

Division of Diabetes Treatment and Prevention

Early Life Nutrition and Risk for Diabetes: A Look at In-Utero Stressors and Vulnerability for Chronic Disease

Susan Bagby, MD

October 2014

Susan Bagby:

Great admiration for what all of you do every day, I just wish I could see you. I really have been privileged in my career to do clinical practice, basic research and medical teaching in an academic setting for over 30 years at OHSU. I literally stumbled into this. I stumbled into this newly emerging area of research that we now know as developmental origins of health and disease, which we fondly, if apologetically, called DOHaD.

Because I had a primary interest all my career in hypertension, I directed hypertension clinics over many years, I was struck in the late 1980s by the increasing prevalence of this perplexing cluster of disorders that we now call metabolic syndrome. And I know all of you know what that is. It's hypertension, obesity, insulin resistance, diabetes and dyslipidemia. It was fascinating. And at about the same time in the early 1990s, the pioneering work of Professor David Barker who is acknowledged as the founder of the DOHaD field was just beginning to show that these metabolic syndrome disorders are really not independent entities. They're biologically related, as David would say, "They're all of a piece" and in fact are tremendously influenced by what happens in very early life by what is called developmental programming.

So in my view, this was a true paradigm shift in our understanding of how chronic disease evolves, what its etiology is, really the only one in my adult medical career, and I dove into it both at the research level, the teaching level, and I've been there ever since. I had the wonderful privilege of working with David Barker. He was on at OHSU, he was a part-time faculty member for the last 20 years and that was a great privilege.

I would ask of you as you listen, in addition to your hat as healthcare provider, that you put on your other hats, your parent hat, your parent-to-be hat perhaps, grandmother, aunts and uncles. Put on your PTA hat or your homeroom hat, because this is a message that I think we need to have permeate our entire culture in order to accomplish the things that we need to accomplish to change. So with that, I will go ahead and remind myself how to advance the slide.

So first what is developmental programming? It's based on the biologic capacity of the normal developing organism to be durably changed by environmental exposures without any change in the inherited genome. That means no change in a gene's DNA sequence. This is the definition of epigenetics, a system which changes gene expression without changing the genome. The environmental exposures that we know of so far that can cause developmental programming are nutrients, both too little and too much; stress with, really, with a capital S, psychosocial stress that's sustained; extremes of oxygen, certainly, chemicals and toxins about which we know not nearly enough.

The mechanisms, the major big picture mechanisms by which this occurs are, first of all, permanent changes in organ structure during development. So, that can't be fixed. The second is this epigenetic

process, so changes in the way genes and sets of genes are expressed, many of which are irreversible but in some cases potentially reversible. So we have a lot to learn there.

The susceptibility to developmental programming varies according to the life course. You're most susceptible as a fetus where organs are developing and things are rapidly changing, still but less so as an infant. Again, still but less so as a child. And then decreasing in teenage and adult years. But I would make the point that we're now beginning to understand that the teenager's brain is really not fully set until about age 25. So we're learning more things about potential risk in teens. But the impact of developmental programming is not that it causes disease, but that it creates increased vulnerability to development of those diseases in later life.

This is a slide I made for myself to try to get my head around it as I was getting into this field. That is, by its basic biology, the nutritional life of the egg is transgenerational. This is one of the important messages in this whole field. What I have here are three generations. Let me see if I can figure out how to do the pointer... I'm not getting my pointer, there it is. I've got three generations. The daughter, color coded in aqua. Here she is as a child, here she is as a fetus in mother's womb. But if you go back beyond that, if you'll recall, the egg that gave rise to that fetus originated in mother's ovary and was actually formed when the mother was in grandmother's womb. So if you think about nutritional forces among others that have long term effects, they go across multiple generations.

This is a very big-picture overview of what I want to talk about. I'll give you the big picture and then we'll come back to some of the details. We're looking at a lifespan of a single individual; in utero, birth, childhood, adulthood. We know that adverse exposures in utero are multiple but the three big ones that we recognize and know about best currently are first of all, undernutrition, classic undernutrition, low-protein low-calorie diet. High calorie malnutrition, we're calling it, you could also call it "maternal-fetal energy excess." The categories there are maternal obesity, maternal high-fat diet, those are often linked but they have separate effects, or overlapping but separate effects, gestational diabetes. And it also thirdly includes psychosocial stress. Again, stress with a capital S, sustained. And I know this audience is very familiar with that in the individuals that you work with.

What we know is that in each case, these developmental programming forces cause abnormal fetal growth. In the case of undernutrition, slowed growth but also asymmetric. I'll tell you more about that. In the case of high-calorie malnutrition, it may often be growth that's too fast but again, it's not normal, it's asymmetric, you get macrosomia which is not a normal state.

We know that amazingly, all of those three forces create similar types of vulnerabilities. They act on similar regulatory systems and systems that relate to how we interact with the environment. But we also know that they can be influenced by the environmental stressors in the postnatal environment. You're born vulnerable, but whether or not you actually express disease will be determined by what you encounter in the postnatal environment. The diseases that I'm going to focus on are the metabolic syndrome diseases, as I alluded to earlier. But will also give you periodically some information that's emerging about behavioral, mental, cognitive defects that are involved as well.

Here's what I'd like to do. I'll tell you about the origins of developmental origins. I'll tell you a little bit about the history which came from human cohort studies, this is a field that started in humans and now has moved back to animal studies as well as ongoing human studies. I'm going to talk about three biologic pathways of disease vulnerability. And these pathways can refer to all three of the major programming forces that I mentioned. But I'm going to, typically in at least the first two, use the undernutrition paradigm because we know so much more about that than we do with the overnutrition and stress paradigms. Change in organ structure, change in homeostatic systems set points, and how they can interact postnatally to amplify the risk of disease. Finally, a very important piece is the recent understanding that these programmed disease vulnerabilities can be in some cases transmitted

transgenerationally, both in the setting of undernutrition, and in the setting of maternal-fetal overnutrition, especially obesity.

So how did this all get started? We go back to David Barker and his team in the UK in the late 1980s, looking at this map. It's a map of coronary heart disease deaths in men in England and Wales that occurred between '68 and '78. What you see are red areas indicating high levels of coronary deaths and green areas indicating low levels, striking differences geographically.

David Barker was renaissance-educated; he had a natural history and anthropology background. He knew that this related to poor land, sparse food, and a lot of urban poverty in these red areas, as compared to the green areas. He asked a genius question, and that was, "These men who are dying in '68 and '78 of coronary disease, what was happening in those areas when they were being formed in the womb?" He looked at that by looking at neonatal mortality in those same areas and found identical patterns, the map looked just like this.

This was really the first time that anyone had ever made a link between chronic diseases and socioeconomic status in early life. This was a huge paradox at that time and I remember this well. We all knew that coronary artery disease was a disease of societal affluence. We thought we knew it. How could then coronary mortality be tracking with socioeconomic disadvantage? The answer for coronary mortality is the same as the answer for all of the metabolic syndrome disease or disorders. That is, that babies who develop under adverse conditions are uniquely susceptible to negative impacts of affluence in a society; high animal protein, fat, sugar, calories.

Again, this was something that was basically rejected by the medical and scientific communities at the time and caused a lot of suffering, actually, for David Barker. But it points to the fact that developmental programming was first recognized because it led to socioeconomic-based health disparity. Most of us now consider that this is at least a major if not the major mechanism by which socioeconomic and psychosocial disadvantage becomes biologically embedded within a population. If you're born, you're wombed under adverse conditions, you don't get a clean plate when you start out in your postnatal life. You're bringing baggage. And these developmentally-based health disparities can in some cases be then transmitted to future generations.

David Barker knew that in order to prove this, he was going to have to find a database that would allow him to connect what happened to the baby and what happened to the adult, as longitudinal rather than cross-sectional data. He looked all over England for that kind of a database and amazingly, he found it in his own mother's home village of Herefordshire. There, this meticulous public health nurse had kept records of births, moms and babies at birth and through the first year. And in small English villages, most people stayed around, at least of those generations. They were there for David Barker and his team to actually recruit and look at their outcomes. He had birth data and data at 50-plus years.

What he was now able to show for the first time is that poor fetal growth increases the risk of chronic disease in later life. This is what that early data looked like, and it was reproduced in populations all over the world. You could look at hypertension; you could look at coronary disease and stroke. You could look at obesity; you could look at glucose intolerance or diabetes, any of these and see this pattern. So you're looking at birth weights and relating it to risk of disease, in this case, blood pressure but it looks the same for clinical hypertension, an inverse relationship between birth weight and disease risk. The lower the birth weight the higher the disease risk. You can see the same pattern for coronary disease and stroke. And this is in an American nurse's study group. A special interest to this group is the pattern with risk of glucose intolerance or diabetes. Again, a steep inverse relationship for birth weight here in pounds and the adjusted odds ratio for diabetes. The lower the birth weight, the higher the risk.

Now, this hatched bar was not in the original data set. I've added that to remind me to tell you that this early data came from older populations that were born in the 30s and 40s and they did not grow up in a milieu that we have today in terms of diet. If we looked at current populations who did grow up in the current milieu, what we see is these high birth weight babies, whereas in the old days those were healthy big babies. Today, those are a mixture of healthy babies and babies who are products of diabetic pregnancies and/or obese pregnancies who have a much greater risk. So we have a kind of J-shaped curve or as my colleague Kent Thornburg says, a Nike swoosh pattern in current populations.

Now, birth weight was a crude surrogate used to indicate poor fetal growth, very crude. In fact, a more appropriate assessment would be looking at asymmetric features of intrauterine growth restriction. In fact, those features are illustrated in these two babies. On the left, the baby is normal. On the right is a growth-restricted baby. That includes a decrease in weight relative to height, so the baby is thin. We know from obstetric literature that when there is impaired nutrient or oxygen to a fetus, there's a stereotypic response, decreasing the blood flow to the organs and abdomen below the diaphragm causing decreasing abdominal girth, and shifting blood flow to better protect the heart and the brain, so-called heart/brain 'sparing'. This of course is essential to fetal survival.

The important thing is that this pattern of asymmetric growth restriction can be present at any birth weight. It's more common in lower birth weight, but you can imagine a baby that was destined to be nine pounds is born at seven pounds because of impairment of normal growth in that baby. That's important to recognize in thinking about what we really care about as indicators of poor fetal growth.

I told you about DOHaD. I told that we use the term fondly but apologetically. It doesn't roll off your tongue easily. The first thing I thought about when I heard about it was this little guy, "dough head". In fact, he's not so inappropriate as an icon because he has a relatively large head. Clearly he had brain sparing. And he's obviously got abdominal obesity, the quintessential central fat of the metabolic syndrome. So I've kept him. This is to just to quickly remind you that I'm going to talk about the metabolic syndrome-related diseases but there are many other diseases coming in current research, which are being related to early life exposure. Just to make you aware of that.

Now, what I'd like to do next is take you through pathways of nutritional programming. I've selected three pathways. They are in fact applicable to any of the three major programming forces that I introduced: undernutrition, high-calorie malnutrition, and psychosocial stressors. But again, because the information is, there's more depth in the undernutrition field, I'm going to use those as examples and then later on we're going to talk about maternal overnutrition, obesity, et cetera.

First is the altered organ structure that's permanent. The second is the altered regulatory system functions that occur during development and then are permanent and postnatal life. And finally, how these two can interact in postnatal life to amplify the risk of disease. This just takes you back now to looking at a single individual across a life course and focusing on fetal undernutrition. Altering the birth phenotype, creating vulnerability modified by what happens in the postnatal environment, and that then determines whether you get overt metabolic disease, and again, focusing on the metabolic cluster.

When you think about organ structure being altered, you have to think about, in utero, the trajectories of organ development. This just shows you those trajectories for several organs. Again, as I mentioned earlier, the brain actually goes all the way up to teens. The pancreas has both prenatal and postnatal phases. I'll focus here on the kidney, which in terms of forming the kidney functional unit, the nephrons, the filtering units, that all takes place before birth. It's done by 36 weeks. The important point is that you cannot form any new nephrons after 36 weeks. Now, what I want to do here is give you a 30,000-foot overview of specific organs and how they are affected by maternal undernutrition and how those effects might play out in postnatal life in terms of metabolic syndrome features or entities.

The kidney, we know with undernutrition has decrease in the number of nephrons. We've known for decades that that's associated with an increase risk of hypertension and kidney disease. In the pancreas, we know from animal studies, there are decreases in the number of beta cells in the islets, the insulin-secreting cells. That of course would impact insulin secretion, reduce the insulin secretion capacity in later life.

Muscle mass turns out to be incredibly important in terms of energy and glucose metabolism. Typically with undernutrition, there is a decrease in muscle mass. You see this in IUGR babies with small arm circumference, for example. We know that that is associated with reduction in basal metabolic rate because the muscle is such a powerhouse of metabolism. We know, and this is easier to show in animal studies, that reduced muscle mass can reduce exercise capacity. It can even reduce the desire to move. And importantly, we know that reduced muscle mass decreases insulin sensitivity because it's a huge organ in terms of its mass and it's a site of insulin receptors which take up glucose. So just decreased muscle mass alone increases insulin resistance. In the heart, the myocardial myocytes, decreased number and this can pose, it's been shown in animal studies to pose a risk for heart failure in later life.

The liver, I can just barely scratch the surface, but we know the lobule numbers are decreased, cell numbers are decreased, and this has powerful impacts on lipid and protein metabolism. In the vasculature, the structural density of the microvascular is reduced, that correlates with higher vascular resistance, and therefore, hypertension. Last but certainly not least, there are anatomical changes in the brain that have been documented in both under- and overnutrition with increase in appetite and hyperactivity of the hypothalamic pituitary adrenal axis and cortisol.

Again, just a big picture view of how when an organ is not formed well early on, that you see reduced functional capacities and disease consequences of that in later life. That's just to briefly remind you of those forming nephron units in the kidney. During development they form in concentric layers. So if you slow that progress with nutrient deficits, you reduce the total number of nephrons that can form. We know that reduction in nephron number can occur in human babies who have experienced intrauterine growth restriction. What you can see here in the orange are those with intrauterine growth restriction, reduced number of nephrons -- reduced number of nephrons in most of those in this small study. Very well-documented in animal studies, this phenomenon of reduced nephron number. Very difficult to show in human studies because you need, they have to be autopsy studies and you have to have a whole kidney to study. This is something that, going forward, the need for non-invasive measuring of number of nephron units is a critical need.

Now, I'm going to leave you with that for now, we'll come back to that. And I want to tell you about the altered regulatory system functions that are influenced by developmental programming. Again, I'll give you a general overview of what those are and then I'll focus down on energy balance and tell you about what David Barker called the "thrifty phenotype."

What we know is that with developmental programming, this whole set of systems that determine our, that sense the environment and determine our response to the environment around us are permanently altered. That includes stress hyperactivity. That means that in response to a sudden noise, in response to socioeconomic stress, this system responds in a hyper-reactive way, you get more cortisol that you otherwise would, and that has health consequences. The same is true for the sympathetic nervous system, it is hyperactive in developmentally programmed individuals and it's both hyperactive in the frequency and the magnitude of its responses.

Now, these are systems that in evolution were designed for acute stress. They act, they do their job, they protect the blood pressure, they get you on the run, fight and flight, but then they go away. In this case, we're talking about a situation where they're programmed chronically to be hyperactive. These are systems where the associated hormones cause increase in oxidative stress. They cause increase

in inflammatory responses. And these two are interactive, one causes the other. We know, also associated with developmental health programming is immune hyperactivity. There's some fascinating information about how that occurs. Some of it relates to the gut microbiome, but it's associated with hyperactive systems which can increase risk for asthma and allergies.

And finally, very, very importantly for metabolic disorders, changes in energy homeostasis. So handling fat, glucose and insulin metabolism, and appetite regulation are all affected. Again, this particular series is true in all three of those major programming forces that we've talked about earlier.

Now we go back again to David Barker, who in 2001 observing both in his human studies as well as ongoing animal studies what he called the "thrifty phenotype." He described this as a fetus which adapts to nutrient deficit by permanently increasing energy utilization efficiency. Okay, let me find myself again here. Increasing energy utilization efficiency, which means that for a given calorie intake you put down more tissue. An increase in appetite-promoting behaviors and circuits in the brain. These would for the most part be promoting survival of the fetus in utero.

On the other hand, when you look postnatally, these permanent adaptations by the fetus, while they may enhance postnatal tolerance to famine and nutrient deficit, they clearly impair the ability of the organism to handle nutrient excess. One of the best examples of this has been described as the rural-to-urban transition. For example, in India, villagers from rural areas had very sparse diets, were very thin, but they did not develop disease, at least not metabolic disease. And when they came, migrated to the city for economic reasons, we have been seeing and continue to see epidemics of metabolic syndrome types of disorders.

If you think about, then, what happens if you were born with an in utero program to have a thrifty phenotype and you were born with this phenotype, you then come into the postnatal environment and there's a reasonable amount of food and it doesn't even have to be rich food. Your increased appetite is going to obligate you to eat more relative to your body weight even if you're born small, and you will undergo accelerated growth. That is, you will cross centiles of growth. And this is a really important concept. Let's say you're born in the 20th percentile of normal birth weight, but because of this entity, this phenomenon, even without developing obesity, you move into the 50th or the 60th percentile. You've crossed centiles and this has increased your body mass to a point that it's bigger than it was thought to be or designed to be in fetal life.

And so, at this point, David Barker asked the question, well, how are these individuals growing? What's the impact of this thrifty phenotype and the impact of accelerated growth on later disease? For this he went to probably the most valuable epidemiologic treasure in the world, and that's the Helsinki cohorts in Finland. He teamed up with a group there that had fabulous public health records kept in the 1930s and 1940s. They had annual child growth data beginning at birth and going through 15 years. And they had socialized medicine with formularies where they could look at hospital records. What they were able to show is that accelerated postnatal growth enhances the risk of chronic disease in later life. This is one of the postnatal stressors that increases risk of disease.

This is one of their first publications, and this is for hypertension. This is a Z-score format. So the overall cohort, this is over 8,000 individuals, the average of their mean for each age would be at zero – these are plotting BMI, weight, and height -- you can see the Z-score score means that the mean is plotted as zero and the group of interest which is 1,400 individuals who developed hypertension as adults, they're now looking back and saying, "Well, how did they grow?" You see that based on this type of presentation that they were born small and they were also both in weight and height, but weight more than height, they're also thin. They grow fairly normally, statistically, through early childhood, but starting at about five years of age you can see that they begin to grow at an accelerated rate and you see the increase in all three of those indices of body weight. They are not obese, but they're growing at an accelerated rate and the only way that you can see that is if you're tracking their weight.

Now, they did something else with a similar group. They again looked at those who were hypertensive, but they divided them and note into those who had only hypertension and those who had both hypertension and diabetes. And again, you see a different early growth pattern. We don't know the reasons for the difference in the growth pattern. Was it something that happened in utero or was it in postnatal life? What we see is that, again, they're born small. But beginning about at the point of accelerated growth, you can see that those who developed hypertension only, had a less-sustained acceleration and they leveled off at very near the average level for body weight. I'm just plotting body weight here, but the other factors look similar including BMI. But those who also developed diabetes had this continued acceleration of their growth. Again, they would have not been overtly obese, in this cohort of individuals who were born in the 30s and the 40s.

Basically, what these studies tell us is that accelerated growth in postnatal life is a risk factor for metabolic disease but it's especially at risk if you're born small, and this just is integrating the two phenomena, and that is birth weight here and BMI in later life here. You can see that you increase your risk if you're born small for a full metabolic syndrome. It's much lower if you're born large. If you're born large and stay small, that's the best place to be. If you're born small, it's very bad to also have accelerated growth in postnatal life. Again, an interaction of what was set up in prenatal life and what you were exposed to in your postnatal life. Again, those accelerated growth patterns were not associated with obesity in children. You could not identify those children unless you were tracking their weight.

This just to show, this is for coronary disease but you can show similar things for diabetes, for obesity, for hypertension. These are all individuals in this graph who were born thin in this case, men born thin. They're showing that if you're born thin but you did not have accelerated growth, that you were much protected at least until you got into a low socioeconomic status. So we're looking at the adult socioeconomic status in these individuals. If you were thin and had rapid growth in childhood, again, you were relatively protected if you were in a high socioeconomic status. But look what happens as you go into the lower socioeconomic strata. You are at increased risk of adverse impacts of poor socioeconomic status. With the undernutrition setting, and in many cases, with the others as well, we know that vulnerability and risk of disease is exacerbated if there is ample food, if there is accelerated postnatal growth, if there's low socioeconomic status.

So finally, then, putting these two together and talking specifically about how kidney nephron number interacts with the thrifty phenotype to enhance the risk of kidney disease. This of course is very important because as all of you know, virtually all of the components of metabolic syndrome are risk factors for chronic kidney disease.

So, low nephron number. What is this contributing to the risk in low birth weight offspring? We've known for decades in nephrology that there needs to be an important relationship between your body mass and the number of nephrons you have. That is your body mass determines what you eat to maintain it, and what your excretory load is that you're putting on the kidney. The number of nephrons determines how you handle that excretory load without biologically adverse consequences. When that mismatch occurs to a significant degree, that creates a substantial risk for developing high blood pressure and kidney disease.

If you look at it from this format, if you have the combination of the thrifty phenotype together with the reduced number of nephrons in the setting of asymmetric growth restriction, you're going to have accelerated growth, increase your body mass, but your number of nephrons cannot change, it's fixed at a low excretory capacity. You have therefore created a mismatch between your body size and the number of nephrons. That occurs even if you don't have obesity. If you do have obesity, and the likelihood if we put the undernutritionally programmed individuals in our current culture, they will also

get obesity that just makes matters worse and increases the risk for hypertension and chronic kidney disease.

We know how that occurs. We know that mismatch creates increased pressure. These are glomeruli, the filtering units of the kidney. There it is, sorry; I'm not very good at this. These are glomeruli. And these are the capillaries, the filtering surfaces within the glomerulus. The high pressure that occurs in the kidney with this mismatch begins to damage the capillaries. And so, you can see here beginning damage. That progresses until that nephron and that glomerulus drops out altogether from fibrosis and damage. Then the remaining nephrons are put under still more pressure. They have to work harder, have higher pressure to get out the daily excretory load.

And so, we see progressive nephron loss. Fewer and fewer functional nephrons are remaining, and this defines clinical progression of chronic kidney disease. In that process fairly early on we'll see hypertension, we won't actually see the creatinine increase early. It's a later finding, something very important to be aware of. We also know that with very minimal levels of chronic kidney disease, there are specific factors associated with high cardiovascular risk imposed by that state. And without any interventions, we're talking about end-stage renal disease and dialysis.

And so, it won't surprise you to see that if we looked at birth weight and the odds ratio for, in this case, end-stage renal disease, and we don't have nearly enough data about this, you can see if you ignore diabetes for a moment, you can see the inverse relationship between birth weight and end-stage renal disease. This is a modern population. This is a young population. They grew up under conditions that we see today with high calories and processed foods. What you can see is in that high birth weight range, where now they're not just healthy babies but also babies of obese and diabetic moms, look what has happened in terms of the risk of end-stage renal disease due specifically to diabetes. This is data that was published in 2000, and you all know what has happened since then. So you can imagine what we're going to be looking at and the task before us in terms of curbing this.

I want to move now to what I know is of special interest to all of you. That is not only the transgenerational transmission of disease risk, but the fact that the most urgent example of that, in fact, is mom's obesity and excess energy states prior to conception that affects the future baby. I'm going to just let you look at this slide on your own because I don't want run out of time. What I'm going to focus on now in terms of transgenerational transmission is up to now we've been looking at forces that are acting at the time of this pregnancy from conception onward that are affecting the health and the metabolic condition of this offspring. But now we're going to move back before that and look at what we've learned about things affecting mom's general nutritional health before she becomes pregnant. So things that happened before the pregnancy happened before conception in this period that influenced the health of this future offspring.

Again, I'll let you look at again on your own. It's very important. But I want to move on to the fact that the most urgent example of this now is maternal obesity and the instances of excess nutrition during pregnancy, pre- and during pregnancy.

Coming back then to both of the nutrition forces which drive developmental programming, with high-calorie malnutrition, we include maternal obesity, including obesity before pregnancy. We include maternal high-fat diet. As you know, high-fat diet in our culture is more than just high-fat but right now it's coded this way. It also includes gestational diabetes. And it probably includes from the HAPO study, as many of you will know about, levels of maternal glucose that are not overtly causing gestational diabetes but are associated with impaired gestational outcomes. That category we know causes abnormal fetal growth. It is typically too fast, as in macrosomia. It is asymmetric. The macrosomic state involves excess fat deposition by the time of birth. It involves altered limb, or ratios, something that has just been recently learned. So we have much to learn there. But it creates the

similar vulnerability in the offspring, an altered phenotype which increases the risk of later disease, and I would say, more even more powerfully than the undernutrition pathway.

Just to give you some data. This is early data showing relationship between maternal body mass index and odds ratio for obesity in offspring. This has been corrected for other aspects of disease to show the increased risk with high maternal BMI. Just to look in overview at some of the consequences of maternal obesity, also true of gestational diabetes for offspring, there are important obstetrical risks. Importantly, some of those obstetrical risks can cause slow fetal growth in offspring as well as other features. And in the offspring, we know there can be large for gestational-aged babies/macrosomia. We know there can, because of complications, be intrauterine growth restriction. We know that these babies have shown to be insulin-resistant in cord blood, so very early insulin resistance. They have excessively fast growth as infants, and they have early onset, meaning in childhood, obesity, hypertension, and diabetes. And of course this continues into adulthood and provides a lot more time for those entities to translate to clinical disease.

Just to give you a hint of research that's ongoing in this area, my colleagues at the Primate Center have a monkey model of high-fat maternal high-fat diet obesity. They show abnormalities in the fetal liver, it's full of fat. It's inflamed and shows increased oxidative stress markers. The neonates have a fatty liver disease phenotype. Although there's less fat, there's fibrosis and inflammation.

The brains of the fetuses are inflamed. They can show changes in the neural appetite circuits and the reward center set points related to appetite and satiation with food. Strikingly, the postnatal behaviors include increased appetite. This is a consistent thing across animal and human literature. They can show extreme preference in these programmed monkeys for high-fat, high-sweet/salty snacks and a real dedication to hoarding those snacks.

There is accelerated infant growth rate just as in humans. There is early excess adiposity, as early as age six months in the monkeys, just as in humans. There is early-onset puberty. And strikingly, there is increased anxiety behaviors in females and aggressive behaviors in males.

We still have a lot to learn. We're going to skip that one, but you can see what's coming. I wanted to point this one out because I think this study is striking and it's in humans and it's very important to the concept of biologic embedding of health disparities. What it says, this is a study looking at ADHD scores and executive function index. For executive function, the higher the score, the lower the executive function. What it's showing you is based on a mother's pre-pregnancy body mass index, obese moms -- although not overweight -- obese moms' offspring at about, I think this is six to seven years of age, have increased ADHD scores and reduced executive function scores. Again, ongoing studies that we need to know a lot more about.

In summary, then, there's a double burden of malnutrition, if you will. One of the big differences is that with high-calorie malnutrition, onset of clinical disease is occurring in childhood. Rapid growth occurs earlier, rapid or early onset of disease. What that means is that when we have young girls, because their mothers were obese, they become obese as children before their reproductive ages. They bring that into the pregnancy and we now have the set up for transgenerational transmission of obesity, diabetes, hypertension, dyslipidemia, and atherosclerotic disease.

This is looking at maternal pre-pregnancy BMI. Metabolic syndrome, full-blown metabolic syndrome in six-year-old offspring, according to maternal BMI, 22% in obese moms. So again, a profound and urgent issue. We're increasing maternal BMI. This is old data. It doesn't begin to show how high it is now. The most recent data that I get is from 31% maternal obesity in Caucasians to 49% in African Americans. Again, it's the worse the lower the socioeconomic status. So again, profoundly disturbing information.

I'm going to wrap up there and I will just focus on two other things. This is our Bob and Charlee Moore Institute for Nutrition & Wellness. We are focusing on young women in adolescence, in college, young adulthood, before conception, during pregnancy, and lactation. And then focusing on young families to get infancy and early childhood as our target audience, I think there are a lot of things that need to be discussed in terms of how we deal with patients, with clients. We need to know obstetric histories in order to identify at-risk individuals. We need to think of babies, children, moms and families as at risk. We need to track infant and childhood size and growth rates because it's the only way we can tell what's really happening in terms of risk.

I look at individual patients and look at centile crossing in terms of what percentile they're in, in terms of their body weight now versus at birth. The children that are at risk need to be monitored in ways that are not routine for pediatricians for the most part, including blood pressure and growth tracking. And we can do this in other settings as well. At the Moore Institute, we're trying to work on referrals for food insecurity, referrals for obesity, referrals for nutrition education. So thank you so much, and I'll stop there.