“Fetal Programming and Adult Health” (2001), by Kevin M. Godfrey and David J.P. Barker

In 2001, Kevin M. Godfrey and David J.P. Barker published the article “Fetal Programming and Adult Health” in Public Health Nutrition, where they identified the significance of maternal nutrition during pregnancy to healthy offspring development. The authors describe the effects of maternal nutrition on fetal programming of cardiovascular disease. Fetal programming is when a specific event during pregnancy has effects on the fetus long after birth. The authors argue that fetuses may adapt to varying shifts in their environment in utero, such as slowed fetal growth in response to malnutrition. While those adaptations can be helpful in utero, the authors assert they may persist into adolescence and adulthood, causing conditions such as high blood pressure or diabetes. Godfrey and Barker assert that fetal adaptations to maternal malnutrition may be implicated in the development of cardiovascular disease in adulthood, and called for future research investigating additional fetal programming variables.

“Fetal Programming and Adult Health” is a review of what was known about the effects of fetal programming on cardiovascular disease at the time of the article’s publication. The authors, Godfrey and Barker, worked together at the University of Southampton in Southampton, England, studying human development and epidemiology, which is the study of what causes health outcomes and diseases throughout populations. They wrote many papers together exploring various fetal programming effects during pregnancy and early life. Godfrey primarily studied methods aimed at improving the growth and development of children early on so as to improve their lifelong health. Barker proposed the Barker Hypothesis, which was one of the first hypotheses proposing the idea for the existence of fetal programming, as a way to explain the developmental causes of diseases.

The authors state that at the time of the article’s publication, people generally believed that low neonatal birthweight was associated with an increased likelihood to develop coronary heart disease and related cardiac disorders in adulthood, including hypertension and type 2 diabetes. Cardiovascular disease refers to all types of diseases affecting the heart, whereas coronary heart disease is specifically diagnosed when there is a blockage in the blood vessels resulting from a buildup of plaque or fat that reduce blood flow to the heart. Hypertension is when blood pressure is abnormally high, meaning that the force of blood pushing against blood vessel walls is consistently elevated. Blood pressure rises when there is less space for it to move due to the buildup of fat. Although Godfrey and Barker discuss the fetal programming association between maternal diet and the eventual development of cardiovascular disease throughout their article, they imply that other researchers were skeptical. The authors state that the general view at the time was that normal variations in maternal diet did not significantly influence fetal growth and development and scientists did not know what caused the association.

Godfrey and Barker split their article into five sections. To begin the article, the authors describe the process of fetal programming and explain how fetal nutrition and fetal growth play a role in the programming of coronary heart disease and other cardiac diseases. They expand upon that in the next section, where they discuss how low birthweight may also have a programming effect on hypertension. Next, the authors describe how type 2 diabetes may be central to understanding the programming effects of fetal growth on cardiovascular disease. In the following section, the authors identify certain factors influencing fetal body size that they used to understand the effects of maternal nutrition on fetal programming. Finally, they highlight the importance of studying maternal diet and body composition when researching fetal programming effects and discuss implications for future research.

Godfrey and Barker begin by describing fetal programming and providing some evidence supporting the idea, particularly focusing on how fetal programming relates to the development of cardiovascular disease. The authors state that the effects of fetal programming may be the result of the fetus adapting to the in utero environment, though they do not state what adaptations take place. That means that the fetus adapted to the pregnant woman's bodily conditions while developing in her uterus. However, while the adaptation may have been useful while in the womb, it has a permanent effect on the fetus, causing a predisposition to the development of certain diseases later in life. For coronary heart disease, they state that predisposition may be the result of fetal adaptation to undernutrition in the womb. That implies that infants who did not get enough nutrients in the womb are more likely to develop coronary heart disease in adulthood. As evidence, the authors cite studies linking signs of undernutrition in the womb to the development of coronary heart disease later in life. Those indicators include low birthweights, low rates of fetal growth, and thinness at birth. Therefore, the authors argue that influences on fetal growth must be important in understanding how fetal programming affects the development of coronary heart disease.

In the next section, the authors describe how there is a positive association between low birthweight and hypertension and describe some possible programming mechanisms underlying that association. In reviewing existing studies, the authors state that almost all studies show that a greater birthweight is associated with a lower blood pressure in adulthood, which indicates a lower likelihood of developing coronary heart disease and other cardiac diseases. Since low birthweight is indicative of restricted growth while in the uterus, the authors describe potential mechanisms by which restricted intrauterine growth may program for hypertension later in life. Restricted intrauterine growth is when a fetus develops smaller than it should because it is growing at a slower rate in the uterus. In the first method described, the authors state that a low birthweight may cause the fetus to have accelerated growth later in childhood in order to catch up. Because blood pressure can rise with age and growth, the accelerated growth spurt could also cause elevated blood pressure. Based on the programming effect, that growth spurt may increase the likelihood of the person to develop more long-term cardiac conditions. Thus, as the low birthweight is the suggested cause, Godfrey and Barker conclude it may have a programming effect on hypertension. Another potential fetal programming mechanism is that the fetus's central stress response system, which also controls blood pressure, is directly altered by impaired fetal growth, which generally applies to atypical fetal growth patterns. The authors state that it is possible that stunted fetal growth may directly affect the central stress response system by permanently resetting how it signals the body to react to stress, causing irreversible dysfunction.

In the following section, Godfrey and Barker describe how type 2 diabetes may be central to understanding the programming effects of fetal growth on coronary heart disease. The authors state that many studies show an association between low birthweight or thinness at birth and diabetes. Type 2 diabetes is a chronic condition that inhibits the body from metabolizing sugar properly due to either resistance to or a lack of insulin. Insulin is a hormone that regulates the movement of sugar into cells, which is a major source of energy for the body. Because of its function, insulin is critical to fetal growth. Since type 2 diabetes is characterized by dysfunctional insulin management, the authors state that it potentially links early growth issues with later development of coronary heart disease. In support of their claim, Godfrey and Barker offer some potential programming mechanisms linking low birthweight and thinness at birth with the development of type 2 diabetes. They explain that one potential mechanism may be in response to undernutrition. A fetus may reduce its dependence on sugar due to a lack of it in the uterus, leading to a permanently altered, sugar-sparing metabolism in adulthood that may eventually lead to type 2 diabetes. Another possibility is that nutrition and other factors determining fetal growth impact the size and functionality of the adult cells producing insulin directly, leading to a permanent insulin deficiency.

Having described the implications of fetal growth and size at birth, Godfrey and Barker then identify certain factors influencing fetal size that they state other researchers have overlooked. The first thing they describe is how much a fetus is supposed to grow, which thereby determines the fetus's need for nutrients. For example, some fetuses require more nutrients for sustaining their current size and future growth. Given the links between fetal size at birth and later development of coronary heart disease, the authors found that the needs for fetal growth were useful in understanding how undernutrition affects fetal size, helping to understand the resulting programming effects.

In the same section, Godfrey and Barker then describe the importance of intergenerational effects, or effects occurring over generations. They describe intergenerational effects in terms of a pattern of heritable in utero adaptations. For example, when pregnant women in several successive generations cannot properly provide nutrients to fetuses, that can have cumulative effects over time, which progressively stunts fetal growth for the next successive generation. Another specific issue that the authors draw attention to is the size of the placenta. The placenta is an organ that develops during pregnancy to provide oxygen and nutrients to the fetus. The size of the placenta is strongly associated with its ability to transfer nutrients to the fetus, which is important to understand how the fetus is nourished and how that may affect the programming of disease. Then, the authors point to the possibility that maternal nutrition may have effects on specific fetal tissues, causing them to develop abnormally. They state that researchers have observed such a phenomenon in animals, but have yet to test it in humans.

Finally, Godfrey and Barker emphasize the importance of studying maternal diet and body composition in relation to fetal programming and discuss implications for future research. Specifically, the authors state that it is important to consider the balance of maternal diet because studies have shown that certain diets alter placental growth, resulting in permanently elevated blood pressure in offspring. They state that maternal body composition during pregnancy is also important to consider because body composition extremes among pregnant woman, when either severely overweight or severely underweight, have demonstrated many negative impacts on the offspring. For example, researchers have found greater death rates by coronary heart disease in people whose mothers had high body weight while pregnant. Godfrey and Barker state that that correlation may be because greater maternal body mass may increase fetal growth, therefore increasing fetal nutrient demand. That means that the larger the fetus gets, the more nutrients it needs to sustain itself. However, if that demand is not met, then the person physiologically may not meet their nutrient need as determined when they were a fetus, thereby causing the fetal adaptation to undernutrition to program for coronary heart disease. In view of their findings, the authors conclude that maternal nutrition greatly affects the fetus. Therefore, they state that further research should be done to identify the biological mechanisms underlying those observations so that specific dietary recommendations could be made for pregnant women in an effort to reduce the development of chronic diseases in their offspring.

Fellow scientists have cited the paper “Fetal Programming and Adult Health” nearly one thousand times since its publication. Researchers who are conducting further studies on the effects of disease programming during pregnancy and throughout early life often cite “Fetal Programming and Adult Health.” However, researchers have also cited the paper in research on the mechanisms and implications of insulin resistance, a component of type 2 diabetes. As of 2021, researchers studying various fetal programming effects continue to cite “Fetal Programming and Adult Health” frequently.

In their article, Godfrey and Barker identified the significance of maternal nutrition during pregnancy in the healthy development of offspring, particularly in the development of coronary heart disease. While the general scientific opinion at the time of publication in 2001 was that normal variation in maternal nutrition did not greatly impact fetal growth and development, the authors provided evidence to challenge that misconception. By identifying gaps in the literature on the topic, Godfrey and Barker have prompted further research in specified areas on the effects of maternal nutrition on offspring development. In doing such, they have motivated researchers to take the next step in identifying the precise relationship between maternal nutrition during pregnancy and disease development in their children.

Sources

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