Title: Childhood and Infant exposure to famine in the Biafran war is associated with hypertension in later life: The Abia NCDS Study

Short Title: Exposure to famine in early childhood and hypertension risk

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Word Count: 3722

Abbreviations:

Abia State Non-Communicable Diseases and Cardiovascular Risk Factors survey, AS-NCD-CRF survey.

AME, Average marginal Effect

DBP, Diastolic Blood Pressure

DOHaD, Developmental Origin of Health and Disease

NCDs, Non-communicable Diseases

SBP, Systolic Blood Pressure

ABSTRACT

There are very few studies in Africans investigating the association between early life exposure to malnutrition and subsequent hypertension in adulthood. We set out to investigate this potential association within an adult cohort who were born around the time of the Biafran War (1968-1970) and subsequent famine in Nigeria.

This was a retrospective analysis of Abia State Non-Communicable Diseases and Cardiovascular Risk Factors (AS-NCD-CRF) Survey, a community-based, cross-sectional study that profiled 386 adults (47.4% men) of Igbo ethnicity born in the decade between January 1965 and December 1974. Based on their date of birth and the timing of the famine, participants were grouped according to their exposure to famine as children (Child-Fam) or in-utero fetus/infant (Fet-Inf-Fam) or no exposure (No-Fam). Binomial logit regression models were fitted to determine the association between famine exposure and hypertension in adulthood.

Overall, 130 participants had hypertension (33.7%). Compared to the No-Fam group (24.4%), the prevalence of hypertension was significantly elevated in both the Child-Fam (43% - adjusted OR 2.47, 95% CI 1.14-5.36) and Fet-Inf-Fam (44.6% - adjusted OR 2.54, 95% CI 1.33-4.86) groups. The risk of hypertension in adulthood was highest among females within the Child-Fam group. However, within the Fet-Inf-Fam group males had a equivalently higher risk than females.

These data suggest that early life exposure to famine and malnutrition in Africa is associated with a markedly increased risk of hypertension in adulthood; with sex-based differences evident. Thus, the importance of avoiding armed conflicts and food in-security in the region cannot be overstated. The legacy effects of the Biafran War clearly show the wider need for ongoing programs that support the

nutritional needs of African mothers, infants and children as well as proactive surveillance programs for the early signs of hypertension in young Africans.

Keywords: famine, fetal-infant malnutrition, Barker's hypothesis, hypertension, Biafra, civil war

INTRODUCTION

Early life and childhood malnutrition have been linked with future increased risk of cardiovascular diseases in adulthood in experimental models.[1,2] Moreover, follow-up studies from survivors of the Dutch famine and the Leningrad siege provide evidence for the role of fetal and childhood undernutrition in cardiovascular diseases in middle age.[3–7] This phenomenon has been aptly explained by the Barker hypothesis.[8–10] Fetal malnutrition leads to a 'thrifty' phenotype in extra-uterine life and a mismatch with the environment during periods of food abundance with resultant accumulation of salt and insulin resistance which leads to increased risk of hypertension and diabetes.[11]

Children in sub-Saharan Africa and many other developing countries continue to suffer and die from malnutrition.[12,13] This is exacerbated by regional conflicts, wars and insurgencies leading to displacement of people, severe disruption of food supplies and poverty. Furthermore, many of these countries are steadily advancing in the epidemiologic transition of diseases and are now facing a double burden of communicable and non-communicable diseases (NCDs). About a third of adults in Nigeria have hypertension which remains uncontrolled in about half of these individuals leading to increased incidence of stroke and resultant morbidity and mortality.[14] This significantly affects the productivity of the active workforce and has enormous economic implications.

Historical conflicts may play an important role in the high prevalence of hypertension in African countries like Nigeria. However, there are very few studies investigating the impact malnutrition and famine exposure early in life on the subsequent cardiovascular health of African men and women. Hult and colleagues[15] previously revealed an increased risk of hypertension and diabetes in adulthood among Igbo residents of Enugu, South-eastern Nigeria, born during the Nigerian civil war (1967-1970) - also known as the ***Nigeria-Biafra War***. This phenomenon represents a natural experiment to investigate the

Developmental Origin of Health and Disease (DOHaD)[16] framework and the Barker hypothesis[10] in those of African ancestry.

Within this context, we aimed to determine the association between famine exposure in early life and hypertension in adulthood by analyzing data from a previous community-based survey conducted in the West-African country of Nigeria. We hypothesized that individuals born or in early childhood during the *Nigeria-Biafra War* (Biafran War) that occurred from July 1967 to Jan 1970 who were subsequently exposed to famine conditions, would have a higher risk of hypertension in adulthood when compared to those born in the five-years following the war.

METHODS

This represents a secondary analysis of data collected as part of the Abia State Non-Communicable Diseases and Cardiovascular Risk Factors (AS-NCD-CRF) Survey. Described in more details previously [17,18], the study comprised a community-based, household survey of people aged ≥15 years living in the southeastern Nigerian State of Abia. For this study, we purposefully focused on study participants of Igbo ethnicity who were born before, during and following the famine that was triggered by Biafran War. The study was approved by the Abia State Ministry of Health Ethics Review Committee and all the participants provided informed consent, in accordance with the Declaration of Helsinki.[19]

The Nigerian Civil War and the Famine in Eastern Nigeria

In brief, the Biafran War was triggered in July 1967 following the secession of the Eastern region of Nigeria as an aftermath of ethnic tensions and pogroms in different parts of the country and the failure of the Aburi accord.[20] The Nigerian government started a “police” offensive initially to halt the secession. This resulted in a full war that led to the opposing Biafran forces being pushed back into a small enclave.[21] With basic supplies purposefully cut-off from the populace living in the enclave of Biafra, one of the

worst humanitarian crises in Africa developed.[21,22] Under difficult circumstances, including interference by both warring parties, famine relief operations were then undertaken by the International Committee of the Red Cross. However, more than 2 million people (including around a million children) died during the conflict, with famine and kwashiorkor major causes of death.[21 21 21] The war and accompanying famine conditions finally ended in January 1970 following the surrender of the Biafran forces and the end of the supply blockade.[15] **Figure 1** below depicts the birth cohort and Biafran famine in the study period.

Setting and Participants

The AS-NCD-CRF survey was conducted between August 2011 and March 2012. A multistage stratified cluster sampling was used to select participants from each of the three senatorial districts in Abia State.[18] Briefly, one rural and one urban local government area (LGA) was randomly selected from Ohafia and Isuikwuato/Bende (Northern), Umuahia North and Ikwuano (Central) and Aba South and Ukwa East (Southern Senatorial Zone).[18]

In each LGA, households and their eligible participants within four randomly selected Enumeration Areas were selected for profiling. Starting from a prominent landmark in the community, trained interviewers proceeded from household to household to interview a minimum of 120 eligible participants in the area. Data were collected using the WHO-STEPwise approach surveillance questionnaire.

Study Data

Once selected, participants were asked about their year of birth, their level of education, smoking, alcohol consumption, exposure to stress, family history of cardiovascular disease, previous diagnosis of hypertension, diabetes, cancers, asthma and any other NCDs.[17] There was no information on participants' birth weight. They were also weighed using a weight balance and also had their height

132 measured.[18] Body mass index (BMI) was then calculated (kg/m^2) and categorized according to WHO
133 thresholds.[23] Waist and hip circumferences were measured using the WHO methodology.[23,24] Blood
134 pressure (BP) measurements were performed with an Omron Digital BP device (Omron M2 BP monitor
135 - Tokyo Japan) following a 5-minute resting period. Three BP reading at 2 minutes intervals were taken;
136 the average of the second and third readings was used for analysis. Systemic hypertension was defined
137 as SBP≥140 mmHg and or DBP≥90 mmHg or normal SBP and DBP in a subject using antihypertensive
138 treatment.[18]

139 **Famine Exposure**

140 The conflict induced famine in Biafra mainly occurred from January 1968 to January 1970 (**Figure 1**).
141 Accordingly, study participants were categorized into three different exposure groups/birth cohorts
142 based on their birth date relative to this specific period. Firstly, those born in the pre-famine period of
143 January 1965 to December 1967 were categorized as being exposed to famine in their early childhood
144 (Child-Fam group). Those born during the specific famine period were categorised as the fetal/infant
145 exposure (Fet-Inf-Fam) group. Individuals born in the transitional period between February 1970 and
146 December 1970 were excluded from the analysis due to uncertainties about their nutritional status.
147 Lastly those born after December 1970 were classified as the non-exposure group (No-Fam)

148 **Statistical Analysis**

149 The distribution of data was tested using the Shappiro-Wilk test and histogram plots. Data are presented
150 as mean (SD), proportions (%) and odds ratio (OR) with 95% confidence intervals (CI) as appropriate.
151 Differences between groups were tested using one-way ANOVA for continuous variables and chi square
152 and exact test for categorical variables. Logistic regression models were used to investigate the
153 association between hypertension in adulthood and famine exposure status. These models were also

adjusted for age, sex, smoking, stress, education, and BMI. We investigated the interaction between sex and exposure to famine on hypertension risk in separate analyses since associations between early life exposures and cardiovascular risk have been shown to vary with gender using the sex × famine exposure status interaction terms. We also investigated possible interaction between sex and BMI, but this was not significant in adjusted model. We further fitted logit regressions to estimate the marginal effects at the mean (MEM) and average marginal effects (AME) by regressing hypertension on exposure to famine and potential explanatory variables. We did this to estimate the predicted probabilities of hypertension in relationship to exposure to famine at different stages of development, and other explanatory variables. The coefficients of the MEM and AME shows the change in probability of hypertension occurring with a unit change in famine exposure while keeping the other covariates within the sample at their means or their individual values respectively. The marginal effect is the difference in the adjusted predictions between each category of famine exposure and the reference unexposed group. The fitted models were robust to the addition of the different explanatory variables and the fully adjusted model is presented. The coefficients of the MEM and AME were comparable and so only the latter are presented. We also plotted the predictive margins of famine exposure and risk of hypertension in adulthood. All data were analyzed using Stata version 17 (StataCorp LLC, Lakeway Drive, College Station, Texas, USA) with plots generated using the Stata and Jasper package (by Matt Arnold) in R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value of <0.05 was considered statistically significant in all analyses while clinical importance was based on the magnitude and direction of effect sizes and 95% CI's.

RESULTS

Cohort Characteristics

The profile of study participants' according to the three pre-specified famine exposure groups is summarized in **Table 1**. Of the 386 participants studied overall, 93 (21.6%) were included in the Child-Fam group, 92 (21.3%) in the Fet-Inf-Fam group and the remaining 201 (46.6%) participants in the No-Fam group, with age-gradients reflecting their year of birth. Overall, there was no difference in education status, smoking or alcohol consumption between groups. However, the Child-Fam group exhibited lower central adiposity compared to the other two groups; despite their being no difference in mean BMI between the three groups (all being the overweight range). Reported exposure to stress in adulthood was significantly higher (78.3%) in the Fam-Child group compared to the Fet-Inf-Fam and No-Fam groups (58.2% and 59.4%, respectively); p=0.01 for the comparison.

Blood Pressure Profiles

Compared to the No-Fam group (24.4%), the prevalence of hypertension was significantly elevated (p=0.001) in both the Child-Fam (43%) and Fet-Inf-Fam (44.6%) groups - see **Table 1.** Consistent with this observation, SBP/DBP levels were significantly higher in the Child-Fam and Fet-Inf-Fam groups. When compared to the No-Fam reference group, the Child-Fam group had a 2.8-fold increased risk of an elevated SBP when adjusting for potential biological and lifestyle confounders. On the same basis, the Fet-Inf-Fam group had an adjusted 1.8-fold risk of an elevated SBP. A similar pattern of higher adjusted risk for elevated DBP, was also found in the two groups – see **Table 2.**

Hypertension

On a crude and then adjusted basis, individuals within the Child-Fam group were 2.3-fold and 2.5-fold more likely to have hypertension in adulthood when compared to the No-Fam group. Similarly, the same

crude and adjusted risk of hypertension in adulthood within the Fet-Inf-Fam groups was 2.5-fold than the No-Fame group - see **Figure 2**.

As shown in **Figure 3**, on a sex-specific basis, after adjustment for potential confounders, within the women (adjusted OR 2.75, 95% CI 1.02-7.41) in the Child-Fam group had a higher risk of hypertension than their male counterparts (OR 2.23, 95% CI 0.55-9.00) when compared to the No-Fam group. Within the Fet-Inf-Fam group, however, this sex-specific trend was reversed with men having a higher adjusted risk than women of having hypertension in adulthood.

Figure 4 presents a forest plot showing the AME of hypertension probability in adulthood. Individuals within the Child-Fam and Inf-Fet-Fam groups had similar predicted probability of hypertension in adulthood; being 20% higher than No-Fam group in adjusted analyses. There was a steep increase in hypertension prevalence with famine exposure, with the highest levels found in the Child-Fam Group. This observed increased risk for hypertension was stronger in women than in men. Overall, on an adjusted basis, individuals within the Child-Fam and Fet-Inf-Fam were at increased risk of hypertension compared to the No-Fam group.

As shown in **Table 3**, the AME of hypertension showed a higher predicted probability in women compared to men (22% vs. 16%) within the Child-Fam group compared to the No-Fam group. Similarly, within the Fet-Inf-Fam group, men had a slightly higher predicted probability of hypertension (21% vs. 19%) than women. The predictive margins of the sex-specific hypertension risk in the 3 study groups/birth cohorts are shown in **Figure 5** below. There was a steep increase in hypertension prevalence with famine exposure which was highest in the Child-Fam group. This increased risk was stronger in women than men within both the Child-Fam and Fet-Inf-Fam groups. The time trend in the risk of hypertension by birth year over the 10 years spanning 1965-1974 is presented in **Figure 6**. Two

peaks of hypertension risk can be seen in those born in 1965 and those born in 1968 at the peak of famine. Thereafter, the risk of hypertension declined. **Figure 7** shows the graphical abstract of the findings.

DISCUSSION

The famine triggered by the Biafran War was a humanitarian disaster. Its legacy continues to haunt Nigeria. In this study, we specifically investigated the risk of hypertension in adulthood among those born in the decade before, during and following the famine. We sought to test and validate the DOHaD framework[16] and the Barker's hypothesis[8,9]; both of which suggest that early life and intrauterine adverse events like malnutrition leads to developmental programming towards vascular diseases later in life. Accordingly, we found an elevated, adjusted risk of adult hypertension within both the Child-Fam and Fet-Inf-Fam groups compared to those born after the famine (No-Fam group). However, we found no evidence to support the pathway postulated by DOHaD[16,25] that early life malnutrition may influence access to education, future socio-economic status, lifestyle and substance consumption. [16,25] Adjusting for lifestyle variables, including emotional stress, did not significantly mediate the increased risk of hypertension among those exposed to famine. Nor was there an association between lifestyle variables and famine exposure. This contrasts with recent findings by Mink *et al*.[25] in the French E3N cohort and the reports by Fransen and colleagues.[25] Furthermore, in contrast to reports from Jyoti and colleagues[26] and Akresh and colleagues[22] we also did not find any association between famine exposure in early life and educational attainment among those who lived through the Biafran War.

The latency framework of the DOHaD proposes a direct link between early life famine exposure and hypertension in adulthood through epigenetic re-programming.[16,25] We sought to explain the role of biological sex in hypertension risk among the famine exposure groups. Within the Child-Fam group,

241 women showed a trend of towards a higher risk of hypertension compared to men, with this pattern
242 reversed within the Fet-Inf-Fam group. Those who experienced famine in childhood and those with fetal-
243 infant malnutrition had similar overall predicted probability of hypertension (20% higher than the No-
244 Fam group) but was similar for the two famine exposed groups. However, there was a markedly higher
245 (6% more) predicted probability of hypertension in women than men within the Child-Fam group.
246 Alternatively, within the Fet-Inf-Fam group, the predicted probability of hypertension tended to be
247 higher in men.
248 Evidence for sex-based differences in the association of early adverse life events and BP have been weak
249 with a meta-regression analysis finding no sex difference in the association between birth weight and
250 systolic BP in later life.[27] Hult and colleagues[15] did not find significant sex differences in risk of
251 hypertension after exposure to the Biafra famine in their study of market subjects in Enugu, Nigeria;
252 even though the average risk of hypertension reported is comparable to ours.[15] It appears that African
253 women are more susceptible to hypertension when they experience malnutrition in childhood.
254 Alternatively, African men appear to be more susceptible to the effects of malnutrition in-utero. These
255 observations are consistent with those of Kuopil and colleagues[28] who studied childhood survivors of the
256 extreme starvation experienced during Leningrad siege in Russia. We may also explain the higher risk in
257 women exposed to malnutrition in childhood by the observation made by Akresh and colleagues [22] that
258 women exposed to the war in their growing years exhibited more stunting, higher overweight risk, earlier
259 age at first birth and lower educational attainment. Our finding of a higher risk and predicted probability
260 of hypertension in females exposed to famine in childhood compares with previous reports from the
261 survivors of the Leningrad siege.[28] It is now well established that the first 12 weeks of pregnancy (the
262 embryonic period) is very critical to future health risk. This is the period when organs like the kidneys,

heart and blood vessels are forming.[29,30] Low birth weight followed by accelerated weight gain in the age group 3-11 years predicted a large difference in the cumulative incidence of hypertension in adulthood in the Helsinki birth cohort.[8] Hypertension may originate from retarded in-utero growth followed by accelerated postnatal growth when exposed to good living conditions.[31] Males who suffer intra-uterine growth restriction are more likely to be born with smaller organs and fewer glomeruli as propounded by David Barker[3,10] and would thus be at high risk of hypertension later in life as shown in our study. There appears to be some specific expression of fetal genes critical to developmental programming in-utero especially when exposed to stress and growth restriction in the early weeks of fetal development.[32–34] Females may be protected by their two X chromosomes unlike males who have only one X chromosome.[35] Protein-energy malnutrition and even small variations in the balance of macronutrients in maternal diet during pregnancy and/or lactation alters BP control of such children through central sympathetic dysfunction and epigenetic modification like hypomethylation of genes e.g. angiotensin II type I receptor and IL-6 genes.[36,37] Moreover in experimental models, there is increased hypoxia inducible factor-1α (HIF-1α) expression in the carotid bodies, hearts and brains of rats exposed to protein-energy malnutrition during pregnancy and/or lactation. High HIF-1α expression is associated with increased risk of hypertension and enhanced activity of peripheral chemoreceptors.[37]

Risk of hypertension is programmed by prenatal and early postnatal experiences with poor maternal nutrition playing key role by restraining fetal growth. Sesso and colleagues[13] have shown the role of childhood malnutrition in increased hypertension risk independent of birth weight. Similar findings have been reported from Brazil.[38] Furthermore, reports of survivors of the Leningrad siege[28], the Great Chinese famine[39] and the Dutch famine[4,5] have previously confirmed the increased risk of hypertension in those with malnutrition in fetal and childhood periods. Malnutrition in early life could initiate

hypertension in adulthood by activation of the renin-angiotensin-aldosterone system, alteration in vascular structure and function, increased sympathoadrenal activity, associated increased heart rate, elevated urinary catecholamines, and reduced vascular compliance.[13] Alternatively, other researchers[3] have failed to show an association between prenatal famine exposure and hypertension in adulthood.

We found a much higher predicted probability of hypertension (20% higher) among those exposed to famine in our cohort when compared to an equivalent report of 2.6% higher reported by Mink and colleagues.[25] This may be because they were unable to distinguish between those who did and didn't experience hunger in childhood within their cohort.[25] By assuming that everyone born in certain periods experienced malnutrition, we may have overestimated the average marginal effects. However, famine was endemic in Biafra during the period 1968-1970 when food supplies were completely shut-off and Biafran lands were unsuitable for cultivation of protein crops.[15,20,21] Consequently, over 2 million children developed kwashiorkor and marasmus with more than 1 million children subsequently dying.[20]

Overall, our result supports a strong association between early life exposure to famine and the development of hypertension in adulthood. Mismatch between the food sufficiency of today's eastern Nigeria and the famine of the 60s may be contributory to the rise in hypertension and stroke-related events observed in eastern Nigeria. We have also shown the sex differences in hypertension risk based on the time of famine exposure during development with the highest risk in males exposed in utero and the highest risk in females exposed during childhood. These findings are especially important today when Nigeria is facing terrorist insurgency in the Northern part of the country with millions displaced from their houses and lands.[40] The victims of the present insurgent crisis are also now facing critical food shortages resulting in childhood malnutrition. In simple terms, preventing such conflicts and consequent

306 famine/malnutrition early in life will improve long-term cardiovascular health and improve life-
307 expectancy in many parts of the Africa continent.

308 The study is not without limitations. It is a cross sectional study and it is difficult to ascertain causality
309 even though we have tried to adjust for important biological and behavioural factors. We assumed that
310 all those born during the period 1965-1970 were automatically exposed to famine and protein-energy
311 malnutrition. This may have led us to overestimate the effects sizes. We were also unable to distinguish
312 between exclusively in-utero versus infant exposure to famine within the cohort. Consequently, our
313 analyses may underestimate the effects of malnutrition in the fetal period given the overlap in famine
314 exposure during infancy (with potentially no exposure to famine in-utero). We were also unable to
315 investigate the effects of malnutrition in different stages of gestation. Of relevance here is the absence
316 of birth weight records and subsequent childhood anthropometric profiling data to more rigorously
317 explore the likely degree and legacy effects of malnutrition exposure in each individual. This is a common
318 problem in developing countries like Nigeria where such historical records are typically non-existent.
319 Although we collected BP data, it was derived from one time-point. This could have led us to
320 overestimate the prevalence of hypertension. Another concern is the validity of estimates if there had
321 been a change in the Biafran population composition due to differential mortality of the least healthy
322 and most vulnerable to famine, then this would have led to underestimation of our effect sizes.

323 Despite these limitations, the strength of the study lies in its focus on a homogenous Igbo population
324 and statistical analyses that generated risk prediction and measurement of potential sex differences in
325 the risk of hypertension in adulthood while controlling for biological and lifestyle variables. Our findings
326 suggest that behavioural lifestyle factors do not play an appreciable role in the association of famine
327 with hypertension in adult life. We were able to demonstrate the direct latency pathway of the

DOHaD.[16,25] We also showed a higher risk of hypertension exposed to famine in-utero exposure, whilst also showing that the highest risk of famine exposure (in respect to hypertension later in life) occurred in females aged under 5-years.

Early life exposure to malnutrition (whether it be as a result of conflict or economic factors) has a long-term, negative legacy effect. To invest in the future of African children and future economic prosperity, therefore, there needs to be a concerted effort to support school feeding programmes alongside proactive health screening programs. This is particularly true in current parts of Nigeria where the threat of insurgency and food insecurity are tragically all too common still.

Data Availability

Additional data collected in the research are available from the corresponding author upon request.

Acknowledgements

The authors thank all the research assistants who participated in the survey.

Authors' Contributions

OSO and ASO conceptualized the study; OSO and OOM designed the study and coordinated the data collection; KS, SS, IIC, UUO, AA, FO, and OAO wrote the first draft of the manuscript; AOB, MFO, OPA, IGE wrote the final manuscript and figures. All author approved the manuscript for submission.

Funding

No funding received

Ethical Approval

The ethical approval was obtained at the Abia State Ministry of Health, Nigeria with reference number: AB/MH/E&HR/1/004/15

Competing interests

The authors declare no competing interests.

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470 **Table 1** shows the study participants' clinical characteristics of the two groups exposed to famine and

471 the unexposed group.

472

Variable	Born 01 Jan 1965-31Dec. 1967 Childhood famine	Born 01 Jan 1968- 31 Jan 1970 Fetal-infant famine	Born 01 Jan 1971- 31 Dec 1974 Unexposed to famine	P value
Number of subjects (431)	93 (21.6%)	92 (21.3%)	201 (46.6%)	
Sex (male) %	47 (50.5%)	50 (54.3)	86 (42.8)	0.15
Age (years)	45.1 (3.9)	42.4 (3.3)	38.4 (2.2)	<0.001**
Smoking (%)	4 (4.3)	7 (7.7)	22 (10.9)	0.16
Alcohol (%)	59 (63.4)	54 (58.7)	113 (56.2)	0.51
Education (%)				
Below secondary	26 (28.0)	27 (29.4)	52(25.9)	0.81
Secondary and above	67 (72.0)	65(70.6)	149 (74.1)	
Feeling stressed %	72 (78.3)	53 (58.2)	117 (59.4)	<0.01*
Family history of CVD	39 (41.9)	33 935.9)	73 (36.3)	0.61
Hypertension (%)	40 (43.0)	41 (44.6)	49 (24.4)	<0.001**
Weight (Kg)	71.1 (15.8)	72.4 (14.0)	69.8 (12.8)	0.07
Height (cm)	163.2 (9.7)	164.9 (8.5)	163.5 (8.4)	0.22
BMI ($Kg/m^{2)}$	26.6 (5.3)	26.5 (4.9)	25.8 (4.5)	0.19
Waist circumference (cm)	86.2 (14.2)	88.1 (16.0)	88.2 (23.4)	<0.001**
Hip circumference (cm)	95.3 (14.9)	97.9 (14.3)	95.0 (17.5)	0.05

Hip-waist ratio	1.0 (0.2)	1.1 (0.1)	1.1 (0.3)	<0.001**
Heart rate (beats/min)	78.3 (11.4)	77.0 (10.0)	77.2 (10.4)	0.51
Systolic BP (mmHg)	135.3 (29.5)	131.3 (21.0)	126.0 (28.5)	<0.01*
Diastolic BP (mmHg)	80.6 (15.7)	79.6 (14.1)	75.6 (17.4)	0.07

473 * p value <0.05; **p value ≤0.001

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Table 2: Odds ratio for hypertension (reference category is the unexposed group).

			All subjects	
			N=386	N=330
Variables	N	n (%)	Crude OR	Adjusted OR
SBP	386	102 (26.4)		
≥140mmhg				
Childhood	93	36 (38.7)	2.80 (1.62-4.85)	2.85 (1.26-6.44)
Fetal-infant	92	29 (31.5)	2.04 (1.16-3.59)	1.76 (0.88-3.53)
Unexposed	201	37 (18.4)	Ref.	Ref.
DBP	386	85 (22.0)		
≥90mmhg				
Childhood	93	26 (28.0)	2.05 (1.14-3.70)	2.57 (1.06-6.19)
Fetal-infant	92	27 (29.3)	2.19 (1.22-3.94)	2.73 (1.30-5.73)
Unexposed	201	32 (15.9)	Ref.	Ref.
Hypertension	386	130 (33.7)		
Childhood	93	40 (43.0)	2.34 (1.39-3.94)	2.47 (1.14-5.36)
Fetal-infant	92	41 (44.6)	2.49 (1.48-4.20)	2.54 (1.33-4.86)
Unexposed	201	49 (24.4)	Ref.	Ref.

SBP: systolic blood pressure, DBP: diastolic blood pressure, HTN: hypertension.

Adjusted model includes famine exposure groups, sex, present age, education attainment (secondary education and above vs. below secondary education), family history of cardiovascular disease, smoking status (Yes vs. No), feeling stressed (Yes vs. No) and body mass index (BMI)

Table 3: Average marginal effects of hypertension stratified by sex (fully adjusted model)

Famine exposure	Average marginal effects (AME); 95%CI	P value
Childhood famine		
Female	0.22 (0.00; 0.44)	0.05
Male	0.16 (-0.12; 0.44)	0.27
Fetal-Infant famine		
Female	0.19 (-0.01; 0.39)	0.06
Male	0.21 (0.01; 0.42)	0.04

Adjusted model includes famine exposure groups, sex, present age, education attainment (secondary education and above vs. below secondary education), family history of cardiovascular disease, smoking status (Yes vs. No), feeling stressed (Yes vs. No) and body mass index (BMI)

Summary Table

What is known about the topic

- Early life and childhood malnutrition is linked to future increased risk of cardiovascular diseases in adulthood in experimental models.
- Fetal malnutrition is associated with the 'thrifty' phenotype in later life and a mismatch with the environment during periods of food abundance resulting in hypertension and diabetes mellitus.
- Regional conflicts, wars and insurgencies in Africa and developing countries lead to displacement of people, severe disruption of food supplies and poverty resulting in early malnutrition in children and young adults. .

What this study adds

- There were significant sex differences in the risk of hypertension with females who experienced famine in childhood having a higher risk of hypertension than males.
- Males born in the transitional period had higher risk of hypertension than females born in the same period.
- Early life famine exposure and malnutrition is associated with sex differences in increased risk of hypertension in middle age.

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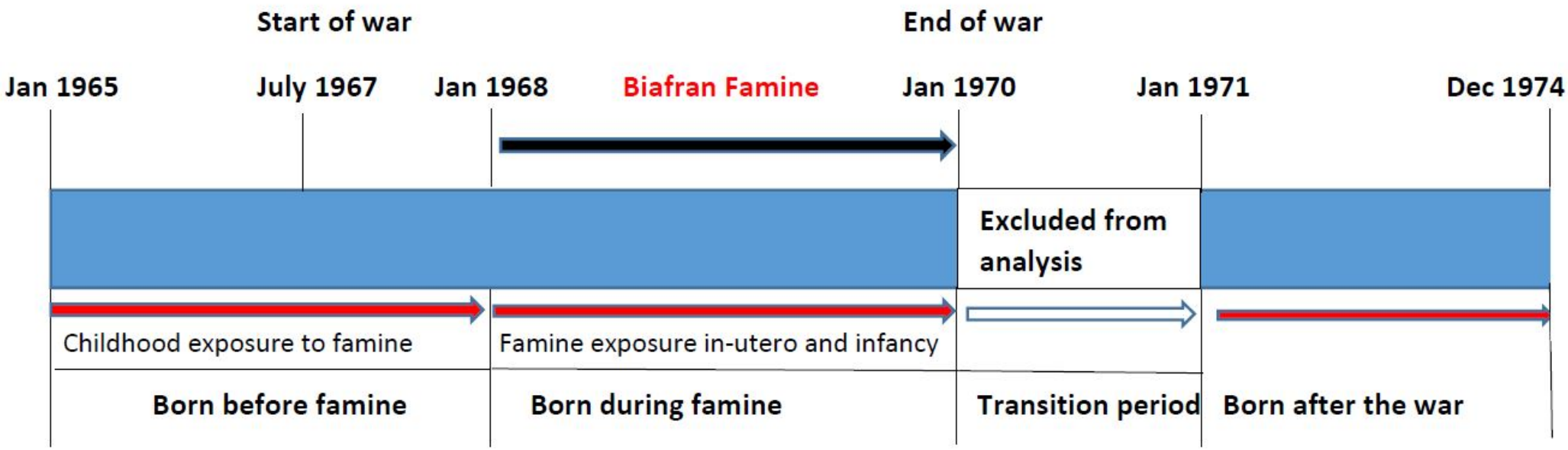
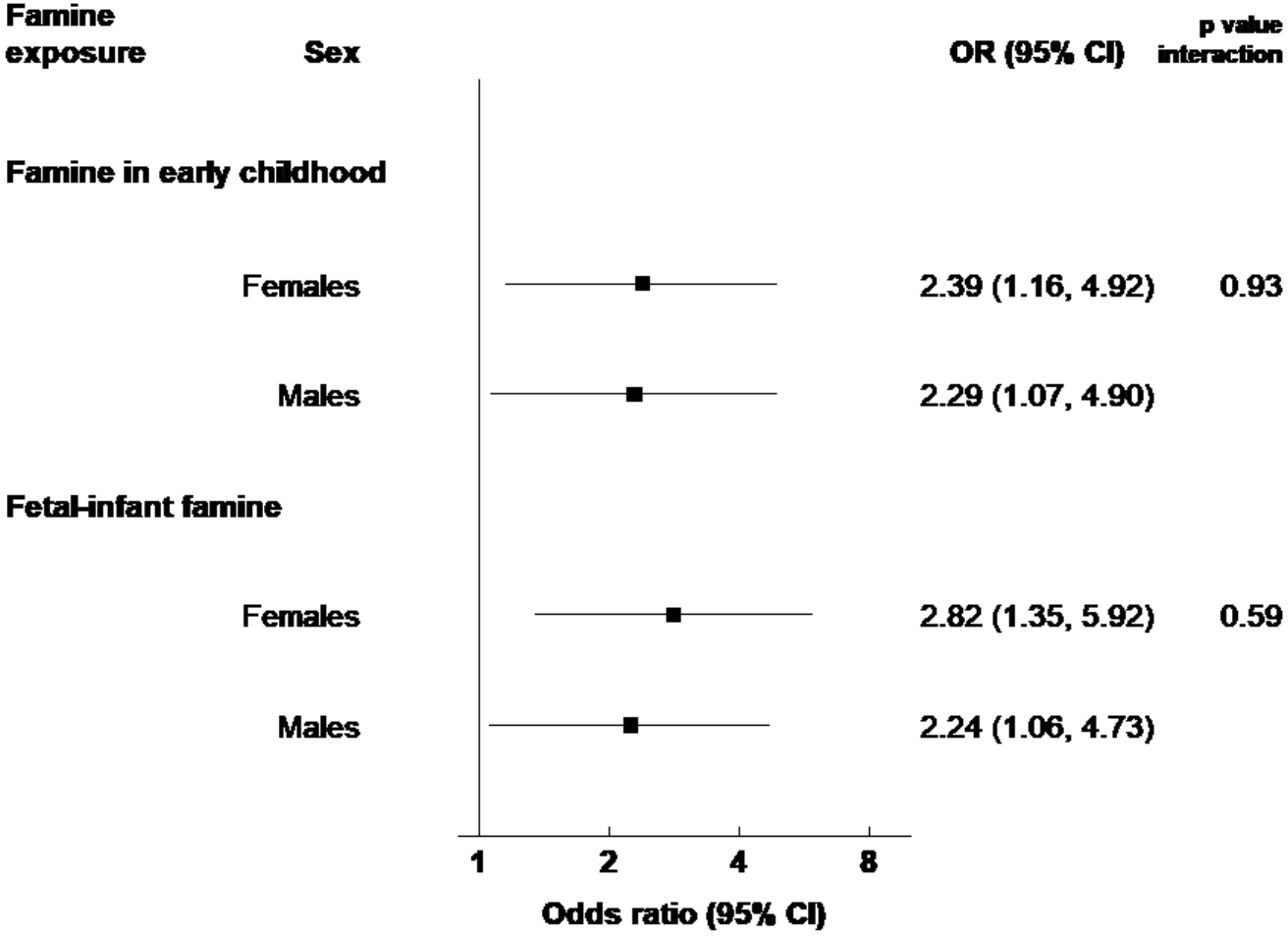
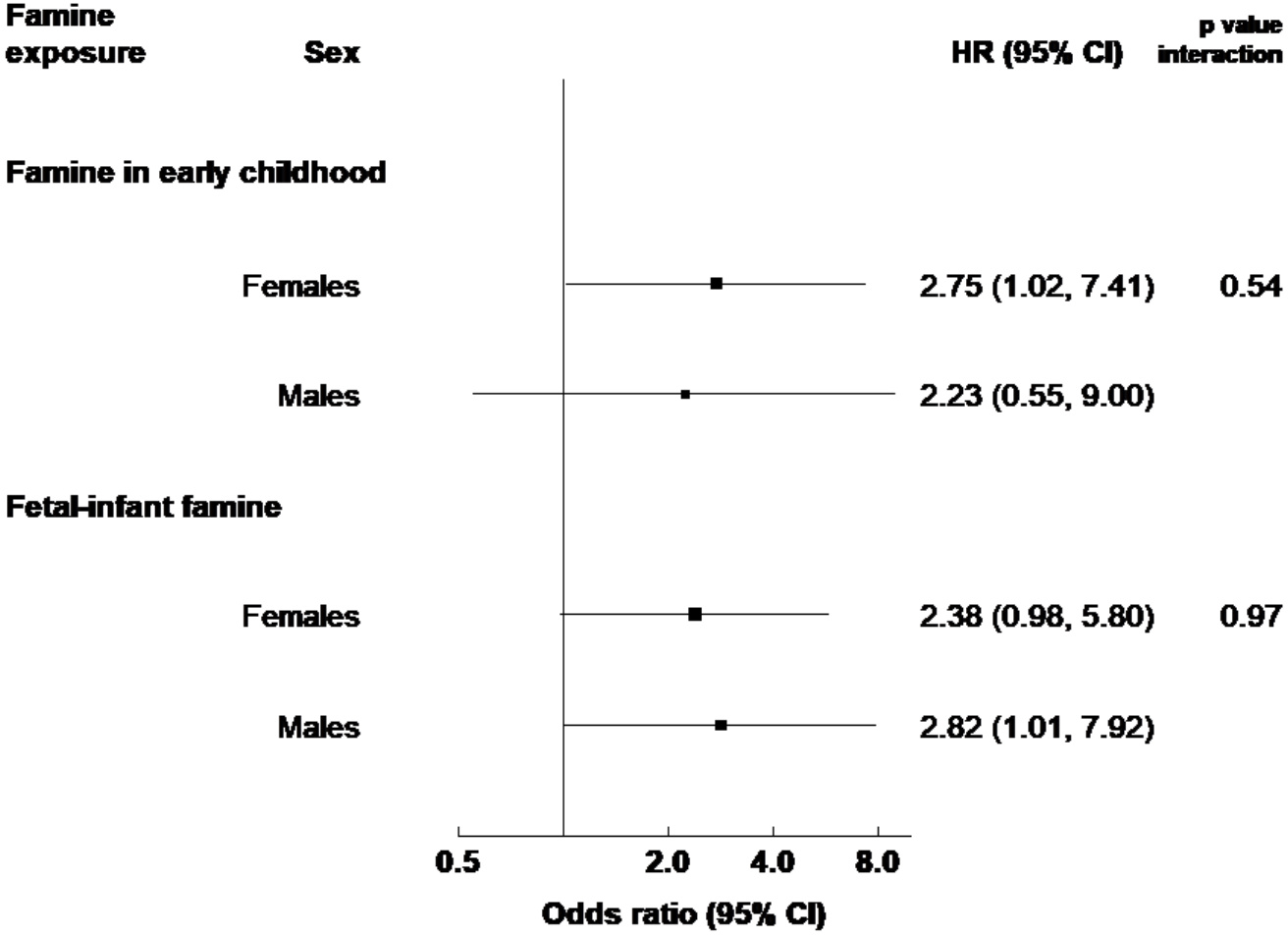
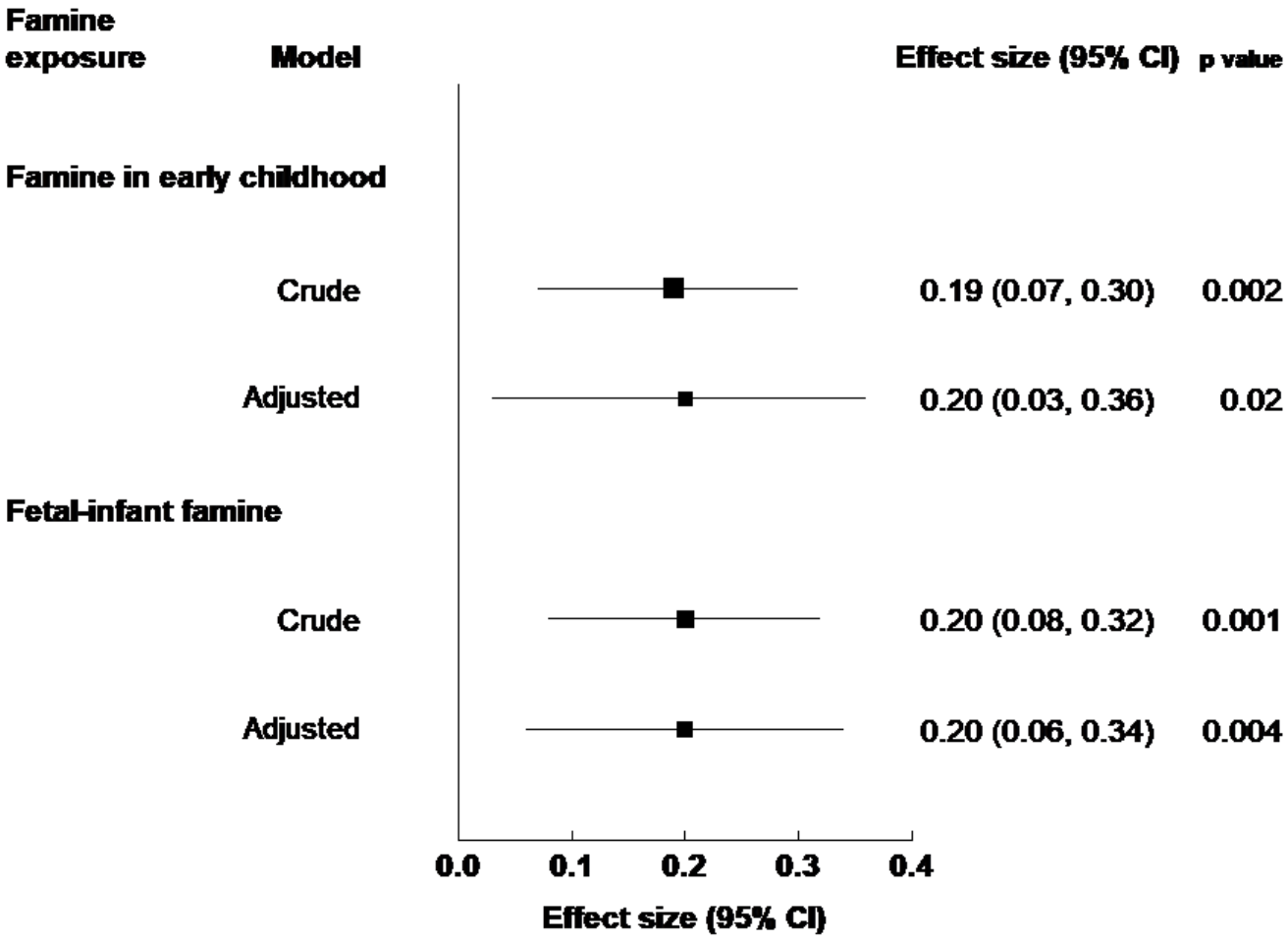
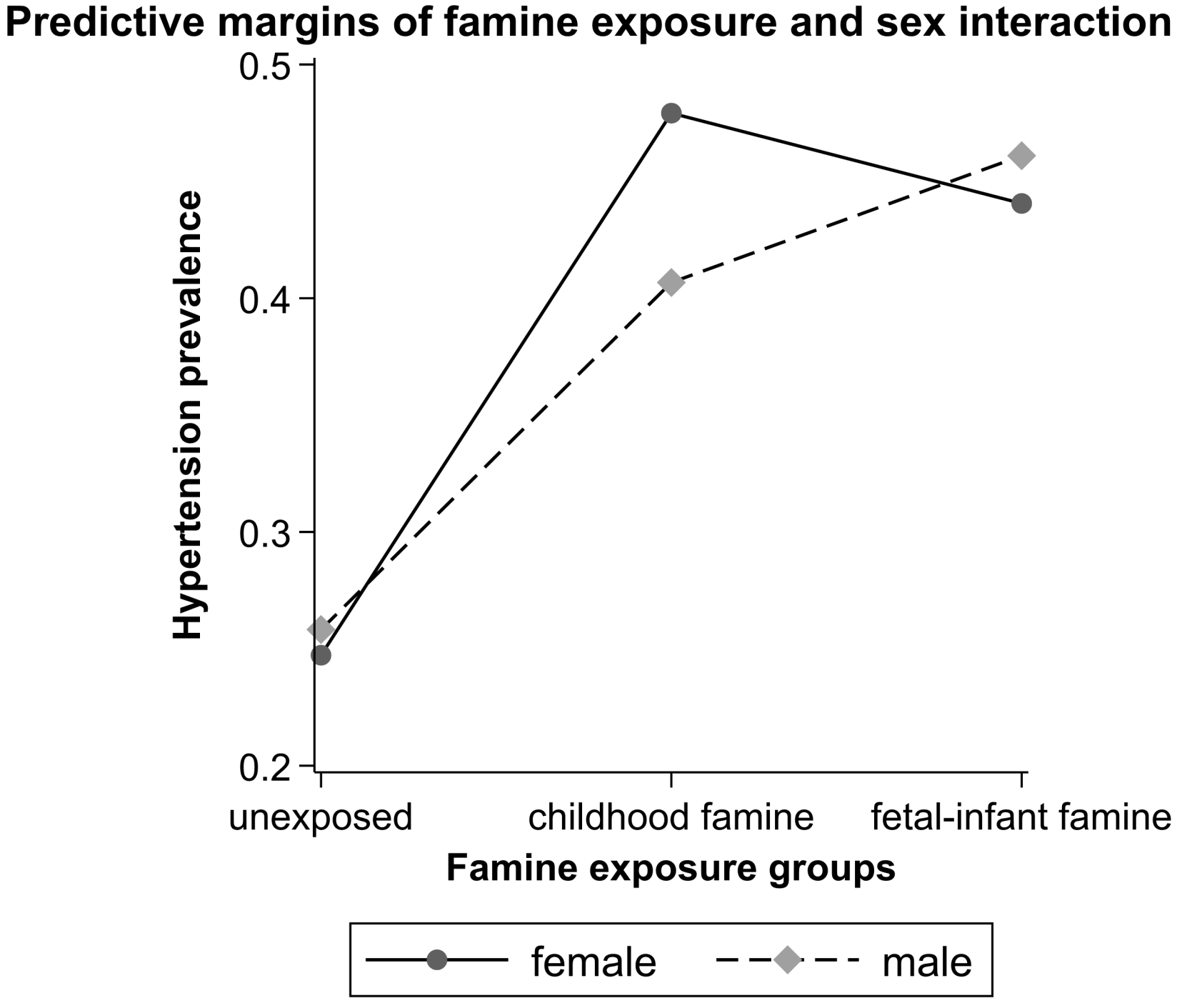
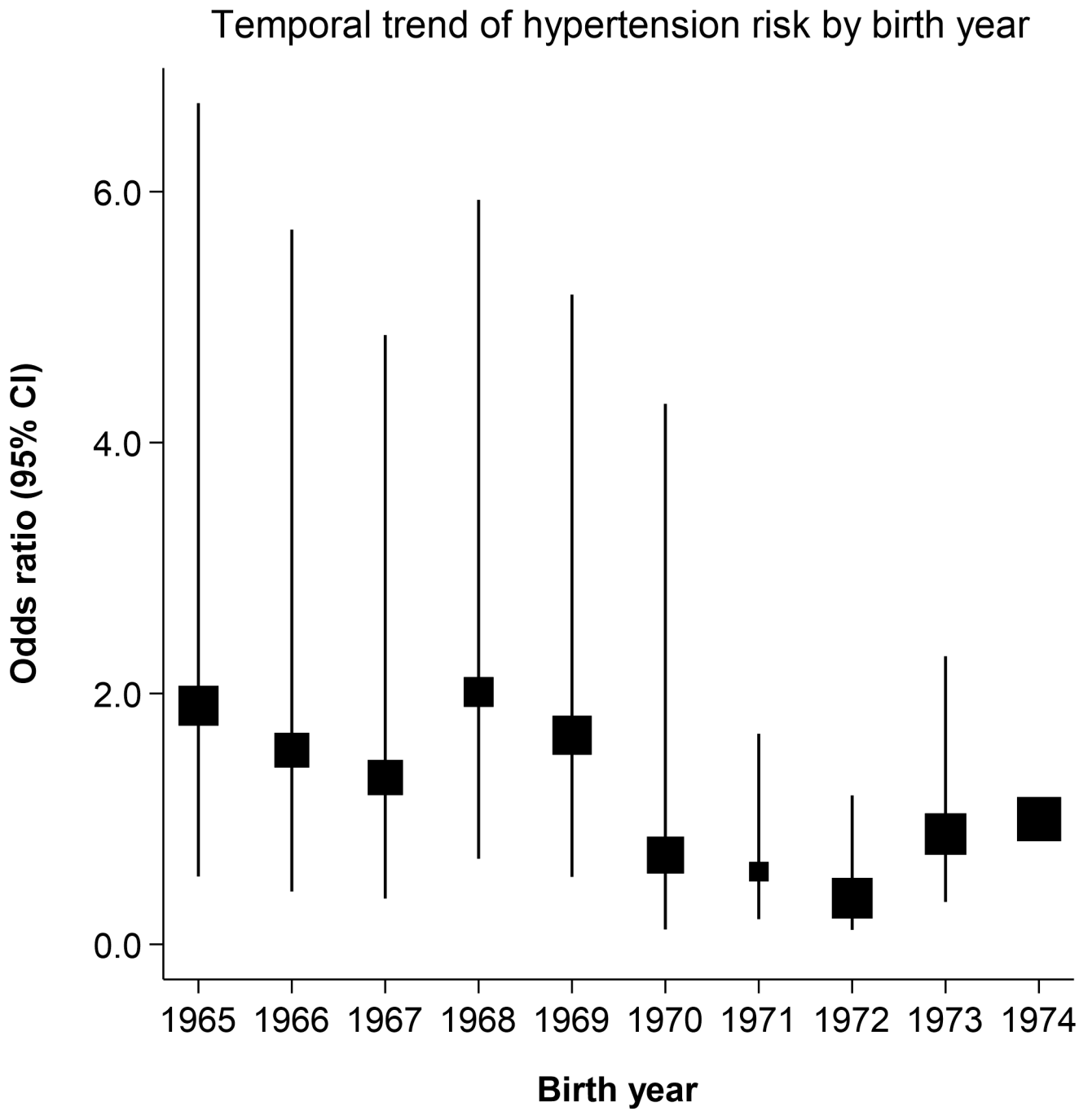

Start of war
End of war
Jan 1965
July 1967
Jan 1968
Biafran Famine
Jan 1970
Jan 1971
Dec 1974
Excluded from analysis
Childhood exposure to famine
Famine exposure in-utero and infancy
Born before famine
Born during famine
Transition period
Born after the war


Famine exposure
Sex
OR (95% CI)
p value interaction
Famine in early childhood
Females
2.39 (1.16, 4.92)
0.93
Males
2.29 (1.07, 4.90)
Fetal-infant famine
Females
2.82 (1.35, 5.92)
0.59
Males
2.24 (1.06, 4.73)
1
2
4
8
Odds ratio (95% CI)


Famine exposure
Sex
HR (95% CI)
p value interaction
Famine in early childhood
Females
2.75 (1.02, 7.41)
0.54
Males
2.23 (0.55, 9.00)
Fetal-infant famine
Females
2.38 (0.98, 5.80)
0.97
Males
2.82 (1.01, 7.92)
0.5
2.0
4.0
8.0
Odds ratio (95% CI)


Famine exposure
Model
Effect size (95% CI)
p value
Famine in early childhood
Crude
0.19 (0.07, 0.30)
0.002
Adjusted
0.20 (0.03, 0.36)
0.02
Fetal-infant famine
Crude
0.20 (0.08, 0.32)
0.001
Adjusted
0.20 (0.06, 0.34)
0.004
0.0
0.1
0.2
0.3
0.4
Effect size (95% CI)


Predictive margins of famine exposure and sex interaction
Hypertension prevalence
0.5
0.4
0.3
0.2
unexposed
childhood famine
fetal-infant famine
Famine exposure groups
female
male


Temporal trend of hypertension risk by birth year
Odds ratio (95% CI)
6.0
4.0
2.0
0.0
1965
1966
1967
1968
1969
1970
1971
1972
1973
1974
Birth year

Famine exposure in childhood	Famine exposure in in-utero and infancy
• Hypertension 43% • Average marginal Effect • -Male: +16% • Female: +22%	• Hypertension 44.6% • Average marginal Effect • -Male: +21% • -Female: +19%
aOR of Hypertension; adjusted for biological and lifestyle variables Male: 2.23 (0.55; 9.00) Female: 2.75 (1.02; 7.41)	aOR of Hypertension; adjusted for biological and lifestyle variables Male: 2.82 (1.01; 7.92) Female: 2.38 (0.98; 5.80)