Barker’s Hypothesis Among the Global Poor: Positive Long-Term Cardiovascular Effects of in Utero Famine Exposure

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ABSTRACT  An influential literature on the Developmental Origins of Health and Disease (DOHaD) has documented that poor conditions in utero lead to higher risk of cardiovascular disease at older ages. Evidence from low-income countries (LICs) has hitherto been missing, despite the fact that adverse in utero conditions are far more common in LICs. We find that Malawians exposed in utero to the 1949 Nyasaland famine have better cardiovascular health 70 years later. These findings highlight the potential context specificity of the DOHaD hypothesis, with in utero adversity having different health implications among aging LIC individuals who were exposed to persistent poverty.

KEYWORDS  Early-life influence on later-life health • Barker hypothesis • Developmental origins of health and disease • Cardiovascular health • Sub-Saharan Africa

Introduction

To the best of our knowledge, this is the first study to document the lasting effects of severe early-life adversity on health at older ages in a low-income country (LIC) cohort that has experienced extreme poverty throughout life (Figure 1, panel a). Contrary to the predominant findings from higher income contexts (Ford et al. 2018; Lumey et al. 2007), our analyses show that persons exposed to in utero adversity during the 1949 Nyasaland famine in Malawi have better cardiovascular health at older ages: they have lower blood pressure (panel b), reduced age-related increase in blood pressure (panel c), lower levels of blood sugar, and fewer stroke symptoms. This result is not driven by mortality selection, but is possibly due to predictive adaptation responses (Gluckman and Hanson 2004) consistent with the Barker hypothesis (Barker 1995): severe early-life adversity in these cohorts might have resulted in increased resilience that partially protected individuals during lives with frequent exposures to poverty and adverse shocks. Against the odds, in this context with widespread life course adversities and high levels of early-life to midlife mortality, individuals exposed to the Nyasaland famine maintained (relatively) better cardiovascular health across multiple domains compared with their peers with less severe in utero adversities.

ELECTRONIC SUPPLEMENTARY MATERIAL  The online version of this article (https://doi.org/10.1215/00703370-11052790) contains supplementary material.
Fig. 1 (a) GDP per capita of the 50 poorest countries in the 1950s, based on cross-sectionally and longitudinally comparable income data over the period 1950–2018; (b) systolic blood pressure among MLSFH respondents; and (c) annual change in systolic blood pressure during 2013–2017. Panel a data are based on the Maddison Project Database 2020 (Bolt and van Zanden 2020). Panel b results are based on an ordinary least-squares regression of systolic blood pressure for year pairs (e.g., 1939 and 1940, 1941 and 1942), gender, region of residence, birth, and a dummy variable for whether the survey was administered in 2017 or 2019. The reference category corresponds to the cohorts with likely in utero exposure to the famine, that is, 1949 and 1950. Panel c results are based on an ordinary least-squares regression of the change in systolic blood pressure from 2013 to 2017 on year pairs, gender, region of residence, and birth. The reference category corresponds to the cohorts with likely in utero exposure to the famine. Panel b and c graphs show 95% confidence intervals with standard errors clustered at the year pair level. BP = blood pressure.

(continued)
The first 1,000 days of life, from conception to age 24 months, is a period of tremendous physiological and neurological development (Engle et al. 2007; Grantham-McGregor et al. 2007). This is also a period of great vulnerability in which early-life adversities may result in long-term health and socioeconomic consequences (Hoddinott et al. 2013). In what became known as the Barker (or Developmental Origins of Health and Disease, DOHaD) hypothesis, a series of studies on the importance of in utero nutrition for health at older ages documented that early-life deprivation is associated with the onset of a number of chronic conditions in late-middle age, including coronary heart disease, diabetes, and hypertension (Barker 1995; Barker et al. 1990). The hypothesized mechanism underlying these early-life origins of later-life health is that different physiological systems and organs—including the cardiovascular system—may not recover from inadequate nutrition at critical periods in fetal development and infancy, which causes long-run health problems from being subsequently exposed to a “standard” diet (Barker 1995; Hoffman et al. 2017). High rates of cardiovascular disease among older persons in middle-income countries are partially attributed to this mechanism (NCD Risk Factor Collaboration 2017).

The impacts of these early-life influences are not mitigated by adult socioeconomic status or health behaviors; instead, they interact. The thrifty phenotype concept (Wells 2007), for example, implies that exposures and behaviors later in life (e.g., diet, physical activity, and socioeconomic contexts) modify the long-term implications of early-life adversities: the greater the discrepancy between early childhood nutritional deprivation and relative nutritional affluence in later life, the greater are the consequences on later-life health.

Most DOHaD research has focused on middle- and high-income countries (MHICs), where cohort studies allow linkages between early-life events and health at older ages (Hoffman et al. 2017). Several studies have documented the negative
effects of early-life adversity on health outcomes later in life by investigating major disruptive events, such as the Dutch famine at the end of World War II (Lumey et al. 2007), the 1918 influenza pandemic (Almond 2006), and the Great Depression (Duque and Schmitz 2020). However, these findings are mixed. Some high-income country studies have shown null effects, including the absence of elevated late-life mortality after famine exposure (Kannisto et al. 1997) or lack of worse health among children born during the American Dust Bowl (Cutler et al. 2007). Frequently cited findings about the negative socioeconomic consequences of exposure to the 1918 influenza pandemic (Almond 2006) have also been called into question, and analyses that control for the lower socioeconomic status of exposed individuals have not found negative effects of exposure to the 1918 pandemic (Beach et al. 2022).

The underrepresentation of LICs in this research, however, is unfortunate for two reasons. First, globally, major sources of negative nutritional shocks in the first 1,000 days are weather fluctuations, which are likely to become more extreme over time (Watts et al. 2018). Despite the greater vulnerability of LIC populations to such fluctuations in early life, few studies have documented their life course impacts. We therefore lack adequate evidence on the long-lasting influences of weather-related early-life shocks among a large and growing population that was highly susceptible to such shocks: individuals born in LICs and now reaching older ages.

Second, the focus on MHICs also implies that analyses might miss important context specificity in the effects of early-life adversities on later-life health (Hoang et al. in press). Importantly, existing MHIC studies mostly investigated individuals whose early-life adversities were followed by better—and often considerably better—health and socioeconomic contexts during later childhood, adulthood, and old ages (e.g., the Dutch hunger-winter cohort (Lumey et al. 2007), individuals born during the Great Depression in the 1930s (Duque and Schmitz 2020), or individuals born during the early 1900s in countries that experienced substantial development during the second half of the twentieth century (Kannisto et al. 1997)). The experiences of these cohorts differ dramatically from the experiences of the global poor upon reaching older ages: their lives were characterized by poverty and adversities throughout (see Figure 1, panel a) For example, the individuals studied in the current research lived most of their lives in subsistence-agricultural contexts with per capita incomes of less than $1 per day (National Statistical Office (Malawi) 2018). Cohort members were born when under-5 mortality was almost one out of three (∼35%) (United Nations 2019), and they have survived sustained poverty, repeated famines, and the HIV/AIDS epidemic. For many in this cohort, this exposure to repeated adversities throughout the life course has given rise at older ages to accelerated aging that entails an earlier onset and faster pace-of-decline of physical, mental, and cognitive health (GBD 2019 Diseases and Injuries Collaborators 2020; Koyanagi et al. 2018; World Health Organization 2015).1

1 In Malawi, economic conditions may have slightly improved in urban areas and for the younger cohorts, though much less than in most other countries with a similar per capita income in the 1940s. However, in our study population of older individuals living in rural villages, conditions remained poor throughout their lives. For example, in our sample, only 3% have secondary education and less than 2% have access to the electricity grid. In general, food security remains an issue, as evidenced by the famines of 2002 (Kamkwamba and Mealer 2016) and 2013.
Early-life adversities may have different consequences on adult health in LICs as compared to MHICs. On one hand, such adversities might matter less in LICs, where adversities are common throughout the life course; on the other hand, individuals exposed to severe in utero adversities might be better protected from worse health at older ages if their life course includes repeated or sustained exposure to adversities. According to the predictive adaptive responses hypothesis (Gluckman and Hanson 2004) and in line with the Barker hypothesis, a fetus affected by an adverse environment responds by making developmental adaptations to improve the odds of survival under analogous conditions after birth. If such conditions do re-occur, then such individuals may be more resilient than individuals living in the same environment but who experienced better conditions in utero. These adaptations may provide benefits that are not immediate but that could prove helpful in a future environment (Lucas 1991). This possibility has been raised in the DOHaD literature, in part from animal studies that have documented predictive adaptive responses based on in utero environments (e.g., in utero nutrient deprivation linked to adaptations for a limited postnatal diet) (Hoffman et al. 2017; Monaghan and Haussmann 2015). Protective health effects of early-life adversities in severely disadvantaged populations, however, have rarely been found. Such patterns are difficult to detect given the focus in DOHaD research on MHICs, where early-life adversities were often followed by improved circumstances in later life. One exception is Barnes et al. (2012), who found that early-life adversity has protective effects on cognition later in life for African Americans, while no association was found for White individuals.2

The 1949 Nyasaland Famine

Malawi is among the poorest countries in the world, with a GDP per capita of around 4% of the global average (Kohler et al. 2020). Now, as in the 1940s, economic activity is centered on rain-fed agriculture. Maize is the main crop, and sweet potatoes and cassava are secondary crops. Tobacco has been the main cash crop since the early twentieth century, creating significant competition for land. All crops are planted at the start of the rainy season, which runs from November to April (see Figure S1, shown in the online supplement, along with all other figures and tables designated with an “S”); harvest time is between April and August. This harvest needs to last for a year until the end of the next growing season, resulting in an annual “hunger season” from December, when food supplies tend to start running low, until the next harvest. Our study cohort was selected to represent this rural context where the majority of Malawians (85%) live in conditions similar to those in other rural sub-Saharan African LICs.

While famines occur with some regularity in Malawi and have been featured in the arts (the film The Boy Who Harnessed the Wind, based on the book by Kamkwamba and Mealer 2016), the 1949 famine was an outlier (Vaughan 1987), as it was preceded by lower than average rainfall in 1948 that led to poor harvests and depleted maize

2 In the Barnes et al. (2012) study, however, early-life adversities are assessed by asking retrospective questions about the childhood environment and are not specific to the in utero period on which the DOHaD literature is often focused.
reserves. Following diminished rainfall in the first part of 1949, the extremely poor 1949 harvest occurred at a time when stored food was already almost exhausted. This culmination of two years of exceedingly low rainfall resulted in the nearly complete loss of the 1949 harvest, extending the annual hunger season from late 1948 until the new harvest in April 1950. While poor rains triggered the famine, as in other cases (Sen 1982), the impacts were exacerbated by other factors: limited access to farmland, poor management by colonial authorities who failed to keep sufficient maize in storage, and a failure to adequately import food (Vaughan 1987). Even though accounts of the famine focus on the Southern Region of Malawi, the resulting crisis was a national one: weather data show much lower than usual levels of precipitation in the Central and Northern Regions as well (Figure S2), colonial harvest records point to clear impacts in the Central Region in addition to the Southern Region, and maize prices increased across the country as a result of redistribution efforts within the context of severely limited national food supplies (Vaughan 1987).

Methods

To identify the long-term health effects of the Nyasaland famine, our analyses investigate individuals who were affected by the famine in utero. The Malawi Longitudinal Study of Family and Health (MLSFH) (Kohler et al. 2015; Kohler et al. 2020) provides a rare dataset enabling these analyses because it (1) captures older respondents, who are often omitted in LIC surveys; (2) provides extensive—and often longitudinal—health measures that cover all aspects of the metabolic syndrome (hypertension, diabetes, heart disease, and obesity), as well as information on mortality after enrollment in the study; and (3) includes study areas—Balaka in the Southern Region and Mchinji in the Central Region—that experienced the largest shortfalls in rain in 1949, while respondents in Rumphi in the Northern Region were affected by the national food supply crisis and overall economic hardships that resulted from the famine (Vaughan 1987).

Since the famine lasted from the start of the hunger season of 1948/1949 (with severe hunger beginning in late 1948) to the harvest of 1950 (in the middle of that year), we consider individuals born in 1949 and 1950 as having experienced in utero exposure to the famine. We compare these individuals with respondents born within ±10 years of the 1949 famine. The main outcome variables of interest are systolic/diastolic blood pressure and blood glucose measured during 2013–2018. Secondary outcomes are anthropometric measures and symptoms of heart disease and stroke.

Malawi Longitudinal Study of Family and Health

The MLSFH is a population-based cohort study with 12 rounds of data collection that provides a rare record of more than two decades of demographic, socioeconomic, and health conditions in one of the world’s poorest countries (Kohler et al. 2015; Kohler et al. 2020). While the MLSFH is not nationally representative, comparisons with the rural samples of the Malawi DHS (National Statistical Office (Malawi) and ICF Macro 2011) and IHS (National Statistical Office (Malawi) 2012) confirm
that the MLSFH study population continues to match closely the characteristics of nationally representative surveys (Kohler et al. 2015; Kohler et al. 2020). The initial MLSFH sample was established using a cluster-random-sampling strategy (Mchinji and Rumphi) and by drawing a subset of an earlier representative population survey (Balaka). Importantly for this study, in 2008 the MLSFH added a sample of parents of the original MLSFH respondents to increase the suitability of the MLSFH for studying intergenerational aspects and the health of older individuals. Currently, the MLSFH study population has been followed up until 2019 (including migration follow-ups), with 2012–2018 data collections focusing on a subset of MLSFH respondents aged 45+, and the 2019 data collection following up on the remaining MLSFH respondents (including older respondents who previously were not included). Cohort Profiles (Kohler et al. 2015; Kohler et al. 2020) provide detailed information about sampling, study instruments, attrition/follow-up rates, and data quality. Non-mortality-related attrition among MLSFH respondents is not different for respondents with in utero exposure to the famine as compared with their peers born in the years before or after the 1949 famine, while the mortality among famine-affected respondents is lower (Table S1). Our analysis sample for Tables 2 and 3 consists of about 850 MLSFH respondents born in 1939–1960 (1949 ± 10 years). Robustness tests use MLSFH respondents born in 1929–1970 (1949 ± 20 years) (Table S2).

Outcomes

The main outcome variables of interest in our study are systolic/diastolic blood pressure and blood glucose. Secondary outcomes of interest include anthropometric measures (weight, height, and waist and hip circumference) and self-reported symptoms of heart disease and stroke. Systolic and diastolic blood pressure were collected in 2013, 2017, and 2019, each round making three measurements using upper-arm blood pressure monitors. We take the average of the three measures and determine hypertension stages 1 + 2 (systolic ≥ 130 mm Hg or diastolic ≥ 80 mm Hg) and stage 2 (systolic ≥ 140 mm Hg or diastolic ≥ 90 mm Hg). Fasting blood glucose levels were collected in 2017. We classify diabetes as blood glucose ≥ 7 mmol/L and (pre)diabetes as glucose ≥ 5.6 mmol/L. Body mass index (BMI) was calculated from measured height and weight. Measured waist and hip circumferences were combined to construct the waist-to-hip ratio (2017 only). Symptoms of stroke were taken from the Questionnaire for Verifying Stroke-Free Status (QVSFS) (Jones et al. 2001) and included sudden weakness in one part of the body, sudden numbness in one part of the body, sudden loss of vision, and sudden loss of ability to speak or ability to understand. For symptoms of heart disease, we relied on the World Health Organization Rose Angina Questionnaire, which elicited experience of chest pain, exertion, and

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3 The MLSFH-MAC (Mature Adults Cohort) screened all respondents for high blood pressure in 2013, 2017, and 2019 following the protocol established by the U.S. Health and Retirement Study (HRS) and using an Omron HEM-780 blood pressure monitor (or comparable device). Three measurements by trained study personnel were taken on the respondent’s left arm, about 45 seconds apart, toward the end of the interview. Data recorded for each measurement included systolic and diastolic blood pressure, pulse, and the time of day the reading was taken. The same model was used over time.
symptom resolution and provides a 0/1 indicator of heart disease (Cook et al. 1989). We used the number of stroke symptoms, the presence of any symptoms, and the Rose angina index as secondary outcomes in our analyses. In all cases, when multiple health measures were available for an individual, we selected the most recent available measure to assess the effect of the famine. In addition, for blood pressure, we also computed the annual changes in blood pressure during 2013–2017 (for respondents surveyed in 2013 and 2017 only; for those surveyed in 2019, no prior blood pressure measurements were available).

The study population is characterized by a relatively high prevalence of hypertension, despite the relative absence of risk factors such as Western diets or obesity (only 5% of individuals in the sample are classified as obese using BMI) (Ciancio et al. 2021; Kohler et al. 2022). Forty-eight percent of individuals in our sample are stage 2 hypertensive, and more than two thirds (71%) are stage 1 or 2 hypertensive. Diabetes is much less prevalent (2%), and we thus focus on being either pre-diabetic (7% prevalence) or diabetic. Forty-two percent report any stroke symptoms (mean number of symptoms = 0.8), and 21% have heart disease according to the Rose angina criteria. Medical diagnoses of stroke or angina are rare (both 2%), most likely reflecting the lack of medical services rather than an overreporting of symptoms. Detailed summary statistics are shown in Table 1.

**Age Measurement and Exposure to the Famine**

For the cohorts exposed to the 1949 famine, neither Malawi nor other sub-Saharan LICs had reliable birth registration (World Bank 2017). Birth years need to be inferred from respondents’ own recollections, which are likely affected by measurement errors (Palamuleni 1995; Rosenzweig 2021). An advantage of our analyses is that we can rely on two different and independent data collection efforts to obtain birth years. Our first analyses (Table 2) rely on the birth years as reflected on Malawi’s National Identity card. These were issued starting in 2017 (World Bank 2017), and the MLSFH has been recording birth years directly from the National IDs since. In cases in which respondents did not have National IDs, Voter Registration cards were used. For individuals in our analysis data, birth years from National IDs are available for 91%, and from Voter Registration cards for 9%. Figure S3 shows a histogram of the birth year distribution of our sample; there is no evidence of heaping at 5- or 10-year intervals.

It is important to recognize that the birth dates on the National ID cards for our analysis sample are based on respondents’ reports to National Registration Bureau staff without external validation via birth registration linkages. Hence, there is also likely measurement error in the birth year information on the National IDs. Our analyses therefore also employ an alternative way to assess exposure to the 1949 famine based on ages reported during the MLSFH surveys. While each age report elicited in a survey is likely subject to some measurement error, individuals in our sample have been asked about their ages multiple times during 1998–2019 (on average, 11 times, with an interquartile range from 9 to 15 times). Rather than relying on a single age

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4 The median standard deviation of age reports is around 1, while the average standard deviation is around 2.
report to infer birth year, we first infer birth year as \textit{survey year – age report} and then estimate a \textit{robust birth year} for each respondent as the median of all available MLSFH birth year data. If measurement/recall error of age is random across different measurements, combining multiple age reports reduces measurement error. The median used to infer robust birth year is also not affected by single outliers, thereby reducing concerns about age heaping. A \textit{robust} measure of each respondent’s age is obtained as \textit{survey year – robust birth year}, providing our “best” (and intertemporally consistent) measure of a respondent’s actual age.

We subsequently determined \textit{in utero} exposure to the 1949 famine from this \textit{robust} age. Because the MLSFH surveys are conducted primarily in June and July, we consider respondents with a 2019 \textit{robust} age of 69 as being exposed \textit{in utero} to the 1949
famine: they were born approximately during the second half of 1949 and the first half of 1950, and thus were in utero during the most severe periods of the famine. The sample selected using robust age shows very similar characteristics (Table S3) to the sample selected using the National ID card.

Finally, we take a different approach and exploit the variation in age reports to create a probability of being in utero during the famine. We create this probability by counting how many age estimates would be in the treatment group over the total number of age estimates. We then run the main specification but with the probability of a dichotomous variable for treatment.

**Analytic Approach**

The effects of famine exposure on subsequent health are estimated using $y_i = \alpha + \beta T_i + \gamma_1 \text{year}_i + \gamma_2 \text{year}_i^2 + \gamma_3 X_i + e_i$, where $y_i$ is health for individual $i$ measured during 2012–2019, $T_i$ is a dichotomous variable for being affected by the famine in utero (born in 1949 or 1950), $\text{year}_i$ is the year of birth minus 1938 (the oldest cohort in our sample), and $X_i$ are individual control variables including gender, region of birth, region of current location, and survey wave dichotomous variables corresponding to the survey wave used for $y_i$. Standard errors are clustered at the year of birth. In the main specification in Tables 2 and 3, we do not include schooling in $X_i$ because schooling is potentially an endogenous pathway variable that could be affected by the famine. The respective results with controls for schooling are reported in Table S4. Additionally, we control for wealth in Table S5.

Potential differential survival to older ages among individuals with famine exposure is investigated using complete (100%) Malawi census data from 1987 and 1998 (Zuberi 2021). Data are aggregated by single-age cohort. Analyses are restricted to cohorts who were between 40 and 60 years old by 1998 (aged 29–49 in 1987). Estimates for differential survival to adulthood are obtained from the census data using $y_i = \alpha + \beta T_i + \gamma_1 \text{age}_i + \gamma_2 \text{age}_i^2 + \gamma_3 d_5 + \gamma_4 d_{10} + e_i$, where $y_i$ is the number of individuals alive in cohort $i$, $T_i$ is a dichotomous variable for being affected by the famine in utero (born in the second semester of 1949 or first semester of 1950), $d_5$ is a dichotomous variable equal to 1 if age is a multiple of 5, and $d_{10}$ is a dichotomous variable equal to 1 if age is a multiple of 10. The dichotomous variables $d_5$ and $d_{10}$ control for the tendency to round ages to 5- or 10-year intervals (Figure S4).

**Results**

*In Utero* Famine Exposure and Long-Term Health

Panel A of Table 2 presents the effects of in utero famine exposure on hypertension and diabetes risk, using birth years (1949 or 1950) from National ID cards. Seventy years after the in utero exposure to the famine, affected individuals have systolic and diastolic blood pressure measurements that are on average 6 mm Hg and 3 mm Hg, respectively, lower than those of individuals without in utero exposure to the famine. These results are both statistically significant and large in magnitude (e.g., for systolic
blood pressure, corresponding to a reduction of 4.5%, or 0.25 standard deviations) and confirm our previous descriptive findings in Figure 1, panel b. Given high average blood pressures of 139 systolic and 85 diastolic in the study population, and the resulting high prevalence of hypertension (71% with systolic >130 mm Hg or diastolic >80 mm Hg), these reductions indicate a positive effect on cardiovascular health. The famine effect, however, is not sufficient to significantly reduce the proportion of people who are hypertensive. Famine exposure leads to a statistically significant decrease in blood glucose of 0.11 mmol/L, but given the overall low prevalence of (pre)diabetes, this effect is not sufficiently large to reduce the proportion of respondents who are (pre)diabetic (blood glucose ≥ 7 mmol/L).
In our study population, blood pressure increased with age by about 0.2 mm Hg per year on average during 2013–2017 (longitudinal measures are available for 561 respondents in our sample). These age gradients are reduced by about 1.9 mm Hg for systolic and 1 mm Hg for diastolic per year for individuals with in utero exposure to the famine (columns 3 and 4 in Table 2, panel A), confirming our previous descriptive findings in Figure 1, panel c. Panel B of Table 2 also documents a negative effect on the number of stroke symptoms, albeit no effect on whether individuals report at least one stroke symptom or using the Rose angina indicator. We find no significant famine effects on anthropometric measures (panel C in Table 2), although the negative coefficient for height is in line with the literature on adverse in utero conditions and stunting (Engle et al. 2007; Grantham-McGregor et al. 2007).

Birth years on National ID cards are potentially subject to measurement or recall error owing to the lack of birth registration for the relevant cohorts. Our analyses in Table 3 therefore identify famine exposure using “robust ages” inferred from the multiple age reports available in the MLSFH. Across most outcomes, the famine effects are estimated more precisely (smaller standard errors) using robust ages rather than birth years from the National IDs. The reductions in systolic and diastolic blood pressure are smaller in magnitude (panel A), but remain statistically significant. The analyses in Table 3 also document a statistically significant reduction in the proportion of respondents who are hypertensive or (pre)diabetic. We observe a negative and statistically significant effect on the probability of reporting any stroke symptom and having heart disease based on the Rose angina metric (panel B). There are also statistically significant negative coefficient estimates for BMI, waist-to-hip ratios, and obesity (panel C).

Finally, we take a different approach and exploit the variation in age reports to create a probability of being exposed during the famine. The results are reported in Table S6. Although the findings are larger in magnitude, we see consistent negative and statistically significant results for blood pressure, change in blood pressure, hypertension stage 1, blood glucose, stroke symptoms, Rose angina score, and BMI.

As discussed in the Introduction, some DOHaD literature focuses on the first 1,000 days from in utero to 2 years of age, and Table S7 presents the health effects of such exposure to the famine. These results point in the same directions as with in utero exposure only but the coefficients are generally smaller and often not statistically significant, with the exception of diastolic blood pressure. This suggests that the effects of the famine are concentrated among those who were affected while in utero.

While we cannot test the mismatch hypothesis directly, we could in principle carry out a mediation or heterogeneity analysis. The hypothesis is that people with lower socioeconomic status should have better outcomes than those with higher status because poor people did not experience a mismatch. Unfortunately, our sample of respondents affected by the famine in utero is small, and any results derived from heterogeneity analysis should be interpreted with caution. Table S9 shows the results of our main specification in which in utero famine exposure is interacted with a variable that takes the value of 1 if the respondent has at least some schooling and 0 otherwise. We do find evidence that supports this hypothesis: our results suggest a larger decrease in blood pressure and diabetes among respondents exposed to the famine in utero and who have no schooling, relative to those similarly exposed but who have at least some level of schooling. With the sample size caveat in mind, these results
Robustness

Our key findings are also robust if analyses additionally control for schooling (Table S4) and wealth (Table S5), and they remain unchanged when extending the analysis sample to include respondents born 20 years before and after the famine (Table S2).
As expected, a placebo analysis for cohorts born in 1951–1952—that is, cohorts with no famine exposure in early life—does not document any long-term health effect (Table S8; cohorts born before 1949 do not provide a valid placebo test as they had some early-life exposure to the famine).

**Survival of Individuals Exposed to the Famine**

A potential concern for the causal interpretation of our results in Tables 2 and 3 is the possibility that individuals exposed to the famine were more likely to die prior to reaching adulthood or older ages. If this were the case, then the survivors of the famine cohort might be healthier owing to additional mortality selection.

No accurate data on infant and under-5 mortality exist for the period around the 1949 Nyasaland famine; yet, since under-5 mortality is estimated to have been approximately 1 in 3 (∼35%) (United Nations 2019), among the highest in the world at that time (Figure S5), a further substantial spike in under-5 mortality seems unlikely (although the age pattern of under-5 mortality might have changed, with more children dying at younger ages; Lee 1990). While we cannot directly estimate variation in under-5 mortality as a result of the famine, analyses of census data allow us to investigate differences in cohort sizes. Using 100% Malawi censuses from 1987 and 1998, we look at whether the cohort that was in utero during the famine is significantly smaller (or larger) than nearby cohorts. To do so, we regress the number of people in each cohort on in utero famine exposure, a linear and quadratic trend for age, and a dummy variable for age being a multiple of 5 or 10 to account for age heaping. The results in Table 4 show that famine-exposed cohorts are not smaller than cohorts born before or after the famine. Because famines and related crises generally depress fertility (Lee 1990), analyses of census data thus do not indicate a reduced survival to adulthood among famine-exposed cohorts.

This conclusion is further supported by analyses of mortality and attrition in the MLSFH cohort itself (Table S1). These analyses focus on respondents who were successfully interviewed in 2008–2010, that is, the survey rounds when MLSFH first expanded to older ages, and focus on three outcomes observed in 2018–2019: being interviewed, being recorded as deceased, and being interviewed conditional on survival. Individuals exposed to the famine were slightly more likely to be surveyed during 2018–2019, and this effect is driven by lower mortality during the period 2008/2010–2018/2019 among famine-exposed respondents (Table S1).

**Discussion and Conclusion**

The Barker (or Developmental Origins of Health and Disease) hypothesis is a prominent life course framework stating that adversities in utero have long-run negative effects on adult health (Barker 1995; Barker et al. 1990). This hypothesis has been extensively studied in high-income countries, where aging studies either elicit early-life contexts in surveys or obtain such information via linkages to external sources, and the DOHaD had substantial influence on understanding the origins of diseases—and specifically noncommunicable diseases—at older ages (Hoffman et al. 2017).
The present study is one of the first, if not the first, to examine the impact of adversities in utero in a persistently low-income context. Importantly, individuals with in utero exposure to the 1949 Nyasaland famine are documented in this study to have better cardiovascular health 70 years after the famine. Specifically, we find significant effects of the famine in reducing systolic and diastolic blood pressures, differences in blood pressures from 2013 to 2017, diabetes risk as measured by glucose levels, and the number of reported stroke symptoms. These results are robust across various analytic specifications and are consistent across alternative inferences of years of birth. Results disappear—as is expected—when using a placebo exposure one year after the famine. Analyses of census and MLSFH attrition data confirm our interpretation that additional mortality selection among famine-affected cohorts is not likely to drive our results. We conjecture that adversities in utero might cause adaptations that turned out to be advantageous regarding cardiovascular health given that individuals were subsequently exposed to persistently low incomes and poor living standards.

These findings need to be interpreted within the context of the cohorts studied. All individuals born prior to 1960 in Malawi faced significant life course adversities. Under-5 mortality for these cohorts was one of the highest in the world, and period life expectancies at birth were around 35 years in the 1950s and remained below 46 years until the early 2000s (United Nations 2019). Survivors to older ages in all of these cohorts are thus very selected. But despite this selection, health at older ages is often poor. For example, hypertension is widespread despite the absence of risk factors such as obesity or Western diets (Kohler et al. 2020; Kohler et al. 2022), mental health is often poor (Kohler et al. 2017), and cognitive decline begins at relatively young old ages (Kohler et al. 2023).

We believe that our findings documenting a positive effect of in utero adversity on later-life cardiovascular health are consistent with epigenetic causes of disease
resulting from a “mismatch” between individuals’ early developmental environment and their later adult environment (Godfrey et al. 2007), thereby causing later-life degenerative diseases via an epigenetic mechanism similar to the Barker hypothesis (Schmitz and Duque 2022). Specifically, in this mismatch hypothesis, the early developmental environment delivers “cues” that trigger predictive adaptive responses (PAR) in the form of epigenetic modifications that affect a later phenotype, which is, therefore, established by early-life gene–environment interactions (Godfrey et al. 2007). When the PAR is “mismatched” with the individual’s actual later mature environment, suboptimal fitness and disease tend to result. The biological mechanism underlying this mismatch hypothesis is likely metabolic or nutritional. For example, the fetus may respond to maternal nutritional deprivation with PARs that are consistent with a poor adult environment, such as reduced somatic growth. Depending on whether the PAR matches the later mature environment, the health consequences are likely to be different.

This mismatch hypothesis has been tested mostly in middle- and high-income contexts, where a mismatch occurs as a result of the sequential occurrence of a deprived developmental environment (owing to, e.g., famine, general unbalanced maternal diet, or maternal infections during pregnancy) and a later (comparatively) rich adult environment. However, much less is known about how a relatively deprived developmental environment affects health across the life course when the latter is also characterized by a relatively poor environment, as is the case in many LICs. The planned extension of the MLSFH is in part motivated by the need to study this and related mechanisms in determining health at older ages in LICs, and future waves of the MLSFH will thus integrate measures of biological (epigenetic) aging within the context of rich socioeconomic data.

Our findings documenting long-term positive effects of in utero famine exposure on cardiovascular health in Malawi are important for two reasons. First, they extend evidence on the DOHaD to persistently low-income contexts that have to date received little attention in this literature. Second, they indicate that the consequences of early-life adversities may be context specific, with possibly opposite consequences of in utero adversities prevailing in persistently low-income and adverse contexts as compared with MHICs. Our results thus highlight the need to further study the implications of early-life adversities on later-life health, including the pathways through which they operate, in LIC populations that face sustained poverty and high levels of morbidity and mortality throughout the life course. Current knowledge from MHIC studies about the developmental origins of health at older ages may not necessarily extend to these populations.

We emphasize that our results should not be construed as evidence against the large body of findings that have documented that early-life adversities have generally negative health and socioeconomic consequences later in life (Barker et al. 1990; Grantham-McGregor et al. 2007; Hoddinott et al. 2013; Hoffman et al. 2017), and that policies that target early-life adversities to improve developmental outcomes of children have high returns and should be prioritized (Engle et al. 2007; Lomborg 2013). In Malawi and globally, recent cohorts did face, and future cohorts are likely to face, much lower levels of early-life and subsequent adversities than the cohorts studied here (Lloyd 2005). Further improving early-life and ongoing environments of recent and future cohorts in Malawi and globally is an important priority. Indeed,
as subsequent adversities are reduced, the impacts of early-life adversities in Malawi are likely to have the negative longer run Barker hypothesis effects on cardiovascular health that have been reported in other contexts with fewer ongoing adversities than experienced by our study cohorts.

Several limitations of our analyses need to be acknowledged. As in other population-based studies in countries that have been persistently very poor, ages and birth years cannot be verified by registration data and individuals’ recall of this information is subject to measurement errors (Palamuleni 1995; Rosenzweig 2021). An advantage of our study is that we can rely on multiple sources of information, including the National ID cards (for birth year) and repeated measures of ages obtained during the MLSFH in 1998–2019. Moreover, measurement errors in years of birth are likely to bias our estimates toward zero (Bound et al. 2001), and our estimated famine effects on later-life health are thus likely conservative. Another limitation is that we are not able to identify the biological and detailed social mechanisms through which the famine worked to affect the health of aging Malawians. Future research that can utilize epigenetic or biomarker data for this cohort might be able to identify possible pathways, but such data are not yet available in the MLSFH or any other LIC aging datasets. Furthermore, we can represent the famine only in terms of the time period when it prevailed in its most severe form, and we lack direct measures of food shortages or localized market prices. These limitations also imply that our analyses probably underestimate the true effects of the famine.

Overall, this study provides important evidence that the most common interpretation of the Barker hypothesis—namely, that in utero adversities translate into worse long-run health—needs to be qualified depending on the context. This interpretation may not hold in LICs with ongoing adversities like Malawi, suggesting that more LIC aging studies are required to better understand health among the aging global poor. Consistent with the Barker hypothesis, early-life scarce conditions may actually provide late-life advantages if the conditions persist over time.

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