COVID-19: BEYOND TOMORROW

The Healthy Brain and Child Development Study—Shedding Light on Opioid Exposure, COVID-19, and Health Disparities

The coronavirus disease 2019 (COVID-19) pandemic highlights longstanding health disparities in the United States. African American individuals contract the disease at much higher rates than White individuals and are nearly twice as likely to die of it. Hispanic/Latinx people and American Indian and Alaska Native people are also overrepresented among confirmed cases. Structural racism fosters vast inequalities among individuals of color, including economic disadvantage as a result of low-paying jobs, discrimination in education and the workforce, underrepresentation in research, and lack of access to adequate health care and healthy foods. These and other associated factors, including the higher prevalence of comorbid conditions, such as obesity, type 2 diabetes, and cardiovascular disease, contribute to the greater morbidity and mortality associated with COVID-19 infection in Black, Latinx, and American Indian and Alaska Native populations.

These inequalities begin before birth and affect an individual’s development. Advances in research methods and data analytics now allow us to study their outcomes in the short term and long term. The Healthy Brain and Child Development (HBCD) Study will be uniquely poised to do so. This large longitudinal study, cofunded by the National Institutes of Health Helping to End Addiction Long-term (HEAL) Initiative and several National Institutes of Health institutes, is preparing to deploy a wide range of research tools to study brain development and physical and mental health beginning during pregnancy and following up children until age 10 years. Among many scientific questions, the HBCD study will directly investigate the associations of adverse environments and socioeconomic disadvantage with the development of both brain and behavior throughout early childhood. The study design will enable collection of many variables, among them severe acute respiratory syndrome coronavirus 2 infection status at the time of pregnancy or thereafter.

During the initial phase of feasibility studies, investigators have already begun to examine the association of the COVID-19 pandemic with prenatal care, family health and well-being, and birth outcomes. The full HBCD study will be informed by these results and will begin participant recruitment in 2022. Approximately 7500 women are expected to be enrolled in their second trimester of pregnancy or right after the birth of their infant, and their children will be followed up with periodic structural and functional brain imaging along with a variety of physical, cognitive, behavioral, and environmental assessments over their first decade of life. Data on medical history and family history will be collected from parents; biospecimen collection (eg, infant teeth, blood, hair) will allow genetic and epigenetic analyses and assays of environmental exposures; and various assessment tools will measure social, emotional, motor, and cognitive development. The data collected from the HBCD population will be made freely available to the scientific research community on an ongoing basis. Access to these data will be promoted to a wide variety of scientists to help answer relevant scientific questions on the consequences of environmental exposures, including fetal or postnatal exposures to drugs, COVID-19 infection, poor nutrition, and social stressors, on brain development and mental health.

The HBCD study was partly prompted by the opioid crisis, which is now claiming more than 50 000 lives every year, as well as the widespread use of other drugs, such as cocaine, methamphetamine, nicotine, alcohol, and cannabis. The HBCD sample will include women who used substances during pregnancy, with a particular focus on opioids but also including cannabis and other drugs alone and in combination. Existing research provides reason to believe that prenatal exposure to some substances or exposure through lactation can adversely affect brain development, but drawing causal inferences from complex environmental influences has not been possible—hence the need for well-controlled longitudinal studies. Importantly, the HBCD sample will include women from similar environmental and socioeconomic backgrounds with no substance exposure, along with participants with lower-risk profiles. Since the study will enroll mothers during pregnancy, the HBCD study will also allow the assessment of the developmental consequences of neonatal drug withdrawal, which now annually affects 8 of every 1000 babies born in hospitals in the US. A complementary effort on a smaller scale, also supported by HEAL, called Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW), is currently under way. Its focus is on babies with neonatal opioid withdrawal syndrome, who will be followed up for 2 years after birth. Results are expected to inform the HBCD study. The HBCD study will also facilitate efforts to understand the consequences of growing up with parents who have substance use disorders, which in some cases involves abuse or neglect, along with the associated social stressors and comorbid psychiatric disorders and other medical conditions, including HIV and COVID-19.

Importantly, the HBCD sample will be ethnically and socioeconomically diverse, to get at the developmental influences of a range of backgrounds and environments. Analyses of data from a larger study of health and brain development in adolescents that is already under way, the Adolescent Brain Cognitive Development study,
already show the measurable outcomes of environmental lead exposure risk, \(^4\) poor-quality neighborhoods, \(^5\) childhood trauma, \(^6\) and parental education level \(^7\) on brain development as measured in early adolescence. Using similar methods adapted for younger children, the HBCD study may provide a much clearer picture than ever before of the developmental outcomes of structural racism and poverty in the first decade of life and how brain development and child health correlate with family circumstances, environmental toxins such as secondhand smoke and lead, physical activity, school quality, nutrition, and other social-environmental factors. The large sample sizes recruited for the Adolescent Brain Cognitive Development study and anticipated for the HBCD study will allow us to disentangle the complex factors that modulate neurodevelopment.

Because the study is being launched amidst the COVID-19 pandemic, it will also provide invaluable information of the consequences of COVID-19 infection, whether to the mother during pregnancy or the child once born. This is important, because it is not yet known if COVID-19 can have long-lasting neurodevelopmental effects in children and/or whether it increases risk of psychiatric disorders, as has been the case for other viral infections. Ongoing studies funded during phase 1 of the HBCD study are using repeated assessments, including multimodal neuroimaging, neurocognitive batteries, family and medical histories, and biospecimen collection, to compare newborns of mothers with and without COVID-19 infection. These infants will also be compared with an existing cohort of infants born prior to January 1, 2020. The associations of timing, symptom severity, and duration in infants exposed to COVID-19, as well as the economic and other stressors on the family, will be examined. Results from the feasibility studies will help delineate the appropriate research questions and outcomes of COVID-19 to be included in the full HBCD protocol.

The HBCD study will be, to our knowledge, the most detailed study of early brain development ever conducted. It will produce baseline developmental data that can be used by pediatricians and neurologists to assess milestones and suggest targets for early interventions. Genetic analysis of biosamples will help researchers start to identify how genes in interaction with the environment influence brain development and modulate risks for mental disorders.

The plasticity of the developing brain makes early childhood one of the most vulnerable to adverse environmental influences. A childhood marked by racial inequity or other socioeconomic disadvantage may have profound effects on neurodevelopment, resulting in lifelong implications. However, the same enhanced neuroplasticity of this developmental period provides unique opportunities for interventions as revealed by prevention research. For example, a supportive parenting intervention delivered to African American parents in rural Georgia was found to eliminate differences in hippocampal and amygdalar volumes that were associated with poverty when measured in their adult children. \(^8\)

As the US deals with a worsening epidemic of overdose deaths from opioids and other drugs and the COVID-19 pandemic and public health experts more systematically confront the long-standing issues of racism and discrimination against marginalized groups and identities, it is crucial to understand how all these factors, alone and in combination, affect an individual’s development in the first years of life and set the trajectories for their future. The knowledge gained from the HBCD study will help inform policy and guide the development of interventions to mitigate the neurodevelopmental effects of adverse environments, including those associated with poverty, deprivation, and structural racism.