
Challenges in Studying the Environmental Factors in Developmental Disabilities

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What Does CDC's National Center on Birth Defects and Developmental Disabilities Do?

CDC's mission is to promote health and quality of life by preventing and controlling disease, injury, and disability. The CDC's National Center on Birth Defects and Developmental Disabilities is specifically charged with the prevention of developmental disabilities (DD) and promotion of health in persons with DDs. Activities related to this mission include developing scientifically sound prevention programs for the DDs we know how to prevent, conducting research to identify the causes of DDs, and identifying ways to promote the health and prevent secondary conditions in those with DDs. Examples of these activities included monitoring the effectiveness of state newborn blood spot screening programs for metabolic and genetic disorders (many of which result in mental retardation (MR) if left untreated) and developing prevention programs targeting women at high risk for an alcohol affected pregnancy and the resulting FAS phenotype.

The Center also has an active research program that monitors the prevalence of mental retardation and other developmental disabilities (cerebral palsy [CP], autism, vision and hearing impairment) and has an epidemiologic centers of excellence program for research on the risk factors and causes of autism; several of the centers have recently incorporated mental retardation also.

Issues and Challenges in the Epidemiologic Research of Developmental Disabilities

One of the primary challenges in DD research is defining the disease outcome. Most DDs are defined on the basis of the child or individual's functioning. There are no biologic markers of the disorder—most are based on outward signs of functional disability. For example, mental retardation is defined on the basis of IQ (and the child's functioning) with mental retardation at the lower tail of the IQ distribution. It is unclear from an etiologic perspective whether a specific agent, for example lead, impacts the entire IQ distribution or whether there are certain subgroups that may be more adversely impacted due to other environmental or genetic factors. Other agents may only impact the lower

tail of the IQ distribution—for example a specific neurotoxic agent that also results in cognitive disability. Another example is autism that is defined as the presence of three key behavior traits. While there is no objective diagnostic test, researchers have worked to develop standardized instruments for eliciting and recording behaviors of the child and obtain information from the parents. Again, as with mental retardation it is not clear if autism is an all or nothing condition—i.e., either you have it or you don't. Can you be a little autistic? We have created diagnostic categories for individuals who have some but not all of the features of autism, but again how a particular agent relates to these various phenotypes are uncertain.

Another challenge to research is that the features of the disorder don't become immediately apparent until the children are older. Again, using our two examples, autism and mental retardation, the average age at diagnosis for autism is not until age 4-5 years and for mental retardation, particularly for mild mental retardation, the age is considerably later—8-9 years. This delayed age at identification is particularly challenging when trying to do research because there is a long lag time between initial exposure—usually prenatal or early childhood—and the diagnosis of the disease. This greatly impacts recall by the parents of past exposure and biologic specimens that may have been available to measure biomarkers of exposure. Also, assembling a retrospective birth cohort is particularly challenging; and what biases are introduced by those study subjects lost to follow up (either due to death or movement out of the study area) needs to be considered. In surveillance or disease tracking which lays the groundwork or foundation for much research, one of the key objectives of this activity is to serve as an early warning signal for potential epidemic exposures. In fact, birth defects surveillance began as a result of the thalidomide epidemic—with the hope that future “epidemics” of birth defects would be prevented. For developmental disabilities surveillance, the long lag between the exposure and the diagnosis or recognition of the disease, make for delayed identification of a “epidemic exposure” and possibly a missed opportunity to identify an exposure due to dilution by factors effected by time as mentioned above.

One final methodologic issue worthy of discussion in the study of DDs is the inter-relatedness between the many DDs. Children with a DD are much more likely to have another DD compared to children without DDs. This is particularly true for certain DDs, such as cerebral palsy and severe MR. We have some evidence to suggest that the etiology of children with multiple DDs is perhaps different than that for children with only one disability. Research into the epidemiology of DD has approached each disorder separately—an integrated approach would, perhaps offer more insight into the underlying causes of these co-occurring DDs.

What Do We Know about Environmental Factors and DDs?

Maternal Behaviors in Pregnancy

Maternal smoking has been linked to mental retardation in a few epidemiologic case-control studies. The magnitude of the increase was 1.6 fold for any smoking with a dose response effect found (increasing to 1.9 fold for one pack per day or more). Other

investigators have examined the impact of maternal smoking on various aspects of cognitive functioning and learning—with mixed results.

It is well known that maternal alcohol use (in high levels) results in Fetal Alcohol Syndrome (FAS)—one of the core features of FAS is neurodevelopmental impairment (manifested as mental retardation in some children.) In children who are still impacted by alcohol but not as severely to have FAS, other neurologic and developmental effects are noted, clinically recognized as fetal alcohol effects or alcohol-related neurodevelopmental disorder. In four recent case series, the proportion of FAS cases with measured IQs ≥ 70 varied from 23 percent to 58 percent and the magnitude of the cognitive deficit appears to be in direct proportion to the extent of the physical features of FAS.

FAS results from heavy and prolonged exposure to alcohol in utero. However, lower levels of exposure are harmful—an average of 2+ drinks per day has been associated with a 7 IQ point decline in children.

Toxic Environmental Exposures:

It is known that several environmental contaminants (i.e., lead, methyl mercury, polychlorinated biphenols) in high doses can produce serious neurologic damage, including CP and MR. The most famous of these were in Minimata Bay, Japan, where fish used as a principle food source, were contaminated with high levels of mercury from industrial runoff and Taiwan and Japan where rice oil use in household cooking was contaminated with PCBs. Assessing the impact on the developing fetus and child to lower levels of these somewhat ubiquitous contaminants has been more challenging. The evidence for lead is perhaps the most clear. Prospective cohort studies of lead exposures have found that among school-age children, a decrease of 2-6 points in mean IQ was associated with previous exposure levels of >20 or >30 $\mu\text{g}/\text{dl}$. Implicit in these findings is that a shift in the IQ distribution due to lead or other toxic environmental exposures would result in a great proportion of children in the population with mental retardation. Alternative explanations for these findings include the inadequate control of socioeconomic correlates of lead exposure and the possibility that children with initially low IQs are more likely to exhibit behaviors that increase their exposure (i.e., pica).

Of the several studies that have examined the impact of in utero and early postnatal exposure (via breast milk) of PCBs and mercury, principally from fish consumption—the outcomes have been less clear. Two of the three major PCB studies have shown persistent effects on cognitive ability in later childhood. In the three long-term studies addressing human exposure to mercury (New Zealand, Seychelles Islands and Faroe Islands), the Faroe Islands and New Zealand studies showed long-term developmental outcomes (motor function, information processing, memory, vocabulary, and attention). Importantly, none of these studies showed an increase in the rates of mental retardation or other serious developmental disability, however it would take a much larger population to examine such effects.

A NAS review of the effects of mercury concluded that there was compelling evidence for subtle neurodevelopmental effects from low levels of in utero exposure of methyl mercury. There was not evidence for a threshold for effects—which included women with maternal hair levels of 1-2 ppm. Translating that to the U.S.—about 10 percent of women of reproductive age has hair mercury levels above 1ppm. In addition, populations who eat larger quantities of fish are clearly in the range that is associated with adverse neurodevelopmental problems.

Conclusions and Recommendations

The impact of the environment on DDs is a challenging research area. The long lag time between exposure (in pregnancy or early childhood) and the development of the DD presents some formidable study design issues. Encouraging prospective population-based studies of uniquely exposed populations will enhance our understanding of the impact of ubiquitous exposures on neurodevelopmental functioning. However, the prospective, targeted studies tend to be small in sample size, limiting the ability to understand how a particular exposure may impact DDs per se. Some of this can be inferred from what we know about “poisoning” episodes—but not all those exist for all outcomes. We can also infer a continuum of response based on our animal models.

Also, many other environmental neurotoxicants have not been adequately studied. Top candidates are chemicals that reproductive age women or young children maybe more commonly exposed to, such as pesticides and phthalates.