nuclei, mitochondria, and endoplasmic reticulum. Consequently, these fibroblasts cannot synthesize new proteins or convert existing ones. The lens protein stored during embryogenesis requires a continuous supply throughout an individual's lifetime. Fetal exposure to famine may induce alterations in lens development-related proteins, potentially impacting postnatal and lifelong lens function. BonavollontàO et al. [33] observed lens damage and cataract formation in rats exposed to fetal malnutrition. Jayaratne SK et al. [34] demonstrated that maternal malnutrition induces oxidative stress in the lens of female mice, a critical mechanism in cataract development. However, this study did not observe significant cataract formation, possibly due to the timing of the examination during childhood rather than adulthood. Kumar D et al. [35] found that fetal malnutrition triggers childhood cataracts, suggesting that maternal malnutrition depletes non-renewable protective substances like glutathione in the lens, leading to early-onset cataracts in childhood. Combining these findings, we hypothesize that prenatal famine exposure may deplete the lens of protective substances, such as glutathione, accelerating oxidative stress and lens aging, ultimately causing the premature formation of ARCs.

Previous studies have indicated a more pronounced impact of prenatal famine exposure on women's health compared to men [24, 26, 27]. These observed sex differences suggest a higher likelihood of ARC in women who experienced fetal famine exposure, aligning with our research findings. The increased prevalence among women may be attributed to the following factors: (1) Women experience a rapid decline in estrogen levels after menopause, losing the protective effects of estrogen, as demonstrated by numerous studies safeguarding against ARCs [36, 37].Consequently, women exposed to famine during gestation exhibit a higher prevalence of ARCs compared to men; (2) the son preference prevalent during China's famine period resulted in families allocating more food and resources to men rather than women. As a consequence, women were more vulnerable to the effects of famine exposure and faced an increased risk of developing ARCs later in life. These sex differences may provide insights into why women are affected by famines differently than men; however, further investigation is warranted.

Despite the advancements in cataract surgery, cataracts remain the primary cause of vision impairment in low- and middle-income countries, accounting for 50% of cases [38]. Statistical data reveals that over 90% of disability-adjusted life years lost due to cataract-induced blindness are concentrated in developing nations [39]. Previous perspectives have linked the higher prevalence of cataracts in these countries to factors such as limited financial resources [39], inadequate education [40], and restricted access to surgical interventions [41, 42]. However, these perspectives have overlooked the significant public health issue of malnutrition, particularly among women. This study provides preliminary evidence suggesting that prenatal malnutrition may contribute to an increased incidence of ARCs at age 60. We propose that prenatal malnutrition could potentially be a contributing factor to the elevated prevalence of cataracts in developing nations, warranting further investigation. These investigation findings accentuate that public health policymakers urgently need to give priority to maternal nutrition in these countries, given the profound and long-lasting effects of such nutrition, even after 60 years.

In the past few decades, an increasing number of studies have confirmed the long-term health impacts of prenatal exposure to the Great Chinese Famine (1959–1961). However, some scholars argue that the results of famine studies may not be reliable enough in terms of the association between famine and adult health problems due to certain limitations in the design and analysis of some famine studies [43, 44]. Therefore, how to conduct scientifically rigorous famine studies has become a key issue in the field [45, 46]. Firstly, the issue of age disparity between groups warrants careful consideration. In most prior studies, participants born during the famine were designated as the famine-exposed group, while those born after the famine were classified as the control group (non-famine exposed). Consequently, participants in the famine-exposed group tended to be older than their counterparts in the non-famine exposed group. However, age is a significant risk factor for various chronic diseases. Thus, conclusions suggesting that famine exposure elevates disease risk may be closely linked to the increased age of participants within the famine-exposed cohort. Li C et al. [47] propose to solve this issue by establishing diverse age-balanced control groups. Consequently, this research compared the prevalence of cataracts between famine-exposed individuals and non-exposed individuals at age 60. Secondly, famine severity is a pivotal indicator in famine research; however, a universally accepted gold standard for its measurement remains to be established. This is due to the multifaceted nature of famine severity, which is influenced not only by the individual nutritional status of pregnant women but also closely linked to broader economic conditions within the population. Given the inadequate medical infrastructure during periods of famine, accurately documenting the personal nutritional status of pregnant women poses significant challenges. Consequently, scholars have proposed various demographic indicators to quantify regional famine intensity, including excess death rate (EDR), cohort size shrinkage index (CSSI), abnormal death proportion, and infant mortality rate. Currently, CSSI is increasingly employed as an indicator for assessing famine severity, likely owing to its derivation from census data regarded as more reliable. Nevertheless, since CSSI may vary based on birth date selection among non-famine groups, this indicator warrants further standardization.

Our study holds several strengths: 1.This study is the first to explore the influence of prenatal famine exposure on the risk of ARC in individuals at the age of 60 and furnishes direct evidence;2. The information for this research was derived from medical records, which are considered to be more trustworthy than data obtained from questionnaires; 3. Chinese identity ID numbers were employed to trace the participants' birthplaces In this study, aiming to prevent the misclassification of famine exposure caused by the disparity between birthplace and current residence. There are certain limitations in this study: 1.The degree of famine constitutes an important indicator in famine research because there may exist significant differences in the intensity of famine endured by individuals even within the same region. Hence, collecting data on the intensity of famine experienced by individuals and establishing a dose-response relationship is conducive to reaching more accurate conclusions. However, this study employed a retrospective design, and the data were not derived from the census database. Thus, many population indicators for quantifying the famine intensity were lacking, which was a major limitation of this study; 2. The data of this study originated from a large-scale comprehensive hospital in Chongqing. Nevertheless, its representativeness might be restricted to some extent, potentially inducing selection bias. A multi-center study would be a preferable solution; 3. this research is confined to the Chinese population; these results might not be applicable to individuals of other ethnic groups.

Conclusions

This study presents initial evidence indicating that prenatal malnutrition may increase susceptibility to ARC at age 60. This insight offers valuable insights offers valuable guidance for public health policymakers in shaping primary prevention strategies for ARCs. Furthermore, prioritizing the enhancement of nutritional status among pregnant women, particularly in developing nations, is crucial. Maternal nutrition significantly influences offspring health, with female offspring being more susceptible, thereby perpetuating a detrimental cycle. Lastly, regular follow-ups and surveys on individuals born during famine are imperative to comprehensively understand and manage the physiological consequences associated with prenatal famine.

Abbreviations

ARC	Age related cataracts
DOHaD	Development origins of health and disease
DOHaD	Development origins of health and disease
LOCS III	Lens Opacities Cataract Classification System III
FBG	Fasting blood glucose
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
TG	Triglycerides
TC	Total cholesterol
HDL	High density lipoprotein
LDL	Low-density lipoprotein

BMI Body mass index
CI Confidence interval
OR Odds ratio

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Author contributions
Y. X. conceptualized the study, designed the experiments, curated and analyzed the data, and drafted and revised the manuscript; X.X. collected and analyzed the data and conducted the investigation; S. W. supervised the project, managed the data, and critically reviewed the manuscript.

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Data availability
All data in this study has been included within this published article.

Declarations

Ethics approval and consent to participate
The Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University has granted approval for this study, and the study protocol and accompanying materials adhere to both medical ethics principles and the requirements outlined in the Declaration of Helsinki. Prior to commencement, participants were provided with a detailed explanation of the study's purpose and gave their informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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