“The Intergenerational Effects of Fetal Programming: Non-genomic Mechanisms for the Inheritance of Low Birth Weight and Cardiovascular Risk” (2004), by Amanda J. Drake and Brian R. Walker

In 2004, Amanda J. Drake and Brian R. Walker published “The Intergenerational Effects of Fetal Programming: Non-genomic Mechanisms for the Inheritance of Low Birth Weight and Cardiovascular Risk,” hereafter, “The Intergenerational Effects,” in the Journal of Endocrinology. In their article, the authors assert that cardiovascular disease may develop via fetal programming, which is when a certain event occurring during a critical point of pregnancy affects the fetus long after birth. Drake and Walker were among the first to show that the programming effects of cardiovascular disease could be sustained across generations through non-genetic means. In “The Intergenerational Effects,” the authors identify how non-genetic mechanisms may perpetuate fetal programming influences over generations, highlighting the importance for further research on fetal programming.

“The Intergenerational Effects” is a review of what was known as of its publication in 2004 about the effects of birth weight and later development of disease across generations. The authors worked together at the University of Edinburgh in Edinburgh, United Kingdom, where they studied how exposure to stress in early development is related to the development of certain diseases. Drake primarily studied how environmental factors affect disease susceptibility, focusing on child life and health. Walker studied the stress hormone cortisol and its relation to cardiovascular disease to seek ways to reduce disease risk. Previously, other researchers, including David Barker, the scientist who introduced the idea of fetal programming in 1995, suggested that fetal programming could have intergenerational effects. Intergenerational means that the effects of a single fetal programming event could affect a lineage of family members across several generations, not just the single fetus that experiences the event.

The authors state that at the time of the article’s publication, many studies had shown an association between low birth weight and the fetus’s development of cardiovascular disease later in life. However, scientists debated about whether that association was the result of fetal programming and environmental effects or a result of genetics. “The Intergenerational Effects” expanded on the idea that the effects could be the result of fetal programming continuing throughout generations, providing evidence and potential explanations for the underlying mechanisms of that process.

While most genetic traits are passed down from parents to offspring, the authors argue that environmental factors rather than genetic processes may cause the development of cardiovascular disease over generations. Genetics is the study of heredity and describes how an individual inherits traits from her parents through the passing on of DNA. DNA is the unique hereditary sequence determining an individual’s traits and appearance. Genes are units of heredity coding for specific traits. Each person has two copies of each gene, one copy inherited from each parent. The process of heredity describes why an offspring has similar traits as her parents and explains how most traits are determined. However, there are other factors that contribute to inheritance, such as an individual’s environment. In fact, the development of nearly all diseases is the result of the way that an individual’s genetics and environment interact.

Environmental factors fall under the category of epigenetics, which is when genes are expressed differently without any change to the DNA sequence itself. For example, researchers have shown that genetics and environmental factors determine a person’s height. Such factors include maternal nutrition and whether the pregnant woman smoked during pregnancy. Epigenetic changes can be inherited through generations as well, and the authors explain how the development of cardiovascular disease may be the result of such effects.

The authors divide "The Intergenerational Effects" into four sections. They first describe the relationship between fetal programming, birth weight, and the later development of cardiovascular disease. They explain that fetal programming affects birth weight directly and that a low birth weight indicates increased risk for cardiovascular disease. Then, the authors build upon the relationship between intergenerational effects and fetal programming by discussing animal studies demonstrating such effects. Next, the authors outline potential factors explaining the intergenerational effects of fetal programming, such as maternal diet and sex-specific factors. Lastly, they discuss the implications of intergenerational effects for certain populations.

First, the authors describe how fetal programming affects birth weight and the later development of cardiovascular disease. They note that previous studies linked the inheritance of low birth weight and the development of hypertension, a cardiovascular disease characterized by abnormally high blood pressure. They also state that existing studies had shown that women who weigh more often have offspring who weigh more, and vice versa. That finding indicated a pattern in weight that continued over generations. Additionally, women with higher blood pressure have been shown to give birth to low-weight infants, who are also at higher risk of developing hypertension. So, the authors suggest that the programming of cardiovascular disease may be the result of a continuous non-genetic process involving intergenerational effects. First, the researchers claim a fetus experiences a stressful event in the womb that causes it to have a low birth weight, via fetal programming. That involves permanent physiological changes to fetal structure. The physiological changes spurred by the low birth weight put the fetus at an increased risk for cardiovascular disease, which is characterized by high blood pressure, an overactive stress response, and other harmful factors that create an adverse in utero environment for the development of the next generation of offspring. The stressful in utero environment for the next generation results from the original fetal programming event that the previous generation experiences. That then perpetuates throughout following generations in the same way.

Next, the authors discuss animal studies that demonstrate the intergenerational effects of fetal programming. First, they describe how continued poor maternal diet has shown to have a compounding effect on birth weight over generations. In a study with rats, researchers found that a continuously malnourished maternal diet consisting of insufficient protein caused lower and lower birth weights over generations, indicating an accumulating, or compounding, intergenerational effect. Next, the authors explain animal studies showing that environmental adversity experienced by one generation could have effects on multiple generations thereafter. In that same rat study, the introduction of a bland diet led to low birth weights immediately, and the low birth weights persisted for two additional generations even after a non-bland diet was reintroduced, further indicating the existence of intergenerational effects. The authors also note that postnatal, or after-birth, programming may have intergenerational effects. For example, in another rodent study, overfeeding of the newly-born rodents during the time directly after birth was shown to have second generation effects as well.

In the following section, the authors describe a number of potential mechanisms explaining the intergenerational effects of fetal programming. As mentioned previously, one idea is that fetal exposure to an adverse in utero environment leads to permanent changes in physiology. In adulthood, those changes in physiology create an adverse environment for the next generation, causing physiological alterations for that individual and its descendants. Another idea is that the maternal diet specifically is the programming effect. Since maternal nutrition affects birth weight directly, the authors state that it must play a considerable role in the observed intergenerational effects. The authors also note that the intergenerational effects of fetal programming may be sex-specific, since existing studies have shown females are more sensitive to those effects. Finally, they discuss some epigenetic possibilities, which is when an organism's appearance is altered with the turning certain genes on or off, without permanently changing the DNA. The mechanism of turning certain genes on or off is called gene expression. They state that studies have shown that environmental influences can permanently affect gene expression and significantly impact growth. Therefore, the authors conclude that environmental factors could influence the expression of genes controlling fetal growth.

In the final section, the authors discuss the implications of intergenerational effects for certain populations. The authors state that theoretically, the intergenerational effects of fetal programming would be advantageous if a population faced the same environmental conditions over several generations. That is because the permanent changes made to fetal structure are adaptive to the stressful in utero environment and serve as preparation for the stressful environment after birth. Developing countries create a special challenge according to the authors. Drake and colleagues state that urban environments, coupled with food and technology advancements, cause people to live more sedentary lifestyles. As a result, the prevalence of cardiovascular disease increases very quickly. On the other hand, improvements of environmental conditions would eventually lead to a decline of such conditions through better maternal health during pregnancy. Better maternal nutrition and health during pregnancy would lead to better fetal growth and development, which would lessen issues caused by low birthweights. Thus, the authors argue that intergenerational effects could have major public health effects for a variety of populations. For those transitioning to a more sedentary lifestyle, the effects would initially be negative because of high rates of stress among pregnant women, but then positive with the betterment of maternal diet across generations.

Researchers within the field of fetal programming have used "The Intergenerational Effects," in further research on intergenerational effects of early life programming of disease. Other researchers have also used the study as background in further epigenetic studies focusing on the evolutionary aspect of intergenerational effects. Additional researchers have used the article in a study on the management of infants with low birth weights. In that study, the authors used "The Intergenerational Effects," to understand the intergenerational effects of fetal programming on low birth weight in order to set a precedent for medical care provided to those at-risk infants. As of 2020, other researchers continue to cite the article, mainly those studying fetal programming effects.

In "The Intergenerational Effects of Fetal Programming: Non-genomic Mechanisms for the Inheritance of Low Birth Weight and Cardiovascular Risk," Drake and Walker identify the significance of intergenerational effects of prenatal programming and offer potential explanations for the process. While scientists previously contested whether the intergenerational effects were the result of genetic inheritance, the authors pointed towards non-genomic mechanisms. In providing evidence for that, they also identified some large-scale implications of intergenerational effects, specifically for transitional populations. Lastly, they pointed out the significance of maternal health, not only for the health of the developing fetus, but also for that of subsequent generations to come.

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