

## Asking the Right Questions

### How Early-Life Exposures Influence Later Development of Disease

Prenatal and early-life environmental insults ranging from malnutrition to toxic exposures can tilt the odds toward development of adverse health effects decades later. These effects likely occur, at least in part, through alterations in an individual's genetic potential to thrive in the environment in which he or she will live—in other words, these early challenges set the bar for what's "normal," and the fetus and infant adapt for a less-than-optimal environment in ways that may contribute to adult-onset disease. A new review examines the evidence for an association between early-life exposures and later disease, and proposes an agenda for future research and risk assessment [*EHP* 120(10):1353–1361; Boekelheide et al.].

One of the most intensively studied instances of adult disease attributable to prenatal circumstances involves children of women who were pregnant during the Dutch famine of 1944–1945. At birth these individuals were small for gestational age, and as adults they had increased incidence of obesity, diabetes, and cardiovascular disease. Furthermore, their children also were small for gestational age, suggesting that such effects can be transmitted across generations, a finding replicated in animal studies of prenatal malnutrition and toxic exposure.

Human and animal studies now link a multitude of early-life hardships, including prematurity, low birth weight, maternal infection during pregnancy, toxic exposures, and malnutrition, to a wide array of

adult-onset diseases. Timing of the insult appears to be an important factor in the consequences. In the Dutch cohort, for example, deprivation in early gestation was associated with coronary heart disease, hypertension, dyslipidemia, and obesity later in life, whereas mid-gestation deprivation was linked with obstructive airway disease and impaired glucose tolerance.

Many adverse outcomes associated with early-life events could be explained by epigenetic changes, in which the genes themselves are unaltered but their expression is persistently blocked, increased, or decreased by environmentally induced molecular tweaks to the components controlling transcription and translation. Such changes could occur directly to a developing fetus or indirectly by, for example, undermining placental function or triggering disease-susceptibility genes. Nonepigenetic changes are also possible, as illustrated by so-called obesogenic chemicals that can activate the key regulator of fat cell growth and development.

Many potential research avenues arise from the accumulating evidence for delayed effects of early-life exposures. Central themes include characterizing epigenetic and nonepigenetic changes that predict disorders, prioritizing investigations, and identifying critical time points with regard to susceptibility. Methods for collecting and analyzing the data alone constitute a research priority, while the ultimate goal is to enable accurate risk assessment. Both experimental evidence in animals and observational human data will be needed to assess causal relationships.

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## Metal Exposure in Child Workers

### Assessing Hazards in Surgical Instrument Manufacturing Workshops

The International Labor Organization estimates that tens of millions of children work in hazardous conditions around the world. In Sialkot, Pakistan, the primary site for surgical instrument production in the developing world, many children labor in dusty workshops producing these items. In a new cross-sectional study researchers report high metal exposures possibly linked to higher rates of respiratory ailments and oxidative DNA damage among children working in 21 Sialkot workshops [*EHP* 120(10):1469–1474; Sughis et al.].

The authors surveyed 104 working children and 75 nonworking schoolchildren aged 10–14 to assess working conditions, exposures to tobacco smoke (active and passive) and to biomass smoke, use of medications, and social class. Urine samples from each participant were analyzed for 20 metals. For 145 children the authors also measured urinary 8-hydroxydeoxyguanosine (8-OHdG), a DNA breakdown product that serves as a biomarker of oxidative stress. They assessed lung function with a pocket spirometer and calculated the average of five consecutive blood pressure readings to classify each child's blood pressure as normal or prehypertensive.

Most of the working children spent 6 days a week in workshops that typically had poor ventilation and lighting, some for up to 12 hours a day. The children mainly ground and polished instruments, and none of them used personal protective equipment.



Twelve-year-old Kabir Qadeer sorts surgery instruments at a workshop in Sialkot, Pakistan.

Compared with the schoolchildren, the working children had higher average urinary concentrations of several steel-related metals. Most notably, chromium levels were 35 times higher in the working children, with values usually exceeding the adult limit of 25 µg/L set by the American Conference of Governmental Industrial Hygienists. Urinary 8-OHdG concentrations did not differ significantly between working children and schoolchildren, although 8-OHdG was significantly correlated with urinary nickel and with overall metal exposure.

The working children reported more respiratory symptoms and asthma than the schoolchildren, but their pulmonary function values were significantly better. The authors suggest several possible explanations, such as the fact that acceptable spirometry results were available for only 37% of the working children compared with 90% of the schoolchildren. No significant differences were seen in blood pressure between the two groups.

The study's strengths include individual biomonitoring of the working children's exposure to metals. Limitations include potential bias in recruitment and difficulty in assessing respiratory end points. The authors write that child labor is a complex issue and that poor parents should not be stigmatized for sending their children to work. Despite a lack of serious health effects observed at the time of study, the findings do present evidence that children may suffer occupational illness in the future, even if they discontinue this work. It is therefore important to implement and enforce measures to reduce hazardous working conditions.

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