Discussion

Ricardo Rueda, MD, PhD

Dr Mardones: Dr Campoy, the results you presented on the effect of arachidonic acid on visual acuity were amazing. Would you comment on those specific results? How many women were involved?

Dr Campoy: These results are from the NUHEAL follow-up study, granted within the EARNEST EU Project framework. The recruitment took place from 2002 to 2004 in three EU countries (Germany, Hungary, and Spain). A total of 312 women were randomized into four groups. One group received 500 mg/day of docosahexaenoic acid (DHA) plus 150 mg of eicosapentaenoic acid (EPA), a second received 400 μg of 5-methyl tetrahydrofolate (5-MTHF), a third received both supplements, and the fourth received placebo. This supplementation began at 20 weeks of pregnancy and continued until delivery, and the mothers received follow-up during this period. After birth, the children received follow-up and still do today. They are 9.5 years old.

At 5.5 years of age, neurodevelopment in these children was examined using the Touwen test and cortical visual evoked potentials (cVEP). The NUHEAL trial reported no differences in the neurological outcome of children at 4 years and 5½ years between children born to mothers receiving fish oil supplements and those who did not. However, better neurological optimality scores in children at 5½ years were seen in those with increasing DHA levels in cord blood. Moreover, children whose mothers had higher DHA percentages in erythrocyte phosphatidyl-ethanolamine (PE) at delivery were more likely to have a Mental Processing Composite (MPC) score of the Kaufman ABC over the 50th percentile at 6.5 years. Results from the VEP examination at 5½ years demonstrate that DHA and particularly arachidonic acid (AA) concentrations in mother's phosphatidyl choline (PC) in red blood cell membranes at delivery determine the visual acuity and retinal maturation in their children at 5½ years of age.

Dr Mardones: How many children participated?

Dr Campoy: If I remember correctly, we have about 170 NUHEAL children participating at 5½ years of age. At the beginning, we saw significant correlations between AA and the different measurement points of the VEP, which we did not believe. However, reviewing the literature, we saw that Dr Sheila Innis and colleagues in Canada also demonstrated that AA is a major factor influencing long-term visual acuity, although they examined this in younger children. So, for us to

see these results in children at 5½ years of age was really interesting. The logistic regression performed in the VEP results of the NUHEAL children demonstrated that after taking into account all of the potential confounders, only mothers' AA in PC in red blood cell membranes at delivery remained, until the end of the analysis, as the most significant factor influencing long-term visual acuity.

Dr Godfrey: Just to clarify, was this looking into the trial data in an observational fashion because AA was not part of the intervention?

Dr Campoy: It was not part of the intervention.

Dr Godfrey: In those studies, were you able to control for the mother's IQ?

Dr Campoy: Yes, so it was surprising that AA was the major factor influencing visual acuity in the 5½-year-old children. The children born to mothers who had a lower level of AA were at a 7.7 times increased risk of having lower visual acuity and retinal maturation at 5½ years of age. This is an important result. We are now processing all these data.

Dr Steckel: My question applies to Dr Campoy's paper, as well as to several others. I did not get a good sense of what the study populations were. I have a sense that they are mainly in rich countries. Is it true that the populations are pretty well-off as a whole? Do we not have large numbers of poor populations or low-income groups that can be studied?

Dr Campoy: Do you mean in the data from the NUHEAL study? These mothers were recruited at three centers in Hungary, Munich, and Spain. The preliminary idea was that mothers in Hungary would have a low intake of fish and so DHA, while those in Germany would have a medium intake and those in Spain a higher intake. However, it was found that the women in Germany and Spain had almost the same intake of fish and those in Hungary a lower intake, but no differences were seen between them in social class or socioeconomic status.

Dr Steckel: My question is about some of the effects you are trying to measure. The statistical significance is a function of the variance of the explanatory variables, and the study population is fairly homogeneous. You will get high standard errors. It would prove useful to involve some groups that are very stressed. The Gambia study was mentioned here, but I think many populations around the world would give us more extremes and variation in the data, which would affect standard errors.

You could see interactions if a person is deficient in protein, for example, in an environment in which several micronutrients are deficient. The consequences could

differ significantly, so studies of populations that are generally in good health except for fish or omega-3 fatty acids would differ from those in populations that are highly stressed.

Dr Campoy: All the mothers are assessed prenatally for dietary intake, and we performed a food questionnaire assessment at 20 and 30 weeks. All of these data are published [Franke C et al. *Br J Nutr.* 2010;103:1648-1656]. We planned the study to see the differences in intake between the three countries, but not the social differences. However, mothers were asked about their socioeconomic status, type of job, etc. The study included mothers in all groups with a low, medium, or high intake of DHA. So, within the DHA-supplemented pregnant women groups, some mothers probably had a higher intake than recommended after the supplementation, but no significant effects were demonstrated after supplementations even higher than 2 g/day of DHA.

Dr Steckel: I suggest that it is perhaps useful to partner with people who work in the developing world. A number of interesting studies are going on, such as one in Ecuador in an Amazon hunter/gatherer population. This population exists under an extremely high disease level, and they are highly stressed. If you could get some of the measures you are interested in into that study, it would prove useful. It is hard to work in the developing world because of the costs, travel, and so on, but some good things could come out of that.

Dr Campoy: Do you know whether the researchers have the structure to measure these kinds of things?

Dr Steckel: I do not know, but they have an elaborate lab setup. They are bringing people out of the jungle and doing blood tests and several metabolic tests. If you are interested, I can give you contact information. I think some good studies are going on in Bangladesh and other countries that stretch the whole idea of the environment. Consider the Tsimane Health and Life History Project, an effort in the Bolivian Amazon directed by Michael Gurven, University of California at Santa Barbara, and Hilliard Kaplan, University of New Mexico.

I also think that, in some sense, the participants of this conference are the appropriate audience for people doing this kind of research because the consequences of deprivation on cognition may be much greater in the developing world than in the rich industrial world. I believe these people in the developing world are those we want to treat. This is where in the next 10, 20, or 30 years we will see a crisis of economic development because of the cognitive or metabolic limitations that arise from pregnancy onward. These are people Abbott Nutrition can help with

nutritional supplements. This population is huge—hundreds of millions or a billion people who live under conditions of extraordinary deprivation. We would want to know how they respond to infections.

Dr Campoy: In fact, the EU Commission asked the NUTRIMENTHE Consortium to produce a report at the end of the project concerning the important impact of nutrition on brain development and mental performance, which will cause exponential damage in the malnourished populations from developing countries. This hereditary damage will determine a relevant qualitative increase of the gap between developed and undeveloped countries, which will separate the latest definitively, even when the economic situation improves. We should take actions as soon as possible to give the developing countries an opportunity for the future.

Dr Mardones: Dr Atkinson, I was surprised that in most of your studies birth length was not considered as an outcome when you provided or supplemented vitamin D or calcium during pregnancy. Would you comment on that, please?

Dr Atkinson: I only can comment from my own personal experience. Unless we have a research assistant standing in the delivery room 24/7, it is difficult to get this information. In our longitudinal birth cohort study, if we are advised of the infant's birth, we measure the length using a length board within 24 hours. However, sometimes such measures are not possible, because mothers go home within 6 hours if the delivery is full term.

Dr Godfrey: In our observational studies, we have measured crown-to-heel birth length, and found it is a challenge to get accurate measurements. I think the ones we have obtained are good. Generally we do not see higher vitamin D status associated with the greater crown-to-heel lengths at birth, so we think it directly affects mineralization more than linear growth per se. Perhaps postnatally, you might see an effect on growth plate that manifests later on, but when we followed up at age 9 years, the children with lower vitamin D status are of the same height as those with a higher vitamin D status, but have reduced bone density and content.

Dr Atkinson: In fact, in the fetal measurement study, no difference in femur length was noted. Rather it was a significantly greater splaying index and metaphyseal cross-sectional area (a pattern of femoral growth that resembled childhood rickets) measured by 3D ultrasound in the fetus at 19 weeks of gestation that was associated with vitamin D deficiency in the mothers [Mahon P et al. *J Bone Miner Res.* 2012;25:14-19]. I agree that we do not have sufficient evidence to say that maternal vitamin D status influences length per se. However, your question was, why do we not measure it? In many cases, it is just impractical in the setting.

Dr Rueda: Dr Atkinson, there are recent reports concerning bone and muscle as a functional unit. In fact, results from Dr Cyrus Cooper in the University of Southampton describe how building bone mass and muscle mass early in life is perhaps an ideal way to prevent osteoporosis and sarcopenia later in life. In the future when we design studies in which we have an ingredient such as vitamin D that might affect not only bone but also muscle, should we consider bone and muscle as a functional unit and try to evaluate the effects on both functional outcomes together?

Dr Atkinson: This is a reasonable proposal, although relevant data are limited as of yet. In the Mysore Parthenon Study that was just published [Rishnaveni GV et al. *Am J Clin Nutr.* 2011;93:628-635], children born to vitamin D-deficient mothers (defined as serum 25OHD <50 nmol/L) had smaller arm-muscle area (thus smaller muscle size) at 5 and 9½ years.

Dr Godfrey: I think with appropriate training and research staff we can take good reliable measurements with a dynamometer in children as young as 4 years of age. I think that going forward, it is important to prove a link between nutrition and sarcopenia. In our studies of elderly populations, it is closely linked with frailty and a whole series of adverse outcomes. We do see associations between size at birth and later muscle mass and grip strength. How those come about we do not know.

Dr Rueda: Dr Campoy, while you mentioned some results about the effect of long-chain polyunsaturated fatty acids on cognitive development in children, results reported in the literature still are controversial. What is your opinion about the potential influence of desaturase polymorphism on these results? Today we know that conversion of precursors (linoleic and linolenic acids) into AA and DHA is not similar in all children, and consequently, desaturase polymorphism is perhaps a main factor influencing those clinical results.

Dr Campoy: I am not saying that nutrition, and specifically AA or DHA, will become the main and unique factors implicated in general neurodevelopment, but they are very important. These results from the NUHEAL cohort and those emerging from the NUTRIMENTHE Project show us that an important relationship between prenatal and postnatal nutrition and brain and behavior development do exist. Moreover, these studies point out that we probably need to define more detailed and focused procedures to measure brain development in each stage. More well-designed studies are needed to demonstrate in which specific areas of the brain a nutrient is needed for optimal development and how this depends on a critical window. We could determine how a deficiency will affect the individual, so we can assess the structural changes produced in the brain and the clinical or the neuropsychological symptoms.

Discussion

In the case of IQ as a sole parameter to evaluate cognition, it is not so clear. The measurement of the IQ in a child will only offer us a very general score of intelligence. From my point of view, IQ is only one of the parameters needed to evaluate cognitive development. To define a child as more intelligent than another, it is necessary to explore many domains. The combination of them will offer us a real score. Even more, the IQ of a child is the result not only of accretion of different fats in the brain, but also the addition of many other nutrients and factors, such as fatty acid desaturase 1 (FADS1) and FADS2 genetic polymorphisms.

The ALSPAC (Avon Longitudinal Study of Parents and Children) study demonstrated that fish intake in the mother during pregnancy is related to offspring IQ, but no associations with maternal blood fatty acids after adjustment were found. Moreover, those children that were homozygous for FADS2 (GG) and were not breastfed had a lower IQ, even below 4 to 6 points with respect to those who received human milk.

We probably will need to include these genetic polymorphisms in future studies to define more precisely the role LCPUFAs (long-chain polyunsaturated fatty acids) have in brain development and also to explore parameters other than IQ, combined with new technologies, in order to measure the real effect of these nutrients on brain development. These new approaches would permit us to establish dosages and critical windows for individualized prevention and therapy.

Dr Koletzko: I fully agree that the effect of the fat polymorphism on both fatty acid levels and plasma, red blood cells, and tissues is a large effect size. In our recent study on the German and Dutch child cohorts, we found large effect sizes, particularly for neonates for AA, but also for DHA. Three percent of DHA variation is explained by these polymorphisms. Perhaps you think that a 3% variation is not large, but if you look at the impact on outcomes, the effects are large. For example, in a European survey, we found that the people with the less common type had only half the risk of dermatitis and allergic rhinitis compared to the people with the other type.

Dr Campoy described the results of research indicating a marked effect of breastfeeding on cognitive development in children at 8 years of age. Children who were breastfed in that study had an IQ advantage over those who were not breastfed. We have seen that in many observational studies from all over the world over the years. We are not sure how to interpret this, because the choice to breastfeed is associated with socioeconomic status, education, and so forth.

I think this study is the first one that gives us confidence that breastfeeding is really causal because if you have the less common variant for fats, if you are less able to

synthesize high AA and DHA, then breastfeeding provides an additional 4.3 IQ point advantage at age 18. That is one third of the standard deviation, which supports the concept that the lipid supply with breastfeeding is causal for cognitive benefit.

My conclusion is that if we do a study on fatty acids, whether it is a cohort study or intervention study, and we have a sizable number of subjects, we must make sure to tier type the subjects.

Dr Rueda: Dr Cunningham-Rundles, you described the importance of the balance between T-helper cells 1 and 2 (Th1, Th2) and the importance of this balance during immune development on promoting an aggressive response against infection or a tolerance response. On the other hand, I believe that the placenta, and more specifically the decidual cells in the placenta, are typically Th2. That is one of the reasons why the mother does not reject the fetus during pregnancy. Is it possible to modulate the Th1 and Th2 balance on decidual cells in the placenta during pregnancy? Also if we modulate that balance, do we have any risk promoting a higher incidence of abortion in those pregnancies when we try to promote a Th1 response to decrease the risk of developing allergy (a typical Th2 response) later in life?

Dr Cunningham-Rundles: I think that is possible. Certainly anything we do that changes cytokine balance we need to do in the context of perinatal life at an appropriate point and in the postbirth period. One of the big mysteries is exactly when to do this intervention because this balance toward Th2 in vitro is clearly beneficial. It just is not the same after birth.

Dr Poston: You mentioned effects of vitamin A and folic acid, but not of vitamin D.

Dr Cunningham-Rundles: We are interested in working on this with children who are likely to have allergic airway disease, but we do not have any data yet.

Dr Godfrey: I would like to follow up on Dr Steckel's points with a question to Dr Cunningham-Rundles. If you look across the developing world, susceptibility to infection and high rates of infection are important factors. In the Gambia studies, one of the seminal papers was published on mortality following birth in hungry versus not hungry women. It showed a delayed effect on mortality—specifically on mortality from infectious diseases after the age of 15 years—pointing toward some perinatal effect on immune development. Does any evidence show what the nature is of the specific exposure or the mechanism that might train that effect?

Discussion

Dr Cunningham-Rundles: I do not know of anything. However, the impact of early undernutrition on thymic development, which manifests itself in early adolescence, is perhaps relevant.

Dr Koletzko: The original hypothesis was to affect undernutrition because it was related to birth in the season when caloric supply was low. I was recently in a discussion that I found quite stimulating that proposed this might relate to a change in early microbiotic exposure because it was a different season of the year and different crops were available.

Dr Godfrey: My recollection was that the researchers looked at subsequent studies for effects on neonatal thymic involving leukocyte responses and found very little, suggesting that perhaps it was postnatal effects from the prenatal nutrition.

Dr Cunningham-Rundles: I think that is true. I am a little hesitant about that study because I have seen some attempts to reproduce it. It seems to occur in only one environment. However, it does seem likely that it is an environmental event, and I think this is a reasonable way to look at it. I only mentioned the study because I think it opens the door to the likelihood that specific areas provide exceptional challenges and that the needs of development still are not understood.

Dr Miller: I would like to build on a theme that I have heard the last couple of days. Dr Koletzko, you talked about variation of normal nutrition, and then we discussed the range of normal. I keep seeing two important areas for us here. One is the rapid change in obesity and diabetes that we are confronted with in the context of evolution during the last decade or two. When we talk about the history of "normal nutrition," most of that was undernutrition, such as nutrition among hunter/gatherers.

Do we have the tools to even understand what public health issues we will face in the next 10 to 20 years given the rapid change we are seeing in what we think is normal nutrition and normal nutritional management? What can we do on the public health side of these issues?

Dr Koletzko: Someone once wrote, it is very difficult to make predictions, especially if they relate to the future. But you are right. The change that has happened in the last 2 decades is not easily paralleled by what happened in the previous 2000 years in terms of the changing body composition of mankind. Many people have speculated and written about the key factors, the triggering factors, and we could probably discuss the prioritization of key factors for the next 2 hours.

What do we expect to happen in the future? Clearly, the consequences of obesity such as the diabetes complex remain a key challenge. As a pediatrician, I particularly worry about behavioral challenges and changes in the immune response. We have seen an epidemic of allergic manifestations with the speed that nobody would have predicted.

The increase in allergic manifestations in China is probably yet to come, but if our hypotheses on hygiene and microbiotic potential and predictors are correct, then China probably will see an explosion of allergy such as Thailand is seeing right now. I am not sure what other people predict as the key challenges for the next 2 decades.

Dr Godfrey: An article written about 30 years ago looked at the range of disorders beyond those we have today, including appendicitis, which has declined over the 20th century, and argues that some powerful forces are at play now. The article predicted that although coronary heart disease is declining in westernized communities, we may soon see a rise in the disease driven by childhood obesity.

In fact, this was a topic at the United Nations' high-level special assembly meeting on the control of noncommunicable diseases in September 2011. According to the Non-Communicable Disease (NCD) Alliance, which includes a group of organizations concerned about diabetes, heart disease, and cancer, legislation is a way to control. Another group of us disagrees with that. We have argued to various government delegations that behavioral components to noncommunicable diseases are a part of the solution. The World Health Organization head for The NCD Alliance is also clear that without a technique for the development of such a component, the chances for halting these changes are not great.

Dr Poston: We have some evidence that pregnancy is an extraordinarily good time to change behavior. Women are susceptible to health messages in pregnancy. For instance, women are susceptible to messages about reduction of alcohol intake during pregnancy in a way that is not possible in any other state. I agree with Dr Godfrey that pregnancy is the time to start.

Dr Riley: Dr Poston, do we know that women are perhaps susceptible during pregnancy and do we know that they maintain that lifestyle after the pregnancy?

Dr Poston: Those studies are in process. Intervention studies are looking carefully at whether women maintain that behavior subsequently, so 6 months postpartum, we will try to find out whether women can maintain these behavioral changes—physical activity and diet. Dr Abrams also will address the potential of behavioral

change affecting the postpartum period and weight retention. Some early evidence suggests that these interventions may have long-lasting effects.

Dr Riley: I was at a conference presented by Dr Atkinson in which a researcher from North Carolina brought up the fact that in the United States only 50% of pregnancies are planned, and that we probably have a chance to make an impact when the pregnancy is planned. If the pregnancy is unplanned, the women may not want to make behavior changes. I do not know whether you have looked at that in England or in any of your other studies.

Dr Poston: We have not.

Dr Catalano: Many issues exist relating to outcomes among women with preexisting diabetes who are planning a pregnancy. This is not something subtle that will happen in 30 years; it is about an increased risk of miscarriage or congenital anomalies. In studies, even in Scandinavian countries, we have seen an effort to improve glucose control prior to a planned pregnancy because of the increased risk of type 1 diabetes in this population. However, the ability to have women with pre-existing diabetes see a physician in order to improve glucose control has not been particularly successful. In California—Dr Abrams, you may want to comment—the Sweet Success program has not proven very successful in enrolling women prior to a planned pregnancy, even though many women are aware of the short-term risks. I believe that programs, even for those women who are planning their pregnancy and know they have a disorder that could have a disastrous outcome, are not quite successful because many women think those bad outcomes will not happen to them. The patients I see, because the risk of having a birth defect is perhaps 5%, 10%, or 15%, think they will fall in the 85% to 95% category that will have a good outcome.

Dr Abrams: I suspect that psychosocial components do exist for women who did not plan their pregnancy and have other things they are working on in their lives, those who do not want to make diet and exercise, or whatever the intervention is, their highest priority. However, I believe that most women want to have a healthy baby, regardless of whether they plan their pregnancy or not, so I think we still have a potential hook to get to them that we usually do not have.

But that said, I believe we are a little shortsighted to think that pregnancy is the time to intervene. We probably need national campaigns to get people aware of the fact that pregnancy is really important. We have to go to the schools and get to children

with the message that pregnancy is an important time, so that it becomes part of our culture and does not hit them for the first time when they become pregnant. Right now, we are using childhood obesity as a way to try to push policy related to obesity, but I tell my friends who work only on childhood obesity that they are too late. I would love to see a groundswell of support for the idea that social policy should recognize the importance of the early pregnancy period. The message has to go beyond the clinical setting.

Dr Marriage: Dr Poston has said that pregnancy is a teachable moment, but we also have looked at research on how great the impact of prepregnancy weight is on subsequent obesity. In my view, perhaps the focus should also include preconception because some women are already obese going into pregnancy. The obesity problem begins in childhood, and it would be beneficial if we could help prevent women from entering pregnancy with excess weight.

Dr Poston: Much effort has gone into trying to teach young people about nutrition and illness, and on the whole, they are not interested. Evidence indicates that if we try to teach them in school, it will not work. We have to do something fairly drastic.

Dr Godfrey has a plan to implement this outside of the school environment to try and change their attitudes.

Dr Godfrey: The science of behavior change is not a perfect science, but it is moving forward beyond what is done for diabetes. We think that an opportunity exists with school children, not just to teach them some things because they often know “five a day” and that sort of information, but to promote behavior change and change attitudes beyond knowledge.

Dr Rueda: What Dr Koletzko mentioned about projects supported by the EU, such as EARNEST or EARLY NUTRITION, is perhaps a way in which we can interact with different communities, different sectors of the population, and promote guidelines that can contribute to that goal of changing behaviors in the general population.

Dr Godfrey: We are trying to get funding for a trial with 4000 school children a year to see whether we can or cannot change what actually goes into their mouths—not just in the days to come, but in the months and years to come—and whether we can change attitudes about physical activity and future pregnancy. It is the sort of question we feel needs an answer.

Dr Abrams: I hope it works, but it is also important to mention that we can try to do

this person by person or we can face the reality that we live in a tempting environment that makes it difficult for many people to avoid obesity. We need social policy changes that go beyond education and beyond behavior change, and those are very hard to make.

I think that governments are going to have to start dealing with social policy changes that create a more healthful environment. It seems unfair that children live in this environment that encourages obesity and then we have to try to teach them to avoid temptations to control their eating. That said, we need to work at both the individual and environmental level.

At the University of California at Berkeley, we have tried to make the food supply better for students. However, although students may say they want healthier food, the pull to fatty, sugary foods does not always match what they say. For example, our students may agree in theory that the government should subsidize healthier food and that the university should not encourage them to eat fast food, but they are not so sure when they realize that this means that they might not find high-fat foods in the dining commons in the middle of the night when they are studying and craving French fries and that the cost of those French fries might increase.

Dr Poston: Case in point, we have just carried out a survey in a deprived area of London where many fast food restaurants are located near schools. That is the environment. How do we negate having fast food shops around schools? We are trying.

Conference attendee: Do these obese children have problems with metabolism, energy, and enthusiasm? When I was younger, I could go 1½ days without eating and with a high-energy level. As we get older and go out shopping, we have to stop and get a cup of coffee and a doughnut because our energy is falling and we are not handling our sugar. Do these young people have a harder time getting the energy to do things because the events that occurred in programming make it harder for them to utilize their calorie resources? Are we up against a very big hurdle? This is not just about changing behavior, and it is not just about moving aside the doughnut shops. It is really about figuring out a way to bring the physiology of these young people back.

Dr Murray: I have worked in weight management with these children for 5 years. I am not convinced that many of the really overweight children had a good conception of either hunger or satiety. I always was impressed with the unstructured nature of their day, the way that sleep times and wake times and mealtimes and snack times blurred throughout the day. We sent a number of these children for

bariatric surgery. After gastric bypass surgery, they understood for the first time what I meant by satiety because the signal was so strong. However, I do not think that many of the overweight children are low on blood sugar and energy. That is not what is driving them. It is much more the psychology of appetite driving them than it is the hunger and satiety cues.

Dr Godfrey: As Dr Koletzko alluded previously, it seems that several different routes to childhood obesity exist. For example, one route is driven by maternal obesity and neonates' demonstrably high adipose tissue at birth. Another route is typified by the original Dutch family data from 1976, which involves undernutrition of the mother in which appetite stimulation in the child occurs through a mismatch route in which the developing fetus is triggered to think that it needs to eat whenever food is available. Such infants are thin at birth but then progressively become fat during childhood. I think this is a complex area, which has a number of metabolic routes to get to a common area.

Dr Poston: In fact, there are studies that show that the offspring of women who get obese in pregnancy grow up with a strange attitude toward satiety. They eat more. We and others have shown that the hypothalamus is structurally changed in the appetite regulator and pathways. In a follow-up observational study that Dr Godfrey and I are involved with, we are looking at satiety in children and relating it to associations with maternal factors such as maternal body mass index. We will do the same with children, because I think extraordinarily good evidence exists for early programming of appetite.