Early nutritional determinants of coronary artery disease: a question of timing?¹,²

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Since its proposal nearly 2 decades ago, the hypothesis that suboptimal maternal and fetal nutrition can have a profound and sustained effect on the health of a person later in life (1) has gained support from human epidemiologic and animal studies. Animal studies aside, much of the evidence is reliant on data from retrospective cohort studies that, in the absence of any accurate measure, used birth weight as a surrogate marker of maternal and fetal nutrition. Birth weight is considered to be a crude and uninformative measure of nutritional status during pregnancy. Despite this major limitation, hundreds of articles have been published that report associations between low birth weight and a wide and heterogeneous range of health outcomes, including hypertension, dyslipidemia, diabetes, renal disease, obesity, osteoporosis, cognitive development, cancer, stroke, and coronary artery disease (CAD). However, because low birth weight and many of the above outcomes are related to lower socioeconomic status (and to all that socioeconomic status represents, such as smoking and poor diet), it is often difficult to know whether the reported associations are indeed causal or, instead, are due to the persistence of adverse circumstances throughout pregnancy. By comparison, the only direct evidence about the possible effect of maternal nutritional status during pregnancy on the health of adult offspring has come from a handful of small, select, retrospective cohorts. The Dutch Famine Birth Cohort Study (4) and, to a lesser extent, the Leningrad Siege Study (5) of World War II have provided most of the information regarding the effects of severe caloric undernutrition in pregnancy on the health of adult offspring. The Dutch famine occurred as a consequence of an embargo on all transport and food supplies to western Netherlands from September 1944 to May 1945. This food blockade severely limited the availability of supplies so much that daily government food rations in some areas decreased the usual dietary intake of the population by >50%. The famine ended when the cities were liberated in the late spring of 1945, whereupon rations returned to normal levels. The adult offspring of women who were pregnant during the Dutch famine have since been the subject of dozens of research publications, including the most recent article by Painter et al (6), which is published in this issue of the Journal. Some of these reports have shown that offspring whose mothers were undernourished during pregnancy had decreased glucose tolerance and dyslipidemia but normal blood pressure. Moreover, on the basis of small subgroup analyses, a differential effect of the timing of maternal exposure to undernutrition was previously reported: persons undernourished in the first trimester were reported to have a greater prevalence of CAD and obesity, those undernourished during early gestation to midgestation were reported to have an increased risk of obstructive lung disease, and those undernourished during mid-to-late gestation were reported to be more insulin resistant and more likely to have impaired renal function.

The study by Painter et al is based on a sample of 975 middle-aged subjects (≈40% of the original cohort), of whom <50% were severely undernourished at some stage during gestation. Overall, CAD was diagnosed in a total of 83 persons. A subgroup analysis showed a significantly greater cumulative incidence of CAD in those exposed to famine during early gestation than in those not exposed to famine (13% compared with 8%) and a younger age at onset in those exposed to famine during early gestation than in those not exposed to famine. However, given the small number of CAD cases within each of the 5 subgroups, the reliability of these findings is uncertain. Concerns about the use of subgroup analysis to highlight statistically significant associations were expressed by the authors of a recent overview of the association of birth weight with blood pressure later in life (7); those authors concluded that “investigators may be more likely to undertake subgroup analyses when overall results are relatively weak.” Nevertheless, the authors used this finding to suggest that maternal nutrition in early gestation is a determinant of subsequent CAD in offspring. They proposed that the effect is mediated through adverse glucose and lipid metabolism, although an examination of Table 2 in the article by Painter et al showed no clear differences in these risk factors between those persons exposed to famine at some point in gestation and those who were not exposed. The findings of Painter et al also contradict the findings of earlier studies in the same study population, which showed that glucose tolerance was more impaired in persons whose mothers were exposed to famine during midgestation or late gestation rather than in early gestation (8).

Interestingly, in another publication by the same group, all-cause mortality in offspring of the subjects in the Dutch Famine Birth Cohort Study were unrelated to famine exposure at any time during pregnancy (9). This finding is shared by that of a follow-up study of adults born during the time of the Leningrad Siege Study, which reported no evidence of excess mortality

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from heart disease (5). Similarly, in a study of birth cohorts born
during a severe famine in Finland, famine exposure throughout
fetal life and early childhood was not associated with increased
all-cause mortality in adulthood, which led the authors to con-
clude that “it seems unlikely that nourishment before birth and
during infancy per se is crucial to adult health” (10). The study by
Painter et al certainly provides food for thought about the early-
life origins of CAD. Nevertheless, the developmental hypothesis
remains controversial and unproven.

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