

## Early Life Exposures and Bone Health and Body Composition

This session was started by Prof Cyrus Cooper who discussed effects of maternal vitamin D supplementation on offspring bone mass. A vitamin D supplementation (1000IU/day) trial resulted in a seasonal effect, where vitamin D increased BMD and BMC and bone area in offspring of mothers treated in winter only. Furthermore, the supplementation also prevented decreases in maternal vitamin D loss normally seen in winter and spring. Dr Lisa Micklesfield discussed some preliminary findings from the Birth to 20 cohort in young South African adults using pQCT, which assesses volumetric BMD and bone geometry rather than the 2D areal density obtained from DXA. Cortical densities were found to be greater at the radius and tibia in females compared to males. Sex significant associations were present, and it seems that early growth as well as current body size determine bone size and density in this cohort. Dr Karin Moritz discussed the effects of alcohol consumption on offspring development. Very high rates of drinking in have been observed in young Australian women (who drink an average of 7 drinks a day at age 18-24!), and the average consumption is 2-3 drinks per day for women. Most pregnancies in this population are unplanned (50%) and high rates of drinking and high rates of fetal alcohol exposure have been observed in Australia. Karin wanted to understand whether exposure to alcohol around the time of conception can program metabolic disease. The rat study conducted showed that alcohol intake up until the time of conception caused lower growth rates, insulin resistance, increased body fat and decreased lean mass in offspring. She now aims to start looking at mechanisms, epigenetics, and mother's biology such as factors in utero that could cause these problems. Prof Susan Carlson discussed maternal DHA supplementation (600mg/day) on children at age 5, and birth weight was higher in the supplemented group. Fat free mass also increased in this group. No effect was observed for fat mass, however an association between gestational weight gain and fat mass was observed in the non-supplemented group only, suggesting a protective effect of supplementation. Prof Hazel Inski, standing in for Janis Baird, discussed the effects of sleep at age 3 years with fat and fat free mass outcomes at 4 years. Increased sleep reduced fat mass by 1.2kg/hour sleep.

Increased sleep also however decreased fat free mass. Less sleep was associated with higher BMI. Hazel cautioned against interventions at this point, as the full effects on body composition are still not well understood. Dr Caroline Childs discussed the effects of maternal Vitamin B status during pregnancy on offspring adiposity at 6 years. Low vitamin B2, B12, and B6 in pregnancy were associated with increased fat mass, But B9 was not associated. Further work is being done looking at potential confounders and causal mechanisms. Dr Robert Levitan looked at the effects of maternal sensitivity (how a mother responds to infant signals) and child BMI. The 7 repeat DRD4 (dopamine 4 receptor gene) allele and plasticity effects of this gene were examined by looking at the MAVAN study in Canada and the Generation R study in Europe. Greater effects of sensitivity on BMI in girls who have the gene have been observed in the Generation R study, but in the MAVAN study they only found this effect for boys. Low maternal sensitivity was associated with high BMI in girls in both cohorts, but further modifications were seen after considering the DRD4 gene. Dr Albert Koulman discussed lipid metabolism in infants and has shown differences in breast fed vs lipid fed offspring where high triglycerides in the mother's milk lead to high small triglycerides in the infant. High cholesterol in mother's milk lead to high large triglycerides in the infant, therefore lipid composition of breast milk affects how infants process lipids. Dr Arend Van Deutekom presented associations between birth weight and infant growth with energy balance behaviours using a systematic review. No association was found between birth weight and energy balance related behaviours (such as energy intake, eating behaviours, physical activity and sedentary behaviours). Generally there was insufficient evidence for the association of infant growth with energy balance related behaviours. He suggested that a shift in focus from birth weight to infant growth should occur, and shift focus from physical activity measurements to sedentary behaviours. Lastly, Simon Schoenbuchner looked at ethnic differences in pubertal bone accrual in Birth to 20 adults using pQCT. Simon wanted to understand if ethnic differences in bone could be due to differences in pubertal timing. Using SITAR curves to model his data, males were found to have a 9 month difference in age at peak height velocity. Site specific differences were found even after adjusting for maturation in boys, and therefore comparisons of skeletal development should take differences in ethnicity and maturity into account.

Proudly brought to you by DOHaD rapporteurs:

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# Developmental Origins of HEALTH AND DISEASE



9th WORLD CONGRESS CAPE TOWN, SOUTH AFRICA

11 NOVEMBER 2015

## Life-Course Economics

This was the first session in economics at a DOHaD conference with presentations from experts in the field.

Karen Hofman from PRICELESS South Africa explored different priority interventions for the first 1000 days with respect to South Africa. The intervention uses the LiST intervention strategy in Kwazulu Natal Province. She pointed out the lack of research related to still births, which occur every two hours in South Africa. Using these proposed interventions for instance; using the full coverage of all LiST interventions could avert 26600 child and newborn deaths in 2030. She finally suggested the establishment of a priority-setting agency. This agency would be responsible for coming up with ways to best use financial resources for universal health coverage, contribute evidence to ensure equity as well as effectiveness and efficiency and lastly understanding of cost-effectiveness, acceptability and feasibility of interventions and how to provide services at high quality. Such a partnership has been formed between PRICELESS SA, NICE international and International Decision Support Initiative (IDSi).

Are returns from early life interventions still high when other things are not equal? Chris Desmond from the HSRC, South Africa says no. Using the analogy of building a house, Chris explained that investing only in early life interventions without changing the later life environment is like starting to build a house and only digging up the foundation and filling it up with concrete. At the end of the day there will be no house no matter how well the foundation is laid. So should we stop investing in early life and early child development? Certainly not. The point is that we cannot stop there. There needs to be follow on comprehensive changes especially in the health and education systems, investing in packages of interventions rather than a single intervention. Continuing with the house analogy, not investing in early child development and aiming for later life would be like trying to build without a foundation. If early life is impacted negatively, the potential for later life is greatly reduced.

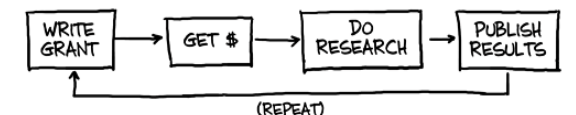
Nicole Ford presented on risk factors affecting child cognitive development in Sub-Saharan Africa. poverty, poor health and an unstimulating environment are a limitation to children reaching their development potential. The impact of these factors can be more pronounced in early life and have lasting impacts on human capital. Factors were combined into 3 main groups; nutrition, environment and maternal-child interaction. Data availability was a major limitation for the study. The authors found that indicators in environment domain provide most support for intervention.

## NOTICES

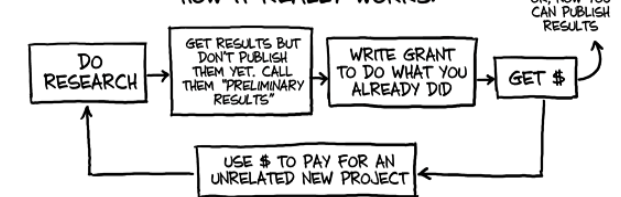
- The award ceremony will take place during the closing session.
- Join the Drum Cafe with your own drum at the end of the closing session!

## THE GRANT CYCLE

HOW IT'S SUPPOSED TO WORK:



HOW IT REALLY WORKS:



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## Methodological challenges for DOHaD studies

Presentations in this session were both theoretically and methodologically highly informative. In this session, common challenges that investigators can anticipate, in longitudinal data analysis in the DOHaD studies and solutions to explaining biologically complex processes were addressed. Emphasis was placed on the "appropriate" use of confounding and mediator variables in explaining pathways or health outcomes that occur between pre-conception and adulthood.

The speakers gave examples how to use different statistical models to finding associations between exposure and health outcomes when confounding variables are appropriately adjusted for in the models. For example, Micheal Kramer showed that the marginal structural model approach (MSM) provided unbiased direct estimates of small-for-gestational-age (SGA) on childhood adiposity when height or BMI were used as intermediates, as opposed to using weight which remained confounded. George Ellison reiterated the fact that study design, and data analysis are processes that should be clearly outlined when embarking on a project to prevent researchers from arriving at incorrect conclusions based on poor planning and overly ambitious methods of analysis. In his presentation he presented findings from a systematic review and meta-analysis of primary observational studies that explored the impact of inappropriate adjustment for mediators in studies that aimed at elucidating causal pathways between exposures and outcomes. They found that a majority of the studies that looked at the relationship between birth weight and blood pressure in later life inappropriately adjusted for mediators that had been incorrectly identified as confounders. These findings highlight the importance of differentiating between confounding and mediator variables in an attempt to prevent false correlations/associations between exposure (i.e. birthweight) and outcome (blood pressure).



## DOHaD and Nutrition: Are we doing enough to improve birth and long term outcomes through maternal nutrition?

During this session, an overview of the current evidence on the role of nutrition in optimising short and long term infant outcomes was provided and key gaps in the research were identified for future prioritisation in this area.

Maternal micronutrient supplementation has well-documented effects on fetal growth and birth outcomes; however, each intervention (balanced protein-energy, iron-folate and multiple micronutrient supplementation) addresses individual nutritional causes of fetal growth restriction. It is important to start considering interventions in combination, rather than as independent of one another, as nutrient deficiencies are generally found in undernourished settings where they present as multiple, rather than single deficiencies. By doing so, we may begin to see the additive effects of providing a comprehensive package of interventions to vulnerable pregnant women, rather than the beneficial, but perhaps limited, effects of isolated interventions.

Additionally, and particularly relevant for DOHaD, evidence for the medium/long term health benefits of early life micronutrient interventions in humans is limited and existing follow-up studies have focused on periods of the life course when overweight/obesity and cardiometabolic risk is still low, i.e. during childhood/adolescence. If we are to gain a deeper understanding of the associations between early pregnancy nutrition and health risk across the life course, preconception and antenatal interventions need more and longer term follow-up, particularly in low-middle income undernourished and transitioning populations.

## DOHaD and Translating Public Health Nutrition Policy into Action: Reaching the Hard to Reach

The DOHaD message has centered on intercepting negative trajectories from as early as conception. This session explored how the research evidence brought forth by DOHaD can be taken up by governments, translate into policy and application of interventions in order to change negative behavior.

Research done in the UK Southampton Women's Survey has shown that maternal diet has an impact on infant growth and health. Increased fat mass (FM) and lower IQ at age four resulted from poor maternal diet. Panel members from the University of Southampton demonstrated how the in the UK they have translated research into action through the Life-Lab intervention, which aims to change negative behaviors in teenagers such as poor diet choice, unhealthy life among other things. The theory behind Life-Lab is that negative behavior (poor diet choice) is much easier to change pre-pregnancy than during or post-pregnancy. The Life-Lab intervention is termed as the "educational intervention" because the teens are first taught in a classroom the theories of how poor health choices have adverse effects later on in life, then the students are allowed to come to the life-lab to scientifically tests those theories, it was shown that teenagers that attend Life-Lab had a change in their attitude and behavior in terms of healthy choices as opposed to teenagers that did not attend the Life-Lab. Another intervention that was tested and proven to be effective in changing female diet choices in Southampton, was changing the way which practitioners communicated the message of healthy nutrition. It was shown that healthy conversation skills changes behavior.

Evidence from Denmark showed that targeting and concentrating government resources on risk populations proved to be effective in changing behavior, it is important for governments to address health inequities as a form of intervention. In Bornholm Denmark a community consisting mainly of low socioeconomic status population, the government partnered with schools & day-care institutions, media and supermarkets in order to drive the message of healthy eating.

## Can we optimise maternal nutrition to minimize epigenetic errors?

The last WHO policy change in guidance for nutritional supplementation of pregnant women was in 1968, namely the use of iron/folic acid supplementation during pregnancy to prevent and treat gestational anaemia. The Cochrane review published on 1 November 2015 is set to change this as the reviewers reported a 'strong basis to guide the replacement of iron, folic acid with multiple-micronutrient supplements for pregnant women in low- and middle income countries.'

At this meeting, Parul Christian of John Hopkins reported that the benefits of multiple-micronutrient supplementation are over and above those seen with iron/folic acid use. A further recommendation was that in food insecure settings where maternal low BMI and low birth weight prevalence is high, balanced protein energy supplementation is needed.

However, we have little data on the use of nutritional supplements during pregnancy as statistics are available from just 28 countries. Mean coverage of iron/folic acid supplementation is only 29%.

Phillip James reports that in The Gambia, nutritional status varies considerably between the dry and rainy season. Maternal preconception concentrations of folate, B2, betaine and the SAM:SAH and the BET:DMG ratios were higher in the rainy season. This would possibly create a greater gene methylation potential.

## Early life exposures and disease

Nephrogenesis begins about 5 weeks after conception, is rapidly ongoing from 20 weeks and is completed at about 34-36 weeks of gestation. Preterm babies may therefore be at risk of a having reduced number of nephrons which is a risk factor of hypertension. A Dutch study was done to investigate the impact of first trimester maternal protein intake on offspring kidney outcomes looking mainly and kidney volume and function. While kidney volume was unaffected, high vegetable protein was associated with higher eGFR. This association needs further research.

Asthma prevalence is on the increase in Western countries with the Lifeways study putting it at about 23%. Evidence shows that allergic disease originates in utero and Karien Viljoen reported results from a study to investigate the role of maternal dietary patterns affect rates of asthma in the offspring, focusing on oily fish, vegetables and Vitamin D. Consumption of oily fish and Vit D were protective against asthma in the offspring.

Lung development starts in utero and continues up to about 20 years of age and therefore disruptions of that process could potentially lead to a decrease in lung function at an earlier age. A Finnish study to investigate the effect of preterm birth on adult lung function found an independent effect of preterm birth and fetal life on lung function not explained or mediated by childhood SES, current lifestyle or manifestation of obstructive airways disease. In the long term, fetal life may lead to increased airway obstruction at the age of peak lung function and manifestation of lung disease at earlier ages.

Over 60% of women of child-bearing age are obese in America and maternal obesity is a risk factor for offspring obesity in later life. In line with this the US Institute of Medicine has guidelines for weight gain in pregnancy. Using data from two USA birth cohorts followed up from the 60s, investigators set out to examine the impact of exceeding current weight gain guidelines on the risk of obesity in female offspring at age 40. According to Lauren Houghton the study showed that exceeding the guidelines tripled the risk of daughters being overweight/obese in midlife. Obesity in the offspring was seen even in girls who were not obese in childhood or young adulthood showing strong evidence that the association is not due to tracking.. Familial confounding was also excluded.

These results confirmed that early life exposures ranging from maternal nutrition to obesity have a significant impact on later disease in the offspring.

## DOHaD and Cardiovascular Disease

Various aspects of cardiovascular disease in childhood in animal and human studies were covered extensively in the Early life factors and cardiovascular disease break out session. Despite having over 12 presentations in this session that spanned almost all continents, the time restrictions on the presenters' time in no way detracted from the overall standard of the papers or the high quality research that was presented. The main thematic areas of focus in this section were foetal growth and growth restriction; metabolic disease; hypertension and heart and vessel imaging to estimate cardiovascular risk. Highlights from this session included the methods used such as latent variable growth curve modelling used by Julian Kagura to explore Early life growth and blood pressure across the life course in urban South Africa. Merida Rodriguez-Lopez used cluster analysis to identify 3 different types of phenotypes among infants exposed to fetal growth restriction. Conditional growth analysis was used to test the association between perinatal growth and energy intake and satiety response at 5-6 years. Looking at non-nutritional exposures, the results from a birth cohort in Preto, Brazil were presented also using directed acyclic graphs (DAGs) and it was found that infants born by Caesarian section were at a higher risk of hypertension than those born naturally. Izzuddin Aris presented findings from a multi-ethnic Asian cohort which aimed to determine the effect of infant weight, length and adiposity gains during early childhood on blood pressure at 36 months. Results showed that infants with rapid gains in weight, length and adiposity were predisposed to higher blood pressure in early childhood.



## Early Life Exposures and Later Outcomes

The principles of DOHaD describe how early life exposures in conception, pregnancy, infancy and childhood can have a significant impact on health and disease risk in later life. The presenters in this session sought to answer the above question by highlighting how early life environments affect children's developmental outcomes such as body composition, cognition and cardiometabolism.

These were some of the findings reported by the speakers:

- Among indicators of physical development at birth, only head-circumference was the most prominent predictor of intelligence as measured by levels of IQ IN 1 year olds.
- It was reported that maternal HIV status was not associated with any outcomes. However, the higher maternal cognitive ability improved cognition in boys and girls. Furthermore, it was reported that boy exclusive breast feeding (i.e. more than 1 years) long term benefits on cognition.
- Early life exposures such severe acute malnutrition have adverse long-term effects on children's physical development (i.e. stunting, body composition associated with increased risk of cardiometabolic disorders and functional impairments).
- Methylation variations of the SLC6A4 gene in the umbilical cord were associated with differences in childhood adiposity as measured by % fat-mass and triceps skinfold.
- The Pune Maternal Nutrition Study (PMNS) showed that measuring femoral length from 18 weeks of gestation can predict stunting at 18 years.
- In the New Delhi Cohort it was found that mother-child versus father-child associations were stronger predictors of cardiometabolic risk, of which they postulated it to be an intergenerational transference through intra-uterine programming.

