



# Neuroscience Advances and the Developmental Origins of Health and Disease Research

Catherine Monk, PhD; Cristina R. Fernández, MD, MPH

Decades ago, when David Barker<sup>1</sup> introduced the developmental origins of health and disease (DOHaD) conceptual model and later demonstrated that the prenatal period is relevant for future well-being, he could not have envisioned that fetal brain imaging would substantiate his claims or that maternal stress would be a potent prenatal exposure affecting health outcomes. Barker's focus was inadequate maternal nutrition, to which he hypothesized fetuses adapt, resulting in programmed changes in physiology and metabolism that contribute to disease risk in adulthood, including coronary heart disease and the related disorders stroke, diabetes, and hypertension.<sup>1</sup> Briefly, lower birth weight, which was viewed as a proxy for nonoptimal maternal nutrition, was found to be associated with increased risk for coronary heart disease years later.<sup>1</sup> When the DOHaD approach was applied to national health records from the World War II-era Dutch Famine and neurodevelopment was added as a disease outcome—showing, for example, far higher rates of schizophrenia in men who had been in utero during the famine rather than the months before or after it—maternal stress was not considered as an additional exposure factor.<sup>2</sup> In the 21st century, DOHaD researchers pivoted, ultimately establishing stress, depression, and anxiety as maternal experiences affecting child prenatal and future development, although to be sure, much of this research was based on maternal report of child outcomes such that the mother was both the source of the independent variable (mood state in pregnancy, often associated with postpartum mood state) and dependent variable (child temperament and emotional or behavioral symptoms) years later.<sup>3</sup> Wu et al<sup>3</sup> build on prior DOHaD research<sup>4</sup> to make substantial contributions to prenatal programming science, with implications for ways to transform the prenatal care ecosystem for 2-generation impact.

Wu et al<sup>3</sup> have 4 key findings. First, higher self-reported perceived stress during pregnancy was inversely associated with the cognitive development domain of the Bayley Scales of Infant Development administered by a licensed psychologist at 18 months old. Second, the volume of the left hippocampus imaged months earlier during gestation accounted for 11% of this association. Third, other characteristics of fetal brain development were associated with 18-month-old development; specifically, local gyrification index was inversely associated with competence, and sulcal depth was inversely associated with infant social-emotional development and competence. Wu et al<sup>3</sup> indicate that their prior work<sup>4</sup> showed that maternal distress is associated with gyrification and sulcal depth, thus suggesting that maternal mental health affects the fetal brain and child outcomes. Fourth, perceived stress during pregnancy was positively associated with parenting stress at 18 months post partum.

This study by Wu et al<sup>3</sup> incorporates cutting-edge neuroscience into DOHaD neurodevelopmental research by directly assessing fetal brain development and showing that it mediates the association between maternal prenatal stress and child cognition and is relevant to other domains of functioning nearly 2 years later. A key outcome associated with maternal stress, cognitive functioning at 18 months, is observer based, consistent with other recent findings<sup>5</sup> that strengthen the rigor of DOHaD research using maternal prenatal mood as an exposure variable. Finally, with the positive associations between prenatal and postnatal distress, Wu et al<sup>3</sup> control for postnatal parenting stress in their models, elegantly isolating prenatal stress as the active agent in

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child outcomes. It is surprising, however, that sex associations were not investigated given the higher rates of learning disabilities in male individuals.

The approach taken by most DOHaD studies is to serially interrogate 1 potential fetal exposure (maternal mood, nutrition, or toxicants) vs the more ecologically valid approach of combining them in the same statistical model, which can be critically important when different exposures share outcomes.<sup>6</sup> This study's<sup>3</sup> consideration of maternal stress as the influencing agent on infant outcomes raises the question, Is maternal stress a marker variable for some other factor? By the authors' own description, stress, the 1 maternal mood domain of 4 assessed (stress, state anxiety, trait anxiety, and depression) that was associated with a child outcome did not reach the severity of a mental disorder.<sup>3</sup> Wu et al<sup>3</sup> used the 10-item Perceived Stress Scale, which asks respondents to determine the extent to which they judged their lives to be unpredictable, uncontrollable, or overloaded during the past month. In this well-resourced, predominantly White, largely college-educated sample, the mean PSS score of 10.7 (of a possible 40) was well below a score of 15 that indicates elevated maternal stress, although scatter plots in the supplemental material show that a portion of the sample scored above 15. As Wu et al<sup>3</sup> suggest, finding an association between maternal prenatal stress and infant cognitive outcomes in the setting of what may be modest stress relative to that of a low-resourced or historically marginalized sample underscores the importance of this research; presumably, with higher stress, and greater social determinants of health burden, the effect sizes would be even greater and of greater concern.

Alternatively, could high endorsement of stress be a marker variable for other, untested factors, such as suboptimal overnutrition or undernutrition related to competing work and household priorities, a busy lifestyle, socioenvironmental barriers to healthy food access, or pregnancy body image concerns? Barker's original work<sup>1</sup> focused on inadequate nutrition in the fetal milieu and its effects on child neurodevelopment; now, state-of-the-art neuroscience techniques are combined with prenatal nutrition assessment to advance DOHaD research. For example, prenatal maternal fatty acid intake is associated with offspring neuronal functioning, intelligence quotient, and cognitive outcomes.<sup>7</sup>

With this important study including fetal brain imaging in DOHaD research, Wu et al<sup>3</sup> underscore that (1) brain development is responsive to variation in utero signals and begins before birth, and (2) so does parenting, since maternal experience affects gestational biology and, consequently, fetal and child outcomes. Ultimately, to obtain specificity regarding prenatal exposures and outcomes, we will need DOHaD neurodevelopmental studies that simultaneously test more than 1 prenatal exposure, include fetal or newborn imaging to identify effects on the brain before postnatal influences, as well as assessments of variation in maternal gestational biology, such as endocrine and inflammatory variables and gut microbiome,<sup>8</sup> to determine the mediating biological pathway between maternal experience and alterations in child brain-behavior functioning.

DOHaD studies such as this have the potential to transform the prenatal and postpartum care ecosystems. The findings of Wu et al<sup>3</sup> encourage a whole-person approach to care that monitors and strengthens a pregnant person's mental well-being and quality of life, as well as their physical health (including nutrition assessment). In addition, helping people experiencing distress and other associated factors in the perinatal period could provide support for parent mental health and the brain development of the fetus and future child, thereby presenting a tremendous opportunity for 2-generational, public health impact.

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#### ARTICLE INFORMATION

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**Corresponding Author:** Catherine Monk, PhD, Department of Obstetrics and Gynecology, Columbia University Vagelos College of Physicians and Surgeons, 622 W 168th St, PH15-1540H, New York, NY 10032 ([cem31@cumc.columbia.edu](mailto:cem31@cumc.columbia.edu)).

**Author Affiliations:** Department of Obstetrics and Gynecology, Columbia University Vagelos College of Physicians and Surgeons, New York, New York (Monk); Division of Behavioral Medicine, Department of Psychiatry, Columbia University Vagelos College of Physicians and Surgeons, New York, New York (Monk); Division of Child and Adolescent Health, Department of Pediatrics, Columbia University Vagelos College of Physicians and Surgeons and New York-Presbyterian, New York, New York (Fernández).

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