6C-5 Autonomic nervous system and baroreflex function in adults after prenatal exposure to the Dutch famine

R.C. Painter[1,2]*, A. Jones[3], S.R. de Rooij[1], C. Osmond[3], J.M. Karemaker[4], D.I.W. Phillips[3], T.J. Roseboom[1]. [1]*Department of Clinical Epidemiology and Biostatistics, Academic Medical Center at the University of Amsterdam, Amsterdam, The Netherlands,* [2]*Department of Obstetrics and Gynaecology, Medical Centre Alkmaar, Alkmaar, The Netherlands,* [3]*MRC Epidemiology Resource Centre at the University of Southampton, Southampton, UK,* [4]*Department of Physiology (Systems Physiology), Academic Medical Center at the University of Amsterdam, Amsterdam, the Netherlands*
E-mail: r.c.painter@amc.uva.nl

Aims: Maternal undernutrition during gestation is associated with exaggerated blood pressure responses to psychological stressors in the offspring. This may be one of the ways in which poor fetal nutrient supply leads to hypertension and cardiovascular disease in adult life. We hypothesized that autonomic nervous system and baroreflex function would be altered among people exposed to famine during gestation.
Study design: Historical birth cohort.
Subjects: Seven hundred cohort members who were prenatally exposed or unexposed to the 1944-'45 Dutch famine underwent a series of 3 psychological stressors (Stroop, mirror-tracing and speech) whilst their blood pressure was recorded continuously using a Finometer or Portapres.
Outcome measures: Normalised indices of autonomic function were derived by spectral analysis (wavelet packet transform). Baroreflex was estimated using an adaptive autoregressive model.
Results: People conceived during the Dutch famine had a greater increment in their low frequency (0.04–0.15 Hz) blood pressure variability during stress compared to unexposed participants (51% extra increase during stress compared to unexposed, 95% CI 10% to 90%, adjusted for gender and BMI). This was not explained by anti-hypertensive drug use, social class or birthweight. Famine exposure in utero was not associated with other measures of autonomic or baroreflex function at rest or during stress.
Conclusions: Our findings indicate that maternal undernutrition during early gestation may lead to increased stress-induced sympathetic nervous system activation.

6C-6 Maternal diets rich in saturated fatty acids result in developmental programming of Na^+, K^+ ATPase activity, gene expression and protein translation in a tissue specific manner

J.A. Armitage[1,2]*, S. Gupta[1], C. Woods[1], R.I. Jensen[1], A.M. Sammuelsson[1], P.D. Taylor[1], L. Poston[1]. [1]*Maternal and Fetal Research Unit, Division of Reproduction and Endocrinology, King's College London, United Kingdom,* [2]*Department of Anatomy and Cell Biology, Monash University, Clayton, Victoria, Australia*
E-mail: james.armitage@med.monash.edu.au

Aims: To investigate whether exposure to various fat-rich diets during development programmes altered Na^+, K^+ ATPase activity in kidney and brain via altered mRNA or protein expression.
Study design: Female *Sprague-Dawley* rats were fed, during pregnancy and suckling, a control fat (4% corn oil) or one of three fat-rich (24%) diets. Fat sources delivered predominantly saturated (SFA), monounsaturated (MUFA) or polyunsaturated (PUFA) fatty acids. Offspring were fed a control diet (4% PUFA) from weaning.
Subjects: Six-month old offspring were euthanased and organs collected (n = 20 per group).
Outcome measures: Na^+, K^+ ATPase activity by colorimetric assay, mRNA expression of α subunit by real time PCR and protein translation by Western blot (α1, α2, α3 and β1 subunits).
Results: SFA offspring had reduced Na^+, K^+ ATPase activity in the renal cortex ($P < 0.05$ vs. other diet groups) and cerebral cortex ($P < 0.05$ vs. control and MUFA offspring). α1 subunit mRNA and total α, α1, α2, α3 or β1 subunit protein were not significantly altered in renal cortex from any diet group. In cerebral frontal cortex, SFA offspring showed reduced ($P < 0.05$) α1 mRNA expression vs. MUFA and PUFA offspring but not controls. SFA offspring had reduced ($P < 0.05$) α1 subunit protein and increased ($P < 0.05$) protein levels of the Na^+, K^+ ATPase modulating protein phospholemman, phosphorylated at serine residue 63 (S63 PLM) vs. controls.
Conclusions: SFA intake during development programmes reduced Na^+, K^+ ATPase activity in brain and kidney, however the mechanisms of action differ. In kidney, activity may be related to membrane biomechanics, in brain, increased PLM and decreased α1 may be responsible.

6C-7 Clinical doses of prenatal glucocorticoids induce profound changes of the renal and cerebral vascular tone in the aged rat

M. Schwab*, D. Reymann, C. Schinzel, O.W. Witte. *Dept. of Neurology, Friedrich Schiller University, Jena, Germany*
E-mail: Matthias.Schwab@med.uni-jena.de

Aims: Prenatal glucocorticoid exposure induces hypertension in the young adult rat (Neuroendocrinology 1996; 64: 412–8) and increases femoral vascular resistance in the postnatal lamb (J Physiol 2003; 547: 61–6). It is not known to what extent altered vascular reactivity accounts for the programming of cardiovascular diseases in the aged rat when they are predominant and if the reactivity of the autoregulated cerebral vasculature is altered. We studied renal arteries (RA) because their vascular tone is involved in modulation of arterial pressure control (Am J Physiol; 2002; 283: R441–50) and middle cerebral arteries (MCA) because depressive disorders that are associated with dysregulation of the HPA axis (J Clin Endocrinol Metab 1997; 82: 234–8) increase stroke mortality (Am J Psychiatry 2003; 160: 1823-9).
Study design: Pregnant dams received saline (n = 6) or 170 μg/kg dexamethasone (n = 6) at day E19 and 20 equivalent to 2×12 mg dexamethasone administered to a 70 kg pregnant woman. Vascular response of the RA and MCA to endothelium-dependent and independent mediators was measured in male offspring at 2.5 years of age using wire myography. Vessels were inspected histologically for intact endothelium.
Results: Basal vasoconstrictor and dilator responses to all mediators were less pronounced in MCA than RA reflecting autoregulation ($p < 0.05$). Contractility but not sensitivity to K^+ and noradrenaline was enhanced in MCA and even more pronounced in RA after prenatal dexamethasone exposure ($p < 0.05$). Relaxation to Ach and PGE_2 after precontraction with noradrenaline was similarly decreased in both vessels ($p < 0.05$).
Conclusions: Prenatal dexamethasone exposure at the dose used clinically to accelerate fetal lung maturation increases the renal and cerebral vascular tone in the aged rat by endothelium-dependent and independent mechanisms. This effect is more pronounced in the renal than in the cerebral circulation.

6D-4 Associations between maternal nutrition during pregnancy and plasma leptin concentrations in rural Indian children; Pune Maternal Nutrition Study

S.S. Naik[1]*, J.A. Deshpande[1], D.S. Bhat[1], C. Joglekar[1], V.U. Deshpande[1], T.M. Deokar[1], S. Rao[1], S.S. Hirve[1], C. Fall[2], C.S. Yajnik[1]. [1]*Diabetes Unit, KEM Hospital & Research Centre, Pune, India,* [2]*MRC Epidemiology Resource Centre, University of Southampton, Southampton, UK*
E-mail: diabetes@vsnl.com

Aim: To study associations between maternal characteristics during pregnancy and plasma leptin concentration in 6-year-old children.
Study design: The Pune Maternal Nutrition Study (PMNS) is a prospective study of maternal nutrition and fetal growth. We recorded maternal pre-pregnancy characteristics, and food intake and physical activity during pregnancy. Circulating levels of nutrients and metabolites were measured twice during pregnancy. Anthropometric measurements on 698 children were carried out at birth and then serially every 6 months. At 6 years body composition and circulating levels of leptin, lipids, and insulin

resistance (HOMA-R) were measured. Ethical approval and consent were obtained.
Subjects: Children born in PMNS.
Outcome measures: Plasma leptin concentrations at 6 years.
Results: Plasma leptin concentration was higher in girls than boys (3.1 vs 2.4 ng/ml, $p < 0.001$). Plasma leptin concentration was associated with adiposity and plasma glucose, lipids, and HOMA-R ($p < 0.01$, all). Those who were born thin (skin folds) but grew rapidly from 3 years had higher plasma leptin concentration. Higher maternal weight gain in early pregnancy and frequent consumption of fruits and milk products at 18 weeks gestation predicted higher leptin concentration ($p < 0.01$), macronutrient intake and physical activity were not related. Higher maternal red cell folate concentrations at 18 & 28 weeks gestation and lower vitamin C concentrations at 28 weeks predicted higher leptin concentration in children at 6 years.
Conclusions: Maternal micronutrient food intake and high circulating folate concentrations in pregnancy predict plasma leptin concentration (and adiposity) in the offspring, suggesting intrauterine nutritional programming of adiposity.

6D-5 Programming of hypothalamic neuropeptide gene expression in rats by early life nutrition

R.L. Cripps[1]*, M.S. Martin-Gronert[1], Z.A. Archer[2], C.N. Hales[1], J.G. Mercer[2], S.E. Ozanne[1]. *[1]Department of Clinical Biochemistry, University of Cambridge, Level 4, Box 232, Addenbrookes Hospital, Hills Road, Cambridge, CB2 2QR, UK, [2]Division of Obesity and Metabolic Health, Rowett Research Institute, Greenburn Road, Bucksburn, Aberdeen, AB21 9SB, Scotland, UK*
E-mail: rlc34@cam.ac.uk

Aims: Early life nutritional experiences are linked to altered susceptibility to obesity. The aim of this study was to see the effect of maternal diet on energy balance hypothalamic neuropeptides in early life.
Study design: Wistar rats were fed a control diet (20% protein) or an isocaloric low protein (LP) diet (8%) during pregnancy. Pups were cross-fostered to give 3 groups, control animals (offspring of control dams during pregnancy and lactation), recuperated animals (offspring of LP dams and suckled in litters of 4 by control dams) and postnatal low protein (PLP) animals (offspring of control dams that were suckled by LP dams in unculled litters).
Subjects: Fed and fasted male rats at weaning.
Outcome measures: Leptin, insulin and glucose were measured and gene expression of energy balance hypothalamic neuropeptides evaluated using *in situ* hybridisation. Significance was determined by one-way ANOVA.
Results: Recuperated pups caught up in size with controls by day 21, yet were hypoleptinemic compared to controls when fed ($p < 0.001$) and showed no drop in leptin concentration on fasting. Despite their lower fed leptin concentration, recuperated animals did not differ from controls in their hypothalamic gene expression. PLP offspring had lower body weight than controls, associated with hypoglycemia, hypoinsulinemia and hypoleptinemia and increased leptin receptor, NPY and AgRP gene expression and decreased POMC and CART gene expression in the ARC (all $p < 0.05$).
Conclusions: These results suggest that the early nutritional environment can affect the regulation of energy balance circuits that could alter future obesity risk.

6D-7 Prenatal exposure to famine and functional bowel disorders

T.K. Klooker[1], B. Braak[1], R.C. Painter[1], S.R. de Rooij[1], R.M. van Elburg[2], R.M. van den Wijngaard[1], G.E. Boeckxstaens[1], T.J. Roseboom[1]*. *[1]Academic Medical Center, Amsterdam, The Netherlands, [2]VU Medical Center, Amsterdam, The Netherlands*

Aims: to assess whether prenatal exposure to the Dutch famine is associated with an increased risk of functional gastrointestinal disorders.
Study design: cohort study.
Subjects: 850 men and women (aged 58) born in the Wilhelmina Gasthuis in Amsterdam around the time of the Dutch famine, whose birth records have been kept.
Outcome measures: Rome II questionnaire.
Results: People exposed to famine in early gestation more often suffered from one or more functional bowel disorder (odds ratio 1.81, 95% confidence interval 1.04–3.15), in particular functional abdominal bloating (odds ratio 2.58, 95% confidence interval 1.27–5.26). Exposure to famine in late or mid gestation was not associated with an increased risk of any functional bowel disorder. Nor was size at birth associated with the risk of functional bowel disorders.
Conclusions: Undernutrition in early (but not in mid or late) gestation appears to negatively affect gut function in later life.

6E-3 Absorption of oral vitamin B-12 in Indians; the Pune Maternal Nutrition Study

D.S. Bhat[1]*, N.V. Thuse[1], C.V. Joglekar[1], A.J. Bhalerao[1], S.S. Naik[1], P.C. Yajnik[1], C. Fall[2], H. Refsum[3], C. Johnston[3], C.S. Yajnik[1]. *[1]Diabetes Unit, KEM Hospital & Research Centre, Pune, India, [2]MRC Epidemiology Resource Centre, University of Southampton, UK, [3]Oxford Centre for Gene Function, Department of Physiology, Anatomy and Genetics, University of Oxford, UK*
E-mail: diabetes@vsnl.com

Aim: Vitamin B12 deficiency is common among Indian mothers and is associated with an increased risk of delivering a small-for-gestational age baby. Vitamin B12 deficiency in Indians may be due to low dietary intake or poor intestinal absorption. We assessed vitamin B12 absorption by measuring the rise in plasma holotranscobalamin concentration after oral vitamin B12.
Study design: Sixty-five families (Group A) received $10\ \mu g \times 3$ doses and 44 families (Group B) received $2\mu g \times 3$ doses of oral B12 every 6 hours. Fasting blood samples were collected before and after the oral dose. Subjects gave signed consent and the Ethical Committee approved the study protocol.
Subjects: 109 families from the Pune Maternal Nutrition Study.
Outcome measures: A rise in plasma holotranscobalamin of $\geqslant$15% and >15pM is considered adequate absorption.
Results: Twenty-seven percent of children, 69% fathers and 49% mothers had low B12 levels (<150pM) at baseline. After oral vitamin B12 there was a >600% rise in plasma holotranscobalamin in group A, and a >300% rise in group B. Vitamin B12 rose by ~45% and ~25% respectively. Ninety-four percent of children and 88% of parents had normal absorption. Pre-dose vitamin B12 was not related to the observed rise in holotranscobalamin. Mean plasma total homocysteine fell significantly (18.6 to 17.4μM and 20.1 to 18.2μM respectively for groups A & B, $p \leqslant 0.003$ for both) during the study.
Conclusions: Intestinal malabsorption is unlikely to be a major cause of the high prevalence of vitamin B12 deficiency in Indians.

6E-4 Body mass index from birth to adulthood and metabolic risk factors for cardiovascular disease; data from the New Delhi Birth Cohort

C.H.D. Fall[1]*, H.P.S. Sachdev[2], C. Osmond[1], R. Lakshmy[3], S.K. Dey Biswas[4], D. Prabhakaran[3], N. Tandon[3], S. Ramji[5], K.S. Reddy[7], D.J.P. Barker[1], S.K. Bhargava[6]. *[1]Medical Research Council Epidemiology Resource Centre, University of Southampton, Southampton, UK, [2]Sitaram Bhartia Institute of Science and Research, New Delhi, India, [3]All India Institute of Medical Sciences, New Delhi, India, [4]Indian Council of Medical Research, New Delhi, India, [5]Maulana Azad Medical College, New Delhi, India, [6]Public Health Foundation of India, New Delhi, India, [7]Department of Paediatrics, Sunder Lal Jain Hospital, New Delhi, India*
E-mail: chdf@mrc.soton.ac.uk

Aims: To examine the relationship of body mass index (BMI) and height at birth and during childhood to risk of adult metabolic syndrome.