

## 9th World Congress on Developmental Origins of Health and Disease

5204

### A global perspective on preventing noncommunicable diseases, childhood overweight and obesity and the relevance to DOHaD

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The prevalence of infant, childhood and adolescent may be plateauing in some high-income countries, but in absolute numbers there are more overweight and obese children living in low- and middle-income countries including 12 million children in Africa. The Political Declaration adopted at the United Nations General Assembly High-level Meeting on Prevention and Control of Non-communicable diseases in 2011 highlighted the importance of multi-sectoral action in reducing the global burden of NCDs. WHO has developed a number plans and targets to address this issue and the WHO Director-General established the Commission on Ending Childhood Obesity to review the emerging science and evidence on the determinants of childhood obesity and develop policy recommendations and a monitoring and accountability framework.

The policy recommendations of the Commission highlight the need for government leadership and political will to protect children from obesity through action on the obesogenic environment and at critical points in the life-course. Tools for implementation, monitoring and accountability will be developed to support countries to put in place these policies.

What will be the relevance of these recommendations to DOHaD in terms of research for policy, new science and the need for data from LMIC and minority groups?

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**Research question:** What is the relationship between teenagers' perceptions of their own health and their actual eating and lifestyle habits?

**Methods:** 379 students aged 13-14 years completed questionnaires about self-beliefs regarding their own health, diet and exercise habits, and engagement with science. Food frequency questionnaire data were analysed using principal components analysis (PCA). Relationships between actual and perceived health behaviours and students' levels of engagement with science were examined.

**Results:** PCA identified a dietary score that summarised compliance with dietary recommendations. It was positively correlated with self-reported health ( $r_p = -0.406$ ,  $p < 0.001$ ). Students' perceptions of the healthiness of their lifestyle were weakly correlated with their amount of moderate/vigorous-intensity physical activity ( $r_p = -0.178$ ,  $p < 0.001$ ), and with low-intensity physical activity ( $r_p = -0.162$ ,  $p < 0.001$ ). Science behaviour and attitude scores (measures of engagement with science) were both positively correlated with the diet score.

**Conclusion:** LifeLab is an innovative educational intervention to change young people's health attitudes and behaviours. It is possible to obtain a dietary score that summarises adolescents' adherence to dietary recommendations, akin to scores used in studies of adults. Improving engagement with science, albeit not in isolation, may be a route to improving health awareness and behaviours in young people.

4900

### LifeLab: Teenagers' self-perceptions of health

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5411

### Implementing a pre-pregnancy lifestyle intervention to reduce the risk of diabetes in young adults: challenges and key-learnings from Malaysia

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In Malaysia, the Jom Mama Project was initiated under a public-private partnership initiative to engage young adults in an intervention to improve the pre-pregnancy health of women to reduce the risk of gestational diabetes and Type 2 diabetes in the next generation. The intervention consists of a novel combination of behaviour change counselling (BCC) through contact with community health promoters (CHPs) and access to a personalised mobile application. The project is currently in the trial implementation stage. One of the key challenges faced was the reception of the intervention program from the target participants. It was found that young married Malaysian adults tend to place higher priorities in their work career than health, which challenged the recruitment strategies. Another barrier encountered was the workload strain and task coordination of the nurses involved in the project who are also concurrently managing their daily task at their clinics. The work schedule of nurses was not as flexible as anticipated, resulting in delays in engaging study participants. Lastly, CHPs found that the learning curve for the training on BCC and E-health was high and more time was needed to familiarise themselves and be confident with the new communication method and use of mobile technologies.

**Conclusion:** Implementing a pre-pregnancy lifestyle intervention for young married adults in a developing country setting requires pragmatic considerations beyond a purist perspective on conducting research, which needs planning for extended time and resources to cater for contextual challenge.

4399

### Optimal periconceptional folate status and human embryonic cerebellar growth trajectories

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**Research question:** Does periconceptional maternal folate status affect human embryonic cerebellar growth?

**Methods:** In a prospective periconception cohort participants filled out questionnaires and received weekly transvaginal 3D-ultrasounds between 7+0 and 12+6 weeks gestational age (GA). Viable non-malformed singleton pregnancies were selected for cerebellar measurements; transcerebellar diameter, (TCD), left and right cerebellar diameters (LCD, RCD). Using linear mixed models we estimated associations between questionnaire data on the moment of maternal folic acid initiation as function of crown-rump length (CRL) and gestational age (GA) and cerebellar measurements. First trimester maternal red blood cell (RBC) folate concentrations were analysed to validate the associations.

**Results:** 263 serial 3D-ultrasound scans of 135 pregnancies were studied. Preconceptional compared to postconceptional initiation of folic acid was associated with larger cerebellar diameters per millimetre increase of CRL (TCD: $\beta=0.260\text{mm}$ , 95% CI = 0.023-0.491,  $p < 0.05$ ; LCD: $\beta=0.171\text{mm}$ , 95% CI = 0.038-0.305,  $p < 0.05$ ; RCD: $\beta=0.156\text{mm}$ , 95% CI = 0.032-0.280,  $p < 0.05$ ) and of proportional cerebellar growth (TCD/CRL: $\beta=0.015\text{mm/mm}$ , 95% CI = 0.005-0.024,  $p < 0.01$ ; LCD/CRL: $\beta=0.012\text{mm/mm}$ , 95% CI = 0.005-0.018,  $p < 0.01$ ; RCD/CRL: $\beta=0.011\text{mm/mm}$ , 95% CI = 0.005-0.017,  $p < 0.01$ ). Cerebellar growth was highest in the third quartile of RBC folate (1538–1813nmol/L).

**Conclusions:** These first findings support the effects of periconceptional maternal folate status on human embryonic brain development. Investigation of the implications of these findings on fetal brain development and postnatal function is recommended.

5350

### Exposure to Maternal Obesity: Predictive-Adaptive Responses in Newborn White (WAT) and Brown (BAT) Adipose Tissue

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Obesity is common among indigenous peoples in the Arctic region, potentially an adaptive response to the cold environment. Among the two primary fat depots, white adipose tissue (WAT) stores excess energy, whereas brown adipose tissue (BAT) expends energy via thermogenesis. Maternal obesity

increases the risk of newborn and adult offspring obesity, though it is unclear if this is a physiologic or pathologic mechanism. We hypothesized that maternal obesity programs offspring adipogenesis via specific effects on both newborn WAT and BAT. We determined the proliferation rate and protein expression of distinguishing genes in WAT and BAT in newborn males of control and obese dams.

**Methods:** Female mice were fed either a control (10% k/cal) or high fat (45% k/cal) diet to create maternal obesity (MO) prior to mating, and diets continued throughout pregnancy and lactation. Newborns were delivered spontaneously, males sacrificed at day one of life, and inguinal WAT and interscapular BAT were collected. Primary WAT and BAT preadipocytes were cultured for proliferation (MTT assay). WAT and BAT protein expression (Western blot) of thermogenic gene (UCP1), adipogenic transcription factors (PPAR $\nu$ , C/EBP $\alpha$ ) and mitochondrial marker (ATP5A) were determined.

**Results:** At 1 day of age, MO males were heavier ( $1.55 \pm 0.09$  vs  $1.31 \pm 0.01$  g;  $P < 0.05$ ) than Controls. In WAT, MO males exhibited decreased preadipocyte proliferation (0.8-fold;  $P < 0.05$ ) though with increased expression of PPAR $\nu$  (1.3-fold;  $P < 0.05$ ) and C/EBP $\alpha$  (1.8-fold;  $P < 0.05$ ). Conversely, in BAT, MO preadipocyte proliferation was increased (1.3-fold;  $P < 0.05$ ) as was the expression of UCP-1 (1.5-fold;  $P < 0.05$ ) and ATP5A (1.7-fold;  $P < 0.05$ ).

**Conclusions:** In MO newborn males, increased WAT PPAR $\nu$  and C/EBP $\alpha$  expression is consistent with enhanced adipogenesis and lipid storage while increased BAT UCP-1 and ATP5A indicate enhanced newborn thermogenesis potential. These findings suggest a predictive-adaptive response in MO newborns facilitating both acute (BAT) and chronic (WAT) benefits of adiposity. Adipogenic programming effects of MO may have evolved for survival benefit.

5029

#### Differential Methylation/Hydroxymethylation of Genes in the Placenta with Maternal Adiposity: Role in Placental Function and Programming of Obesity

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**Research question:** Understanding the mechanism whereby the obesogenic intrauterine environment affects placental function may help prevent intergenerational transmission of obesity. We generated genome-scale distribution maps of methylated (5mC, repressive) and hydroxymethylated (5hmC, permissive) genes in human placentas of obese and healthy weight pregnancies.

**Methods:** Genomic DNA was isolated from randomly sampled placental villous tissue of 10 pre-pregnancy obese and 10 lean

women. Methylated and hydroxymethylated DNA was applied separately to NimbleGen 2.1M methylation arrays.

**Results:** Increased numbers of 5mC and decreased numbers of 5hmC regions were found throughout the genome in obese vs healthy weight groups but especially prominent in Chr17 and 19, including the GH-CSH (17q24) and the PSG (19q13) gene clusters. Hyper-methylated genes in obese pregnancies associated with defense response, cell adhesion, female pregnancy and lipid digestion. Hyper-hydroxymethylated genes in lean placentas associated with hormone secretion, defense or inflammatory response, TNF $\alpha$  production and insulin secretion. With a VENN diagram we found 262 genes with increased 5mC/decreased 5hmC and 17 genes with decreased 5mC/increased 5hmC suggesting regulation by ten eleven translocase enzymes.

**Conclusion:** Differential methylation/hydroxymethylation of genes that have vital roles in the control of maternal metabolism, fetal growth and placental development is found in the placenta with maternal obesity.

4917

#### Sexually dimorphic influence of first trimester phthalate and phenol exposure on gene regulation in human placenta

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**Research question:** Prenatal exposure to endocrine disrupting chemicals (EDCs) may disrupt hormone homeostasis during critical windows of development, shaping adult disease susceptibilities. We explored whether exposure to phthalates and phenols, which may have detrimental health effects induce changes in placental physiology, which may contribute to intrauterine programming of these phenotypes.

**Methods:** We assessed genome-wide changes in methylation and gene expression in 171 human placentas from the Harvard Epigenetic Birth Cohort. Associations with first trimester urinary metabolites of 11 phthalates and 8 phenols were assessed separately in the placentas of males and females due to potential effect modification by sex-specific patterns of methylation associated with cell growth and differentiation.

**Results:** We identified changes in methylation and expression among genes implicated in metabolism and cellular organization for both males and females. However, the specific EDCs with the greatest influence on these pathways varied by sex, and between methylation and expression patterns.

**Conclusions:** This study represents the first investigation into the influence of phenols and phthalates on genome-wide regulation in human placental tissue. Notably, our study provides novel evidence for the molecular basis of the impact of

prenatal phthalate and phenol exposure on human placental function and possibly fetal (re)programming.

5353

### Paternal obesity: fetal and placental outcomes

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**Background/Aims:** Paternal obesity has been shown to induce changes in offspring phenotype via the paternal epigenome. Since the formation of the placenta relies on both paternally- and maternally-derived genes, we investigated the effects of paternal obesity on placental gene expression.

**Methods:** Male C57Bl6 mice were fed a control (n = 5) or high fat diet (OB, n = 5; 60%kcal fat) for 6 weeks before mating with control female mice. At embryonic day 18.5, maternal, fetal serum, and placental tissues were collected.

**Results:** OB fathers showed increased body weight, fat depots and higher glucose levels compared to control fathers (p < 0.05); sperm counts were reduced but not statistically significant. Paternal obesity resulted in hyperglycemia in female but not male fetuses. Male placenta from OB fathers had higher mRNA levels of genes mediating Th17 inflammatory pathways (CD4, FOXP3, IL-22, TGFBR1 Trkc, NOD1) and decreased levels of genes involved in placentation (Wnt2, VIP, VPAC1, MMP 1,9). OB female placenta showed reduced levels of genes involved in ER stress and placentation.

**Conclusion:** Paternal obesity imposed sex-specific changes in fetal glycemia and placental gene patterns. It appears that male placenta are more vulnerable to paternal obesity-induced changes in inflammatory/immune signaling.

5451

### Maternal obesity alters placental gene expression in a sex-specific manner

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**Aim:** High fat (HF) diet intake during pregnancy results in fetal and postnatal metabolic dysfunction and obesity. In the present study we investigated placental gene expression.

**Methods:** Female C57BL/6 mice were fed a control or a HF diet (60% kCal fat) for 6 weeks prior to mating. On embryonic (E) day 18.5, dams were sacrificed, fetal and placental tissue was collected. In a subset of mothers, intestinal permeability assessed using a 4-kDa tracer assay.

**Results:** Females fed a HF diet were heavier at mating and remained heavier over pregnancy. Maternal blood glucose at E18.5, fetal weight and sex ratio did not differ between groups. Maternal intestinal permeability increased with pregnancy, but did not change further with HF diet. HF female placentae had increased mRNA levels of apoptotic-related genes (Bax, Bcl2, Bad), and genes associated with ER stress (Calreticulin, FKB13, HSP47, HSP27). HF male placentae showed reduced levels of genes involved in autophagy and inflammation.

**Conclusion:** We show pregnancy-induced increases in maternal gut permeability but this was not further altered by diet. Maternal obesity induced sex specific changes in placental gene expression; where female but not male, placentae were more vulnerable to obesity induced apoptotic-related genes changes and ER stress.

4633

### Low maternal B12 associates with higher leptin in maternal adipose tissue, placental tissue and cord blood

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**Research question:** In line with the developmental programming hypothesis, evidences show that maternal vitaminB12 deficiency at periods of development influence metabolic status and degree of metabolic syndrome of the offspring into adulthood. Our recent study showed that low maternal vitaminB12

was associated with adverse cord blood lipid profile and higher BMI which provided the clue to explore the link between the adiposity marker, leptin, and vitamin B12. We hypothesize that maternal B12 might program leptin levels in-utero. Therefore we investigated whether maternal B12 levels associate with leptin in maternal adipose tissue, placental tissue and cord blood.

**Methods:** Paired maternal venous and cord blood samples (n = 91), adipose tissue (n = 42) and placental tissue (n = 83) were collected at delivery. Serum vitamin B12 was determined by electro-chemiluminescent immunoassay. Leptin levels were measured by ELISA.

**Results:** B12 deficiency (<150 pmol/L) was common (mothers-40%; neonates-29%). In regression analysis, adjusted for likely confounders, maternal B12 independently associated with neonatal leptin (= -0.662; p = 0.002; R<sup>2</sup> = 12.7%). Leptin gene expression was higher in adipose tissue and placental tissue from mothers with low B12.

**Conclusion:** Our study highlights that low maternal B12 associates with higher leptin in cord blood, maternal adipose tissue and placental tissue, suggesting leptin gene could represent a mechanism of adverse programming either in the placental tissue or maternal adipose tissue.

4454

#### Cord blood levels of Placental Growth Factor; a novel biomarker for the identification of fetal growth restriction

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**Research question:** Distinction between fetuses who are growth restricted (FGR) from those who are not is vital. In this study we assessed whether cord blood levels of placental growth factor (PLGF) can serve as a tool to retrospectively identify fetal growth restriction.

**Methods:** This study was embedded in the Generation R study, a large prospective population based cohort study. Live singletons with data available concerning fetal growth and cord blood PLGF levels were included (n = 3462). To adjust for gestational age PLGF multiple of the median (MoM) values were calculated. Using repeated measurements analyses growth curves of neonates with a PLGF MoM level < p10 were compared with neonates with a PLGF MoM level > p10.

**Results:** Median PLGF MoM level was 1.0 (3.2). Neonates with a PLGF MoM level < p10 (i.e. 0.67) showed a significantly different fetal growth pattern (p = 0.02) showing a deviation from the growth curve from approximately 30 weeks of gestation onwards. This resulted in a significantly lower birthweight of 0.58 SD (90% range 0.46-0.70, p < 0.001) and an increased risk for a deviating growth curve of ≥30 percentiles (OR 1.60, 95% CI 1.21-2.11, p < 0.01).

**Conclusion:** Cord blood PLGF might be a promising biomarker in retrospectively determine fetal growth restriction.

4927

#### Exploring the Developmental Overnutrition hypothesis using Mendelian randomization in three birth cohorts

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**Research question:** The developmental overnutrition hypothesis suggests mechanisms by which intra-uterine conditions related to high levels of maternal glucose and other fuels affect lifelong risk of offspring fatness. We aimed to assess whether there is a causal, intra-uterine effect of maternal body mass index (BMI) on offspring BMI.

**Methods:** Mendelian randomization (MR) analysis of the association between pre-pregnancy maternal BMI and offspring BMI at age 7 was performed in three birth cohorts (N = 6,997) using a weighted allele score generated from 32 BMI-associated genetic variants. Results from the three cohorts were meta-analysed and compared with multivariable regression associations.

**Results:** In multivariable regression analysis, a one SD (~4 kg/m<sup>2</sup>) greater maternal pre-pregnancy BMI was associated with a 0.29 SD (0.26, 0.31) (~0.75 kg/m<sup>2</sup>) increase in offspring BMI, with a slightly weaker association in analyses adjusted for additional confounders (0.23 SD (0.20, 0.26); N = 4,724). In crude MR analysis, the equivalent estimate was 0.57 SD (0.41, 0.72). However, this effect was largely attenuated when offspring genotype was taken into account (0.10 SD; -0.08, 0.28).

**Conclusion:** Our findings provide no strong evidence that an increase in maternal early pregnancy BMI has a causal effect on later offspring BMI in childhood via intrauterine mechanisms.

4921

### Does genetic variation contribute to the architecture of gestational weight gain?

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Greater gestational weight gain (GWG) is associated with adverse offspring health. Whilst there are no previous studies of heritability, phenotypes that would plausibly influence it (e.g. BMI and birth weight) are heritable. Our aim was to investigate the genetic influences of GWG.

We calculated the proportion of variance explained by genome-wide single nucleotide polymorphisms (SNPs) in the ALSPAC cohort (N=7,192) for early (0-20 weeks gestation), late (20-28+) and total (0-28+) GWG. We performed a genome-wide meta-analysis from 12 studies from maternal (N=7,681 - 10,555) and offspring (N=8,819 - 16,471) samples.

19% of the variability in early GWG can be explained by SNPs in the maternal genome; this increases to 24% by late pregnancy. Variants near the Pregnancy Specific Beta-1-Glycoprotein 5 (PSG5) gene reached genome-wide significance ( $P=1.71 \times 10^{-8}$ ) for total GWG in the offspring genome. An additional 10 loci reached suggestive levels of significance ( $P < 10^{-5}$ , maternal and/or offspring genome). Of the 11 GWG loci, two are associated with BMI in the GIANT consortium (Bonferroni  $P < 0.005$ ). Additionally, two robustly associated BMI SNPs were nominally positively associated with GWG ( $P < 5.15 \times 10^{-4}$ ).

A substantial proportion of the variability in GWG can be explained by common genetic variation, which partly overlaps with the genetic architecture of BMI.

4506

### Does maternal antenatal distress predict placental gene expression of 11 $\beta$ -HSD2, MAO-A, NR3C1 and SLC6A4?

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**Objective:** Antenatal distress (including depression and anxiety) is associated with an increase in risk of adverse fetal and infant development, and it is possible that these effects are mediated via altered expression of key placental enzymes and receptors, such as 11 $\beta$ -HSD2, MAO-A, glucocorticoid

receptor (NR3C1) and serotonin transporter (SLC6A4). This study aims to further characterise this association.

**Methods:** Pregnant women were recruited prior to elective caesarean and assessed for anxiety, depression and life events. Placental gene expression was analysed (N=83). Results were adjusted for confounding variables including maternal age, gestational age and birth weight.

**Results:** There was an association between antenatal anxiety and increased gene expression of NR3C1 ( $\beta = 0.25$ ,  $p = 0.04$ ). There was no association between maternal anxiety and gene expression of 11 $\beta$ -HSD2, MAO-A, or SLC6A4 in the whole group. However, subgroup analyses of the Caucasian group demonstrated a significant association between the number of antenatal life events and decreased gene expression of 11 $\beta$ -HSD2 ( $\beta = -0.32$ ,  $p = 0.02$ ).

**Conclusions:** This study demonstrates an increase in placental NR3C1 gene expression following antenatal anxiety exposure. Additionally, there were associations between aspects of maternal distress and decrease in placental 11 $\beta$ -HSD2. Placental NR3C1 functioning may be one potential mechanism by which antenatal anxiety affects fetal development.

4622

### Impact of paternal cholestasis on the sperm epigenome

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**Research question:** Paternal metabolic status has been shown to impact disease susceptibility in the offspring. We hypothesised that paternal cholestasis disturbs intratesticular homeostasis and impacts the epigenome of paternal germ cells.

**Methods:** 7-9 week old C57BL/6 fertile male mice were fed a normal chow (NC) diet  $\pm$  supplementation with 0.5% cholic acid (CA), for 6 or 10 weeks. At completion of feeding, we studied the effects of cholestasis on sperm and testes. Sperm DNA damage, global DNA methylation and hydroxymethylation and sperm microRNA content were assessed.

**Results:** CA feeding significantly increased sperm DNA damage after 10 weeks ( $n = 5-6$ ,  $p$ -value  $\leq 0.05$ ) and caused an increase in mRNA expression of the apoptotic marker FasL in the testes ( $n = 5-6$ ,  $p$ -value  $\leq 0.05$ ). Assessment of global sperm DNA methylation and hydroxymethylation showed a trend for

decreased 5-mC% and 5-hmC% DNA content after 6 and 10 weeks of CA diet (n=5-6). Altered sperm miR-34c\_1 content was also observed (n=5-6).

**Conclusion:** Long-term male cholestasis was associated with DNA damage in the sperm, accompanied by increased apoptosis in the testes. Global sperm DNA methylation, hydroxymethylation and microRNA content were affected by male cholestasis. Ongoing studies investigate whether this has an impact on the phenotype of the offspring.

4431

### The effect of dietary fat on age related changes on the liver DNA methylome across generations

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Increased energy intake over three generations can induce compensatory metabolic adjustments in young adults, associated with altered DNA methylation regulation. We hypothesised that such changes in DNA methylation in young adults are perturbed during ageing contingent on diet.

Female C57BL/6 F0 mice were fed 5% or 21% fat diets (w/w) throughout pregnancy and lactation. Female F1 offspring were fed the same diet as their dams and mated at d90. This was repeated until the F3 Offspring were at d90 and d456. The liver methylome was analysed by MeDIPSeq.

In F1, ageing induced 48 differentially methylated regions (DMRs) in the 5% fat group and 288 DMRs in the 21% fat group. In F3, ageing induced 6 DMRS in the 5% fat group and 415 DMRs in the 21% fat group. Pathways significantly altered include Cancer and insulin signaling.

The effect of ageing on DNA methylation was greater in mice fed a high fat diet than a low fat diet. This effect was reduced across generations in the low fat group, but exacerbated by feeding a high fat diet. Overall, these findings show that the effect of dietary fat on the DNA methylome across generations is specific to the level of intake.

4395

### Common genetic variants and kidney outcomes in children and adults

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**Aim:** Kidney measures in early life are associated with kidney disease in later life. We hypothesized that these associations are partly explained by common genetic variants that lead to smaller kidneys with lower kidney function in early childhood and kidney disease in adulthood.

**Methods:** We examined in a population-based prospective cohort study among 4,119 children the associations of a weighted genetic risk score combining 27 previously identified common genetic variants related to kidney function in adults with kidney outcomes in children aged 6.0 years (95%range 5.7-7.8). Kidney outcomes included combined kidney volume, glomerular filtration rate (eGFR) based on creatinine levels, and microalbuminuria based on albumin-creatinine urine levels.

**Results:** The genetic risk score based on variants related to impaired kidney function in adults was associated with smaller combined kidney volume and with lower eGFR in children. Per additional average risk allele, combined kidney volume was -0.43 cm<sup>3</sup> (95% CI -0.66; -0.21) smaller and eGFR was -0.42 ml/min/1.73m<sup>2</sup> (95%CI -0.61; -0.23) lower.

**Conclusion:** These observations suggest that common genetic variants related to impaired kidney function in adults lead to subclinical changes in childhood kidney outcomes. The well-known associations of kidney measures in early life with kidney disease in later life may be partly explained by common genetic variants.

4628

### Prenatal nutritional supplementation effects on fetal growth and birth outcomes in rural Gambia: the Early Nutrition and Immune Development trial

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**Research question:** Does prenatal micronutrient and/or protein & energy supplementation improve fetal growth and birth outcomes in malnourished populations?

**Methods:** The study was a randomized trial (ISRCTN49285450) in 875 women with four arms receiving supplementation from <20 weeks gestation (Iron-folate (FeFol), multiple micronutrients (MMN), protein-energy (PE), PE & MMN). Regression was used to examine between-arm differences in fetal biometry Z-scores (INTERGROWTH standards) at 20 and 30 weeks and neonatal anthropometry Z-scores (WHO standards), testing for effect modification by maternal height and BMI at booking.

**Results:** PE supplementation was differentially associated with fetal biometry at 20 and 30 weeks. For example, compared to

the FeFol arm, the two arms receiving PE had greater femur length Z-scores at 20 weeks (beta 0.21; 95% CI 0.05 to 0.38) but only greater head circumference Z-scores at 30 weeks (0.13; 0.00 to 0.25). These differences did not result in the PE arms being heavier or larger at birth and there was limited evidence of effect modification by maternal height and BMI.

**Conclusion:** Sensitive periods for fetal growth may not be consistent for all anthropometric measures. More research is needed to understand the timing and type of intervention that will have longer lasting protective effects.

#### 4600

##### **Early-Onset Overweight after Maternal Obesity Increases Insulin, Intrinsic Renal Leptin Signaling and Metabolic Programming of the Kidney**

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**Research question:** Obesity is associated with low-grade inflammation and diseases, e.g. arterial hypertension and diabetes. Whether maternal obesity is mechanistically linked to renal dysfunction of the offspring remains elusive. We therefore queried if maternal obesity induces metabolic programming of structure, function and adipocytokine-signaling in kidneys of the offspring.

**Methods:** Female wildtype mice were fed with high-fat diet (HFD) or standard chow (Control). The offspring were sacrificed at postnatal day (P) 21 and P70 to obtain serum, kidneys and white adipose tissue (WAT). Intraperitoneal glucose tolerance was assessed at P21 and P70. Renal function was assessed in metabolic cages at P70.

**Results:** The HFD group exhibited 2-fold increased WAT, impaired glucose tolerance, and increased serum leptin (2-fold) and insulin (4-fold) at P21. Intrinsic-renal leptin expression (10-fold) and signalling, proliferation (PCNA, CyclinD1) and profibrotic markers were greater in HFD than Control. Moreover, HFD showed a greater renal deposition of ECM (collagen) than Control. At P70 HFD exhibited a reduction of fractional and total sodium excretion by 50% and a decreased glomerular filtration rate ( $p < 0.07$ ).

**Conclusion:** Our findings show a novel link between maternal obesity and metabolic programming of renal structure and function in the offspring, potentially via intrinsic-renal leptin and insulin signaling.

#### 4651

##### **Counter-regulatory cytokine expression and preterm birth: a case-control study nested in a cohort study (BRISA Birth Cohort, Brazil)**

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**Research question:** Currently known risk factors explain a fraction of preterm birth (PTB). Few studies have looked at associations between counter-regulatory cytokine (CRC) expression and PTB and the results are conflicting. Our objective was to investigate the association of CRC - Interleukin 10 (IL-10) and Transforming Growth Factor  $\beta$  (TGF- $\beta$ ) with PTB.

**Methods:** This was a case-control study nested in a prospective cohort study, called BRISA. Women with singleton pregnancies were interviewed from 22 to 25 weeks of gestational age (GA). A blood sample was collected and gynecological examination was performed. Serum IL-10 and TGF- $\beta$  were determined using cytometric bead array. All PTB estimated by ultrasound dating performed  $< 20$  weeks of gestational age were considered cases. Controls were selected by simple random sampling from the rest of the cohort, at a 2:1 ratio.

**Results:** The study included 327 pregnant women, 109 cases and 218 controls. Low levels of IL-10 (OR = 3.96) or TGF- $\beta$  (OR = 23.21) or both simultaneously (OR = 94.28) were associated with increasing odds of PTB, even after adjustment for confounding.

**Conclusion:** Decreased CRC is a risk factor for PTB. Low IL-10/TGF- $\beta$  levels from 22 to 25 weeks of GA could be used as early predictors of PTB, especially among primiparous.



4957

### Maternal Obesity negatively impacts on fetal kidney development, maternal health and birth outcomes in an Indigenous Australian cohort

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**Research question:** Chronic disease in Indigenous populations is prolific. The leading cause of chronic disease is obesity. Implications of obesity on birth outcomes are poorly understood as is the impact of maternal obesity on fetal organ development.

**Methods:** This is a prospective longitudinal maternal/infant cohort. Height, weight, BMI, %Body fat, fetal ultrasounds, with fetal kidney measures, and maternal health and birth outcomes were recorded.

**Results:** Median weight and BMI of the cohort was 85.34kg (range: 45-148kg) and 30.74kg/m<sup>2</sup> (15-52 kg/m<sup>2</sup>), and % body fat was 43.65% (17-63%). Maternal BMI was associated with infant birth weight ( $\rho = 0.32$ ;  $p = 0.005$ ) but not timing of birth. Both BMI and %body fat were negatively associated with combined kidney volume/estimated fetal weight ratio ( $\rho = -0.357$ ,  $p = 0.016$  and  $\rho = -0.406$ ,  $p = 0.014$ ). 6.2% of the cohort developed gestational diabetes (GDM) and delivered earlier ( $p = 0.002$ ) and babies had a median birth-weight centile that was significantly greater than those without GDM ( $p = 0.031$ ). GDM women had higher urinary protein/creatinine and albumin/creatinine ( $p = 0.047$  and  $p = 0.024$ ). There was no effect on fetal kidneys.

**Conclusion:** This Indigenous cohort is at significantly increased risk of future development of chronic disease in both the mother and her offspring and highlight the urgent need for reducing obesity in this population.

4705

### Alcohol exposure during the periconceptional period programs renal dysfunction in aged female rats

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**Research question:** Prenatal alcohol exposure, a major social issue, has deleterious effects on the developing brain though effects on the kidney are not well understood. The periconceptional

period is a poorly understood but critical window of development. We aimed to determine the effects of alcohol exposure during this period (PCEtOH) on offspring kidney function in aged rats.

**Methods:** Rats received a liquid diet +/- 12.5% v/v ethanol from four days before mating to embryonic day four. Offspring kidneys were collected at postnatal day 30 (PN30) and 19 months (19m). Nephron endowment was quantified at PN30. Renal function and gene/protein expression/localisation was measured (19m) during basal and dehydrated conditions.

**Results:** Nephron number and relative kidney weight were reduced in male PCEtOH offspring at PN30 ( $P < 0.05$ ). Urine flow increased in PCEtOH females at 19m ( $P < 0.05$ ) during basal and dehydrated conditions ( $P < 0.05$ ). Renal AVPR2 mRNA and protein levels and AQP2 mRNA levels increased in female PCEtOH offspring ( $P < 0.05$ ) with reduced AQP2 levels at the apical membrane of the collecting duct.

**Conclusion:** PCEtOH exposure reduced nephron number in males. Female PCEtOH offspring were susceptible to renal disease with ageing, associated with changes in renal gene expression and AQP2 localisation.

4948

### Using donor eggs eliminates the risk of congenital heart defects after IVF/ICSI

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**Background:** Congenital heart defects (CHD) remain a leading cause of morbidity and mortality. An established association with maternal age could be due to either maternal factors or the aging oocyte.

**Methods:** A cohort of all patients in South Australia receiving infertility treatment 1986 - 2002 were linked to the state-wide birth defects registry. Some 4,260 births after infertility treatment including 1,394 after IVF and 911 after ICSI were compared to 292,141 births from spontaneous conceptions. Odds ratios were calculated.

**Results:** Fertilisation by IVF/ICSI was associated with CHD (OR = 1.49 1.18-1.88). There was a monotonic rise in risk of CHD across 5-year age groups for Age 40-44 vs Age 20-24 (OR = 1.48, 1.19-1.85).

Compared to natural conceptions, use of a donor oocyte during IVF/ICSI was not associated with the risk of CHD after assisted conception (OR = 1.00, 0.47-2.11). However, for women using their own egg, the risk was increased (OR = 1.50, 1.17-1.93). This was attenuated only slightly after adjustment for maternal age, parity and baby sex (OR = 1.41, 1.09-1.82).

**Conclusion:** Oocyte factors appear to be very important for the specific risk of congenital heart defects in babies conceived through assisted conception, and not maternal factors directly.

4406

### Periconceptional maternal smoking reduces growth of the human embryonic head

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**Research question:** Can we create reliable embryonic growth trajectories of the embryonic head to predict fetal head size and to assess effects of periconceptional maternal conditions?

**Methods:** In a periconception cohort we studied the embryonic head longitudinally between 9+0 and 12+6 weeks gestational age (GA) using 3D-ultrasound. Using a virtual reality system crown-rump-length (CRL), embryonic volume (EV), head volume, biparietal diameter (BPD) and occipitofrontal diameter (OFD) were measured longitudinally. Reference-curves and regression lines were created investigating associations between HV and HV/EV, and GA, CRL and EV. Z-scores were calculated to correlate embryonic HV and HC with fetal HC obtained from structural anomaly scans. Linear mixed models estimated the associations between maternal conditions and embryonic HV.

**Results:** 303 (73%) 3D-ultrasound scans from 149 pregnancies were eligible for embryonic head measurements (ICC > 0.99). Correlations were assessed between embryonic and fetal head measurements (HC:q = 0.617; HV:q = 0.660). A significantly negative association between maternal periconceptional smoking ( $\beta = -0.0276\text{mm}^3$  95% CI = -0.0066; -0.2373  $p < 0.05$ ), and significant positive associations between maternal age ( $\beta = 0.0043\text{mm}^3$  95% CI = 0.0008; 0.0399  $p = 0.01$ ), maternal periconceptional use of alcohol ( $\beta = 0.0141\text{mm}^3$  95% CI = 0.0033; 0.0261  $p < 0.01$ ) and HV were established.

**Conclusions:** Growth of the human embryonic head is most strongly and negatively associated with periconceptional smoking and positively associated with maternal age and use of alcohol.

4473

### Prenatal markers of neonatal fat mass, a systematic review

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**Research question:** Which early and late prenatal markers of neonatal fat mass have been identified to date?

**Methods:** A systematic literature search was conducted to identify studies on prenatal markers of neonatal fat mass. Inclusion criteria were 1) original reports, written in English, 2) measurable prenatal markers and 3) neonatal fat mass measurement within one month after birth, using the four-compartment model, MRI, DXA or air displacement plethysmography. Two reviewers independently performed study selection, assessment on methodological (QUADAS-II) and statistical quality and appraisal of clinical applicability.

**Results:** Of 2333 studies primarily identified by the search strategy, 16 studies were included. Only 4 studies were of adequate quality. Due to substantial methodological heterogeneity, performance of a meta-analysis was not possible. Investigated markers were maternal characteristics, ultrasound measurements and biochemical markers in the 2nd and 3rd trimester. Markers of interest, assessed in  $\geq 2$  studies of adequate quality, were maternal BMI, fasting glucose and HbA1c, all with conflicting results. Clinically applicability was appraised poor for all markers.

**Conclusion:** Although significant associations were found, no useful marker has been identified to date, due to poor methodological and statistical quality, inconsistent results and, particularly, poor appraisal of clinical applicability. Remarkably, no study investigated periconceptional markers.

4525

### How to define fetal growth restriction? An observational study exploring clinical implications of misclassification

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**Research question:** Fetal growth restriction (FGR) is frequently incorrectly classified as a neonate born small for gestational age (SGA, birthweight < p10). The distinction between fetuses who are truly growth restricted from those who aren't is essential. We investigated to which extent misclassification occurs.

**Methods:** This study was embedded in the Generation R study, a large prospective population-based cohort study. Live singletons were included (n = 8451). Neonates were divided into 4 groups; SGA with FGR, SGA without FGR, non-SGA (i.e. normal birthweight) with FGR and non-SGA without FGR. Five cut-offs were used to define FGR: decrease in fetal weight of 30/35/40/45 or 50 percentiles during pregnancy. Misclassification and postnatal catch-up growth at the age of 2 years were assessed.

**Results:** Depending on the used cut-off, of the non-SGA fetuses 9.7-26.6% were in fact growth restricted. Of the SGA fetuses 56.6-81.9% weren't growth restricted and thus constitutionally small. Non-SGA fetuses with FGR had an increased risk of catch-up growth with OR's ranging from 2.0-2.7 (all  $p < 0.001$ ).

**Conclusion:** Using birthweight  $< p10$  to define FGR leads to misclassification. Attention is needed for growth restricted fetuses with a normal birthweight considering their risk of catch-up growth and therefore their increased risk for unfavorable cardiovascular outcomes.

4977

### What do we know about body composition in healthy infants? A review of the literature

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**Research question:** What do we know about the distribution of fat and fat-free mass in the first 2 years of life?

**Methods:** PubMed was searched for human studies of healthy, singleton, term infants whose body composition was measured with reference methods between birth and 24 months of age. Papers that reported means and variances were included in a quantitative synthesis. Random-effects models were used to explore heterogeneity.

**Results:** The review included 83 papers (and is currently being updated), including 69 that were appropriate for meta-analysis. These 69 papers included information on 144 samples and 656 total measurements to analyse.

**Conclusion:** Most studies were small, conducted in the first few months after birth, and as a whole provided little information about changes in body composition during infancy. Few studies aimed to collect reference data, and the apparent variability in estimates of fat mass suggest that those that did were likely undersized for this purpose. Studies were predominately conducted in the USA, and overwhelmingly describe Caucasian populations. The between-study heterogeneity is substantial and cannot be explained by reported study level characteristics, illustrating the need for a high-quality international standard.

4658

### Intrauterine Growth and Early Childhood Development: Evidence from the Sao Paulo Western Region Cohort

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**Research question:** To estimate the associations between intrauterine growth and gestational lengths and children's physical and cognitive development at 15 months of age.

**Methods:** We combined clinical records on gestational length and intrauterine growth with a detailed assessment of children's development conducted at children's home 15 months after birth. We assessed children's physical growth (height-for-age z-score), gross motor skill development (Saving Brains Scale) as well as overall cognitive and socio-emotional development (Ages and Stages Questionnaire-ASQ).

**Results:** Prematurity was negatively associated with height for age (beta = -0.385  $p < 0.05$ ), gross motor skills (beta = -0.378  $p < 0.01$ ) and overall development (beta = -0.411  $p < 0.05$ ). We also found a significant association between small for gestation age and height for age (beta = -0.730  $p < 0.05$ ). We also found significant gender differences, with female children on average less likely to be stunted (probability difference 0.0436  $p < 0.05$ ) and higher ASQ scores (beta = 0.229  $p < 0.01$ ).

**Conclusion:** The findings presented suggest that children delivered prematurely or experiencing intrauterine growth restrictions are not able to fully catch up in their development in the first year of their life. Further studies are needed to understand the gender-based results.

4988

### Pregnancy and postpartum islet beta-cell function in African women attending the Antenatal Clinic in the Charlotte Maxeke Johannesburg Academic hospital

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**Research question:** We evaluated beta-cell function and insulin resistance during and after pregnancy in urban African pregnant women attending the Charlotte Maxeke Hospital Antenatal Clinic.

**Methods:** Between 20-24 (V1) and 30-36 (V2) gestational weeks, and six months after delivery (V3), 108 women participated in a standard 75 g OGTT. Blood samples were analysed for glucose (GLC), proinsulin (PI) and insulin (INS). Areas-under-the-curve (AUC) and related indices were calculated.

**Results:** Postprandial insulin resistance (AUC-GLC  $\times$  AUC-INS) increased significantly between V1 and V2 (29.416.9 $\times 10^{-3}$  vs 46.831.7 $\times 10^{-3}$  mmol2l-2min2;  $p < 0.0001$ ). At V3, the AUC-GLC  $\times$  AUC-INS declined significantly to levels similar to those seen at V1 (29.5  $\pm$  18.2 $\times 10^{-3}$  mmol2l-2min2;  $p < 0.0001$  vs. V2). The AUC-PI:AUC-INS, which was used as a measure of  $\beta$ -cell PI processing efficiency, decreased significantly between V1 and V2 (16.6  $\pm$  7.6 $\times 10^{-3}$  vs 14.7  $\pm$  7.3 $\times 10^{-3}$ ;  $p = 0.0004$ ), reflecting increased PI conversion to INS with progression through pregnancy. Between V2 and V3 the variable increased significantly (27.5  $\pm$  12.9 $\times 10^{-3}$ ;  $p < 0.0001$  vs. V2), reflecting a reduction in PI conversion to INS after delivery.

**Conclusion:** These results demonstrate that during pregnancy increasing insulin resistance is offset by the increased conversion of PI to INS. After pregnancy, insulin resistance declines and is mirrored by reduced processing of PI to INS.

5020

### Role of prenatal factors and postnatal growth on insulin sensitivity and beta-cell function in Afro-Caribbean youth: Vulnerable Windows Cohort Study

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**Research question:** We investigated whether prenatal factors and postnatal growth are associated with insulin sensitivity (IS) and beta-cell function (BCF) in Afro-Caribbean youth.

**Methods:** We measured anthropometry in a birth cohort at birth, 3 monthly to 2 years and then 6 monthly. We measured IS with the Matsuda index and BCF by the oral disposition index (oDI) during oral glucose tolerance testing in 293 non-diabetic youth (age 17.8 ± 0.9 yrs; BMI 22.6 ± 4.8 kg/m<sup>2</sup>).

**Results:** In age, sex, and current BMI-adjusted multivariate analyses, growth in weight during late infancy (6 months - 2 years), and growth in height during late infancy and childhood (2-8 years) were positively associated with fasting glucose (P-values < 0.05), but not 2-hour glucose. Growth in weight during childhood was inversely associated with the Matsuda index (P = 0.007). Birth size was not associated with the Matsuda index. Maternal weight gain in pregnancy was inversely associated with oDI (P = 0.004) while BMI at birth was positively associated (P = 0.04) with oDI.

**Conclusion:** Greater maternal weight gain in pregnancy and lower birth BMI are associated with reduced beta-cell function in youth. However, faster postnatal growth is associated with lower insulin sensitivity.

4733

### Human Fetal Kidney Volume in Pregnancies Complicated by Gestational Diabetes

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**Background:** Gestational diabetes (GDM) is associated with adverse perinatal outcomes and long-term health risks for the offspring. However, studies examining fetal kidney development in human pregnancies complicated by maternal glucose intolerance are lacking.

**Method:** A prospective study was undertaken at Monash Medical Centre, Monash Health. Fetal biometry and kidney size were measured by obstetric ultrasound at 32-34 weeks in a multi-ethnic group of women with GDM (n = 35) or without (n = 41). Fetal kidney volume was calculated using the approximation of an ellipsoid.

**Results:** Maternal age and BMI were similar in non-GDM and GDM women. Estimated fetal weight (EFW) percentile was lower in GDM pregnancies (P = 0.0002) and remained lower at birth (P = 0.01). There was no difference in absolute fetal kidney volume (P = 0.62). Following adjustment for EFW, fetal kidney volume was larger in GDM pregnancies (P = 0.03).

**Conclusion:** Unexpectedly, lower EFW and birth weight were reported in GDM pregnancies. Interestingly, body weight is considered one of the best predictors of kidney volume and length, yet our preliminary data indicate that kidney size was not proportionately reduced in GDM pregnancies. The study is ongoing and we are beginning to collect urine samples to assess renal function in babies born to women with GDM.

4653

### 'Thin-fat' fetal phenotype at 20 weeks of life in GDM pregnancies - Novel evidence from an Indian Cohort

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**Research question:** What are the differences in fetal size in early pregnancy between GDM and control.

**Methods:** Serial fetal biometry was performed GDM women and controls at 18-20 weeks and 28-32 weeks. At each visit, abdominal and head circumference (AC) & (HC), femur length (FL) and abdominal wall thickness (AWT) was measured along with collection of maternal data.

**Results:** 193 women with GDM and 184 controls had complete anthropometric and maternal demographic data. Scans were performed at 20.5 (±1.7) and 32.7 (±1.4) weeks.

At 20-weeks GDM group had higher AWT 2.6 (0.5) vs 2.3 (0.4) p < 0.001 despite smaller measures of all other anthropometric variables. Mean (SD) mm GDM vs Control: AC: 148.9 (29)

vs 155.1 (19.7),  $p=0.01$ , HC: 171.8 (32.9) vs 179.7 (21.9),  $p=0.006$ , FL: 32.9 (7.1) vs 34.5 (4.5),  $p=0.01$ . These differences persisted despite adjustment for age, BMI, height, gestational age, sex and FPG. Similar significant differences persisted at 28-32 weeks. Gestational age and sex adjusted birthweights (BW) of the two groups were similar ( $p=0.56$ ).

**Conclusion:** Smaller size with increased abdominal fat is seen as early as 20 weeks in fetuses of GDM mothers, even prior to GDM diagnosis. Adiposity may potentially be a significant contributor to BW in GDM. AW could serve as an early marker of GDM.

4983

### Fetal macrosomia and early childhood obesity- findings from the Growing Up in Ireland Cohort Study

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**Research questions:** What is the prevalence of macrosomia and GDM in infants in Ireland? What is the association between macrosomia and early childhood obesity?

**Methods:** This population-based cohort study was carried out in over 8,000 nine month old infants and their caregivers in Ireland and included 2 waves. We performed an ordered logit regression analysis to determine the association between macrosomia and childhood obesity in 3 year old children.

**Results:** Seventeen percent ( $n=1417$ ) of the infants were macrosomic while the incidence of GDM was 3%. At the age of 3 years old, 24% ( $n=1971$ ) of the children were overweight or obese. The multivariate adjusted odds ratio (OR) of childhood obesity was 2.14 (95% CI: 1.82-2.50) in macrosomic babies and 2.59 for extreme macrosomic (95% CI: 2.02-3.32). Other significant risk factors were rapid weight gain from birth to 3 years, high gestational weight gain, maternal obesity, starting solids between 4-5 months, smoking throughout pregnancy, and paternal obesity.

**Conclusion:** Macrosomia is an independent risk factor of early childhood obesity. Public health strategies targeting the period before and during pregnancy are essential for the early prevention of obesity. The high prevalence of macrosomia may be indicative of undiagnosed GDM in Ireland.

4687

### Ethnic Differences in Fetal Growth Patterns in GDM: Novel Data from the UK

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**Research question:** Are there ethnic differences in fetal growth patterns in GDM?

**Methods:** Multicentre retrospective data collection was undertaken for all women with GDM between 2008-2012. Fetal biometric data was obtained at 28, 32, 36 weeks gestation for 125 SA and 142 WC.

**Results:** Compared to WC, SA had had lower BMI ( $28.5 \pm 6.1$  vs  $32.2 \pm 7.4 \text{ kg/m}^2$ ), height (159, IQR: 155-163 vs 165, IQR: 160-169cm), less likely to smoke (1.3 vs 17.5%), had lighter babies ( $3226.5 \pm 588$  vs  $3419.4 \pm 630 \text{ g}$ ) despite higher FPG ( $5.3 \pm 0.7$  vs  $5.1 \pm 0.76$ ) and 2hPG ( $8.1 \pm 2.1$  vs  $7.6 \pm 1.9$ ) mmol/l ( $p < 0.01$  for all).

At 28 weeks, abdominal-circumference (AC) for SA and WC were similar ( $243.4 \pm 18$  vs  $247 \pm 16$  vs  $248.3 \pm 23$ ,  $p=0.19$ ). At 32 and 36 weeks, AC of SA was lower than WC despite adjustment for maternal BMI, height, glucose values at OGTT and offspring sex ( $p=0.03$ ;  $p=0.007$ ). Head circumference (HC) was similar in both at all gestations. Both HC/AC ratio and femur-length/AC ratio was higher in SA at 28 and 36 weeks after full adjustment ( $p < 0.02$ ).

**Conclusions:** Despite smaller overall size, SA showed evidence of abdominal adiposity in early fetal life. With progressing gestation there was a pattern of growth restriction with sparing of HC and lower AC compared to WC, signifying a possible adverse intra-uterine environment.

4437

### Associations of maternal and paternal depression and anxiety with offspring anxiety disorder at age 18 years

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**Objective:** Evidence suggests that maternal depression and anxiety in pregnancy are associated with increased risk of childhood behavioural and emotional problems in offspring; it remains unclear to what extent this is due to a maternal biological impact on fetal development. In this study, we compare associations between maternal and paternal antenatal depression and anxiety with offspring anxiety disorders, thus controlling for some genetic and shared environmental factors.

**Methods:** We used data from the ALSPAC population cohort including measures of antenatal parental depression and anxiety. At 18 years, offspring completed the CIS-R interview, yielding diagnoses for anxiety disorders. Results were adjusted for confounding variables including parental postnatal depression and anxiety.

**Results:** Children of women with antenatal depression (18 weeks gestation), had an increased risk of anxiety disorders at 18 years of age (11.1% vs 6.2%; adj. OR 1.75 (1.19, 2.58);  $p=0.01$ ). Children of women with antenatal anxiety had increased risk of co-morbid anxiety and depression (adj. OR 1.39 (1.06, 1.82);  $p=0.02$ ). No such associations were found with paternal antenatal depression or anxiety.

**Conclusions:** The differences in the associations between maternal and paternal mood during pregnancy and anxiety in young adults supports the hypothesis that fetal programming may account, at least in part, for this observation.

4497

### Maternal dietary patterns and postpartum depression, a prospective study of 56,303 women in the Norwegian Mother and Child Cohort Study

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**Research question:** Maternal diet has been indicated among potential risk factors for postpartum depression (PPD). The aim of this study was to examine whether maternal dietary patterns were associated with PPD.

**Methods:** In the Norwegian Mother and Child Cohort Study, 56,303 women reported dietary intake during pregnancy using a food frequency questionnaire and answered the Edinburgh Postpartum Depression Scale six months postpartum. Dietary pattern scores were assigned using i) an a-priori approach assessing adherence to a New Nordic Diet (NND) and ii) a data-driven approach grouping together correlated food intakes, which identified three patterns denoted 'prudent', 'western' and 'traditional'.

**Results:** The prevalence of PPD was 10.6%. High versus low adherence to the NND (score tertiles) was associated with 17% lower risk of PPD [adjusted odds ratio (OR): 0.83 (95%CI: 0.77, 0.89)]. High versus low scores on the 'prudent' and 'western' dietary patterns were associated with 13 and 15% increased risk, while high scores on the 'traditional' pattern was associated with lower risk of PPD [OR: 0.84 (95%CI: 0.78, 0.91)].

**Conclusion:** Our findings suggest that maternal diet modifies the risk of PPD, pointing to meal frequency and consumption of traditional Nordic food items as important aspects of a healthy diet.

4442

### Maternal Depressive Symptoms During Pregnancy and the Risk of Childhood Obesity: a 15 Year Prospective Birth Cohort Study

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**Research question:** Is maternal depression during pregnancy associated with risk of obesity in offspring?

**Methods:** Pregnant women of Kaiser Permanente in the San Francisco area were recruited from 1996-1999. Extensive in-utero exposures were prospectively ascertained from interviews and EMR data. Depressive symptoms were ascertained by CESD. Among offspring, 496 were followed over 11 years for weight and height recorded in their medical records (9 measurements per child, on average). Obesity was defined as BMI  $\geq$ 95th percentile based on age- and gender-specific CDC criteria.

**Results:** After controlling for confounders, offspring of mothers with depressive symptoms (CESD  $\geq$ 16) in pregnancy had more than 60 percent higher risk of obesity than those whose mothers did not: odds ratio (OR)=1.61, 95% confidence interval (CI)=1.09-2.40. The association was stronger for persistent (OR=1.94, 95% CI=1.11-3.37) than transitory obesity (OR=1.50, 0.94-2.41). There was a dose-response relationship: OR=1.76 for CESD 16-29, and OR=2.77 for CESD  $\geq$ 30. The association appeared to be stronger among mothers with higher pre-pregnancy BMI ( $\geq$ 25), minority race/ethnicity, and younger age. There was no gender difference (sex dimorphism).

**Conclusion:** This prospective birth cohort study revealed that maternal depression in pregnancy may impact fetal programming of childhood growth, increasing risk of childhood obesity.

4499

### Maternal pre-pregnancy obesity and maternal depressive symptoms 6 months after delivery

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**Research question:** We examined if maternal pre-pregnancy overweight and obesity are associated with depressive symptoms 6 months postpartum, independently of prenatal depressive symptoms.

**Methods:** Our study sample comprised 1306 pregnant women participating in the Prediction and Prevention of Preeclampsia

Study (PREDO). According to birth register data, 967 were normal weight (BMI < 25.00 kg/m<sup>2</sup>), 259 overweight (25.00–29.99 kg/m<sup>2</sup>), and 80 obese (≥ 30.00 kg/m<sup>2</sup>) before pregnancy. The women filled in the Center for Epidemiological Studies Depression Scale biweekly throughout pregnancy from 12–13th gestational week onwards and at six months postpartum.

**Results:** In comparison to normal weight counterparts, women who were overweight (mean difference, [MD] = 0.22 in standard deviation [SD] units, 95% Confidence Interval [95% CI] 0.09–0.35, *P* = .001) or obese (MD = 0.32 SD units, 95% CI 0.10–0.54, *P* = .005) before pregnancy had higher levels of depressive symptoms 6 months postpartum. The effects remained after adjustments for maternal age, parity and education level (*P*-values ≤ .006), and further adjustments for depressive symptoms during pregnancy (*P*-values ≤ .04).

**Conclusion:** Maternal pre-pregnancy overweight and obesity carry risks for postpartum depressive symptoms, independently of maternal prenatal depressive symptoms. Interventions targeting overweight and obese mothers during and after pregnancy may benefit also the psychological well-being of the mothers.

4770

#### Ante-partum and post-partum depression among women living in slums in Mumbai, India

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**Research question:** Prospective studies in India have found the prevalence of depression among pregnant women to be 16–23% and 11–14% in the post-partum period. Our objectives were to assess the prevalence of depression in the pre and post-partum period among mothers living in Mumbai slums, and to study determinants of depression.

**Methods:** Women enrolled in the Mumbai Maternal Nutrition Project (*n* = 365) were interviewed at 28–31 weeks of pregnancy and again 30–60 days post-delivery. The Edinburgh Post-natal Depression Scale (EPDS) was used to assess depression (defined as >15). We used regression models to study associations between depression and potential determinants.

**Results:** Mean (SD) EPDS score was 10.3 (5.0) during pregnancy and 9.8 (4.7) post-partum. The prevalence of depression was 18.1% and 15.1% respectively, 6.6% were depressed at both time points. Women of lower education level were at higher risk of depression (*p* = 0.003). Other factors related to an increased risk of both ante- and post-natal depression were financial worries and perceived lack of family support (*p* < 0.05). Sex of the baby was not associated with depression.

**Conclusions:** The prevalence of depressive symptoms is high among pregnant and post-partum women in this population. Risk factors were similar to those found in other populations.

4964

#### Antenatal Maternal Mental Health Predicts Preschoolers' Neuronal Firing during an Executive Functioning Task

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**Research question:** Antenatal symptoms of depressed mood and anxiety predict offspring brain development, important to executive functioning (EF). We ask whether normative variation in maternal mental health predicts preschoolers' neuronal firing during an EF task.

**Methods:** Pregnant women participating in "Growing Up in Singapore Towards Healthy Outcomes" completed mental health questionnaires. At 3.5 years of age, a subset of their children participated in an electrophysiological test yielding neuronal firing patterns likely reflective of cognitive inhibition.

**Results:** After controlling for accuracy and neuronal firing at baseline, increased symptoms of antenatal depression and state anxiety significantly predicted less coordinated neuronal firing at test (State Anxiety: *B* = 0.261, *p* = 0.013, *n* = 71; Depression: *B* = 0.231, *p* = 0.021, *n* = 72); trait anxiety marginally predicted (*B* = 0.184, *p* = 0.078, *n* = 70). Neither depression nor anxiety between three and twenty-four months postpartum significantly associated with neuronal firing.

**Conclusion:** Even subtle differences in maternal anxiety and depression, specifically during the antenatal period, may affect offspring EF. As previous research suggests links between poor EF and psychopathology, these results suggest a cognitive mechanism for the inter-generational transmission of internalizing disorders.

4815

#### Effect of early nutrition on later cognition: human milk nutrients at 3 months of age predict declarative memory abilities at 2 and 3 years of age

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**Research question:** We hypothesized that docosahexaenoic acid (DHA) and free choline intake at 3 months of age in exclusively breastfed infants and their interaction would predict the ability to recall ordered sequential steps in toddlerhood.

**Methods:** Participants ( $n = 121$ ) from a study of human milk nutrients and cognition returned to the lab for follow-up at 26 and 38 months old. Eighty-nine had full data. Using an imitation paradigm, toddlers were tested for declarative memory abilities immediately, after 20 minutes, after one week, and after a refresher demonstration at the 1-week delay session. Multivariate regressions were conducted by age controlling for months exclusively breastfed and predicting the four recall scores by DHA, free choline, and DHA X free choline.

**Results:** For 2-year-olds, the ability to immediately recall ordered steps was related to DHA ( $p = 0.05$ ) and DHA X choline ( $p < 0.05$ ). The ability of 2-year-olds to recall ordered steps after relearning at the 1-week delay was related to DHA ( $p < 0.05$ ) and DHA X choline ( $p < 0.05$ ). In 3-year-olds, DHA, choline, and their interaction predicted (all  $p < 0.05$ ) relearning of the steps with no significance in ordering the steps.

**Conclusion:** Early human milk nutrients have long-lasting effects on declarative memory abilities.

4717

#### **Effects of iron and n-3 fatty acid supplementation, alone and in combination, on cognition and behavior in South African school children**

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**Research question:** We investigated the effects of iron and n-3 fatty acid (FA) supplementation, alone and in combination, on cognition and behaviour in South African school children with poor iron and n-3 FA status.

**Methods:** Children ( $n = 321$ , 6-11 years) were allocated to receive 1) iron plus a mixture of docosahexaenoic acid and eicosapentaenoic acid (DHA+EPA), 2) iron plus placebo, 3) placebo plus DHA+EPA, or 4) placebo plus placebo as oral supplements (4/wk) for 8.5 months. Cognition was assessed at baseline and endpoint. In a sub-sample ( $n = 98$ ), teacher-rated classroom behaviour was determined, and physical activity was measured during school days using accelerometers.

**Results:** Iron supplementation increased performance in a test of verbal memory. DHA+EPA supplementation showed no benefits on any of the cognitive tests, but decreased physical activity counts and increased sedentary physical activity during morning class time. DHA+EPA did not affect teacher-rated

behaviour, but lower physical activity during morning class time was associated with lower levels of teacher-rated hyperactivity and oppositional behaviour at endpoint.

**Conclusions:** Our result suggest that in children with poor iron and n-3 FA status, iron may improve verbal memory, while DHA+EPA may decrease physical activity levels during class time, associated with improved behaviour.

4586

#### **Maternal cortisol concentrations during pregnancy and newborn amygdala volume**

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**Research question:** Alterations in limbic brain structures are associated with neuropsychiatric disorders. In the broader context of the importance of the intrauterine environment in shaping brain development we have previously presented the first evidence in humans that elevated maternal cortisol concentrations during pregnancy are associated in children with amygdala volume and affective problems. We sought in this study to determine whether this effect is already evident in the newborn brain, a time when postnatal influences could not have yet confounded any associations with prenatal influences.

**Methods:** Data from an on-going prospective, longitudinal study in pregnant women and their newborn children will be presented ( $N = 80$ ). 5 ambulatory measures of cortisol over the course of 4 days in each trimester of pregnancy were collected, and newborn brain magnetic resonance imaging scans were acquired for quantification of amygdala volumes applying a semi-automatic segmentation protocol.

**Results:** The preliminary data suggest that after adjusting for potential confounders higher maternal cortisol concentrations during pregnancy are associated with larger amygdala volumes in newborn infants, with this effect being stronger in female than in male offspring.

**Conclusion:** These findings replicate previous observations and suggest a role of maternal gestational glucocorticoid concentrations in programing her offspring's susceptibility for affective disorders.

5043

#### **Markers of allostatic load associate with adverse pregnancy and offspring outcomes in rats**

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**Research question:** Allostatic load is an index of multisystem physiologic risk that can be used as a measure of the cumulative toll (the ‘wear and tear’) of physiologic and psychological stress. It assumes multisystemic interactions including transgenerational inheritance and incorporates subclinical biomarkers of neuroendocrine, inflammatory, and metabolic function into a single index score. We developed a new model of allostatic load in pregnant Long-Evans rats and hypothesized that markers of allostatic load are risk factors for preterm birth and are passed on to subsequent generations.

**Methods:** Pregnant dams were untreated controls (saline injected) or treated to stress (swimming and restraint) from gestational days 12-18 alone, interleukin (IL)-1 $\beta$  alone or both stress + IL1 $\beta$ . The timing of gestation, pregnancy outcomes, behaviour and neurological assessments were monitored.

**Results:** Stress alone or IL1 $\beta$  alone had no effect upon gestational length or adverse outcomes whereas stress + IL1 $\beta$  dams had more preterm deliveries and more adverse outcomes. Offspring from stressed, IL1 $\beta$  and stress + IL1 $\beta$ -treated dams displayed behavioural, neurological and neurodevelopmental changes compared to offspring from control dams. Frequently stress + IL1 $\beta$  produced the worst results.

**Conclusion:** Allostatic load markers associate with adverse pregnancy and offspring outcomes and may be used to predict risk.

4509

#### **Do maternal anxiety and mindfulness during pregnancy affect infant cognition and emotion? Results from a brain imaging study**

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**Research question:** We examined the effect of both negative (i.e., maternal anxiety) and positive (i.e., maternal mindfulness) prenatal exposure on infant auditory attention and multimodal processing of emotional information.

**Methods:** Measurements were conducted with n = 79 to 82 mother-infant pairs. Mothers completed the Symptom Checklist (SCL-90, anxiety subscale), State-Trait Anxiety Inventory and Freiburg Mindfulness Inventory. We recorded event-related potentials (ERPs) in the nine-month-old infants, using an auditory oddball paradigm with a standard tone and three types of deviants and an auditory/visual paradigm presenting fearful and happy face/voice pairs. Repeated measures mixed-model ANCOVAs were run on the mean ERPs

amplitudes (influence of gender, alcohol intake, birth weight was controlled for).

**Results:** For ERP responses elicited by standard sounds, anxiety was positively associated with the N250 amplitude while mindfulness was negatively associated with the N250 amplitude; mindfulness was also positively associated with the P150 amplitude. Larger P350 amplitudes were revealed in response to fearful vocalizations regardless of visual prime type.

**Conclusion:** Infants prenatally exposed to high maternal anxiety devote more attentional resources to repeated sounds with lower information content and process fear-related stimuli more extensively. These processes might underlie infant vigilance and anxiety. Importantly, higher mindfulness in pregnancy has some opposite effects.

4500

#### **Fatty fish intake during pregnancy and postpartum depression in the Norwegian Mother and Child Cohort Study**

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**Research question:** Intake of seafood during pregnancy has been indicated to reduce the risk of postpartum depression (PPD). The aim of this study was to examine whether maternal intake of fatty fish was associated with PPD.

**Methods:** In the Norwegian Mother and Child Cohort Study, 56,303 women reported dietary intake during pregnancy and answered the Edinburgh Postpartum Depression Scale six months postpartum. Dietary intake of fatty fish was calculated and OR for risk of PPD was evaluated using logistic regression.

**Results:** The prevalence of PPD was 10.6% and mean intake of fatty fish was 84 g per week, which is less than one fatty fish dinner per week. Intake of between 140–280 g fatty fish per week reduced the risk of PPD compared with intake of 35 g or less [adjusted odds ratio (OR): 0.79 (95% CI: 0.72, 0.86)]. Increasing fatty fish intake further was not associated with reduced risk of PPD. Adjusting for lean fish intake or use of EPA+DHA supplements had little impact on the association.

**Conclusion:** Intake of 1-2 servings of fatty fish per week during pregnancy was associated with reduced risk of PPD. This association was not affected by long chain n-3 fatty acids supplementation.

4702

#### **Overweight and obesity: life course and multigenerational studies**

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**Introduction:** Optimal birth size and good health in early life is an important health outcome in its own right and is also one predictor of subsequent health and education. Current methodological developments in life course epidemiology create unique opportunities to investigate how early circumstances and exposures shape later outcomes and how parental and grandparental characteristics influence health and social outcomes of descendant generations.

**Methods:** We attempt to model continuities in birth outcome and body size across generations together with social mobility patterns in a dynamic way that allows for bidirectional and time changing effects. In this way, we aim to examine the scope for breaking the “chains of risk” between generations, and to highlight new potential ways to reduce long term inequalities. We mainly use data from the Uppsala Birth Cohort Multigenerational Study ([www.chess.su.se/ubcosmg/](http://www.chess.su.se/ubcosmg/)) and other linked register data where we can apply a life course and intergenerational approach to analysis.

**Results:** Multiple sub-studies demonstrate associations between social and health characteristics across more than two generations. Examples include social patterning of pre-pregnancy body mass index, weight gain in pregnancy, size at birth, childhood overweight and obesity as well as incidence of diagnosed eating disorders.

**Conclusion:** When mechanisms by which poor health and adverse parental (and grandparental) socioeconomic position translate into social and health disadvantage in the offspring.

4154

#### **Grandparents cardiovascular risk factor profiles are associated with grandchildren’s anthropometric measures at age 5 and 9 years in the Lifeways Cross-Generation Cohort Study**

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**Research question:** Three generation cohort studies are rare. To assess whether the cardiovascular disease (CVD) risk factor profile of grandparents of 4 lineages at 10 year follow-up relate to the body mass index (BMI), waist circumference (WC) or lipoprotein profile of their grandchildren.

**Methods:** In a sub-sample of 153 families in Dublin, both grandparents and children were examined to a standardised

clinical protocol; bloods were taken from all grandparents and 43 children. Pearson’s correlation coefficients are reported.

**Results:** Children’s BMI aged 5 and aged 9 was associated with that of grandparents ( $r = .206, p = .011$  and  $r = .198, p = .035$ ) as was child’s WC aged 9 ( $r = .224, p = .017$ ). Grandparents’ WC was associated with that of child aged 5 and 9 also. Grandparents’ HBaIC was associated with child’s WC aged 5. Grandparents’ HDL cholesterol was inversely ( $p < .03$ ) and LDL cholesterol positively associated with child’s BMI and WC at both timepoints ( $p < .04$ ). The maternal grandmother (MGM) had the most consistent association, additionally having significant associations between child’s total cholesterol and LDL cholesterol and her own ( $p < 0.02$ ).

**Conclusion:** These highly novel data show clustering of CVD risk factors in families across generations, most consistently for the MGM.

5351

#### **Maternal Obesity Programs Offspring Hyperphagia via Enhanced Appetite and Reduced Anorexigenic Neurons**

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As the prevalence of obesity among pregnant women continues to rise, increasing number of children are exposed to an ‘obese intrauterine environment’ during development. Maternal obesity increases the risk of offspring obesity, due in part to altered development of appetite regulatory neurons in hypothalamic arcuate nucleus (ARC). The ARC contains two populations of neurons, derived from neural stem cell (NSC) progenitors, which have opposing actions on food intake: orexigenic (AgRP; agouti-related protein) and anorexigenic (POMC; pro-opiomelanocortin). The development of these neurons from is regulated by bHLH neuroproliferative factor (Hes1) which promotes NSC proliferation and inhibits downstream bHLH neurodifferentiation factors (Mash1, Ngn3). Ngn3 further promotes the development of anorexigenic POMC neurons, while inhibiting AgRP expression. We hypothesized that (1) maternal obesity impacts fetal hypothalamic ARC development, increasing expression of appetite (AgRP) versus satiety (POMC) neurons, and (2) these changes are mediated by Hes1 and Mash1/Ngn3.

**Methods:** Female mice were fed either a control (10% k/cal) or high fat (45% k/cal) diet to create maternal obesity (MO) prior to mating, and diets continued throughout pregnancy and lactation. Newborns were delivered spontaneously, males sacrificed at day one of life, and brains collected. Hypothalamus was dissected and protein expression analyzed (Western Blot) for Hes1 (neuroproliferation), Mash1 and Ngn3 (neurodifferentiation), and AgRP and POMC expression.

**Results:** At 1 day of age, MO males were significantly heavier ( $1.55 \pm 0.09$  vs  $1.31 \pm 0.01$  g) than Controls. MO males exhibited decreased hypothalamic expression of Hes1 (0.6-fold) and Ngn3 (0.8-fold) with increased expression of Mash1 (2.8-fold). Consistent with these changes, expression of AgRP was significantly increased (1.5-fold) and POMC was significantly reduced (0.7-fold).

**Conclusions:** MO offspring appetite regulation is biased toward orexigenic, and away from anorexigenic neurons, resulting in excess appetite, reduced satiety and development of obesity. The putative underlying mechanism involves reduced Hes1 which promotes premature neuronal differentiation as evident by increased Mash1. Reduced Ngn3 expression impairs anorexigenic POMC neuronal development, resulting in increased AgRP expression. Early modifications of the maternal nutrient environment may prevent altered development of appetite regulation.

4411

#### Maternal trans fatty acid status in relation to birth outcomes in a multi-ethnic Asian population

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**Research question:** Does maternal elaidic acid (the main industrially produced trans fatty acid) status influence birth outcomes?

**Methods:** Maternal blood samples ( $n = 999$ ; 26th-28th week gestation) were analyzed for plasma fatty acids using gas chromatography. Relationships between maternal plasma phosphatidylcholine elaidic acid (% total fatty acids) and duration of gestation and neonatal anthropometry were assessed by multivariable regression analysis.

**Results:** Women in the highest quartile of elaidic acid status (median: 1.75%) had an odds ratio (OR) for delivering small for gestational age infants (SGA; <10th percentile for gestational age) of 2.25 (95% confidence interval (CI): 1.22, 4.15), as compared with women in the lowest quartile (median: 1.16%). Similarly, the highest quartile of elaidic acid status was associated with a 134.6 g (95% CI: 70.4, 198.8) lower birth weight and a 0.52 cm (95% CI: 0.19, 0.85) shorter birth length as compared with the lowest quartile. In contrast, maternal elaidic acid status was not associated with duration of gestation at birth and preterm delivery (<37 weeks).

**Conclusion:** Higher maternal elaidic acid status was associated with lower birth weight, shorter birth length, and a higher risk of delivering SGA infants, suggesting that high trans fat intake during pregnancy may affect fetal growth.

4428

#### Maternal Retinal Vasculature Is Indicative For Subsequent Fetal Growth And Birth Size At Birth

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**Objective:** We aimed to study the maternal retinal microvasculature at mid-trimester and its relationship with subsequent fetal growth and birth size.

**Methods:** We recruited 732 pregnant women aged 18-46 years in the first trimester with singleton pregnancies. All had retinal photography and fetal scan performed at 26-28 weeks gestation, and subsequent fetal scan at 32-34 weeks gestation. Infant anthropometric measurements were done at birth. Retinal microvasculature was measured using computer software from the retinal photographs.

**Results:** In multiple linear regression models, each 10  $\mu\text{m}$  narrowing in maternal retinal arteriolar caliber was associated with decreases of 1.36 mm in fetal head circumference at 32-34 weeks gestation, as well as decreases of 1.50 mm and 2.30 mm in infant head circumference and birth length at delivery, respectively. Each standard deviation decrease in maternal retinal arteriolar fractal dimension was associated with decreases of 1.55 mm in fetal head circumference at 32-34 weeks gestation, as well as decreases of 1.08 mm and 46.42 g in infant head circumference and birth weight at delivery, respectively.

**Conclusions:** Narrower retinal arteriolar caliber and a sparser retinal vascular network in mothers, reflecting a suboptimal uteroplacental microvasculature during mid-pregnancy, were associated with poorer fetal growth and birth size.

#### 4449

### **BMI in early pregnancy is more important for fetal growth than metabolic factors in early pregnancy and longitudinal changes during pregnancy**

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**Research question:** BMI influences fetal growth and changes in glucose and lipid metabolism during pregnancy. We hypothesized that metabolic factors present in early pregnancy and longitudinal changes are associated with fetal growth.

**Methods:** 1031 healthy women were followed prospectively and categorized according to BMI; BMI < 25 (n = 628), BMI 25-30 (n = 286) and BMI > 30 (n = 89). BMI, gestational weight gain (GWG), fasting plasma glucose (FPG), insulin and lipids (cholesterol, HDL, LDL, triglycerides) were measured longitudinally at 15 weeks (v1), 31 weeks (v3) and 36 weeks (v4). Outcomes were birthweight (BW), placental weight (PW) and fetal-placental-ratio (FPR). Analyses were done by linear regression models.

**Results:** Fetal growth outcomes(g) differed between groups; BMI < 25; BW 3510 (548), PW 692 (153), FPR 5.21 (0.9), BMI 25-30; BW 3706 (577), PW 736 (148), FPR 5.15 (0.8) and BMI > 30; BW 3757 (644), PW 768 (644), FPR 4.99 (0.8).

Maternal metabolic factors associated with FPR (B, 95% CI, p-value); BMIv1 -0.02, -0.03-0.0, p = 0.045,  $\Delta\text{HDL}$  cholesterol 0.5, 0.2-0.7, p < 0.001.

Maternal metabolic factors associated with BW; BMIv1 21.8, 14.3-29.5, p < 0.001, GWG 2.5, 15.6-31.4, p < 0.001, FPGv1 179.2, 95.6-262.7, p < 0.001,  $\Delta\text{FPG}$  148.5, 75.2-221.8, p < 0.001,  $\Delta\text{HDL}$  -284.5, -369.6-199.5, p < 0.001.

Maternal metabolic factors associated with PW; BMIv1 5.6, 2.8-8.4, p < 0.001, insulinv1 0.5, 0.5-1.0, p = 0.3, GWG 5.0, 2.2-7.8, p < 0.001,  $\Delta\text{HDL}$  -119.2, -151.9-86.4, p < 0.001.

**Conclusion:** Among metabolic factors present in early pregnancy and longitudinal changes associated with measures of fetal growth, BMI is consistently an important factor. When adjusted for BMI in early pregnancy most metabolic factors are less significant. Therefore, a healthy BMI should be encouraged before pregnancy.

#### 4490

### **Association between maternal mid-gestation vitamin D and offspring's abdominal adiposity**

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**Research question:** To study the association between maternal mid-gestation vitamin D status and offspring neonatal abdominal adipose tissue volumes.

**Methods:** 204 mother-offspring pairs without gestational diabetes who were born  $\geq 34$  weeks gestation and  $\geq 2000\text{g}$  had complete data for maternal 25-OH vitamin D at 26-28 weeks, neonatal abdominal adipose tissue (AAT) volumes by MRI and fat mass by PEAPOD air displacement plethysmography 7-21 days postpartum. MRI AAT was classified into superficial (sSAT), deep subcutaneous (dSAT) and internal adipose tissue (IAT). Vitamin D was classified based on Endocrine Society Clinical practice guideline 2011 (<50 nmol/L: deficient, 50-72.5 nmol/L: insufficient and >72.5 nmol/L: sufficient).

**Results:** Adjusting for maternal and fetal confounders, neonates in the 3 maternal vitamin D groups had similar total body fat mass by PEAPOD. dSAT was greater in neonates of vitamin D deficient and insufficient groups compared to those of sufficient group (by 2.0 (95% CI: 0.03-4.0) and 2.0 (0.4-3.6) ml, respectively). sSAT was greater in neonates of deficient

group compared to neonates of sufficient group (by 7.9 (0.5-15.3) ml). IAT was similar among neonates of 3 vitamin D groups.

**Conclusion:** Maternal mid-gestation vitamin D deficiency is associated with greater superficial and deep subcutaneous adipose tissue volumes in neonates.

4523

### **Influence of maternal gestational hypertensive disorders on microvasculature in school-age children. The Generation R Study**

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**Aims:** To examine the associations of maternal blood pressure development and hypertensive disorders during pregnancy with microvasculature adaptations in childhood

**Methods and results:** In a population-based prospective cohort study from early pregnancy onwards among 3,748 pregnant mothers and their children, we measured maternal blood pressure in different periods of pregnancy. Information about gestational hypertensive disorders was obtained from medical records. At the age of 6 years, retinal arteriolar and venular calibers were measured from retinal photographs. Higher maternal systolic and diastolic blood pressure in early pregnancy were associated with childhood retinal arteriolar narrowing (differences: -0.08 SDS (95% CI -0.12, -0.04) and -0.05 SDS (95% CI -0.09, -0.01), per SDS increase in systolic and diastolic blood pressure, respectively). These associations were independent from maternal blood pressure in mid- or late pregnancy. Maternal blood pressure in mid-pregnancy was not independently associated with childhood retinal vessel calibers, whereas higher maternal systolic blood pressure in late pregnancy was associated with childhood narrower retinal venular caliber only (p-value < 0.05). Children of mothers with gestational hypertensive disorders tended to have narrower retinal arteriolar caliber (difference: -0.13 SDS (95% CI -0.27, 0.01)).

**Conclusions:** Our results suggest that higher maternal blood pressure during pregnancy is associated with persistent microvasculature adaptations in their children. Further studies are needed to replicate these observations and to examine the long-term consequences.

4527

### **Maternal polyunsaturated fatty acid levels during pregnancy and childhood adiposity**

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**Research question:** To examine the associations of maternal polyunsaturated fatty acid levels during pregnancy with general and abdominal childhood fat distribution measures.

**Methods:** In a population-based prospective cohort study among 4,830 mothers and their children, we measured maternal second trimester n-3 and n-6 PUFA plasma levels. At the median age of 6.0 years (95% range, 5.6–7.9), we measured childhood body mass index, fat mass percentage, android/gynoid fat ratio with dual-energy x-ray absorptiometry, and pre-peritoneal abdominal fat area with ultrasound.

**Results:** We observed that higher maternal total n-3 PUFA levels, and specifically eicosapentaenoic acid, docosapentaenoic acid, docosahexaenoic acid levels, were associated with lower childhood total body fat percentage and lower android/gynoid fat mass ratio (p-values < 0.05), but not with childhood body mass index and abdominal pre-peritoneal fat mass area. Higher maternal total n-6 PUFA levels and specifically dihomo-gamma linolenic acid were associated with a higher childhood total body fat percentage, android/gynoid fat mass ratio and abdominal pre-peritoneal fat mass area (p-values < 0.05), but not with childhood body mass index.

**Conclusion:** Our findings suggest that lower maternal n-3 PUFA levels and higher n-6 PUFA levels during pregnancy are associated with higher total body fat and abdominal fat levels in childhood.

4530

### **The relation between anemia in different trimesters and changes in the placental vascularization, Northeastern Tanzania**

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**Research question:** The first and second trimesters during pregnancy are time points where anemia could have a profound effect on the placental and fetal development. The aim of this study is to evaluate how anemia in the first and second trimester of pregnancy will influence the villous branching of the placenta as compared to third trimester anemia. Furthermore, the effect of anemia on the Vascular Endothelial Growth Factor (VEGF) and the Placental Growth Factor (PlGF)-balance will be evaluated.

**Method:** This sub-study is a part of a major project entitled 'FOETALforNCD – foetal exposure and epidemiological transition: the role of anaemia in early life for non-communicable diseases in later life'. Placental biopsies from women with different hemoglobin (Hb) levels (Hb  $\leq$  8 g/dL; Hb 8.1-10.9 g/dL and Hb  $\geq$  11 g/dL) and blood samples collected at 20 weeks gestational age (GA) from women included in the FOETALforNCD study will be analyzed.

Development of the placental vasculature will be investigated using stereological and immunohistological examination of placental biopsies. The PlGF/VEGF-balance will be quantified by enzyme-linked immunosorbent assay in Tanzania.

**Results and conclusion:** Data collection is on-going. Preliminary results from 10 placental examinations and VEGF/PlGF results from 74 women will be presented.

4528

#### **Dynamics of second trimester anaemia with foetal growth and birth outcome in a longitudinal study in Tanzania**

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**Research question:** Anaemia during pregnancy is highly prevalent in Africa and reduces birth weight (BW), which might increase the risk of non-communicable diseases later in life. The most vulnerable time-point for anaemia in pregnancy is not well established.

**Methods:** A cohort of 896 women with singleton pregnancy were followed from a gestational age (GA) of <24 weeks. Foetal growth was estimated throughout pregnancy using ultrasound. Full hematology count and screening for malaria was

performed at every contact. Data on maternal anthropometry and birth outcome were collected. Severe-moderate anaemia was defined as HB  $\leq$  8g/dL.

**Results:** In total, 16.5% (148) of the women suffered from severe-moderate anaemia at some time-point during pregnancy. Microcytic hypochromic anaemia, indicative of micronutrient deficiency, was predominant. Ninety-four women (10.5%) experienced severe-moderate anaemia in the 2nd trimester, which was associated with reduced foetal growth in the 3rd trimester (-9,4g/day\*kg; p=0,026), reduced BW (-139g, p=0,012), and increased risk of being small for gestational age (OR 2,4 p=0,007) (adjusted for Body Mass Index, GA at delivery, newborn's sex, and exposure to malaria). A similar effect was not observed in women suffering anaemia in the 3rd trimester.

**Conclusion:** Severe-moderate anaemia in the 2nd trimester has the most detrimental effect on birth outcome.

4579

#### **Dissecting the relationship between depression and adiposity in young adult offspring: the Western Australian Pregnancy Cohort (Raine) Study**

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**Research question:** There is an increase in mental health related issues in younger populations, a strong bidirectional correlation between depression and obesity; maternal smoking in pregnancy association with offspring behavioral disorders and obesity. Does the interplay between negative emotional states with prenatal (maternal smoking) and postnatal (hormonal contraceptive usage in girls) psycho-social factors affect depression correlation with BMI at age 20?

**Methods:** The effect of maternal smoking on young adult BMI was assessed as a function of depression, anxiety, and stress score (DASS) in the offspring males, and females using and not using hormonal contraceptive (HC) among offspring participants aged 20 years in Western Australian Pregnancy Cohort (Raine) Study.

**Results:** The change in the DASS and BMI slopes, between HC user vs. HC non-user female and male vs. HC non-user female in the maternal non-smokers and corresponding change in the mothers smoking group was significant with respective estimates of [-0.14 (95% CI -0.26 -0.02)] and [-0.21 (95% CI -0.32 -0.10)] for HC user female and males.

**Conclusions:** We found a positive correlation between DASS and BMI at age 20. Non-HC user females, with a mother who smoked during the pregnancy, showed the strongest positive relationship between DASS and BMI.

5144

**Characterising Public Understanding of DOHaD to Inform Communication Strategies**Jacquie Bay<sup>1</sup>, Robyn Dixon<sup>2</sup>, Sarah Morgan<sup>3</sup>, Clare Wall<sup>4</sup>, Masahito Oyamada<sup>5</sup><sup>1</sup>Liggins Institute, University of Auckland, New Zealand; <sup>2</sup>Faculty of Medical and Health Sciences, University of Auckland, New Zealand; <sup>3</sup>Liggins Institute, University of Auckland, New Zealand; <sup>4</sup>Faculty of Medical and Health Sciences, University of Auckland, New Zealand; <sup>5</sup>Fuji Women's University, Japan**Research question:** To characterize the level of understanding of DOHaD concepts in an urban adult population in New Zealand.**Methods:** A structured questionnaire was used to ascertain knowledge of DOHaD concepts in the general public. Structured oral interviews were conducted outside of a popular retail store in socio-economically varied suburbs of the city of Auckland, New Zealand.**Results:** The cohort (n = 900) shows a relatively low level of understanding of DOHaD concepts. In comparison to common public health messages, such as 'the food we eat affects our health and wellbeing', the DOHaD messages of 'the food a mother eats during pregnancy may affect the health of the baby through to adulthood' is about a third lower (98% to 60%). In comparison, 80% of the cohort agreed that the tobacco smoke exposure of the mother and father would affect the health of the child in adulthood.**Conclusion:** Given that 11% of premature morbidity and mortality in New Zealand is caused by the 4 main NCDs (Cancers, diabetes, cardiovascular diseases and chronic respiratory diseases), these data highlight the need for public health interventions, centred on DOHaD concept translation. Validation of the survey tool across a range of contexts offers potential for future intervention impact comparison.

4655

**First Trimester Prediction of GDM using maternal characteristics: Scope for improvement? Preliminary Results from the PRiDE study**Hema Venkataraman<sup>1</sup>, Kate Myler<sup>2</sup>, Emma Marston<sup>3</sup>, Nithya Sukumar<sup>4</sup><sup>1</sup>University of Warwick; <sup>2</sup>University of Warwick; <sup>3</sup>University of Warwick; <sup>4</sup>University of Warwick**Research question:** To assess the first trimester prediction of GDM using maternal characteristics.**Methods:** Data from the PRiDE study was used to design a model to predict GDM defined by NICE (FPG-5.6, 2hPG-7.8) or IADPSG (FPG-5.1, 2hPG-8.5) criteria. The basic model consisted of the NICE selective screening criteria i.e. Family history (FH) of GDM, BMI  $\geq$  30, previous

macrosomia/stillbirth (pMS), ethnic minority (BME) and previous GDM (pGDM).

**Results:** Of 953 women, GDM prevalence was 14.9% and 12% by IADPSG and NICE respectively.

Overall prevalence of screening criteria: BME-24.1%, FH-41.1%, pMS-3.7%, pGDM-5.9% and Obesity-57%. Prevalence in GDM group (NICE vs IADPSG): BME (19.5%, 22.9%), FH (41.6%, 41.4%), pMS (2.7%, 4.3%), pGDM (15.8%, 11.4%) and obesity (63.7%, 67.9%).

pGDM (OR: NICE-5.5, IADPSG-3.6) and age (OR: NICE-1.08, IADPSG-1.06) (P &lt; 0.02 for all) were strong predictors of GDM by both groups. Obesity (OR: 2.6, p = 0.01), Waist-circumference (WC) (OR: 1.02, p = 0.02) and FH (OR: 1.5, p = 0.01) were predictors of GDM by IADPSG criteria only.

The basic model predicted 5.6% and 4.6% of variance in GDM diagnosis by NICE and IADPSG, improving to 8.8% and 6.8% with addition of maternal age.

**Conclusion:** GDM prediction is suboptimal with currently available screening factors. Age should be included in selective screening criteria. Objective measures of maternal adiposity may improve prediction of GDM by IADPSG.

4672

**Maternal lipids and hormones concentration throughout pregnancy and birth weight: a prospective cohort**Dayana Rodrigues Farias<sup>1</sup>, Ana Beatriz Franco-Sena<sup>2</sup>, Christian Henrique Dias-Silva<sup>3</sup>, Thatiana de Jesus Pereira Pinto<sup>4</sup>, Livia Costa de Oliveira<sup>5</sup>, Gilberto Kac<sup>6</sup><sup>1</sup>Rio de Janeiro Federal University; <sup>2</sup>Rio de Janeiro Federal University; <sup>3</sup>Rio de Janeiro Federal University; <sup>4</sup>Rio de Janeiro Federal University; <sup>5</sup>Rio de Janeiro Federal University; <sup>6</sup>Federal University of Rio de Janeiro**Research question:** Are maternal lipids, leptin and adiponectin throughout pregnancy associated with infants' birth weight (BW)?**Methods:** Prospective cohort of 182 pregnant women followed three times during pregnancy and one at postpartum. Infants' BW was obtained from the child vaccination booklet. Maternal serum concentrations of total cholesterol (TC), HDL-c and triglycerides were assayed by the enzymatic colorimetric method and LDL-c was calculated. Plasma leptin and adiponectin were also estimated. We assessed lipids and hormones as absolute concentrations and relative changes. Statistical analyses included crude and adjusted linear regression models.**Results:** LDL-c concentrations and TC/HDL-c and LDL-c/HDL-c ratios at the second and the third trimesters were positively associated with BW. Relative variation of LDL-c and LDL-c/HDL-c and TC/HDL-c ratios from the first to the second trimester and the overall pregnancy change were positively associated with infants' BW while changes in HDL-c (from first to second trimester and overall) were negatively associated. Leptin was positively associated with BW in the first trimester while the

relative variation from the first to the second trimester was negatively associated.

**Conclusion:** Maternal LDL-c, HDL-c and leptin concentrations and LDL-c/HDL-c and TC/HDL-c ratios during pregnancy were significantly associated with infants' BW, even after adjustment for confounders.

4557

### **Fetal liver blood flow in mid-gestation is prospectively associated with newborn adiposity**

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**Research question:** Variation in the relative distribution and shunting of umbilical venous blood flow perfusing the fetal liver has been proposed as one mechanism underlying fetal programming of health and disease risk. We hypothesized that fetal liver blood flow (fLBF) in mid-gestation influences fetal growth and predicts newborn adiposity.

**Methods:** Fetal ultrasound was performed in 56 mother-child dyads at 30 ± 1.2 wks gestational age (GA) for biometry and fLBF. fLBF was derived by subtracting umbilical vein flow from ductus venosus flow. Newborn percent total body fat (NB %BF) was quantified using dual-energy X-ray absorptiometry (DXA) within the first month of life (3.7 ± 1.5wks). Stepwise multiple regression analyses were performed to determine the associations between fLBF, biometry, and NB%BF. Covariates included GA at ultrasound, GA at birth, postnatal age at DXA, maternal age, parity, SES, race/ethnicity, pre-pregnancy BMI, gestational weight gain and obstetric complications.

**Results:** Greater fLBF was significantly associated with larger fetal abdominal circumference ( $\beta = 0.23$ ,  $p = 0.014$ ), higher estimated fetal weight ( $\beta = 0.27$ ,  $p = 0.001$ ) and higher NB%BF ( $\beta = 0.38$ ,  $p = 0.002$ ).

**Conclusion:** Greater fLBF in mid-gestation is associated with increased fetal growth, and also accounts for a significant proportion of the variance in newborn adiposity, providing

further evidence that intrauterine developmental processes program risks for infant obesity.

4801

### **Premature weaning impairs beta cell regeneration later in life**

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It has been proposed that events during fetal life may predispose to adult metabolic disease, and specifically to  $\beta$ -cell failure. However the effects of conditions during early postnatal life were not studied. We examined the impact of premature weaning on glucose homeostasis and the regenerative potential of  $\beta$ -cells in mice.

Wild-type mice weaned prematurely (at postnatal day 17) show normal body weight and glucose tolerance, even when placed on high fat diet for up to 3 months. To examine the potential of  $\beta$ -cells to cope with severe injury, we utilized transgenic Insulin-rtTA/TET-DTA mice, in which the majority of  $\beta$ -cells can be ablated following the administration of doxycycline.  $\beta$ -cell ablation in 4 weeks-old mice spontaneously weaned to high-carbohydrate chow led to a robust regenerative response of  $\beta$ -cells and recovery of normoglycemia, as previously reported. Strikingly, premature weaning at P17 led to failure of  $\beta$ -cell regeneration in the majority of mice. Adult Akita mice bearing a folding mutation in the Ins2 gene were more severely diabetic if weaned prematurely.

We propose that  $\beta$ -cells require a minimum time of exposure to a fatty component of milk to gain long term potential for regeneration and survival. The findings may have public health implications regarding the importance of breast feeding.

4551

### **Maternal flaxseed oil supplementation during lactation programs adipose tissue inflammation in male adults rats but not in female**

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**Research question:** We aimed to evaluate if maternal flaxseed oil supplementation during lactation affects adipose tissue inflammation in male and female offspring at adulthood.

**Methods:** Lactating rats were divided: control (C), 7% soybean oil; hyper 19% soybean oil (HS) and hyper 17% flaxseed oil + 2% soybean oil (HF). After weaning, the male and female offspring received a standard diet until 180 days old (PN 180), when we collected the adipose tissue.



**Results:** Male rats presented lower adiponectin in HF (-61%) and HS (-60%), lower PPAR- $\gamma$  in HF (-42%) and HS (-51%), higher TNF- $\alpha$  in HF (3.5 fold vs C; 4 fold vs HS), higher IL-6 (2.7 fold vs C; 2 fold vs HS), higher IL-1 $\beta$  (2 fold vs C and HS) and higher IL-10 (2 fold vs C and HS) mRNA expression in epididymal adipose tissue. The HF female presented higher leptin (+82%) and lower adiponectin (-59%), TNF- $\alpha$  (-70% vs C), IL-6 (-58% vs C) and IL-1 $\beta$  (-70%) mRNA expression in ovarian adipose tissue.

**Conclusion:** Flaxseed oil during lactation cause a sexual dimorphism at adulthood, characterized by increased adipose tissue inflammation markers, while the female shows a decrease in these cytokines.

4596

### Short chain fatty acids in human milk influence infancy anthropometry outcomes

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**Research question:** Putative protective effects of human breast milk (HM) on later reduced obesity risk are likely to be complex and multifactorial. We investigated whether short chain fatty acids (SCFAs), known to promote energy expenditure, are associated with infancy anthropometrics.

**Methods:** We studied 641 HM hindmilk samples in a prospective birth cohort. Body size at 3 and 12 months, using weight, length and skinfold thickness z-scores, was related to HM SCFA measured by 1H-nuclear magnetic resonance spectroscopy (NMR).

**Results:** NMR peaks for HM butyrate, acetate, formic acid, but not propionate, were detected. Overall, SCFAs were unrelated to infant sex, maternal BMI, mode of delivery, gestational age and birth-weight. However, butyrate peaks were higher in HM from exclusively breast-feeding mothers than those mixed-feeding ( $p = 0.003$ ).

HM butyrate was inversely related to 12-month skinfolds ( $rs -1.0$ ,  $p = 0.02$ ), 12-month BMI ( $rs -0.09$ ,  $p = 0.04$ ), 3-12 month skinfolds gain ( $rs -0.1$ ,  $p = 0.002$ ), 3-12 month weight gain ( $rs -1.1$ ,  $p = 0.01$ ). HM acetate and formic acid showed similar but less pronounced associations with adiposity.

**Conclusions:** SCFAs, specifically butyrate, potentially resulting from maternal/HM microbiome variation may play a role in weight gain and adiposity. Confirmation of these findings,

and exploration of HM SCFA origin may be critical to future strategies to reduce rapid infancy weight gain.

4630

### The effect of exclusive breastfeeding on growth in rural Gambian infants: Data from the ENID trial (ISRCTN49285450)

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**Research question:** Does adherence to the WHO's exclusive breastfeeding (EBF) recommendation improve infant growth in rural Gambia?

**Methods:** Feeding pattern information was collected weekly for 778 infants from birth to 1 year of age, categorizing infants as EBF if only breast milk was given in the first 6 months. EBF status was entered into sex-adjusted multilevel models to test its association with weight-for-age and length-for-age growth curves describing 8,476 serial observations of weight and 8,524 of length collected monthly. The same was done for waist circumference and skinfold variables with 7,867 observations.

**Results:** Although evidence exists that the shape of the estimated weight and length curves differed by EBF status, the estimated differences in weight and length between EBF and non-EBF infants were small at birth, 6 months, and 1 year of age with all 95% confidence intervals crossing zero. The same effect was seen for estimated waist circumference and adiposity curves, however the evidence was stronger for waist circumference at 6 months and for adiposity at 1 year.

**Conclusion:** EBF to 6 months of age among Gambian infants may result in greater adiposity. In this environment, this effect might serve as a natural protection against infections around weaning age.

4677

### To what extent do secular trends toward obesogenic infant growth trajectories reflect changes in feeding practices in American Samoa?

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**Research question:** Dramatic increases in obesity prevalence have occurred in American Samoa since the 1970s, reflecting trends in the Pacific region as a whole. Our aim was to determine whether these trends are reflected in infant growth trajectories and how changing infant feeding practices may influence infant growth.

**Methods:** We compared multilevel weight-for-age and length-for-age growth curves from birth to 15 months of age, and the effects of infant feeding (breastfed, formula- or mixed-fed) on the curves, in two cohorts of term, singleton Samoan infants born in 1976-1982 (n = 6,267) and 2001-2008 (n = 795) in American Samoa.

**Results:** While birth weight was similar, the 2001-2008 cohort grew faster in infancy; by 4-months the 2001-2008 cohort were approximately 120g heavier and almost a centimeter longer than the 1976-1982 cohort. By 12-months they were over 300g heavier and almost 3cm longer. Duration of exclusive breastfeeding was longer among the 1976-1978 cohort and mixed-feeding was practiced more widely among the contemporary group, accounting for some of the differences in infant growth.

**Conclusion:** Secular trends towards larger body size in this population can be detected as early as infancy. Changing infant feeding practices is a likely contributor to these trends.

#### 4862

##### **Birth socio-economic status (SES) is more strongly associated with BMI/body fat than changing SES birth to 16 years in South African adolescents**

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**Research question:** How does household SES and change in household SES from infancy to adolescence associate with obesity risk in urban South African adolescents?

**Methods:** The study included 847 male and 911 female participants aged 17/18 years from the South African Birth to Twenty cohort with household SES measures from infancy to 16 years, birthweight, BMI and DXA assessed body fat values (kg) at 17/18 years. Structural equation modelling was applied to study the relationship between birth SES and socio-demographic environment, birthweight, growth in SES over the period and BMI/body fat at ages 17/18 years.

**Results:** We reveal significant change in SES within the cohort. However, change in SES is not significantly associated with either BMI or body fat. Infancy SES is associated directly with

BMI (standardised coefficient = 0.13 (se = 0.05)) and body fat (standardised coefficient = 0.15 (se = 0.05)) in boys, and indirectly with BMI in girls through its association with birthweight (standardised coefficient = 0.06 (se = 0.03)).

**Conclusion:** This is the first paper to consider SES change in a transitioning environment at more than 2 time points and to relate this to obesity risk prospectively. Our findings reveal that changing SES in the early life-course does not build on significant risks for obesity associated with infancy SES.

#### 5409

##### **Early Life Growth and Blood Pressure across the Life-course in urban South Africa**

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Early life growth is associated with a single measurement of blood pressure (BP); but its association with life course BP trajectories remain unclear. This study seeks to assess association between early life growth and BP trajectories between childhood and adulthood using Birth to Twenty cohort anthropometric data from childhood to 18 years for black participants.

Relative weight gain (RWG) at ages 0-2, 2-4, 4-18 years was computed from regression of current weight on previous weight independent of height. Latent variable growth curve modelling was used to identify distinct trajectories for systolic (SBP) and diastolic (DBP) blood pressure, separately for boys (n = 932) and girls (n = 1005). Relative risk ratios (RR) obtained from multinomial logistic regressions was used to describe the association between early life growth and BP trajectories.

Three trajectories of SBP and DBP were identified: low, moderate and elevated for boys and girls, separately. RWG in infancy was associated increased risk of being in the moderate SBP trajectory; boys (RR 1.37, 95% CI 1.09 to 1.71) and girls (RR 1.40, 95%CI 1.12 to 1.76) and DBP trajectory for both boys (RR 1.41, 95%CI 1.14 to 1.75) and girls (RR 1.27 95% CI 1.03 to 1.57). In addition, RWG in infancy significantly predicted the elevated SBP trajectory in boys; 1.93-fold (95% CI 1.24 to 2.99) and a 2-fold increased risk for the elevated DBP trajectory in girls (RR:2.09, 95%CI 1.06 to 4.11). In girls, RWG in mid-childhood was significantly associated with 67% increased risk of being in the elevated SBP trajectory

compared to the low trajectory (RR 1.67, 95% CI 1.20 to 2.32). Being small for gestational age was not statistically significant in all the models.

This study suggests that relative weight gain in early life may program an individual into moderate to elevated life course BP trajectories.

4408

### Fetal growth restriction induces different cardiac phenotypes

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**Aim:** To identify different cardiac phenotypes induced by fetal growth restriction (FGR).

**Methods:** A cohort study was conducted in 126 FGR and 64 adequate for gestational age (AGA) including fetal cardiac morphometry, perinatal characteristics and postnatal mean blood pressure (BP) and aortic intima media thickness (aIMT) assessment. To identify cardiac phenotypes among FGR, a cluster analysis was performed based on fetal left ventricular sphericity index (LVSI) and left ventricular wall thickness selected (LVWT).

**Results:** FGR showed signs of cardiac remodeling when compared to AGA. Cluster analysis identified 3 different cardiac phenotypes among FGR. The most prevalent phenotype (54%) was characterized by a 'globular' heart with the lowest LVSI, 29% showed an 'elongated' heart with mild changes in cardiac morphometry and 17% showed a 'hypertrophic' phenotype with the highest LVWT and cardiac size. The hypertrophic cluster presented the worst perinatal and postnatal outcomes including the highest prevalence of

pre-eclampsia, the lowest gestational age at birth, Apgar score, and birthweight and the highest values of BP (elongated: 71 mmHg (68-79), globular: 70 (66-79) and hypertrophic: 78 (69-80)) and aIMT (elongated: 0.55 (0.05), globular: 0.57 (0.07) and hypertrophic: 0.58 (0.01)).

**Conclusions:** FGR induced at least 3 different cardiac phenotypes. The hypertrophic cluster showed the worst perinatal outcome. Cardiac phenotypic classification may improve identification of those FGR cases at highest short-term and long-term risk.

4415

### Effect of infant weight, length and adiposity gains during early childhood with blood pressure at 36-months

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**Research question:** To examine associations between weight, length and adiposity gains in early childhood with blood pressure (BP) at 36-months in a multi-ethnic Asian cohort, and if this was mediated by obesity-related gene variants.

**Methods:** In 649 children with BP measurements and genotyped for obesity-related variants (MC3R, MC4R, FTO), anthropometric measurements of weight, length, abdominal circumference, triceps and subscapular skinfolds were collected at birth, 3-, 12-, 18- and 36-months. Conditional changes between timepoints were calculated, and variables of interest were assessed using linear regression.

**Results:** Birth anthropometry was not associated with BP at 36-months. Greater conditional gains in weight, length and adiposity, particularly during later ages (12-36, 18-36 months), were associated with higher systolic and diastolic BP, and had a

50-89% greater likelihood of having BP > 90th percentile at age 36-months ( $p < 0.01$  for all). Greater subscapular skinfold gains in early childhood were more strongly related to higher BP at 36-months for those who carried minor allele variants for MC3R rs3746619 ( $p$  for interaction = 0.018).

**Conclusion:** Offspring who gain weight, length and adiposity faster than their peers, especially from the second year, are predisposed to higher blood pressure in early childhood. The effect of subscapular skinfold gain may in part be mediated by MC3R genotype.

4366

### The association of perinatal growth with energy intake and satiety response at 5-6 years of age; The ABCD study

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Perinatal effects on later energy intake and eating behavior have been implicated to play a role in the developmental origins of obesity. We assessed the confounder-adjusted associations of birth weight and postnatal growth with parent-reported energy intake and satiety response subscore at 5-6 years, in 2,227 children. Conditional weight gain in early infancy (1-3 and 3-6 months) and childhood (12 months to 5 years) was negatively associated with energy intake, with 24.0kcal/day (95% CI: 1.8; 46.1) and 79.5kcal/day (95% CI: 29.4; 129.7) more intake for each Z-score weight gain in infancy and childhood, respectively. Conditional height gain during 0-1, 1-3 months and 12 months to 5 years was negatively associated with energy intake ( $\beta$  at least -35.1kcal/day per Z-score height gain [95%CI: -58.4; -11.8]). Conditional weight gain in all growth periods was negatively associated with satiety response, with incremental effect sizes from -0.03 (95%CI: -0.06; -0.002) in infancy to -0.12 (95%CI: -0.19; -0.06) in childhood. Our findings suggest that excessive early weight gain are associated with increased childhood energy intake and diminished satiety response. Rapid height gain seems to be beneficial for energy intake. Obesity prevention strategies addressing the optimization of childhood feeding patterns should also focus on optimization of childhood growth.

4925

### The association of infant growth with energy intake and satiety response at 5-6 years of age - The ABCD study

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**Background:** Energy intake and eating behavior in later life may be affected by early (infant) growth.

**Objectives:** To assess the associations of early growth with mean daily energy intake and satiety response at 5-6 years of age.

**Methods:** Data of 2227 children from the Amsterdam Born Children and their Development-study were used. Exposures were gestational age-adjusted birth weight z-score, conditional weight and conditional height gain between 0-1, 1-3, 3-6, 6-12 months and 1-5 years. Outcomes were energy intake and satiety response, obtained from Food Frequency Questionnaires and Child Eating Behavior Questionnaires.

**Results:** Mean energy intake was 1531 ( $\pm 338$ ) kcal/day, mean satiety response sub-score 2.37 ( $\pm 0.50$ ) on a 4-point Likert-scale. Conditional weight gain in early infancy (1-3 and 3-6 months) and childhood (12 months to 5 years) were positively associated with energy intake at age 5-6. Conditional height gain during 0-1, 1-3 months and 12 months to 5 years was negatively associated with energy intake. Conditional weight gain in all periods was negatively associated with satiety response. Birth weight was not associated with either energy intake or satiety response.

**Conclusion:** Accelerated infant and childhood weight gain is associated with increased energy intake and diminished satiety response at 5 years.

4489

### Vascular dysfunction in offspring born from dams of advanced maternal age

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**Introduction:** Advanced maternal age ( $\geq 35$  years) is increasing and associated with adverse maternal and fetal outcomes. Long-term vascular function is compromised in offspring born from adverse intrauterine environments. We hypothesised that adult offspring from aged dams have altered vascular function. **Methods:** Aged female Sprague Dawley rats (9.5 months) and young controls (4 months) were mated with young males. Vascular function was assessed in adult, male and female offspring. Endothelium-dependent vasodilation to methylcholine (MCh) and vasoconstriction to phenylephrine (PE) were determined in the absence or presence of inhibitors of nitric oxide (NO) synthase or cyclooxygenase.

**Results:** Female offspring demonstrated a tendency to increased PE-induced vasoconstriction (percent change in area-under-curve (AUC); 51.6%) that was not observed in males (4.4%). Conversely, MCh-induced vasodilation tended to be decreased in male (-32.7%) but not female (5.0%) offspring. While the contribution of NO to vasodilation was unaltered by maternal age in either sex, the contribution of

vasodilatory prostaglandins was reduced only in female offspring (delta AUC; young:  $45.0 \pm 2.3$  vs. aged:  $3.2 \pm 28.5$ ). **Conclusion:** Offspring of aged dams showed sex-specific impairment of vascular function which may predispose them to cardiovascular disease. A redundancy of vasodilator mechanisms in female offspring may provide protection from the detrimental effects of a compromised pregnancy.

4544

### Sexual Dimorphism in Fetal Cardiac Growth Response to Intrauterine Growth Restriction (IUGR)

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**Research question:** Poor fetal nutrition predisposes to adult cardiovascular disease (CVD). We have developed a baboon model of maternal undernutrition-induced IUGR in male and female fetuses. We hypothesized that IUGR affects fetal cardiac structure and growth.

**Methods:** Six control pregnant baboons ate ad libitum, and six nutrient restricted baboons - a reduced diet (70% of control) from 0.16 gestation (G) through pregnancy resulting in IUGR. Fetuses (3 males and 3 females per group) were euthanized at C-section at 0.9G. Histology was assessed by trichrome staining. Pro-fibrotic, inflammatory and autophagic markers were measured by Western Blot.

**Results:** Accumulation of cardiac fibrosis was inversely correlated with birthweight in male but not female IUGRs ( $r = -0.831$ ,  $p = 0.01$ ). IUGR males had 3-fold increase in matricellular protein thrombospondin (TSP)-1, whereas IUGR females showed a 6-fold increase in transforming growth factor- $\beta$ . Pro-inflammatory NF $\kappa$ B was increased 4-fold in female IUGRs vs. controls. In males and females, levels of autophagic markers ATG7 and LC3 positively correlated with birthweight ( $r = 0.68$ ,  $p = 0.02$ ) suggesting reduced autophagy in IUGRs. Impaired autophagy is considered detrimental and might lead to cardiac remodeling.

**Conclusion:** There is a sexual dimorphism in cardiac fibrosis and autophagy in IUGR, which may program offspring for CVD later in life.

4635

### Cesarean section as an independent risk factor for hypertension among young adults

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**Research question:** Cesarean section (C-section) delivery has been identified as an important risk factor for noncommunicable diseases in adulthood. The aim of this study was to assess the presence of the association between c-section and hypertension (HT) later in adulthood.

**Methods:** a prospective birth cohort was followed up in the city of Ribeirao Preto, Brazil. Blood pressure measurements were obtained from 1141 adult subjects in 2002/04. These individuals had been recruited in 1978/79 for this birth cohort and had had a second assessment in 1987/98, at age 9-11 years. Several socio-demographic and anthropometric variables were collected at the three different times. Risk ratio was assessed by Poisson regression.

**Results:** There was a significant difference in the percentage of hypertensive subjects according to the type of delivery (c-section: 12.4%; vaginal: 8.2%;  $p = 0.022$ ). The non-adjusted risk ratio was 1.56 (95% CI 1.05-2.31). After adjustments for socio-demographic and anthropometric variables the estimate was RR = 1.51 (95% CI 1.01-2.26).

**Conclusion:** In this cohort it has been observed that individuals who were born by c-section had a 51% higher risk of hypertension compared to those who were born by vaginal delivery.

4710

### The effect of prenatal hypoxia and a postnatal high-salt diet on microvascular structure and function

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**Research question:** Cardiovascular disease programmed in utero may be exacerbated by a postnatal "second-hit". We examined the impact of exposure to prenatal hypoxia coupled with a postnatal high-salt diet on microvascular structure and function.

**Methods:** Pregnant CD1 mice were housed in a hypoxic chamber (12% O<sub>2</sub>; N = 11, HYP) or control (21% O<sub>2</sub>; N = 11, CON) environment from embryonic day 14.5 to 19.5 (birth). From 10 weeks of age, a subset of animals was placed on a life-long high-salt diet (5% NaCl). Offspring were culled at 12 months of age and mesenteric arteries dissected for pressurized myography. Kidney sections were stained with Masson's Trichrome and Verhoeff's Van Gieson stain to assess collagen and elastic fiber content, respectively.

**Results:** HYP offspring birth weight was reduced by 7% compared to CON. HYP offspring had impaired endothelial function, but no change to vascular structure and mechanics. Prenatal hypoxia and postnatal high-salt diet combined caused a leftward shift in the stress-strain relationship, suggesting stiffening of mesenteric vasculature. Increased perivascular fibrosis and reduced elastin deposition in renal arteries was observed.

**Conclusion:** Prenatal hypoxia programmed endothelial dysfunction in male and female offspring. A high-salt diet had an additive deleterious effect on structural but not functional characteristics in both sexes.

#### 4965

##### **Maternal early pregnancy lipid profile and offspring's lipids and glycaemic control at age 5-6 years: the ABCD-study**

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**Research question:** Does maternal early pregnancy lipid profile influence offspring's lipids and glycaemic control and does offspring's fat percentage mediate this association?

**Methods:** 1133 mother-child pairs were included from the prospective ABCD-study. Maternal non-fasting lipids were collected in early pregnancy: triglycerides, total cholesterol (TC), Apolipoprotein A1 (ApoA1), Apolipoprotein B (ApoB) and free fatty acids (FFA). Fasting triglycerides, TC, high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose and C-peptide were assessed in offspring aged 5-6 years and HOMA2-IR was calculated.

**Results:** After adjustments for covariates, the strongest associations were found between maternal TC and offspring's TC (boys;  $\beta = 0.137$ ; 95% CI: 0.070-0.203, girls;  $\beta = 0.267$ ; 95% CI: 0.198-0.335) and LDL (boys;  $\beta = 0.112$ ; 95% CI: 0.050-0.174, girls;  $\beta = 0.251$ ; 95% CI: 0.186-0.317), maternal ApoB and offspring's TC (boys;  $\beta = 0.628$ ; 95% CI: 0.301-0.956, girls;  $\beta = 1.108$ ; 95% CI: 0.750-1.465), maternal ApoA1 and offspring's HDL (only boys;  $\beta = 0.222$ ; 95% CI: 0.101-0.343), and maternal ApoB and offspring's LDL (boys;  $\beta = 0.695$ ; 95% CI: 0.338-1.001, girls;  $\beta = 1.208$ ; 95% CI: 0.878-1.537). No significant associations between maternal lipids and offspring's glycaemic control, nor a mediating role of fat percentage were found.

**Conclusion:** Maternal early pregnancy lipid profile is associated with offspring's lipid profile in childhood. Overall, stronger associations were found for girls. These associations could be a reflection of foetal programming, however the role of genetics and environment cannot be excluded.

#### 4752

##### **Association between in utero HIV and ART exposure and assessment of vascular damage in infancy: a feasibility study**

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**Research question:** Perinatal environmental factors are critical in later health outcomes. HIV and anti-retroviral treatment (ART) are associated with increased cardiovascular (CV) risk. This pilot study assessed the feasibility of measuring aortic intima media thickness (aIMT) in infants with and without in utero exposure to HIV and ART in a resource-limited setting.

**Methods:** Participants were recruited as part of an ongoing birth cohort study in South-Africa. Aortic IMT was measured using standardized trans-abdominal ultrasound. Feasibility and quality was assessed by a priori parameters. Differences between HIV-exposure groups were described.

**Results:** Sixty-nine children (6-24 weeks) were included; 19 (27.5%) were HIV and ART exposed. Feasibility scored well on all predetermined aspects. Overall quality of the aIMT images was good; 59 images (86%) were rated average, good or excellent. Mean aIMT in HIV exposed infants was 439  $\mu$ m

versus 420 in the unexposed group. Power analysis indicated a group size of 500 to permit significant difference of aIMT at 0.80 power level.

**Conclusion:** Assessment of aIMT is feasible and well-tolerated in infants in a resource-limited setting. Larger studies of aIMT in infancy are warranted to investigate whether HIV or its treatment are associated with early cardiovascular disease risk.

5013

### Aortic, coronary and carotid dimensions, intima media thickness and stiffness in 6-year-old children born extremely preterm

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**Research question:** Does arterial growth, ageing and elasticity differ in 6-year-old children born extremely preterm (EXP, n = 178, mean gestational age 24.9 weeks, mean birth weight 782 g) compared with same-aged control children born at term (n = 172).

**Methods:** We determined end-diastolic diameters (D) of the abdominal aorta (AA), the coronary arteries (CA), and common carotid arteries (CCA), as well as carotid intima media thickness (cIMT) by ultrasonography. Relative (%) systo-diastolic diameter change (strain) of AA and CCA were also calculated as indicators of arterial elasticity.

**Results:** AAD was 7.3 mm in EXP and 8.1 mm in controls (p

4452

### Trajectories of early development and adult intelligence

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**Research question:** To investigate associations between physical development at birth, developmental milestones assessed at 1- and 3-years follow-ups and young adult intelligence, and to explore whether the effects of development at birth and at 1-year are mediated by later stages of development.

**Methods:** Physical development and milestones were assessed for the 9125 children in the Copenhagen Perinatal Cohort. A subsample of the cohort comprising 1155 individuals participated in a follow-up when they were aged 20-34 years and were administered the Wechsler Adult Intelligence Scale.

**Results:** Among indicators of physical development at birth, only head-circumference significantly predicted IQ (p < 0.001); among 1-year milestones, milestones related to standing and walking predicted IQ (p = 0.01); and among 3-year milestones, milestones related to especially language development significant predicted IQ (p < 0.001). In a model including all predictors, head-circumference and milestones related to language and social interactions were the only significant predictors. Any effects of 1-year milestones seemed to be mediated through 3-year milestones.

**Conclusion:** Among indicators of physical development at birth, head circumference appears to be the most important predictor of intelligence. Effects of attainment of 1-year milestones may be mediated through later behavioral development as assessed at the 3-year follow-up.

5414

### Exclusive breastfeeding, HIV exposure, and development at primary school-age in a large, rural, cohort in South Africa

Ruth Bland

**Research question:** To investigate whether exclusive breastfeeding and other early life factors, including maternal HIV, were associated with child development at ages 7-11 years.

**Methods:** The Vertical Transmission Study (VTS) supported HIV-positive and negative women in EBF; in 2013 HIV-negative VTS children (345 HIV-exposed, 596 HIV-unexposed), were assessed on cognition, executive function, and emotional-behavioural functioning. Same-aged HIV-negative children (n=629) from the local Demographic Platform provided comparative population means. For each outcome we split the VTS sample into scores above or at/below the population mean. We modelled each outcome using logistic regression analyses, allowing for early life factors (including maternal HIV), overall and stratified by child sex.

**Results:** Six months EBF vs ≤1, was associated with fewer conduct disorders (anti-social behaviour) (aOR 0.44 [95% CI 0.2-0.7]) in both sexes. For boys, 2-5 months EBF vs ≤1 was associated with improved cognition on the Learning sub-scale scores (aOR 2.07 [95% CI 0.9-4.2]) and fewer externalising problems (general behaviour problems) (aOR 0.48 [95% CI 0.2-1.0]). Improved cognition in both sexes was associated

with higher maternal cognitive ability (aOR 1.43 [95% CI 1.0-1.9] Sequential, 1.74 [95% CI 1.2-2.3] Planning sub-scales). Maternal HIV status was not associated with any outcomes.

**Conclusion:** Exclusive breastfeeding has long term benefits particularly for boys.

#### 5410

##### **Long-term Effects of Acute Malnutrition on Growth, Body Composition and Function**

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**Background:** Given evidence of early nutritional exposures affecting long-term adult health, it is vital that treatment of severe acute malnutrition (SAM) starts looking beyond short-term mortality outcomes. We followed-up 462 Malawian children seven years after an episode of SAM, comparing them to age/sex matched community controls. Multivariable linear regression was used to compare study groups.

**Results:** 320/462(82%) case children were recruited. They were significantly more stunted and underweight than controls (height-for-age Z-score -1.8 vs -1.3,  $p < 0.001$ ). Cases have preserved head circumference, torso growth but compromised limb growth, compared to controls. Waist-hip ratio is significantly higher for cases than controls (0.91 vs 0.89,  $p = 0.01$ ), and lean mass assessed by bioelectrical impedance vector analysis is significantly lower. Case children have evidence of functional impairment with hand-grip strength significantly weaker (12.7kg vs 13.8kg,  $p = 0.01$ ) and some deficit in steps taken per day. However lung function assessed by spirometry appears unaffected compared to controls.

**Conclusions:** SAM may be associated with a number of adverse long-term effects, including stunting, body composition associated with higher risk of cardiometabolic disorders, and functional impairments. Preservation of torso height, lung function and head circumference indicate sparing of some vital organs. Going forward, it is crucial to identify effective strategies for improving long-term outcomes in SAM survivors.

#### 4969

##### **Perinatal methylation of the serotonin transporter SLC6A4 is a predictor of childhood adiposity**

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**Research question:** Developmental influences can alter epigenetic processes to induce long-term metabolic effects in the offspring, suggesting that early life epigenetic marks may allow the identification of individuals at risk of later metabolic disease. Using a genome wide initial screen, we identified methylation differences in umbilical cord (UC) that were predictive of later adiposity, followed by replication studies in UC, cord blood and adult adipose tissue.

**Methods:** UC DNA was extracted from infants in the Southampton Women's Survey (SWS) and analysed using a MBD array. 93 differentially methylated regions (DMRs) associated with childhood adiposity were identified. The DMR within the serotonin transporter SLC6A4 was validated by pyrosequencing across a range of perinatal and adult tissues.

**Results:** Increased UC and cord blood methylation of SLC6A4 was associated with lower % fat-mass ( $n = 418$ ,  $p = 0.001$ ) and triceps skinfold thickness ( $n = 281$ ,  $p = 0.013$ ) in the children at 6 years of age. Methylation of SLC6A4 also differed between adipose tissue from obese versus lean adults ( $n = 65$ ,  $p = 0.042$ ).

**Conclusion:** SLC6A4 plays an important role in energy balance. Thus the association of SLC6A4 methylation with both childhood and adult fat mass suggests that altered methylation may contribute significantly to the development of adiposity.

#### 4939

##### **Maternal dietary supplementation with canola oil during lactation delays the loss of uncoupling protein 1 in the offspring's adipose tissue**

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**Research question:** Brown adipose tissue is a potential target to combat obesity, because it rapidly expends energy by non-shivering thermogenesis, a process mediated by uncoupling protein (UCP)1. Conjugated linoleic acid (CLA) increases UCP1 in vitro and the amount present in maternal milk is dependent on the mother's diet. Our study in sheep was designed to investigate whether maternal dietary supplementation with canola oil (which increases milk CLA content) delays the loss of UCP1 in suckling offspring.

**Methods:** From delivery, mother sheep were fed, a standard diet+3% canola oil. Each mother raised twins, which were tissue sampled at 7 and 28 days of age. Perirenal adipose tissue was analysed using immunohistochemistry to determine the relative abundance of UCP1 for each animal.

**Results:** Offspring of mothers receiving canola possessed fat with more UCP1 at 28 days, than controls, as there were no significant changes in its relative amount with age (7d:  $37.0 \pm 3.5\%$ ; 28d:  $29.4 \pm 3.8\%$ ) compared with 24% reduction in controls (7d:  $37.8 \pm 3.2\%$ ; 28d:  $13.9 \pm 1.2\%$  ( $p < 0.0001$ )). Total fat mass was unaffected.

**Conclusion:** Exposure to raised CLA through suckling milk delays the loss of perirenal UCP1 during infancy. This has been suggested to be protective against excess white fat deposition in later.

4958

#### Growth trajectories in early childhood, their relationship with antenatal and postnatal factors, and development of obesity by age 9 years

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**Research question:** We aimed to: identify groups of children with distinct trajectories of growth in early childhood; examine associations between trajectories and body size at age 9; and assess effects of antenatal and postnatal exposures on growth trajectories.

**Methods:** 557 children contributed serial height and weight measurements from birth to 9 years. Latent class growth models were used to derive distinct groups of growth trajectories from birth to age  $3\frac{1}{2}$ . GLMs were used to explore

(i) relationships between the groups and body size at age 9 years and (ii) antenatal and postnatal predictors of growth trajectory groups.

**Results:** Four discrete growth trajectory groups were identified (low, intermediate, high, accelerating). Relative to the intermediate group, the low group had reduced z-BMI (-0.75 SD; 95% CI -1.02, -0.47), and the high and accelerating groups had increased z-BMI at age 9 (high: 0.70 SD; 95% CI 0.49, 0.92; accelerating: 1.64 SD; 95% CI 1.16, 2.11). Maternal obesity in early pregnancy was associated with a near quadrupling of risk of membership of the accelerating growth group (OR 3.72; 95% CI 1.15, 12.05).

**Conclusions:** Efforts to prevent childhood obesity could be embedded within population-wide strategies that also pay attention to healthy weight for women in their reproductive years.

4955

#### Association between linear growth and fat and lean tissue gain during childhood and cardiometabolic outcomes in Indian adolescents

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**Research question:** To determine the independent associations of linear growth and fat and lean tissue gain during discrete age periods from birth to adolescence with cardiometabolic outcomes in Indian adolescents.

**Methods:** Adolescents from a birth cohort (N=545) had anthropometry and measurements of plasma glucose, insulin and lipid concentrations and blood pressure at 13.5y. Insulin resistance (HOMA-IR) was calculated. These outcomes were examined in relation to conditional SD scores representing linear growth, and fat and lean tissue gain during 0-1, 1-2, 2-5, 5-9.5 and 9.5-13.5y in 414 children who had measurements at all these ages and were born to normal glucose tolerant mothers

**Results:** Faster fat gain particularly during 5-9.5y was associated with higher total (fat%) and central body fat (waist-hip ratio;  $P < 0.001$ ). Faster fat gain during later childhood years was also associated with higher systolic blood pressure (5-9.5y) and HOMA-IR (5-9.5 and 9.5-13.5y;  $P < 0.001$ ). There was no association of faster infant growth with cardiometabolic risk factors.

**Conclusion:** In this first longitudinal data to separate the effects of lean and fat tissue growth in childhood, we found that especially fat gain in late childhood/adolescence increases cardiometabolic risk. Factors which increase rate of infant growth may have no adverse cardiometabolic effects.

4952

**Stunting at 18 years is predicted by femur length in utero: Pune Maternal Nutrition Study (PMNS)**

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**Research question:** Is stunting evident at birth or during intra-uterine life?

**Methods:** Length and height measurements were available in children in the PMNS from 18 weeks of gestation (ultrasound) till 18 years age. Parental measurements were also available.

**Results:** At 18 years, 69 of 663 participants were stunted (height for age)

4949

**Components of height and the intergenerational change in height as predictors of body composition and cardiovascular risk in young Indian adults**

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**Research question:** We investigated the relationships between components of height, change in intergenerational parental height, and cardiovascular (CVD) risk and whether these associations may be explained by body composition.

**Methods:** We studied 357 young adults and their parents in the Pune Children's Study. We measured weight, total height, leg length, sitting height, plasma glucose, insulin and lipids, blood pressure, carotid intima media thickness (IMT) and pulse wave velocity (PWV). Lean and fat mass were measured by dual x-ray absorptiometry.

**Results:** Total height and leg length were directly related to lean mass while sitting height was directly related to both lean and fat mass (p0.001 for all). Leg length was inversely related to blood pressure, 120-minute glucose and PWV, independent of lean and fat mass (p0.05 for all). Sitting height was directly related to blood pressure, triglycerides and IMT, and inversely to PWV; these relationships were attenuated on adjustment for lean and fat mass. Mid-parental height and intergenerational change in height were inversely related to PWV.

**Conclusions:** Shorter adult leg length and greater sitting height are associated with a more adverse CVD risk factor profile. The mechanisms need further study but our findings suggest a role for lean and fat mass.

4937

**Comparison of mother - child versus father - child associations for cardiometabolic risk - New Delhi Birth Cohort, India**

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**Background:** Evidence is inconsistent regarding differences between mother-child versus father-child associations for cardiometabolic risk. We examined these intergenerational associations in the New Delhi Birth Cohort.

**Methods:** The study population consisted of male and female members (F1) of the New Delhi Birth Cohort (n = 1100, male-59.3%) and their offspring F2 (n = 1242, mean age (SD) = 7.7 (3.9), male-56.9%), whose anthropometric and biochemical measurements were collected. Multiple regression analyses with adjustment for confounders and familial clustering was used to test parental - offspring associations in pooled analyses and separately for male and female parents.

**Results:** There is a significant association between parental and offspring cardiometabolic risk factors, after adjusting for confounders. When stratified by parent gender, female parent-child associations were stronger compared to male parent, for measures of adiposity ( $\beta$  co- eff (95% CIs, female and male) were: BMI = 0.27 (0.20-0.34) and 0.16 (0.08-0.24), waist circumference = 0.31 (0.24-0.38) and 0.18 (0.10-0.27), hip circumference = 0.35 (0.25-0.44) and 0.28 (0.19-0.37), blood pressure: systolic blood pressure = 0.24 (0.1-0.4) and 0.16 (0.08-0.24), diastolic blood pressure = 0.18 (0.04-0.31) and 0.11 (0.01-0.22) and biochemical markers: fasting glucose = 0.31 (0.04-0.58) and 0.15 (0.06-0.25), HDL-cholesterol = 0.38 (0.11-0.65) and 0.12 (-0.18-0.42).

**Conclusions:** The stronger female parent-child as compared to male-parent child associations point to intergenerational mechanisms, possibly through intra-uterine programming that have an additive effect over and above genetic and shared household lifestyle and behavioural effects.

4712

### Periconceptional alcohol exposure contributes to increased adiposity in male offspring

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**Research question:** Maternal alcohol consumption around conception can contribute to insulin resistance in rats but the effects on obesity are unknown.

**Methods:** Rats were fed a control or ethanol (12.5% EtOH v/v) diet from 4 days prior to mating until 4 days of gestation. A subset of offspring was subsequently fed a HFD from 3 months of age. A DXA-scan was performed at 7 months and plasma was collected at 8 months before animals were killed for tissue collection.

**Results:** EtOH caused an increase in total body fat mass in males that was exacerbated by a high fat diet, whereas in females, only a HFD increased fat mass. EtOH was associated with a greater incidence of microvesicular steatosis and hepatic inflammation in male, but not female offspring. Plasma triglycerides, HDL and cholesterol were increased in EtOH-exposed male offspring and LDL, cholesterol and leptin in EtOH-exposed female offspring. mRNA levels of Tnf- $\alpha$  in visceral adipose were increased in both sexes of the EtOH group.

**Conclusion:** EtOH programmed phenotypes were similar to those caused by consumption of a postnatal HFD, particularly in male offspring. These results have important implications for women who have consumed.

4654

### Maternal Docosahexaenoic Acid (DHA) Supplementation and Body Composition at Age 5 Years

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**Research question:** Does DHA intake during pregnancy program child body composition?

**Methods:** We conducted a Phase III placebo-controlled, randomized trial of maternal DHA supplementation (600 mg/day) starting before 20 weeks gestation and continuing until birth. We followed the growth and development of 190 children and 152 of these had fat mass (FM) and fat free mass (FFM) determined by air displacement plethysmography (ADP) at 5 years. After birth, all children consumed DHA and arachidonic acid from human milk or infant formula for the first year of life. Linear regression was used to explore the effect of DHA supplementation by treatment group and interactions with prospective predictors of child body composition.

**Results:** Children whose mothers were assigned to DHA had significantly higher FFM than those whose mothers were assigned to placebo ( $15.14 \pm 2.11$  kg vs  $14.48 \pm 2.22$  kg,  $p = 0.051$ ). The association between gestational weight gain (GWG) and FM differed by group (pinteraction = 0.043), wherein greater GWG predicted higher FM in the placebo group ( $p = 0.049$ ), but not in the DHA-supplemented group.

**Conclusion:** DHA supplementation during pregnancy increased offspring FFM at 5 years and attenuated the increase in 5-year FM related to gestational weight gain.

4364

### The Association of Birth weight and Infant growth with Energy Balance-Related Behavior. A Systematic Review and Best-evidence Synthesis of Human Data

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Low birth weight and accelerated postnatal weight gain are associated with later obesity risk, but the underlying mechanisms are unknown. We conducted a systematic review to assess the available evidence on the association of perinatal growth with energy balance-related behavior in humans. Studies were included if they reported on the association of (i) birth size or (ii) infant growth with later (i) energy intake, (ii) eating behaviors, (iii) physical activity (PA) or (iv) sedentary behavior (SB) in humans. Thirty eligible studies were identified through four major electronic databases. We found no evidence for an association of birth weight with later energy intake, eating behavior, PA or SB. Other birth size measures and infant growth were unrelated with PA as well. However, we found moderate evidence that extreme birth weights (at both ends of the spectrum) are associated with lower PA levels at a later age. We found insufficient evidence for an association of other birth size measures, extreme birth sizes or infant growth with energy intake, eating behavior or SB.

Further original, high-quality research is required to address these associations, as a better understanding of the mechanisms underlying the developmental origins of obesity may guide public health strategies for successful prevention and surveillance of obesity.

## 5025

### Low B-vitamin status during pregnancy is associated with greater offspring adiposity in childhood

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**Research question:** Is maternal B-vitamin status during pregnancy associated with offspring adiposity?

**Methods:** In a prospective UK population-based mother-offspring cohort (Southampton Women's Survey) 497 mother-child pairs had measurements of maternal serum micronutrient status at 34 weeks gestation (vitamin B6 (pyridoxal-5-phosphate) by reverse-phase high performance liquid chromatography, folate and vitamin B12 by automated immunoassay, riboflavin by LC-MS/MS). We analysed low status for vitamins B6 (below 20 nmol/L), B12 (below 200 ng/L) and folate (below 6.8 nmol/L), and serum riboflavin (continuous variable) in relation to child's %fat mass (from DXA scans at ages 4 and 6 years, appropriately adjusted for child sex and age).

**Results:** Maternal folate status was not associated with offspring adiposity but low vitamin B6 status (below 20 vs equal or greater 20 nmol/L) was associated with greater child %fat mass at ages 4 and 6 years (28.9% vs 27.9%,  $p=0.082$ ; 25.8% vs 24.3%,  $p=0.012$ , respectively), as was low vitamin B12 (below 200 vs equal or greater 200 ng/L) status (29.0% vs 27.9%,  $p=0.046$ ; 25.5% vs 24.8%,  $p=0.12$ , respectively). Lower maternal late pregnancy serum riboflavin was associated with higher child's %fat mass (age 4 years  $r=-0.11$ ,  $p=0.054$ , age 6 years  $r=-0.11$ ,  $p=0.021$ ).

**Conclusion:** Lower maternal B-group status during late pregnancy has associations with adiposity in the offspring.

## 4867

### A DRD4 Gene by Maternal Sensitivity Interaction Predicts Risk for Overweight or Obesity in Two Independent Cohorts of Pre-School Children

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**Background:** The 7-repeat allele of the dopamine-4 receptor gene (DRD4) increases susceptibility to a variety of environmental influences, including maternal sensitivity. The current study examines whether pre-schoolers who carry the 7R allele are more influenced by maternal sensitivity as it relates to overweight/obesity risk.

**Method:** Two longitudinal birth cohorts were analyzed i.e. the Maternal Adversity Vulnerability and Neurodevelopment (MAVAN) project in Canada and the Generation-Rotterdam (GEN-R) study in the Netherlands. Maternal sensitivity was coded by trained raters based on video-taped interactions of mothers and their infants. Linear mixed-effects models and standard multiple regression techniques were used to predict both continuous BMI z-scores and membership in higher BMI categories at 48 months of age.

**Results:** As hypothesized, in both cohorts, pre-schoolers who carried the 7R allele were more strongly influenced by maternal sensitivity regarding overweight/obesity risk. In the Canadian sample this was strongly evident in girls, while in the Dutch sample it was apparent in boys. In the Canadian girls in particular, there was evidence for a differential susceptibility effect, with 7R carriers exposed to high maternal sensitivity having a very low chance of being at a higher BMI, and vice-versa.

**Conclusions:** Children who carry the 7-repeat allele of DRD4 appear to be more influenced by low maternal sensitivity as it relates to overweight/obesity risk. This adds further support to the theory that the 7R allele is a "plasticity gene" variant that can

increase susceptibility to a variety of environmental influences, including maternal sensitivity. Children identified as 7R carriers in the first year of life may have particular benefit from early obesity prevention programs aimed at enhancing sensitive mother-infant interactions.

4882

### The lipid class cross-talk during dietary fat metabolism in breast-fed infants.

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**Research question:** The lipid metabolism of breast-fed infants is significantly different to that of formula fed infants. Breast-fed infants have higher levels of specific sphingomyelins (SM (36:2)) and lower levels of specific triglycerides like TG (54:2). We want to understand which components in the diet are driving these differences in lipid metabolism.

**Methods:** Breast-milk samples and infant plasma samples from 30 mother-infant pairs were obtained 12 weeks post-partum in rural Gambia. Samples were extracted with an organic solvent and profiled by direct infusion mass spectrometry, using chip based nanospray and high-resolution mass spectrometry.

**Results:** Breast-milk lipids showed strong associations with specific plasma lipids, from different classes. Smaller triglycerides and diglycerides in breast-milk correlated with sphingomyelins e.g. SM (36:2) but not with plasma triglycerides. Higher levels of the breast-milk sphingomyelin SM (34:2) associated with higher levels of plasma triglycerides e.g. TG (54:2). These results suggest that the lipid composition of the infant's diet has a profound influence on which pathways are activated, to metabolise and repackage the dietary fatty acids.

**Conclusion:** It is well-documented that changes to fatty acid composition of milk affect infant development. Our study shows for the first time that intact dietary lipids in breast-milk determine how dietary fat is metabolised.

4887

### Duration of sleep at 3 years of age is associated with lean and fat mass at 4 years of age: the Southampton Women's Survey

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**Research question:** What is the relationship between child's sleep at age 3 years and their body composition at 4 years?

**Methods:** Prospective cohort study of 900 children (475 boys, 425 girls) born to Southampton Women's Survey (SWS) participants recruited between 20-34 years of age and followed through their pregnancies and beyond. Total sleep duration at age 3 years was derived from parental report of night sleep and nap time duration. Body composition was assessed by DXA at 4 years.

**Results:** Mean total sleep duration was 11.5 hours. In linear regression analyses, adjusted for confounding factors (maternal educational attainment, pre-pregnancy BMI, smoking during pregnancy, child's age, sex, height at the time of DXA (except analyses of BMI), age last breastfed, dietary quality at 3 years, TV watching and hours actively on the move) shorter sleep duration (hours) was associated with higher BMI (kg/m<sup>2</sup>) ( $\beta = -0.211$ , 95% CI -0.332, -0.089) and greater fat mass ( $\beta = -0.105$  (-0.215, -0.005)) but also with greater lean mass ( $\beta = -0.129$  (-0.214, -0.045)).

**Conclusion:** Previous research suggested the association between shorter sleep and higher body mass index was due to an effect on adiposity. Our findings suggest that the relationship might also be determined by an effect of muscle.

4979

### Ethnic differences in adolescent male skeletal growth persist after adjustment for maturational timing

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It is unclear how differing patterns of growth and maturation affect adolescent changes in bone size or density. We previously reported ethnic differences in maturational timing among South African males in the Birth To Twenty cohort (BTT), as well as skeletal differences during adolescence. We aim to determine to what extent these skeletal differences are determined by maturational timing.

In 255 boys from BTT, cortical volumetric (v)BMD and cortical/total cross-sectional areas (CSA) of the radius and tibia were measured annually by peripheral quantitative computed tomography (12.3-22.2 years). Each parameter was modelled longitudinally against 'biological age' (years since peak height velocity, PHV) to adjust for maturational differences.

Black boys had greater cortical vBMD throughout, despite some convergence. Cortical CSA was equal at PHV, but diverged as a result of faster growth in white boys. Total CSA already differed at PHV, with black boys having relatively narrower radii but wider tibiae. Faster growth among white boys meant that their total CSA was greater in late adolescence. Ethnic differences in long bone development are not only a result of variation in maturational timing. Potential implications for adult skeletal health and fracture risk will require further investigation.

4407

### **Benzyl Butyl Phthalate (BBP)-foe or friend? An Epigenetic View**

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Benzyl butyl phthalate (BBP) is a common plasticizer used in household products and food packaging industries. The epigenetic effect of BBP exposure in the development of diabetes or obesity remains unknown. Mesenchymal stem cells and preadipocytes were treated with different doses of BBP for several time points. RNA, microRNA, histone, and protein were extracted and analyzed at different time-points. Several computational docking analysis were carried out.

After 8 days of differentiation, the cells exposed to BBP had higher number of differentiated adipocytes compared to control. We showed for the first time that adipogenic genes were up regulated while Sirtuin (epigenetic and metabolic modulator) and insulin signaling genes were significantly down regulated. Our results also indicate that BBP is capable of inducing adipogenesis by itself in the committed preadipocytes and drive the stem cells towards adipogenic lineage. BBP disrupted insulin signaling genes and microRNAs in insulin pathway. Our molecular docking studies also demonstrate BBP as a potential antagonist of Sirt3 and insulin receptor.

BBP can be an obesogen as well as diabetogen. Uncovering the effect of BBP on important epigenetic metabolic regulator(s) could lead to therapeutic interventions and would have a major impact on diabetes pandemic in the present and future generations.

4534

### **NIH efforts to advance research focused on early life factors and cancer development**

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**Research question:** Most cancer research in human populations has focused on a range of exposures in the middle to last 25th percentile of the lifespan. While this narrow age range yields the highest number of cancer cases, it is a phase of life in which cancer prevention efforts are more difficult and perhaps less effective. The emerging evidence that early life exposures affect cancer development later in life calls for a refocusing of efforts targeting the early life spectrum. This paradigm shift in cancer research has the potential to translate into substantial gains in cancer prevention and control.

**Methods:** Staff at the National Cancer Institute has utilized workshops and collaborations with NIH partners to advance research opportunities targeting early life factors and cancer.

**Results:** Specific NIH funding opportunity announcements (FOAs) focused on early life factors and cancer development has been published.

**Conclusion:** Advancement of cancer research efforts focused on early life factors and the links to cancer have been slow, but successful with new FOAs for investigators in the United States and globally.

4394

### **First trimester maternal protein intake and childhood kidney outcomes. The Generation R Study**

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**Research question:** To examine the associations of total, animal and vegetable maternal protein intake during pregnancy with kidney volume and function in school-age children.

**Methods:** This study was performed in 3,650 pregnant women and their children participating in a population-based cohort study from early life onwards. First trimester energy adjusted maternal protein intake was assessed with a food frequency questionnaire. At the child's age of 6 years, we assessed kidney volume, estimated glomerular filtration rate (eGFR) using serum creatinine and cystatin C levels, and microalbuminuria using urine albumin-creatinine ratios.

**Results:** First trimester maternal total protein intake was associated with a higher childhood creatinine-based eGFR (0.06 (95% CI 0.01, 0.12) ml/min/1.73m<sup>2</sup> per gram of protein intake). This association was mainly driven by vegetable protein intake (0.22 (95% CI 0.10, 0.35) ml/min/1.73m<sup>2</sup> per gram of vegetable protein intake). These associations were not explained by protein intake in early childhood. First trimester maternal protein intake was not associated with childhood kidney volume, cystatin C-based eGFR or the risk of microalbuminuria.

**Conclusion:** Our findings suggest that higher total and vegetable, but not animal, maternal protein intake during first trimester of pregnancy is associated with a higher eGFR in childhood.

4341

#### Maternal nutrient intake during pregnancy and asthma risk in offspring over a 10 year period

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**Research question:** Which dietary patterns in the maternal pregnancy diet influence childhood asthma risk over a 10yr period?

**Methods:** n = 897 mother-child pairs from the Lifeways birth cohort, with data on nutrient intake during pregnancy and asthma status respectively, were included in analysis. Data on socio-economic and morbidity indicators over 10yr follow-up on mothers and the index child were collected through self-administered questionnaires. Data were modelled to Generalised Linear Mixed Models (GLMM); personal id was modelled as random effect with random intercepts and slopes over time for individuals. GP diagnosed asthma status at any time-point over 10 years was related to maternal pregnancy nutrition.

**Results:** In the final GLMM, pregnancy intake of oily fish was significantly protective of asthma risk (OR 0.16, 95% CI 0.03-0.94). Vegetable intake in Q1 versus Q4 (OR 1.70, 95% CI 1.08-2.66) suggested a significant increase in the odds of offspring asthma. A higher vitamin D intake significantly reduced the odds (OR 0.95, 95% CI 0.92-0.99).

**Conclusion:** This analysis suggests that maternal pregnancy diet may influence asthma risk offspring at any time-point over a 10yr follow-up, with oily fish, vegetable and vitamin D intake suggesting a protective effect after adjusting for total dietary energy and socio-economic factors.

4412

#### Maternal plasma PUFA status during pregnancy and trajectory of postnatal growth in children from the GUSTO cohort

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**Research question:** Polyunsaturated fatty acids (PUFA) are needed for foetal and postnatal development, including growth. Few observational studies have investigated associations between maternal PUFA status and longitudinal trajectories of offspring postnatal growth.

**Methods:** In 1169 children from the GUSTO mother-offspring cohort, individual length/height (cm) and weight (kg) growth trajectories were fitted from birth to age 4 years using the Jenss-Bayley nonlinear model combined with a mixed effect approach. Parameters summing up the individual trajectories were related to maternal plasma phosphatidylcholine PUFA levels (% fatty acids) at 26-28 weeks gestation, using linear regression adjusted for main known confounders.

**Results:** Among 965 mother-child pairs with full data, higher maternal linoleic acid was associated with greater birth length (B per 5% increase [95% CI] 0.21 [0.07; 0.35] cm) and birth weight (0.026 [0.005; 0.048] kg). Offspring weight gain velocity beyond 2 years of age was greater in those with higher maternal docosahexaenoic acid (B per 5% increase 0.17 [0.04; 0.31] kg/y) and lower total omega-6 (B per 5% increase -0.08 [-0.16; -0.002] kg/y) levels.

**Conclusion:** The strength of observed associations was weak, but they nevertheless suggest that prenatal exposure to PUFA could influence postnatal trajectories of weight and length/height in early childhood.

4588

#### Does fish oil supplementation in late pregnancy prevent offspring asthma? Experience from a Danish randomized controlled trial with 25 years of follow-up

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**Research question:** Does fish oil supplementation in late pregnancy prevent offspring asthma in a long-term perspective?

**Methods:** In 1990, 533 pregnant women were randomly assigned to receive fish oil (FO) (n = 266) (2.7 g long-chain n-3 fatty acids daily), olive oil (OO) (n = 136), or no oil (n = 131). During a 25-year follow-up period, information about offspring use of asthma medication and asthma hospitalizations was extracted from two population-based disease registries with complete follow-up. In intention-to-treat analyses using Cox regression, we estimated the effect of fish oil relative to that of olive oil on offspring asthma medication use and hospitalizations. Furthermore, in 2008 when the offspring were 18-19 years old, lung function was measured by spirometry in a subset (n = 243, 45%) of offspring.

**Results:** During 25 years of follow-up, 14% of offspring received asthma medications and 5% had been hospitalized. The hazard ratios of asthma medication use and asthma hospitalizations were HR = 0.54 (0.32-0.90) and HR = 0.31 (0.13-0.75), respectively, in the FO group compared to the OO group. No effect was seen on lung function in the subset of offspring with lung function measurements at 18-19 years of age.

**Conclusion:** Fish oil supplementation in late pregnancy may prevent offspring asthma.

#### 5415

##### **Growth in 7-11 year old HIV-exposed and unexposed children in rural South Africa**

Brian Houle

**Research question:** To investigate the association of HIV exposure and other early life and child growth aged 7-11 years.

**Methods:** The Vertical Transmission Study (VTS) supported HIV-positive and negative women to exclusively breastfeed (2001-2006); in 2013 the height, weight and body fat of HIV-negative VTS children (345 exposed and 596 unexposed), and a comparison group of same-aged HIV-negative children from the local demographic site (n = 629) were measured. We compared age-standardised median z-scores (or raw scores adjusted for age and sex for body fat) by HIV exposure as well as using internationally recognised cut-offs, examined distributional differences using relative distributions, and explored early life factors using linear regressions for the VTS sample.

**Results:** There were no significant differences by HIV exposure for any indicator. Relative distributions showed little inequality in the distributions by HIV exposure. Normal, as opposed to low birthweight, was associated with increased BMI and body fat. Being born in a peri-urban, as opposed to rural, household ( $\beta = 1.13$ ;  $p = 0.009$ ) with a fridge ( $\beta = 0.77$ ;  $p = 0.050$ ) increased body fat, while being exclusively breastfed for 6 vs < 1 month decreased body fat ( $\beta = -1.19$ ;  $p = 0.055$ ).

**Conclusion:** There was no effect of HIV exposure on the growth of children in mid childhood.

#### 4819

##### **Effect of Preterm birth and intrauterine life on adulthood lung function: A clinical follow-up of births (1985-89) in Finland**

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**Research question:** Fetal origins of lung function and obstructive lung disorder have been proposed. To what extent the adulthood lung function is related to preterm birth (whole range) or underlying pregnancy conditions remains unsolved.

**Methods:** Participants came from the preterm birth study 'ESTER', a cohort of individuals born in Northern Finland (1985-89), which examines association between gestational age (GA), intrauterine exposures, and adulthood health. Participants were grouped by GA at birth: <34wks (n = 139), 34 < 37wks (n = 239), ≥37wks (n = 341). At mean age of 23yrs they underwent spirometry (Medikro®) (FVC, FEV1, FEV/FVC) and provided details of pulmonary health history. Lung function was expressed as z-score, as according to global standards.

**Results:** Preterm-born had poorer adulthood lung function compared to full-term (34 wks: FEV1: -0.443 (95% CI: -0.639, -0.247), FEV/FVC: -0.288 (95% CI: -0.472, -0.104), 34 < 37wks: FEV/FVC: -0.134 (95% CI: -0.284, 0.020) (adjs. age, sex, cohort). Multivariate regression modelling suggested preterm birth as the strongest determinant of adulthood lung function, with very little effect of maternal pregnancy conditions (gestational diabetes, hypertension, asthma, smoking), or subject's smoking-habit and physical activity.



**Conclusion:** Preterm birth is associated with obstructive airflow in young adult life, suggesting a raised risk of earlier decline in lung function, and possibly an earlier development of chronic obstructive pulmonary disease later in life.

4865

### Cardiometabolic and Pulmonary Outcomes among Children Exposed to the World Trade Center

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Although chemical and psychosocial stressors may contribute to cardiometabolic and pulmonary disease, physical effects of early life exposure to the World Trade Center (WTC) attacks have not been examined. We compared cardiometabolic and pulmonary outcomes in adolescents from the WTC Health Registry (n = 120) who were <8 on 9/11/01 with a frequency-matched comparison group (n = 83). Registry adolescents had similar demographics and exposure patterns compared to Registry adolescents as a whole, except our participants had higher family income (p = 0.01). Registry adolescents were more likely to meet criteria for probable post-traumatic stress disorder (p < .02). They did not differ on HOMA-IR, triglycerides, blood pressure, brachial artery distensibility (BAD) or pulse wave velocity. Total lung capacity, functional residual capacity (FRC) and residual volume (RV) were all lower (0.46-0.54 SD units, p = 0.008-0.03), though spirometry and oscillometry did not differ. As both WTC registry adolescents (81%) and comparison adolescents (12%) reported WTC exposures we conducted multivariate analyses by exposure, which revealed 3.59-fold prehypertension (p = 0.008); reduced BAD (-0.075, p = 0.01); and reductions in FRC and RV among those reporting, non-dust, traumatic WTC exposures. While interpretation is limited at this early phase of the study, our findings suggest urgency for longitudinal examination as this vulnerable population ages into adulthood.

4723

### Mother's weight gain in pregnancy is related to daughters being overweight 40 years later

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**Research Question:** Exceeding the Institute of Medicine's (IOM) guidelines for pregnancy weight gain has been related to childhood and adolescent weight. However, whether the effects extend to midlife is less clear.

**Methods:** Between 2005-2008, we recruited 1,108 daughters of mothers who were originally part of two 1960s birth cohorts. We classified maternal pregnancy weight gain as greater than vs. less than/equal to the guidelines. We used logistic regression to estimate associations of maternal pregnancy weight gain with daughters' overweight status (body mass index (BMI  $\geq$  25)) at a mean age of 44, accounting for maternal pre-pregnant BMI, and daughter's body size at birth and childhood.

**Results:** Compared to mothers with a pre-pregnancy BMI < 25 who did not exceed guidelines, mothers who exceeded guidelines and were either not overweight, overweight, or obese were 2.1(1.0-4.6), 5.6 (2.4-12.7) and 6.9 (2.0-23.8) times more likely to have overweight daughters, respectively. The association between weight gain and having a daughter who was overweight in her forties remained even in daughters who were not overweight at birth, childhood or as young adults (OR=3.9; 95% CI = 1.5-10.0).

**Conclusion:** Obesity prevention before pregnancy and strategies to keep weight gain during pregnancy within the IOM guidelines might prevent overweight in daughters 40 years after birth.

4847

### Does Fetal Growth Restriction Cause Later Obesity? Pitfalls in Analyzing Mediators as Confounders

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**Research question:** Do infants born small-for-gestational-age (SGA) birth have increased or decreased adiposity in childhood and adulthood?

**Methods:** In a 11.5-year follow-up of 17,046 Belarusian children, we compared three approaches to analyzing the association between SGA vs appropriate-for-gestational age birth on adiposity (skinfold thicknesses and bioelectrical impedance measure of body fat). The first approach estimates the total effect of SGA on adiposity and adjusts for baseline covariates only. The second uses additional regression adjustment for concurrent height, weight, or BMI at follow-up.

The third uses a marginal structural model (MSM) to estimate the controlled direct effect of SGA on adiposity.

**Results:** The first approach yielded negative associations between SGA birth and all adiposity outcomes. Regression modeling of intermediates reversed (i.e., to positive) the SGA-adiposity association. The MSM approach yielded unbiased estimates of the independent (direct) effect of SGA birth when modeled on height or BMI but remained confounded when modeled on weight.

**Conclusion:** Regression adjustment for anthropometric intermediates yielded reversed (positive) associations between SGA birth and later adiposity, owing to selection bias caused by collider stratification. The MSM approach provided valid estimates of controlled direct effect when using height or BMI as the intermediate, but not with weight.

4721

**Inappropriate adjustment for mediators in analyses exploring the relationship between birth weight and blood pressure in later life: A systematic review and meta-analysis**

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**Research question:** The aim of the present study was to explore the impact of inappropriate adjustment for mediators (i.e. covariates falling on the causal pathway between exposure and outcome) on the observed adjusted relationship between birth weight and blood pressure in later life.

**Methods:** The study involved a systematic review and meta-analysis of primary observational studies identified by combining search terms used in previous systematic reviews conducted by the authors (RH) and others. Data extraction focussed on the timing and measurement of exposure (birth weight), outcome (blood pressure) and covariates (whether confounders, mediators or competing exposures). To identify which of the measured covariates were likely to act as confounders, mediators or competing exposures in the relationship between birth weight and blood pressure a Directed Acyclic Graph was constructed using [www.dagitty.net](http://www.dagitty.net) and all of the covariates measured by any of the primary studies. Meta-analyses were conducted on published unadjusted and adjusted coefficient estimates, the latter disaggregated into estimates generated from under-, over- and appropriately-adjusted analyses.

**Results:** Very few of the published analyses reported adjusted coefficients generated by appropriately-adjusted multivariable statistical models; most reporting adjusted coefficients from over-adjusted models (i.e. models that inappropriately adjusted for mediators that had been incorrectly identified as confounders).

5404

**Best Buys in the first 1000 Days for South Africa**

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After two decades of political democracy, SA has made strides to address poverty and inequality - results of policies for child grants and free care for children under 6 and pregnant women. However, largely attributable to the HIV epidemic, SA will not meet MDGs 4 and 5. The critical first 1000 days of a child's life sets the stage for health over a lifetime. Ensuring that we prioritize the key interventions during this period will enable SA to save more mothers lives during pregnancy and delivery and child lives in the post- 2015 SDG era. Furthermore, understanding the associated costs will enable appropriate budget bids from Health to Treasury. Using the Lives Saved (LiST) Tool we identified priority interventions for mothers, children and newborns that would save additional lives using different scenarios for scale up by 2030; the majority to be provided in the first two years. Half of the childhood interventions are nutrition related; exclusive breastfeeding, therapeutic and appropriate complementary feeding, water connection in the home and hand washing with soap. Other related analyses demonstrate the cost and impact of family planning and diarrhoeal interventions at both the national and provincial level. Strategic gains could be realized by targeting these interventions in "hotspots" with vulnerable populations and on districts with the worst MDG outcomes. The establishment of the Office of Health Standards Compliance to monitor compliance with norms and standards for quality healthcare delivery is an important first step on the road to universal health coverage, but little attention has been focused on the establishment of a formal priority-setting agency, such as HITAP in Thailand. Using this as a model could help to impact the first 1000 days for South African children.

5408

**Returns to early life interventions: Are they still high when other things are not equal?**

Chris Chris Desmond

*Health Science Research Council*

There are high returns to investing in interventions which improve ECD. This has been repeated so often that it is now rarely questioned. This paper critically evaluates the source of high returns and highlights the importance of subsequent complementary interventions in realizing the best returns. ECD investments have such high returns because they improve the rate of return of all subsequent interventions. But when those subsequent interventions are not there, or are of poor quality, the returns from ECD are not so large. This may explain why the benefits of similar ECD interventions, which

have a similar impact at the time, are seen to endure in some contexts and fade in others. In contexts where the benefits of ECD interventions fade, these interventions should not be dismissed as low return investments. Rather, evaluators need to consider the evaluation of sets of interventions, which collectively will generate the high returns which have come to be expected from ECD investments. The key is in the identification of what interventions over the life of the child work most effectively together; this requires a move away from a narrow focus on immediate returns in the early years to one which asks how the maximum impact can be gained over the life of the child.

5403

### Lifecourse evolution of diabetes related phenotypes in Indians: Pune Studies

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Current ideas of aetiology of type 2 diabetes are largely based on a genetic susceptibility and precipitation by obesogenic lifestyle, usually in the adult age. India is one of the world capitals of diabetes. Indians develop diabetes at a younger age and at much lower levels of obesity compared to Europeans. Our research showed that higher susceptibility of Indians to diabetes, is partly related to their excess adiposity (body fat percent) and associated insulin resistance. We further showed that the 'thin-fat' Indian phenotype expresses at birth, and is related to maternal factors (size, nutrition, activity etc), and that this may be influenced by 'epigenetic' factors. Influence of maternal methyl donor nutrition and I-C metabolism on offspring phenotype excited lot of interest.

We have now completed 21 year follow up in the Pune Children's Study (PCS, urban), and 18 year follow up in the Pune Maternal Nutrition Study (PMNS, rural). In the PCS we found that diabetes related phenotypes (glucose tolerance, insulin resistance disposition index, adiposity and central adiposity) were influenced by small size at birth and large size in later life in the urban cohort. Moreover, childhood insulin resistance was a risk factor for increased risk of diabetes and cardiovascular risk factors at 21 years of age.

We found a high prevalence of prediabetes (25%, ADA criteria) in 18 y old PMNS participants (37% in males, 18% in females). Prediabetic individuals were centrally more obese (waist circumference, and subcutaneous abdominal fat on MRI, but not visceral fat) compared to the normoglycemic, and had higher fasting glucose and lower disposition index at 6 and 12 years of age, but similar insulin resistance. The prediabetic were born 2 days earlier (273 v 271 days) and their mothers had lower plasma triglyceride concentrations during pregnancy.

MRI abdominal fat measurements at 18 years of age showed that there was larger amount of subcutaneous (SAT) than visceral (VAT) fat. SAT at 18y was predicted by higher adiposity at 6 and 12 years of age (DXA) and by higher maternal folate but lower vit

B12 and vit D levels, and lower physical activity during pregnancy. Dermatographic pattern of the participants (higher md15, established between 11-19 weeks of gestation, and previously associated with risk of diabetes) was also associated with SAT. In the world's first description of the life-course evolution of diabetes related risk factors we found that maternal-fetal under-nutrition and minimally preterm delivery increased the risk. The related phenotypes were evident by 6 years of age. Our results support a case for 'primordial' prevention, in addition to improving the lifestyle of adults.

4416

### Short stature in black South African adults and cardiometabolic risk: evidence from adults of Sotho descent

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**Research question:** to investigate the association between adult height and cardiometabolic risk in black South Africans.

**Methods:** Adults from Sotho descent (746 men, 1415 women) were included from the North-West and Free State provinces. Socio-demographic and anthropometric measurements were collected. Short stature was defined as height < -2 standard deviations of the sex-specific medians at 19y (WHO reference). Fasting blood glucose, cholesterol, triglycerides and HDL-cholesterol and blood pressure were measured. The criteria for cardiometabolic risk were as for the metabolic syndrome. The odds of short stature to be associated with increased cardiometabolic risk were assessed in men and women and within BMI categories.

**Results:** 19.2 % of men and 13.8% of women were short. There were no significant differences between cardiometabolic risk markers of short vs. normal stature participants. Short overweight participants had greater odds of increased serum triglycerides than short normal weight ones, of high fasting glucose in men and of low HDL-cholesterol in women. Short overweight women had significantly higher fasting triglycerides than overweight women of normal height.

**Conclusion:** There was no association between adult height and cardiometabolic risk in black South Africans. However, in the overweight group, short women had higher fasting triglycerides than women of normal height.

4966

### Maternal caffeine intake during pregnancy, early growth and body fat distribution at school-age. The Generation R Study

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**Research question:** We examined the associations of maternal caffeine intake during pregnancy with early growth patterns, and body fat outcomes and insulin levels at school-age.

**Methods:** This study was embedded in a population-based cohort followed from early pregnancy onwards among 7,857 mothers and their children. We assessed maternal caffeine intake by questionnaires in each trimester of pregnancy. Growth characteristics were repeatedly measured from birth to 6 years. At 6 years, we measured body fat distribution outcomes and insulin levels.

**Results:** Compared to children whose mothers consumed less than 2 units of caffeine per day during pregnancy, those whose mothers consumed 6 or more units of caffeine per day tended to have a lower weight at birth, but higher weight and body mass index gain from birth to 6 years, resulting in a higher body mass index, total body fat mass and android/gynoid fat mass ratio at the age of 6 years. Also, these children tended to have an increased risk of overweight at 6 years. Maternal caffeine intake during pregnancy was not consistently associated with childhood insulin levels.

**Conclusion:** High levels of maternal caffeine intake during pregnancy affect childhood growth patterns and body fat distribution, but not insulin levels.

#### 4393

##### Effect of postnatal nutrition on cardiovascular remodeling induced by fetal growth restriction

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**Objective:** To determine the influence of postnatal nutrition on cardiovascular remodeling induced by fetal growth restriction (FGR).

**Methods:** A cohort study including 81 children with birth-weight <10 centile (FGR) and 121 with adequate fetal growth (AGA). Cardiovascular end-points were left ventricular sphericity index (LVSI), carotid intima-media thickness (cIMT) and blood pressure (BP) at 4-5 years of age. The combined effect of FGR and postnatal variables -including breastfeeding, fat dietary intake and body-mass index (BMI)- on cardiovascular end-points was assessed by linear and robust regressions

**Results:** LVSI was significantly lower, while cIMT and blood pressure were significantly higher in IUGR as compared to controls. Breastfeeding >6 months (coefficient 0.0982) and healthy-fat dietary intake (coefficient -0.0128) showed an independent beneficial effect on LVSI and cIMT respectively. Overweight/obesity induced an additional increment of 1 SD on cIMT in FGR children (interaction coefficient 0.0307) when compared with its effect in AGA. BMI increased systolic BP (coefficient 0.7830) while weight catch-up increased diastolic BP (coefficient 4.8929).

**Conclusions:** Postnatal environment has an effect of cardiovascular remodeling of fetal origin. Breastfeeding >6 months improved cardiac remodeling in AGA and IUGR as well as healthy fat ratio improved vascular remodeling. Overweight/obesity potentiated the effect of IUGR on vascular remodeling.

#### 4369

##### Sex differences in the association between foetal growth and child attention at age four: specific vulnerability of girls

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**Research question:** Impaired foetal growth may provide an early indication of risk of child attention problems. However, despite both foetal growth and child attention problems differing by sex, few studies have examined sex differences in this association. This study examined sex differences in the association between foetal growth indices and attention problems at age four, in a prospective birth-cohort from a middle-income country.

**Methods:** A total of 3749 neonates from the 2004 Pelotas Birth Cohort (Brazil) with foetal growth indices collected at

birth were assessed using the Child Behaviour Checklist. Ordinal logistic regression, adjusting for maternal, demographic, gestational, perinatal, and child nutrition/mother-child morbidity, was conducted separately for girls and boys.

**Results:** In girls, attention problems were associated with being born small-for-gestational-age (OR = 1.40, CI = 1.08-1.82,  $p = .012$ ), with a small head circumference (OR = 1.52, CI = 1.11-2.08,  $p = .009$ ), or a low ponderal index (OR = 1.29, CI = 1.08-1.54,  $p = .005$ ). There were no associations identified between attention difficulties and any foetal growth indices in boys.

**Conclusion:** Girls with impaired foetal growth may be particularly at risk of later attention difficulties. This is consistent with emerging research that female foetuses may be more vulnerable to certain sub-optimal intrauterine environments, inducing epigenetic changes that lead to disturbed growth and long-term developmental impairment.

4477

#### Maternal Mid-Pregnancy Trans Fatty Acids and Pregnancy Outcomes

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**Research Question:** We investigated the association between maternal trans-C18:1 fatty acid concentrations during pregnancy and pregnancy outcomes.

**Methods:** Participants were 6,695 pregnant women and newborns from the Generation R Study, Rotterdam, the Netherlands (born in 2002–2006). Maternal mid-pregnancy (gestational age 20.7 weeks, SD 1.2) trans-C18:1 fatty acid concentrations in plasma were related to gestational age-adjusted birth weight SD-scores, placental weight, and pre-eclampsia. Also, we explored potential time-trends of the association of maternal trans-C18:1 concentrations on birth weight, given the Dutch industry-initiative to lower TFA food content during the inclusion period.

**Results:** A higher maternal trans-C18:1 concentration was associated with a lower birth weight (adjusted  $\beta$  -0.10, 95% CI -0.15; -0.04,  $P < 0.001$ ), placental weight (adjusted  $\beta$  -10.65, 95% CI -20.23; -1.07,  $P = 0.03$ ) and a higher risk of pre-eclampsia (adjusted odds 1.65, 95% CI 1.10; 2.49,  $P = 0.02$ ). In our population, the median trans-C18:1 concentration decreased with 31% over time. However, the association between the trans-C18:1 concentration standardized per birth year, and birth weight was comparable between birth-year cohorts.

**Conclusion:** A higher maternal mid-pregnancy trans-C18:1 fatty acid concentration was associated with more adverse pregnancy outcomes. Although the intake of TFA in our

population decreased during the inclusion period, the association with adverse pregnancy outcomes persisted even at lower maternal trans-C18:1 fatty acid concentrations.

5105

#### Large fetuses of obese woman show higher plasma levels of adiponectin, express adiponectin receptor 1 and show an inactive enos in human umbilical artery endothelial cells.

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We studied the correlation of fetal plasma adiponectin levels with birth weight in large-for-gestational-age fetuses of obese women (L/O) and adequate-for-gestational-age fetuses of normal weight women (A/N). We also compared Adiponectin Receptor-1 (AdipoR1) and eNOS expression and activation in Human Umbilical Artery Endothelial Cells (HUAEC) from both groups.

Plasma cord blood and HUAEC were obtained from the umbilical cord of term single pregnancies of A/N and L/O. Fetal plasma adiponectin levels were measured by ELISA. The mRNA of both AdipoR1 and eNOS were measured by qPCR. AdipoR1, eNOS and phospho-eNOS (Ser1177) protein expression by Western blot and ELISA.

Fetal plasma adiponectin levels were increased in L/O compared to A/N group and positively correlated to maternal BMI and fetal birth weight. mRNA and protein expression of AdipoR1 and eNOS are increased in HUAEC from L/O. Phospho-eNOS, and phospho-eNOS/eNOS ratio decreased in HUAEC from L/O.

Fetal circulating adiponectin levels show a positive correlation with fetal weight. In HUAEC the increase in AdipoR1 could be a signal of increased Adiponectin sensitivity. Finally, the over-expression of eNOS in L/O paralleled by a low activity of the enzyme could be associated to sub-clinical vascular compromise and fetal programming of endothelial dysfunction.

4674

#### Leisure-time physical activity in young adults born preterm - The ESTER Study

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**Research question:** Adults born with very low birth weight (< 1500 g) report less physical activity (PA) and are less fit than their term-born peers. We examined whether self-reported PA is decreased among preterm-born adults and whether this extends to all degrees of prematurity.

**Methods:** At the age of 23.1 (SD 1.4) years 656 participants of the ESTER Study completed a modified Kuopio Ischemic Heart Disease Risk Factor Study-questionnaire on 12-month PA. 123 participants were born early preterm (EPT, < 34 wk GA), 215 late preterm (LPT, 34-36 wk GA) and 318 were term-born controls. Group differences were examined by linear regression.

**Results:** As compared with controls, EPT group reported 30.1% (95% CI 14.2-43.1) lower volume of leisure-time PA (MET<sub>h</sub>/year), to which both lower conditioning and non-conditioning PA contributed. This resulted in 29.0% (13.4-41.7) lower energy expenditure (kcal/year). Also the volume and energy expenditure of vigorous PA (MET ≥ 6) were lower among EPT group. Differences in LPT group compared with controls were not statistically significant. Adjustments for early life confounders or current mediating factors did not change the results.

**Conclusion:** Young adults born early preterm report engaging in less LTPA compared with term-born controls which may predispose them to cardiometabolic and other chronic diseases.

#### 4815

##### **Effect of early nutrition on later cognition: human milk nutrients at 3 months of age predict declarative memory abilities at 2 and 3 years of age**

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**Research question:** We hypothesized that docosahexaenoic acid (DHA) and free choline intake at 3 months of age in exclusively breastfed infants and their interaction would predict the ability to recall ordered sequential steps in toddlerhood.

**Methods:** Participants (n = 121) from a study of human milk nutrients and cognition returned to the lab for follow-up at 26 and 38 months old. Eighty-nine had full data. Using an imitation paradigm, toddlers were tested for declarative memory abilities immediately, after 20 minutes, after one week, and after a refresher demonstration at the 1-week delay session. Multivariate regressions were conducted by age controlling for months exclusively breastfed and predicting the four recall scores by DHA, free choline, and DHA X free choline.

**Results:** For 2-year-olds, the ability to immediately recall ordered steps was related to DHA (p = 0.05) and DHA X choline (p < 0.05). The ability of 2-year-olds to recall ordered steps after relearning at the 1-week delay was related to DHA (p < 0.05) and DHA X choline (p < 0.05). In 3-year-olds, DHA, choline, and their interaction predicted (all p < 0.05) relearning of the steps with no significance in ordering the steps.

**Conclusion:** Early human milk nutrients have long-lasting effects on declarative memory abilities.

#### 4890

##### **Intergenerational change in anthropometry of children and adolescents in New Delhi Birth Cohort, India**

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**Research question:** Evaluate intergenerational change in anthropometry and its predictors in an Indian urban cohort.

**Methods:** Using Cole's LMS approach on longitudinal anthropometry (6-monthly intervals from 0-21 years) of 8181 F1 generation, growth charts were derived. These were used to compute age and gender specific F2 generation (children of F1) anthropometric Z scores between 0 and 21 years. For comparison, F1 Z score was interpolated at the exact date of anthropometry of F2, using F1 neighbouring anthropometric Z scores within a specified window. Intergenerational change was quantified using mixed modeling (accounting for siblings and multiple F2 measurements) in five age groups (0-5, 5-7.5, 7.5-10, 10-12.5, >12.5 yrs) adjusting for gender of child and parent.

**Results:** 2,236 (F2-F1) comparisons in 1523 pairs (> 400 each group) were analyzed. There was a significant increase in height (0.66 to 1.19 SD), weight (0.84 to 1.31 SD) and BMI (0.31 to 1.15 SD) in F2 generation at all ages. Age, socio-economic status and birth and measurement periods were significantly associated with intergenerational change in anthropometry.

**Conclusion:** Over one generation, there was substantial increase in anthropometry. A lower increase in BMI in <7.5 years suggests that children grew up (became taller) before growing out (becoming wider).

4767

### Longitudinal Associations between affective problems and eating disturbances in South African adolescents

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**Research questions:** Do South African adolescents with affective problems have a higher risk of later eating disturbances?

**Methods:** Participants were 486 boys and 545 girls who were part of a larger longitudinal study in South Africa. Affective problems were assessed using the Youth Self Report (YSR) at year 14; eating disturbances were measured using the Eating Attitudes Test-26 (EAT-26) at years 13 and 17.

**Results:** Girls with affective problems at year 14 were more likely to report eating disturbances at year 17 [OR = 3.22], even after adjusting for age, BMI, and household SES. Associations were not significant for boys. There is a significant increase in eating disturbances in both girls with and without affective problems from 13 to 17 years. Although there is no difference in EAT-26 scores at age 13, by age 17, girls with affective problems at year 14 report significantly higher EAT-26 scores than girls without affective problems.

**Conclusion:** Depression increases drastically during adolescences, particularly for girls, and is associated with a host of other psychological problems such as eating disorders. We provide longitudinal evidence from a South African study to support Western findings that girls with signs of early depression are at risk.

4724

### Maternal pregnancy factors and menarche in girls with a family history of breast cancer: The Legacy Girls Study

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**Research question:** Maternal pregnancy factors (age, weight gain, and body mass index (BMI)) are associated with menarche, a breast cancer risk factor, but it is unknown whether these associations are similar across the spectrum of breast cancer risk.

**Methods:** Using the LEGACY girls study cohort of 1,040 girls aged 6-13, we examined the association between maternal pregnancy factors and menarche. Approximately half of the cohort was enriched with a family history of breast cancer and the remaining half was of average risk.

**Results:** After adjusting for age, race and site, earlier menarche was associated with older maternal age (Odds Ratio (OR) = 3.12, 95% CI = 1.30-7.46 per year of age), high maternal BMI (OR = 1.06, 95% CI = 1.00-1.13, and lower pregnancy weight gain (<14 lbs compared to more, OR = 3.38, 95% CI = 1.19-9.60). There were no statistically significant interactions by family history.

**Conclusion:** Maternal and pregnancy-related factors were associated with menarche in a cohort of girls enriched with a family history of breast cancer. This suggests that modifiable factors such as pregnancy weight gain are important across the spectrum of breast cancer risk and not just in girls at average risk for breast cancer.

4951

### Does change in components of childhood height influence cardiovascular risk and cognitive function in Indian adolescents?

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**Research question:** We investigated whether change in height components is related to cardiovascular (CVD) and cognitive outcomes in Indian adolescents.

**Methods:** We derived conditional SD scores for leg length and sitting height at 0-2, 2-5, 5-9.5 and 9.5-13.5y in 487 children from the Parthenon Study. Lean and fat mass (bio-impedance), plasma glucose, insulin and lipid concentrations, blood pressure (BP), and cognitive function were measured at 13.5y.

**Results:** Greater increase in leg length and sitting height at all ages were related to higher lean mass ( $p < 0.01$ ). Increase in leg length and sitting height up to 5y was associated with higher fat mass ( $p < 0.01$ ) but the direction of the relationship with leg length reversed subsequently. Overall, increase in leg length and sitting height in early life (birth, 0-2y) was associated with lower CVD risk and better cognitive performance. An increase in leg length between 5-9.5y was associated with lower systolic BP; greater increase in sitting height was associated with higher systolic (5-9.5y) and diastolic BP (9.5-13.5y) ( $p < 0.05$  for all). Adjusting for body composition attenuated the relationships with sitting height.

**Conclusions:** An increase in height components in early life, and in leg length between 5-9y appears beneficial. Body composition may mediate relationships with CVD.

4959

#### **Birth weight, postnatal weight gain and cortisol responses to stress in Indian adolescents**

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**Research question:** To explore the associations between birth weight and postnatal weight gain, and adolescent cortisol responses during the Trier Social Stress Test for children (TSST-C).

**Methods:** Adolescents from an Indian birth cohort (N = 243; age: 13.5y) performed 5-minutes each of a public speaking and a mental arithmetic task in front of two unfamiliar 'evaluators' (TSST-C). Salivary cortisol concentrations were measured at baseline and at 0, 10, 20, 30 and 60 minutes after TSST-C. Cortisol increment from baseline at these points (stress-response) were examined in association with birth weight and conditional SD scores representing weight gain during 0-1, 1-2, 2-5, 5-9.5 and 9.5-13.5y using linear mixed-model analysis.

**Results:** In boys, lower birth weight (P0.02, adjusted for age, socio-economic status, and maternal gestational diabetes) and greater weight gain during 5-9.5y and 9.5-13.5y (P 0.05) was associated with higher cortisol stress-response, especially 20 minutes after TSST-C. Adjusting for pubertal stage attenuated the latter associations. In girls, greater weight gain from 2-5y was associated with lower cortisol responses at all time points after completing TSST-C (P 0.02).

**Conclusions:** Reduced fetal growth and accelerated weight gain during later childhood may increase neuro-endocrinal stress-responses in boys. Early weight gain up to 5y may be protective against stress-induced morbidity.

4972

#### **The association of childhood growth trajectories with left ventricular mass and left atrial size in adolescence**

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**Research question:** Are childhood growth trajectories related to cardiac structure in adolescence?

**Methods:** Linear spline multilevel modelling was used to estimate associations of weight, height, and weight-for-height trajectories from birth to age 10 with left ventricular mass indexed to height<sup>2.7</sup> (LVMI) and left atrial antero-posterior diameter indexed to height (LAI) assessed by echocardiography in 17 year-olds from a UK Birth cohort (N = 1,498). We adjusted for appropriate confounders.

**Results:** Birthweight was weakly positively related to LVMI and LAI; childhood weight trajectories began to show associations after age 3 years, with the strongest association for weight gain between 3-7 years: 1SD higher weight gain associated with 0.28SD higher LVMI, p

4429

#### **Prenatal exposure to maternal anxiety is associated with DNA methylation signatures in adolescence**

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**Research question:** Prenatal maternal anxiety disorders have been associated with adverse mental health outcomes in offspring. However, the molecular pathway by which this process occurs has not yet been elucidated. We sought to investigate whether epigenetic mechanisms could underlie the transmission of prenatal maternal anxiety to offspring's mental health.

**Methods:** Participants were recruited from the Wisconsin Study of Families and Work, a prospective cohort study of child development. Prenatal maternal anxiety was assessed during the second trimester of pregnancy using the Spielberger



State-Trait Anxiety Inventory. DNA from buccal cells that were collected when offspring were 18 years old was extracted and interrogated on the Illumina 450K BeadChip Array. Linear regressions of DNA methylation against prenatal maternal anxiety were conducted, with adjustment for sex, ethnicity, and maternal age. Pathway analysis was conducted using Gene Ontology (GO).

**Results:** A highly positively skewed p-value distribution was found for prenatal maternal anxiety. The top genes associating with prenatal maternal anxiety included NR3C1, the gene encoding the glucocorticoid receptor, and were significantly enriched for GO biological processes involving cellular developmental process and regulation of developmental growth.

**Conclusion:** These findings support the idea that epigenetic mechanisms may be involved in fetal programming of mental health.

4989

#### Early-life adversity and healthy ageing

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**Question:** Is early-life adversity associated with ageing in mid-life?

**Methods:** Participants were mothers from a UK birth cohort who attended a research clinic in mid-life (n = 1,730, mean age 51 years). We studied associations of self-reported paternal occupational social class (OSC), parental physical or mental illness, alcoholism, death, separation or imprisonment and own experience of childhood illness, physical or sexual abuse and physical or emotional neglect with cardiovascular health (body mass index (BMI), fat mass, and systolic blood pressure), cognitive (logical memory and verbal fluency) and physical function (timed 3-meter walk, grip strength). Analyses were repeated adjusting for adult household OSC to assess potential mediation.

**Results:** Low paternal OSC was associated with lower logical memory, verbal fluency and grip strength scores, and higher BMI and fat mass (p-values

4722

#### The health in later life of Channel Islanders exposed to the 1940-45 German occupation and siege

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Ledds Medical School

**Research question:** The Channel Islands Occupation Birth Cohorts Study set out to examine whether exposure to the 1940-45 occupation and siege influenced the long term health of this population.

**Methods:** To-date analyses have been conducted on three separate cohorts, linking data from multiple sources (including birth records, population registration documents, health care utilisation data and death notifications) to assess whether exposure to the occupation in early life was associated, in later life, with higher: blood pressure; blood glucose levels; total blood cholesterol concentrations; body mass index; rates of hospital admission for acute cardiovascular events; all-cause and/or cause-specific mortality; and rates of poor self-reported health.

**Results:** These analyses suggest that there is some evidence of an increased risk of metabolic dysfunction, elevated body mass index, hospital admissions for acute cardiovascular events, mortality and self-reported health, while the absence of an increased risk of elevated blood pressure or total blood cholesterol levels may partly reflect ongoing challenges associated with linking sufficient numbers of individuals across enough of the available datasets to generate samples for analysis that are sufficiently large and sufficiently well-specified to permit robust analysis.

4703

#### Early life determinants of mortality in a cohort of 12,564 men and women born in Uppsala 1915-1929

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**Introduction:** This paper studies the association between perinatal health and all-cause mortality by specific age intervals, assessing the contribution of maternal socioeconomic characteristics and the presence of maternal-level confounding.

**Material and methods:** Our study is based on a cohort of 12,564 singletons born between 1915 and 1929 at the Uppsala University Hospital. We fitted Cox regression models to estimate age-varying hazard ratios of mortality and 95% confidence intervals for absolute and relative birthweight and gestational age. We conducted between and within-family survival analyses to assess maternal-level confounding.

**Results:** This study provides evidence that light, small, and preterm newborns have a higher risk of mortality, although these associations vary by age and measure under scrutiny. The associations with birthweight and gestational age were confirmed in the sibling analysis analyses, indicating that any residual maternal confounding is limited. There was a small indication of negative confounding of low birthweight on infant mortality, leading to underestimation.

**Conclusions:** Our findings support the interpretation that policies oriented towards improving population health should invest in birth outcomes and hence, in maternal health.

4401

**Gender differences of age-related morbidity and mortality: on the way to ontopathogenic model**

Viktor Goudochnikov

*Council of International Society for DOHaD*

Earlier we have evaluated age-related dynamics and gender differences of morbidity and mortality caused by various diseases in southern region of Brazil. The aim of our present work was to perform systematic re-evaluation of these gender differences, in order to justify the necessity of elaborating the ontopathogenic model. The data retrieved from DataSus were used again, but in the present work the attention was paid mainly to feminine fraction. In general, females predominated in morbidity caused by hypertension, diabetes mellitus, affective disorders, bronchial asthma, cholecystitis, whereas the males predominated in morbidity provoked by myocardial infarction, schizophrenia, chronic obstructive pulmonary disease, gastro-duodenal ulcers. Expressive gender differences were observed for morbidity and mortality provoked by some non-reproductive cancer types and infectious diseases. In many cases feminine fraction has shown clear-cut age-related dynamics related to menopausal transition. Our future research efforts should be directed to elaborating ontopathogenic model that has to describe the causes and mechanisms of various diseases during entire ontogeny. Moreover, since considerable evidence indicates an important role of glucocorticoids in mechanisms of programming/imprinting phenomena, as well as in etiopathology of various disorders, we suggest to consider the contribution to ontopathogenic model of these hormones, together with other bioregulators.

4430

**Increased dietary fat across generations leads to loss of metabolic homeostasis with ageing and an aged transcriptome in young adults**Samuel Hoile<sup>1</sup>, Leonie Grenfell<sup>2</sup>, Mark Hanson<sup>3</sup>, Karen Lillycrop<sup>4</sup>, Graham Burdge<sup>5</sup><sup>1</sup>*University of Southampton;* <sup>2</sup>*University of Southampton;*<sup>3</sup>*University of Southampton;* <sup>4</sup>*University of Southampton;*<sup>5</sup>*University of Southampton*

Transition onto a modified diet over several generations can induce compensatory metabolic adjustments in young adults, associated with altered gene transcription. We hypothesised that compensatory changes in young adults are lost during ageing contingent on dietary macronutrient content. Female C57BL/6 F0 mice were fed 5% or 21% fat diets (w/w) throughout pregnancy and lactation. Female offspring were fed the same diet as their dams until the F3 generation. Young adult (d90) and ageing (d456) offspring were studied

for growth markers, metabolism and liver transcriptome (microarray).

Phenotype was unchanged at d90. Liver weight, glucose and bHB concentration were altered by diet and generation in ageing, suggesting loss of metabolic control. Gene expression differences between d90 dietary groups was greater in F1 (698 genes) compared to F3 (23) offspring. There effect of generation was greater in the 5% lineage (520) compared to the 21% lineage (17). The effect of age was greatest in the F1 5% group (1340).

Dietary macronutrient content altered metabolic phenotype across generations after reaching adulthood; implying loss of homeostasis with ageing. Gene expression data suggests increased dietary fat led to an aged transcriptome, which occurred within one generation for 21% fat and over three generations for 5% fat.

4785

**Understanding the inter-connection between body image, socio-demography and the development of obesity across lifespan in South Africa: SANHANES-1**

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*Human Sciences Research Council*

**Research question:** What are the factors that differentiate body image across lifespan in South Africa? Particular focus is given to the explanation of the nexus between body mass index, weight concerns and socio-demographic factors.

**Methods:** A cross-sectional survey and a second analysis of data for participants in the SANHANES-1. Body image (BI) was investigated and compared to the body mass index (BMI), socio-demographic variables and attempts to lose / gain weight. Data were analysed using STATA version 11.0 and results are presented as %, means, 95% confidence intervals, p-values and odds ratios.

**Results:** South Africans at the extreme ends of BMI have alarming negative BI (i.e. have largely distorted BI and are highly dissatisfied by it). To be specific, those South Africans who view themselves as underweight overestimate their body size and prefer to be bigger. On the other hand, those who view themselves as obese underestimate their body size and prefer to be smaller. As a result, they engage in weight gain / loss attempts, by mainly adjusting their dietary intake and physical activity. Income, gender and ethnicity seem to have the highest effects on body image, followed by race, age, marital status and to the lesser extent by urbanization.

**Conclusions:** Body mass index seems to differentiate BI in South Africa. Body mass index is influenced by socio-demography, thus it may appear as if socio-demographic factors have the most effect on BI. This calls for a need for targeted interventions to reduce unemployment, dispel myths regarding social stereotypes attached to the weight status and advocate positive body image in the country.

4532

### The UPBEAT trial. A Complex Intervention of Diet and Physical Activity in 1555 Obese Pregnant Women

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**Research question:** Obesity in pregnancy and excessive gestational weight gain (GWG) have been associated with increased risk of obesity in the offspring. Randomised trials of maternal interventions are required to establish effectiveness in prevention of offspring obesity.

**Methods:** 1555 pregnant women (mean BMI 36.3 kg/m<sup>2</sup>) were randomized (15+0 to 18+6 weeks' gestation) to standard antenatal care or a health trainer delivered intervention (weekly, 8 weeks) of dietary advice (low glycemic index) and physical activity.

**Results:** Compared to standard care, the intervention (mean 7 sessions/woman) reduced dietary glycemic load by 26.3 units (95% CI -31.6 to -20.9)(19% lower), saturated fat intake (% energy) by 1.03% (-1.35 to -0.70)(8% lower) and total energy intake by 1.08MJ (-1.36 to -0.80)(14% lower). Protein intake increased ( $p < 0.001$ ) and total carbohydrate intake ( $p = 0.02$ ) fell. Physical activity improved by 295 metabolic equivalents mins/wk (112.1 to 477.6) (21.3% higher). Maternal GWG was reduced by 0.55 kg (-1.1 to 0.0). The sum of skinfold thicknesses decreased ( $p = 0.010$ ). The intervention did not reduce gestational diabetes or large-for-gestational-age delivery.

**Conclusion:** The UPBEAT intervention provides a safe strategy to improve diet, physical activity, GWG and body fat. 6months and 3yr childhood follow-up is underway.

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4445

### M-Health improves fertility and (pre)pregnancy lifestyle behaviors in couples

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**Research question:** Does the m-Health coaching platform 'Smarter Pregnancy'(www.slimmerzwanger.nl) empower couples

to improve lifestyle behaviors during the (pre)pregnancy period with beneficial effects on the chance of pregnancy?

**Methods:** Patients visiting the outpatient clinic at of the Erasmus MC or midwifery practice in Rotterdam contemplating pregnancy ( $n = 1,275$ ) or being pregnant ( $n = 603$ ) were offered a free-subscription to 'Smarter Pregnancy'. After identification of inadequate lifestyles the personal coaching program (6 months) was generated using SMS, E-mail and additional screening moments tailored to improve these behaviors. Data of 2,003 patients were analyzed using multiple imputation and generalized estimating equations (GEE) with independent correlations. We modeled and estimated the changes from inadequate to adequate behavior over time. To determine the effect of behavioral changes on the chance of pregnancy we used a joint model in which risk scores were modeled simultaneous with pregnancy rates.

**Results:** After 6 months of coaching the percentage of patients with adequate behaviors (vegetable, fruit, folic acid, quit smoking and alcohol use) increased by 18.6 to 65.8%. Improvement of each inadequate behavior increased the chance of pregnancy up to 40%.

**Conclusion:** M-Health empowers (pre)pregnant couples to improve lifestyle and pregnancy chance.

4938

### Combatting the Transgenerational risk of Non-communicable diseases in Transitioning societies -from evidence to action with Case studies from India

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**Background:** Evidence from transitioning societies points to life-course influences on disease risk. Should we now move from evidence to action with interventions tailored to these societies?

**Methods:** Indian birth cohort studies have shown that parental influences and child's own circumstances are determinants of future disease. Later life factors, including dietary and lifestyle behaviours are also important. Should we shift our focus to evidence – based policies and interventions tailored to combat these life-course determinants of transgenerational risk? We review a potential multi-tier approach with ongoing/new individual, household and community-level interventions that could change disease patterns in future generations of transitioning societies.

**Results and Conclusions:** Non-communicable diseases share a number of common risk factors. A complete package of services delivered through a decentralized system is warranted. This includes universalization of maternal and under-5 nutrition supplementation to improve pre-pregnant nutritional status of young girls and women, improved ante-natal care and institutional deliveries, complete immunization and good

breast-feeding practices, reduction in childhood infections from appropriate water, sanitation and hygiene measures, controlling indoor and ambient air pollution, school curricula advocating the right foods, physical activity, abstinence from tobacco, alcohol and drugs and increasing awareness of and uptake of health care services and social support.

4464

**Effect of a prenatal lifestyle intervention on infant size up to 1 year of age: results of the Norwegian Fit for Delivery randomized controlled trial**

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**Research question:** Does the Norwegian Fit for Delivery (NFFD) lifestyle intervention in pregnancy affect birth weight and growth during the first year of life?

**Methods:** The NFFD randomized controlled trial was performed between 2009-2014. Inclusion criteria were nulliparity, age  $\geq 18$  years, singleton pregnancy  $\leq 20$  gestational-weeks, pre-pregnancy BMI  $\geq 19$  kg/m<sup>2</sup>, literacy in Norwegian or English, and signed informed consent. Pre-existing diabetes and inability to exercise were exclusion criteria. The intervention group (n = 296) received dietary counseling twice by telephone and access to twice-weekly exercise groups; the control group (n = 295) received routine prenatal care. Babies were weighed and measured at delivery and 6 and 12 months postpartum. Data was analyzed using two-sided t-test.

**Result:** 557 babies were delivered at term (279 intervention, 278 control). There was no difference in weight between groups at birth (3.47 vs. 3.52 kg, mean diff -0.05 kg, 95% CI -0.12, 0.03, p = 0.20), 6 months (8.07 vs. 8.13 kg, p = 0.50) or 12 months (9.97 vs. 10.06 kg, p = 0.37). Mean length was identical for both groups at delivery (50.2 cm) and 6 months (69.0 cm), and equivalent at 12 months (77.1 vs. 77.3 cm, p = 0.58).

**Conclusion:** The NFFD intervention had no significant effect on infant size during the first year.

4631

**The Role of Food Security on Nutritional Status and health during Critical Periods of Growth and Development**

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Recent research suggests that the timing and intensity of food insecurity and hunger can have differential effects on infant,

child, and teenage nutritional status and health. Furthermore, the ways in which households and communities attempt to cope with problems of food access may mitigate or exacerbate these effects. The aim of this presentation is to review the literature on the role of food insecurity on nutritional status and health during the life course, with a focus on early environment adversity. In addition to discussing the literature on the consequences of food insecurity associated with under-nutrition, there will also be an examination of the food insecurity-obesity paradox, a phenomenon that is associated with the nutrition transition. The presenters will use case studies from their own research in Southern Africa and Central America as examples. Moreover, there will be a discussion on familial and community networks as potential coping strategies to ameliorate food insecurity and hunger. Finally, examples of food-related and non-food related coping responses will be examined and whether these behaviors are effective responses to food insecurity and hunger. A critical biocultural approach from anthropology will be used to frame this presentation.

4976

**A review of maternal, neonatal, infant and child health interventions within the first 1000 days of life: What can South Africa learn from other countries?**

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**Research question:** South Africa (SA) has notable political commitment through policies and guideline documents on maternal, neonatal and child health (MNCH) outcomes yet when compared to other lower middle income countries (LMIC), MNCH mortality rates are still high. There needs to be a more efficient country specific method to prioritise MNCH interventions learning from other LMICs and focussing on the first 1 000 days of life.

**Method:** This systematic literature review employed an exhaustive search strategy, wide range of databases, rigorous quality criteria and SA applicability. Results: Thirty two articles and 15 interventions were partially or non-aligned. Examples of these were preventing teenage pregnancies, community participation and the effectiveness of community of health workers, postnatal care, training and integration of care. Experts in the field of MNCH and implementers within the SA context discussed the applicability of the non-aligned interventions for developing packages of care. These intervention packages were added to the SA Primary Health Care (PHC) re-engineering strategy model as directives for cadres of staff to strengthen and support health systems.

**Conclusions:** These interventions highlight gaps in SA and provides directives on integrating and packaging service provision for MNCH care across the first 1000 days and levels of care.

4936

**Vascular and metabolic studies in children whose fathers had premature cardiovascular disease**

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**Research question:** Are the metabolic and vascular profiles of children whose fathers had premature cardiovascular disease (PCD) different when compared with an age-, gender- and BMI-matched healthy cohort?

**Methods:** A cross-sectional study comparing well children whose fathers have had PCD, either myocardial infarction or coronary artery bypass grafting before aged 56 years [subjects, n=53] and children of healthy parents, free from clinical

cardiovascular disease [controls, n=39]. Inclusion criteria for participants included 8-14.0 years old and healthy.

Anthropometrics, medical history, family history, exercise habits, carotid IMT-(cIMT) were recorded. Endothelial function was assessed by peripheral applanation tonometry-(RH-PAT).

24-hour ambulatory blood pressure recordings were performed. Blood pressure indices were calculated to control for gender and height [BPI(height)] as well as gender and age [BPI(age)].

Fasting lipids, lipoproteins, HbA1C and fibrinogen were measured. Oral glucose tolerance testing (OGTT) was performed, measures of insulin sensitivity were derived.

**Results:** Compared with matched controls our subjects have: higher alanine aminotransferase (p=0.004) and fibrinogen (p=0.049) levels, lower RH-PAT scores (p=0.005) indicating relative endothelial dysfunction as well as higher diastolic blood pressures (p=0.009). Differences in fasting glucose (p=0.08) and insulin sensitivity (p=0.27) did not reach statistical significance. Fasting lipids and lipoproteins were similar.

**Conclusion:** The results of this pilot study show early impaired vascular and metabolic health in well young children whose fathers have PCD.