Social Science & Medicine 327 (2023) 115940

Contents lists available at ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

Opioids ease my pain: Early-life malnutrition and elderly outcomes

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ARTICLE INFO

Handling Editor: Social Epidemiology Editorial Office

JEL classification:
I12
J13
J16
Q51
Q53

Keywords:
Health and early life
Opioid use roots
Deaths of despair
WWII and Iran

ABSTRACT

Despite a large body of evidence showing that early-life malnutrition influences adult outcomes, there is no evidence that early-life starvation causes use of opioids. Studying the long-term effects of a food shortage in Iran caused by WWII, we find that the rate of people who use drugs in this cohort increased significantly higher than in surrounding cohorts. Then, we examine a broad spectrum of outcomes for this cohort to shed light on potential causes of opioid use in the survivors of this cohort. Our findings suggest that pain contributes significantly to opioid use.

1. Introduction

Studies have examined the roots of the U.S.'s drug abuse problem, particularly opioids (Currie and Schwandt, 2021), but little is known about drug abuse in developing countries. According to the United Nations' World Drug Report, 269 million people aged 15–64 had used drugs in the last year (5.4 percent of the global population). By 2030, the number of people abusing drugs worldwide is expected to increase by 11%, with developing countries seeing the greatest growth (UNODC, 2021). Iran is an important part of the global supply chain for opioids because it is close to Afghanistan and has used opium since the 18th century (Hansen, 2001; UNODC, 2007). This has made Iran one of the world's top consumers of opium and its derivatives (Soroosh et al., 2019), similar to the U.S., where opioid misuse is higher than in other developed countries.

In this study, we first examine the relationship between birth during the Iranian famine and opioid use later in life. We find that people born during the famine are more likely to use illegal drugs in the category of opioids (opium and heroin, but no stimulants). To our knowledge, this is the first paper that investigates early-life malnutrition and opioid use later in life. Second, we look at several outcomes for survivors in the treatment group. This is because studies have shown that being malnourished in early life can hurt many aspects of a person's human capital and may lead to drug abuse later in life (Almond et al., 2018; Almond and Currie, 2011; Kyriopoulos et al., 2019). While the treatment cohort survivors do not show a significant decline in educational attainment, they report adverse health, especially for the pain and physical conditions that they have. These findings are based on the 28-item General Health Questionnaire and health-related quality of life. The survivors in the treatment cohort are also about 0.6 cm shorter than those in the cohorts around them. Considering these findings, survivors likely abused opioids in the treatment cohort as pain relievers for their physical problems. Our study is based on detailed and unique survey data from 96,141 people in Tehran collected as part of the WHO global project called Health Equity Assessment and Response Tool (HEART). The 936 survivors in the treatment group were all born during the 1941–1943 food shortages.

A few studies have examined the link between early-life shock and drug abuse. However, this literature leaves unclear what drives these addictive behaviors or whether drug abuse is directly impacted by early-life malnutrition or is derived indirectly from physical or mental health deterioration. Our paper shows that opioid abuse may derive from pain and physical health deterioration inherited from early-life malnutrition. To relate our study to the previous literature, we specifically test three possible hypotheses:

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https://doi.org/10.1016/j.socscimed.2023.115940
Received 22 December 2022; Received in revised form 8 April 2023; Accepted 29 April 2023
Available online 8 May 2023

1. *The treatment cohort survivors have a higher opioid use rate because they are less educated, so they are socioeconomically disadvantaged.* Early-life shocks have an impact on learning and cognitive abilities (Bharadwaj et al., 2013; Ding and He, 2021; Fritze et al., 2014), and insufficient education can lead to increased drug abuse rates. It is often suggested, especially in the U.S., that opioid misuse disproportionately affects the less educated (Case and Deaton, 2015). We examine the years of schooling of the treatment cohort to test this hypothesis.
2. *The treatment cohort survivors are more likely to use opioids because they suffer from mental health problems.* There is evidence of the long-term impact of early-life shocks on mental health (Adhvaryu et al., 2019). We analyzed the treatment cohort's mental health using one of the most commonly used psychological assessment measures, the 28-item General Health Questionnaire (Goldberg et al., 1997; Huang et al., 2013).
3. *The treatment cohort survivors are more likely to use opioids because they have a physical disorder and suffer more pain.* Organs and tissues undergo rapid development in the nine months in utero. Undernutrition during gestation influences the structure and function of organs and tissues and raises the risk of chronic degenerative disorders (De Rooij et al., 2021). In order to measure their physical health, we examine the height and pain of the treatment cohort.

While we find strong evidence for Hypotheses 2 and 3, we do not find any for Hypothesis 1. This finding suggests that, even in the absence of significant educational inequality, early-life famine exposure can degenerate health and lead to opioid abuse in the elderly.

2. Literature

We contribute to two literature strands. The literature on early-life circumstances and long-term outcomes, particularly early-life malnutrition, and the literature on drug abuse, particularly opioid use and pain management. Early-life nutrition and health are critical to a person's life trajectory and human capital formation (Almond et al., 2018). In the fetal origins hypothesis (FOH) framework, D.J. Barker first claimed that chronic diseases have their origins in fetal development (Barker, 1992). Over the next few decades, the long-term effects of the fetal origin hypothesis were studied in a variety of fields, including physical health (Hoynes et al., 2016; Karimi et al., 2021; Lee, 2014), chronic health (Barker, 1998; Costa et al., 2007), earnings and labor supply capabilities (Isen et al., 2017; Shah and Steinberg, 2017), and mental illness (Ding and He, 2021; Dinkelman, 2017; Song et al., 2009). The Chinese famine of 1959–61 caused millions of deaths nationwide. Early-life exposure to Chinese famine was linked to metabolic syndromes (Zheng et al., 2012), chronic kidney disease (Lv et al., 2020), and premature aging (Wang et al., 2019). In studies, mental illness and depression were significantly associated with exposure to the Chinese famine (C. Li et al., 2018; Y. Li et al., 2018). The most similar study to ours that of Huang et al. (2013) used the 12-item General Health Questionnaire (GHQ-12) and found a large cohort effect for women. Natural selection in utero during the famine might obscure the detrimental effects of famine exposure on men's mental health. The Dutch famine of 1944–45 generated natural experiments to assess the consequences of prenatal undernutrition on later life. Studies reveal that the cohort exposed to the Dutch famine in utero in any stage of gestation suffered from cardiovascular disease, glucose intolerance, and other physical health outcomes, even without birth weight decreases (De Rooij et al., 2021). The Dutch famine also increased the risk of schizophrenia in adulthood, as well as other psychiatric disorders, including major affective disorders, antisocial personality disorder, and general mental illness that is not diagnosis-specific, among famine survivors' children (Susser and St Clair, 2013). In the most similar study to our context, Franzek et al. (2008) studied the relationship between prenatal exposure to famine during the Dutch Hunger Winter of 1944–45 and addiction to alcohol or drug abuse later in life. They used the data of those born in 1944–1947 who had registered with an addiction problem (alcohol and drug abuse) in the Dutch Mental Health Care Organization database and found that prenatal exposure to famine is associated with addiction later in life.

Most studies on drug abuse have focused on the U.S. because the "opioid epidemic" there is exceptionally alarming. Various factors contribute to the opioid epidemic, including chronic pain, poor health, and lack of access to chronic pain management (Friebel et al., 2022; Thompson-Lastad and Rubin, 2020). We look at data from Iran since secular trends in drug abuse, including opioid abuse, have been projected for developing countries. While malnutrition is more prevalent in developing countries, it is important to figure out if early-life malnutrition and its effects are linked to drug abuse and how that happens so that policy solutions can be made.

3. Historical setting

Iran experienced a severe food shortage that lasted two years—longer than the Dutch Hunger Winter (one year) but shorter than the Great Leap Forward Famine in China (three years). The food crisis in Iran was triggered by the Anglo–Soviet attack on Iran during WWII and the country's occupation. The Anglo–Soviet attack on Iran was a coordinated attack by the British Empire and the Soviet Union on the neutral country of Iran on August 25, 1941. Iran surrendered in less than one week and agreed to a ceasefire on August 30, 1941. The Allies had occupied the country since September 1941 and provided a massive stream of over 5 million tons of material to the Soviet Union. The occupation took more than four years; however, the first two years of the occupation, from September 1941 to September 1943, were noticeable for three facts (Farrokh, 2011; Foran, 1993): the highest recorded inflation rate in the history of the country; a severe food shortage; and several bread riots in the country.

Although a large body of literature uses the Dutch Hunger Winter and Great Leap Forward Famine in China as natural experiments to evaluate the long-term impact of early-life starvation, only one study looked at Iran's food crisis during World War II (Dadgar et al., 2020b). The study found a 1-cm drop in height for people born between September 1941 and 1943. As in the previous study in Iran, we consider those born between September 23, 1941, and September 23, 1943, to be the treatment cohort. (We provide details of the timing and the food crisis in the online appendix.) In this study, despite much evidence documenting economic shock and the food crisis between fall 1941 and summer 1943, we could not find strong evidence of other severe social-economic distress, such as violence. Therefore, we think the most serious impact of the famine exposure is the malnutrition of mothers and their offspring.

4. Data

The data for this study was collected as part of a global project called Urban Health Equity Assessment and Response Tool (HEART) in October 2011 in Tehran, Iran. HEART is a project formed by the WHO Center for Health Development in Kobe, Japan, in collaboration with local offices of WHO and cities worldwide. The second wave in 2011–12 was conducted in 15 cities, mostly in low- and middle-income countries, and addressed urban health inequalities in different dimensions (Prasad et al., 2015). The data was used in several studies to examine health aspects in Tehran, one of the world's largest cities (Dadgar et al., 2020a, b; Karimi et al., 2020).

Sampling strategy. To get representative samples of individuals from all 22 of Tehran's districts, a method called "stratified multistage cluster sampling" was used. In Tehran's districts, blocks are randomly selected based on the number of households in each neighborhood. Each block is defined as eight households in sub-districts in Tehran. The survey has two parts. The first part applies to all household members, and the second to one household member. In the first part of the survey, all members of all eight households were questioned, but only one member is questioned in the second part. In the second part, the age and gender of the people chosen from the households were taken into account by making a table with eight cells, two columns for male and female, and four age groups: 15–25 years, 26–44 years, 45–64 years, and 65 years and older. One person from each gender and age group must attend to represent age groups over 15. Finally, 33915 households containing 118464 people were inspected. The birth dates of 22323 people were not described and omitted from our study, leaving 96141 individuals. As we discussed, Iran has traditionally had a problem with opium and its derivatives, like opioid abuse, and Tehran ranks among the top ten Iranian cities regarding these drugs' consumption. Urban HEART countries might customize indicators to local needs. Iran attached the use of illicit drugs to the standard questionnaire. It is important to mention that the mental health (GHQ-28) and pain (HRQoL) indices are only requested from one person per household. Individuals with heights outside the range of 0.5–99.5 percentiles are excluded from the height analysis to reduce the number of unacceptable height numbers. However, the direction and significance of the results are the same for other acceptable height ranges and the whole sample (see online appendix Table A2).

Illicit drug use (IDU). Part 8 of the questionnaire asks about using illegal drugs: Has a household member over 13 ever used opioids or other substances such as or X-stimulant pills?

If yes, answer: Which member(s) of the household? (By code).

Which of the following is true (both are possible)?

1. Opium or derivatives like heroin
2. Stimulants such as cannabis, cocaine, methamphetamine, or pills such as ecstasy.

Choose the consumption pattern in the last month.

A. 1–3 times in a month
B. 1–3 in a week
C. 1–3 in a day.
D. I don't remember

We identify the household members who used opioids or stimulants in the last month if they chose any of these consumption patterns as illicit drug users (IDU = 1). However, as we show, the rise in drug use was observed only in the consumption patterns of the first category (opioids), not the second (stimulants). According to the questionnaire, we cannot separate opium from heroin.

Education. The survey divides people's education into eight groups: illiterate, some primary school, some secondary school, some high school, diploma, associate's degree, bachelor's degree, and master's degree or above. These eight categories allow us to estimate the schooling years. Therefore, we consider the following years of schooling based on the average number of years of each period in Iran: 0, 2, 5, 8, 12, 15, 18, and 22.

Mental health. Our study uses the 28-item General Health Questionnaire (GHQ-28) to assess the mental health of the treatment cohort. The GHQ is among the most common ways to determine psychosocial well-being and screen for mental symptoms (Goldberg and Williams, 1991). It is widely used for screening nonspecific psychiatric morbidity and has been translated into many languages (Hankins, 2008). In various nonclinical settings, its validity and reliability are acceptable as a screening instrument for psychiatric disorders (Griffith and Jones, 2019; Huang et al., 2010). Items were chosen to address four main areas in the design of the GHQ-28: somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression (Goldberg and Hillier, 1979). The GHQ-28 examines breakdowns in normal function that result in an inability to engage in usual, healthy activities. It has been shown that the elements of psychological well-being are the same across cultures and that the factor structure is the same across cultures and different samples (Goldberg et al., 1997; Werneke et al., 2000).

The GHQ-28's factor analysis revealed four seven-item subscales:

Somatic symptoms (items 1–7);

Anxiety/insomnia (items 8–14);

Social dysfunction (items 15–21);

Severe depression (items 22–28).

Scoring: For each question, the respondent is asked to score how he or she feels based on the following criteria:

Much better than usual: 1.

Almost better than usual: 2.

Same as usual: 3.

Much worse than usual: 4.

The scoring system used in the questionnaire runs from 1 to 4, but we transpose it to a scale of 0, 1, 2, and 3, which is similar to the original scoring system (Goldberg and Hillier, 1979). The 28-question version has a minimum score of 0 and a maximum score of 84. Scores that are higher suggest that the person is more distressed.

Physical health (height and pain). The established negative relationship between height and morbidity and mortality from various diseases may be partially due to the fetal and early-life nutritional environment (Barker, 1995; Barker et al., 1990; Fogel, 1994). Thus, nutritional deficiency in early life may signal physical degeneration and an increased risk of specific diseases in the elderly. We also use height in this study as a physical health indicator.

The survey also includes a measure for pain by asking: "How much did the pain interfere with your normal activities?" (1 = never, 5 = always).

This question is part of the health-related quality of life (HRQoL) survey from the Center for Disease Control and Prevention.

Table 1 summarizes statistics on our variables of interest and principal covariates. It indicates a significant amount of variation in all study covariates and outcomes.

Covariates (control variables). Our mean respondent was born in early 1978, which means the mean age at the end of 2011 was 34. About half of the sample is male, 98 percent are Iranians, and 93 percent are Persian. The districts of Tehran are arranged almost in ascending order from north to south.

Table 1
Summary statistics.

	Mean	Std. Dev.	Min	Max	Obs
Covariates					
Birth Year	1977	19.22	1921	2011	96141
Age Years	34.20	19.221	0	90.571	96141
Male	.504	.5	0	1	96141
Iranian	.983	.13	0	1	96141
Persian	.928	.258	0	1	96141
District			1	22	95974
Outcomes					
Schooling years	9.796	6.128	0	22	92792
Mental Health (GHQ-28)	28.789	11.874	0	84	23754
Pain (HRQoL)	2.407	1.061	1	5	26863
Height	162.754	18.536	46	195	86404
Illicit Drug Use	.4%	.064	0	1	96141
Number of Drug Users (In the last month used illicit Drug)					
	A 1-3 in a month	B 1-3 in a week	C 1-3 in a day		D don't remember
Opioids N = 330	89	49	174		18
Stimulants N = 136	34	28	71		3

Total Number of Drug Users = 400 *(Note: 66 individuals consume both opioids and stimulants.)*.

Notes: Mental health (GHQ-28) and Pain (HRQoL) indices are only requested from one person per household. Individuals with heights outside the range of 0.5–99.5 percentiles are excluded from the height analysis to reduce the number of unacceptable height numbers.

Sources: Authors' calculations using Urban HEART 2011 in Tehran.

Outcome variable. Across all groups, the IDU rate is 0.4%, and 0.52% for adults over 18, which is relatively low. However, there are some points to consider to understand this small number. In our survey, IDU was defined as using illicit drugs (opium, heroin, ecstasy) in the last month. This definition differs from the standard drug abuse definition. The standard definition refers to using various drugs, including cannabis, marijuana, and some legal substances, for the last 12 months. There is still the possibility of underreporting use of these drugs due to adverse social norms and the illegality of substance abuse. The undersigned report affects all age groups and may not significantly affect our study.

5. Empirical strategy

The following section describes two types of evidence. First, the raw data are presented in a series of figures showing outcomes by age. They show that outcomes are a smooth function of age for the younger cohorts that escaped the famine shock, but a discontinuity for those born during the famine of 1941–1943 is observable. Second, the deviation of outcomes from a smooth cohort trend are evaluated by comparing them with surrounding cohorts. Our sample and specific setting allow us to validate the results with several robustness tests and to reduce the analytical challenges in natural experiments discussed in the literature (Xu et al., 2016). (see online appendix).

5.1. Data illustration

When the survey was conducted, members of the treatment cohort were between 68 and 70 years old. Fig. 1, panel b, shows that, in the whole sample, age predicts the rate of opioid use, except in the case of the treatment cohort. Between the lines, there is a jump in the IDU rate. The vertical lines isolate the data from people in our 2011 survey who were around 68–70 years old, meaning they were born from 1941 to 1943 during the Iran famine of the Second World War. In Fig. 1, Panel a, data are grouped according to people born within two years of one another, with each point being the average rate of IDU for the two-year group. Birth cohorts are from September 23, 1939 (the start of quarter 4) to September 23, 1961 (the end of quarter 3).

The average rate of IDU for people aged 50 to 72 is 0.54%, but the treatment cohort is estimated to have a 0.77% IDU rate. In fact, in the treatment cohort, the IDU rate is approximately 43% higher than the average for people aged 50 to 72. The increase is even more dramatic relative to the two surrounding cohorts. We discuss how this rise in the IDU rate is associated with physical and mental health symptoms in the treatment cohort.

Fig. 2 shows the other outcomes for individuals in Tehran in the age range of 30–72. First, it shows that individuals' outcomes are a continuous function of their age, at least before famine exposure. The quadratic polynomial could fit our data and has a smooth trend before age 68.04, as indicated by the vertical line. In addition, Fig. 2 shows a departure from the trend for some outcomes. Fig. 2, Panel a, displays the average years of schooling. Schooling years decline with age. The treatment cohort maintains this trend, but for health outcomes, we have a different story. Fig. 2 Panels b–d show three more health outcomes. Health outcomes are smooth with age but discontinuous between 68 and 70. This discontinuity is more significant for pain in panel d.

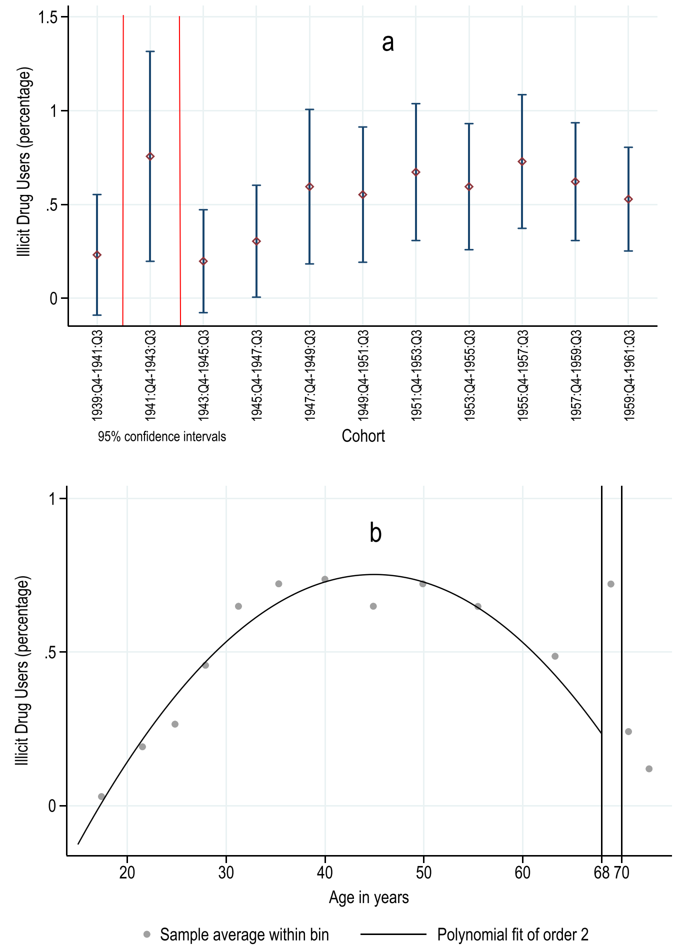

Fig. 1. Panel a: sample mean illicit drug use (IDU) rate of Iranians in biennial birth cohorts from September 1939 to 1961. Data are grouped according to people born within two years of one another, with each point being the average rate of IDU for the two-year group. Panel b: IDU percentage by age in Tehran 2011. Sample average within a bin and a polynomial fit of order 2. Sources: findings of the author from the Urban HEART 2011 in Tehran.

5.2. Specification

Cohort studies are used most often to study the long-term health effects of famine exposure in childhood by comparing exposed and surrounding cohorts. To minimize changes in confounders over time, we first restrict the sample to Iranians born 24 months before, 24 months during, and 24 months after the shock and examine their outcomes with a simple *t*-test. We then use the simple model in Equation (1) while adding covariates (control variables) and indicators (fixed effects) to the model. The following equation results:

$$y_i = \beta_0 + \beta_1 Exposure_i + \Theta X_i + \varepsilon_i \quad (1)$$

Where y_i represents our interesting outcomes for an individual i, β_1 is our interest coefficient that measures the impact of the famine exposure on the outcome, *Exposure* is a dummy for birthdays between 23/09/1941 and 23/09/1943, inclusive., X_i indicates baseline characteristics of the individuals that potentially influence outcomes. These covariates are the exact age, gender, and ethnicity dummies for being Iranian and speaking Persian. Residence may affect drug use if these drugs are easier to obtain in some areas. Thus, we add district indicators (fixed effects) to our model to improve estimation accuracy. Our empirical strategy identifies the effect of being born between September 23, 1941, and September 23, 1943, in Iran, assuming that no other lifetime events should affect treatment and control groups in a different way. If early-life exposure to the famine affects the outcome, β_1 as the coefficient of the dummy variable for those born between 23/09/1941 and 23/09/1943 becomes significant and shows the impact of the famine exposure on outcome.

6. Findings

Table 2 shows the absolute values of outcomes in this study for the treatment and surrounding cohorts, as well as a simple *t*-test between

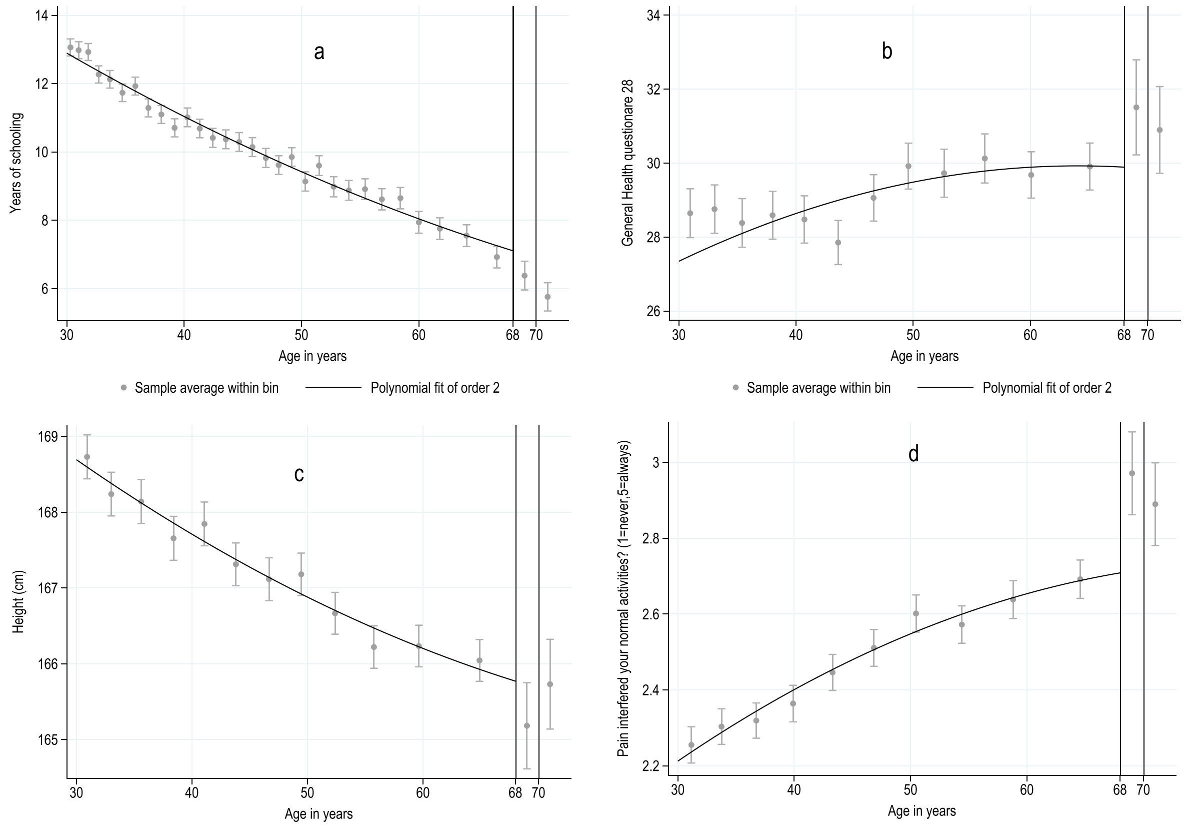

Fig. 2. Relationship between age and study outcomes. A: schooling years; b: GHQ-28; c: height; d: pain index. Note: Sample average within a bin and a polynomial fit of order 2.
Sources: findings of the author from the Urban HEART 2011 in Tehran.

Table 2
Outcome means comparison with simple *t*-test between treatment and surrounding cohorts.

Born between September	Treatment 1941–1943	Surrounding cohorts 1939–41 & 1943-45	t-statistic	p-value
Observations	936	1892		
(1) Illicit Drug Use *(IDU)*	.77 [.3]	.22 [.1]	2.15	.031
(2) Education				
Schooling years	6.34 [0.21]	6.27 [0.15]	0.28	0.78
(3) Mental health measured by General Health 28 Goldberg (the higher the score, the worse the health)				
Somatic symptoms**	8.50 [.23]	7.86 [.15]	2.37	0.017
Anxiety/insomnia	7.15 [.27]	6.77 [.17]	1.18	0.238
Social dysfunction	13.57 [.17]	13.34 [.13]	1.02	0.30
Severe depression	2.43 [.20]	2.26 [.12]	0.74	0.45
GHQ-28*	31.67 [.64]	30.23 [.43]	1.88	0.06
(4) Physical health measured by height and pain				
Height	165.24 [.28]	165.77 [.20]	−1.50	0.13
Pain** (HRQoL)	2.97 [.055]	2.80 [.038]	2.38	0.017

Notes: See notes and source under Table 1. Standard errors are in brackets. ***p < .01, **p < .05, *p < .1.

them. Table 3 provides results in the regression form to ease the comparison of outcomes and add covariates for the robustness test. Famine exposure in early life increase IDU rates and have a negative impact on mental and physical health.

Main outcome. The first part of Table 2 reports the rate of IDU. In the treatment cohort, the rate of IDU is 0.77%, about three times higher than in the surrounding cohorts (0.22%). We report IDU as our main outcome of interest in Columns 1–3 in Table 3. Covariates are not controlled for Column 1. The comparison in the regression form leads to the difference between IDU in the treatment and surrounding cohorts. In the second column, we add the covariates. They are the exact age and are dummies for sex, being Iranian and Persian speakers. We call the two last dummies together "ethnicity." It is important to mention that not all Iranians speak Persian, and most non-Iranians in Iran are Afghan immigrants, and they speak Persian (Table A1 in the appendix provides covariate coefficients.). In Column 3, district-indicators are included. All models generate similar results above the.5% IDU rate increase. In Table 2, the coefficients are significant at the 5% level. The significance level rises from 5% to 10% due to robust standard errors in column 2 and district clustered standard errors in column 3.

Education. The second part of Table 2 shows the schooling years of the treatment cohort and the surrounding cohorts. The average schooling years in the treatment cohort is 6.35, and in the surrounding cohorts, 6.27. Treatment cohort schooling years are not significantly different from surrounding cohort. We also examined the original education categories and the illiteracy rate. None of them show the impact of famine on the treatment cohort's education (See Table A3 in the online appendix.).

Mental Health. As shown in the third part of Table 2 and Columns 4–6 of Table 3, mean GHQ-28 scores are about 1.4 units higher in the treatment cohort survivors. Based on Cohen's effect size criteria (Cohen,

Table 3
Impacts of time of birth: Early-life shock on IDU and health outcomes.

	IDU			Mental Health			Physical Health					
	Illicit Drug Use			(GHQ28)			Height (cm)			Pain(HRQoL)		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Famine Exposure	.0055*	.0054*	.0051*	1.44*	1.35*	1.31*	−.53	−.60**	−.58**	.16**	.15**	.14**
	(.0030)	(.0030)	(.0027)	(.777)	(.768)	(.679)	(.35)	(.28)	(.184)	(.067)	(.067)	(.066)
Obs	2828	2828	2825	1007	1007	1005	2595	2595	2592	1162	1162	1160
R-sq	.0016	.004	.0093	.004	.026	.073	.001	.38	.391	.005	.067	.076
Covariates (exact age, sex, ethnicity) and District Indicators (fixed effects)												
Covariates	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes
District FE	No	No	Yes	No	No	Yes	No	No	Yes	No	No	Yes

Notes: See notes and source under Table 1. All regressions are ordinary least squares (OLS). Robust standard errors are in parenthesis in the columns without FE. Standard errors are clustered in the level of district when district indicators are added (Column 3, 6, 9, 12). Covariates are exact age, sex, ethnicity dummies. p < .01, **p < .05, *p < .1.

1992), this estimated impact has an effect size of 1.88 (1.4 divided by 0.76, the standard error of GHQ scores), which is very large. This means that the risk of mental illness is higher for people who lived through the treatment cohort. The GHQ-28 coefficient is significant at the 10% level in all models in Table 3 Columns 4–6.

Height. The fourth part of Table 2 indicates that the average height of people who survived in the treatment cohort is 165.24 cm, compared to 165.77 cm in the surrounding cohorts. This difference is not statistically significant before controlling for sex, but the height is strongly sex-dependent. Adding covariates in Columns 7–9 of Table 3, shows survivors in the treatment cohort are about 0.6 cm (with covariates) shorter than those in the surrounding cohorts, and the coefficient becomes significant at a 5% level. This finding is consistent and not statistically different from the 0.97 cm found in another study about the Iranian famine of 1941–1943.

Pain. The largest difference between the treatment group and its surrounding cohorts is in the level of pain they report. The HRQoL pain score is reported in the last line of Table 2 and columns 10–12 of Table 3. The pain level felt by survivors in the treatment cohort was more than two standard deviations higher than the pain level felt by survivors in the surrounding cohorts. The difference is large and statistically significant at the 2% level (p-value <.017). Based on Cohen's effect size criteria (Cohen, 1992), this is the biggest cohort effect we find in this study. This estimated impact has an effect size of 2.27 (0.15 divided by 0.065, the standard error of HRQoL scores on pain), which is quite large.

Mental health subscales. As discussed in the data section, the GHQ-28 items fall into four main categories: somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression. In the second part of Table 2, we report the subscale scores. The largest difference between the treatment and control groups is in the somatic symptom scores, including questions about pain and physical activity. The differences in the other three subcategories are neither large nor statistically significant. This finding shows again that physical problems are a major cause of the poorer mental health scores of people who were in the treatment cohort.

Analysis of illicit drug types that increased in the treatment group also suggests the treatment cohort uses them for pain relief. Table 4 shows that opioids, not stimulants, increased IDUs in the treatment group. It shows an increase in all opioid consumption patterns (a, b, c, and d); however, only the increase in pattern A is statistically significant. Interestingly, all stimulant users reported opioid use as well.

Overview of robustness tests. We run several robustness tests on our results. Our findings show these results are stable. Here, we give an overview of the robustness tests. More details can be found in the online appendix of the paper.

Testing for systematic differences in the survivors of the treatment cohort. Evaluating the impact of early-life events, including famines, typically involves some other major identification challenges. Parents with higher socioeconomic status may avoid fertility or pregnancy during a shortage. In this case, the adverse early-life famine exposure would be overestimated as a result. In contrast, treated individuals may die sooner, while healthier subsamples survive. This leads to underestimating the negative impact of the shock. These mechanisms may be difficult to rule out, and Xu et al. (2016) discuss that using famine as a natural experiment does not guarantee accurate statistics about early-life malnutrition's long-term effects. This section provides evidence showing no systematic difference between the treatment and control cohorts of survivors. In Table 5, we examine whether individuals in the treatment cohort and surrounding cohorts have had a systematic difference in their baseline observable confounders. Table 5 summarizes the baseline variables of treatment and surrounding cohorts and their confidence intervals. The first two rows report the number of observations in each cohort and the average age of each cohort. The difference between cohorts is two years. Due to population trends and the fact that

Table 4
Impacts of time of birth: Early-life famine exposure on illicit opioid consumption patterns and stimulants.

	Illicit Opioid Use Consumption patterns in the last month											
	A.1-3 times in a month			B.1-3 times in a week			C. 1–3 times in a day			D. don't remember		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Famine Exposure	.0032**	.0032**	.003**	.0005	.0005	.0004	.0006	.0006	.0005	.0011	.0011	.0011
	(.0013)	(.0013)	(.0013)	(.0011)	(.0011)	(.0011)	(.0017)	(.0017)	(.0017)	(.0008)	(.0008)	(.0008)
	Illicit stimulants Use (total)											
	.0011	.0011	.0011									
	(.0008)	(.0008)	(.0008)									
Obs	2828	2828	2825	1007	1007	1005	2595	2595	2592	1162	1162	1160
R-sq	.0016	.004	.0093	.004	.026	.073	.001	.38	.391	.005	.067	.076
Covariates (exact age, sex, ethnicity) and District Indicators (fixed effects)												
Covariates	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes
District FE	No	No	Yes	No	No	Yes	No	No	Yes	No	No	Yes

Notes: See notes and source under Table 1. All regressions are ordinary least squares (OLS). Covariates are exact age, sex, ethnicity dummies. p < .01, **p < .05, *p < .1.

Table 5
Treatment and surrounding cohorts' characteristics mean and CI 95%.

Born between September:	(Before) 1939–1941	(Treatment) 1941–1943	(After) 1943–1945
Observations	872	936	1020
Baseline characteristics			
Age by years	70.95	69.1	67.02
Ratio of men	58	56	54
(per 100)	(55,62)	(53,60)	(51,57)
Non-Iranian	9	10	8
(per 1000)	(4,17)	(4,17)	(2,14)
Non-Persian Language	9	8	8
(per 100)	(7,11)	(6,10)	(6,10)
Father's Education	1.73	1.75	1.83
Min = 1; Max = 5	(1.67, 1.80)	(1.68, 1.81)	(1.77, 1.9)
Other Potential outcomes			
Home owner	86	83	85
(per 100)	(84,89)	(81,86)	(83,88)
Lowest Income category	46	48	45
(per 100)	(43,50)	(44,51)	(42,48)
Retired	54	48	49
(per 100)	(50,57)	(45,52)	(46,52)
Married	78	79	82
(per 100)	(76,81)	(77,82)	(79,84)
Illiterate	28	25	20
(per 100)	(25,31)	(22,28)	(17,23)

Note: See notes and source under Table 1. All t-tests are not significant in any baseline or other potential outcomes of the treatment cohort and surrounding cohorts.

older cohorts contain fewer living members due to aging, there are fewer observations for the older cohorts. We cannot find a drop in the number of survivors in the treatment cohort. The ratio of male-to-female live births may be influenced by environmental factors during human conception and gestation (Catalano and Bruckner, 2005). The proportions of males and Iranians in the cohorts and their confidence intervals have been reported in the next rows. Information about the father's level of education was queried in five categories: illiterate, primary school educated, less than a high school diploma, high school diploma, and university degree. The baseline confounders of the treatment and surrounding cohorts do not differ significantly. In the second part of Table 5, we also look at other potential treatment outcomes and the surrounding cohort. The treatment cohort also has lower rates of owning a home, being in the lowest income category, and retiring than the two cohorts on either side. However, the differences are not statistically significant, probably due to the sample size.

It has been shown that opioid use disorders can vary depending on where people live (Yang et al., 2022). We could not find a significant difference between the living districts in the treatment and surrounding cohorts that are depicted in Fig. 3.

In addition, we add district indicators to all specifications, and the results do not change. It is important to point out that we do not have access to data on where individuals were born. Our observations are limited to the place of residence, which may be the same for some of them. The estimated coefficients are not affected when we add covariates to our models. Therefore, increases in IDU and declines in health status among individuals in the treatment cohort cannot be explained by age, gender, ethnicity, or the district of the city in which they live. Selection may lessen the effects of childhood famine on adults, but our findings show this is not enough to make the early life scars go away completely.

Placebo tests. As another robustness examination, we do a placebo test. We first made three dummies for age ranges of 58–60, 48 to 50, and 38 to 40 and compared them with their surrounding cohorts as the main analysis for 68 to 70. For example, for ages 56–60, the surrounding cohorts are 56–58 and 60–62. We add covariates and district indicators as the main analyses. The results are provided in Table 6 and do not

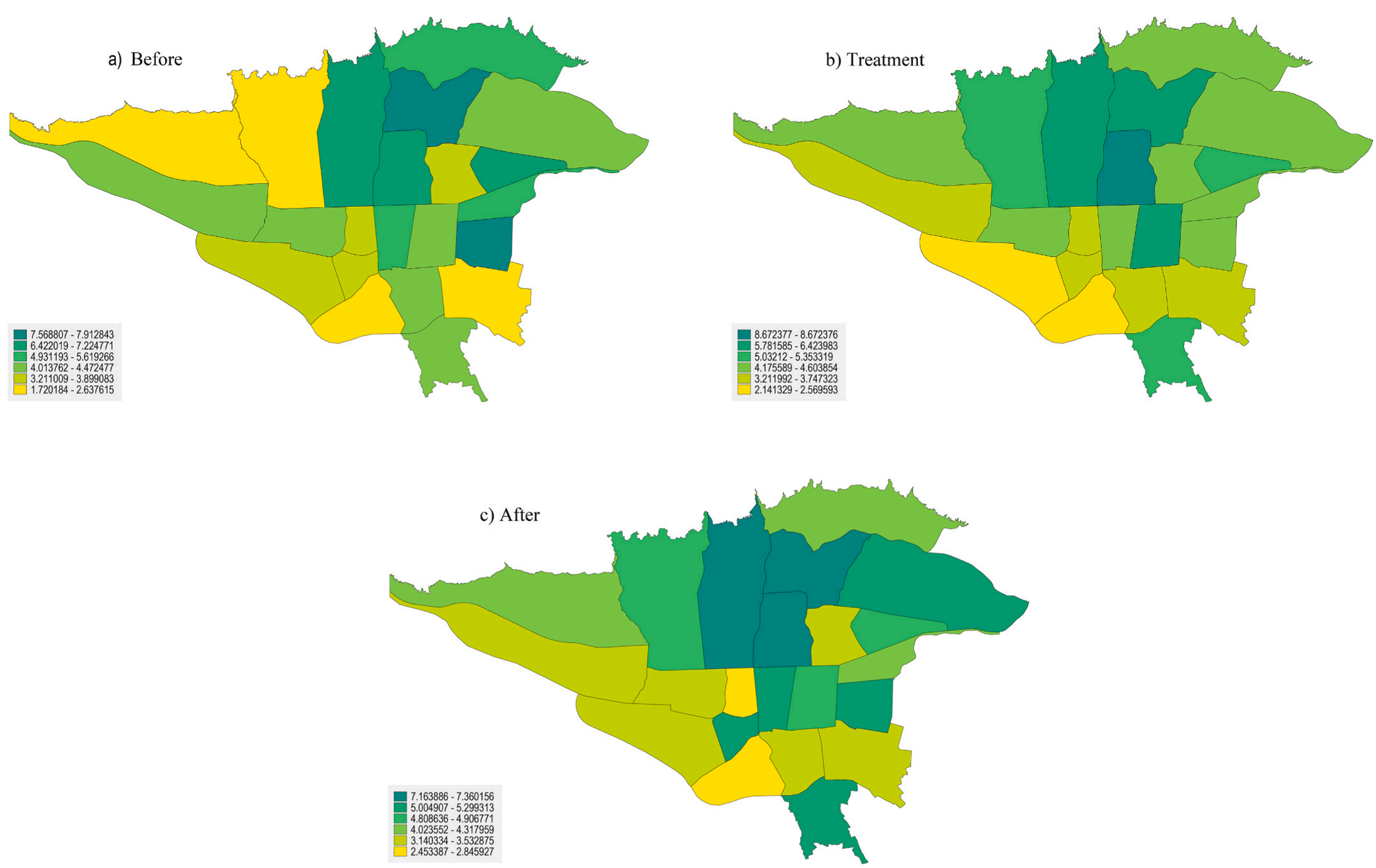

Fig. 3. District of residence for individuals in treatment and surrounding cohorts. The time and the number of observations are the same as in Table 5.

Table 6
Placebo test for time of birth: impact of three age groups on illicit drug use.

	Illicit Drug Use			Illicit Drug Use			Illicit drug Use		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Age 58 to 60	.00071	.001	.00125						
	(.00214)	(.00213)	(.00218)						
Age 48 to 50				.00268	.00271	.00299			
				(.00184)	(.00184)	(.00201)			
Age 38 to 40							−.00258	−.00219	−.00213
							(.0016)	(.00159)	(.00219)
Observations	5639	5639	5626	8129	8129	8116	8550	8550	8535
R-squared	.00002	.00638	.01322	.0003	.00575	.01055	.00025	.00765	.01073
Covariates	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes
District FE	No	No	Yes	No	No	Yes	No	No	Yes

Notes: See notes and source under Table 1. Similar to the main analysis for each age group, the surrounding cohorts (control group) are those born two years before and two years after the placebo age. All regressions are ordinary least squares (OLS). Covariates are exact age, sex, ethnicity dummies. ***p < .01, **p < .05, *p < .1.

significantly impact any of these age groups. This placebo test again shows that our results are not accidental.

Event study. The final robustness test is the event-study analysis. In this analysis, we show how the coefficients of year-of-birth dummies vary around the time of famine. In this setting, a coefficient designates each period. Zero if individuals were born in the year (12 months) leading up to the famine. One is born during the first year of the famine; two during the second year of the famine; three are born in the first year after the famine, and so on. The results in Fig. 4 show how the coefficients evolved around the famine. Fig. 4-panel b is the same analysis, but only this period changed from one year to two years, and one indicates the famine period.

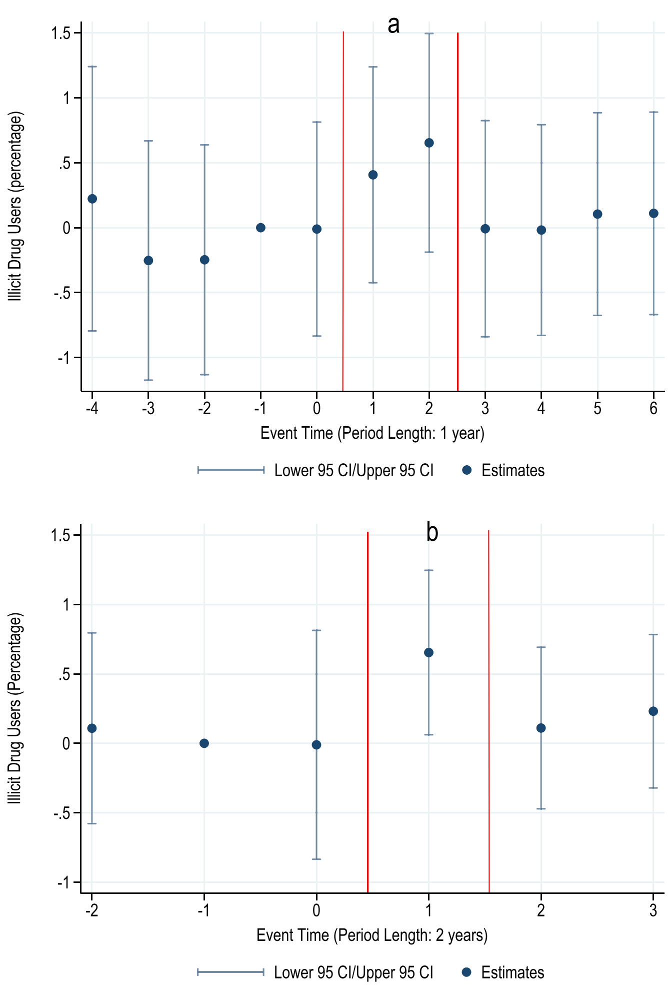

Fig. 4. In Panel a, the coefficient designating each year is shown. One is born during the first year of the famine, two during the second year of the famine. In panel b, the coefficient designating two years is shown. One is born during the famine, and two during the two years after the famine. Sources: findings of the author from the Urban HEART 2011 in Tehran.

Alternative specifications. Our results are also robust to the alternative specifications if we add birth year fixed effects or use a quadratic polynomial of age and use non-Iranians in Iran as a control group (see the online appendix, Section II).

7. Discussion

The Life path to opioid use. In several ways, malnutrition in early life could, directly or indirectly, lead to opioid use later in life. According to other studies, opioid abuse could be caused by poor health or low socioeconomic performance over a lifetime triggered by fetal or early-life environmental changes (Almond et al., 2018). On the other hand, other studies (Shonkoff et al., 2012; Shonkoff and Levitt, 2010) show that some mental functions are encoded during fetal development, which can directly cause an increase in the risk of opioid use. The findings of this study show that even though the treatment cohort survivors' education level was not decreased in our setting, there is a big difference in their health. Even if a few people who use opioids are taken out of the sample, the negative health effects we find for survivors in the treatment cohort do not change. So, this finding shows that opioid use is not to blame for the poor health of the survivors in the treatment cohort, but the opposite may be true. Looking at broad health outcomes, the most significant difference between the treatment and control cohorts is in somatic symptoms and pain scores. There are no statistically significant differences between anxiety, social dysfunction, and severe depression, which are the other three subscales of the GHQ-28. The fact that the treatment cohort survivors do not show lower education means that the full effects of malnutrition in early life may show up later in life or that people with less education could not survive in our context.

Limitations and potential threats. While this study examines the long-term effects of early-life starvation, the results regarding opioid use may not be accurate. Illegal drugs like opium and heroin are hard to study because their use is so rare in the population (about 0.5%). In addition, the use of these drugs is a big disadvantage due to the social norms of the country. Self-reported IDUs in the survey may suffer strongly from under-reporting measurement errors. Another limitation of this study is that we do not know whether the food crisis affected individual mothers. While the famine affected the entire country, some citizens might have been spared the effects of the food crisis. Due to the small number of survivors in the treatment cohort, we lack sufficient power to study them by sex separately for all outcomes. Still, HRQoL pain scores, which have the highest cohort effect, are the same for both male and female subsamples. It is statistically significant for both males and females, at 10%. We also have another restriction: the members of our treatment cohort are 68–70 years old. Studies show early-life conditions predict survival to advanced ages (Preston et al., 1998), and we can only examine survivors in this cohort. As the treatment cohort individuals were already in their late 60s, there may have been excess mortality among this group over the previous 20–30 years, which may result in underestimating the effect of malnutrition. The survivors in the treatment cohort have not reported using opioids as a pain killer or for other reasons like recreation. Despite these weaknesses, we still conclude that early-life malnutrition severely affects long-term outcomes. Considering the reduced form used in this study, we may interpret the estimated effect as the average between exposed and non-exposed groups. Therefore, the precise estimation of the treatment cohort is probably larger than what we found in our study.

Other studies. The findings of our physical health study align with another study on Iran's famine from 1941 to 1943, which found a 1-cm decline in the height of people in Iran (Dadgar et al., 2020a, b). Mental health findings in our study are consistent with studies in other settings. A study by Huang et al. (2013) examined the potential impact of exposure to the 1959–1961 Chinese Famine using the GHQ-12 in 4972 Chinese born between 1956 and 1963. They found that women born during the famine had higher GHQ-12 scores with a large effect size based on Cohen's criteria for effect and, therefore, more risk of mental illness. One study found that negative income shock at birth significantly increases the risk of severe mental distress, as measured by the Kessler Scale (Adhvaryu et al., 2019). In WWII famine studies, men exposed to the Dutch famine during early gestation had more anxiety and depression symptoms (De Rooij et al., 2021). Finally, in the drug and alcohol context, the findings of Franzek et al. (2009) suggest that prenatal exposure to the Dutch famine during the first trimester is associated with addiction later in life.

8. Conclusion and implications

We looked at how malnutrition in early life affects the use of illegal drugs and how this use might be caused. Early-life malnutrition increases aged opioid use, not stimulant use. Early-life nutrition is well known to affect physical and mental development, but this study adds to the growing body of evidence that it also affects opioid abuse in adulthood. It is challenging to test all of the mechanisms that can be responsible for this rise in opioid abuse, but we used a rich dataset to find some clues. The rise in opioid abuse in our context is associated with physical and mental health problems but not education. Somatic symptoms and pain scores differ significantly between the treatment and control cohorts. This study shows that survivors in the Iran Famine-exposed cohort have pain and are likely to use opioids to treat it. It is important to note that our context differs from that of the US. In the US, opioid misuse is mostly due to overprescribing opioid painkillers. The opioids in this study, however, are not prescribed in Iran; users purchase and smoke them illegally. Opioids might have the same purpose of pain management, but they are prepared in very different ways, with different policy implications. It is recommended to legislate prescriptions for doctors in the United States. Our findings show that pain in Iran leads people to accept the high risk of punishment for buying drugs and purchasing them illegally from the black market. Accordingly, this study suggests offering alternative pain medications to unhealthy individuals to reduce the risk of this black and unregulated market for illicit drugs.

Data availability

Data is available online.

Appendix A. Supplementary data and evidence

The data for this article can be found online at https://data.mendeley.com/datasets/x68pjr22rp.10.17632/x68pjr22rp.1

Supplementary evidence to this article can be found online at https://doi.org/10.1016/j.socscimed.2023.115940.

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