BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038977
Article Type:	Original research
Date Submitted by the Author:	02-Apr-2020
Complete List of Authors:	Arage, Getachew; Belachew, Tefera; Jimma University College of Public Health and Medical Sciences, Nutrition and Dietetics Abera, Mubarek; Jimma University College of Public Health and Medical Sciences, Psychiatry Abdulhay , Fedilu ; Jimma University College of Public Health and Medical Sciences, Obstetrics and Gynecology Abdulahi, Misra; Jimma University College of Public Health and Medical Sciences, Department of Population and Family Heath Hassen , Kalkidan; Jimma University College of Public Health and Medical Sciences, Nutrition and Dietetics
Keywords:	Nutritional support < GASTROENTEROLOGY, Adult neurology < NEUROLOGY, NUTRITION & DIETETICS

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Effects of early life exposure to Famine on adulthood cognitive function in Ethiopia: A historical cohort study in Northeast Ethiopia

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Abstract

Objective: Earlier famine studies, as natural experiments, had tested the association between famine exposure during early life and adulthood cognitive function and reported variable findings. Hence, we sought to identify, (1) whether exposed to Ethiopian Great Famine during prenatal life had effect on cognitive function in adults, (2) whether this effect was associated with postnatal exposure to famine.

Setting: Raya Kobo district, North Wollo zone, northeast Ethiopia.

Participants: Adult men and women (n=1047) recruited to a historical cohort study with multistage stratified random sampling technique. Participants were divided into prenatal exposed, postnatal exposed (1-2 years during the famine) and non- exposed groups. Self-reported birth date and age of the participants was used to classify status of famine exposure.

Outcome measures: The primary outcome measures of this study was cognitive function in adults after early life exposure to famine. The Secondary outcome measures included whether this effect was specific to gestational or postnatal exposure windows. Montreal Cognitive Assessment (MoCA) tool was used to assess participants cognitive function.

Results: Adults having early life famine exposure were 3.2 points decreased cognitive test score (β= -3.2, 95% CI: -4.1, -2.3). Famine exposure at postnatal period was associated with decreased cognitive test score (β= -4.83, 95% CI: -6.37, -3.29) adjusted for all possible studied covariates. However, similar results were not observed in the prenatal exposed groups (β= -0.62, 95% CI: -2.77, 1.54).

Conclusions: Famine exposure during early life, specifically postnatal exposure window was associated with adulthood cognitive function. This study therefore highlights the importance of improving nutritional status during the postnatal period of child growth and development in ways that stimulate adulthood cognitive function. This finding also provides further evidence for the hypothesis of developmental origin of adult disease. further studies are needed to elucidate the potential mechanism behind this association.

Keywords: Famine exposure, early life adulthood, cognitive function, Ethiopia

Strengths and limitations of this study

- This is the first study investigate the relationship between early life exposure to famine and adulthood cognitive function in Ethiopia.
- Considering timing of exposure in assessing the effect of famine exposure in early life on adulthood cognitive function is also one of strength of the study. However, our study acknowledges the following limitations.
- The findings might be partly biased by self-selection effects. It is plausible that potential participants couldn't participate because of health related problems, and others may have already died due to the exposure.
- Exposure to the famine was defined using the self-reported birth date and age, thus recall bias cannot be ruled out. However, it is at our utmost belief that the exceptional catastrophic period of the famine, named as ''Kefu Qan'' by the local people or translated as known as "Evil Days in the memory of the survivors and the world could not forgettable.
- The long-term consequence of the famine likely depend on the severity of the exposure within the household which could not be measured due to the global nature of the famine where no household was invulnerable.
- Finally, factors such as parent-child bond, early childhood experiences and trauma have not been accounted for as potential confounding factors.

Introduction

Ethiopia had passed through long and troubled history of famines due to desertification and frequent severe rainfall failure (1). Notably, a widespread famine affected the country from 1983- 1985, where its epicenter was the northeast region of the country namely, Tigray and Wollo (2-4). It was ranked as "Great Famine" due to its global impact in famine scale and also known as the "Great Ethiopian Famine" due to its unprecedented high causality compared with any famine ever happened in Ethiopia or Africa (5, 6). In the memory of the famine survivors, it was named as ''Kefu Qan'' or translated as known as "Evil Days" (7). Over half a million deaths were occurred during the famine (8).

Cognition represents a complex set of higher mental functions controlled by the brain, which includes attention, memory, thinking, learning, and perception (9). Nutrition during early life is the fundamental determinants of neuro-developmental process. Malnutrition during this critical period of growth and development alters brain structure and neuronal connectivity and more prone to neurodevelopmental impairments (10). The human brain began to form at about two weeks during prenatal life and reach 80% of its adult size by the first two years after birth. Consequently, neurodevelopmental impairment in early life affects later performance of adults ability to learn and productivity (11, 12)

The broader understanding of the devastating short term consequences of famine such as mass migrations of people in search of food, social breakdown, loss of personal pride and morality were clearly known (13). However, the long term impact of the famine exposure is yet to be explored. Elsewhere, famine exposure in the early life, particularly the prenatal and postnatal period is the stages with magnificent growth and development, thus any change during this period could affect adulthood cognitive function (10, 14).

Adulthood cognitive function is thought to be the result of complex interactions between genetic and environmental factors including nutrition and psychosocial adversities in early life (15, 16) and behavioral related factors in later life such as physical activity, smoking, alcohol drinking, socioeconomic, demographic and dietary pattern (17, 18).

Nevertheless, context specific factors specifically those related to intrinsic attributes of once biology are usually neglected, as those are considered as non-modifiable (19). Investigators, such as Barker and his colleagues, have introduced a theory called "fetal origin of adult diseases (FOAD)" or "developmental origins of health and disease (DOHaD)" to explain the adulthood diseases resulted from early life nutritional insult (20, 21).

Empirical understanding of the link between adulthood cognitive function with early life adverse environment requires natural environment such as famine, migration, stress and disaster(22). A number of studies have reported the association between famine exposure in early life and cognitive function in adult life (23-26).

One of the best opportunity to deeply understand the long term consequence of early life adverse exposure is famine. More specifically, global famine such as the "Great Ethiopian Famine" of 1983-85 can be taken as a natural exposure to explore the long term assaults of early life undernutrition. Presumably, such studies may explain the cognitive related problems in Ethiopia and also give more insights on the hypothesis called DOHaD. As far as the authors' best search, no study has been ever conducted or documented to explore the nutrition and cognitive function of these segment of the population thus far. Hence, we conducted this study to evaluate the effects of prenatal and postnatal exposure to famine on adulthood cognitive function among the survivors of the 1983-85 global famine in Northeast Ethiopia.

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Methods and Materials

Study setting, design and period

The study was conducted in North Wollo Zone, Raya Kobo District, Northeast Ethiopia. Exposure status for the area, Raya Kobo District was selected purposively as this place was the epicenter of 1983-85 Great Ethiopian famine (2). The district has an estimated total population of 228,798 and has 36 kebeles (lowest administrative unit in the district), four of which are urban and the rest are rural kebeles of the district. A historical cohort study design was employed from March 15, to April 30, 2019 to investigate the effect of prenatal and postnatal famine exposure on adulthood cognitive function.

Study Participants

The study participants to this study were people who have been exposed to the 1983-85 great Ethiopian famine.

Patient and public involvement

Patents were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Measurements

Exposure measurement

The main exposure variable is early life exposure to the 1983-85 Great Ethiopian famine. Self-reported birth date and age of the participants were used to classify famine exposure status. Based on the timing of exposure, there were prenatal and postnatal exposures to famine. Famine exposure windows were determined using the famine start and end dates previously described (2). Accordingly, the study participants were categorized into three groups: non-exposed group (age =30-32 years, birth year = 1987 – 1988, n=357), prenatal exposed group (age =34-36, birth year = 1983, 1985, n= 359), postnatal-exposed group (age = 37-38, birth year = 1981-1983, birth- two years old during the famine, n= 356) (supplementary file 1). For this study, a total of 1072 participants were recruited with the guidance of developmental army and health extension workers of the community. Finally, 1047 participants who had completed data on all variables required

in the analysis were used for statistical comparison. Multistage stratified random sampling technique was used to reach the final sample size **(figure 1).** Participants born immediately after the end of famine were uncategorized and considered as the transitional period because of uncertainties in their exposure to famine and this helps to reduce misclassification bias. Thus, subjects born between 8 September 1986 to 30 August 1987 were excluded from the study. Adults displaced to other area of the country and those who were in other location during the famine and seriously ill were excluded from the study.

Outcome measurement

The outcome of the study was cognitive test performance among adult participants. Montreal Cognitive Assessment (MoCA)-basic tool was used to assess subjects' cognitive performance (27). Eight data collectors were involved in assessing the cognitive function of participants and each hold a minimum of diploma in clinical nursing and have significant experience as a research nurse. Three days of training on administration of the test and scoring of the test result was provided for the selected data collectors. The questionnaire was first prepared in English and then translated into Amharic (the local language) and back into English to ensure consistency.

Covariate measurement

A household wealth index score was generated from durable assets owned by the household using principal component analysis Physical activity was assessed by using the International Physical Activity Questionnaire (IPAQ). Participants who uses a specified substance (smoking, drinking and Khat chewing) in the past three months and once in their life time were considered as current users and ever users respectively (28). Height of the study subjects was measured to the nearest 0.1 cm using a stadiometer (Seca®, Germany) with the subjects positioned at the Frankfurt Plane and the four points (heel, calf, buttocks and shoulder) touching the vertical stand and their shoes taken off. Weight was measured using portable battery operated Seca® digital scale. Body mass index (BMI) was calculated as the weight in kilogram divided by height in meters squared (kg/m^2). Dietary pattern was assessed using unquantified food frequency questionnaire (FFQ) composed of 38 food types covering the main food consumed in the study area. As there is no Ethiopian classification of food groups, the 38 food items of the food

frequency questionnaire were grouped into seven groups [cereals, vegetables and fruits, dairy products, protein foods, oils, others] according to the Food and Agricultural organization (FAO) food groups. A dietary pattern was derived by using K-means cluster analysis. Two major dietary patterns were identified the healthy and unhealthy dietary pattern' based on the participant's fruits and vegetable consumption. The healthy dietary pattern indicates high consumption of fruits and vegetables and the unhealthy dietary pattern indicates low fruits and vegetables consumptions.

Statically analysis

The data was double entered to Epidata 3.1 and exported to SPSS version 25 ([SPSS Inc. version 25, Chicago, Illinois] for analysis. Continuous variables were reported as mean and standard deviation (± SD) when normally distributed or medians and interquartile ranges (IQR) for skewed distribution. Categorical variables were described as percentages and compared using Pearson chi-square test. Differences in mean cognitive test score among different groups were compared using analysis of variance (ANOVA) or T-test.

Linea regression analysis was used to examine the association between famine exposure in earl life and cognitive test score. The estimate (β-coefficients) and 95% CI were reported to describe the associations. Covariates were selected based on evidence from existing literature and the presence of biologically plausible relationships between the covariates and the outcome variable. When the regression coefficients of the exposure variables changed more than 10% after adding a variable and when the covariate was significantly associated with the outcome, this covariate was considered as a confounder and included in further models. Five sets of regression models were developed. Model 1: included the outcome and the main exposure variable (famine exposure status). Model 2: built on model one by adding sex and age. Model 3: built on model 2 by adding educational status, wealth index, marital status, residency and occupational status. Model 4: built on model 3 by adding smoking status, drinking status, Khat chewing status and physical activity. Model 5 (full adjusted model) built on model 4 by adding body mass index and dietary pattern. The rationale of the different models was to observe changes in the association between the main exposure and outcome variable when different sets of covariates were accounted for in the model. The outcome variable, cognitive test score

was tested for normality using a P-P plot and a steam leaf diagram, and all potential confounders were tested for linearity with the outcome variable using scatter plots. Multicollinearity diagnosis was checked by using variance inflation factor (VIF<10). Moreover, stratified analysis with sex was performed and the interaction of famine exposed groups with residency was performed by likelihood ratio test. P-values presented were based on two-tailed test and $P < 0.05$ was considered statistically significant.

Results

Background characteristics

A total of 1047 adults had complete data for all variables included in the analysis. Six hundred ninety-seven (66.6%) of the participants were exposed and 350 (34.4%) of the were non-exposed group. Of these, 350 (33.4%), 348 (33.2%) and 349 (33.3%) were non-exposed, prenatal-exposed and postnatal-exposed respectively. The mean (±SD) ages for exposed and non-exposed groups were 35.3 (1.4) and 31.2(0.70). The mean (± SD) age of non-exposed, prenatal exposed and postnatal exposed groups were 31.20 (0.66), 35.05 (0.86) and 37.60 (0.86) respectively. The mean (± SD) ages for males and females were 34.29 (2.79) and 34.89 (2.79). Two-hundred ten (36.0%) were females exposed to famine during postnatal period (**Table 1).**

Cognitive test score

The mean (±SD) cognitive test score among the non-exposed and exposed groups were 21.11 ± 6.90 and 17.95 ± 7.43 respectively. While, the mean (± SD) cognitive test score based on the time of exposure for each group were as follows: Prenatal exposed 19. 43± 6.60, postnatal 16.48 ± 6.7. There were differences in cognitive test score between non-exposed groups and famine exposed groups (p-value < 0.001) **(Table 2).** Exposure to famine during postnatal had significantly lower cognitive test score **(Figure 2).** The mean (± SD) cognitive score was 18.37 ± 7.24 for non-exposed female and 14.58 ± 7.92 for postnatal exposed females. The mean (± SD) cognitive score was 23.67 ± 5.42 for non-exposed male and 19.36 ± 7.00 for postnatal exposed male **(Figure 3).**

Association between famine exposure in early life and adulthood cognitive functions

Compared with the non-exposed group, the exposed group had low cognitive score. Adults having early life famine exposure were 3.2 points decreased cognitive test score (β= -3.2, 95% CI: -4.1, -2.3). Exposure to famine during postnatal life was associated with a 4.83 points decrease in cognitive test score (β= -4.83, 95% CI: -6.37, -3.29) in the full adjusted model **(Table 3).** However, Exposure to famine during prenatal period was not significantly associated with adulthood cognitive test score. Males had higher cognitive test score (β= 1.22, 95% CI: 0.34, 2.11) in the final model (result not shown). The effect of famine exposure in early life was not modified by sex and residency (*P interaction > 0.05)* (result not shown)

Role of covariates

Although different models were developed to account for different sets of potential confounders, the association between postnatal famine exposure and adulthood cognitive function remained significant. The highest risk for decreased cognitive test score (β = 4.16, 95% CI (-5.18, -3.13) was observed after adjusted for sex and age at early childhood exposed group. Moreover, male sex and higher education (secondary and above) were positively associated with increased cognitive test score. Meanwhile, household wealth index was associated decreased score of cognitive test (data not shown).

Discussion

The main concern of this study was to examine the association between early life famine exposure and adulthood cognitive function. The focus of this article was thus the contribution of factors beyond socioeconomic, demographic, psychosocial adversaries in early life and other established determinants of adulthood cognitive function (17, 18, 29). We found that being exposed to famine during postnatal life was associated with decreased cognitive test score by 4.83 points when examining the association between famine exposure in early life with adulthood cognitive function using simple linear regression. This finding have been confounded by other predictors of cognitive status in adults. Then we adjusted for potential confounders including sex, age, body mass index, dietary pattern, smoking status, drinking status, Khat chewing status and physical activity, educational status, marital status, residency, occupational status and wealth index.

However, in all the adjusted models famine exposure in early childhood remained significant. On the contrary, famine exposure during prenatal period was not associated with adulthood cognitive test score in the final model. Male sex and educational status was positively associated cognitive function, while wealth index was negatively associated with it.

The finding that postnatal exposure to famine, but not prenatal exposure was associated with adulthood cognitive indicate the role of adequate nutrition during postnatal period (birth to 24 months of postnatal life) for determine adulthood cognitive function. This doesn't rule out the importance of nutrition during prenatal period on the cognitive status of adults. Although, there was no statistically significant association between prenatal famine exposure and adulthood cognitive function in final linear regression model, the mean cognitive test score was lower, as compared to the non-exposed group (mean difference = 1.68).

The following reasons may explain the associations of postnatal famine exposure, but not prenatal exposure on adulthood cognitive function: The first two years of postnatal period is the time for fastest growth and development of brain and double its size both of which are accompanied by highest energy and protein demand in human life (30). For instance, the development of the frontal lobes which is responsible for higher cognitive functions including planning, sequencing and self-regulation appears to occur in growth spurts during the first two years of life after birth (31). Thus nutritional deprivation during early life hampers the growth and development of the brain resulting in restricted cognitive functions during later in life (32). Moreover, malnutrition during the first two years of life affects growth, motor development and behavior of children to explore their environment through which it influence the maturity of the brain in early in postnatal life (33). Protein- energy malnutrition during the postnatal period resulted in smaller brain size related with fewer neurons, simpler synaptic connections and reduced concentration of neurotransmitters growth factors altogether contribute for poorer long term cognitive outcomes (34).

The mechanisms whereby early life famine exposure affects adulthood cognitive function was still unclear. Nonetheless, we comprehended the following reasons to explain the associations. Exposure to moderate to severe malnutrition in early life could alter

permanently the structure and function of the brain which could increases the risk of neuro cognitive impairment in early childhood period and the association may persist into adult life. The Developmental origin of health and diseases hypothesis indicates that malnourishment during fetal phase and first two years after birth could increase the risk of neurodegenerative disease in later life (35). Thus, malnourishment during the very beginning of life could result in a permanent deficit to brain structures (10, 14, 27). Animal studies(36, 37) and human studies (23, 26, 38, 39) have provided strong evidence for the hypothesis. In addition, epigenetic changes might be another potential mechanism that facilitated to understand the association between famine exposure in early life and the risk of cognitive impairment in adult life (40, 41). In Barbados Nutrition Study (BNS, long lasting DNA methylation changes associated with liability for defective attention and cognition in adult life was observed (42).

The findings in the present study was consistent with studies conducted in China famine birth cohort of the year 1959-61 (24, 25, 38). However, it was inconsistent with the study conducted in another Chines study (23). These variations could be explained by the heterogeneity of test tools. Mini-Mental Status examination (MMSE) was used to measure genitive function in Chinese study. The present study uses Montreal Cognitive assessment (MoCA) to measure cognitive function. Our study also observed that famine exposure during prenatal period was not associated with adulthood cognitive function. The finding is consistent with study of Dutch famine birth cohort study, (de Groot et al.,2010) reported that that there is no association between famine exposure in prenatal life and cognitive decline in adults (43). Similarly, a follow up study conducted in Hertfordshire revealed that cognitive performance in adult life was not associated with impaired fetal growth (44).

The presents study findings may extend our understanding of the long term impact of undernutrition and also lay the justification to extend our understanding of the genetic and epigenetic mechanisms of nutrition related cognitive impairment in later life. More interestingly, these findings may partly explain the reason behind cognitive related problems in Ethiopia, a country known for history of chronic food insecurity. Furthermore, these findings may help policy makers to lay context specific strategies peculiar to famine exposed regions of the country.

Conclusion

Famine exposure during early life, specifically postnatal exposure window was associated with adulthood cognitive function. This study therefore highlights the importance of improving nutritional status during the postnatal period of child growth and development in ways that stimulate adulthood cognitive function. This finding also provides further evidence for the hypothesis of developmental origin of adult disease. further studies are needed to elucidate the potential mechanism behind this association.

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Acknowledgements we would like to acknowledge the Institute of Health, Jimma University for funding the study. We are also grateful to the study participants for their dedicated time and volunteer participation.

Funding The study was funded by Jimma University, Institute of Health. The funder has no role in the design, implementation, analysis, and in the interpretation or write up of the manuscript.

Data sharing statement Extra data is available from the corresponding author on request.

Contributorship statement Getachew Arage and Dr. Kalkidan Hassen conceived and planned the study. Getachew Arage, Prof. Tefera Belachew, Dr. Mubarek Abera, Dr. Fedilu Abdulhay, Misra Abdulahi and Dr. Kalkidan Hassen implemented the study. Getachew Arage and Dr. Kalkidan Hassen did the analysis. Getachew Arage drafted the manuscript. Dr. Mubarek Abera, prof. Tefera Belachew, Dr. Fedilu Abdulhay, Misra Abdulahi and Dr. Kalkidan Hassen reviewed the manuscript. All authors gave input to the manuscript, read and approved the final version.

Consent for publication This is not applicable as the study does not have individual person's data.

Conflict of interest interests The authors declare no conflicts of interest

Ethics approval Ethical clearance was obtained from Institutional Review Board of Jimma University (Ref. No. JHRPGD/660/2019).

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List of tables

Table 1: Background characteristics of the study participants according to Ethiopian famine exposure status, Northeast Ethiopia, 2019 (n= 1047)

Variables	Non-exposed group n = 350	Prenatal exposed group n = 348	postnatal exposed n= 349	*P- value*
Age in years, mean ±SD	31.20 ±.0.66	35.05 ±.0.86	37.62 ± 0.50	<0.001*
Sex, n (%)				
Female	169 (48.3%)	205 (58.9%)	210 (60.2%)	0.002*
Male	181(51.7%)	143 (41.1%)	139 (39.8%)	
Residence, n (%)				
Urban	53 (15.2%)	70 (20.1%)	69 (19.7%)	0.165
Rural	297 (84.8%)	278 (79.8%)	280 (80.3%)	
Educational status				
Cannot read and write	87 (24.8%)	138 (39.6%)	165(47.3%)	
Primary school	66 (18.8%)	86 (24.7%)	84 (24.1%)	
Secondary school	116 (33.2%)	72 (20.7%)	57 (16.3%)	<0.001*
Above secondary school	81(23.2%)	52 (14.9%)	43 (12.3%)	
Household wealth index, n (%)				
Low	70 (20.0%)	76 (21.8%)	108 (30.9%)	
Medium	58 (16.6%)	55 (15.8%)	48 (13.7%)	0.011*
High	222 (63.4%)	217 (62.4%)	193 (55.4%)	
Marital status , n (%)				
Single	102 (29.2%)	54 (15.5%)	59 (16.9%)	
Married	220(62.8%)	230 (66.1%)	238 (68.2%	<0.001*
Divorced/Widowed	28 (8.0%)	64 (13.4%)	52 (9.2%)	
Current drinker, n (%)				
Yes	237 (67.7%)	220 (63.2%)	164 (46.9%)	0.001*
No	113 (32.3%)	128 (36.8%)	186 (53.3%)	
Ever drinker, n (%)				
Yes	110 (31.4%)	122 (35.1%)	182 (52.2%)	0.001*
No	240 (68.6%)	226 (64.9%)	167 (47.1%)	
Dietary pattern, n (%)				
Healthy	125 (35.7%)	113 (32.4%)	89 (25.5%)	
Unhealthy	225 (64.2%)	235 (67.5%)	260 (74.5%)	0.012*
Physical activity level, n (%)				
Low	6 (1.7%)	4 (1.2%)	51 (14.6%)	
Moderate	28 (8.0%)	40 (11.5%)	77 (22.1%)	<0.001*
High	316 (90.3%)	304 (87.3%)	221(63.3%)	
BMI (kg/m$^{2)}$, mean ±SD)	23.3 ± 4.83	23.06 ±5.21	23.36 ±.4.60	0.025*

P-value represents Independent Samples t-tests for continuous variables or χ2-test for categorical variables
** P < 0.05*

Table 2: Cognitive test score according to Ethiopian famine exposure status, Northeast Ethiopia, 2019 (n= 1047)

Famine exposure status	Score	p-value
Non- exposed	21.11± 6. 90	
Exposed	17.95± 7. 43	< 0.001*
Prenatal exposed	19. 43± 6.60	
Postnatal exposed	16.48± 6.7	

* Indicates statistical significant

Table 3: Relation between famine exposure in early life and adulthood cognitive function, Northeast Ethiopia, 2019 (n= 1047)

Models	Prenatal exposed	postnatal exposed	p-value
Model 1	-1.68 (-2.74, -0.62)	-4.63 (-5.69, -3.57)	*<0.001*
R^2(adjusted)		0.065	
Model 2	-1.26(-0.23, -0.74)	-4.16(-5.18, -3.13)	*0.002*
R^2(adjusted)		0.13	
Model 3	-0.56(-3.08, -1.94)	-1.79 (-3.36, -0.57)	*0.006*
R^2(adjusted)		0.16	
Model 4	-0.58(-2.74, -1.57)	-2.22 (-2.99, -2.46)	*<0.001*
R^2(adjusted)		0.37	
Model 5	-0.62(-2.77, 1.54)	-4.83 (-6.37, -3.29)*	*<0.001*
R^2(adjusted)		0.39	

Data are β-coefficients (95% confidence interval) from multiple linear regression analysis

All β-coefficients are related to the non-exposed groups

Model 1 Cognitive test score adjusted for famine exposure status

Model 2 adjusted for sex and age

Model 3 Adjusted for educational status, wealth index, marital status

Model 4 Adjusted for smoking status, drinking status, Khat chewing status and physical activity

Model 5 Adjusted for body mass index and dietary pattern.

Window of exposure to the 1983-1985 Ethiopian Great Famine cohorts, North Wollo Zone, 2019.

Date of birth (dd/mm/yyy)	Exposure to the famine (August 1983, August 1985)	Age during the famine	Age in 2019 (Current age)
During famine 08/August/1983-30/August /1985 (n=348)	Prenatal exposed	Famine exposure during the famine period	34-36
Post-famine 08/September/1986-30/August/1987	Transition (Washout period)	One years after the famine	33
Pre-famine 08/September/1981-08/August/1983 (n=349)	Postnatal exposed	Birth-two years during the famine	37-38
Post-famine 08/September/1987-08/October/1988 (n= 350)	Non- exposed (reference group)	Two years after the famine	30-32
Tota1 sample size		1047	

Dd: days, mm: months, yy: years

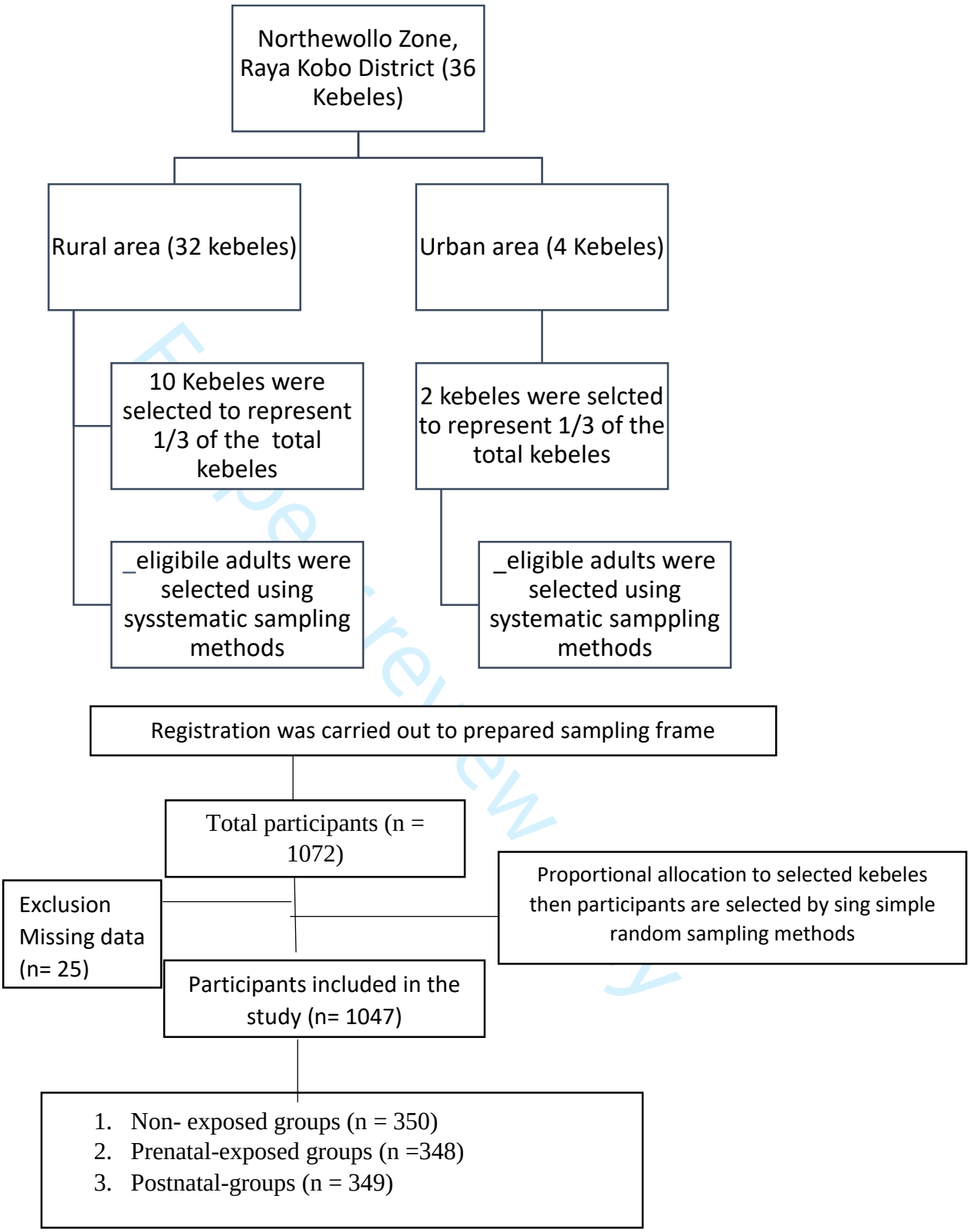

Figure 1: Flowchart showing how the final sample size was reached

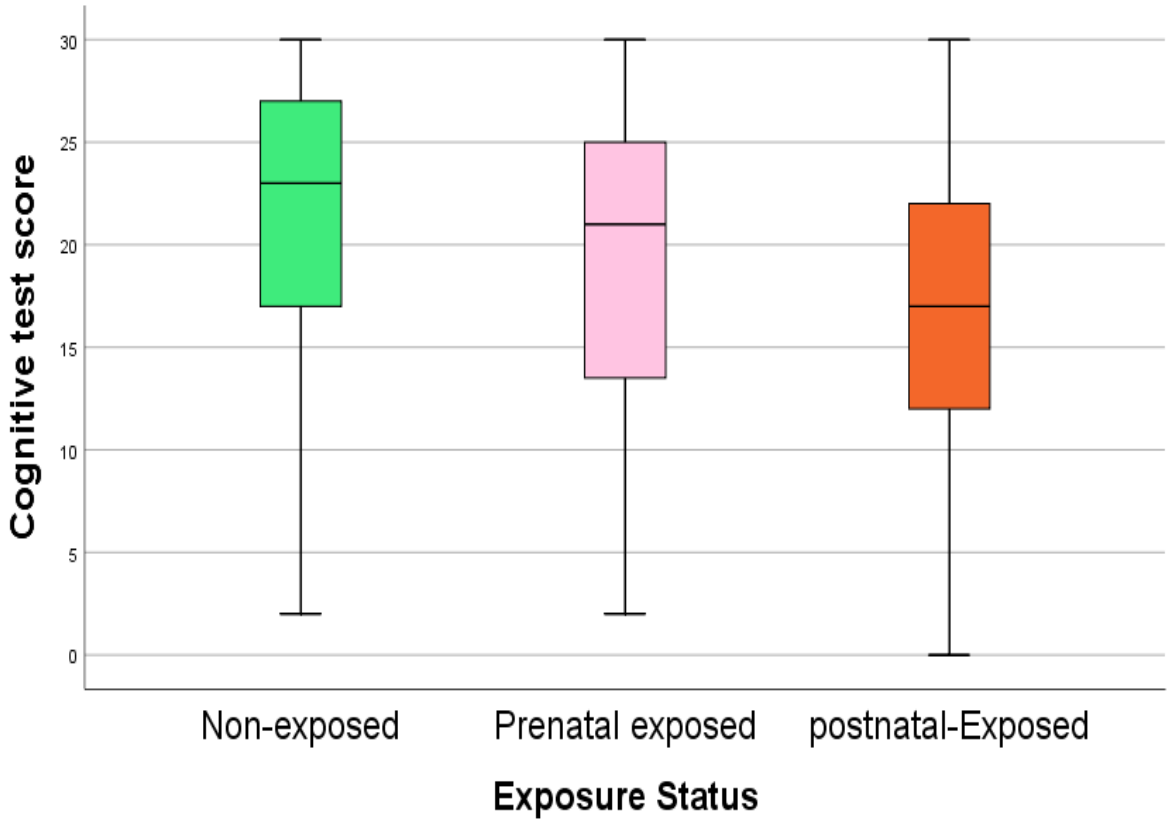

Figure 2. Distribution of cognitive test score by famine exposure status, Northeast Ethiopia, 2019 (n= 1047)

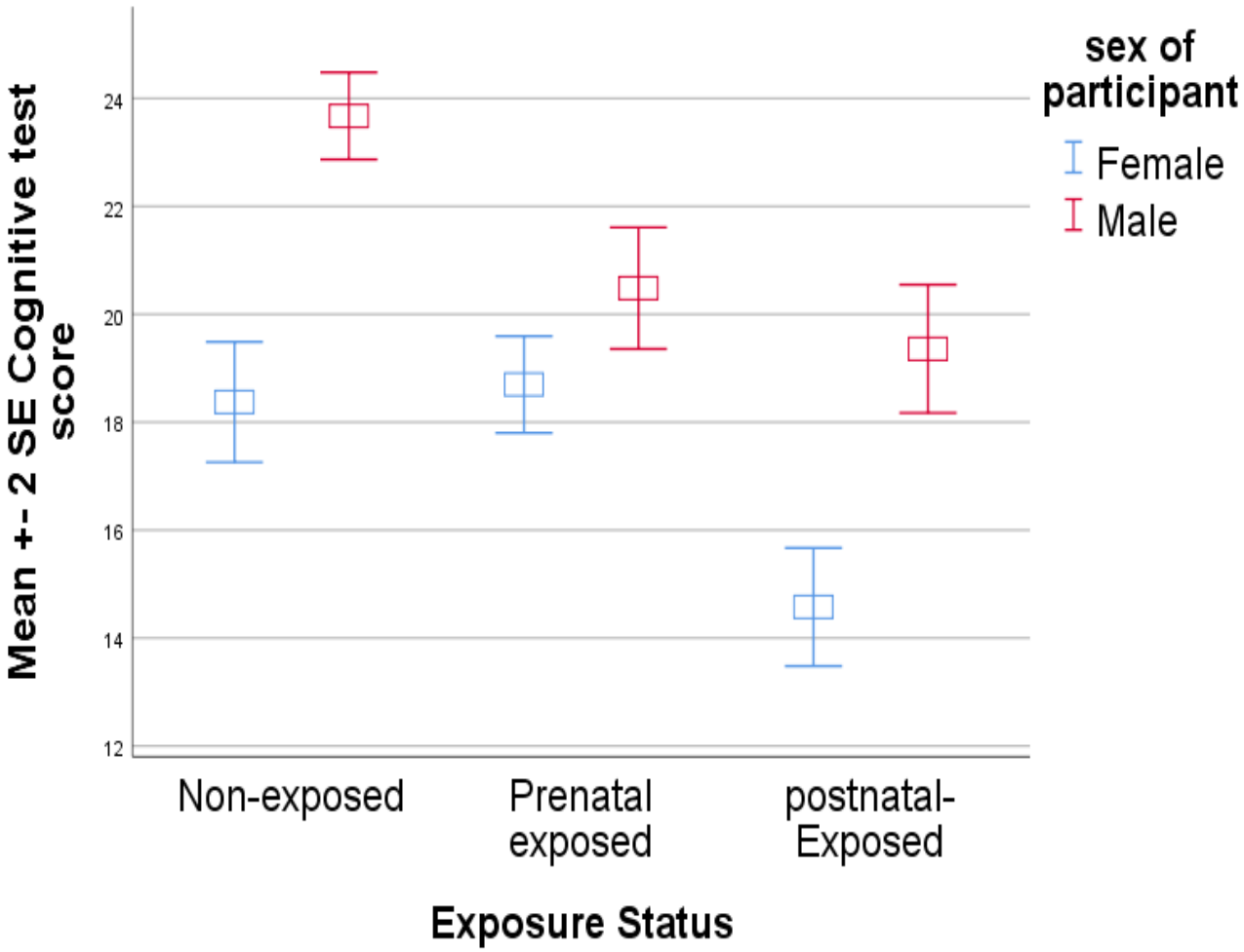

Figure 3: The mean and standard deviation of cognitive test score among famine exposed and non-exposed groups stratified by sex, northeast Ethiopia, 2019 (n = 1047)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038977.R1
Article Type:	Original research
Date Submitted by the Author:	22-Jun-2020
Complete List of Authors:	Arage, Getachew; Belachew, Tefera; Jimma University College of Public Health and Medical Sciences, Nutrition and Dietetics Abera, Mubarek; Jimma University College of Public Health and Medical Sciences, Psychiatry Abdulhay , Fedilu ; Jimma University College of Public Health and Medical Sciences, Obstetrics and Gynecology Abdulahi, Misra; Jimma University College of Public Health and Medical Sciences, Department of Population and Family Heath Hassen , Kalkidan; Jimma University College of Public Health and Medical Sciences, Nutrition and Dietetics
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Mental health
Keywords:	Nutritional support < GASTROENTEROLOGY, Adult neurology < NEUROLOGY, NUTRITION & DIETETICS

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Consequences of early life exposure to the 1983-1985 Ethiopian Great Famine on cognitive function in adults: a historical cohort study

Getachew Arage[1*2], Tefera Belachew[2], Mubarek Abera[3], Fedilu Abdulhay[4], Misra Abdulahi[5], Kalkidan Hassen Abate[1]

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Abstract

Objectives: To investigate the association between early life famine exposure and cognitive function in adults.

Design: Historical cohort study

Setting: Raya Kobo District, North Wollo Zone, Northeast Ethiopia.

Participants: We recruited 1047 adult men and women aged 30-38 years who had history of early life exposure to Ethiopian great famine. Based on self-reported age and birth date, participants were categorized into famine exposed in early life (prenatal/postnatal) and non-exposed groups.

Outcome measures: The primary outcome measure of this study was cognitive function in adults after early life exposure to famine. Cognitive function was measured using Montreal Cognitive Assessment (MCA)—basic. Associations between exposure and outcome variables were examined by linear regression analysis models.

Results: Adjusted for covariates, early life exposure to famine showed 1.29 (β = -1.29; 95% CI: -2.16, -0.52) points lower cognitive function score compared to non-exposed. Based on sub-analysis for timing of famine exposure, postnatal exposure to famine resulted in 2.26 (β = -2.26; 95% CI -3.12, -1.36) points lower cognitive function score compared to non-exposed groups. Prenatal famine exposure had 1.26 (β = -1.26; 95% CI -2.35, 0.94) points lower cognitive function score although not statistically significant.

Conclusions: Famine exposure in early life was associated with cognitive functions in adults. While the overall finings highlight the importance of optimal nutrition in early life for brain growth and development, the association observed between postnatal famine exposure and adult cognitive function may indicate the relative importance of learning and experience during early childhood for optimal brain development after birth. Further studies are needed to elucidate the potential mechanism behind this association.

Strengths and limitations of this study

- This is the first study to examine the effect of early life famine exposure on adulthood cognitive function in low income country, Ethiopia.
- To control for selection bias, a one year transitional (washout) period was considered.
- Severity of exposure at individual level was not considered
- Early childhood experiences, parent-child bond, and health status during early life didn't considered
- Birth weight and maternal factors including behavioral risk factors, psychological stress and infection didn't not considered

Introduction

Cognitive functions are a complex sets of higher mental activities controlled by the brain; and includes attention, memory, thinking, learning, and perception (1, 2). Rapid growth and development of the human brain (brain growth spurt) occurs during fetal and early postnatal (first 2 years of age) life. At birth, the brain already grown its 25% of adult size , and by the age of 2-3 years it grows 80% of its adult size (3, 4). As such the growth and subsequent functions of the brain can greatly be influenced by prenatal and postnatal environments such as malnutrition and other adverse life experiences (5). Nutrients are essentials for the formation of the building blocks of neurotransmitters, cell proliferation, deoxyribonucleic acid (DNA) synthesis, and enzyme in the brain (1). Malnutrition in the postnatal period affects child's ability to interact and explore with the environment which interferes with language, motor and social skills development; all of which are the foundation block for adult cognitive capacities (5, 6).

Currently the burden of neurological and mental health disorders are alarmingly increasing, particularly, with a higher pace in Sub-Saharan African countries (7, 8). According to the 2016 Global Burden of Disease (GBD) report, neurological disorders were the leading cause of Disability-Adjusted Life Years (DALYs) (9). In Ethiopia high prevalence of cognitive impairment was observed among adults living with underlying medical disorders such as HIV/ AIDS, and diabetes mellitus (10-12).

Early scientists Barker and colleagues introduced a theory called "Fetal Origin of Adult Diseases (FOAD)" or "Developmental Origins of Health and Disease (DOHaD)" to explain the long term consequences of early life undernutrition on adult health and diseases such as cognitive function (13-15).

Famine study provides an opportunity to examine the association between early life nutrition and its long term effects on adult diseases including cognitive function. Previous famine studies have contributed substantial evidence on the association between famine exposure in early life and cognitive function in adults, and reported heterogeneous findings (16-20).

The 1983-1985 Ethiopian Great Famine was one of Africa's most severe famines that caused over half a million deaths (21, 22). It affects the whole Ethiopia and returns to normal year (but some problems in certain villages) during September 1986 – September 1987 (21). Hence, we conducted this study to investigate the effects of early life exposure

to famine (prenatal and first 2 years of postnatal life**)** on cognitive function in adults among survivors of the Ethiopian Great famine in Wollo province, Ethiopia.

Methods and Materials

Study setting and design

The study setting has been described in detail elsewhere (23). Briefly, the study was conducted in Raya Kobo District, northeast Ethiopia, which was the epicenter for the 1983-1985 Ethiopian great famine (21). A historical cohort study design was employed from March 15 to April 30, 2019.

Study participants and sampling

Adult men and women aged 30-38 years who had history of early life exposure to famine were the study participants**.** Self-reported age and birth date were used to categorize famine exposure status. The start and end dates of the famine was used to define windows for famine exposure (21). Thus, the study participants were categorized into two groups: Early life exposed, age from 34 to 38 years with birth date between September 8, 1981 to August 30, 1985; non-exposed, age from 30 to 32 years with birth date between September 8, 1987 to October 8, 1988. The early life famine exposed groups were further grouped into prenatally exposed, age from 34 to 36 years with birth date between August 8, 1983 to August 30, 1985 and postnatal-exposed, age from 37 to 38 years with birth date between September 8, 1981 to August 8, 1983. In order to get optimal washout period between exposed and non-exposed groups, participants born immediately after end of the famine (between 8, September 1986 to 30, August 1987) were excluded from this study **(supplementary file1).** Additionally, adults who were displaced to other area of the country and those who were in other location during the famine and participants with deformity (Kyphosis, Scoliosis, and limb deformity) were excluded from the study.

Two population mean formula using G-Power 3.0.10 and taking type one error 5%, 80% power, a design effect of 1.5 and calculated effect size of 0.1817 was used to calculate the sample size. Assuming the mean (± SD) of general cognition score in exposed groups 12.06 (3.50) and non-exposed groups 11.40 (3.76) from a study conducted in China (17), the total calculated sample size was 1071 (714 exposed and 357 non-exposed groups). We included 1047 (697 exposed and 350 non-exposed groups) participants who had a

complete data on all variables required in the analysis. Multistage stratified random sampling technique was used to select the study participants **(Figure 1)**.

Patient and public involvement

There was no direct public or patient involvement in the design and implementation of this study.

Data collections and measurement

Pretested and structured questionnaire was used to collect socio-demographic/economic data and lifestyle factors of participants using face-to-face interview. The questionnaire was first prepared in English and then translated into Amharic (the local language) and back into English to ensure consistency. Eight trained clinical nurses collected the data.

Main exposure variable

The main exposure variable, early life (prenatal and first 2 years of post-natal life) exposure to the 1983-85 Ethiopian great famine was determined using the age and birth date of participants. We considered the participants is prenatal exposed (intrauterine life or born during the famine), postnatal exposed (first 2 years of age during the famine) and non-exposed (born after the famine).

Outcome measure

The primary outcome variable, cognitive function was measured using the Montreal Cognitive Assessment (MoCA)-basic. MoCA enables the assessment of different domains of cognitive function including perception, thinking, reasoning and memory. It has high reliability in individuals who are illiterate and have low-educational status (24). The cognitive function score for each item was added to get the total score; then the mean score was computed.

Covariates

Additionally, various sets of covariates including participants sex, age, educational status, marital status, residence, occupational status, wealth index, dietary pattern, substance use and physical activity were collected. We define household wealth index, substance use and physical activity similar to previous study (23). Dietary pattern was assessed using qualitative food frequency questionnaire (FFQ). Participants were asked to report the

frequency of consumption of each food per day, per week or per month using the past one year as a reference (25). Two major dietary patterns, healthy and unhealthy, were derived through K-means cluster analysis. The detail for assessing dietary patterns has been described as supplementary file **(Supplementary file 2)**. History of raised blood pressure and diabetes were assessed by interviewing adults. Body mass index (BMI) was calculated as the weight in kilogram divided by height in meters squared (kg/m^2). Blood pressure was measured in triplicate using digital blood pressure measurement after 5 minutes of rest. Sex of the participants and residency were considered as potential effect modifiers.

Statistical Analysis

The data were doubly entered to Epidata 3.1 and exported to SPSS version 25 ([SPSS Inc., Chicago, Illinois] for analysis. Percentages were used to described categorical variables while mean and standard deviation (± SD) or medians and interquartile ranges (IQR) were used to described continuous variables. Differences in mean cognitive function score among different groups of early life was compared using one-way and two-way analysis of variance (ANOVA) or T-test.

A series of linear regression analyses with robust statistical procedures were conducted to evaluate association between the three exposure categories (early life, prenatal or postnatal exposure) and cognitive function in adults. The estimate (β-coefficients) and 95% CI were reported to describe the associations. Three sets of regression models were developed. Model 1: included the outcome and the main exposure variable (famine exposure status). Model 2: built on model one by adding sex, age, residence and educational status. Model 3: full adjusted model built on model two by adding body mass index, dietary pattern, increased blood pressure, physical activity, cigarette smoking, alcohol drinking, history of hypertension, diabetes and effect modifiers. The rationale of the different models was to observe changes in the association between the main exposure and outcome variable when different sets of covariates were accounted in the model. The outcome variable, cognitive function score was tested for normality using a P-P plot and a steam leaf diagram, and all potential confounders were tested for linearity with the outcome variable using scatter plots. Effect modification by sex and residence were assessed by including interaction terms for both famines exposed groups. P-values

presented were based on two-tailed test and $P < 0.05$ was considered statistically significant.

Results

Background characteristics

A total of 1047 participants (697 exposed and 350 non- exposed groups) were enrolled to the study. The mean (± SD) ages for early life exposed and non-exposed groups were 36.30 (± 1.5) and 31.2 (± 0.6), respectively. Four-hundred-fifteen (59.5%) of the participants were females exposed to famine. Five-hundred-fifty-eight (80.1%) of the participants were rural residents exposed to famine. Three-hundred-three (43.5%) of them can't read and write among early life exposed groups **(Table 1).**

Cognitive function

The mean (± SD) cognitive function score among early life exposed and non-exposed groups were 17.95 ± 7.43 and 21.11 ± 6.90 respectively. Based on the time of exposure to famine, the mean cognitive function score for prenatal and postnatal exposed group was 19.43 ± 6.60 and 16.48 ± 6.70 respectively. Among early exposed groups, the mean cognitive test score was 16.61 ± 7.50 for females and 19.93 ± 6.87 for males whereas it was 18.53 ± 6. 92 for urban and 15.65 ± 8.84 for rural residents (**Table 2**).

Early life famine exposure and cognitive function in adults

Multivariable linear regression analysis was used to detect the association between cognitive function and the famine exposure in early life **(Table 3)**. After adjusted for the main exposure variable (Model 1), the cognitive function score in early life, prenatal and postnatal exposed groups were lowered by 3.16 (β = -3.16; 95% CI: -4.09, -2.28), 1.68 (β = -1.68; 95% CI: -2.74, -0.62) and 4.66 (β = -4.66; 95% CI: -5.76, -3.55) points respectively compared to non-exposed groups. After adjusted for sex, age, residence and educational status (Model 2), the score of cognitive function was lowered by 1.12 (β = -1.12; 95% CI: -1.89, -0.33), 1.27 (β = -1.27; 95% CI: 2.27, -0.12) and 2.18 (β = -2.18; 95% CI: -3.11, -1.27) points in early life, prenatal and post-natal exposed groups respectively. In the fully adjusted model (Model 3), early life exposure to famine showed 1.29 (β = -1.29; 95% CI: -2.16, -0.52) points lower cognitive function score compared to non-exposed. Postnatal exposure resulted in 2.26 points

reduction (β = -2.26; 95% CI: -3.12, -1.36) while prenatal exposure resulted in 1.26-point reduction (β = -1.26; 95% CI: -2.35, 0.94) in cognitive function scores although the later was not statistically significant. The effect of famine exposure in early life was not modified by sex and residency (*P interaction > 0.05)* (results not shown).

Role of covariates

Different models were used to account for different sets of potential confounders. But, he association between early life famine exposure and adulthood cognitive function continued significant. The highest effect of famine exposure on low cognitive function score (β = -3.16; 95% CI (-4.09, -2.28) was observed in unadjusted regression model (**Table 3**). Moreover, male sex and educational status of secondary and above were positively associated cognitive function. Rural residency and unhealthy dietary pattern was negatively associated with cognitive function in adults **(Table 4).**

Discussion

The main goal of this study was to examine the association between early life famine exposure and cognitive function in adults. The focus of this article is therefore to describe the contributions of factors beyond early childhood experience and adult lifestyles, which affects cognitive function of adults (2, 26, 27).

When examining the association between famine exposure in early life with cognitive function in adults using multivariable linear regression models, adults who had early life exposure to famine were 1.29 points lowered cognitive function score. This association might have been confounded by other predictors of cognitive function in adults. To account for this, we adjusted for potential confounders. However, in all of these adjusted models the observed association remained significant after adjustment for potential confounders. A sub-analysis by timing of exposure, we found that adults who had prenatal famine exposure resulted in 1.26 points lowered cognitive function score compared to non-exposed though not statistically significant. Similarly, postnatal exposure to famine had 2.26 points decreased cognitive function score after adjusted for all possible covariates.

Our findings showed that early life exposure to famine negatively affected adult cognitive function. Although much is not known about the mechanisms how early life famine exposure affects cognitive function in adult life, this might be explained by the potential capacity of adverse life experience during early life that could have impaired the growth and development of the brain, which can affect cognitive function across the life span (28). In addition, epigenetic changes during early life is another potential mechanism that facilitated to understand the association between famine exposure in early life and the risk of altered cognitive function in adults (29, 30). In Barbados Nutrition Study, long lasting DNA methylation changes due to early childhood malnutrition was associated with liability for defective attention and cognition in adults (31).

The finding that postnatal exposure to famine, but not prenatal exposure was associated with cognitive function in adults can be discussed from the following three perspectives. Firstly, from the biological point of view, the first two years of postnatal life is a period of the fastest brain development compared to other periods, and accompanied by highest energy demands of the brain (3, 4, 32). The frontal lobe, which is the center for higher cognitive functions including planning, sequencing and self-regulation appears to occur in growth spurts during the first two years of life after birth (4). The study of Georgieff et al., (2006) reported that protein- energy malnutrition during the postnatal period resulted in smaller brain size related with fewer neurons, simpler synaptic connections and reduced concentration of neurotransmitters, and growth factors altogether contribute for poorer long term cognitive outcomes (33). Moreover, this might be due to the fact that nutrient supply to the brain might not be affected unlike other organs. As a result, under-nutrition during prenatal life couldn't have a profound effect on cognitive decline in adults (15).

Secondly, from the behavioral point of view, malnourishment during the first two years of life has been associated with immaturity of the brain likely due to lack of stimulus from deprived environments and lack of opportunity to play, communication and explore to their environment (6). Moreover, the mother could not have the capacity to actively engage their young children to play and communication as the mother themselves have affected by the famine. Thus, the lack of opportunity to get engaged and to explore the environment as a secondary complication of the malnutrition from famine might rather

explain the lower cognitive function in adulthood. Impaired exploratory behavior and motor development can further compromise and potentiate early damage of the brain (34). Thirdly, those children who experienced famine in their postnatal life could have higher risk of stunting. Studies show that stunting in early life is associated with poor cognitive function in later life (35, 36). Furthermore, the implication of sever famine like Ethiopian great famine affects children in early life is not only related with insufficient foods. It also affects the quality of parent-child bond, social development and a child's ability to interact with the environment, which determine cognitive function in the long run (2, 4, 21).

In this study, we observed that the scores on the Montreal Cognitive Assessment are all below standard cut off scores, even in the unexposed group. Therefore, it is important to notice different factors responsible for lower score in the overall population. Ethiopia is known by high burden of stunting among children (37). The ability to get adequate nutrition is the commonest problem in Ethiopia. Consequently, early childhood stunting is negatively associated with cognitive function in adults (35, 36). Moreover, factors such as parental schooling, wealth, size at birth, duration of breast feeding, health problems of early childhood (diarrhea, malaria, acute respiratory illness, malaria) have impact on cognitive function in later life. All of which could have affected the outcome among the overall populations (2, 38).

The observed association between early life famine exposure and cognitive function in adults was consistent with studies conducted in the Chinese famine exposed birth cohorts of the year 1959–1961 (16, 17, 20), Dutch famine (19) and Ghana famine (39). The study participants during the Chinese, Ghana and Ethiopian famine were selected from the settings known for chronic malnutrition. The finding that prenatal exposure to famine was not associated with cognitive function is consistent with other Dutch famine study (40) and Hertfordshire follow up study (41). Nonetheless, our finding is inconsistent with other Chines famine study (18). These variations could be explained by the heterogeneity of test tools. Comprehensive neuropsychological tests, containing the Telephone Interview of Cognitive Status (TICS-10), word recall, and pentagon drawing was used to estimate cognitive performance in Chinese study (18), as Montreal Cognitive Assessment was used in Ethiopian study.

The presents study finding has implications for the global rise of neurodevelopmental problems. It adds for understanding of the links between early life and later health, and examines the role of nutrition in utero and postnatal life in the etiology of decreasing cognitive function in later life More remarkably, these findings are used to plan effective ways of improving cognitive function of adults in Ethiopia, a country known for high prevalence of malnourishment during early life (37). Additionally, these findings may help policy makers to establish context specific strategies particular to famine prone regions of the country.

There are several limitations of our study. First, the findings might be partly biased by survival bias. It is plausible that potential participants couldn't participate because of health related problems, and others may have already died due to the exposure. Second, exposure to the famine was defined using the self-reported birth date and age, thus recall bias cannot be ruled out. However, it is at our utmost belief that the exceptional catastrophic period of the famine, named as ''Kefu Qan'' in the memory of the survivors and the world could not be forgettable. Third, severity of exposure at individual level was not considered although the long-term consequence of famine depends on the severity of the exposure within the household. Fourth, the study didn't capture early childhood experiences such as parent-child bond, parenting style and neonatal problems such as asphyxia, hypoglycemia, hypothermia, preterm, which causes brain damage and predispose to reduced cognitive function in later life. Finally, reduced in cognitive function could be worsening with age. However, the prolonged Ethiopian great famine affected almost the whole Ethiopia (21), making it impossible to identify a control group that was not affected by famine. To overcome this limitation, age adjustment was conducted in the multivariate model. Despite all these limitations, our study is the first to investigate long-term consequences of early life exposure to famine in the context of low income countries like Ethiopia.

In conclusion, famine exposure during early life was positively associated with cognitive function in adults. More specifically, postnatal famine exposure was associated with decreased cognitive function. Although there was no statistically significant association between prenatal exposure to famine and cognitive function in adults, a decrease in cognitive test score was observed. The study will potentially lead to better nutritional interventions during intrauterine period and the first two years of postnatal life. The

mechanism through which famine exposure during early life influenced adult cognitive function needs additional study in a similar context.

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Acknowledgements The authors would like to acknowledge the Institute of Health, Jimma University for funding the study. The authors are also grateful to the study participants for their dedicated time and volunteer participation

Contributorship Getachew Arage (GA), Kalkidan Hassen Abate (KHA), and Mubarek Abera (MA) conceived and planned the study. GA implemented and supervised the field work. Fedilu Abdulhay (FA) and Misra Abdulahi (MAB) were involved in data cleaning and verification. GA, KHA and MA did the analysis and interpretation. GA, FA and MAB drafted the manuscript. MA, KHA,Tefera Belachew (TB) and MAB critically revised the manuscript. All authors have reviewed the manuscript and approved the final version for submission.

Funding The study was funded by Jimma University, Institute of Health. The funder has no role in the design, implementation, analysis, and in the interpretation and write up of the findings

Competing interests None declared.

Ethics approval Ethical approval was obtained from Institutional Review Board of Jimma University (Ref. No. JHRPGD/660/2019).

Data sharing statement Extra data is available from the corresponding author on request.

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List of tables

Table 2: Distribution of cognitive test score by famine exposure status, sex of participant and residency, Northeast Ethiopia, 2019 (n= 1047)

Variables	Early life exposed§	Prenatal exposed	Postnatal exposed	Non-exposed	P-value
Cognitive test score,	17.95 ± 7. 43	19.43 ± 6.60	16.48 ± 6.70	21.11 ± 6. 90	< 0.001

Table 1: Background characteristics of the study participants according to Ethiopian famine exposure status, Northeast Ethiopia, 2019 (n= 1047)

Variables	Early life exposed§ n = 697	Prenatal exposed group n = 348	Postnatal exposed n= 349	Non- exposed group n = 350	P- value
Age, (years), mean ± SD	36.3 ± 1.5	35.05 ± 0.8	37.62 ± 0.5	31.20 ± 0.6	< 0.001*
Sex, n (%)					
Female	415 (59.5%)	205 (58.9%)	210 (60.2%)	169 (48.3%)	0.002*
Male	282 (40.5%)	143 (41.1%)	139 (39.8%)	181 (51.7%)	
Residence, n (%)					
Urban	139 (19.9%)	70 (20.1%)	69 (19.7%)	53 (15.2%)	0.165
Rural	558 (80.1%)	278 (79.8%)	280 (80.3%)	297 (84.8%)	
Educational status					
Cannot read and write	303 (43.5%)	138 (39.6%)	165 (47.3%)	87 (24.8%)	
Primary school	170 (24.4%)	86 (24.7%)	84 (24.1%)	66 (18.8%)	
Secondary school	129 (18.5%)	72 (20.7%)	57 (16.3%)	116 (33.2%)	< 0.001*
Secondary and above	95 (13.6%)	52 (14.9%)	43 (12.3%)	81(23.2%)	
Household wealth index, n (%)					
Low	184 (26.4%)	76 (21.8%)	108 (30.9%)	70 (20.0%)	
Medium	103 (14.7%)	55 (15.8%)	48 (13.7%)	58 (16.6%)	0.011*
High	410 (58.8%)	217 (62.4%)	193 (55.4%)	222 (63.4%)	
Marital status , n (%)					
Single	113 (15.5%)	54 (15.5%)	59 (16.9%)	102 (29.2%)	
Married	468 (67.2%)	230 (66.1%)	238 (68.2%	220 (62.8%)	< 0.001*
Divorced/Widowed	116 (17.4%)	64 (18.4%)	52 (14.8%)	28 (8.0%)	
Current drinker, n (%)					
Yes	384 (55.1%)	220 (63.2%)	164 (46.9%)	237 (67.7%)	
No	313 (44.9%)	128 (36.8%)	185 (53.1%)	113 (32.3%)	0.001*
Dietary pattern, n (%)					
Healthy	202 (28.9%)	113 (32.4%)	89 (25.5%)	125 (35.7%)	
Unhealthy	495 (71.1%)	235 (67.5%)	260 (74.5%)	225 (64.2%)	0.012*
Physical activity level, n (%)					
Low	55 (7.8%)	4 (1.2%)	51 (14.6%)	6 (1.7%)	
Moderate	117 (16.8%)	40 (11.5%)	77 (22.1%)	28 (8.0%)	< 0.001*
High	525 (75.4%)	304 (87.3%)	221 (63.3%)	316 (90.3%)	
BMI (kg/m^2), mean ± SD	23.3 ± 4.9	23.06 ± 5.21	23.36 ± 4.60	23.3 ± 4.83	0.025*
History of Diabetes mellitus					
Yes	115 (16.5%)	15 (4.3%)	100 (28.6%)	14 (4.0%)	
No	582 (83.5%)	333 (95.6%)	249 (71.4%)	336 (96.0%)	< 0.001*

§ Prenatal and postnatal exposed, P-value—represents Independent Samples t-tests for continuous variables or $\chi 2$-test for categorical variables, * Statistical significance

mean ± SD					
Sex					
Female	16.61 ± 7.50	18.70. ± 6.42	14.53 ± 7.94	18.37 ± 7.24	0.031
Male	19.93 ± 6.87	20.48. ± 6.74	19.36 ± 7.02	23.67 ± 5.41	
Residence					
Urban	18.53 ± 6. 92	19.48 ± 6.62	17.57 ± 7.12	21.47± 6. 81	0.673
Rural	15.65 ± 8.84	19.24 ± 6.53	11.90 ± 9.43	19.13 ± 6.79	

§ Prenatal and postnatal exposed, P-value—represents Independent Samples t-tests or Two-way ANOVA for continuous variables

Table 3: Associations between early life famine exposure and cognitive function in adults, North Wollo Zone, Raya Kobo district, Northeast Ethiopia, 2019.

Models	Early life exposed§	Prenatal exposed	postnatal exposed	Non-exposed
Model 1	-3.16 (-4.09, -2.28)	-1.68 (-2.74, -0.62)	-4.66 (-5.76, -3.55)	Ref.

Table 4: Multivariable linear regression model predicting cognitive function of adults in North Wollo Zone, Raya Kobo district, Northeast Ethiopia, 2019.

Variables	Early life exposed	Non-exposed	P-value
Sex of participants (male)	2.75 (1.83, 3.67)	Ref.	< 0.001
Place of residence (rural)	-1.57 (-2.75, -0.38)	Ref.	0. 010
Educational status (Secondary and	3.15 (2.69, 3.61)	Ref.	< 0.001
R^2(	0.04	0.02	0.08	Ref.
adjusted)				
Model 2	-1.12 (-1. 89, -0.33)	-1.27 (-2.27, -0.12)	-2.18 (-3. 11, -1.27)	Ref.
R^2(	0.36	0.35	0. 42	Ref.
adjusted)				
Model 3	-1.29 (-2.16, -0. 52)	-1.26 (-2.35, 0.94)	-2. 26 (-3.12, -1. 36)	Ref.
R^2(	0.37	0. 36	0. 45	Ref.
adjusted)				

§ Prenatal and postnatal exposed, Ref—Reference

Data are β-coefficients (95% confidence interval) from multiple linear regression analysis

All β-coefficients are related to the non-exposed groups

Model 1: Cognitive test score with famine exposure (unadjusted for any covariate)

Model 2: adjusted for sex, age, residence and educational status

Model 3: Adjusted for body mass index, dietary pattern, increased blood pressure, physical activity, cigarette smoking, alcohol drinking, history of chronic diseases and effect modifiers

above)			
Dietary pattern (unhealthy)	-1.84 (-2.80, -0.88)	Ref.	< 0.001
History of diabetes mellitus	-1.13 (-2.47, -0.204)	Ref.	0.09
Adjusted $R^2 = 0.45$, Ref—Reference,			

Figure legends

Figure 1. Flow diagram representing sample recruitment.

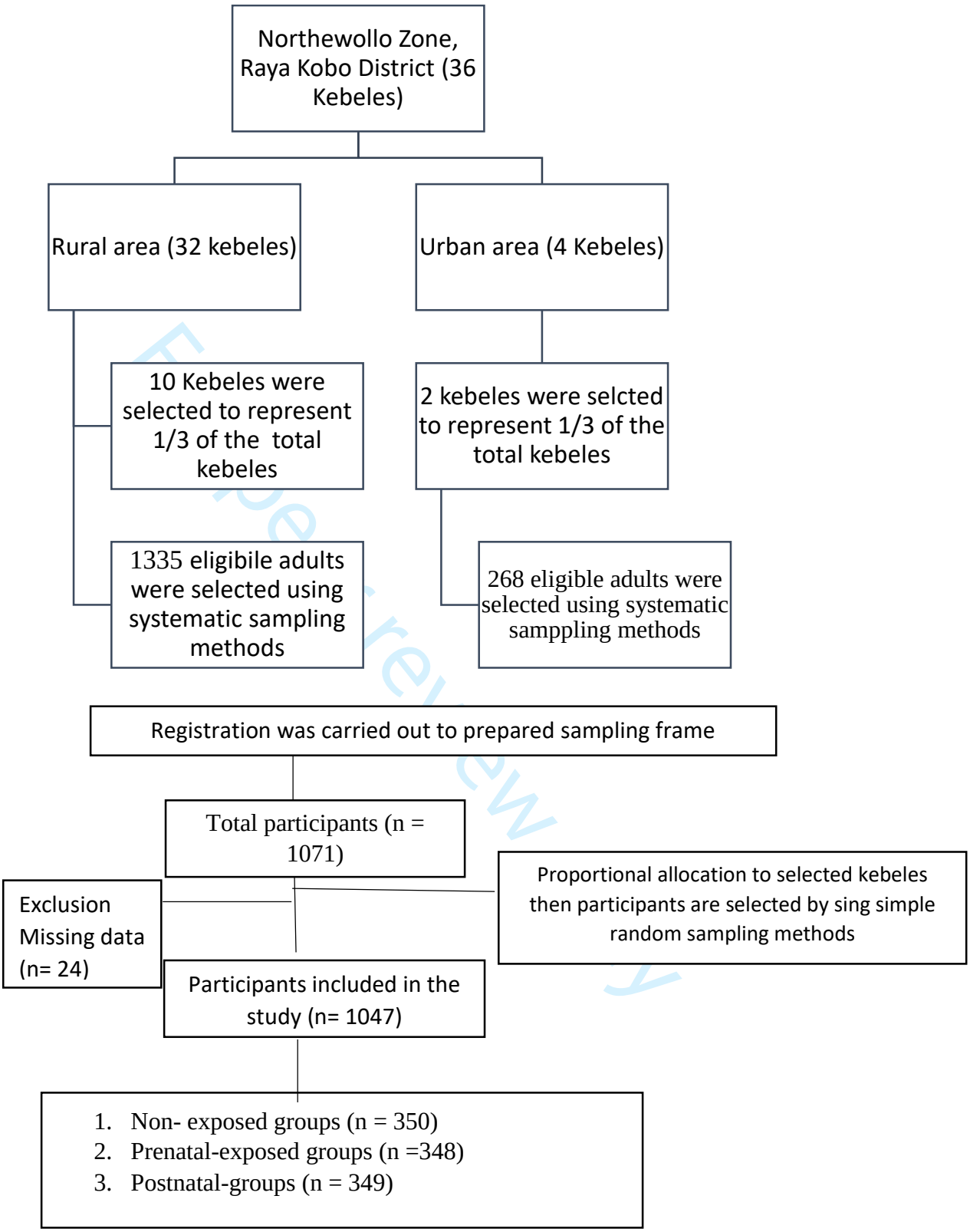

Figure 1. Flow diagram representing sample recruitment.

Window of exposure to the 1983-1985 Ethiopian Great Famine cohorts, North Wollo Zone, 2019.

Date of birth (dd/mm/yyy)	Exposure to the famine (August 1983, August 1985)	Age during the famine	Age in 2019 (Current age)
During famine 08/August/1983-30/August /1985 (n=348)	Prenatal exposed	Famine exposure during the famine period	34-36
Post-famine 08/September/1986-30/August/1987	Transition (Washout period)	One years after the famine	33
Pre-famine 08/September/1981-08/August/1983 (n=349)	Postnatal exposed	Birth-two years during the famine	37-38
Post-famine 08/September/1987-08/October/1988 (n= 350)	Non- exposed (reference group)	Two years after the famine	30-32
Tota1 sample size		1047	

Dd: days, mm: months, yy: years

Dietary assessment

Dietary pattern was assessed using qualitative food frequency questionnaire (FFQ) composed of 38 food items covering the main foods consumed in the study area (Aragie and Genanu, 2017, Selinus, 1971). Furthermore, the lists of food items were developed based on an extensive interview of the key informants who know the culture and the types of foods consumed in the study area. Participants were asked to report the frequency of consumption of each food per day, per week or per month using the past one year as a reference (Rodríguez et al., 2002). The consumption of each food item per day was not taken as a cut-off point to define consumers because of the large variation of dietary habit in the community over the days of the week. Rather, adults were coded as a ‘‘consumer’’ of a food item if they had consumed the food item at least once per week. As there is no Ethiopian classification of food groups, the 38 food items were grouped into six groups [cereals, vegetables and fruits, dairy products, protein foods, oils, others] according to the) FAO food groups (Assessment, 2018).

Means (± SD) intake of food groups per week in any given week during the last one year before the survey by famine exposure status, North Wollo Zone, Raya Kobo district, Northeast Ethiopia, 2019.

Food groups	Early life exposed[§]	Prenatal exposed	postnatal exposed	Non-exposed
Cereals	1.00 ± 0.09	1.00 ± 0.03	1.00 ± 0.00	1.00 ± 0.9
Vegetables and fruits	0.19 ± 0.40	0.17 ± 0.05	0.39 ± 0.70	0.48 ± 0.65
Protein source food (both plant and animal)	0.18 ± 0.01	0.19 ± 0.60	0.20 ± 0.08	0.36 ± 0.60
Oils	0.80 ± 0.50	0.89 ± 0.60	0.50 ± 0.03	1.00 ± 0.15
Others*	0.92 ± 0.52	1.00 ± 4.9	0.70 ± 0.30	1.00 ± 0.89

[§] Prenatal and postnatal exposed

T-test was done to assess the differences between famine exposed and non-exposed groups by intake of the different food groups. The food items were grouped according to Food and Agricultural organization (FAO). Means (± SD) indicates the frequency of consumption of the different food groups per week between food famine exposed and non-exposed groups

* spices, condiments, beverages

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STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study Design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5 N/A N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study Size	10	Explain how the study size was arrived at	6
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A N/A N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	N/A
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key Results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

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

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.