Original Article

Egg intake in extremely undernourished Chinese women during reproductive age and subsequent nonfatal perimenopausal coronary events

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Background and Objectives: Chinese women in rural areas who are currently ≥55 years old have experienced extreme undernutrition during their childbearing age. Their specific experiences provided us with a natural quasi-experimental field for assessing the effects of consuming eggs to obtain nutrients during the childbearing period on preventing nonfatal coronary events (NCE) during the postmenopausal period in the framework of life course epidemiology. **Methods and Study Design:** A population-based matched case–control design for NCE was conducted in Yiyuan County, Shandong Province, China. In this study, 462 women with NCE (cases; onset age ≥55 years) were included from the Active Surveillance System for Chronic Diseases, and 462 age-matched women without NCE and stroke (controls) from the same village were included. Conditional logistic model analysis was used to determine the association between egg intake and NCE during the postmenopausal period in 3 specific life-periods, namely age 18 to 49 years (childbearing period), age 50 years to NCE onset (perimenopausal and postmenopausal period), and age 18 years to NCE onset (total period). **Results:** We found that ≥12 eggs vs. 0 egg intake per month under extreme undernutrition status during childbearing period exhibited a strong preventive effect against NCE during the postmenopausal period (OR=0.588, 95% CI=0.358-0.964). The window of protective effect was in the age 28 to 49 years, suggesting a critical period model of life course epidemiology. **Conclusions:** Egg intake under extreme undernutrition status during the childbearing period plays a critical role in preventing NCE during the postmenopausal period.

Key Words: egg intake, nonfatal coronary events, life course epidemiology, undernutrition, postmenopausal period

INTRODUCTION

From the clinical and epidemiologic perspectives, modifiable risk factors, such as body mass index (BMI) and behaviors, are of greater interest to public health intervention than nonmodifiable mortality risk factors, such as advanced age and male sex, for cardiovascular disease (CVD), because they can be controlled or treated. The global INTERHEART study indicated that 9 modifiable risk factors, namely dyslipidemia, smoking, diabetes mellitus, hypertension, abdominal obesity, psychosocial stress, poor diet, physical inactivity, and alcohol consumption, accounted for >90% of the risk for a first myocardial infarction.[1] In particular, the association between undernutrition and CVD has been identified in epidemiological and experimental studies, which showed that undernutrition in early life (in the prenatal period, infancy, or childhood) was a crucial predisposing factor for CVD development.[2,3] The results of a well-known large-scale and long-term Helsinki birth cohort study in which 8760 participants were followed up from birth to the age of 54 years or to an elderly age demonstrated that growth pattern predisposing individuals to coronary heart disease (CHD) was characterized by a small body size at birth and thinness throughout infancy up to 2 years of age.[4-7] Similarly, an animal study showed that rats subjected to protein malnutrition during the prenatal and infantile period exhibited an increase in the cardiovascular sympathetic tone, which contributed to the elevation of arterial pressure in 90-day-old rats.[3] Furthermore, male rats with intrauterine growth restriction caused by the maternal low-protein diet showed decreased liver weight at birth and high levels of circulating and hepatic cholesterol at 40 weeks of age.[8] These results indicate the hypothesis that undernutrition experienced in early life causes CVD at a later stage, while obtaining adequate nutrition prevents CVD development in a later stage in life, should be tested.

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In rural China, particularly, women aged ≥55 years had experienced major social and economic changes from their childbearing period (which would have occurred between the 1950s and 1980s) to their later postmenopausal period (middle 1980s-). Naturally, most of them experienced extreme shortage of nutrition during their childbearing period due to natural disasters as well as political unrest that occurred between the 1950s and 1980s in China. For example, the Great Leap Forward famine during 1959-1961 was the costliest famine in human history, which resulted in approximately 30 million deaths,[9,10] and the Chinese Cultural Revolution of 1966-1976 caused a large-scale social and political shock with profound effects on the daily lives of the population. Owing to the extreme shortage of economic resources, most Chinese women in rural areas consumed food in insufficient quantities.[9] Moreover, for thousands of years, Chinese culture has exhibited a preference for male children; consequently, families allocated more resources to their sons than to their daughters during lean times;[11] the nutritional resources were first allocated in the following order: the son, daughter, husband's parents, wife's parents, husband, and wife. In addition, these women in the childbearing age not only had inadequate nutrition for themselves but had to consecutively nurture multiple children; hence, they were doubly vulnerable to malnutrition.[12] During the era of extreme shortage of nutrition, eggs were the main source of high-quality protein mainly because they were easily available in rural China. However, owing to rapid development since the 1980s due to the policies of reform and liberalization, women in rural China who experienced undernutrition in their young age received sufficient nutrition during the onset of their postmenopausal period.[13] Thus, their specific experiences provided us a natural experimental field for assessing the effect of obtaining nutrition through egg intake during the childbearing period on preventing nonfatal coronary events (NCE) during the postmenopausal period in the framework of life course epidemiology.

Life course epidemiology mainly focuses on the long-term effects on later health or disease risk of physical or social exposures during gestation, childhood, adolescence, young adulthood, and later adult life.[14] The following 4 models are commonly emphasized in life course approaches. Model 1, a critical period model assumes that an insult during a specific period of development has lifelong effects on the structure or function of organs, tissues, and body systems.[15] Model 2 involves a critical period model with later effect modifiers, wherein later life factors may modify early risk.[15,16] By contrast, Model 3, which considers the gradual accumulation of risk, refers to how risk factors at each life stage combine to increase disease risk and that separate and independent insults gradually cause long-term damage to health.[15] Finally, Model 4 considers the accumulation of risk with correlated insults and supposes that risk factors that tend to cluster in socially patterned ways may increase the risk of adult disease, perhaps through chains or pathways of risk over time, where one adverse (or protective) experience tends to lead to another adverse (or protective) experience in a cumulative manner.[15] In this study, the optimal life course model was identified for elucidating the effects of egg intake during the childbearing period on preventing NCE during the postmenopausal period among Chinese women in rural areas.

Theoretically, for our study, the ideal design would be a large birth cohort with continuous reliable and valid data collection from birth to childhood, adolescence, the childbearing period, and the postmenopausal period. However, because it was not possible to determine the nutritional status in the cases and controls during their childhood, adolescence, and childbearing period by actual measurement, a retrospective case–control study was the only feasible study design. Although the recall bias was unavoidable for the case–control design, participants may easily recall and report their exposure experiences and critical turning points continuously, including egg intake and other lifestyle factors (eg, smoking, drinking, and diet) through their adolescence, childbearing age, and postmenopausal period. Studies have shown that a case–control design was successfully used to elucidate the effects of accumulated exposures to tobacco and alcohol throughout the participants' lifetimes on the incidence of cancers.[17,18]

Therefore, a population-based matched case-control design for NCE was conducted in Yiyuan County of Yimeng Mountainous Area, Shandong province, China, with 462 women with NCE (cases) and 462 women without (controls) NCE who were ≥55 years old and had highly homogeneous lifestyles. All the cases and controls had experienced extreme shortage of nutrition during the childbearing period (age 18-49 years) and a nutrition balance (surplus) in the perimenopausal and postmenopausal period (age ≥50 years); the postmenopausal age was defined as ≥55 years based on a large-scale epidemiological investigation in Chinese women in rural areas.[19] Our proposed Lifespan Risk Exposure Measurement Instrument (LREMI)[20] was used to collect exposure experiences, such as egg intake and other lifestyle factors, from the age of 18 years to occurrence of NCE. Various strategies of conditional logistic model analysis were used to determine the association between egg intake and NCE during the postmenopausal period in the 3 specific life-periods, namely age 18 to 49 years (childbearing period), age 50 years to occurrence of NCE (perimenopause and postmenopausal period), and age 18 years to occurrence of NCE (total period). In this study, the effect of obtaining nutrients through egg intake during the childbearing period on preventing NCE during the postmenopausal period was assessed and the optimal life course epidemiological model was elucidated.

METHODS

Study design and participants

Our study was conducted in Yiyuan County of Yimeng Mountainous Area, Shandong province, China, based on the Active Surveillance System for Chronic Diseases (ASSCD). Yiyuan County is located in the hinterland of Yimeng Mountainous Area and is a state-grade poverty-stricken county. Residents in this small area exhibit highly homogeneous lifestyles, and have high homogeneity in their smoking habits, drinking habits, diets, and physical activities. The area provided us with a natural experimental population for controlling these potential confounders efficiently, expecting to achieve their statistical equilibrium through age matching. The ASSCD was established in 2007 for the surveillance of chronic diseases (eg, stroke and NCE) in the entire population. All NCE cases were from this surveillance database (female and onset age ≥55 years), and age-matched (±3 years) controls without NCE and stroke from the same village.

NCE was defined as angina or nonfatal myocardial infarction in the ASSCD system. All the cases had received diagnosis at a local hospital and were reported into the ASSCD system by the doctors. All participants were validated by their village doctors.

Procedures for data collection

The LREMI, which was created by our life course epidemiology research group[20] was applied to record the dynamic changing exposure to egg intake and other factors (smoking habit, alcohol consumption, diet, and physical activities) and their turning point (cutoff) across an individual's life course from age 18 years to occurrence of NCE. An app in the iOS system was developed to help collect data of lifespan exposure and experiences of the participants. A video presents the process of collecting data from a 75-year-old woman regarding egg intake by using the LREMI app. (Supplementary File–Video 1).The actual process of investigating egg intake comprised the following steps: 1) enquiring about the current egg-intake status of the respondent (frequency of egg intake, no. of eggs consumed) and filling out the questionnaire; 2) identifying the starting point (time) of the current egg-intake status for identifying the first turning point; 3) obtaining the egg-intake status before the first turning point and its duration by using the method in step 1, thereby establishing the second turning point; and 4) repeating the entire process until the egg-intake status at the age of 18 years was obtained. Information of the respondents' smoking habit, alcohol consumption, other dietary variables (tea, fruit, vegetables, meat, soybeans and soy products, fish and aquatic products, and coarse grains), physical activities, history of diseases (obesity, diabetes, hypertension, hyperlipidemia, and stroke) was collected using a similar method. Figure 1 illustrates the turning points in the life span of a 75-year-old woman who was considered a representative respondent.

The life course from the age of 18 years to the occurrence of NCE (total period) was divided into 2 periods, namely the childbearing period (period 1; age 18 to 49 years) and the perimenopause and postmenopausal period (period 2; age 50 years to occurrence of NCE).[19] The egg intake of an individual was measured by counting the number of eggs consumed per month year by year during the 3 defined periods. Exposure to other factors, including smoking habit, alcohol consumption, and diet, was also calculated using a similar method (see column 1 in Table 2).

Statistical analysis

The sociodemographic characteristics, anthropometric measurements, and reproductive factors were summarized in the case and control groups. Similarly, for case and control groups, the distribution of egg intake and other potential confounding factors was also summarized in period 1, period 2, and the total period. The differences between case and control groups were analyzed using the paired t test for continuous variables and the McNemar test for categorical variables.

Various strategies of multivariate conditional logistic analysis were used for assessing the effect of egg intake during period 1, period 2 and the total period on preventing NCE during the postmenopausal period and for elucidating its optimal life course epidemiological model. The odds ratio (OR) (95% CI) in every year (or the cumulative effect) from the age of 18 years to the occurrence of NCE were projected onto the dimensionality of the entire life course to visualize the optional life course epidemiological model.

All data were analyzed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA). All the statistical tests were two-sided, and $p \leq 0.05$ was considered statistically significant.

RESULTS

Table 1 summarizes the current characteristics of the NCE-related factors in the 462 cases and 462 controls. The results revealed a high homogeneity (education level, marital status, occupation, income levels, and repro-

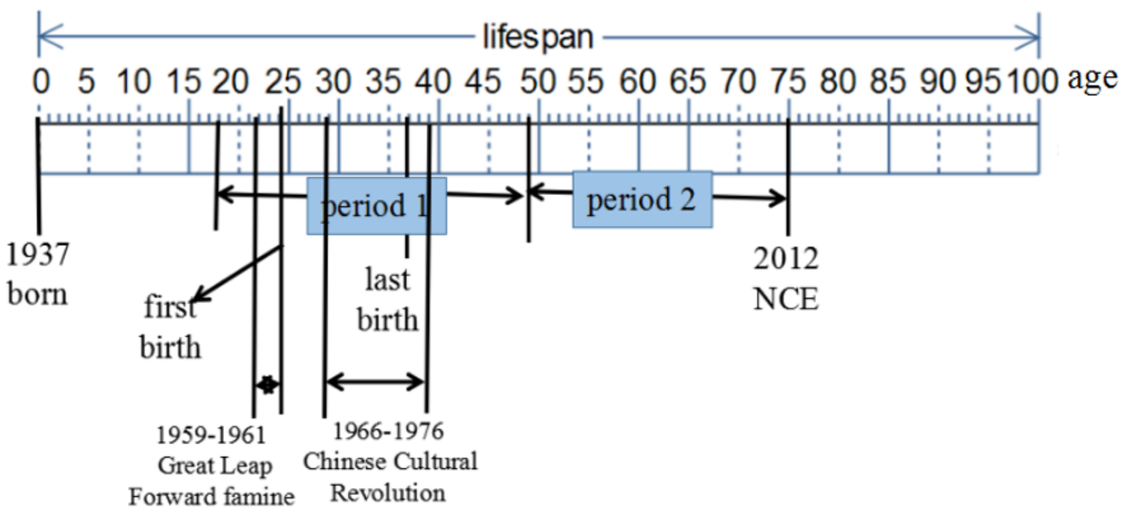

Figure 1. The life span turning points for a 75-year-old women

Table 1. Current characteristics of NCE-related factors in the case and control groups

	Case (n=462)	Control (n=462)	*p* value
Age (years)	69.7±6.9	69.7±6.9	0.117
Education level			0.383
Illiterate	382 (83.6%)	377 (82.7%)	
Primary school	68 (14.9%)	67 (14.7%)	
Middle school or higher	7 (1.5%)	12 (2.6%)	
Marital status			0.083
Married	315 (69.2%)	337 (74.1%)	
Widowed/divorced	140 (30.8%)	118 (25.9%)	
Occupation			0.746
Farmer	436 (95.4%)	441 (95.9%)	
Others	21 (4.6%)	19 (4.1%)	
Per capita annual incomes (yuan)			0.134
<1000	144 (31.2%)	152 (32.9%)	
1000-3000	159 (34.5%)	135 (29.2%)	
3000-10000	116 (25.1%)	127 (27.5%)	
≥10000	43 (9.3%)	48 (10.4%)	
Parity	4.0±1.7	4.0±1.8	0.582
Age at first birth	23.2±2.9	23.3±2.8	0.570
Age at last birth	32.3±5.2	32.2±5.1	0..858
Breast-fed periods in the whole life (months)	81.9±49.9	80.8±48.7	0.800
BMI (kg/m^2)			0.012
<24	190 (41.2%)	227 (50.8%)	
24-28	177 (38.4%)	151 (33.8%)	
>28	94 (20.4%)	69 (15.4%)	
Hypertension	357 (77.3%)	193 (41.8%)	<0.001
Diabetes	131 (28.4%)	37 (8.0%)	<0.001
Hyperlipidemia	124 (26.8%)	52 (11.3%)	<0.001

Data are n (%) and mean (SD). *p* for differences determined using the paired *t* test (for continuous variables) and McNemar test (for categorical variables)

ductive factors) between the 2 groups although the 2 groups were only matched for the factor of age in this study. However, significant differences between the case and control groups were detected in prevalence of obesity (x^2=11.0, p=0.012), hypertension (x^2=106, p<0.001), diabetes (x^2=56.6, p<0.001), and dyslipidemia (x^2=35.0, p<0.0001).

Table 2 presents a comparison of egg intake and other potential confounding factors between the case and control groups in period 1, period 2, and the total period. In period 1, clearly, the average number of egg consumed in a month in the case group (3.7±6.6) was significantly lower than that in the control group (5.1±9.1) with p=0.007. A significant difference was also detected in the total period between the 2 groups (5.1±7.2 vs 6.6±9.7, p=0.01). However, the difference was not statistically significant in period 2 (p=0.057). None of the potential confounding factors, including smoking, alcohol consumption, tea consumption, physical activities, fruit consumption, vegetable consumption, meat consumption, fish consumption, and consumption of bean products, differed significantly between the case and control groups in all the 3 periods, except for the intake of coarse gain in period 2 (p=0.03).

Table 3 shows the association between egg intake and NCE by using various strategies of multivariate conditional logistic analysis in period 1, period 2, and the total period. When the potential confounding factors were not adjusted (Model 1), the protective effect of egg intake on NCE was only detected in period 1, with an OR of 0.59 (95% CI 0.36-0.96) at the compared level of egg intake of ≥12 per month vs egg intake = 0 per month. After adjustment for confounding factors, including lifestyle factors (tobacco smoking, alcohol consumption, tea consumption, and occupational physical activities), parity, and dietary factors (consumption of fruits, vegetables, meat, fish, coarse grain, and soy products) in Model 2, the protective effect was still powerful with an OR of 0.58 (95% CI 0.34-1.00) in period 1. By contrast, such an effect was neither observed in period 2 (OR=0.82, 95% CI 0.54-1.23) nor in the total period (OR=0.69, 95% CI 0.42-1.12). These results suggested that obtaining nutrients though egg intake in an extreme undernutrition status during the childbearing period (period 1) had a powerful protective effect on preventing NCE during the postmenopausal period.

To identify the critical period for supplementing nutrients by egg intake, the ORs (95% CI) in every year from the age of 18 years to the occurrence of NCE were estimated through conditional logistic regression (Figure 2). A significant window of protective effect was observed between the age 28 to 49 years with ORs <1.00, which suggested a critical period model from the perspective of life course epidemiology. Furthermore, the accumulative effects of egg intake per year during this window were estimated (Figure 3), and an increasing effect was observed with the extension of the window period, which indicated an accumulative effect of egg intake in this critical period.

To further explore whether the effect of egg intake in the aforementioned critical period (28 to 49 years) could be modified by potential modification factors in period 2, including egg intake and the 4 risk factor of NCE (obesity, hypertension, diabetes, and hyperlipidemia), the con-

Table 2. Characteristics of egg intake and other potential confounding factors in period 1, period 2, and the total period in the case and control groups

	Period 1			Period 2			Total-period		
	Case	Control	*p* value	Case	Control	*p* value	Case	Control	*p* value
Egg intake (eggs/month)	3.7±6.6	5.1±9.1	0.007	8.2±13.0	9.0±13.3	0.057	5.1±7.2	6..6±9.7	0.010
Smoking status			0.847			0.602			0.612
Never smoker	448 (97.0%)	447 (96.75%)		445 (96.3%)	443 (95.9%)		444 (96.1%)	442 (95.7%)	
Former or current smoker	14 (3.0%)	15 (3.25%)		17 (3.7%)	19 (4.1%)		18 (3.9%)	20 (4.3%)	
Alcohol drinking status			0.362			0.431			0.448
Never drinker	434 (93.9%)	426 (92.2%)		422 (91.3%)	414 (89.6%)		419 (90.7%)	411 (89.0%)	
Former or current drinker	28 (6.1%)	36 (7.8%)		40 (8.4%)	48 (10.4%)		43 (9.3%)	51 (11.0%)	
Tea drinking status			1.000			0.240			0.240
Never tea drinker	341 (73.8%)	342 (74.0%)		266 (57.6%)	250 (54.1%)		266 (57.6%)	248 (53.7%)	
Former or current tea drinker	121 (26.2%)	120 (26.0%)		196 (42.4%)	212 (45.9%)		196 (42.4%)	214 (46.3%)	
Physical activity (MET hours/day)	44.0±48.8	42.5±25.6	0.645	30.8±41.2	30.4±16.6	0.930	39.2±44.5	38.2±21.5	0.732
Fruit (50 g/month)	20.9±38.9	17.8±31.1	0.127	30.4±52.7	29.8±50.5	0.830	23.8±39.3	21.2±32.5	0.208
Vegetables (50 g/day)	9.6±7.3	9.3±7.5	0.676	8.6±5.7	8.5±5.7	0.890	9.2±6.3	9.0±6.6	0.676
Coarse grain (50 g/day)	10.3±7.0	9.5±7.1	0.128	6.2±5.3	5.3±5.3	0.030	9.0±5.8	8.1±6.1	0.079
Meat (50 g/month)	3.7±9.5	4.0±11.8	0.722	5.8±17.6	6.6±16.3	0.441	4.4±11.2	4.8±11.9	0.649
Fish (50 g/month)	1.5±5.1	2.0±5.8	0.127	2.0±5.9	2.5±6.7	0.275	1.6±4.9	2.2±5.7	0.145
Bean products (50 g/month)	15.0±41.1	11.5±32.3	0.095	10.4±24.8	8.7±21.7	0.275	13.5±34..3	10.5±27.3	0.157

Data are n (%) and mean (SD). *p* values for differences determined using the paired sample t test for continuous variables and McNemar test for categorical variables.

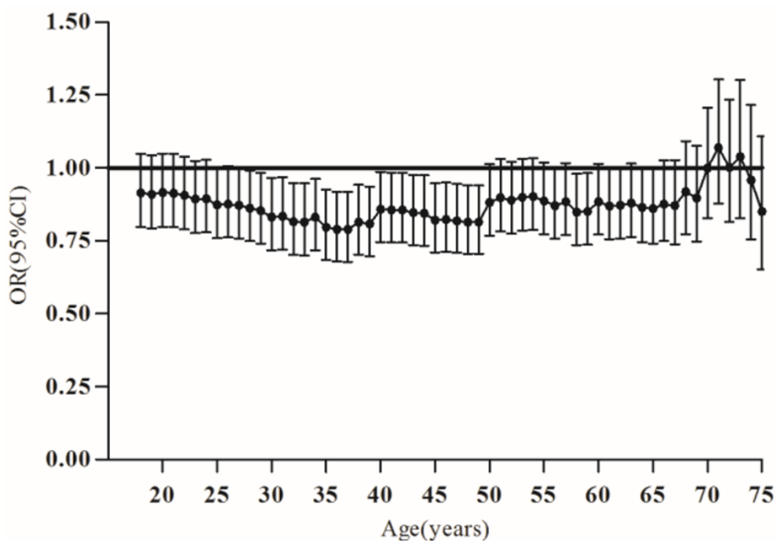

Figure 2. The odds ratio (95%CI) for association of egg intake in every year with NCE.

Table 3. Odd ratios and their 95% CI from conditional logistic regression analysis for association of egg intake during period 1, period 2, and the total period with NCE during the postmenopausal period

	Period 1		Period 2		Total-period	
	Model 1†	Model 2‡	Model 1†	Model 2‡	Model 1†	Model 2‡
Egg intake (eggs/month)						
0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
0.01-4	1.12 (0.81, 1.56)	1.18 (0.81, 1.71)	1.02 (0.71, 1.45)	1.19 (0.80, 1.78)	1.05 (0.76, 1.47)	1.22 (0.84,1.78)
4.01-12	0.86 (0.60, 1.23)	0.89 (0.59, 1.34)	1.00 (0.70, 1.42)	1.09 (0.78, 1.63)	0.88 (0.61, 1.25)	0.93 (0.62,1.40)
≥12	0.59 (0.36, 0.96)	0.58 (0.34, 1.00)	0.74 (0.51, 1.05)	0.82 (0.54, 1.23)	0.68 (0.44, 1.05)	0.69 (0.42,1.12)
Parity		1.05 (0.92, 1.19)		1.06 (0.94, 1.21)		1.07 (0.94, 1.22)
Smoking (yes vs no)		0.85 (0.36, 1.99)		0.84 (0.40, 1.75)		0.84 (0.41, 1.72)
Alcohol drinking (yes vs no)		0.84 (0.48, 1.49)		1.08 (0.66, 1.79)		1.05 (0.65, 1.70)
Tea drinking (yes vs no)		1.21 (0.86, 1.70)		0.95 (0.71, 1.27)		0.96 (0.72, 1.28)
Physical activity		1.00 (1.00, 1.00)		1.00 (1.00, 1.01)		1.00 (1.00, 1.01)
Fruit		1.00 (1.00, 1.01)		1.00 (1.00, 1.00)		1.00 (1.00, 1.01)
Vegetables		0.99 (0.97, 1.01)		0.99 (0.96, 1.01)		0.99 (0.97, 1.02)
Coarse grain		1.01 (0.99, 1.04)		1.03 (1.00, 1.06)		1.02 (1.00, 1.05)
Meat		1.00 (0.99, 1.01)		1.00 (0.99, 1.01)		1.00 (0.99, 1.02)
Fish		0.99 (0.96, 1.02)		1.00 (0.97, 1.02)		0.99 (0.96, 1.02)
Bean products		1.00 (1.00, 1.00)		1.00 (0.99, 1.01)		1.00 (1.00, 1.01)

†Model 1 comprised univariate conditional logistic regression analysis for egg consumption during period 1, period 2, and the total period.
‡Model 2 comprised multivariate analysis adjusted for lifestyle factors (tobacco smoking, alcohol consumption, tea consumption, and occupational physical activities), parity and dietary factors (consumption of fruit, meat, fish, coarse grain, and bean products) during period 1, period 2, and the total period.

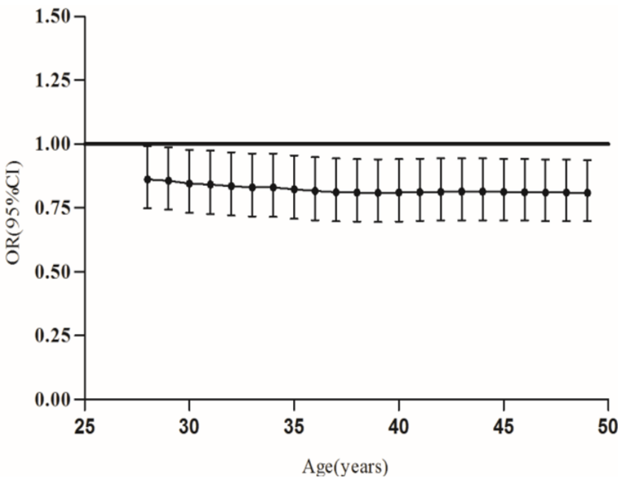

Figure 3. The accumulative effects of egg intake by year on NCE during the critical period (age of 28 to 49).

ditional logistic model with interaction terms was built for each effect modifier. However, no significant effect modification was detected for these factors (Table 4), suggesting that the protective effect of obtaining nutrients through egg intake under extreme undernutrition status during the aforementioned critical period was not affected by the exposure status in period 2.

DISCUSSION

Various epidemiological and experimental studies have confirmed that undernutrition in early life was a crucial predisposing factor for the development of CVD.[2-8] These results indicate the hypothesis that experiencing undernutrition in early life causes CVD in later life, while supplementing nutrition in early life prevents CVD in later life. Chinese women in rural areas who are currently ≥55 years old had experienced extreme undernutrition and shifted to nutrition balance (surplus).[9-13] This provided us a natural experimental field to verify the above hypothesis in the framework of life course epidemiology in which we assessed the effect of obtaining nutrients through egg intake during the childbearing period on preventing NCE during the postmenopausal period. In this life course epidemiological study with a matched case–control design, we used our proposed LREMI and found that obtaining nutrients through egg intake under extreme undernutrition status during childbearing period (period 1) had powerful protective effect on preventing NCE during the postmenopausal period with OR (95% CI) of 0.588 (0.358, 0.964). Furthermore, a window of a significant protective effect with ORs of <1.00 was identified in the life period of age 28 years to age 49 years (Figure 2 and Figure 3), suggesting a critical period model in the perspective of life course epidemiology.[14,15] The effect modification analysis

Table 4. ORs and their 95% CI of the modification effects of potential modification factors in period 2 on egg intake in the critical period (28 to 49 years)

		OR(95%CI)	*p* value
Egg	Egg†	1.00 (0.97, 1.03)	0.928
	Egg‡	1.00 (0.99, 1.02)	0.644
	Egg† x Egg‡	1.00 (1.00, 1.00)	0.139
Obesity	Egg†	0 .98 (0.96, 1.00)	0.105
	Obesity	1.38 (1.12, 1.72)	0.003
	Egg† x Obesity	0.99 (0.97, 1.01)	0.440
Hypertension	Egg†	0.98 (0.94, 1.01)	0.123
	Hypertension	4.06 (2.82, 5.85)	0.000
	Egg† x Hypertension	1.02 (0.98, 1.07)	0.245
Diabetes	Egg†	0.98 (0.96, 1.00)	0.014
	Diabetes	3.75 (2.39, 5.87)	0.000
	Egg† x Diabetes	1.01 (0.97, 1.06)	0.590
Hyperlipidemia	Egg†	0.98 (0.96, 1.00)	0.022
	Hyperlipidemia	2.58 (1.73, 3.85)	0.000
	Egg† x Hyperlipidemia	1.02 (0.98, 1.07)	0.383

†Average egg intake from the age of 28 years to 49 years.
‡Average egg intake during period 2.

revealed that this protective effect of egg intake under extreme undernutrition status during the above critical period was not affected by the exposure status in the postmenopausal period. In conclusion, our study evidenced that egg intake under extreme undernutrition status, as a main source of high-quality protein, could play a critical role in protecting vascular function and preventing CVD in later life.

The Chinese diet between the 1950s and 1980s was characterized by a high carbohydrate content, moderate dietary fiber content, and low animal protein content. Combined with high fertility rate and long lactation, the aforementioned diet strongly suggests that rural Chinese women experienced extreme nutrition deficiency, particularly of animal-derived nutrients, during their childbearing period between the 1950s and the 1980s. This matched case–control study showed that specifically eggs, and not any other animal product, were responsible for preventing NCE. The reason may be that rural Chinese women consumed significantly less meat and fish during their childbearing period between the 1950s and the 1980s than did women in Western countries.[21] Eggs are more readily available than meat and fish, because many rural families raised chickens. Egg is an inexpensive and low-calorie source of nutrients, including high-quality protein, essential fatty acids, and various vitamins and minerals, lecithin, and choline, which can lower the risk of cardiovascular disease or have numerous important physiologic functions,[22-26] and an experimental study confirmed that eggs contain a substance that inhibits angiotensin-converting enzyme for protective vascular function.[27] These functions might be more critical and more powerful in an extreme undernutrition status for maintaining vascular function and preventing from coronary atherosclerosis. By contrast, although a large egg contains approximately 210 mg of cholesterol,[28] eating 12 eggs per month in an extreme undernutrition status was far from the recommended cholesterol intake.[29] In addition, various studies have shown that egg intake promotes the formation of large LDL, which is a form that is less atherosclerotic and HDL subclasses.[30-36] These data suggest that dietary cholesterol provided by eggs enhances reverse cholesterol transport.[37] Qin et al (2018) found that daily egg consumption was associated with low risks of CVD, ischemic heart disease, hemorrhagic stroke, and ischemic stroke among Chinese middle-aged adults.[38]

The case and control groups were highly homogeneous although they were only matched for age. These homogeneous factors included socioeconomic, anthropometric, reproductive, lifestyle-related, and most diet-related factors. This homogenous status was observed because the participants belonged to a relatively isolated mountainous area with similar living standards, and their habits were not influenced by external factors. More importantly, China's food system during the 1950s-1980s was dominated by small farms and ration stores,[39] and both type and quantity of supplies were limited and equally distributed. This homogeneous life experience between the case and control groups was beneficial for highlighting the protective effect of obtaining nutrition through egg intake in an extreme undernutrition status during the childbearing period on preventing NCE during the postmenopausal period. Even in a highly homogeneous environment, microscopic differences were observed between individuals. Some of the reasons for the differences are differences in the number of family laborers, because a large number of laborers obtained a large number of resources; the status of women in marriage and family life; and the burden of raising children and supporting elderly family members.

Biases, particularly the recall bias, were inevitable in this case–control study due to long-term recalling exposures. However, lifestyle factors, such as egg intake, smoking habits, drinking habits, and diet, were common. Usually, it is easy for participants to recall their exposure experiences and critical turning point continuously by using our proposed LREMI. In addition, we trained investigators in data collection to ensure the reliability of the results. However, various biases still existed. Therefore, additional experimental animal studies should be conducted for confirming our proposed hypothesis.

Conclusion

Our finding suggested that consumption of >12 eggs per month during the childbearing period when the women experience nutritional deficiency could independently reduce the risk of NCE in women aged ≥55 years. The critical period for this protective effect was 28 to 49 years and a cumulative effect was observed during this period. Eggs are an inexpensive and low-calorie source of nutrients for people in rural China, especially for rural women. Suggestions for limiting egg intake in China should be made prudently. Additional experimental animal studies should be conducted for confirming our hypothesis.

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REFERENCES

1. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364:937-52. doi: 10.1016/S0140-6736(04)17018-9.
2. Barker DJ. Fetal programming of coronary heart disease. Trends Endocrinol Metab. 2002;13:364-8. doi: 10.1016/S1043-2760(02)00689-6.
3. Barros MA, De Brito AJ, Nogueira VO, Wanderley AG, Costa-Silva JH. Maternal low-protein diet induces changes in the cardiovascular autonomic modulation in male rat offspring. Nutr Metab Cardiovasc Dis. 2014;25:123-30. doi: 10.1016/j.numecd.2014.07.011.
4. Barker DJ, Osmond C, Forsen TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. N Engl J Med. 2005;353:1802-9. doi: 10.1056/NEJMoa044160.
5. Eriksson JG. Early growth and coronary heart disease and type 2 diabetes: findings from the Helsinki Birth Cohort Study (HBCS). Am J Clin Nutr. 2011;94(6 Suppl):1799S-1802S. doi: 10.3945/ajcn.110.000638.
6. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early growth and coronary heart disease in later life: longitudinal study. BMJ. 2001;322:949-53. doi: 10.1136/bmj.322.7292.949.
7. Kajantie E, Barker DJP, Osmond C, Forsen T, Eriksson JG. Growth before 2 years of age and serum lipids 60 years later: The Helsinki Birth Cohort Study. Int J Epidemiol. 2008; 37:280-9. doi: 10.1093/ije/dyn012.
8. Liu X, Qi Y, Tian B, Chen D, Gao H, Xi C et al. Maternal protein restriction induces alterations in hepatic tumor necrosis factor-alpha/CYP7A1 signaling and disorders regulation of cholesterol metabolism in the adult rat offspring. J Clin Biochem Nutr. 2014;55:40-7. doi: 10.3164/jcbn.13-100.
9. Cai Y, Feng W. Famine, social disruption, and involuntary fetal loss: evidence from Chinese survey data. Demography. 2005;42:301-22. doi: 10.1353/dem.2005.0010.
10. Song S. Does famine have a long-term effect on cohort mortality? Evidence from the 1959-1961 great leap forward famine in China. J Biosoc Sci. 2009;41:469-91. doi: 10.1017/S0021932009003332.
11. Mu R, Zhang X. Why does the Great Chinese Famine affect the male and female survivors differently? Mortality selection versus son preference. Econ Hum Biol. 2011;9:92-105. doi: 10.1016/j.ehb.2010.07.003.
12. Delisle HF. Poverty: the double burden of malnutrition in mothers and the intergenerational impact. Ann N Y Acad Sci. 2008;1136:172-84. doi: 10.1196/annals.1425.026.
13. Zhai F, Wang H, Du S, He Y, Wang Z, Ge K et al. Prospective study on nutrition transition in China. Nutr Rev. 2009;67(Suppl 1):S56-61. doi: 10.1111/j.1753-4887.2009.00160.x.
14. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31:285-93. doi: 10.1093/ije/31.2.285.
15. Kuh D, Ben-Shlomo Y. A life course approach to chronic disease epidemiology. 2nd ed. New York: Oxford University Press; 2004.
16. Frankel S, Elwood P, Sweetnam P, Yarnell J, Smith GD. Birthweight, body-mass index in middle age, and incident coronary heart disease. Lancet. 1996;348:1478-80. doi: 10.1016/S0140-6736(96)03482-4.
17. Luchtenborg M, White KK, Wilkens L, Kolonel LN, Le Marchand L. Smoking and colorectal cancer: different effects by type of cigarettes? Cancer Epidemiol Biomarkers Prev. 2007;16:1341-7. doi: 10.1158/1055-9965.EPI-06-0519.
18. Vigen C, Bernstein L, Wu AH. Occupational physical activity and risk of adenocarcinomas of the esophagus and stomach. Int J Cancer. 2006;118:1004-9. doi: 10.1002/ijc.21419.
19. Lewington S, Li L, Murugasen S, Hong LS, Yang L, Guo Y et al. Temporal trends of main reproductive characteristics in ten urban and rural regions of China: the China Kadoorie Biobank study of 300 000 women. Int J Epidemiol. 2014; 43:1252-62. doi: 10.1093/ije/dyu035.
20. Ding LJ, Liu RH, Ji XK, Yuan ZS, Zhang T, Xue FZ. Lifespan risk exposure measurement instrument: a feasible and effective tool for life course epidemiology research. Biomed Environ Sci. 2017;30:59-63. doi: 10.3967/bes2017.007.
21. Guallar-Castillon P, Rodriguez-Artalejo F, Tormo MJ, Sanchez MJ, Rodriguez L, Quiros JR et al. Major dietary patterns and risk of coronary heart disease in middle-aged persons from a Mediterranean country: the EPIC-Spain cohort study. Nutr Metab Cardiovasc Dis. 2012;22:192-9. doi: 10.1016/j.numecd.2010.06.004.
22. Rimm EB, Stampfer MJ, Ascherio A, Giovannucci E, Colditz GA, Willett WC. Vitamin E consumption and the risk of coronary heart disease in men. N Engl J Med. 1993;328:1450-6. doi: 10.1056/NEJM199305203282003.
23. Bolton-Smith C, Woodward M, Tunstall-Pedoe H. The Scottish Heart Health Study. Dietary intake by food frequency questionnaire and odds ratios for coronary heart disease risk. II. The antioxidant vitamins and fibre. Eur J Clin Nutr. 1992;46:85-93.
24. Voutilainen S, Rissanen TH, Virtanen J, Lakka TA, Salonen JT. Low dietary folate intake is associated with an excess incidence of acute coronary events: The Kuopio Ischemic Heart Disease Risk Factor Study. Circulation. 2001;103: 2674-80. doi: 10.1161/01.CIR.103.22.2674.

25. Ishihara J, Iso H, Inoue M, Iwasaki M, Okada K, Kita Y et al. Intake of folate, vitamin B6 and vitamin B12 and the risk of CHD: the Japan Public Health Center-Based Prospective Study Cohort I. J Am Coll Nutr. 2008;27:127-36.
26. Knekt P, Ritz J, Pereira MA, O'Reilly EJ, Augustsson K, Fraser GE et al. Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts. Am J Clin Nutr. 2004;80:1508-20. doi: 10.1134/S0036024409120024.
27. Majumder K, Wu J. Angiotensin I converting enzyme inhibitory peptides from simulated\r in vitro\r gastrointestinal digestion of cooked eggs. J Agr Food Chem. 2009;57:471-7. doi: 10.1021/jf8028557.
28. Barraj L, Tran N, Mink P. A comparison of egg consumption with other modifiable coronary heart disease lifestyle risk factors: a relative risk apportionment study. Risk Anal. 2009;29:401-15. doi: 10.1111/j.1539-6924.2008.01149.x.
29. Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation. 2006;114:82-96. doi: 10.1161/circulationaha.106.176158.
30. Berneis K, Rizzo M. LDL size: does it matter? Swiss Med Wkly. 2004;134:720-4. doi: 2004/49/smw-10813.
31. Koba S, Hirano T, Ito Y, Tsunoda F, Yokota Y, Ban Y et al. Significance of small dense low-density lipoprotein-cholesterol concentrations in relation to the severity of coronary heart diseases. Atherosclerosis. 2006;189:206-14. doi: 10.1016/j.atherosclerosis.2005.12.002.
32. Pascot A, Lemieux I, Prud'Homme D, Tremblay A, Nadeau A, Couillard C et al. Reduced HDL particle size as an additional feature of the atherogenic dyslipidemia of abdominal obesity. J Lipid Res. 2001;42:2007-14. doi: 10.1089/107999001317205268
33. Greene CM, Waters D, Clark RM, Contois JH, Fernandez ML. Plasma LDL and HDL characteristics and carotenoid content are positively influenced by egg consumption in an elderly population. Nutr Metab (Lond). 2006;3:6. doi: 10.1186/1743-7075-3-6.
34. Mutungi G, Waters D, Ratliff J, Puglisi M, Clark RM, Volek JS et al. Eggs distinctly modulate plasma carotenoid and lipoprotein subclasses in adult men following a carbohydrate-restricted diet. J Nutr Biochem. 2010;21:261-7. doi: 10.1016/j.jnutbio.2008.12.011.
35. Kanter MM, Kris-Etherton PM, Fernandez ML, Vickers KC, Katz DL. Exploring the factors that affect blood cholesterol and heart disease risk: is dietary cholesterol as bad for you as history leads us to believe? Adv Nutr. 2012;3:711-7. doi: 10.3945/an.111.001321.
36. Eftekhar S, Parsaei H, Keshavarzi Z, Yazdi AT, Hadjzadeh MA, Rajabzadeh A et al. The prevention and treatment effects of egg yolk high density lipoprotein on the formation of atherosclerosis plaque in rabbits. Iran J Basic Med Sci. 2015;18:343-9. doi: 10.1016/j.jnucmat.2015.07.038.
37. Fernandez ML. Effects of eggs on plasma lipoproteins in healthy populations. Food Funct. 2010;1:156. doi: 10.1039/C0FO00088D.
38. Qin C, Lv J, Guo Y, Bian Z, Si J, Yang L et al. Associations of egg consumption with cardiovascular disease in a cohort study of 0.5 million Chinese adults. Heart. 2018;104:1756-63. doi: 10.1136/heartjnl-2017-312651.
39. Zhai FY, Du SF, Wang ZH, Zhang JG, Du WW, Popkin BM. Dynamics of the Chinese diet and the role of urbanicity, 1991-2011. Obes Rev. 2014;15(Suppl 1):16-26. doi: 10.1111/obr.12124.