

The Effects of Maternal Diet and Inflammation on Offspring Brain Development, Part 1

By Alice Graham, M.S., Ph.D. and Damien Fair, PA-C, Ph.D.

The roots of psychiatric disorders can be traced back to the prenatal period. The prenatal period is characterized by rapid fetal brain development with all major brain structures in place by the time of birth. This creates both opportunity, in terms of supporting healthy brain development, and vulnerability to adverse maternal conditions that might affect the brain. The development of the fetus and fetal brain can be guided by environmental influences due to biological signaling between the mother, placenta and fetus. Inflammatory proteins play an important role in this signaling. Levels of inflammation in the mother can be elevated for multiple reasons, including heightened body mass index and experiences of stress. Heightened inflammation in the mother can be passed on to the fetus through actions involving the placenta. Inflammatory signaling proteins in turn play an important role in many processes involved in fetal brain development, including differentiation of brain cells and growth of connections between these cells.

While the effects of heightened inflammation during pregnancy on brain development and long term behavior have been well documented in research with animals, we have recently published a series of studies providing evidence for these effects in humans. Our recent work suggests that elevated maternal inflammation during pregnancy can affect the structure and function of the newborn brain. We have examined the brain shortly after birth because this allows us to be able to begin to understand potential effects of the prenatal environment, versus the postnatal environment. We use magnetic resonance imaging (MRI) to study the newborn brain. We have found that heightened chronic maternal inflammation during pregnancy is related to differences in the newborn amygdala, a brain region important for processing stress and emotion, as well as social functioning. These differences in the newborn amygdala are in turn related to difficulties regulating behavior when children are two years of age. Interestingly, we have also found that heightened

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Director's Message

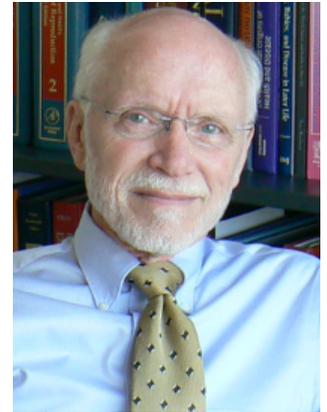
Over the last year, I have had the opportunity to speak to many lay and scientific audiences. I often say that atmospheric warming offers the greatest danger to the human race. Well-read people know that reams of scientific evidence points to human activity as the primary culprit. People across the globe must address this issue in the near future to avoid disastrous consequences. What will it take to convince the science skeptics that action is required?

I also make the point that a second danger also demands our concern. Over the past 30 years, chronic diseases like heart disease, type 2 diabetes and obesity have replaced diseases caused by infectious agents (germs) as the primary cause of death. In 1900 over 50% of all deaths were caused by infections; life expectancy at birth was a mere 50 years. By 2010, infectious diseases accounted for less than 1% of all deaths and life expectancy had climbed to 80 years.

At the turn of the 21st century the outlook for the health of the human race appeared to be bright. Little did we know that our expectation of living for 80 years would be so severely challenged. Beginning in 2016, the Centers for Disease Control and Prevention announced that life expectancy was decreasing for the first time in decades. Increases in chronic diseases were the primary cause. The decrease has continued every year since and the downward trend is expected to continue. Babies born today are likely to have shorter lives than their parents.

Epidemiological data from 190 countries all point to poor nutrition as the ultimate cause of most chronic diseases. The industrialization of food has made it possible to provide calories for large populations but this has come at the expense of providing required nutrients. Good tasting

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Kent Thornburg, Ph.D.



Maternal Diet and Inflammation Affect Offspring Brain Development

Part 1 *(continued from page 1)*

Inflammation is closely linked to the overall organization of the newborn brain into systems which affect later emerging cognitive abilities. We have conducted this work in collaboration with colleagues at University of California, Irvine and Charite University of Medicine in Berlin. The results have been published in *Biological Psychiatry*, *Neuroimage* and *Nature Neuroscience* and were highlighted in a press release by the National Institute of Mental Health.



In collaboration with Elinor Sullivan, Ph.D., at the OHSU Oregon National Primate Research Center, we have extended this work to non-human primate models, which allows for a more controlled experimental setting. This translation between human research and animal work provides additional support for the links between heightened inflammation during pregnancy and alterations in the infant brain. We have learned that inflammation during pregnancy can alter the trajectory of brain development following birth and later in life. This study was recently published in the journal, *Cerebral Cortex*.

We are currently examining whether an intervention using psychotherapy during pregnancy has potential to reduce maternal inflammation and support healthy fetal brain development. This work is particularly important given the increasing awareness of the burden of mental health disorders during pregnancy, as well as challenges with heightened body mass index and poor physical health, which are associated with heightened inflammation. We hope to continue to refine our understanding of the effects of maternal inflammation during pregnancy on the developing brain with an eye towards identification of interventions to support brain development and long term health outcomes.

Maternal Diet and Inflammation Affect Offspring Brain Development

Part 2 **By Elinor Sullivan, Ph.D.**

Elinor Sullivan, Ph.D., associate professor, Department of Psychiatry, Division of Neuroscience, Oregon National Primate Research Center, OHSU, and Joel Nigg, Ph.D., professor, Department of Psychiatry, OHSU, are collaborating to discover prenatal environmental factors that influence the risk for children developing neurodevelopmental and psychiatric disorders.

Attention-Deficit Hyperactivity Disorder (ADHD) and related learning deficits in children are a major public health concern. At present, psychologists and psychiatrists lack effective prevention strategies and interventions. Consequently, these medical conditions impose enormous burdens on affected families as they struggle for health care, education and legal assistance.

Epidemiological studies have demonstrated that babies whose mothers have conditions like obesity, poor nutrition, gestational diabetes or hypertension are more likely to experience neurodevelopmental disorders. The mechanisms for this association remain largely unknown. New evidence suggests that these conditions cause maternal inflammation that impairs the development of the fetus. The study led by Sullivan and Nigg, known as the PEACH Study – Prenatal Environment and Child Health, is funded by the National Institute of Mental Health. Three hundred pregnant women will be recruited to examine the role of inflammation as a mechanism by which maternal obesity and diet are influencing the child's brain development and his/her risk for a behavioral disorder. Sullivan and Nigg are seeking to discover the strongest predictors of infant and toddler behavior that are associated with neurodevelopmental disorders in order to find new approaches to prevent or treat mental health problems in children.

Our team has recently shown that a high maternal body mass index (BMI) before pregnancy was associated with altered emotional states in six-month-old infants. High blood levels of omega-3 fatty acids in pregnancy were associated with better emotional status and thus buffered children against the negative consequences of excess fat tissue in the mother. These results suggest that omega-3 supplementation during pregnancy may protect against offspring behavioral risk associated with increased maternal obesity.



Director's Message

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calories are cheap but nutrients are expensive.

It has now become clear that a chronic disease epidemic is spreading across the globe. Populations in the U.S. are among the leaders in increasing chronic disease rates. In the mid 90's, type 2 diabetes took a large upswing so that the American Diabetes Association recently estimated that 13% of the U.S. population has the disease. Diabetes leads to cardiovascular disease, the leading cause of death worldwide. Diabetes is associated with obesity, which is largely driven by non-nutritious, sugar, salt and fat laden diets across all layers of society, in addition to other factors.

Between 1990 and 2015, the number of people with obesity has more than tripled in Oregon and the number of people with diabetes has more than doubled. Because of this, the Oregon Health Authority suggests that the number of people with heart disease will quadruple over the next few decades.

Scientists in OHSU's Center for Developmental Health are seeking the biological causes of this condition. They also know that in the short term, the epidemic can be reversed by changing the nutritional intake of future mothers and fathers. The key word is prevention.

The Center for Developmental Health is joining forces with another center in the Knight Cardiovascular Institute, the Center for Preventive Cardiology, to spread OHSU's mission of caring about the health of all Oregonians. Check out our websites: www.ohsu.edu/heart and <https://www.ohsu.edu/knight-cardiovascular-institute/center-preventive-cardiology-research>.



Most of us feel helpless in combating global warming but everyone can spread the word within their own communities about the upcoming crisis. The same is true for the chronic disease epidemic. The message is especially important for young men and women who will be reproducing. Women who are pregnant and lactating need unlimited access to delicious healthy food. Let us know if you can help.

Save the date: May 21, 2020
David J.P. Barker Memorial Lecture:
The Impact of Famine on Lifetime Health



The impact of the German occupation of The Netherlands during World War II continues to this day. You may recall from history class that the occupation began in 1940 and lasted until May 1945 when Allied troops liberated the people of The Netherlands. In September of 1944 the exiled Dutch government called for a railway strike to slow the German Army and Germany retaliated by cutting off the country's food supply, thus the winter of 1944-45 is known as the Dutch Hunger Winter. Rations fell below 1000 calories per day by November and were as low as 500 calories per day by April. Sadly, about 20,000 Dutch people died during the winter. Food supplies were immediately reestablished when the Allied troops arrived. Because the exact dates of the famine are known and the population had good nutrition before and after the hunger winter, it is possible to study the enduring effects of famine on population health.

Tessa Roseboom, Ph.D., professor of Early Development and Health at Academic Medical Center in Amsterdam, has received international recognition for her studies on the health effects of the famine during early development. The Dutch have kept detailed health records of their citizens, enabling her to follow the children who were in their mothers' wombs during the famine. Her studies found that children who were conceived during that winter have increased risk of diabetes, heart disease, high blood pressure and hospitalization as adults and higher lifetime rates of obesity.

The Knight Cardiovascular Institute has invited Dr. Roseboom to deliver the 2020 Barker Memorial Lecture at 5:30 p.m. on May 21, 2020, location to be determined. Dr. Roseboom will discuss the effects of the war including differences in long term disease outcomes of people who were developing in the womb during the famine. Please email heart@ohsu.edu if you would like more information when available.

Pregnancy Complications are Predictors of Cardiovascular Disease Risk

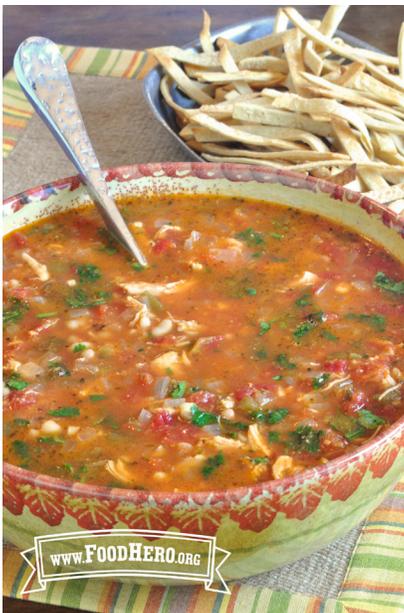
On April 4, 2019, the OHSU Knight Cardiovascular Institute welcomed Janet Catov, Ph.D., M.S., associate professor of Obstetrics, Gynecology & Reproductive Sciences at the University of Pittsburgh, to deliver the *David J.P. Barker Memorial Lecture*.

According to Dr. Catov, *“Heart disease is the leading killer of women, and it manifests differently in women compared to men. We are interested in what pregnancy can teach us about heart disease in women, and how to take that information and improve pregnancy health and women’s long term health.”*

Recent research by the Catov laboratory explored the relationship between preterm birth and maternal cardiovascular risk factors. Her epidemiological studies have shown that women who have pregnancy related hypertension, preterm birth or preeclampsia have an increased risk for cardiovascular disease in midlife. She explained that the increasing rates of pregnancy disorders predict an increase in cardiovascular disease risk among affected women and that we now have the opportunity to improve their future pregnancy outcomes and long term health.



Chicken Enchilada Soup Recipe Courtesy of Food Hero



This issue’s healthy recipe is one of hundreds available at FoodHero.org. Food Hero is an initiative of Oregon’s Supplemental Nutrition Assistance Program Education (SNAP-Ed) program and was developed by Oregon State University Extension Service. Their mission is to help low-income Oregonians improve their health by increasing their consumption of fruits and vegetables.

Recipes on the website use common, inexpensive ingredients,

and are easy to prepare. Many have been taste-tested and approved by kids and families.

In addition to recipes, the site includes a blog with advice on shopping and storing seasonal foods, resources for kids, and access to the Food Hero Monthly magazine. Nutrition information and additional recipes can be found on the Food Hero website - <https://foodhero.org/>.

Ingredients

2 teaspoons oil
1 cup chopped onion (about 1 medium)
2 cloves garlic, minced, or 1/2 teaspoon garlic powder
1 teaspoon ground cumin
1 can (16 ounces) navy beans
1 can (28 ounces) diced tomatoes
2 cans (14.5 ounce each) fat-free chicken broth (see notes)
1 can (8 ounces) tomato sauce
2 cans (4 ounces each) chopped green chilies
2 teaspoons dried oregano
2 cups chopped cooked chicken
1/2 cup chopped fresh cilantro
1 cup shredded cheese
10 thin corn tortillas

Directions

1. Heat oil in a large pot. Add onion, garlic, and cumin, and sauté until onion is softened but not browned.
2. Drain and rinse beans. Add drained beans, tomatoes with liquid, and chicken broth. Heat to a boil. Reduce heat.
3. Stir in tomato sauce, chilies, oregano, and chicken. Simmer 15 minutes.
4. When ready to serve, stir in cilantro and 1 cup cheese until melted. Serve tortilla strips on the side as a soup topping.
5. Refrigerate leftovers within 2 hours.

Notes

- Broth can be canned or made using bouillon. For each cup of broth use 1 cup very hot water and 1 teaspoon or 1 cube bouillon.
- To make tortilla strips, stack tortillas and cut in half. Cut each half-stack into thin strips. Spread strips on a baking sheet. Bake at 350 degrees, tossing frequently, for 15 minutes or until crispy and starting to lightly brown
- Can substitute other beans, meat or meat substitutes, vegetables and also add or subtract spices to taste.

Nutrition in Pregnancy Conference

We now know that development before birth and through the first two years is critical in establishing later life risk for chronic diseases including heart disease, obesity and diabetes. However, specific guidelines detailing the nutritional needs of women before and during pregnancy and lactation are lacking.

To address this issue, the OHSU Moore Institute for Nutrition & Wellness held a Nutrition in Pregnancy conference in Washington, DC in May 2019. They invited 28 international scientists, clinicians and policy experts to discuss nutritional needs before and during pregnancy and lactation, and how early nutrition impact the lifelong health of both the mother and her offspring.

The conference was attended by representatives from many academic institutions and

important organizations including the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Institute of Allergy and Infectious Diseases, the Academy of Nutrition and Dietetics, the March of Dimes, the American College of Obstetrics & Gynecology (ACOG), the United States Department of Agriculture (USDA), the Bill & Melinda Gates Foundation, 1000 Days and the Center for Science in the Public Interest.

The experts addressed the social issues that affect the dietary choices of women and agreed that addressing these issues is important for the health of both the mother and her offspring. It was clear that improving women's nutrition, before conception, during pregnancy and through lactation, will improve the health of the next generation and will require a concerted effort by research scientists, health care providers, policy makers and community leaders.

Participants agreed that it is imperative that health care providers discuss nutrition with women of reproductive age. They reached consensus on several issues, including the importance of balanced nutrition before conception, through pregnancy and early childhood, the harm that can be caused by fad diets, and the importance of a prenatal multi-vitamin supplement before and during pregnancy that includes iodine, folic acid, iron and vitamins D and B12.

A full consensus statement from the meeting is being prepared for publication and key points are being sent to the U.S.D.A. 2020 Dietary Guidelines Advisory Committee. The 2020-2025 Dietary Guidelines for Americans will include recommendations for nutrition during pregnancy and infancy for the first time.

The Nutrition in Pregnancy conference was supported by the OHSU Bob and Charlee Moore Institute for Nutrition & Wellness, the Vitamix Foundation, the March of Dimes and the International Society for Developmental Origins of Health and Disease.



The Heart Beat

Please contact us by email at heart@ohsu.edu or by phone at 503-494-2382 if you would prefer to receive this newsletter by email or if you would like to receive information about lectures and events at the Center for Developmental Health

Food Pharmacy at OHSU Center for Preventive Cardiology

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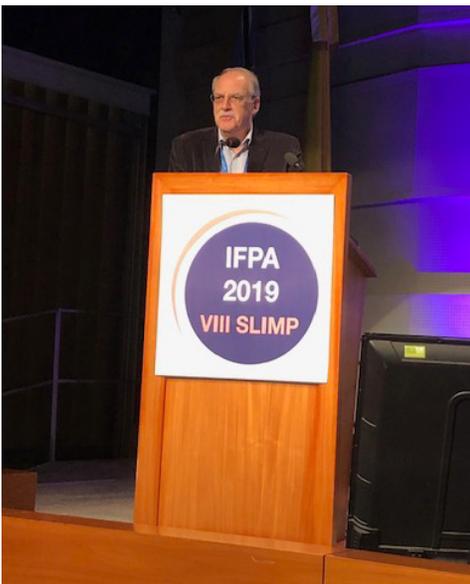


classes taught by chefs and doctors. The Food Pharmacy is designed to bridge the gap between knowing what to do and actually doing it, something which far too many of us struggle with.

Variations of food pharmacy programs are becoming increasingly popular, with 13 such programs in Oregon alone. What sets this Food Pharmacy apart, though, is that it will be open to all CPC patients regardless of socioeconomic status (other criteria for entry do apply). There is no doubt that income barriers contribute to insufficient fruit and vegetable intake, however 89% of adults at the highest income level still do not meet the recommended vegetable intake. There are clearly additional barriers beyond economics.

The CPC's program will investigate how increased access to fruits and vegetables affects their use and consumption, regardless of participants' level of food security. It will also track changes in cardiovascular risk markers such as weight, blood pressure, and cholesterol levels. The potential impact of the program is profound, as one participant of a previous iteration of CPC's Food Pharmacy discovered. Following a massive heart attack, she struggled to follow the recommended heart-healthy diet. Yet after receiving free fruits and vegetables for three months, those recommendations became a reality. When discussing her experience with the program, she stated, "I'm excited about vegetables for the first time in my entire life, and I'm 66 years old. Who knew? I have a love of vegetables I wouldn't have had if I had not gone into the Food Pharmacy program."

Dr. Fazio and Ms. Severson have worked to establish the CPC's Food Pharmacy as a resource that does more than simply make healthy food more accessible. By also providing education and support, the program improves the quality of life of each participant and promotes the health of the entire community.



Myatt receives IFPA Award in Buenos Aires, Argentina

Awards and Recognitions

Leslie Myatt, Ph.D., FRCOG, Center for Developmental Health Scientist and Moore Institute associate director, was presented with the senior scientist award in placentology at the 2019 IFPA conference in Buenos Aires, Argentina.

The "IFPA Award in Placentology" acknowledges outstanding contributions to the field of placentology in all its aspects, including the relationship between the fetus and the mother, by established investigators who are normally within 20 years of receipt of their highest degree.

Myatt served as president of the International Federation of Placenta Associations (IFPA) from 2002 to 2004 and hosted the annual meeting at OHSU in 2016.

He studies the effects of maternal obesity, gestational diabetes and sexual dimorphism on mitochondrial respiration in the placenta and their relationship to epigenetic regulation of placental function and fetal programming.

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Checks should be made payable to OHSU Foundation and mailed to Center for Developmental Health, Oregon Health & Science University, 3030 S.W. Moody Avenue, Mail Code MDYMI, Portland OR 97201. Online donations can be made at www.ohsu.edu/heart.

We appreciate the generosity of our many thoughtful donors.
Below is a list of recent memorial & honorary donations:

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From Juanita Struble*

*In memory of Griffin Huber
From Richard and Patty Evans*

*In memory of Jack See
From Juanita Struble*

*In honor of Dr. Kent Thornburg
From Gordon and Clea Crisman*

*In memory of Gerrit van Gelder
From Juanita Struble*

*In honor of Dr. Kent Thornburg
From Richard and Diane Lowensohn*

*In memory of Mrs. Gray Johnson
From Juanita Struble*

Awards and Recognitions

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Kent Thornburg, Ph.D., director of the Center for Developmental Health and Moore Institute, was awarded the David Barker Medal by the International Society for Developmental Origins of Health and Disease (DOHaD) at the Society’s 2019 meeting in Melbourne, Australia.

The David Barker Medal is the society’s highest honor. It is awarded every two years to a scientist who has made an outstanding contribution to the scientific development and broader leadership of the field of developmental origins of health and disease.

OHSU’s place as an international leader in the field of DOHaD is a direct result of Barker’s pioneering work and his and Thornburg’s decades long collaboration. Together, they published over 30 scientific papers significantly contributing to moving the DOHaD work from concept to established science. Thornburg continues to be an international leader in the field and their collaborative discoveries set the stage for the explosion of research that has happened since.



Thornburg with Mary Barker, BSc, MSc B.Sc., M.Sc., Ph.D., C. Psychol., daughter of the late David Barker.



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Food Pharmacy at OHSU Center for Preventive Cardiology

by Tracy Severson, R.D., L.D.

Most of us know that eating enough fruits and vegetables is instrumental to good health, yet we typically are also aware that we aren't quite eating enough. In fact, only about 10% of Americans meet the recommended daily intake for fruits and vegetables. OHSU's Center for Preventive Cardiology (CPC) is working to change this.

The CPC strives to reduce the burden of cardiovascular disease among Oregonians. The Center's director, Sergio Fazio, M.D., Ph.D., believes that good nutrition is the foundation for maintaining healthy hearts. Yet while nutrition education is important, he feels that innovative strategies must be developed to promote large-scale improvements in dietary intake and, subsequently, reduce rates of chronic disease.

The CPC has started a Food Pharmacy program that goes beyond simply telling patients about the importance of a healthy diet. Their Food Pharmacy actually increases access to fruits and vegetables and teaches patients how to easily prepare the produce. Every week for three months, qualifying CPC patients will receive free home deliveries of fresh fruits and vegetables. Participants will meet with the CPC's registered dietitian, Tracy Severson, for nutrition education and have access to the Heart Protection Kitchen, CPC's free cooking

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