Undernutrition and chronic disease: the 1944-1945 Dutch famine
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Hunger and non-communicable chronic diseases: a grim combination?

Submitted

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Both hunger and non-communicable chronic diseases (NCCD) are growing worldwide health challenges. While hunger and NCCD are substantial global health threats in their own right, there is evidence that the two are directly related and that undernutrition during critical periods of early growth and development increases the risk of various chronic diseases throughout life. Such relations may further aggravate health prospects for the longer term. Here we provide a global orientation on hunger and NCCD, with an emphasis on low-and-middle-income (LMI) countries, where both problems often coexist.

**HUNGER FROM A GLOBAL PERSPECTIVE**

Despite ample countermeasures over recent decades\(^1\), hunger and malnutrition are still the number one global health threat, with more victims than from AIDS, malaria, and tuberculosis combined\(^2\). In 2000, 189 countries adopted the United Nations Millennium Declaration and formed a new global partnership to reduce extreme poverty, hunger, disease, lack of shelter and exclusion and to promote gender equality, health, education, and environmental sustainability\(^3\). In this declaration eight time-bound targets were set, known as the Millennium Development Goals (MDG)\(^3\). The first MDG is to eradicate extreme hunger and poverty.

The United Nations Food and Agriculture Organization estimated that 925 million people suffered from hunger worldwide in 2011\(^4\). Every four seconds someone dies of its direct consequences\(^5\). Of all hungry people 25% are children. Each year, undernutrition causes five million infant deaths in LMI countries\(^6\), 146 million underweight children\(^7\), and up to 17 million underweight newborns\(^7\). For a global distribution of hunger see Figure 1.
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FIGURE 1  Global distribution of undernutrition between 2006 and 2008 according to the Food and Agriculture Organization of the United Nations.  
CAUSES OF HUNGER

Dominant causes of hunger are natural disasters, such as floods and tropical storms, and prolonged periods of drought in combination with sharp rises in food prices. Environmental over-exploitation, such as deforestation, overcropping, and overgrazing, and lack of agricultural infrastructure aggravate the problem. The importance of a well functioning infrastructure is exemplified by better than average agricultural growth in LMI countries that are on track of reaching the first MDG, underscoring the need for proper roads, warehouses, and irrigation systems in countries that lag behind. While most LMI countries strongly depend on agriculture, governments often focus economically on urban development.

Human conflict, including war, is another important cause of food shortage. To date, war is estimated to cause over 35% of total global food shortages, a doubling since 1992. There is an unfortunate list of recent cases of famine caused by natural disasters or war. Last year, for example, a prolonged drought, sharp rises in food prices, and armed conflict in Somalia have caused the most severe famine in 60 years in the Horn of Africa. The drought caused crop failures and heavy livestock losses jeopardizing the livelihoods of millions. In the Horn of Africa alone, over 320,000 children are severely malnourished to date. In July 2010, more than 20% of Pakistan was flooded, resulting in severe undernutrition, especially among women and children.

These are just two of many recent examples underscoring acute undernutrition as a heavy burden for LMI countries. Although in some LMI countries progress is being made in reducing the number of hungry people, it is not fast enough in most. MDG 1, to halve the proportion of hungry people between 1990 and 2015, is unlikely to be reached. The current food and financial crises will aggravate the problem and it must be feared that hunger will continue to be a major health threat in the developing world for decades to come.

TRANSITION FROM COMMUNICABLE TO NON-COMMUNICABLE CHRONIC DISEASES

particularly in LMI countries there is a shift from communicable to non-communicable chronic diseases, such as cardiovascular disease, cancer, and chronic respiratory disease. In Africa, NCCD mortality is expected to exceed mortality from communicable, maternal, perinatal, and nutritional diseases by 2030.
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The greatest part of all worldwide global NCCD disease mortality now occurs in LMI countries, some 80% due to cardiovascular and diabetic diseases, some 70% due to cancer, and some 90% due to chronic obstructive pulmonary disease. The increase in cancer incidence by 2030 is estimated to be 82% in low-income and 70% in lower-middle-income countries, as compared to 58% in upper-middle-income and 40% in high-income countries. There may be several explanations for this increase of NCCD in developing countries. People in LMI countries benefit less from prevention efforts and have less access to effective health care services than people in developed countries. Also, risk factors for NCCD, such as cardiovascular disease, are typically on the increase in LMI countries. A global distribution of major NCCD is depicted in Figures 2A and 2B.

The NCCD transition now specifically affects health and economies in LMI countries. For example, in the next ten years, the estimated losses in national income due to heart disease, stroke, and diabetes in China will be $558 billion. Poverty is a major propellant of the problem. In general, the poorest are at the highest risk of developing chronic diseases and of premature death, while globally some 100 million people are pushed into poverty each year due to health services costs.
FIGURE 2A  Age standardized (per 100,000 population) death rates for non-communicable diseases worldwide in 2008 among females according to the World Health Organization.

Date accessed: 27 October 2011.
FIGURE 2B
Age standardized (per 100,000 population) death rates for non-communicable diseases worldwide in 2008 among males according to the World Health Organization.

DEVELOPMENTAL PROGRAMMING

Society and science have long focused on short-term health consequences of undernutrition. However, a large body of scientific evidence demonstrates a link between undernutrition during critical periods of growth and development and risk of NCCD. A driving force has been the developmental origins of health and disease (DOHaD) hypothesis, postulated by Professor David Barker in the early 1980s. This hypothesis proposes that undernutrition during important periods of growth and development results in early adaptations in structure and function of the body. These adaptations may be beneficial for short-term survival, but can also increase the risk of NCCD in the long-term.

Substantial evidence now supports the hypothesis for intrauterine factors. Low birth weight, a marker of impaired fetal growth rate and unfavorable fetal environment, is consistently found related to an increased risk of cardiovascular disease and type 2 diabetes. In agreement, small size at birth has been associated with risk factors for cardiovascular disease and type 2 diabetes, such as hypertension, hypercholesterolemia, impaired glucose tolerance, and insulin resistance. Since size at birth is the product of maternal, placental, and fetal factors, it is difficult to define the impact of each of these factors on the risk of NCCD in later life. To overcome this problem, historic periods of famine have been used to investigate the effects of undernutrition on health in adult life.

HUNGER AND NON-COMMUNICABLE CHRONIC DISEASES:
HISTORICAL EVIDENCE FROM FAMINE STUDIES

In our view, knowledge of health outcomes of historic periods of famine has direct relevance to societies where hunger and NCCD coexist to date. Several historic periods of famine have been used to investigate long-term health effects of acute undernutrition during important periods of growth and development. A first example is the great Chinese famine (late 1950s-early 1960s). The most severe period was between 1959 and 1961. Early life exposure to the Chinese famine has been associated with an increased risk of hypertension, overweight, metabolic syndrome, hyperglycemia, and schizophrenia.

During World War II, the siege of Leningrad by German troops (1941-1944) made the population of Leningrad suffer from severe undernutrition. Food was rationed from the beginning of the war to as low as 300 kcal per day during the winter of 1941-1942. Girls and boys exposed
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to the latter period during (pre-)adolescence had higher later life systolic blood pressure levels than unexposed individuals\(^{10}\). Exposed boys also experienced higher mortality from ischemic heart disease and cerebrovascular disease\(^{35}\). Girls exposed between 10 and 18 years of age had higher mortality from breast cancer than unexposed girls\(^{32}\).

A third example is the occupation of the UK Channel Islands, including the island of Guernsey, by the German army during World War II. Food supplies for Guernsey became severely limited after Allied invasion of France in June 1944, enforcing rationing at some 1,200 kcal per day until liberation in May 1945\(^{36}\). Such exposure in childhood, adolescence, and young adulthood was shown associated with an increased risk of cardiovascular disease in later life\(^{37}\). Girls exposed to this nutritional deprivation in pre-adolescence experienced later menarche and higher risk of breast cancer than girls that had been evacuated from Guernsey\(^{38}\).

Each of these above examples can best be called an ecological study, without individual estimates of famine exposure and confounders. To overcome that limitation, we used the Dutch famine as a ‘natural experiment’ in history to investigate the long-term health effects of early life acute undernutrition. The Dutch famine evolved from World War II and the harsh 1944-1945 winter, leading to blockage of food transport from the rural East to the urban West of the Netherlands. As a result, the food situation in the West deteriorated rapidly from October 1944 onwards. Between December 1944 and April 1945, the official rations varied between 400 and 800 kcal per day\(^{39}\). On May 5\(^{\text{th}}\) 1945 the Netherlands was liberated, ending the famine abruptly. Both pre- and postnatal famine exposure were associated with an increased breast cancer risk\(^{40,41}\). Postnatal famine exposure was also associated with mediating factors for this increased breast cancer risk\(^{42-44}\). Famine exposure in the prenatal period was related to an increased risk of obesity\(^{45,46}\), an atherogenic lipid profile\(^{47,48}\), an impaired glucose tolerance\(^{49,50}\), an increased risk of coronary heart disease\(^{51}\), and (cause-specific) mortality\(^{52}\). Famine exposure in childhood, adolescence, or young adulthood was related to an increased risk of obesity\(^{53}\), type 2 diabetes\(^{54}\), coronary heart disease\(^{55}\), and COPD\(^{56}\).

As most historical evidence stems from the developed world one might suspect that findings about famine and NCCD are somehow specific for such regions. It can be questioned whether the long-term effects on adult health have to attributed to total reduction in kilocalories, imbalance between different nutrients, or a shortage of one or two specific nutrients. We know that during the Dutch famine the relative amount of proteins, fats, and carbohydrates remained essentially unchanged\(^{57}\). This implies that, at least in the Dutch famine study, total caloric restriction – instead of restriction of specific nutrients – is responsible for the long-term health consequences.
From the abovementioned studies, it is difficult to discern if long-term health effects result from undernutrition as such or from the combination of acute undernutrition and adequate nutrition later on. Therefore, it can be questioned whether such acute famine exposures compare to states of chronic undernutrition often found in poor countries. Research within such areas seems to confirm such comparability. A study in three Gambian villages has shown that people born during the ‘wet’ (hungry) season are ten times more likely to die prematurely than people born during the ‘dry’ (harvest) season\(^5\). Famine exposure in sub-Saharan Biafra was associated with increased blood pressure levels and increased risks for diabetes mellitus among 40 year old Nigerians\(^6\). Indian babies are the smallest in the world; with one-third being low birth weight\(^6\). There is also a phenomenal increase of type 2 diabetes and coronary heart disease among Indians\(^6,61\). It is predicted that by 2025 one in five diabetic patients in the world will be Indian\(^6,61\). Various studies in India have shown that early life undernutrition importantly contributes to chronic disease proneness, for instance through rapid postnatal catch-up growth\(^6,61\). We therefore believe that historic evidence generalizes to those parts of the world where famine and rising NCCD rates coexist to date.

**IMPLICATIONS FOR DEVELOPING COUNTRIES**

The number of people suffering from NCCD will increase steeply in the future\(^13\), and we believe this partly reflects long-term effects of widespread hunger. Although it is hard to conceive of human experimentation on this issue, there is substantial non-experimental and animal evidence of a causal link between undernutrition in early life and NCCD in later life. According to the results of the Dutch famine study, more than 10% of the people who suffered from coronary heart disease in the cohort could have been prevented had they not been exposed to undernutrition during their early life. For type 2 diabetes and chronic obstructive airways disease this would even be 25% of cases, whereas for obesity it would be about 5%. Clearly, extrapolation of such excess risks to the developing world requires caution, but it seems likely that prevention of hunger and undernutrition, especially among pregnant women and children, is not only of immediate relevance but may also help in reducing the number of people that will suffer from NCCD in future generations. Given the variety of sources it may be unfeasible to completely eradicate famine and undernutrition in the short run. We believe, however, that there is sufficient evidence to consider famine victims as higher risk groups for later life NCCD, and as targets for preventive interventions. Both a continued battle against famine and preventive care for affected generations, including for example screening for high blood pressure and low-cost life-saving interventions like aspirin\(^6\), can prohibit famine and NCCD from becoming a grim combination in the developing world.
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