Undernutrition in adolescence and risk of cardiovascular disease

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This editorial refers to ‘Cardiovascular consequences of famine in the young’, by A.F.M. van Abeelen et al., on page 538

According to the most recent update from the United Nations Food and Agriculture Organization, 925 million people worldwide are undernourished. Undernutrition during pregnancy in developing countries leads to 1 in 6 infants born with low birth weight. This is not only a risk factor for neonatal deaths, but could also lead to increased risk of chronic diseases later in life. More recently, the global financial and economic crisis along with increasing food prices has meant that many families in developed countries may also now struggle to provide adequate nutritional support to their offspring, albeit to a lesser degree. This is highlighted by a recent survey presented by the Association of Teachers and Lecturers which found that primary, secondary, and college teachers in the UK who responded to the survey believed that three-quarters of their students arrived hungry, and that these numbers had increased since the start of the global recession.

As early as the 1940s, Ancel Keys put forward his hypotheses about the physiological and psychological effects of a limited diet. Keys’ Minnesota Starvation Experiment took 36 men (conscientious objectors to the war) aged 22–33 years, and was divided into three phases: a 12 week control phase, where physiological observations were collected to establish a baseline for each subject; a 24 week starvation phase, during which the caloric intake of each subject was drastically reduced; and finally a recovery phase, where they were assigned to various rehabilitative diets to re-nourish the volunteers. The key motivation for the study was to guide the Allied relief assistance to famine victims. With the Second World War drawing to a close, many of the Allied forces were encountering starved civilians who had survived on an extremely limited diet. It was one of the first to show the importance of diet alone in determining basic physiological functions, e.g. blood pressure, cholesterol level, and resting heart rate, and went on to show the effectiveness of dietary rehabilitation strategies.

Studies investigating the effects of limited diet have largely focused on the sensitivity of fetal growth to maternal undernutrition during specific periods of pregnancy, in particular gestation. Evidence from experimental, clinical, and epidemiological studies has shown a strong relationship between malnutrition during intrauterine development and increased risk of cardiovascular and metabolic disease in later life. Throughout development the body can change structure and function permanently in response to environmental influences such as nutritional availability in order to produce the best phenotype for the predicted later environment. The mechanisms are incompletely delineated, but it is hypothesized that the underlying mechanism for bringing about these changes are epigenetic modifications which can lead to changes in gene expression without modification of the underlying DNA. This ‘re-programming’ following environmental exposure can then influence later metabolic or physiological functions in adult life.

Importantly, there is now increasing evidence that a mismatch in environmental pressures, such as malnutrition in early life followed by overnutrition in adult life, impairs the ability of the individual to respond to the environmental challenges, and may lead to an increased risk of disease (see Figure 1). For instance, in the early 1980s, David Barker and others proposed over a series of studies that an adverse fetal environment followed by the availability of high-calorie food and reductions in energy expenditure in adulthood would lead to greater risk of adult chronic disease, an idea referred to as the Barker Hypothesis.

The adolescent years, which have the highest growth velocity after infancy, have been highlighted as being more sensitive to environmental pressures than early development. A study of almost 6000 men and women in Norway indicated that poverty in childhood and adolescence, followed by later prosperity, was associated with the subsequent development of risk factors for cardiovascular disease.
Given the ethics of assessing the effect of malnutrition on adverse outcomes, studies of the physiological effects of poor nutrition are mostly observational and retrospective. The majority of these are based on disasters such as the Chinese and Dutch famines or the siege of Leningrad.

The Dutch Famine of 1944–45 was caused by a combination of factors including failed crops, the harsh winter, and the war which was preventing the transport and delivery of food. As a result, adults exposed to the calorie restriction had an average intake of 400–800 kcal a day during the peak of the famine. van Abeelen et al.14 hypothesized that in addition to embryonic years, malnutrition during adolescence may also increase the risk of cardiovascular disease later in life. They present data on almost 8000 women from the Prospect-EPIC cohort aged between 0 and 21 years of age who were exposed to the Dutch famine. Subjects were divided retrospectively into three age categories: 0–9 years, 10–17 years, and 18–21 years, corresponding to childhood, adolescence, and young adulthood, respectively. Their results show that greater exposure to the famine resulted in a 38% increased risk of cardiovascular disease in adult life. This increased risk was particularly evident when looking at the adolescent age range when compared with women of the same age with no exposure to famine [hazard ratio (HR) 1.38; 95% confidence interval (CI) 1.03–1.84 before adjustment for confounders]. In contrast, they found a decreased risk of stroke for women exposed to the famine when compared with unexposed women, particularly in the childhood and young adulthood groups (HR 0.79; 95% CI 0.61–1.02 before adjustment for confounders). These results add further weight to the suggestion that adolescence is a particularly sensitive period open to epigenetic modifications and that dietary mismatch in post-famine nutritional availability contributes to coronary disease risk.

Earlier this year a similar study by Li et al.14 focused on almost 8000 men and women who had been exposed to the Chinese famine of 1959–61. Like the Dutch Famine, malnutrition was imposed on the population for a period of time. In Li’s study they divided the cohort into a number of exposure groups defined as non-exposed, fetal exposed, and early childhood, mid-childhood, or late childhood exposed. They concluded that participants who were born in severely affected famine areas and had Western dietary habits in adulthood or were overweight in adulthood had a particularly high risk of metabolic syndrome in later life. Data also exist from almost 6000 men and women who were exposed to the siege of Leningrad where higher mortality from ischaemic heart disease and cerebrovascular disease was observed in men exposed at age 6–8 and 9–15, respectively.15 Taken together there appear to be consistent data showing that nutritional status in childhood may impact significantly on chronic disease processes in later life. The findings of these recent studies could have significant practical impact on immigrant populations who try to adapt to the relatively more affluent and nutritionally rich environments, particularly those escaping man-made and natural catastrophes. For instance, first-generation Asians in the UK have a higher incidence of cardiovascular disease than Caucasian counterparts.16 As cardiovascular disease carries the largest economic and population burden in developed countries and is fast approaching similar importance in developing countries, further work is now needed to better understand the mechanisms behind these associations and devise public health strategies which could have a significant impact on disease burden in years to come.

**Summary**

The relative roles played by genetic and environmental factors, and the interaction between the two, remain the subject of much current debate. The van Abeelen study and others are beginning to show us the importance of developmental adaptations in response to undernutrition to the susceptibility to cardiovascular disease. This adaptive response is even more significant for those experiencing a mismatched rich nutritional environment in later life.

**Conflict of interest:** none declared.

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CARDIOVASCULAR FLASHLIGHT

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Takayasu arteritis presenting with extensive bilateral aneurysms of the common carotid arteries

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A 17-year-old female patient was referred to our institution for vascular evaluation. She had presented to the general practitioner with a sore throat and elevated inflammatory markers. Prior to hospital admission, additional symptoms appeared despite antibiotic treatment: night sweat, cervical pain, and upper extremity claudication.

During clinical examination, a whirring bruit audible at auscultation led to subsequent ultrasound of the supraaortic arteries. Figure A shows a sonographic cross-sectional view of a partially thrombosed right common carotid artery (CCA) aneurysm with a maximum diameter of 27.1 mm. As the longitudinal view of the left CCA in Figure B reveals, the wall diameter measured 4.8 mm due to extensive intima-media thickening. By using magnetic resonance angiography (MRA), suspicion of large-vessel vasculitis was substantiated. Magnetic resonance angiography demonstrated a clinical picture pathognomonic for TA with inflammatory vessel wall changes resulting in stenoses (Figure C, arrows) and aneurysmatic dilations (Figure D, arrows) of the aorta and high-calibre arteries arising thereof.

The extent of these aneurysms is pronounced. Yet, extracranial carotid aneurysms are per se a rare finding with TA. Most frequently affected are the aorta, the subclavian artery, and the brachiocephalic trunk.

Therapeutic options may include medication, endovascular revascularization, and surgical measures. Within the present concept, high-dose corticosteroids are applied to de-escalate acute exacerbations, whereas infliximab and methotrexate serve as the maintenance treatment. Furthermore, antiplatelet therapy was established. Since TA has been stable, no interventional or surgical approaches have yet been conducted. Follow-up in this patient involves continuous laboratory assessment, quarterly ultrasound, and annual MRA.

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